AI-Statistical Machine Learning Approaches to Liver Disease Prediction

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Proposed Solution:

The improvement of patient care, research, and policy is significantly impacted by medical diagnoses. Medical practitioners employ a variety of pathological techniques to make diagnoses based on medical records and the conditions of the patients. Disease identification has been significantly enhanced by the application of artificial intelligence and machine learning in conjunction with clinical data. Data- driven, machine learning (ML) techniques can be used to test current approaches and support researchers in potentially innovative judgments. The goal of this work was to use ML algorithms to derive meaningful predictors of liver disease from the medical data of 615 persons**.** Liver diseases avert the normal function of the liver. Mainly due to the large amount of alcohol consumption liver disease arises. Early prediction of liver disease using classification algorithms is an efficacious task that can help the doctors to diagnose the disease within a short duration of time. Discovering the existence of liver disease at an early stage is a complex task for the doctors. The main objective of this project is to analyze the parameters of various classification algorithms and compare their predictive accuracies so as to find out the best classifier for determining the liver disease. This Project examines data from liver patients concentrating on relationships between a key list of liver enzymes, proteins, age and gender using them to try and predict the likeliness of liver disease. Here we are building a model by applying various machine learning algorithms find the best accurate model. And integrate to flask based web application. User can predict the disease by entering parameters in the web application**.**

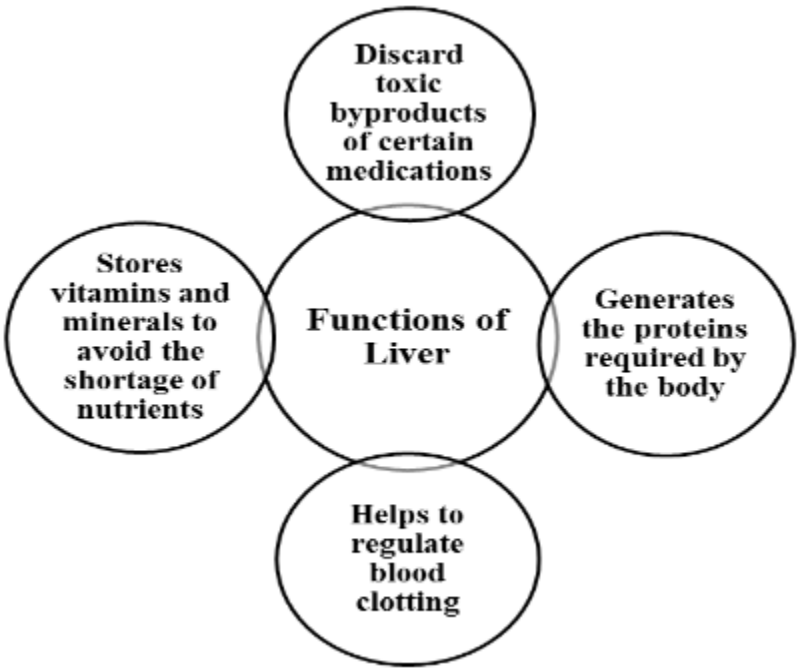
Idea of Prediction of Liver Disease Using Different Classification Algorithms:

Abstract:

Liver diseases averts the normal function of the liver. Mainly due to the large amount of alcohol consumption liver disease arises. Early prediction of liver disease using classification algorithms is an efficacious task that can help the doctors to diagnose the disease within a short duration of time. Discovering the existence of liver disease at an early stage is a complex task for the doctors. The main objective of this paper is to analyse the parameters of various classification algorithms and compare their predictive accuracies so as to find out the best classifier for determining the liver disease. This paper focuses on the related works of various authors on liver disease such that algorithms were implemented using Weka tool that is a machine learning software written in Java. Various attributes that are essential in the prediction of liver disease were examined and the dataset of liver patients were also evaluated. This paper compares various classification algorithms such as Random Forest, Logistic Regression and Separation Algorithm with an aim to identify the best technique. Based on this study, Random Forest with the highest accuracy outperformed the other algorithms and can be further utilised in the prediction of liver disease.

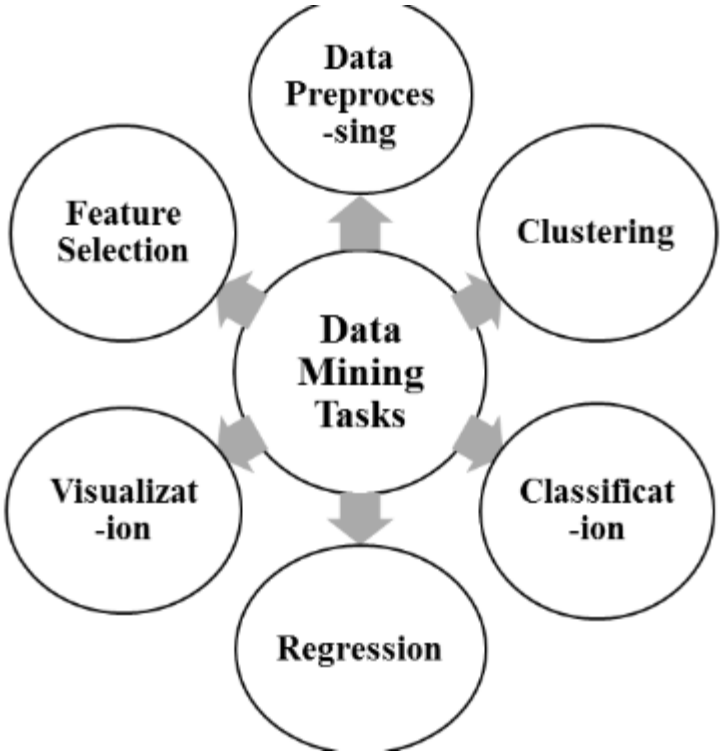
INTRODUCTION:

Healthcare is an efficacious part of a country's economy. It makes a provision to improve the health by taking the certain essential measures into consideration. It is mainly composed of the Primary Care, Secondary Care and Tertiary Care Thus, ―The main aim behind the Healthcare System is to deliver the best quality of services and to predict the diseases at an early stage.‖ Liver is an essential organ of our body. There is a great need for an early detection of liver disease so as to prevent complete liver failure, which can result in patient's death. For the proper diagnosis, it is necessary to evaluate some of the main attributes of liver patient's dataset Some of the main attributes of liver disease include, ―Total_bilirubin, direct_bilirubin, alkaline_phosphotas, total_protein, albumin and globulin ratio. It is the challenging task for doctors to accurately predict the liver disease. Various classification techniques are used to classify the data and predict the liver disease through the datasets of liver patients. Having access to classification algorithms with large amount of data will help clinicians make better decisions and ultimately improve patient outcomes with an accurate prediction of liver disease. This paper shows a survey about the classification techniques that can be used for the prediction of liver disease and gives an idea for future work, that which classification technique can be utilised further for diagnosis of the liver disease.



Tool Used Weka Tool:

Weka is an efficient machine learning software which is written in java and developed at Waikato. It is used to classify various parameters when different algorithmic approaches are applied based on the datasets. It is an accumulation of visualization tools and algorithms that can be utilised for analysing the data and predictive modelling. Classification algorithms are implemented using Weka that are utilised for the prediction of liver disease at an early stage [3]. The experimental results of classification algorithms provide ease to the doctors through the provision of accurate patient's pathological status.



Classification Algorithms Used Random Forest:

Random forests is a supervised machine learning algorithm that supports both classification and regression tasks. It mainly deals with the construction of multiple decision trees. It follows a basic approach where a dataset is divided into a batch of random datasets such that a decision tree is built for each random datasets . Thus, —The forest is an ensemble of decision trees that are trained and all of them come up with a decision such that a majority vote is considered which results in a final single decision. It can operate on large data set and maintains the accuracy for missing data.

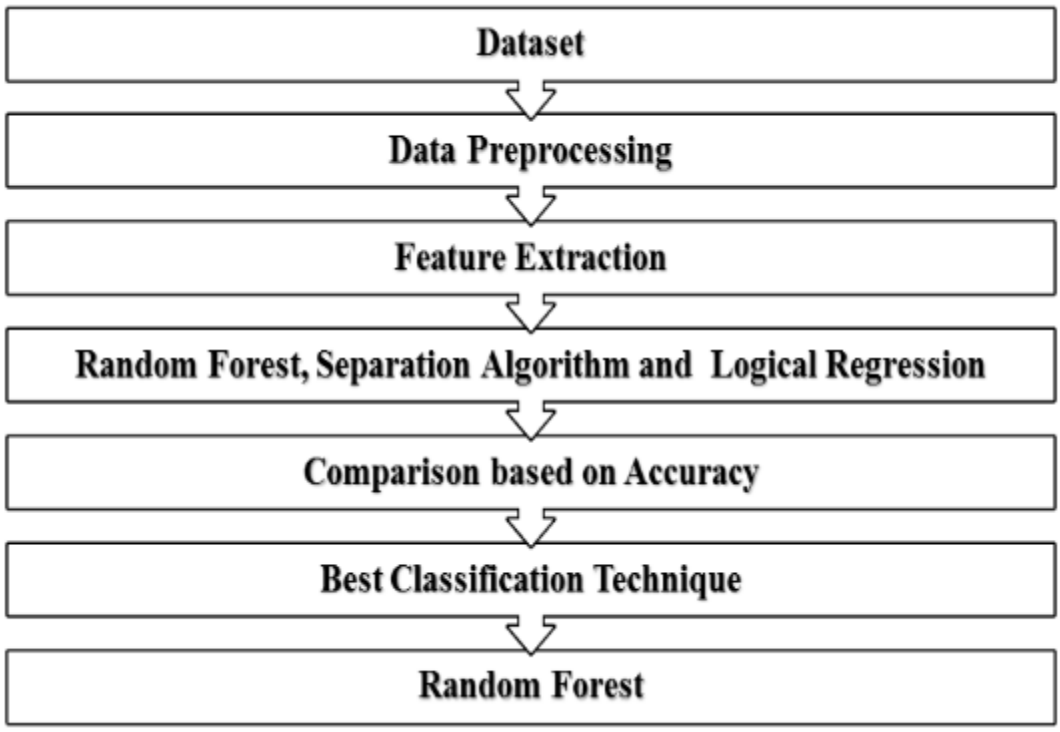
Logistic Regression:

Logistic Regression is a supervised machine learning algorithm that is used for classification. It is utilised for predictive modeling and helps to calculate the possibility of a particular event taking place. It mainly deals with the prediction of binary outcomes for a given set of independent variables and determines the discrete values. It performs the binary classification and predicts the future outcomes based on training from the previous output.

Separation:

Algorithm

Separation algorithm is a novel approach that mainly deals with an idea to first treat every data point as a fundamental entity. It mainly signifies that, —Every data point is separated which may be d-dimensional from every other point by hyper planes such that no two points are unseparated by at least one hyper plane. This algorithm is non-iterative and demonstrate an approach that once the data points are separated by planes then these planes are utilised to classify the data points. C. Methodology In this section, a flow diagram is demonstrated which consist of various classification algorithms that are evaluated and compared on the basis of accuracy parameter. The algorithms are analysed so as to find the best classifier, which can be further used to predict the liver disease. On the basis of accuracy, Random Forest algorithm with 100% accuracy outperformed other algorithms.



The remaining portion of the paper is organized as follows, —Section I consists of Introduction that describes about the tool used and various classifiers that are required for an accurate prediction along with the methodology that contains a flowchart, Section II consists of Literature Survey that provides a description of the work performed by several authors and also include a table comparing the work of several authors, Section III consists of a Conclusion that describes about the accomplishment of this study by providing the best classification technique that can be utilised for an accurate prediction of liver disease and followed by References.

Table 1. Comparison Table of parameters used in different Classification Algorithms for Liver Disease Prediction.

Features	***Hoon Jin et al. (2014)***				***Ayesha Pathan et al. (2018)***				***Tapas Ranjan Baitharu et al. (2016)***			
Objective	To evaluate the results of classification algorithms for better prediction of liver disease.				To implement different classification algorithms using Weka in order to predict the liver disorder.				To forecast liver disease from Liver Function Test dataset using various classification algorithms.			
Dataset	UCI Repository **(Liver Disease Dataset).**				UCI Repository **(Liver Disease Dataset).**				UCI Repository **(Liver Disease Dataset).**			
Concerned Disease	Liver Disease				Liver Disease				Liver Disease			
Environment Used	Weka				Weka				Weka			
Attributes Used	11				11				7			
Algorithms Used	**Naïve Bayes**	**Decision Tree**	**Multilayer Perceptron**	**k-NN**	**Naïve Bayes**	**Ada Boost**	**J48**	**Random Forest**	**J48**	**ZeroR**	**Naïve Bayes**	**Multilayer Perceptron**
Specificity	0.952	0.352	0.303	0.467	-	-	-	-	-	-	-	-
Sensitivity	0.374	0.831	0.829	0.727	-	-	-	-	-	-	-	-
TP Rate	-	-	-	-	-	-	-	-	-	-	-	-
Precision	95.1	76.3	74.9	77.4	0.796%	0.508	0.872	1	-	-	-	-
F Measure	-	-	-	-	0.56	0.594	0.872	1	-	-	-	-
Accuracy	53.9	69.4	67.9	65.3	55.84%	71.31%	87.46%	100%	68.97	57.971	62.8986	60.2899
Error Rate	-	-	-	-	44.16%	28.69%	12.54%	0.00%	-	-	-	-
Recall	-	-	-	-	0.558	0.713	0.875	1	-	-	-	-
Kappa Statistics	-	-	-	-	-	-	-	-	0.3401	0	0.153	0.4023
Mean Absolute Error	-	-	-	-	-	-	-	-	0.3673	0.4874	0.4597	0.3543
Root Mean Squared Error	-	-	-	-	-	-	-	-	0.5025	0.4936	0.5083	0.4523
Relative Absolute Error	-	-	-	-	-	-	-	-	75.3511	100	102.9673	72.68
Best Algorithm	Naïve Bayes				Random Forest				Multilayer perceptron			
Result	In terms of precision, Naïve Bayes gave better classification results. Also, appropriate algorithms were evaluated and analysed for prediction of the liver disease.				Random Forest Algorithm gave better performance results as compared to other algorithms.				In terms of accuracy, multilayer perceptron gave best classification results as compared to other classifiers.			

Business Intelligence framework to support Chronic Liver Disease Treatment:

ABSTRACT:

Business Intelligence (BI) framework designs the architecture of business intelligence information system which uses expert systems and Artificial Intelligence technology to support clinical decision and draw the strategy against chronic liver disease in Egypt. It makes integrated diagnostic and medical advice bases on the collected patient's information, providing reference for the clinical medical officers. This paper aims to support decision function and in particular utilization of

historical data laboratory and outcome data processed through artificial intelligence tools. The combination of historical data and predictive tools provides valuable information in the hands of physicians as they develop a course of treatment for a patient.

INTRODUCTION:

The framework of business intelligence system aims to support clinical decision for national strategy against chronic liver disease in Egypt. Liver fibrosis is a chronic disease that results from viral hepatitis, fatty liver disease, alcohol abuse or autoimmune and genetic liver disease. Chronic infection with hepatitis C virus (HCV) is one of the most common causes of cirrhosis in the world today. Assessment of fibrosis is important in chronic hepatitis C for a number of reasons including decision-making regarding treatment and predicting prognosis. The Arab Republic of Egypt has the highest prevalence of hepatitis C in the world. The national prevalence rate of hepatitis C virus (HCV) antibody positivity has been estimated to be between 10-13% according to a study published on August 2010 in the National Academy of Sciences. Chronic HCV is the main cause of liver cirrhosis and liver cancer in Egypt and, indeed, one of the top five leading causes of death. Genotype 4 represents over 90% of cases in Egypt. Non-invasive methods have been extensively developed in recent years as alternatives to liver biopsy for predicting liver fibrosis in patients with chronic hepatitis C, the most validated being

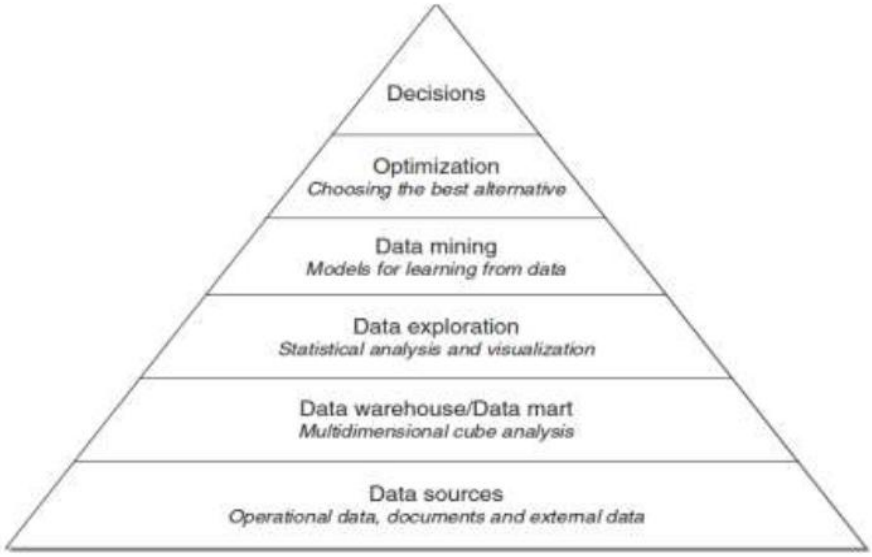
FibroTest (FT) and ActiTest (AT) (Biopredictive, Paris, France).

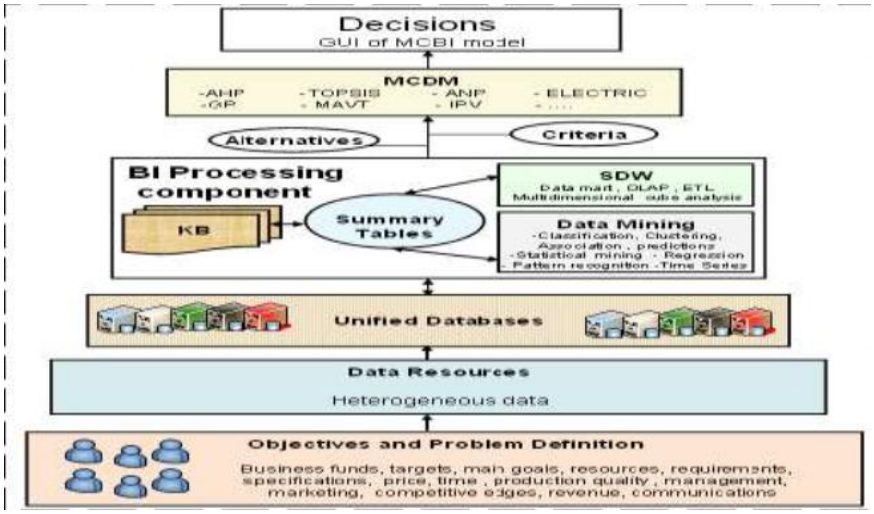
FT measures the degree of fibrosis and combines five serum biochemical markers (Alpha2-macroglobulin, haptoglobin, gamma glutamyltranspeptidase (GGT), total bilirubin, and apolipoprotein A1) with the patient's age and sex. The outcomes describe the degree of fibrosis [FT unit range from 0-no fibrosis to 1-cirhosis]. AT measures the degree of necrosis and inflammation by combining the above measures with ALT [AT unit range from 0- no inflammation to 1- high degree of inflammation] This paper is divided into six sections. Section 2 presents background and literature reviews for previous work in biomedical for chronic liver disease and business intelligence system. Problem definitions and Research methodology are presented in section 3. Section 4 presents the proposed business intelligence framework to treat the chronic liver disease. Section 5 presents the case study for deployment of business intelligence framework to treat the chronic liver. Finally, conclusions and future work are presented in section

BACKGROUD AND PREVIOUS WORK:

The "gold standard" for assessing fibrosis, liver biopsy (LB), is recommended prior to the initiation of antiviral therapy; in addition, it is vital for monitoring fibrosis progression. Unfortunately, this procedure is invasive, prone to complications, including hemorrhage and death, and has a high risk of sampling error.

Biochemical markers for liver fibrosis (FT) and necroinflammatory features ActiTest (AT) are an alternative to LB, in patients with chronic hepatitis C. Since September 2002, FT and AT has been used in several countries as an alternative to liver biopsy in order to estimate liver fibrosis and necroinflammatory activity in chronic viral hepatitis C. Several prospective studies have validated these panels of tests in chronic viral hepatitis C and demonstrated its predictive value and the better benefit: risk ratio than biopsy.





Social impact:

Liver Transplantation in Patients with Alcoholic Liver Disease:

REVIEW Liver Transplantation in Patients With Alcoholic Liver Disease Michael R. LuceyDivision of Gastroenterology and Hematology, Department of Medicine, University of Wisconsin, Madison, Walkthrough alcoholic liver disease (ALD) is one of the most common indications for liver transplantation (LT), there are stillunresolved controversies about the goals of treatment, the referral, evaluation, and selection of patients with ALD for LT,and their care after LT. It is uncertain whether there is a large unmet need for LT among patients with ALD because of theunmeasured effects of recent drinking, relapse, and recovery with abstinence in this population. A careful assessment ofthe extrahepatic effects of alcohol-related end-organ damage is needed for ALD patients who are referred for an LT evalua-tion. Although there clearly is a relationship between the length of sobriety and future abstinence, the present methods forpredicting future drinking are inexact. The survival of ALD patients after LT is as good as the survival of non-ALD patients,although patients with coincident ALD and hepatitis C virus have higher mortality and morbidity rates. After LT, ALD patientshave an increased risk of developing malignancies and cardiovascular disease. These risks appear to be linked to cigarettesmoking. Covert drinking occurs both before and after transplantation, and approximately 20% of patients return to harmfuldrinking after LT. Harmful drinking after LT (instead of slips) causes liver damage and reduces survival. Better therapies for controlling addictions to alcohol and nicotine are needed for ALD patients. Alcoholic liver disease (ALD) is the second most com-mon diagnosis for patients undergoing liver trans-plantation (LT) in the United States and Europe.1,2ALD, either alone or in combination with a hepatitis

Cvirus (HCV) infection, accounted for 20% of all pri-mary transplants in the United States between 1988and 2009 (>19,000 recipients). This is a remarkablenumber, especially when it is contrasted with the pre-diction made at the landmark National Institutes ofHealth consensus conference in 1984 that not manypatients with ALD would be selected for LT.3More-over, the outcomes for patients who undergo trans-plantation for ALD are at least as good as those forpatients with most other diagnoses and are betterthan those for patients with HCV.4However, the appa-rent success of LT for ALD masks a more complexreality. There are still unresolved controversies aboutLT for patients with ALD. In this review, I address sev-eral of these contentious issues, which include the fol-lowing: the goals of treatment; the referral, evaluation,and selection of patients for LT; and the impact of thediagnosis of ALD on care after LT.

GOALS OF TREATMENT:

The goal of LT is the treatment of life-threatening liverfailure or cancer that is intractable to medical man-agement. The medical management of ALD starts withabstinence from alcohol. Patients with alcoholism whoremain abstinent can recover from advanced liver fail-ure, and stable liver function can be reestablishedwith the resolution of portal hypertension.5,6Unfortu-nately, alcoholism is a disease of relapses andremissions, and this pattern persists even after life-threatening episodes such as variceal hemorrhage.7The frequency of recovery from decompensated liver failure due to ALD is restricted by the frequency ofdrinking relapses.8A therapeutic formulationaddressing LT for ALD needs to encompass the psy-chological and somatic health of potential candidates.In other words, LT should be seen as a treatment ofend-stage liver failure within a comprehensive careprogram that addresses the management of addic-tions to alcohol, cigarettes, and any other addictivedrugs.

REFERRAL OF ALD PATIENTS FORAN LT EVALUATION:

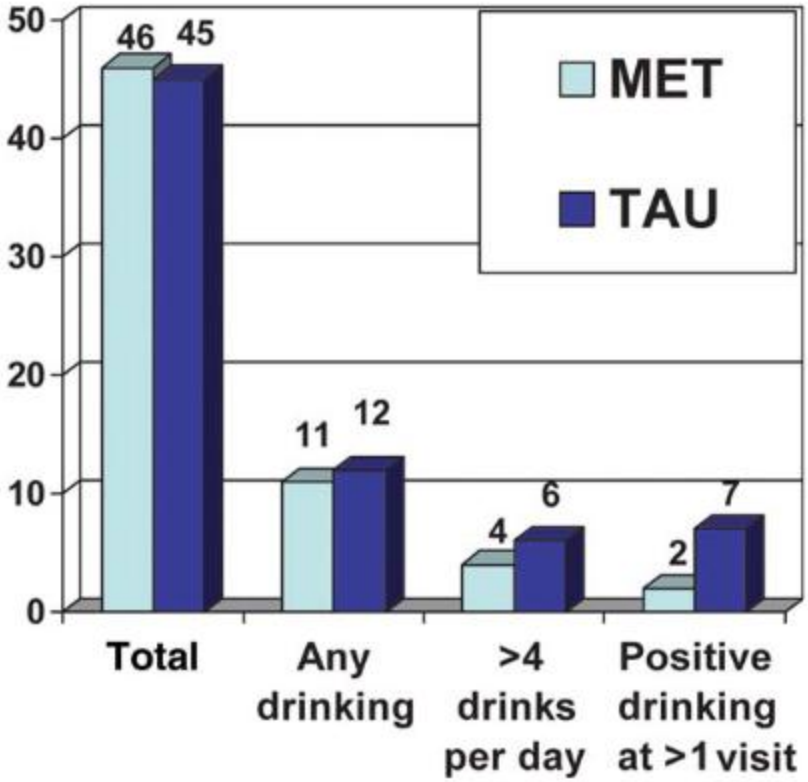
The combined prevalence of alcohol abuse and de-pendence in the United States has been estimated tobe 84.5 cases per 1000 persons who are 18 yearsold or older; this translates into approximately 18million adults at risk for ALD.9The estimated age-adjusted death rate related to liver cirrhosis in 2005was 9.2 deaths per 1000 persons; this translatesinto approximately 27,000 deaths.9In 2004, liverdisease (not including viral hepatitis) accounted for2.4 million ambulatory care visits, and it was thethird most common digestive diagnosis on hospitaldischarge records.10Although these data do not pro-vide a precise estimate of the prevalence of patientswith life-threatening ALD who are suitable candi-dates for LT, previous researchers have asserted thatALD patients are under-referred for LT in the UnitedStates.11On the other hand, data documenting the processof referral and evaluation for patients with problemdrinking are inconclusive on this point. Julapalliet al.12described a cohort of 199 patients with liverdisease who received their medical care at a largemetropolitan Veteran Affairs medical center, albeit onewithout an LT program, between October 2001 andSeptember 2003. All members of the cohort met theguidelines for referral for possible LT; nevertheless,despite 300 clinical encounters, only 15 patients wereeventually referred for evaluation. Even when thosepatients with a history of recent alcohol use wereremoved from consideration, the presence of

ALD wasa significant negative determinant for the considera-tion of an LT referral. In contrast, in a retrospectivestudy of patients at a community hospital in SouthWales, United Kingdom from 1987 to 1990, althoughALD was the most common diagnosis among patientswho were not referred to an LT unit, continuing drink-ing was the usual explanation; the writers consideredthis to be appropriate.13Similarly, when Veldt et al.8undertook a prospective assessment of patientsadmitted to a French inpatient liver unit on accountof alcohol-associated liver failure, the combination ofdeath during the initial hospital stay, recovery withabstinence, and alcoholic relapse during the immedi-ate follow-up meant that very few actual transplantcandidates emerged. Thus, whether there is an unmetneed for transplantation in patients with liver failuredue to ALD remains unanswered.

LT FOR PATIENTS WITH SEVEREALCOHOLIC HEPATITIS:

Patients with severe alcoholic hepatitis present partic-ular challenges to transplant teams because theyhave invariably consumed alcohol in the previousmonth. Patients who fail to respond to corticosteroidshave a very high 90-day mortality rate. Previously, in the 1997 American Society of Transplantation/American Association for the Study of Liver Diseasesguidelines, alcoholic hepatitis was an absolute contra-indication to placement on the transplant waiting list;this is also the position endorsed by the UK Liver Ad-visory Group.20,33 However, data are emerging from aEuropean multicenter study about a carefully selectedgroup of patients suffering from their first episode ofsevere alcoholic hepatitis. These

patients, for whommedical treatment had failed but who had received afavorable psychosocial assessment, had excellent in-termediate-term survival and a low frequency ofharmful drinking after LT.41Consequently, transplantgroups on both sides of the Atlantic have argued forplacement on the LT waiting list for the occasionalpatients with life-threatening alcoholic hepatitis whomeet these stringent criteria

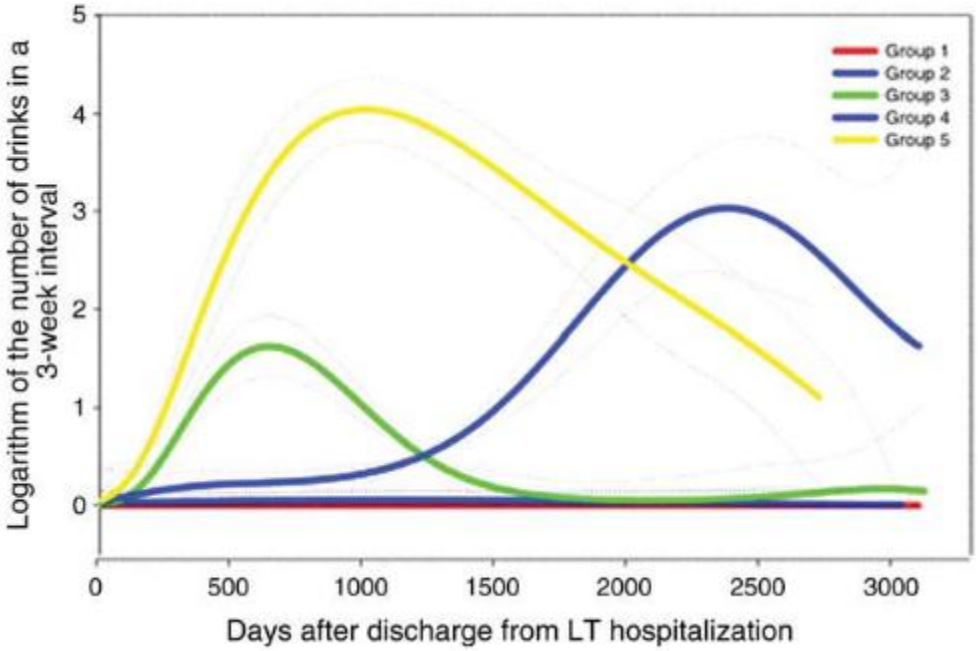


MORTALITY AND MORBIDITYAFTER LT IN ALD PATIENTS:

ALD patients selected for LT in the United States havepretransplant and posttransplant survival rates simi-lar to those of LT recipients without a diagnosis ofALD.2,4An analysis of large multicenter databasesfrom the United States and Europe showed greatermortality in patients with comorbid ALD and HCV,2,4although this was not found in a single-center se-ries.44It is possible that the advent of more effica-cious therapies for HCV either before or after trans-plantation will improve the survival of

comorbidpatients.Although ALD patients have survival rates similarto those of LT recipients without ALD, the causes ofdeath after transplantation differ between recipientswith ALD and recipients without ALD. A retrospectiveanalysis of the European Liver Transplant Registry byBurra et al.2showed that cardiovascular causes andde novo malignancies were significantly overrepre-sented in patients who had undergone transplanta-tion for ALD versus recipients without ALD. Similarly,Watt et al.45showed that in a prospective cohort of780 primary graft recipients, ALD was significantlyassociated with the risk of cardiovascular death 1year after LT.45Studies from the European LiverTransplant Registry and several single centers suggestthat patients who undergo transplantation for ALDhave an increased incidence of de novo cancers aftertransplantation, and these cancers are associatedwith worse survival.46–49These studies do not showan association between new-onset cancers and alco-holic relapse. In some but not all of these studies,new tumors were concentrated in the aerodigestivetract. The stratification of cardiovascular deaths andnew-onset cancers of the aerodigestive tract inpatients receiving LT for ALD strongly hints at acausal linkage with cigarette smoking. Smoking isprevalent in ALD patients undergoing an evaluationfor LT, and DiMartini et al.50showed that recipientsof LT for ALD who were smokers before transplanta-tion quickly reestablish smoking at addictive levels. Ifthe link between cigarette smoking and death from ei-ther cancer or cardiovascular disease is correct, itpoints the way to improving posttransplant healththrough the promotion of smoking cessation in LTrecipients with alcoholism and in all LT recipients. Evidence of alcoholic relapse in conjunction with afailure to take immunosuppressant is patchy. Someaccounts have suggested an association between alco-holic relapse and so-called noncompliance, whereasothers have contended that

noncompliance is no morecommon in these patients than in patients withoutALD



Silymarin as Supportive Treatment in Liver Diseases: A Narrative Review:

Abstract:

Silymarin, an extract from milk thistle seeds, has been used for centuries to treat hepatic conditions. Preclinical data indicate that silymarin can reduce oxidative stress and consequent cytotoxicity, thereby protecting intact liver cells or cells not yet irreversibly damaged. Eurosil 85® is a proprietary formulation developed to maximize the oral bioavailability of silymarin. Most of the clinical research on silymarin has used this formulation. Silymarin acts as a free radical scavenger and modulates enzymes associated with the development of cellular damage, fibrosis and cirrhosis. These hepatoprotective effects were observed in clinical studies in patients with alcoholic or non-alcoholic fatty liver disease, including patients with

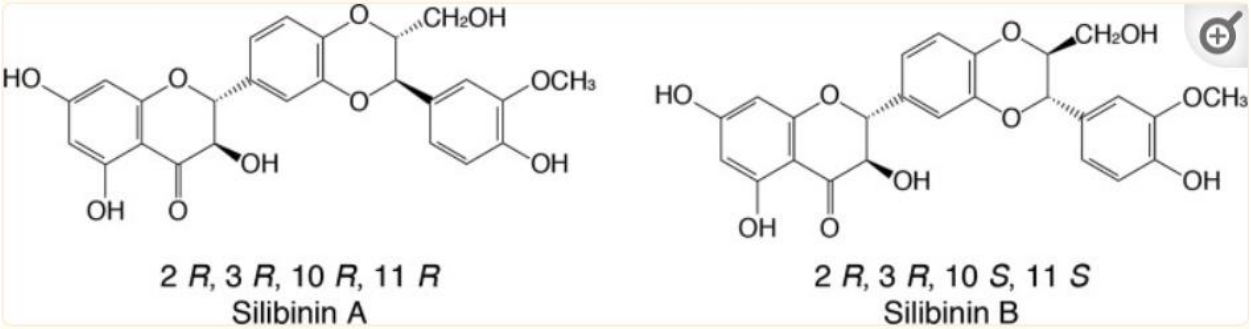
cirrhosis. In a pooled analysis of trials in patients with cirrhosis, silymarin treatment was associated with a significant reduction in liver-related deaths. Moreover, in patients with diabetes and alcoholic cirrhosis, silymarin was also able to improve glycemic parameters. Patients with drug-induced liver injuries were also successfully treated with silymarin. Silymarin is generally very well tolerated, with a low incidence of adverse events and no treatment-related serious adverse events or deaths reported in clinical trials. For maximum benefit, treatment with silymarin should be initiated as early as possible in patients with fatty liver disease and other distinct liver disease manifestations such as acute liver failure, when the regenerative potential of the liver is still high and when removal of oxidative stress, the cause of cytotoxicity, can achieve the best results.

Silymarin Pharmacology

Chemistry

Silymarin is an extract from the dried seeds and fruits of the milk thistle plant (*S. marianum*). Milk thistle has been used medicinally in Europe since the first century AD. Its medicinal properties were mentioned in the writings of the Greek physician and botanist Dioscorides (40–90 AD), who recommended it as a treatment for snakebite. The sixteenth century English herbalist Nicholas Culpeper recommended milk thistle for jaundice and for expelling stones. By the nineteenth century, a German scientist, Johannes Gottfried Rademacher, had shown that extracts or 'tinctures' from milk thistle seeds were beneficial for treating patients with liver disorders . The milk thistle extract silymarin is a complex mixture of plant-derived compounds identified as mostly flavonolignans, flavonoids (taxifolin, quercetin) and polyphenolic molecules . These compounds are known to be antioxidants in addition to having several other biologic properties . The four main flavonolignan isomers in silymarin are silibinin, isosilibinin,

silichristin and silidianin, but the most prevalent and biologically active of these is silibinin (also called silybin). Approximately 50–60% of the silymarin complex is silibinin, with the other flavonolignan isomers comprising about 35%: silichristin (~ 20%), silidianin (~ 10%) and isosilibinin (~ 5%) Silibinin is a polyphenolic flavonoid antioxidant with the molecular formula of $C_{25}H_{22}O_{10}$ and with a molecular weight of 482.44 g/mol . Silibinin itself is mixture of two diastereomers, silibinin A and silibinin B, in an approximately equimolar ratio. It undergoes phase I and phase II biotransformation in the liver. During phase II, multiple conjugation reactions have been observed that include the formation of glucuronide and glucuronide sulfate derivatives



Silymarin was first isolated in 1968 by German scientists at the University of Munich and then described and patented by the German herbal medicine manufacturer Madaus as a specific treatment "against liver diseases". The first commercial preparation of silymarin was developed by Rottapharm/Madaus (Cologne, Germany) and complies with the analytical specifications reported in the European Pharmacopoeia 01/2005 under "Milk Thistle fruit." It is registered as a drug for liver diseases in many countries in Europe, Asia, America, Africa and Australia. Different forms, including capsules and tablets, are available with different dosages; the recommended daily dosage (depending on the commercial formulation

used) is between 420 and 600 mg, and the majority of clinical trials have been conducted with a dosage of 140 mg three times a day.

Pharmacokinetics:

Crude silymarin extract is lipophilic and poorly soluble in water, so only about 20–50% is absorbed from the gastrointestinal tract after ingestion For this reason, formulation scientists have endeavored to improve the oral bioavailability and solubility of silymarin preparations, but the commercially available silymarin-containing products differ significantly in their content, dissolution and oral bioavailability of the active ingredient silibinin . In 1995, Rottapharm/Madaus invented a co-precipitation processing method that produced a high-quality silymarin (90–96% purity; approximately 60% of the content being silibinin) with an enhanced dissolution profile (> 90% of silibinin liberated by the co-precipitate); this advanced processing method was subsequently patented in 2014 under the trade name Eurosil 85® . Most of the published clinical research on silymarin has used this standardized pharmaceutical preparation. The silymarin formulation derived using the Eurosil 85® extraction method contains 60% silibinin and has a bio-dissolution of up to 85%. Therefore, the commercially available silymarin capsule, at a daily dosage of 3 capsules, provides 420 mg of silymarin, corresponding to 250 mg of silibinin .Silymarin from this specific orally administered formulation is rapidly absorbed; the peak plasma concentration of silibinin is reached about 2–4 h after oral administration, and its plasma half-life is approximately 6 h . It has been established that 3–7% of orally administrated silibinin is excreted in an unchanged form in the urine . After gastrointestinal absorption silibinin and the other components of silymarin are rapidly metabolized by phase I and phase II biotransformation reactions in liver cells and undergo extensive enterohepatic circulation: about 80% of silibinin is excreted as glucuronide and sulfate conjugates with bile . It is assumed that 20–40% of bile silibinin is recovered, whereas the remaining part is excreted via feces .

Silymarin was assessed for drug–drug interaction and for cytochrome P450 (CYP450) induction or inhibition by permeability studies with Caco-2 cells and by studies with human primary hepatocytes and with human liver microsomes, respectively . At a supratherapeutic concentration (1 μmol/l), there was negligible inhibition of the CYP450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9 and 2E1, minor (< 20%) inhibition of CYP 3A4 and moderate (< 40%) inhibition of CYP 2C19 and 2D6. The authors concluded that, since the therapeutic concentration of silibinin is ~ 0.2 μmol/l, silymarin is unlikely to cause hepatic drug–drug interactions at the standard dose . Results of trials in healthy volunteers and/or clinical trials suggest that milk thistle does not affect CYP 1A2, 2C9, 2D6, 2E1, 3A4 or 3A5 . In two multiple-dose pharmacokinetic studies, silymarin (160–450 mg every 8 h) did not reduce levels of the CYP 3A4 substrate indinavir. However, as our knowledge in this area is incomplete, patients taking silymarin along with CYP450 enzyme substrates should be advised to watch for signs of drug–drug interactions. Because silymarin has been shown to lower elevated blood glucose and hemoglobin A1c levels in patients with diabetes, there is theoretical potential for an additive risk of hypoglycemia in patients taking antidiabetic drugs . However, there is no documented hypoglycemia and no clinical evidence of this additive effect. Other theoretical drug interactions with silymarin, based on laboratory/animal studies, include inference with estrogen therapy (in animal studies, silymarin binds to estrogen receptor beta), reduced clearance of glucuronidated drugs (in laboratory studies, milk thistle inhibited uridine diphosphoglucuronosyl transferase) and increased absorption of P-glycoprotein substrates (in vitro, milk thistle can inhibit P-glycoprotein activity). Silymarin and silibinin have the potential to interact with statins; in vitro they inhibit both organic anion transporting polypeptide 1B1 (transports statins into the liver) and breast cancer resistance protein (transports statins from the liver to the bile) . However, silymarin (140 mg, 3 times a day) did not alter the pharmacokinetics of a single 10-mg dose of rosuvastatin in a study in healthy males . In a trial in hepatically impaired renal transplant patients, silymarin reduced the apparent clearance of the immunosuppressant sirolimus.

Pharmacodynamics:

Several pharmacologic actions of silibinin have been identified including antioxidant properties, anti-inflammatory properties, antifibrotic effects and insulin resistance modulation.

Antioxidant Properties :

The production of reactive oxygen species (ROS) is a natural consequence of a variety of essential biochemical reactions in the liver, mostly related to the processes involved in detoxification. Exposure to high levels of toxins (e.g., alcohol, hepatotoxic drugs) or intensive oxidation of free fatty acids (i.e., insulin resistance) leads to abnormal production of ROS; the endogenous antioxidants may also become depleted. For example, it is widely acknowledged that ethanol promotes the formation of various free radicals in several cell types, including hepatocytes, Kupffer cells, endothelial cells and infiltrating inflammatory leukocytes . The consequent imbalance, with persistent presence of ROS that are not neutralized by endogenous antioxidants, creates a condition called “oxidative stress”, which is implicated in the pathogenesis of a variety of liver disorders including liver fibrosis . In vitro, silibinin is found to be a potent scavenger of ROS, such as hydroxyl and peroxyl anions and hypochlorous acid, in various model systems, such as rat liver microsomes , as well as human platelets, leukocytes, endothelial cells , erythrocytes and fibroblasts . In addition, superoxide anion radicals and nitric oxide were inhibited in isolated Kupffer cells after treatment with silibinin (concentration at which 50% inhibition occurs of 80 μmol/l) . Silymarin may augment the generation of glutathione in the liver via an increase in substrate availability (i.e. cysteine) for its biosynthesis, which subsequently contributes to the enhancement of its antioxidant capacity in liver tissues. Silymarin protects liver cells by a number of mechanisms. First, it stabilizes membrane permeability through inhibition of lipid peroxidation, thereby helping the liver to maintain levels of its own protective antioxidant, glutathione . Silymarin also protects against injury from various toxic

chemicals such as carbon tetrachloride for example, by inhibiting the production of tumor necrosis factor-alpha (TNF-α), interferon-gamma, interleukin (IL)-2 and IL-4 as a consequence of blocking hepatic nuclear factor kappa B ($NF\kappa_B$) activation Silymarin is able to reduce the cellular uptake of xenobiotics, including mushroom poisons, by blocking organic ion uptake transporters on the surface of hepatocytes It also inhibits TNF-α expression, for example, when induced by α-amanitin toxin from poisonous mushrooms The hepatoprotective properties of silibinin are widely attributed to these antioxidant activities

Anti-Inflammatory Properties

Chronic inflammation has been associated with progressive hepatic fibrosis and the development of cirrhosis and oxidative stress may be the common underlying mechanism in the initiation and progression of hepatic inflammation in various liver disorders .NF-κB is an important transcriptional regulator of the inflammatory response and plays an essential role in regulating inflammatory signaling pathways in the liver . Moreover, NF-κB is activated in virtually every chronic liver disease, including AFLD , NAFLD viral hepatitis and biliary liver disease There is increasing evidence that demonstrates the overall inhibition by silymarin of inflammatory mediators such as NF-κB and inflammatory metabolites (e.g., prostaglandin E2 [PGE_2] and leukotriene B_4 [LTB_4]) . Kupffer cells are resident liver macrophages that appear to be involved in innate immune responses and host defense through the expression and secretion of inflammatory mediators . In isolated rat Kupffer cells, silymarin weakly inhibited PGE_2 formation but strongly inhibited LTB_4 formation, even at low concentrations (15 μmol/l). This selective inhibition of LTB_4 formation by Kupffer cells and possibly other cell types may account for the anti-inflammatory potential of silymarin.

Antifibrotic Effects

Silibinin has demonstrated antifibrogenic effects in animal and in vitro models Hepatic fibrogenesis, which results from chronic liver tissue damage, is characterized by activation of hepatic stellate cells (HSCs), a

liver-specific type of pericyte. Activated HSCs develop into myofibroblasts, which are responsible for the deposition of collagen fibers leading to liver cirrhosis. In an in vitro model of human hepatic fibrogenesis, silibinin demonstrated antifibrogenic properties by dose-dependently inhibiting the growth factor-induced production of pro-collagen in activated human HSC . The antifibrogenic effect of silymarin has also been confirmed in an animal model of alcohol-induced hepatic fibrosis in non-human primates receiving chronic treatment with alcohol . In this study, baboons were fed alcohol (50% of daily calories) for 3 years with a nutritionally adequate diet, which resulted in an increase of collagen type I in hepatic biopsy samples. Results showed that concomitant administration of silymarin significantly reduced the alcohol-induced increase in hepatic collagen type I .

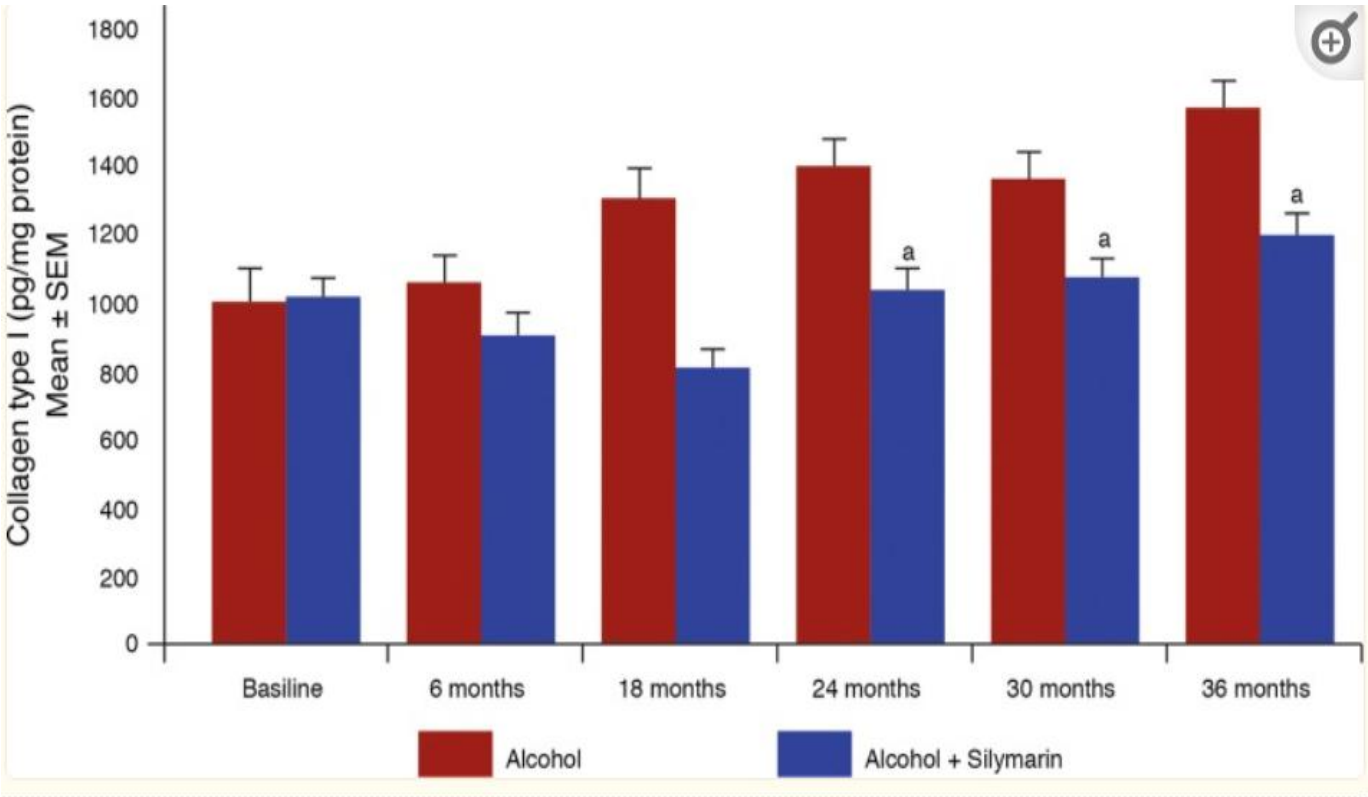


Table 1

Clinical trials with silymarin in patients with liver cirrhosis and/or alcoholic liver disease

References	Condition	*n*	Treatment (*n*)	Duration	Outcome with silymarin
Salmi et al. [61]	Liver disease (78% with daily alcohol use)	97	Silymarin 420 mg/day (47) Placebo (50)	4 weeks	Improvement in ALT, AST, liver function parameters and liver histology
Trinchet et al. [58]	ALD (50% with cirrhosis)	116	Silymarin 420 mg/day (57) Placebo (59)	3 months	No significant effect
Ferenci et al. [55]	ALD or NAFLD (70% with cirrhosis)	170	Silymarin[a] 420 mg/day (87) Placebo (59)	Median 41 months	Improvement in 4-year survival; survival differences most marked in patients with ALD and cirrhosis, and those with low severity disease (Child class A)
Feher et al. [62]	ALD	36	Silymarin[a] (17) Placebo (19)	6 months	↓ in ALT, AST, bilirubin and procollagen synthesis
Muzes et al.	ALD	NA	Silymarin[a] 420	6 months	Improvement of anti-oxidative

Table 2

Studies investigating the impact of silymarin on survival in patients with cirrhosis

Data from [13], adapted with permission from Saller et al. [13]

References	Silymarin dose (mg/day)	*n*	Patient/disease characteristics	Treatment duration (mo)	Liver-related mortality	
					Silymarin (% patients)	Placebo (% patients)
Ferenci et al. [55]	420	170	Liver cirrhosis etiology: alcoholic/non-alcoholic 92/78 Child classification: A, 89; B, 69; C, 12	24	18.4[a]	37.3
Trinchet et al. [58]	420	116	Alcoholic hepatitis, 58 with cirrhosis Baseline histology scores: fibrosis, 3; alcoholic hepatitis, 5	3	1.8	5.1
Bunout et al. [60]	280	71	Alcoholic hepatic insufficiency (24/29 patients with biopsy data had cirrhosis)	15	13.2	12.2
Pares et al. [57]	450	200	Alcoholic cirrhosis	24	9.4	14.6