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Clinical Naturopathy

An evidence-based guide to practice

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Jerome Sarris & Jon Wardle

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Contents

Preface

As we look back on the past decade since the first edition in 2010, a lot has evolved in the field of Naturopathy. Not only has research in the therapies and practices employed by naturopaths grown considerably, more and more studies now also emphasise the value of 'whole practice' naturopathy—or the application of naturopathic approaches to healing. Naturopaths are increasingly being recognised as research leaders, with successful applications to highly competitive conventional funding schemes such as the National Health and Medical Research Council (NHMRC) in Australia or the National Institutes of Health in the United States. Naturopathy is recognised as one of the major traditional systems of medicine by the World Health Organization, and the profession has made remarkable strides globally through initiatives such as the World Naturopathic Federation.

This third edition aims to retain much of what is familiar and well-loved from previous editions, updated with the most recent research as well as some new content that reflects the evolution of naturopathic practice. We hope to have captured this evolution, but no doubt the text will still need to evolve further in future editions to keep pace with contemporary practice. As discussed in the preface of the previous editions, we do recognise that the field should not sacrifice the core philosophical tenants that place it as a unique healing system in the pursuit of 'evidence-based medicine'. This third edition is still focused on reconnecting more with the fundamentals of naturopathy, as well as pushing the scientific boundaries even further.

Patients rarely fit into textbook examples, and individualisation of treatment is integral to naturopathic philosophy. Feedback from students and practitioners noted that case studies in the first edition tended to funnel readers towards predetermined outcomes, and often obscured the flexibility of options presented in the chapter material. As such, the case studies were omitted in the second edition and in this edition. However, we are pleased to have assisted recently in the creation of *Clinical Naturopathy: Case Studies*, which allowed a collection of clinically-relevant cases to be enshrined, as well as unshackle these case studies from the constraints of fitting into discrete textbook chapters so that they could more truly reflect the inter-systems approaches to diagnosis and treatment seen in naturopathic practice.

We respect that the practise of naturopathic medicine is complex and individualised, and thus acknowledge that this text does not provide a definitive 'how-to' guide. As with all previous and subsequent editions, the purpose of this text is to articulate evidence-based clinical practice (principles, treatment protocols and interventions) in a reader-friendly format for practitioners, academics and students. We have aimed to develop a resource that is comprehensive enough to serve as a robust resource reference, but compact enough to be carried around as desired and to be a useful tool to be used in practice. It is a book we hope will be thumbed through extensively, rather than one that spends most of its life on a shelf.

A strength of this text that we have maintained is that it explores the key principles and philosophies used in modern naturopathy for treating a range of conditions. The essence of this is detailed in the 'key treatment protocols' section in each chapter. An additional strength is the critical evaluation of the current evidence of both diagnostic and practice methods, and naturopathic interventions (whether they come from the

conventional or complementary sphere). This differentiates *Clinical Naturopathy: An Evidence-Based Guide to Practice* from some other publications that, while informative, often do not provide an evidence-based, referenced analysis of the treatment protocols underpinning the therapeutic use of naturopathic interventions.

Of course, we do acknowledge some limitations. First, it is recognised that it is not possible to detail all diseases and disorders that are encountered in clinical practice. As any naturopathic clinician will know, people are treated, not diseases, and each person manifests a unique combination of variations of signs and symptoms rather than an isolated textbook-diagnosed disease. Regardless, categorisation by major diseases and illnesses provides a useful framework with which to discuss naturopathic treatment protocols and interventions. The protocols and principles discussed in each chapter will in many cases be clinically relevant to the treatment of various other conditions where similar underlying causes exist. To assist readers we have made some of the major links of these between chapters overt, but we also acknowledge that there are far more than has been detailed.

As this is meant to be a clinical reference, rather than a purely academic tome or research publication, detailed analysis of each and every trial has not been entered into. However, all treatments have been duly referenced and readers, as always, are encouraged to explore these further. A selection of relevant further reading has been listed by individual contributors for those who wish to undertake additional investigation of the chapter content. It can also be noted that we focus primarily on the major evidence from clinical trials over that of *in vivo* or *in vitro* studies. Traditional evidence is also discussed when relevant. It will be apparent to readers that not every method, diagnostic technique or intervention included in this book has solid clinical evidence, and some herbal medicines or nutrients rely largely on traditional evidence. However, we feel as though it would be remiss to ignore those treatments and practices based on traditional evidence that form core parts of modern naturopathic practice in strict deference to modern scientific evidence.

Research in the naturopathic medicine field is still slowly advancing. Much of the research on complementary medicines is being led by naturopaths themselves—with the World Naturopathic Federation identifying over 2000 peer-reviewed medical research publications authored by naturopaths. The number of naturopathic 'whole practice' trials has increased from six studies with a total 692 patients showing the effectiveness of naturopathic 'whole practice' care at the time of our second edition to 33 trials with a total of 9859 patients at the time of publication of this edition. There is much work remaining, but the momentum and trajectory of naturopathic research is very promising.

The future direction of naturopathy and its components more broadly appears positive, with mainstream acceptance—including government regulation or degree education—evolving in countries such as Australia, Brazil, Canada, Germany, India, Mexico, Spain, South Africa, the United Kingdom and the United States. To maintain the development of the profession and to enable more effective healers, education is paramount. *Clinical Naturopathy: An Evidence-Based Guide to Practice*, 3rd edition is developed to be at the forefront of naturopathic education in the 21st century. This book is designed for naturopaths, allied health or conventional medical practitioners, researchers and anyone with an interest in the principles, practices and treatments of naturopathic medicine. We are pleased with this third edition and the fantastic contributions from the leaders in our field, and feel honoured that this may in part contribute to shaping better healthcare.

Jerome Sarris and Jon Wardle

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CHAPTER 7

Liver dysfunction and disease

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OVERVIEW

It is important to understand the functions of the liver, the systemic implications of liver disease and the importance of also treating the liver as an adjunct to other conditions, such as metabolic syndrome and hormone dysregulation.

The liver is involved in the metabolism of carbohydrates, proteins and fats. It converts simple carbohydrates in the form of fructose and galactose to glucose and then converts glucose to glycogen for storage. If carbohydrate intake exceeds requirements sugars are converted to triglycerides (TG), contributing to dyslipidaemia.[1]

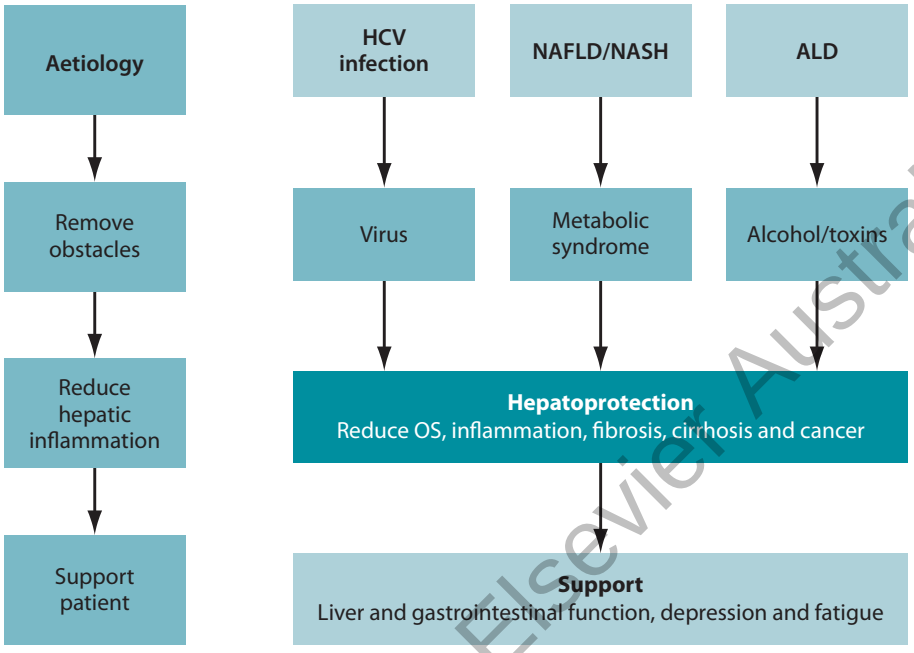
Protein metabolism in the liver is responsible for the synthesis of non-essential amino acids and functional proteins such as: fibrinogen and prothrombin for clotting; transferrins and lipoproteins for transport of iron and cholesterol, respectively; albumin for maintaining oncotic pressure; and globulins for immune function. Amino acids are also important for maintaining blood pH. If protein metabolism in the liver is disturbed this can lead to: bleeding disorders such as oesophageal varices and excess bruising; ascites due to low albumin and reduced oncotic pressure; impaired immune function; anaemia and fatigue as seen in non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and hepatitis C virus (HCV) infection.

The liver is also involved in the production and regulation of triglycerides, phospholipids, lipoproteins and cholesterol. It metabolises fats by lipolysis and transforms fatty acids via β-oxidation to acetyl-CoA, the substrate for energy production via the Krebs cycle. The liver stores fat-soluble vitamins (A, D, E, K) and other vitamins and minerals (B12, Zn, Fe, Cu, Mg). The liver converts carotene to vitamin A, folate to 5-methyl tetrahydrofolic acid and vitamin D to 25-hydroxycholecalciferol.

The liver synthesises bile, which emulsifies lipids and fat-soluble vitamins in the intestines to aid digestion and prevent cholesterol precipitation in the gallbladder. Bile synthesis and excretion is also a mechanism for reducing excess cholesterol. Another major role of the liver is the metabolism and detoxification of: alcohol; synthetic and natural drugs; steroidal hormones such as the corticosteroids, testosterone, progesterone and oestrogen; non-steroidal hormones such as thyroid hormones; and insulin and growth hormones. It also converts ammonia to urea.[1]

Common pathways of liver disease

Liver diseases can have a variety of causes but can progress through similar pathology, therefore different aetiologies of liver disease can have common treatments, as shown in Figure 7.1.



HCV = hepatitis C virus; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; ALD = alcoholic liver disease

Figure 7.1
Common pathology and treatment in liver diseases

Aetiologies

- Viral infection—hepatitis (A, B, C, D, E)
- NAFLD/non-alcoholic steatohepatitis (NASH), dysregulated free fatty acid (FFA) metabolism and accumulation due to obesity, insulin resistance and metabolic syndrome
- ALD, accumulation of toxins due to excess alcohol consumption

Common pathology

- *Hepatitis (B and C).* Increased oxidative stress as a direct consequence of the virus and indirectly as a result of the immune response.
- *NAFLD and NASH.* Increased oxidative stress as a result of FFA accumulation and lipid peroxidation, exacerbated by increased inflammatory cytokines from adipose tissue, damages the liver.
- *ALD.* Increased oxidative stress as a result of toxins.

Common treatment—reduction of hepatic inflammation

Oxidative stress in liver disease accelerates inflammation, fibrosis and necrosis, creating additional oxidative stress, which causes further damage to proteins, DNA, lipids and sensitises redox-regulated necrotic cell signalling pathways, affecting gene expression[2] and

causing mitochondrial dysfunction and pathology.[3] Increased oxidative stress leads to reduced liver function and can progress through fibrosis to cirrhosis and possibly cancer.

Liver disease can lead to metabolic syndrome with dysglycaemia or dyslipidaemia and increases in the frequency of comorbidities.[4]

Treatment based on reducing oxidative stress, inflammation, regulating digestive dysfunction and supporting fatigue will assist in the treatment of most chronic liver diseases.

Common comorbidities

- Metabolic syndrome
- Cardiovascular disease
- Depression and fatigue
- Hormonal dysregulation
- Dyspepsia

NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is the hepatic manifestation of metabolic syndrome.[5–7] The Asia-Pacific Guidelines on NAFLD recommend that the term NAFLD is retained for cases of fatty liver associated with the metabolic complications of over-nutrition, usually with central obesity and overweight.[8] NAFLD is the most common liver disease worldwide in adults and children.[9] NAFLD usually occurs in the fourth or fifth decade of life and is predominantly asymptomatic. NAFLD may progress from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis. An estimated 20–35% of the general population has steatosis, 10% developing more progressive NASH, which is associated with increased risk of cardiovascular and liver-related mortality.[10]

The prevalence of NAFLD is higher among the obese and patients with type 2 diabetes. In fact in a cohort of NAFLD patients, 50% had diabetes, 44% had hypertension and 12% had previous vascular disease.[11] The environmental factors involved in NAFLD and metabolic syndrome are diet, physical activity and gut microflora. Metabolic syndrome with dysglycaemia, dyslipidaemia and obesity results in an increase in the level of FFAs from the breakdown of adipose tissue and from the metabolism of excess dietary carbohydrates (hyperlipidaemia); this dysregulation leads to lipotoxicity in the liver, causing oxidative stress and liver inflammation.[10]

Signs and symptoms

- Fatigue[7] and depression[12]
- Right upper quadrant pain or discomfort or fullness, possibly due to stretching of the hepatic capsule and hepatomegaly[9]
- Metabolic syndrome[7]—type 2 diabetes mellitus, insulin resistance (IR), hyperlipidaemia and obesity
- Acanthosis nigricans,[9] a cutaneous manifestation of IR, was found in 12% of NAFLD patients. This regional hyperpigmentation is typically found in adults around the neck, over knuckles, elbows and knees and offers the clinician and patients a physical clue as to the presence of IR.[13]

Pathophysiology

The hallmark of NAFLD is the deposition of excess FFAs within hepatocytes and is associated with the loss of insulin sensitivity.[14] There are theories as to whether the fat

accumulation in the hepatocytes occurs first or IR; the literature is moving towards the theory that IR occurs first.[7,10]

Hepatic FFAs' concentration is increased by the following.[15,16]

- Obesity and IR cause excess FFAs in the liver from adipose tissue—60%.
- IR increases *de novo* lipogenesis (DNL) from excess dietary carbohydrates—25%.
- Poor diet increases dietary fatty acids—15%.
- Lipotoxicity, oxidative stress and mitochondrial damage results in decreased hepatic β-oxidation of FFAs.[17]
- Steatosis reduces very low density lipoprotein (VLDL) synthesis, export and clearance of FFAs.

Excess FFAs accumulate in the liver, leading to macrovesicular steatosis and lipid-induced cellular injury, worsening hepatic IR and reducing hepatic function; this contributes to a vicious cycle.[7,10] Both IR and obesity are pro-inflammatory conditions, resulting in high oxidative stress exacerbated by the aldehyde by-products of lipid peroxidation, which increase the production of pro-inflammatory cytokines and recruit inflammatory cells into the liver.[10]

In summary, the pathophysiology of NAFLD is complex and includes IR, disrupted lipid, protein and carbohydrate homoeostasis, oxidative stress, FFA-mediated lipotoxicity, defects in mitochondrial function, endoplasmic reticulum stress, cytokine mediated toxicity, inflammation and fibrosis.[17]

Diagnosis

A diagnosis of NAFLD requires confirmation of hepatic steatosis, with the additional exclusion of excessive intake of alcohol. The alternative causes for fatty liver (genetic, viral, metabolic, drug) must be excluded before a diagnosis of NAFLD can be made.[10]

Clinically, elevated liver transaminases, gamma glutamyl-transpeptidase (GGT), hypertriglyceridaemia, ferritin[9] and numerous weight-loss and weight-gain cycles would alert the practitioner to a possible NAFLD diagnosis. Serum ferritin is elevated in 20–50% of NAFLD patients and the raised transferrin saturation (> 55%) occurs in 5–10% of patients; both may reflect hepatic steatosis and fibrosis due to oxidative stress and inflammation. Hypertriglyceridaemia is often present in more than 50% of NAFLD patients.[9] Refer to Appendix 5 for more information on laboratory reference values.

An ultrasound of the liver, computed tomography and magnetic resonance imaging will detect moderate to severe steatosis (> 30% steatosis). A liver biopsy may be necessary to quantify the degree and stage of hepatic steatosis and fibrosis. The presence of more than 5% of steatotic hepatocytes in a section of liver tissue from a liver biopsy is the accepted minimum standard for a histological diagnosis of NAFLD.[18]

DIFFERENTIAL DIAGNOSIS—NAFLD

- Non-alcoholic steatosis
- ALD[7]
- HCV
- Wilson's disease[7]
- Cardiovascular disease
- Gallbladder disease
- Irritable bowel syndrome

Risk factors

Practitioners should be aware of the existence of conditions that commonly co-occur with NAFLD. The presence of NAFLD is an independent risk factor for coronary artery disease.[19] The hepatic metabolism of methionine is perturbed in NASH,[20] which may provide a reason for the increased coronary artery risk in this population. Recently polycystic ovarian syndrome was proposed as the ovarian manifestation of metabolic syndrome.[21]

Risk factors for mortality in NAFLD patients are the presence of cirrhosis, impaired fasting glycaemia or diabetes.[22]

NAFLD: at-risk groups

- Histological NASH on diagnosis[22]
- Metabolic syndrome[4,5]
- Major health conditions (especially cardiovascular disease)[19,20]
- Older age[22]
- Smokers[23]

Conventional treatment

A 2017 attempted network Cochrane meta-analysis looking at the pharmacological interventions for non-alcohol related fatty liver disease concluded that due to the very low quality evidence, the effectiveness of pharmacological treatments for people with NAFLD, including those with steatohepatitis, are uncertain.[24] Although there is no pharmacological agent approved for treating NAFLD, vitamin E (in patients without type 2 diabetes mellitus) and thiazolidinedione pioglitazone (in patients with and without type 2 diabetes mellitus) have shown the most consistent results in randomised controlled trials.[25] However, a recent systematic review of the use of thiazolidinediones (peroxisome proliferator activator receptor-γ agonists) in NAFLD concluded that while they modestly improve fibrosis and hepatocellular ballooning, it is at the cost of significant weight gain. In seven randomised trials the average weight gain was 4.4 kg (CI, 2.6–5.2 kg).[26] There is an increased cardiovascular risk with rosiglitazone. Other side effects are fluid retention and osteoporosis. The evidence that insulin-sensitising drugs are able to modify the natural history of NAFLD is not currently available.[27]

Key treatment protocols

The first goal is to address the metabolic syndrome picture and reverse the lipotoxicity and insulin resistance via lifestyle interventions[25,28] using diet and exercise.

At the same time it is important to protect the liver from oxidative stress and subsequent inflammation and fibrosis, as well as supporting liver function and healing. Supporting the digestive system will reduce the dyspeptic symptoms of NAFLD thereby improving client wellbeing and nutrient status. Two of the major symptoms of NAFLD are fatigue and depression so in order to motivate the client to make positive lifestyle choices the treatment protocol needs to address these issues.

Naturopathic Treatment Aims

- Encourage beneficial dietary and lifestyle changes.
- Treat the underlying metabolic causes:
  - modulate fatty acid pathways
  - regulate blood glucose
  - reduce weight.
- Reduce hepatic inflammation:
  - reduce oxidative stress.
- Reduce systemic inflammation.
- Reduce the likelihood of fibrosis.
- Support liver function.
- Support digestive function.
- Support mood and energy levels.

Encourage beneficial dietary and lifestyle changes

Dietary and lifestyle advice

Identifying and removing potential liver stresses is one of the first steps in instigating beneficial lifestyle changes, such as alcohol moderation and smoking cessation. The 2016 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical guidelines for the management of NAFLD state that lifestyle correction is mandatory in all patients. The EASL-EASD-EASO guidelines plus other studies recommend the Mediterranean diet and state that it can achieve benefits even without calorie restriction and weight loss.[29–31] The diet needs to be low in carbohydrates and particularly low in high-fructose corn syrup as fructose is lipogenic and stimulates triglyceride synthesis.[32] Where there is a high-fructose diet, especially with soft drink consumption, all the signs relating to NAFLD are present: increased blood glucose, triglyceride, alanine aminotransferase (ALT), cholesterol, weight and hepatic steatosis. In NASH patients high fructose ingestion was associated with hepatic insulin resistance and higher fibrosis.[33] High-fructose diets increase hepatic reactive oxygen species (ROS) and macrophage aggregation, resulting in TGF-beta-1 signalled collagen deposition and hepatic fibrosis.[34] This potentially leads to decreased copper absorption and a resulting deficiency.[33,35]

The diet should also be high in protein, fibre, good fats, antioxidants and anti-inflammatory foods such as lean meat and fresh vegetables to regulate blood glucose levels and support antioxidant status, bowel and liver function. High-protein diets prevent and reverse steatosis independently of fat and carbohydrate intake more efficiently than a 20% reduction in energy intake.[36] The effect appears to result from small, synergistic increases in lipid and branched-chain amino acids (BCAA) catabolism, and a decrease in cell stress. Similarly, low-carbohydrate diets are useful in reducing circulating insulin levels and decreased intrahepatic triglycerides (IHTG) due to enhanced lipolysis and fatty acid oxidation.[37] Studies involving low-carbohydrate diets with less than 50 g/day of carbohydrate saw a reduction in insulin sensitivity and decreased endogenous glucose production rate—more than an isocaloric low-fat diet—and encouraged hepatic and visceral fat loss. Attention to nutrition status is important as malnutrition accounts for more than 60% of patients with severe liver failure and negatively affects clinical outcomes in terms of survival and complications.[38]

Exercise or physical activity

Exercise of sufficient duration and intensity will reduce adipose tissue therefore reducing a source of adipose-derived FFAs; it also enhances insulin sensitivity. Exercise will increase muscle mass, adiponectin and the biogenesis of mitochondria. **Endurance exercise** uses muscles that use triglycerides for energy rather than carbohydrates and therefore there is an overall decrease of FFAs and an increase in the β-oxidation of FFAs in NAFLD.[16,27,39,40]

There is emerging and growing evidence for the effectiveness of increasing physical activity reducing hepatic fat content,[27] regardless of whether it is resistance based or aerobic or combined with diet and weight loss. Therefore it is important to find some form of exercise that is physically possible for the patient. **Resistance exercise** independent of weight loss is also associated with significant reduction in hepatic fat[40] and may improve insulin sensitivity more than aerobic exercise alone.[39] Resistance exercise may be more accessible to some patients than aerobic exercise and may achieve better compliance than diet; therefore, it is a more sustainable treatment option.[40,41]

Aerobic exercise training and dietary restriction can positively affect NAFLD when weight loss approximating 4–9% of body weight is achieved; an inverse correlation between NAFLD and physical activity or fitness levels has also been demonstrated.[16,27,39] Weight loss, irrespective of diet, reduces aminotransferases in obese women with NAFLD[42] and 7–10% weight loss coincided with significant histological improvement of liver disease.[43] Therefore a combination of exercise, diet and weight loss is synergistic in the amelioration of liver disease in NAFLD.[44]

A systematic review with meta-analysis concluded that exercise is efficacious in modifying liver fat in adults. Interventions ranged from 2–24 weeks in duration and prescribed exercise on two to six days per week at intensities between 45% and 85% of VO_{2peak}.[27] The review could not report an improvement in ALT due to many ALT measures being normal at baseline and because studies with positive results were excluded due to lack of a control group. In a study that lacked a control group a near 50% reduction in ALT was achieved in patients who complied with the prescribed exercise regimen, indicating reduced liver inflammation.[45] The exercise regimen consisted of aerobic exercise for 30 minutes per day at a heart rate of 60–70% of maximal for at least five days a week for three months.

In rodents regular exercise reduced DNL, increased β-oxidation and increased the removal and clearance of FFAs via VLDL. Sedentary behaviour, on the other hand, resulted in the reduced oxidation of fatty acids and mitochondrial activity with the up-regulation of fatty acid synthesis.[16,27]

Kistler et al. suggest that intensity of exercise may be more important than duration or total volume of exercise in the treatment of NAFLD, with vigorous activity associated with significantly lower odds of fibrosis.[46] The suggested mechanisms for the benefits of vigorous exercise over moderate are that vigorous exercise increases adiponectin and AMP-activated protein kinase (AMP-kinase) in the liver, which increases fatty acid oxidation, decreases glucose production, regulates mitochondrial biogenesis and reduces inflammation and fibrosis.[46,47] Decrease in adiponectin plays a significant role in metabolic disorders such as obesity, type 2 diabetes, coronary heart disease and metabolic syndrome due to its insulin sensitising, anti-inflammatory and anti-atherogenic properties.[48] Decreases in adiponectin and increases in leptin in metabolic syndrome and obesity are linked to fibrosis in NAFLD.[49] Coker et al.[50] found that exercise training with calorie restriction achieved better results in visceral fat loss, weight loss and improvements in insulin resistance than calorie restriction alone.

Treat the underlying metabolic causes

Modulate fatty acid pathways and regulate blood glucose

In obese individuals it is important to reduce adipose tissue as a source of FFAs as well as to control insulin resistance that results in excess lipolysis of adipose tissue. Also, controlling insulin resistance will help decrease rates of DNL from carbohydrate metabolism. Exercise can reduce adipose tissue, and improvements in insulin resistance combined with a diet containing low carbohydrates and healthy fats are essential to improving NAFLD. Strong evidence exists for **omega-3 fatty acids**[51] reducing hepatic fat content in children with NAFLD. **Vitamin E (natural)**[52,53] as a fat-soluble antioxidant is also useful in reducing lipid peroxidation in NAFLD.

Whole ***Curcuma longa*** oleoresin up-regulated the expression of genes related to glycolysis, β-oxidation and cholesterol metabolism in obese diabetic KKAy mice and

down-regulated the gluconeogenesis related genes (see Chapter 19 on diabetes for more information).[54] In a recent trial, participants received an amorphous dispersion curcumin formulation (500 mg/day equivalent to 70 mg curcumin) or matched placebo for a period of eight weeks. Curcumin achieved a significant reduction in liver fat content (78.9% improvement in the curcumin versus 27.5% improvement in the placebo group). There were also significant reductions in cholesterol, triglycerides, body mass index, glucose and glycated haemoglobin, and liver inflammation.[55] Berberine is a plant alkaloid with several pharmacological activities, including antimicrobial, antidiabetic, hypoglycemic, hypocholesterolemic, anti-tumoral, immunomodulatory properties, anti-inflammatory and antioxidant.[56–59] Berberine improves mitochondrial function[56] and inhibits hepatic lipogenesis.[57]

Reduce hepatic inflammation

The inflammatory process causes oxidative stress and vice versa, driving liver disease progression. Therefore a key treatment goal in NAFLD is to reduce hepatic inflammation and oxidative stress by using hepatoprotective herbal medicines with specific hepatic anti-inflammatory and antioxidant activity. Hepatoprotection is defined as more than just antioxidant and anti-inflammatory effects; it also includes several non-mutually exclusive biological activities including antifibrotic, antiviral and immunomodulatory functions.[60]

One of the ways that oxidative stress damage can be reduced is through hormesis. It is postulated that hormesis is a mechanism by which phytochemical adaptogens such as ***Astragalus membranaceus*** and antioxidant-rich plants such as ***Silybum marianum*** strengthen mitochondria by improving the β-oxidation of FFAs, increasing energy and stamina.[61] In calorie restriction, exercise and hormesis, increased ROS up-regulates adaptive responses. This results in a net reduction in ROS due to the stimulation of antioxidant defences and detoxification.[62] This adaptation or preconditioning of the mitochondria has been named 'mitochondrial hormesis' or 'mitohormesis'.[62–64] These hormetic pathways, activated by phytochemicals, include the sirtuin-FOXO pathway, the NF-kappa B pathway and the Nrf-2/ARE pathway.[61] Surh[65] terms this exogenous form of hormesis 'xenohormesis'.[61,66] Bitter foods such as dandelion coffee, rocket and radicchio also have a hormetic effect as well as stimulate digestion and aid dyspepsia.

Silymarin (an active constituent of *Silybum marianum*) protects cells against oxidative stress by stabilising cell membranes, radical scavenging, chelating iron and supporting endogenous antioxidants such as glutathione.[67] *Silybum marianum* also has anti-inflammatory[68,69] and antifibrotic[70,71] effects through the reduction of inflammatory cytokines and TNF-α as well as hypoglycaemic, choleretic and cholagogic actions. The latter two actions help remove fat from the liver through the fatty acid metabolism pathways, thereby preventing deposition of fat in the liver.

Curcuma longa interrupts insulin signalling, which stimulates hepatic stellate cell activation (a key element in fibrogenesis), suppresses the gene expression of type I collagen and also increases the *de novo* synthesis of glutathione, thereby exerting anti-inflammatory, antioxidant, antidiabetic and antifibrotic effects.[72] The antioxidant and anti-inflammatory actions of **baicalin** and ***Scutellaria baicalensis*** make it a very useful clinical tool in NAFLD[73] and ALD[74] management.

Baicalin, the active ingredient in *Scutellaria baicalensis*, has been shown to reduce dyslipidaemia and hepatic lipid accumulation, improve hepatic steatosis and reduce visceral fat mass in vivo.[73]

Glycyrrhiza glabra has an anti-inflammatory effect in NAFLD by lowering elevated ALT and aspartate aminotransferase (AST) in a randomised, double-blind, placebo-controlled clinical trial.[75] The biologically active metabolite of **glycyrrhizin** (18 beta-glycyrrhetinic acid [GA]) prevented FFA-induced lipid accumulation and toxicity by stabilising the lysosomal membranes, inhibiting cathepsin B activity and inhibiting mitochondrial cytochrome *c* release.[76] Another preparation of GA (**carbenoxolone**, 3-hemisuccinate of glycyrrhetinic acid) inhibited pro-inflammatory cytokine expression, inhibited FFA-induced ROS formation and reversed FFA-induced mitochondrial membrane depolarisation in HepG2 cells. GA also prevented the development of fatty liver by inhibiting the sterol regulatory element binding protein 1c (SREBP-1c) expression and activity via antiapoptotic mechanisms and the inhibition of inflammatory cytokines and ROS formation in the liver.[77]

Grapeseed extract improved markers of inflammation and glycaemia in obese type 2 diabetes mellitus patients[78] and reduced ALT and improved grade of steatosis in NAFLD patients.[79] (See Chapter 19 on diabetes and Chapters 11–13 on the cardiovascular system for more information.)

Both omega-3[51] and **vitamin E (natural)**[52] have shown some effectiveness in reducing inflammation in NAFLD and/or NASH. Deficiencies in vitamin E lead to an increased risk of developing advanced inflammation (6.5-fold) and lower riboflavin intake is associated with increased risk of advanced steatosis (6.2-fold) compared with those chronic hepatitis C patients with adequate intakes.[80]

Accumulation of lipids in the hepatocyte impairs the metabolic capacity of the mitochondria, leading to a buildup of reduced electron transport chain substrates and lipid peroxidation, leading to increased ROS.[81] Therefore stimulation of mitochondrial function through **L-carnitine**,[82,83] **alpha lipoic acid**[84] and **coenzyme Q10**[85] may be effective in NAFLD and other liver conditions associated with mitochondrial dysfunction. **Melatonin** (5 mg) and **tryptophan** (500 mg) twice daily for four weeks reduced the plasma levels of pro-inflammatory cytokines in NASH.[86]

Support liver function

Herbs that support liver function such as ***Silybum marianum***, ***Berberis aristata***,[87] ***Cynara scolymus***,[88] ***Curcuma longa***[54] and ***Schisandra chinensis*** also help support the production and elimination of bile that promotes the elimination of cholesterol, which lowers FFAs (see Table 7.1 and Figure 7.2).[89] See the following liver detoxification section for herbs and nutrients specific to supporting detoxification. **SAMe**[90] supports methylation and has shown some effectiveness in NAFLD and NASH. **N-acetylcysteine** (600 mg/day) reduced ALT in NAFLD patients and improved liver function through supporting glutathione production.[91]

Reduced dietary protein intake is an independent predictor of complications in cirrhosis.[117,118] In those with liver cirrhosis with low serum albumin or globulin, extra **protein**, approximately 1.0–1.2 g of protein per kilogram of body weight,[119] is required to assist the liver to synthesise proteins. Compromised liver function will also result in reduced protein synthesis, possibly resulting in signs such as prolonged prothrombin time due to reduced synthesis of clotting factors. The provision of a night-time feed to cirrhotic patients led to a body protein increment of about 2 kg of lean tissue sustained over 12 months.[120]

Support liver detoxification

A protocol to enhance liver detoxification is an adjunct treatment to all acute and chronic inflammatory conditions and conditions associated with hormone imbalance through

the removal of exogenous and endogenous toxins that may cause oxidative stress, drive inflammation and act as carcinogens.

Liver detoxification refers to the phase I, phase II and phase III enzymes in the liver. Phase I enzymes activate both toxins and drugs, potentially increasing the effects of both. Phase II enzymes conjugate the metabolites of phase I, making them more water soluble and available for excretion, thereby reducing toxic metabolites and the need for therapeutic drugs.[121] Phase III involves the mobilisation of the products of phase II from the intracellular environment to the extracellular environment for excretion as bile, urine, sweat and via the lungs. Toxic compounds such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), polycyclic aromatics and beta-naphthoflavone induce both phase I and phase II activity.[122] Conversely, therapeutic interventions tend to inhibit phase I and induce phase II, protecting the body from a buildup of the toxic metabolites of phase I (Table 7.1 and Figure 7.2).

Table 7.1
Required nutrients, inducers and inhibitors of phase I and phase II[92]

	Required nutrients	Induced by	Inhibited by
Phase I	B2, B3, B6, B9, B12 Branched-chain amino acids Glutathione Bioflavonoids Phospholipids	Tobacco[93] Omeprazole Ethanol *Hypericum perforatum* (hyperforin)[94] Caffeine (CYP1A2)[95] High-protein diet[96] Charcoal-broiled food[93] Flavonoids[97] *Rosmarinus officinalis*[98]	Grapefruit juice[99] Oranges[99,100] Legumes Quinidine Erythromycin Fluvoxamine *Carum carvi*[101] Brassica family[102] Bioflavonoids[94] *Cuminum cyminum*[101] *Taraxacum officinale* *Allium sativum*[103,104] *Schisandra chinensis*[105] *Glycyrrhiza glabra*[106] *Withania somnifera* *Curcuma longa* *Foeniculum vulgare*[107] *Cynara scolymus* *Silybum marianum*[108]
Phase II	Acetylation: B5 Methylation: B6, B9, B12, SAMe and betaine Conjugation: amino acids Glucuronidation: taurine and glucoronic acid Glutathione: glutamate, cysteine and glycine Sulfation: glutathione, cysteine and methionine	Caffeine[109] *Cymbopogon citratus* (citral) *Salvia officinalis* *Camellia sinensis* *Thymus vulgare* *Zingiber officinale*[110] Brassica family[111] Bioflavonoids[94] *Cuminum cyminum*[101] *Taraxacum officinale* *Allium sativum*[103,104] *Schisandra chinensis*[112,113] *Humulus lupus*[114] *Glycyrrhiza glabra*[115] *Rosmarinus officinalis*[116] *Withania somnifera* *Curcuma longa* *Silybum marianum*[113] N-acetylcysteine	Deficiencies in selenium, zinc, B1, B2, molybdenum Low-protein diet, NSAIDs, aspirin

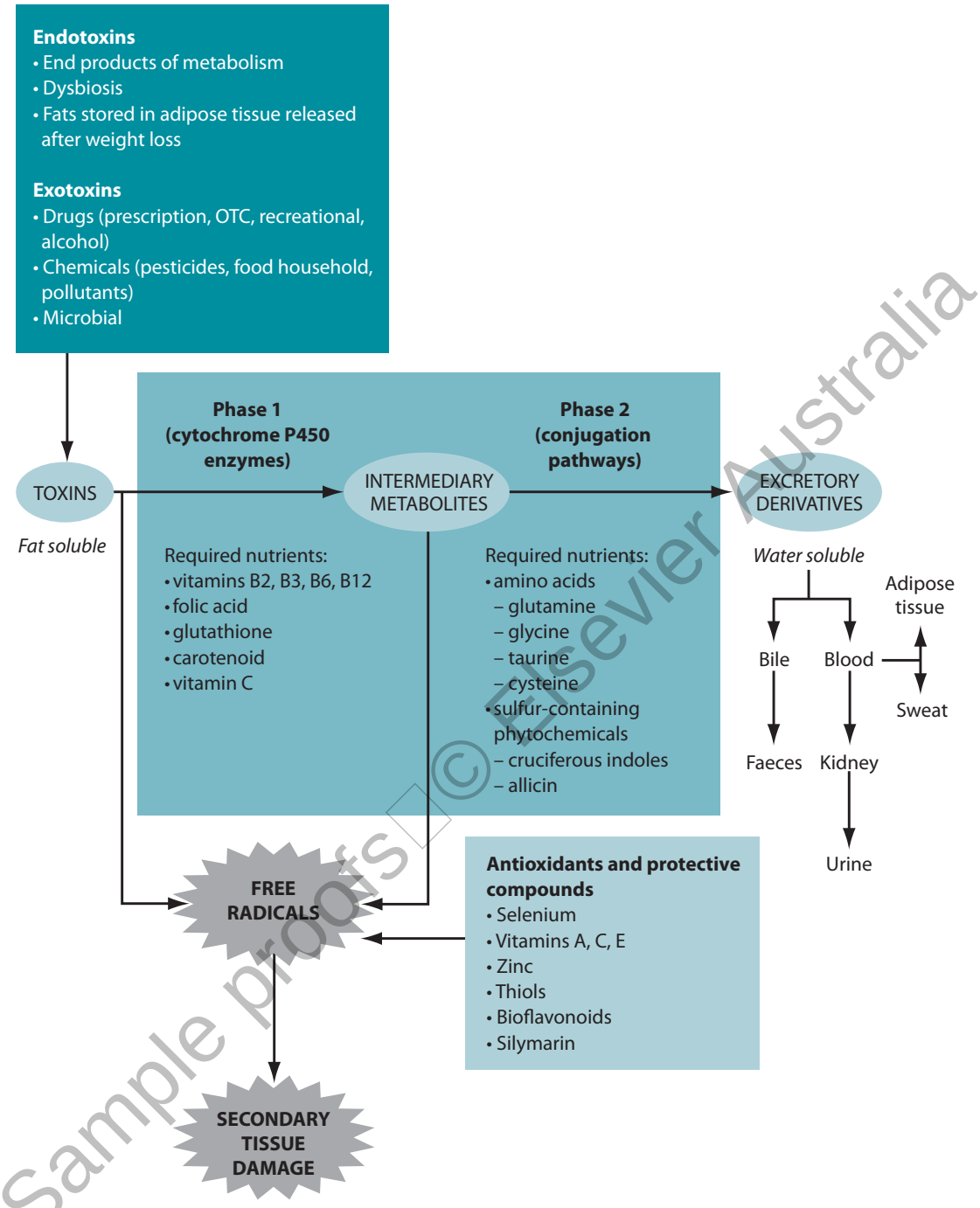


Figure 7.2
Biochemical and nutritional factors affecting liver metabolism

A detoxification protocol requires, first of all, a healthy diet and good digestive function to reduce the intake and maximise the output of toxins. This should be combined with lifestyle changes such as exercise and relaxation and be supported by foods, nutrients and herbs that optimise liver function by balancing phase I and phase II enzyme activity and providing antioxidants' protection.

A **healthy diet** (see Chapter 3 on wellness) is essential in effective detoxification. A diet high in fibre and water will promote the elimination of waste products and reduce the enterohepatic circulation of toxins. Enterohepatic circulation involves reabsorbing substances through the gastrointestinal tract rather than excreting them. This can be particularly problematic with the reabsorption of hormones excreted via the bile, such as oestrogen, leading to hormone imbalances. **Probiotics** and **prebiotics** can help gastrointestinal tract function and reduce the formation of endotoxins such as ethanol and lipopolysaccharide (LPS).[123]

Foods containing **flavonoids** (e.g. kaempferol, diosmetin, theaflavin and biochanin A) can inhibit the metabolic activation of procarcinogens by phase I enzymes and some dietary flavonoids (e.g. naringenin, quercetin, biochanin A and phenylchalcones) can stimulate the detoxification of carcinogens by inducing phase II enzymes.[94] A review cautions that a number of studies have demonstrated inhibition and induction effects on drug bioavailability by flavonoids, raising concerns about the safe use of flavonoid supplements that are not subject to legal regulations.[97] ***Allium sativum*** can be beneficial through an inhibitory effect on phase I[124] and an induction effect on phase II[103] enzymes as well as increasing the synthesis of endogenous antioxidants and glutathione via Nrf2/ARE[104] and is therefore very useful in detoxification and easily accessible as a food. Another food example is the phytochemical phenethyl isothiocyanate, a constituent of **cruciferous vegetables** that can modulate cytochrome P450 composition in human liver at concentrations that can be achieved by dietary intake.[102] This can antagonise the carcinogenicity of chemicals that rely on the CYP1 family for their bioactivation such as heterocyclic amines and polycyclic aromatic hydrocarbons.[102]

Teas can be used to hydrate and to gently cleanse the body, with various herbal teas and dandelion root coffee potential choices. Also the use of **culinary herbs and spices** such as turmeric, cumin, fenugreek, rosemary and sage is a great way to introduce a variety of herbs into the diet. Diets low in **protein** may predispose patients to lowered liver detoxification, as key amino acids are involved in these liver processes.[36,119] Increasing crude protein intake will also help to improve availability of amino acid precursors for conjugation.

Fasting is also known to enhance the detoxification process,[125] in part because the main source of energy is hydrolysed fatty acid tissue from adipose tissue stores, where many toxins are stored.[126] However, due prudence needs to be displayed, as fasting may liberate toxins faster than they can be eliminated (because in part the adequate substrates from phase II detoxification may be missing or compromised) and may potentially endanger the patient.

Hydrotherapy is thought to increase filtration through the liver by encouraging blood circulation, in addition to aiding excretion through sweating.[126] Sauna therapy has also been used to encourage elimination through the skin, with substantial elimination and significant clinical improvement thought possible through this mechanism.[125,127] **Sauna** exposure of 5–15 minutes per day is safe and effective in enhancing detoxification, though caution is advised in patients with recent myocardial infarction or other serious cardiovascular complications, and patients need to be advised that eliminating toxins through the skin may initially irritate (though ultimately improve) conditions such as

atopic dermatitis.[128] Many nutrients, particularly trace elements such as zinc, copper, iron and chromium as well as electrolytes, may be lost through sweating and may need monitoring or replacement.

Some herbs have a history of use for detoxification and are used in traditional herbal medicine for their role in supporting liver function including ***Silybum marianum***, ***Cynara scolymus***, ***Bupleurum falcatum***, ***Schisandra chinensis***, ***Peumus boldo*** and ***Taraxacum officinale***. Herbs such as *Silybum marianum* and *Schisandra chinensis* can increase levels of Nrf2 either by stimulating its release or inhibiting its proteolytic breakdown. Activated Nrf2 translocates into the nucleus where it interacts with small MAF family proteins bound to the antioxidant response element (ARE), allowing transcription of target genes including those that regulate antioxidant and phase II enzymes.[113]

Exercise will also promote hepatic biotransformation processes.[129,130]

Detoxification is also an area in which unproven and often ineffective remedies are aggressively marketed, both to practitioners and to patients, implying careful consideration before their use in clinical practice.[131] Therefore, while detoxification regimens may provide a clinically valuable adjuvant to treatment, naturopathic practitioners should be sure to focus on more relevant primary treatment aims in the clinical setting. More extreme detoxification methods can be very dangerous and should be avoided. While it is true that many traditional methods may fall into this category, it should also be acknowledged that these traditions were born of a time when environmental toxic burdens were far lower and would have resulted in fewer side effects and lower risk.

Support digestive function

Dyspeptic symptoms associated with NAFLD include burping, bloating, reflux, flatulence and indigestion with intolerances to fatty foods. Common herbal medicines used to stimulate secretion of bile and pancreatic enzymes are ***Gentiana lutea*** and ***Cynara scolymus***. Bitter foods such as dandelion coffee, rocket, radicchio, watercress, radish, cauliflower and the rest of the Brassicaceae family also stimulate digestion. Cholagogues aid digestion and carminatives reduce spasm and wind. Dysbiosis plays a role in the pathogenesis of liver disease through inflammation and damage to the epithelial cells of the intestines. This damage can then expose the liver to intestinally derived toxins such as ethanol and lipopolysaccharides (LPS), which drive inflammation in the liver.[123]

Probiotics, **prebiotics** and **increased dietary fibre** can be used to help restore intestinal flora balance and function to the gastrointestinal tract. They can be useful in reducing the enterohepatic reabsorption of toxins from the gastrointestinal tract. The inclusion of a range of probiotics such as ***Lactobacillus bulgaricus*** and ***Streptococcus thermophilus*** reduce hepatic necroinflammation in NAFLD patients.[132] ***Bifidobacterium longum*** with FOS and lifestyle modification significantly reduced tumour necrosis factor alpha (TNF-α), C-reactive protein (CRP), serum AST levels, HOMA-IR, serum endotoxin, steatosis and NASH activity score[133] (see Chapters 4–6 on the gastrointestinal system for more detail).

Support mood and energy levels

A number of epidemiological studies have found links between chronic liver diseases such as NAFLD and hepatitis B and C with depression.[144,145] Weinstein et al. suggest that NAFLD and HCV patients have a higher prevalence of depression than the wider population.[12]

Probiotics

Dysbiosis of the gut microbiota affects the pathogenesis and progression of NAFLD and NASH.[134–137] Gut microbiota-mediated inflammation of the intestinal mucosa leads to compromised intestinal permeability and impairment in mucosal immune function.[138] Compromised intestinal permeability means that bacterial products such as lipopolysaccharide (LPS) and toxins are carried to the liver via the portal circulation and can trigger an immune response, oxidative stress, inflammation, fibrosis and promote insulin resistance, obesity and metabolic syndrome.[139–142] A specific mechanism of injury that can occur in NAFLD is the microbiota converting choline into methylamines; this reduced availability of choline reduces the export of VLDL from the liver and increases fat accumulation and ROS.[135,140]

Evidence suggests that diet and lifestyle factors which are known to exacerbate NAFLD may do this by changing the gut microbiota.[140,141] Poor diets, which are low in fibre and high in fats and sugars, reduce gut motility and that affects the microbiota and intestinal permeability which further degrades gut motility. A high-fat diet increases inflammatory microbiota and causes an increase in bile acids, which then increase intestinal permeability.[7] A high-fructose diet increases bacteria that can extract energy from complex polysaccharides resulting in an increase of free fatty acids reaching the liver, with consequent hepatic lipogenesis.[140] Changes to diet within a few days lead to a change in microbiota; however, if the diet reverts so do the microbiota. Therefore, changes to diet need to be sustainable, containing plenty of plant food and fermented foods.

The use of probiotics improves the pathology of NAFLD in animal models, and to some extent in human models probiotics led to decreases in liver fat and serum ALT and lipid levels and improvements in inflammation, liver fibrosis, oxidative stress and insulin resistance.[140,142,143] In an animal intervention, the authors concluded that probiotics can improve intestinal integrity, ameliorate dysbiosis, improve liver pathology and reduce gut endotoxemia and the consequent inflammatory response by the Kupffer cells in the liver.[137] A review of the literature concluded that probiotics could ameliorate hepatic steatosis via reduction in inflammation; reduce endotoxemia by inhibiting epithelial invasion, maintaining intestinal barrier integrity and the production of antimicrobial peptides; and enhance insulin sensitivity.[135]

Depression and mood disorders are often seen in obesity and diabetes mellitus, two of the major metabolic pictures seen in NAFLD. While mood disorders are not always present, they are relevant to some sufferers of chronic liver disease and symptoms must be supported. (See also Chapter 15 on depression and Chapter 18 on stress and fatigue.)

Integrative medical considerations

After a thorough naturopathic consultation, it may become apparent that the patient has a number of risk factors and symptoms that suggest the presence of NAFLD. If this diagnosis is not confirmed at the time of their initial consultation, a referral to a general practitioner in the first instance would be worthwhile for further investigation.

Refer for liver ultrasound or further medical care if there are signs of:

- severe fluctuations in weight (loss and gain)
- elevated GGT
- elevated ALT
- raised triglycerides
- raised ferritin.

Clinical summary

Refer to the naturopathic treatment decision tree (Figure 7.3) regarding clinical decisions in the treatment and management of liver disease. From the thorough case history taking and observation of the clinical signs and symptoms of liver disease, a

potential diagnosis of NAFLD may be apparent. It would be useful to confirm the diagnosis of NAFLD with a general practitioner, who may refer the patient for biochemical tests and liver ultrasound or liver biopsy if indicated. An individualised treatment plan considering causation, age, sex, culture, current dietary and lifestyle factors and family and social history should be discussed with the patient. This treatment plan would address the underlying causes (alcohol, viral infection, metabolic syndrome), support liver and digestive function, reduce inflammation and oxidative stress, address obstacles to healing and encourage beneficial dietary and lifestyle changes.

OTHER LIVER AND BILIARY DISEASES

Hepatitis

According to the World Health Organisation (WHO), an estimated 71 million people have chronic hepatitis C infection.[146] Chronic hepatitis C can lead to hepatic fibrosis, cirrhosis and hepatocellular carcinoma. It is the leading cause of liver transplantation in Australia.[147] Estimates indicate that 25 per cent of those infected with hepatitis C will clear the virus, with 75 per cent having chronic infection.[148] Clinical symptoms of chronic hepatitis C include fatigue,[149] right upper quadrant pain or discomfort, nausea, malaise, anorexia, pruritus, weight loss, arthralgia, musculoskeletal pain, night sweats and dry eyes (sicca syndrome). Extrahepatic manifestations of chronic hepatitis C are: mixed cryoglobulinaemia, glomerulonephritis, porphyria cutanea tarda, low-grade malignant lymphoma, autoimmune thyroiditis, Sjögren's syndrome, lichen planus, aplastic anaemia, polyarteritis nodosa, erythema nodosum, idiopathic pulmonary fibrosis and diabetes mellitus.[150] The pathophysiology of chronic hepatitis C is multifactorial and the key players are the hepatitis C virus directly, the immune response to HCV infection and oxidative stress.

DIFFERENTIAL DIAGNOSIS

- Chronic fatigue syndrome
- Fibromyalgia
- NAFLD
- NASH
- Autoimmune hepatitis

Risk factors[151]

Modifiable risk factors include:

- intravenous drug and tobacco use
- blood transfusions
- tattoos
- needle-stick injuries
- steatosis
- insulin resistance, type 2 diabetes
- body mass index (BMI) over 25.

Non-modifiable risk factors include:

- age at acquisition of HCV infection
- age and necrosis stage at liver biopsy
- gender (male)
- duration of infection
- ALT levels ranging from 1.5–5 times the upper limit of normal (ULN), ALT > 70 IU/L and genetics (immune function and interferon sensitivity).

Conventional treatment

- Since 2013/2014 direct acting antivirals (DAAs) have become the gold standard of treatment for CHC, leading to sustained viral response (SVR) in 91% of CHC patients in 12 weeks.[152] However, treatment response does depend on the HCV genotype, the presence or otherwise of cirrhosis and whether the patient is treatment naïve or treatment experienced.[152–156]
- Overall, the adverse events associated with DAAs are mild: nausea, fatigue and anaemia. However, Sofosbuvir (NS5B polymerase inhibitor) is contraindicated in patients with severe renal impairment (it is metabolised through the kidneys).[157–159]
- There is also some controversy as to whether the direct-acting antivirals increase the incidence or recurrence[160,161] of hepatocellular carcinomas or not[162–164] particularly in patients with cirrhosis.

Within the hepatitis C population, one subtype of the virus (HCV genotype 3) is difficult to treat despite the advances in the new direct-acting antivirals for the other hepatitis C genotypes (1, 2, 4, 5 and 6) so the complementary medicine treatment of this subtype still has relevance.[152–155]

Key treatment protocols

- From a naturopathic clinical perspective, the goal of supporting treatment of chronic hepatitis C is to reduce oxidative stress caused by the hepatitis C virus (proteins) and the inflammatory mediators produced by the ineffectual immune response to the virus and thereby reduce disease progression in the form of inflammation, fibrosis, cirrhosis and potentially cancer.
- Encourage beneficial dietary and lifestyle changes. (See the NAFLD section earlier in this chapter and Chapter 3 on wellness.)
- Antiviral and immune support. An immediate, strong and persistent CD4+ T-cell response[166,167] and a vigorous multispecific cytotoxic T lymphocyte response[167–170] against multiple HCV epitopes coupled with a predominant T helper 1 cytokine profile is more likely to encourage viral clearance in response to acute HCV infection.[171] Herbal medicines such as ***Astragalus membranaceus***,[172] ***Echinacea* spp.**[173] and ***Phyllanthus amarus***[174] which influence the Th1–Th2 balance may assist in both acute and chronic hepatitis C infection. **Zinc** and **vitamin E** are particularly important for an effective immune response. **Intravenous silibinin** has shown direct anti-HCV activity in chronic hepatitis C patients who were previous non-responders to standard therapy[175] and to prevent HCV re-infection after liver transplantation.[176]
- The treatment strategies to reduce hepatic inflammation and oxidative stress, support liver function and digestive function and alleviate depression and fatigue are outlined in the NAFLD treatment protocol section.

- Use of specific nutraceuticals. Studies have shown that 2 g **L-carnitine** taken concurrently with interferon and ribavirin for 12 months helped chronic hepatitis C patients clear the hepatitis C virus and reduced fatty liver and fibrosis by 70%.[177] The sustained virological response was also greater in the L-carnitine group (46%) compared with the interferon and ribavirin group (39%). A total 800 IU **vitamin D3** per day given at the same time as pegylated interferon and ribavirin helped liver transplant patients with chronic hepatitis C achieve greater rates of SVR.[178] Between 50% and 73% of chronic hepatitis C patients were deficient in vitamin D3.[179,180] Correcting vitamin D deficiency before antiviral therapy is recommended[178] as low vitamin D is linked to severe liver fibrosis and low levels of SVR on interferon-based therapy.[180]

Cholecystitis

Cholelithiasis is the medical term for the presence of gallstones in the gallbladder. An estimated 14–20% of Australians will develop gallstones in their lifetime. There are three main types of gallstones: cholesterol stones—70% cholesterol crystals; black pigment stones—calcium bilirubinate present in haemolytic disorders; and brown pigment stones—linked to bacterial or helminthic infection in the biliary tree.[181]

In respect to aetiology and pathophysiology, hypersecretion of cholesterol and the hyposecretion of bile acids and phosphatidylcholine (lecithin)[182,183] causes the bile to contain more cholesterol than the bile salts and phospholipids can solubilise. Chemical components of bile precipitate in the gallbladder and occasionally in the bile duct[181] to form microscopic cholesterol-rich vesicles.[183] Pathogenic development of these cholesterol-rich vesicles into macroscopic gallstones has been linked to hypomotility and excess biliary mucin excretion,[184] which is linked to hepatic cholesterol hypersecretion and a cycle of lithogenesis. Gallstones are asymptomatic in 60–80% of cases and, of those, only 10–20% will develop symptoms. Gallstone-associated pain can increase the risk of complications such as acute cholecystitis, cholangitis and pancreatitis.

Cholecystitis can be classified as acute or chronic. Acute cholecystitis is indicated if the pain lasts longer than 12 hours, and may be due to gallstone impaction in the cystic duct. The clinical presentations include fever, upper abdominal pain with marked tenderness and guarding in the right upper quadrant, especially with pain on palpation combined with inspiration, known as Murphy's sign due to elevated pressure within the gallbladder due to obstruction.[185] Chronic cholecystitis (or cholelithiasis) is the most common clinical presentation of symptomatic gallstones and presents as episodic biliary pain usually in the right upper abdominal quadrant or epigastric area, which can radiate to the right subscapular area, midback or right shoulder. Episodes of biliary pain generally last between 30 minutes and a few hours and episodes may occur daily or every few months. Nausea is common, but vomiting and fevers are not.

DIFFERENTIAL DIAGNOSIS

- Angina pectoris
- Appendicitis
- Bowel obstruction
- Epigastric pain from myocardial infarction
- Gastro-oesophageal reflux
- Irritable bowel syndrome
- Liver disease
- Oesophagitis
- Pancreatitis
- Peptic ulcer disease

Source: Portincasa et al. 2006[186]

Risk factors

- Age—increased biliary cholesterol secretion due to a decrease in cholesterol 7-α-hydroxylase activity[187] and decreased biliary salt excretion[188]
- Obesity—increased biliary secretion of bile from the liver with cholesterol supersaturation[186]
- Females—in pregnancy, endogenous oestrogens linked to increased hepatic cholesterol uptake and synthesis, gallbladder hypomotility and decreased cholesterol 7-α-hydroxylase activity.[181,185] The risk for women is two to three times that of males of the same age.[185,189] Women with a BMI over 32 are six times more likely to develop gallstones than women with a BMI over 22[190]
- Rapid weight loss and weight cycling and a prolonged fat-restricted diet is thought to exacerbate gallbladder stasis
- Diet—high carbohydrates in the diet[182] and high triglyceride levels in the blood[183] are linked to gallstone formation
- Dyspepsia—particularly *Helicobacter* species and slow transit time

Conventional treatment[191]

- An ultrasound is the common diagnostic tool.
- A cholescintigraphy scan is also used.
- If acute cholecystitis is suspected, refer the patient to their general practitioner or a hospital emergency department.
- Current medical treatment for cholelithiasis is surgery. Single incision laparoscopic cholecystectomy (SILC) is associated with a 90.7% success rate and a 6.1% complication rate. Critical reviews of clinical guidelines for gallstones have been articulated in the literature.[192–194]

Key treatment protocols

- Encourage beneficial dietary and lifestyle changes. (See Chapter 3 on wellness.)
- Promote optimal bile formation in the liver with choleretics such as ***Curcuma longa***,[195] ***Cynara scolymus*** and ***Peumus boldo***.
- Promote effective gallbladder motility and function with cholagogues such as ***Cynara scolymus, Peumus boldo*** and ***Taraxacum officinale***.
- As a specific for cholelithiasis use the cholerectic and cholagogue ***Peumus boldo.***
- Reduce bile and cholesterol reabsorption in the small intestine by reducing cholesterol intake, synthesis and output with niacin (B3),[196] red yeast rice,[197,198] ***Cynara scolymus***,[199] ***Taraxacum officinale***,[200] fibre and probiotics.
- Support optimal digestive function. See Chapters 4–6 on the gastrointestinal system.
- There is limited evidence of the role of Chinese herbal medicines in the treatment of cholecystitis[201] and cholelithiasis.

Pancreatitis

Pancreatitis is a progressive inflammatory disease characterised by irreversible destruction of exocrine pancreatic tissue.[202] Repeated episodes of acute pancreatitis lead to tissue remodelling and fibrosis.[202] Pancreatitis can be due to obstruction of the pancreatic duct. Obstruction leads to an overproduction of ROS in pancreatic acinar cells, affecting the mitochondria and inducing apoptosis and necrosis.[203,204] Alcohol is the most common

cause of pancreatitis. Excessive alcohol consumption may cause the deposition of protein plugs in the pancreatic ducts, leading to obstruction. The presence of gallstones account for 25–40% of cases of pancreatitis; gallstone impaction at the ampulla of Vater causes hypertension in the pancreatic duct, initiating inflammation.[205] Infectious organisms account for 10% of acute pancreatitis cases, including viruses (e.g. mumps, Coxsackie B and hepatitis), bacteria (e.g. *Mycoplasma pneumoniae* and leptospirosis) and parasites (e.g. *Ascaris lumbricoides, Fasciola hepatica,* and hydatid disease).[206]

Autoimmune pancreatitis is a chronic fibroinflammatory disease of the pancreas. There are two main subtypes. Autoimmune type 1 is a multi-organ disease associated with immunoglobulin G4 (IgG4) and may include proximal bile duct strictures, retroperitoneal fibrosis, renal and salivary gland lesions and swelling of the pancreas. Autoimmune type 2 is a pancreas-specific disorder without systemic involvement.[207]

Pancreatitis usually presents with abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back). Serum lipase or amylase activity elevated more than three times the upper limit of normal (ULN) is a common finding. Characteristic findings of acute pancreatitis are revealed on contrast-enhanced computed tomography and magnetic resonance imaging or transabdominal ultrasonography.[208] The most common clinical presentation of chronic pancreatitis is midepigastric postprandial pain that radiates to the back that is relieved by sitting upright or leaning forwards.[209] Steatorrhoea, malabsorption, vitamin deficiencies (A, D, E, K, B12), diabetes, weight loss or obstructive jaundice may be present.[209,210]

DIFFERENTIAL DIAGNOSIS

- Acute cholecystitis
- Acute pancreatitis
- Intestinal ischaemia or infarction
- Obstruction of the common bile duct
- Pancreatic cancer
- Peptic ulcers or gastritis
- Renal insufficiency

Source: Nair et al. 2007[209]

Risk factors

- Excessive alcohol consumption—leads to endoplasmic reticulum stress and abnormal unfolded protein responses in pancreas, up-regulation of autophagy and ROS[211]
- Cholelithiasis
- Abdominal trauma
- Infectious organisms: viruses, bacteria and parasites[206]
- Hyperlipidaemia
- Viral infections
- Medications (azathioprine, thiazides and oestrogens)
- Obesity and smoking increase the risk of progression to severe pancreatitis[212]
- Genetics—patients with mutations in genes linked to cationic and anionic trypsinogen, serine protease inhibitor Kazal 1, cystic fibrosis transmembrane conductance

regulator, chymotrypsinogen C and calcium-sensing receptor have been shown to be at increased risk of pancreatitis[212]
- Environmental (petrochemical fumes)[210]
- Untreated acute pancreatitis
- Possible autoimmune factor
- HIV/AIDS (comorbid factors and HAART)[213]

Conventional treatment

- Autoimmune pancreatitis: corticosteroids[207]
- Strong opioids for acute pain
- Removal of gallstones
- Antimicrobials—broad-spectrum antibiotics
- No effective treatment for chronic pancreatitis pain
- Acute: restoration of blood volume and electrolyte balance, replace fluids and minimise pancreatic ischaemia[212]
- Enteral feeding[212] to support/avoid malnutrition and development of chronic pancreatitis
- If pancreatitis with hypertriglyceridaemia: weight loss, exercise, blood sugar control, lipid-restriction diet

Key treatment protocols

- *Encourage beneficial dietary and lifestyle changes.* Cease alcohol and tobacco use. Eat low-fat and small meals.[209] (See Chapter 3 on wellness.)
- *Reduce oxidative stress and pain.* Daily antioxidant supplementation of 600 mcg selenium, 0.54 g ascorbic acid, 9000 IU beta-carotene, 270 IU alpha-tocopherol and 2 g methionine was effective in the reduction of pain and oxidative stress of chronic pancreatitis.[210]
- *Reduce inflammation.* In experimental pancreatitis (rat model) curcumin reduced inflammation via inhibition of NF-kappa-B and activator protein-1,[214] and *Taraxacum officinale* reduced IL-6 and TNF-α levels in acute pancreatitis.[215] A TCM formulation targeting pancreatitis contained: *Bupleurum falcatum* (anti-inflammatory), *Glycyrrhiza glabra* (anti-inflammatory and secretin-stimulating), *Panax ginseng* (tonic and free radical scavenging antioxidant) and *Paeonia lactiflora* (proton pump inhibition). This herbal combination improved pancreatic ischaemia.[216]

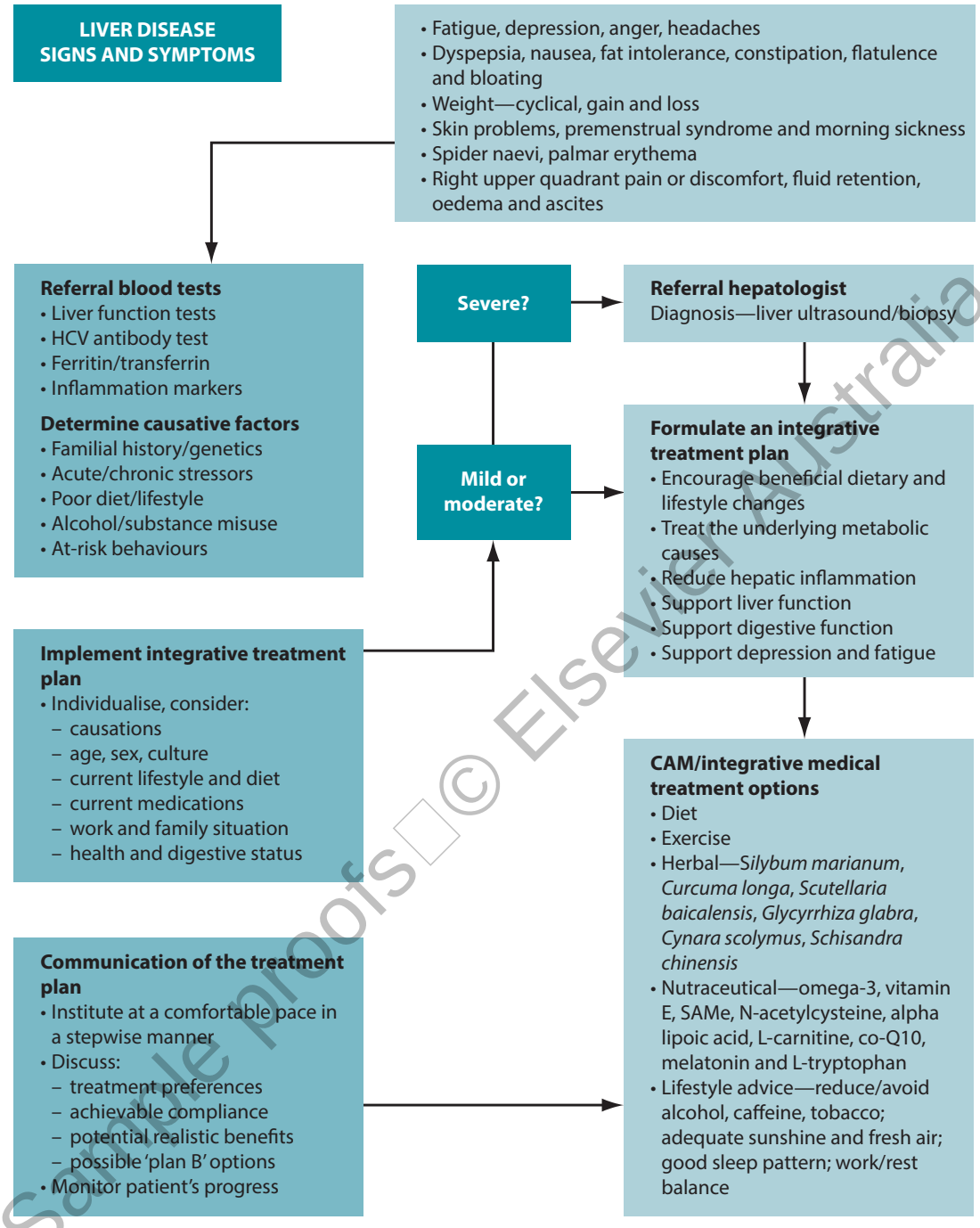


Figure 7.3
Naturopathic treatment decision tree—liver disease

Table 7.2
Review of the major evidence for liver disease

Intervention	Mechanisms of action	Literature	Summary of results	Comment
Realsil: Silybin 94 mg, phosphatidylcholine 194 mg and α-tocopherol 30 mg	Inhibits and scavenges free radicals; protects lipid membranes; regulates cell signalling pathways involved in obesity and insulin resistance; reduces cell migration, TGF-beta-induced synthesis of procollagen type I and secretion of MMP-2 phosphatidylcholine protects against oxidative stress-mediated liver damage	Loguerico et al. 2012[217]	Significant normalisation of ALT, AST and GGT over 12 months Blood glucose was 31% lower in the treated group compared with placebo	Realsil significantly reduced liver inflammation and improved dysglycaemia in NAFLD patients without increases in body weight
Silybum marianum (active isolate: silibinin) Silibinin	Antiviral, antioxidant, anti-inflammatory, hepatoprotective and antifibrotic effects	Fried et al. 2012[218] Guedj et al. 2012[219] Kim et al. 2012[220] Polyak et al. 2010[221] Salomone et al. 2017[222] Wah et al. 2017[223] Zhong et al. 2017[224]	A range of studies have revealed activities that may be beneficial in liver dysfunction and disease including reduced inflammatory cytokines activity: IL-4, IL-10, TNF-α, IFN-γ, VEGF-A, TGF-β and NF-κB activity Silibinin has prevented viral infection Silibinin inhibited TGF-β induced *de novo* synthesis of pro-collagen I Silibinin inhibits de novo lipogenesis, restores NAD^+ levels, induces SIRT1/AMPK signaling and promotes mitochondrial β-oxidation in vivo and in vitro[222] Positive efficacy to reduce transaminases levels in NAFLD patients[224]	Intravenous use of silibinin is promising as an antiviral in HCV[175]
Scutellaria baicalensis (active isolate: baicalin)	Baicalin ameliorates ischaemia/reperfusion-induced hepatocellular damage by suppressing TLR4-mediated inflammatory responses in ALD[74] Alleviates palmitic-acid-induced cytotoxicity in AML-12 cells via suppression of ER stress and TXNIP/NLRP3 inflammasome activation[225]	Guo et al. 2009[73] Kim et al. 2012[74] Zhang et al. 2017[225]	Results have found baicalin reduces dyslipidaemia, hepatic lipid accumulation and visceral fat mass in vivo, improves hepatic steatosis[73] Reduced serum ALT, TNF-α and IL-6 in alcoholic fatty liver	The antioxidant and anti-inflammatory actions of baicalin and *Scutellaria baicalensis* make it a very useful clinical tool in NAFLD[73] and ALD[74]

Table 7.2
Review of the major evidence for liver disease (continued)

Intervention	Mechanisms of action	Literature	Summary of results	Comment
Curcuma longa	Shown in a range of studies to have antioxidant, anti-inflammatory and anti-fibrotic actions	Ak et al. 2008[226] Honda et al. 2006[54] Rahmani et al. 2016[227] Chenari et al. 2017[228]	Antioxidant, radical scavenging and metal chelating effects in animal models Prevented thioacetamide-induced cirrhosis, and hepatic fibrosis, inhibited hepatic stellate cell (HSC) activation Suppressed connective tissue growth factor expression in HSC activation	*Curcuma longa* reduces liver injury through down-regulation of inflammatory processes[229]
Cynara scolymus	Shown in a range of studies to have antioxidant, anti-inflammatory, choleretic and hepatoprotective actions, which may be of benefit for a range of liver conditions Anti-hyperglycemic, hypolipidemic	Speroni et al. 2003[88] Qiang et al. 2012[199] Ben Salem et al. 2017[230] Mocelin et al. 2016[231] Sahebkar et al. 2018[232]	Normalisation of AST and ALT Reduction of histological changes and accumulation of triglycerides[88] Lowered hamster plasma cholesterol levels by a mechanism involving the greater excretion of fecal bile acids and neutral sterols after feeding for 42 days[199]	Lowers cholesterol and triglyceride levels through stimulating bile production and flow
Glycyrrhiza glabra	Shown in a range of studies to have several beneficial actions for liver conditions including antiviral, anti-inflammatory and hepatoprotective effects Antimicrobial, antioxidative, antidiabetic, anticancer activities as well as immunomodulatory, gastro-protective, neuro-protective and cardio-protective effects	Hajiaghamohammadi et al. 2012[75] Wu et al. 2008[76] Rhee et al. 2012[77] Wang et al. 2013[233] Hosseinzadeh et al. 2017[234]	Lowered ALT and AST Prevented lipotoxicity and regulated apoptosis Reversed FFA-induced mitochondrial membrane depolarisation in HepG2 cells	Glycyrrhiza's anti-inflammatory and protective actions have significant benefits in treating NAFLD via altering gene expression pathways seen in fibrosis and reducing hepatic inflammation
Schisandra chinensis	Shown in a range of studies to have antioxidant, hepatoprotective, antiobesity and antidiabetic actions, which may benefit several liver conditions Hypolipidemic	Pan et al. 2008[89] Park et al. 2012[235] Chung et al. 2017[236]	Decreased hepatic total cholesterol and triglyceride levels (by up to 50% and 52%, respectively) in hypercholesterolaemic mice[89] Antiobesity action: reduced the accumulation of cellular triglycerides and induced inhibited differentiation and adipogenesis in 3T3-L1 cells in high-fat diet rats[229]	Hepatoprotective, especially in terms of lipid metabolism

Table 7.2
Review of the major evidence for liver disease (continued)

Intervention	Mechanisms of action	Literature	Summary of results	Comment
Alpha-lipoic acid 300–600 mg/day	Improves glucose uptake via up-regulation of GLUT4 receptors Antioxidant—scavenger and up-regulation of endogenous antioxidants via Nrf2/ARE Antifibrotic via inhibition of TGF-β and anti-inflammatory via inhibition of TNF-α induced NF-κB	Kaya-Dagistanlia et al. 2013[237] Castro et al. 2012[84] Hultberg et al. 2006[238] Min et al. 2010[239] Petersen Shay et al. 2008[240] Kim et al. 2004[241] Pilar Valdecantos et al. 2015[242]	Antidiabetic, antihyperlpdaemic, antioxidant, anti-inflammatory, antifibrotic	Decrease in fatty degeneration, inflammation and cell vacuolisation in hepatocytes
L-carnitine	Modulator of fatty acid transport and oxidation Improves beta-oxidation through protection and stimulation of mitochondrial function	Meta-analysis NAFLD Musso et al. 2010[243] Fujisawa et al. 2017[244]	Improves insulin sensitivity, modulates lipid profiles, glucose metabolism, oxidative stress and is anti-inflammatory and antifibrotic	Improves insulin sensitivity and promotes beta-oxidation
Berberine	Antimicrobial, antidiabetic, hypoglycemic, hypocholesterolemic, anti-tumoral, immunomodulatory properties, anti-inflammatory and antioxidant	Zhu et al. 2016[56] Zhao et al. 2017[57] Pirillo et al. 2015[58] Wei et al. 2017[59]	Berberine improves mitochondrial function[56] and inhibited hepatic lipogenesis[57]	Berberine is found in *Berberis vulgaris, Mahonia aquifolium, Hydrastis canadensis, Phellodendron amurense, Coptis chinensis, Eschscholzia californica*
Probiotics	Reduction of aminotransferases Immune support: inhibition of epithelial invasion, bacterial translocation, production of antimicrobial peptides Enhancement of insulin sensitivity Reduction in hepatic inflammation/steatosis, suppression of the TNFα/IKK-β signaling pathway, reduction of activity of Jun N-terminal kinase, decrease DNA binding activity of NF-κB	Doulberis et al. 2017[135]	Amelioration of hepatic steatosis and endotoxemia, prevention of NAFLD progression and tumorigenesis	Encouraging, though preliminary evidence which needs further study

KEY POINTS

- There is a cyclic relationship between metabolic syndrome and liver disease.
- Oxidative stress and inflammation drives pathology in liver disease and pancreatitis. This reduces liver and pancreatic function with systemic consequences for health.
- Effective detoxification can regulate hormones and have anti-carcinogenic effects through inhibition of phase I and induction of phase II enzymes.[94,102]
- Adjunctive naturopathic protocols, herbal medicines, nutraceuticals, probiotics, Mediterranean diet, exercise and lifestyle can attenuate disease progression by reducing inflammation and oxidative stress driven liver diseases such as NAFLD, NASH, ALD and HCV.

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