

Clinical Nutrition & Supplements For Non-Alcoholic Fatty Liver Disease (NAFLD)

Original | Clinical Research White Paper

June 2023 | Saju Joseph MD FACS, Devan A. Patel PharmD, Jill Barat PharmD, Teri A. Standridge B.S., Vinay Patel M.D.

Clinical Nutrition & Supplements For Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD, or non-alcoholic fatty liver disorder, is a serious health issue that affects millions of people worldwide. This condition can be difficult to treat with traditional medical approaches and requires significant lifestyle changes to manage appropriately.

In addition to lifestyle modifications, there are several potential drug and supplement treatments that may be beneficial in some cases of NAFLD. However, there have been limited long-term efficacy studies and no definitive evidence of their effectiveness.

More recently, increasing attention is being paid to the use of dietary supplements as a potential treatment for alleviating symptoms related to NAFLD. The availability and minimal side effects associated with this approach make supplements an attractive alternative. As such, further research into the benefits of dietary supplementation may prove invaluable.

Overview of Nonalcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the accumulation of fat in the liver cells of people who don't consume alcohol.¹ People who are overweight or obese are most likely to suffer from this condition as obesity is caused by an imbalance in energy regulation, which often leads to increased inflammation in the body. Left untreated, NAFLD can lead to a more serious condition known as non-alcoholic steatohepatitis (NASH).

NASH (non-alcoholic steatohepatitis) is a more severe form of NAFLD that can occur when fat accumulates in the liver and causes inflammation.² This inflammation can lead to fibrosis (scarring) of the liver, which could eventually progress to cirrhosis (liver failure). People with NASH are at an increased risk of developing liver cancer.

The most common symptoms of NASH are fatigue, malaise and occasionally mild abdominal. More severe symptoms include jaundice (yellowing of the eyes and skin), itching, and swelling in the legs or abdomen. More often, there are no symptoms of either NAFLD or NASH until the disease progresses to a more serious condition.

Who Is Most at Risk for NAFLD?

People who are overweight or obese, and those with insulin resistance and diabetes are most at risk of developing non-alcoholic fatty liver disease (NAFLD).³ People who have high cholesterol, high triglycerides, metabolic syndrome, and polycystic ovarian syndrome may also be more likely to develop NAFLD.⁴ Additionally, individuals who take certain medications, such as steroids or tamoxifen, have an increased risk of developing fatty liver disease. Also, other lifestyle causes could include a sedentary lifestyle, increased ingestion of processed foods including high fructose corn syrup, and a high fat/carbohydrate diet.



Management of NAFLD

NAFLD can be reversed or managed if identified early on. The primary recommendation for the management of NAFLD is weight loss through diet and exercise, as research has demonstrated that obesity is a major risk factor for NAFLD.

Nutrition plays a critical role in managing both the risk factors for this disease and its progression. Individuals should focus on leading a healthy lifestyle with a balanced diet rich in whole plant foods such as fruits, vegetables, legumes, nuts, and healthy fats, and minimizing highly processed foods.

Exercise also has benefits for not only maintaining a healthy weight but also supporting lean muscle growth. This combination can reduce inflammation associated with obesity, helping to reduce risk factors involved with the development of NAFLD.

Medications for NAFLD

Currently, there is no medical cure for NAFLD. Lifestyle changes are most effective, however, there are some prescription medications that are useful for managing NAFLD and its symptoms.

Insulin Sensitizers

The most used medications for NAFLD are those that help regulate insulin resistance (IR). IR is a condition in which the body doesn't respond to the hormone insulin properly. Insulin helps the body use and manage glucose (sugar) for energy, but when the body becomes insulin resistant, the glucose accumulates more into the blood, in turn causing higher concentrations and leading to diabetic complications. IR can cause a host of problems, including fatty liver disease.⁵ Medications for IR can help improve insulin sensitivity, which in turn can help reduce the risk of developing NAFLD/NASH.

Rosiglitazone and pioglitazone are both insulin sensitizers. A randomized controlled trial showed that rosiglitazone improved steatosis and aminotransferase levels in patients with NASH.⁶ However, the use of rosiglitazone is restricted due to its increased risk of heart attack (ischemic heart disease). The European Medicines Agency prohibits its use, and the FDA highly restricts its use in the United States.

Pioglitazone, at a dosage of 30 or 45 mg/d, has been shown to improve serum aminotransferase levels and liver histology in NASH patients in randomized controlled trials.⁷⁻⁸ However, fibrosis improvement was not significant. US guidelines recommend pioglitazone for patients with Diabetes and biopsy-proven NASH patients. Pioglitazone does, however, have

side effects such as weight gain, edema, heart failure, and bone density reduction, which often limits its use.

Furthermore, one prior study did suggest the risk of bladder cancer increases if pioglitazone is used for more than 2 years. Other studies have refuted this. France and Germany prohibit pioglitazone usage for new patients, while the FDA advises caution if there is a history of bladder cancer and avoidance if active cancer is present.

Metformin is a medication used to treat type 2 diabetes mellitus by increasing insulin sensitivity. It also reduces hepatic gluconeogenesis and triglyceride production. Studies show it improved fatty liver disease in mice and NAFLD/NASH patients.⁹ However, a randomized trial found no significant improvement in liver histology in NAFLD patients.¹⁰ It was also ineffective in reducing ALT levels in pediatric NAFLD patients.¹¹ American guidelines do not currently recommend it for adult NAFLD treatment.

Lipid Lowering Drugs (Statins)

NAFLD is linked to obesity and dyslipidemia, an imbalance of lipids, such as cholesterol. Statins are used to treat dyslipidemia by preventing cholesterol synthesis. Statins may also have anti-inflammatory effects and can be used to treat NAFLD. Atorvastatin and simvastatin are two types of statins. A pilot study showed that atorvastatin treatment significantly reduced serum aminotransferase and lipid levels in all patients with NAFLD, but a histological assessment was not done.¹²

In various clinical studies, the effects of atorvastatin and simvastatin on patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) were examined. Atorvastatin combined with antioxidants showed a significant reduction in hepatic steatosis risk after four years of treatment.¹³ However, some patients with biopsy-proven NASH with hyperlipidemia had increased fibrosis stage with atorvastatin administration. On the other hand, simvastatin treatment did not result in significant improvements in NASH patients.¹⁴

The effectiveness of statins for NAFLD/NASH is not yet fully confirmed. Statins can reduce lipid levels in the liver and peripheral areas. When fat is removed from the liver, serum aminotransferase levels may briefly increase, but this does not lead to liver injury. Over time, decreased fat deposition in the liver lowers serum aminotransferase levels. Despite a temporary increase in serum aminotransferase levels after statin treatment, discontinuing treatment is unnecessary. It's not recommended to use statins to treat NASH until randomized controlled trials confirm their efficacy.

Pentoxifylline

Pentoxifylline is a medication used to treat peripheral vascular disease. It helps increase blood flow to certain areas of the body, such as the arms and legs. Pentoxifylline has been studied as

a potential treatment for NAFLD/NASH due to its ability to inhibit the synthesis of TNF- α , which is believed to play a role in the progression of NAFLD. Recent research has also demonstrated that pentoxifylline can reduce levels of oxidized lipid products in NASH patients.¹⁵

In initial tests, the use of pentoxifylline for twelve months showed a significant decrease in serum AST and ALT levels among NASH patients.¹⁶⁻¹⁷ However, randomized controlled trials have produced conflicting results. Van Wagner et al found that administering pentoxifylline at a dosage of 1200 mg per day for twelve months did not result in reduced aminotransferase levels in NASH patients when compared to a placebo.¹⁸

A study by Zein et al found that administering pentoxifylline (1200 mg/d) for 12 months improved histological features of NASH (steatosis, lobular inflammation, NAS, and fibrosis) compared to placebo.¹⁹ However, larger randomized controlled trials are necessary to confirm the effects of pentoxifylline on NAFLD/NASH. Caution is required when administering pentoxifylline due to its adverse effects, such as nausea and vomiting.

Ursodeoxycholic acid


Ursodeoxycholic acid (UDCA) is a bile acid with protective properties. It has been studied for its effects on NAFLD/NASH. Recent randomized controlled trials have shown that treatment with high-dose UDCA for a period of 12 months can improve aminotransferase levels, serum fibrosis markers, and selected metabolic parameters in NASH patients.²⁰ However, there was no histological assessment performed in this study.

Another randomized controlled trial found that a combination of UDCA and vitamin E improved serum AST and ALT levels and hepatic steatosis in patients with NASH after two years of treatment.²¹ However, American guidelines do not recommend UDCA for the treatment of NAFLD or NASH.

Angiotensin receptor blockers

The renin-angiotensin-aldosterone system (RAAS) affects insulin sensitivity and is linked to NAFLD/NASH development. Angiotensin II type 1 blockers, such as telmisartan, valsartan, and losartan, have been studied for their effects on NAFLD. Telmisartan was found to reduce steatohepatitis progression by suppressing macrophage infiltration into the liver.²²

In a clinical trial, both telmisartan and valsartan lowered serum ALT levels, HOMA-IR, and NAS for NASH patients with metabolic syndrome.²³ Telmisartan had a stronger effect on HOMA-IR and NAS as compared to valsartan. The results suggest that these medications may be beneficial for treating NAFLD/NASH patients with metabolic syndrome, but further research is needed to confirm their efficacy and safety for clinical use.



A combination treatment of losartan and deferasirox showed a decrease in NASH progression in rats.²⁴ Losartan was found to improve serum aminotransferase levels and liver histology in a clinical trial. However, in an open-label trial, combination therapy with rosiglitazone and losartan did not show greater benefits than rosiglitazone alone.²⁵ Further randomized controlled trials are needed to confirm the effects of angiotensin receptor blockers on NAFLD/NASH. Additionally, the use of angiotensin receptor blockers for normotensive patients should be approached with caution due to their hypotensive effects.

Dietary Supplementation for NAFLD

Recent attention has been given to the potential benefits of dietary supplements in slowing the progression of NAFLD. These substances are widely available and have minimal side effects. Below, we'll discuss some of the most researched dietary supplements for improving NAFLD.


B12 (methylcobalamin)

Vitamin B12, also known as cobalamin, is an essential water-soluble vitamin that plays a crucial role in the metabolism of fatty acids, amino acids, and carbohydrates. Recent studies have shown that vitamin B12 may help to reverse NAFLD and improve liver function.²⁶

One of the primary mechanisms by which vitamin B12 may help to reverse NAFLD is through its role in the methionine cycle. The methionine cycle is a metabolic pathway that is responsible for the synthesis of S-adenosylmethionine (SAME), a key molecule that is involved in numerous methylation reactions in the body. Methylation is a critical process that regulates the expression of genes, repairs DNA damage, and detoxifies harmful substances. In people with NAFLD, the methionine cycle is disrupted, leading to a buildup of toxic metabolites and oxidative stress. Vitamin B12 helps to restore the methionine cycle by facilitating the conversion of homocysteine to methionine, which in turn leads to the production of SAME.²⁷

Vitamin B12 is also an anti-inflammatory. Chronic inflammation is a key contributor to the development and progression of NAFLD. Vitamin B12 has been shown to reduce the production of pro-inflammatory cytokines and increase the production of anti-inflammatory cytokines, which helps to reduce inflammation in the liver.²⁸

In addition to its role in the methionine cycle and its anti-inflammatory properties, vitamin B12 also helps to improve liver function by reducing oxidative stress and improving lipid metabolism. Oxidative stress is a condition in which there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. In individuals with NAFLD, oxidative stress is increased, leading to damage to liver cells and inflammation.



Vitamin B12 helps to reduce oxidative stress by acting as a cofactor to produce glutathione, a powerful antioxidant. Furthermore, vitamin B12 helps to improve lipid metabolism by facilitating the breakdown of fatty acids and the conversion of triglycerides into energy.²⁹

L-Methylfolate

L-Methylfolate is a type of folate, a B vitamin that the body needs and cannot produce by itself. It is vital for various metabolic processes, including DNA synthesis, cell proliferation, and homocysteine metabolism. Studies have observed low levels of L-Methylfolate in individuals with NAFLD, indicating a possible link between the deficiency and the disease's development.³⁰ Interestingly, supplementing with L-Methylfolate has been shown to improve liver function, reduce inflammation, and promote weight loss in people with NAFLD.³¹

One of the ways that L-Methylfolate may help in managing NAFLD is by reducing oxidative stress in the liver.³² L-Methylfolate acts as an antioxidant, neutralizing harmful chemicals and helping to prevent liver damage from free radicals. L-Methylfolate may also aid in managing NAFLD by lowering the levels of homocysteine in the blood.³³

Homocysteine is an amino acid that is toxic to the liver at high levels. Low levels of L-Methylfolate are associated with the accumulation of homocysteine in the body. L-Methylfolate helps to break down homocysteine into less harmful substances, reducing the toxic load on the liver.

L-Methylfolate has also been shown to suppress the production of pro-inflammatory molecules, reducing inflammation in the liver, and promoting healing.³⁴ Finally, L-Methylfolate may aid in NAFLD by improving insulin sensitivity.³⁵

Vitamin E

Vitamin E is a powerful antioxidant that helps protect cells from damage caused by free radicals.³⁶ Free radicals are molecules that can cause damage to cells and tissues in the body, leading to inflammation and disease. By neutralizing these free radicals, vitamin E can help prevent further damage to liver cells and reduce inflammation.

Research also suggests that vitamin E may help reduce the accumulation of fat in the liver by increasing the breakdown of fats and improving liver function. It may also help reduce insulin resistance, which is a common risk factor for NAFLD.³⁷

When it comes to dosage, studies have found that a daily dose of 800 IU of vitamin E for at least 6 months can help improve liver function and reduce inflammation in people with NAFLD.³⁸ However, it is important to note that high doses of vitamin E can be harmful, so it is important to speak with a healthcare professional before starting any vitamin E supplementation.

Vitamin D

Research has shown that vitamin D supplementation can help improve the liver's function, decrease inflammation, and reduce fat accumulation.³⁹ Vitamin D can also improve insulin resistance, which is a key factor in the development of NAFLD.⁴⁰

Moreover, vitamin D has potent antioxidant properties that can protect liver cells from oxidative damage, a common consequence of NAFLD. The antioxidant properties of vitamin D can also help reduce the risk of liver cancer, which is a severe complication of NAFLD.⁴¹

In addition, vitamin D has been found to enhance the immune response and reduce inflammation in the liver.⁴² By doing so, vitamin D may help prevent the progression of NAFLD to more severe liver diseases, such as cirrhosis or liver failure.

Chromium Picolinate

Chromium Picolinate, an essential trace mineral, has been extensively researched for its various potential health benefits, including its use in the treatment of non-alcoholic fatty liver disease (NAFLD).

Several studies have suggested that supplementing with Chromium Picolinate can improve the symptoms of NAFLD, largely by enhancing insulin sensitivity and reducing inflammation.⁴³


One of the key mechanisms by which Chromium Picolinate may help improve NAFLD is through its effect on insulin. Chromium Picolinate has been shown to enhance insulin sensitivity by improving glucose uptake into cells and increasing the activity of insulin signaling pathways.⁴⁴

Another way in which Chromium Picolinate may help improve NAFLD is through its anti-inflammatory properties. Chromium Picolinate has been shown to reduce inflammation in the liver by inhibiting the production of pro-inflammatory cytokines and increasing the activity of antioxidant enzymes.⁴⁵

Furthermore, several studies have suggested that Chromium Picolinate supplementation can lead to significant reductions in liver fat content and improved liver function in patients with NAFLD.⁴⁶

Zinc Picolinate

Zinc picolinate is a form of zinc that has been shown to have potential benefits for individuals with NAFLD. Zinc is an essential mineral that plays a key role in many biological processes in the body, including metabolism, immune function, and antioxidant activity.



One of the ways zinc picolinate may help NAFLD is by reducing inflammation. Inflammation is a common characteristic of NAFLD and is thought to play a key role in its development and progression. Studies have shown that zinc supplementation can reduce markers of inflammation in the liver, potentially slowing or reversing the damage caused by NAFLD.⁴⁷

Zinc picolinate may also help improve insulin sensitivity, which could help reduce liver fat accumulation and improve liver function.⁴⁸ In addition, zinc picolinate may have antioxidant properties that could benefit individuals with NAFLD. Zinc is an important cofactor for many antioxidant enzymes in the body, and supplementation with zinc picolinate has been shown to increase antioxidant activity in some studies.⁴⁹

Overall, while more research is needed, zinc picolinate appears to have potential benefits for individuals with NAFLD. It may help reduce inflammation, improve insulin sensitivity, and increase antioxidant activity, all of which could help improve liver function and slow the progression of NAFLD.

Turmeric

Turmeric, a widely used spice in Asian cuisine, may hold immense potential in combating non-alcoholic fatty liver disease (NAFLD). The most active compound within turmeric is curcumin, which possesses antioxidant, anti-inflammatory, and lipid-lowering properties that may help with NAFLD.


Research has shown that curcumin can prevent the accumulation of fat in the liver by decreasing the expression of genes responsible for lipid metabolism.⁵⁰ Additionally, curcumin has been found to be effective in reducing liver inflammation, thus preventing further liver damage.⁵¹

Turmeric also helps in regulating blood glucose levels, which is beneficial for individuals with NAFLD as they tend to have IR, leading to increased blood glucose levels.⁵² Furthermore, curcumin may help improve liver function by protecting liver cells from damage caused by free radicals, which contribute to the development and progression of NAFLD.⁵³

In addition to its liver-protective properties, turmeric has been found to have the potential in preventing other chronic diseases such as cardiovascular disease, diabetes, and cancer, which are often associated with NAFLD.⁵⁴

Overall, the use of turmeric as a natural remedy for NAFLD is promising due to its anti-inflammatory, antioxidant, and lipid-lowering properties. However, more research is needed to determine the optimal dose and duration of consumption for maximum impact.

Milk Thistle



Milk thistle is an herbal supplement that has been extensively researched for its potential in treating various liver conditions, including NAFLD. Milk thistle contains an active ingredient called silymarin, which is a potent antioxidant and anti-inflammatory compound. Studies have shown that silymarin helps reduce liver inflammation, which may significantly improve the symptoms of NAFLD.⁵⁵ Additionally, silymarin also promotes the growth of new liver cells, which aids in repairing any damage caused by the disease.⁵⁶

Furthermore, milk thistle has been found to have lipid-lowering effects.⁵⁷ It helps reduce levels of harmful cholesterol and triglycerides in the blood, which, when elevated, can contribute to the development of NAFLD.

In a clinical trial conducted on patients with NAFLD, it was found that milk thistle supplementation significantly decreased liver enzyme levels, which are key indicators of liver inflammation and damage.⁵⁸ Moreover, milk thistle supplements may also improve IR.⁵⁹

While more research is needed to fully understand the benefits of milk thistle in treating NAFLD, the available evidence suggests that milk thistle may be beneficial for improving liver function and reducing inflammation in those with this condition.

Chanca Piedra


Chanca Piedra, also known as *Phyllanthus niruri*, is a plant that grows in tropical regions and has been used in traditional medicine for centuries. It is known for its ability to promote liver health and has been used to treat liver-related conditions such as hepatitis, jaundice, and gallstones. Recent studies have also shown that it may be effective in treating NAFLD.

Animal studies have shown that chanca piedra can improve symptoms of NAFLD by lowering liver fat accumulation and providing antioxidant properties.⁶⁰ The plant contains compounds such as flavonoids, alkaloids, and lignans, which have been shown to have antioxidant, anti-inflammatory, and hepatoprotective properties.

The mechanisms by which Chanca Piedra may be able to help NAFLD are not fully understood, but it is believed that its compounds may help to protect the liver cells from damage, reduce inflammation, and improve fat metabolism. Additionally, it may also be able to regulate insulin sensitivity.⁶¹

Overall, Chanca Piedra appears to be a promising natural supplement for NAFLD. Its ability to reduce liver fat accumulation, improve liver function, and reduce inflammation makes it a promising avenue for further research.

Ginger Root Extract



Ginger root extract, derived from the underground stem of the *Zingiber officinale* plant, has been shown to have beneficial effects on NAFLD.

One way ginger root extract can help alleviate NAFLD is by targeting inflammation. Ginger root extract contains potent anti-inflammatory compounds such as gingerols and shogaols. These compounds help reduce pro-inflammatory cytokines that contribute to liver damage.⁶² Moreover, gingerol has been shown to modulate the expression of genes involved in inflammation, further highlighting its anti-inflammatory properties.⁶³

Another way ginger root extract can benefit NAFLD is by regulating lipid metabolism. Studies have demonstrated that ginger can alter the expression of genes involved in lipid metabolism, leading to decreased lipid accumulation in the liver.⁶⁴ Gingerols and shogaols can also help lower serum lipid levels, which can be beneficial for people with NAFLD.⁶⁵

Finally, ginger root extract has hepatoprotective properties and may help prevent liver damage. In animal models, ginger extract has been shown to attenuate oxidative stress, reduce liver enzyme levels, and improve liver histology.⁶⁶ These effects are attributed to ginger's antioxidant properties, which may protect liver cells from oxidative damage.

Dandelion Root Extract


Dandelion root has been used for centuries as a natural remedy for a wide range of health issues, including liver problems. The root contains a wide spectrum of nutrients and compounds that are known to be highly beneficial for liver health, including inulin, taraxacin, and choline, to name just a few.

Research has shown that dandelion root can help to promote liver function by increasing the production of bile, which is essential for digestion and the breakdown of fats.⁶⁷ It is also thought to help reduce inflammation in the liver, which is a key factor in the development of non-alcoholic fatty liver disease.⁶⁸

Other ways in which dandelion root may help to improve liver health include its ability to enhance the liver's ability to detoxify harmful substances, such as environmental pollutants, alcohol, and drugs.⁶⁹ It has also been shown to help prevent the build-up of fat in the liver, which is a common feature of nonalcoholic fatty liver disease.⁷⁰

L-Cysteine HCL

L-Cysteine HCL, a natural amino acid, has been found to be effective in treating NAFLD.⁷¹ It works by reducing oxidative stress and inflammation in the liver, which can cause damage to liver cells.⁷² L-Cysteine HCL achieves this by enhancing glutathione production, the body's most potent antioxidant. Glutathione is known to play a crucial role in detoxifying the liver. It defends the liver against free radicals and other toxic substances that it encounters. As a result,



L-Cysteine HCL helps to prevent liver cell injury, thereby reducing the risk of liver damage and disease progression.

In addition to its antioxidant properties, L-Cysteine HCL also improves insulin sensitivity.⁷³ By improving insulin sensitivity, L-Cysteine HCL reduces the risk of developing NAFLD and slows down the progression of the disease in patients who already have it.⁷⁴ Another benefit of L-Cysteine HCL is its ability to reduce the levels of lipids in the blood.⁷⁵ By lowering lipid levels, L-Cysteine HCL may reduce the risk of liver damage and disease progression.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a nutrient naturally found in the mitochondria of cells and is known to play a vital role in energy production. Recent studies have shown that CoQ10 can offer promising benefits in the treatment of NAFLD.⁷⁶

CoQ10 acts as an antioxidant and anti-inflammatory. By inhibiting the production of pro-inflammatory cytokines, CoQ10 can help to reduce liver damage, inflammation, and fibrosis, ultimately leading to improvement in liver function.⁷⁷

Studies have also shown that CoQ10 supplementation can also improve insulin sensitivity.⁷⁸ CoQ10 can help to increase the uptake and utilization of glucose in the liver, which not only improves insulin sensitivity but can reduce the accumulation of liver fat.

Further research is needed to fully understand the mechanisms underlying the beneficial effects of CoQ10 in NAFLD, but current evidence suggests that it could be a valuable addition to the treatment regimen for NAFLD.

Bioperine

Bioperine is a bioactive compound extracted from the fruit of black pepper. It acts as a bioenhancer, which means it can enhance the bioavailability and absorption of other nutrients and compounds in the body. Studies have shown that bioperine can improve the absorption of several nutrients that may aid in liver health, such as curcumin, resveratrol, and silymarin.⁷⁹

Furthermore, bioperine has been shown to have anti-inflammatory and antioxidant properties.⁸⁰ By reducing inflammation, bioperine may help alleviate the damage to liver cells caused by NAFLD.

Moreover, bioperine has been found to have a protective effect against liver damage induced by alcohol and toxins.⁸¹ It can regulate the levels of liver enzymes, which are markers of liver damage, and improve liver function.⁸² This suggests that bioperine may also have a beneficial effect on NAFLD, as it shares many pathological features with alcohol-induced liver disease.



BergaCynFF® (Bergamont (Citrus bergamia) and Cynara cardunculus (artichokes))

BergaCynFF® is a natural, plant-based supplement formulated to support liver health and aid in the prevention and treatment of NAFLD. It contains a unique blend of ingredients, including artichoke leaf extract, bergamot fruit extract, and fennel seed extract, which work together to support liver function and promote fat metabolism.

Artichoke leaf extract is a potent antioxidant that has been shown to protect liver cells from oxidative stress.⁸³ It also aids in the digestion of fats by promoting the secretion of bile, a liquid that helps to break down fats during digestion.⁸⁴ Bergamot fruit extract contains compounds known as polyphenols, which have been found to improve lipid metabolism and reduce inflammation in the liver, thereby supporting liver health.⁸⁵ Fennel seed extract is a rich source of fiber that helps to promote digestion and curb appetite, which may aid in weight management.

Studies have demonstrated the effectiveness of BergaCynFF® in improving liver function and reducing the accumulation of fat in the liver. In a randomized controlled trial, participants with NAFLD who took BergaCynFF® showed significant improvements in oxidative stress and inflammation, compared to those in the placebo group.⁸⁶ Another study found that BergaCynFF® supplementation resulted in a significant reduction in liver enzyme levels and liver fat content among individuals with NAFLD.⁸⁷

BergaCynFF® is a safe and effective natural supplement that may aid in the prevention and treatment of NAFLD. Its unique blend of natural ingredients work together to support liver health, promote fat metabolism, and reduce inflammation, making it a valuable addition to any NAFLD treatment plan.

Conclusion

NAFLD remains a difficult condition to treat. Lifestyle changes are often necessary for improving health and reversing fatty liver. However, making lifestyle changes proves difficult for many people. Certain prescription medications may address conditions related to NAFLD (such as diabetes or high cholesterol), therefore reducing some symptoms of fatty liver.

Unfortunately, medications are not always highly effective in treating NAFLD specifically. Furthermore, many prescription medications come with unwanted side effects.

Dietary supplements are continually being researched for their possible effectiveness in treating NAFLD. Certain nutrients and herbs have shown promise in fighting fatty liver symptoms and addressing health conditions that can lead to NAFLD.

Dietary supplements are an attractive addition to a NAFLD regimen because they are generally safe to use and tend to produce few negative side effects. Though more research is necessary to prove their level of efficacy, supplements plus lifestyle changes may be an effective and holistic approach to addressing NAFLD.

References:

1. "Nonalcoholic Fatty Liver Disease (NAFLD) & NASH - NIDDK." National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, <https://www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash>. Accessed 16 May 2023.
2. "Nonalcoholic Steatohepatitis (NASH)." Stanford Health Care, <https://stanfordhealthcare.org/medical-conditions/liver-kidneys-and-urinary-system/nonalcoholic-steatohepatitis-nash.html>. Accessed 16 May 2023.
3. "Risk factors for NAFLD - Non-Alcoholic Fatty Liver Disease." NCBI, <https://www.ncbi.nlm.nih.gov/books/NBK384735/>. Accessed 16 May 2023.
4. Vassilatou, Evangeline. "Nonalcoholic fatty liver disease and polycystic ovary syndrome." NCBI, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093689/>. Accessed 16 May 2023.
5. "Nonalcoholic Fatty Liver Disease and Insulin Resistance: New Insights and Potential New Treatments." NCBI, 14 April 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5409726/>. Accessed 16 May 2023.
6. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, Podevin P, Lacorte JM, Bernhardt C, Bruckert E, Grimaldi A, Poynard T; LIDO Study Group. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology*. 2008 Jul;135(1):100-10. doi: 10.1053/j.gastro.2008.03.078. Epub 2008 Apr 8. PMID: 18503774.
7. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006 Nov 30;355(22):2297-307. doi: 10.1056/NEJMoa060326. PMID: 17135584.
8. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for

- nonalcoholic steatohepatitis. *N Engl J Med*. 2010 May 6;362(18):1675-85. doi: 10.1056/NEJMoa0907929. Epub 2010 Apr 28. PMID: 20427778; PMCID: PMC2928471.
9. Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin-deficient mice. *Nat Med*. 2000 Sep;6(9):998-1003. doi: 10.1038/79697. PMID: 10973319.
10. Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjørø K, Haaland T, Løberg EM, Birkeland K. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. *Scand J Gastroenterol*. 2009;44(7):853-60. doi: 10.1080/00365520902845268. PMID: 19811343.
11. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, Abrams SH, Scheimann AO, Sanyal AJ, Chalasani N, Tonascia J, Ünalp A, Clark JM, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; Nonalcoholic Steatohepatitis Clinical Research Network. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 2011 Apr 27;305(16):1659-68. doi: 10.1001/jama.2011.520. PMID: 21521847; PMCID: PMC3110082.
12. Gómez-Domínguez E, Gisbert JP, Moreno-Monteagudo JA, García-Buey L, Moreno-Otero R. A pilot study of atorvastatin treatment in dyslipemid, non-alcoholic fatty liver patients. *Aliment Pharmacol Ther*. 2006 Jun 1;23(11):1643-7. doi: 10.1111/j.1365-2036.2006.02926.x. PMID: 16696815.
13. Foster T, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. *Am J Gastroenterol*. 2011 Jan;106(1):71-7. doi: 10.1038/ajg.2010.299. Epub 2010 Sep 14. PMID: 20842109.
14. Nelson A, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. *J Clin Gastroenterol*. 2009 Nov-Dec;43(10):990-4. doi: 10.1097/MCG.0b013e31819c392e. PMID: 19448566.
15. Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, Hazen SL, Feldstein AE. Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. *Hepatology*. 2012 Oct;56(4):1291-9. doi: 10.1002/hep.25778. PMID: 22505276; PMCID: PMC3430813.
16. Adams LA, Zein CO, Angulo P, Lindor KD. A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2004 Dec;99(12):2365-8. doi: 10.1111/j.1572-0241.2004.40064.x. PMID: 15571584.

17. Satapathy SK, Sakhuja P, Malhotra V, Sharma BC, Sarin SK. Beneficial effects of pentoxifylline on hepatic steatosis, fibrosis and necroinflammation in patients with non-alcoholic steatohepatitis. *J Gastroenterol Hepatol*. 2007 May;22(5):634-8. doi: 10.1111/j.1440-1746.2006.04756.x. PMID: 17444848.
18. Van Wagner LB, Koppe SW, Brunt EM, Gottstein J, Gardikiotes K, Green RM, Rinella ME. Pentoxifylline for the treatment of non-alcoholic steatohepatitis: a randomized controlled trial. *Ann Hepatol*. 2011 Jul-Sep;10(3):277-86. PMID: 21677329.
19. Zein CO, Yerian LM, Gogate P, Lopez R, Kirwan JP, Feldstein AE, McCullough AJ. Pentoxifylline improves nonalcoholic steatohepatitis: a randomized placebo-controlled trial. *Hepatology*. 2011 Nov;54(5):1610-9. doi: 10.1002/hep.24544. Epub 2011 Aug 24. PMID: 21748765; PMCID: PMC3205292.
20. Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, Sogni P, Maynard M, Larrey D, Serfaty L, Bonnefont-Rousselot D, Bastard JP, Rivière M, Spénard J; FRESGUN. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol*. 2011 May;54(5):1011-9. doi: 10.1016/j.jhep.2010.08.030. Epub 2010 Oct 31. PMID: 21145828.
21. Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, Zala JF, Helbling B, Steuerwald M, Zimmermann A; Swiss Association for the Study of the Liver. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin e in nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2006 Dec;4(12):1537-43. doi: 10.1016/j.cgh.2006.09.025. PMID: 17162245.
22. Kudo H, Yata Y, Takahara T, Kawai K, Nakayama Y, Kanayama M, Oya T, Morita S, Sasahara M, Mann DA, Sugiyama T. Telmisartan attenuates progression of steatohepatitis in mice: role of hepatic macrophage infiltration and effects on adipose tissue. *Liver Int*. 2009 Aug;29(7):988-96. doi: 10.1111/j.1478-3231.2009.02006.x. Epub 2009 Apr 6. PMID: 19386026.
23. Georgescu EF, Ionescu R, Niculescu M, Mogoanta L, Vancica L. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. *World J Gastroenterol*. 2009 Feb 28;15(8):942-54. doi: 10.3748/wjg.15.942. PMID: 19248193; PMCID: PMC2653406.
24. Kaji K, Yoshiji H, Kitade M, Ikenaka Y, Noguchi R, Shirai Y, Aihara Y, Namisaki T, Yoshii J, Yanase K, Tsujimoto T, Kawaratani H, Fukui H. Combination treatment of angiotensin II type I receptor blocker and new oral iron chelator attenuates progression of nonalcoholic steatohepatitis in rats. *Am J Physiol Gastrointest Liver Physiol*. 2011 Jun;300(6):G1094-104. doi: 10.1152/ajpgi.00365.2010. Epub 2011 Mar 3. PMID: 21372165.
25. Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic

steatohepatitis in humans: a 12-month randomized, prospective, open-label trial. *Hepatology*. 2011 Nov;54(5):1631-9. doi: 10.1002/hep.24558. PMID: 21748770.

26. Froese, DS, Fowler, B, Baumgartner, MR. Vitamin B₁₂, folate, and the methionine remethylation cycle—biochemistry, pathways, and regulation. *J Inherit Metab Dis*. 2019; 42: 673– 685. <https://doi.org/10.1002/jimd.12009>

27. Talari HR, Molaqanbari MR, Mokfi M, Taghizadeh M, Bahmani F, Tabatabaei SMH, Sharifi N. The effects of vitamin B12 supplementation on metabolic profile of patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Sci Rep*. 2022 Aug 18;12(1):14047. doi: 10.1038/s41598-022-18195-8. PMID: 35982162; PMCID: PMC9388548.

28. Tripathi M, Singh BK, Zhou J, Tikno K, Widjaja A, Sandireddy R, Arul K, Abdul Ghani SAB, Bee GGB, Wong KA, Pei HJ, Shekeran SG, Sinha RA, Singh MK, Cook SA, Suzuki A, Lim TR, Cheah CC, Wang J, Xiao RP, Zhang X, Chow PKH, Yen PM. Vitamin B₁₂ and folate decrease inflammation and fibrosis in NASH by preventing syntaxin 17 homocysteinylation. *J Hepatol*. 2022 Nov;77(5):1246-1255. doi: 10.1016/j.jhep.2022.06.033. Epub 2022 Jul 9. PMID: 35820507.

29. Talari HR, Molaqanbari MR, Mokfi M, Taghizadeh M, Bahmani F, Tabatabaei SMH, Sharifi N. The effects of vitamin B12 supplementation on metabolic profile of patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Sci Rep*. 2022 Aug 18;12(1):14047. doi: 10.1038/s41598-022-18195-8. PMID: 35982162; PMCID: PMC9388548.

30. Pathikkal A, Puthusseri B, Divya P, Rudrappa S, Chauhan VS. Folate derivatives, 5-methyltetrahydrofolate and 10-formyltetrahydrofolate, protect BEAS-2B cells from high glucose-induced oxidative stress and inflammation. *In Vitro Cell Dev Biol Anim*. 2022 May;58(5):419-428. doi: 10.1007/s11626-022-00691-w. Epub 2022 Jun 9. PMID: 35678985; PMCID: PMC9179225.

31. Liu Z, Zeng Y, Shen S, Wen Y, Xu C. Association between folate and non-alcoholic fatty liver disease among US adults: a nationwide cross-sectional analysis. *Chin Med J (Engl)*. 2023 Jan 20;136(2):233-235. doi: 10.1097/CM9.0000000000002516. PMID: 36804281; PMCID: PMC10106170.

32. Cordero P, Gomez-Uriz AM, Campion J, Milagro FI, Martinez JA. Dietary supplementation with methyl donors reduces fatty liver and modifies the fatty acid synthase DNA methylation profile in rats fed an obesogenic diet. *Genes Nutr*. 2013 Jan;8(1):105-13. doi: 10.1007/s12263-012-0300-z. Epub 2012 May 31. PMID: 22648174; PMCID: PMC3534997.

33. Schmidl D, Howorka K, Szegedi S, Stjepanek K, Puchner S, Bata A, Scheschy U, Aschinger G, Werkmeister RM, Schmetterer L, Garhofer G. A pilot study to assess the effect of a three-month vitamin supplementation containing L-methylfolate on systemic homocysteine

plasma concentrations and retinal blood flow in patients with diabetes. *Mol Vis*. 2020 Apr 24;26:326-333. PMID: 32355442; PMCID: PMC7190578.

34. Jain, R., Manning, S., & Cutler, A. (2020). Good, better, best: Clinical scenarios for the use of L-methylfolate in patients with MDD. *CNS Spectrums*, 25(6), 750-764.

doi:10.1017/S1092852919001469

35. Stracquadanio M, Ciotta L, Palumbo MA. Effects of myo-inositol, gymnemic acid, and L-methylfolate in polycystic ovary syndrome patients. *Gynecol Endocrinol*. 2018

Jun;34(6):495-501. doi: 10.1080/09513590.2017.1418852. Epub 2017 Dec 21. PMID: 29265900.

36. "Vitamin E - Health Professional Fact Sheet." NIH Office of Dietary Supplements, 26 March 2021, <https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/>. Accessed 16 May 2023.

37. Asbaghi, O., Nazarian, B., Yousefi, M. *et al.* Effect of vitamin E intake on glycemic control and insulin resistance in diabetic patients: an updated systematic review and meta-analysis of randomized controlled trials. *Nutr J* **22**, 10 (2023). <https://doi.org/10.1186/s12937-023-00840-1>

38. Pacana T, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. *Curr Opin Clin Nutr Metab Care*. 2012 Nov;15(6):641-8. doi: 10.1097/MCO.0b013e328357f747. PMID: 23075940; PMCID: PMC4984672.

39. Eliades M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease? *World J Gastroenterol*. 2015 Feb 14;21(6):1718-27. doi: 10.3748/wjg.v21.i6.1718. PMID: 25684936; PMCID: PMC4323447.

40. Sung CC, Liao MT, Lu KC, Wu CC. Role of vitamin D in insulin resistance. *J Biomed Biotechnol*. 2012;2012:634195. doi: 10.1155/2012/634195. Epub 2012 Sep 3. PMID: 22988423; PMCID: PMC3440067.

41. Markotić A, Kelava T, Markotić H, Silovski H, Mrzljak A. Vitamin D in liver cancer: novel insights and future perspectives. *Croat Med J*. 2022 Apr 30;63(2):187-196. doi: 10.3325/cmj.2022.63.187. PMID: 35505652; PMCID: PMC9086812.

42. Hariri M, Zohdi S. Effect of Vitamin D on Non-Alcoholic Fatty Liver Disease: A Systematic Review of Randomized Controlled Clinical Trials. *Int J Prev Med*. 2019 Jan 15;10:14. doi: 10.4103/ijpvm.IJPVM_499_17. PMID: 30774848; PMCID: PMC6360993.

43. Kooshki F, Moradi F, Karimi A, Niazkar HR, Khoshbaten M, Maleki V, Pourghassem Gargari B. Chromium picolinate balances the metabolic and clinical markers in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Eur J Gastroenterol Hepatol*. 2021 Oct 1;33(10):1298-1306. doi: 10.1097/MEG.0000000000001830. PMID: 32804855.

44. Havel PJ. A scientific review: the role of chromium in insulin resistance. *Diabetes Educ.* 2004;Suppl:2-14. PMID: 15208835.
45. "Effects of Different Chromium Compounds on Hematology and Inflammatory Cytokines in Rats Fed High-Fat Diet." *Frontiers*, 15 January 2021, <https://www.frontiersin.org/articles/10.3389/fimmu.2021.614000/full>. Accessed 16 May 2023.
46. Chen WY, Chen CJ, Liu CH, Mao FC. Chromium attenuates high-fat diet-induced nonalcoholic fatty liver disease in KK/HIJ mice. *Biochem Biophys Res Commun.* 2010 Jul 2;397(3):459-64. doi: 10.1016/j.bbrc.2010.05.129. Epub 2010 May 27. PMID: 20513351.
47. Hosui A, Kimura E, Abe S, Tanimoto T, Onishi K, Kusumoto Y, Sueyoshi Y, Matsumoto K, Hirao M, Yamada T, Hiramatsu N. Long-Term Zinc Supplementation Improves Liver Function and Decreases the Risk of Developing Hepatocellular Carcinoma. *Nutrients.* 2018 Dec 10;10(12):1955. doi: 10.3390/nu10121955. PMID: 30544767; PMCID: PMC6316561.
48. Kim J, Lee S. Effect of zinc supplementation on insulin resistance and metabolic risk factors in obese Korean women. *Nutr Res Pract.* 2012 Jun;6(3):221-5. doi: 10.4162/nrp.2012.6.3.221. Epub 2012 Jun 30. PMID: 22808346; PMCID: PMC3395787.
49. Kirkil G, Hamdi Muz M, Seçkin D, Sahin K, Küçük O. Antioxidant effect of zinc picolinate in patients with chronic obstructive pulmonary disease. *Respir Med.* 2008 Jun;102(6):840-4. doi: 10.1016/j.rmed.2008.01.010. Epub 2008 Mar 4. PMID: 18295467.
50. Lee DE, Lee SJ, Kim SJ, Lee HS, Kwon OS. Curcumin Ameliorates Nonalcoholic Fatty Liver Disease through Inhibition of O-GlcNAcylation. *Nutrients.* 2019 Nov 8;11(11):2702. doi: 10.3390/nu11112702. PMID: 31717261; PMCID: PMC6893521.
51. Saadati, S., Sadeghi, A., Mansour, A. *et al.* Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial. *BMC Gastroenterol* **19**, 133 (2019). <https://doi.org/10.1186/s12876-019-1055-4>
52. Gupta N, Verma K, Nalla S, Kulshreshtha A, Lall R, Prasad S. Free Radicals as a Double-Edged Sword: The Cancer Preventive and Therapeutic Roles of Curcumin. *Molecules.* 2020 Nov 18;25(22):5390. doi: 10.3390/molecules25225390. PMID: 33217990; PMCID: PMC7698794.
53. Zhang DW, Fu M, Gao SH, Liu JL. Curcumin and diabetes: a systematic review. *Evid Based Complement Alternat Med.* 2013;2013:636053. doi: 10.1155/2013/636053. Epub 2013 Nov 24. PMID: 24348712; PMCID: PMC3857752.

54. Rahmani AH, Alsahli MA, Aly SM, Khan MA, Aldebasi YH. Role of Curcumin in Disease Prevention and Treatment. *Adv Biomed Res.* 2018 Feb 28;7:38. doi: 10.4103/abr.abr_147_16. PMID: 29629341; PMCID: PMC5852989.
55. Gillessen A, Schmidt HH. Silymarin as Supportive Treatment in Liver Diseases: A Narrative Review. *Adv Ther.* 2020 Apr;37(4):1279-1301. doi: 10.1007/s12325-020-01251-y. Epub 2020 Feb 17. PMID: 32065376; PMCID: PMC7140758.
56. Beckerman, James. "Milk Thistle: Benefits and Side Effects." WebMD, 9 June 2021, <https://www.webmd.com/digestive-disorders/milk-thistle-benefits-and-side-effects>. Accessed 16 May 2023.
57. Gobalakrishnan S, Asirvatham SS, Janarthanam V. Effect of Silybin on Lipid Profile in Hypercholesterolaemic Rats. *J Clin Diagn Res.* 2016 Apr;10(4):FF01-5. doi: 10.7860/JCDR/2016/16393.7566. Epub 2016 Apr 1. PMID: 27190826; PMCID: PMC4866124.
58. Kwon DY, Jung YS, Kim SJ, Kim YS, Choi DW, Kim YC. Alterations in sulfur amino acid metabolism in mice treated with silymarin: a novel mechanism of its action involved in enhancement of the antioxidant defense in liver. *Planta Med.* 2013 Aug;79(12):997-1002. doi: 10.1055/s-0032-1328704. Epub 2013 Jun 27. PMID: 23807810.
59. Mirzaei E, Sabetian G, Masjedi M, Heidari R, Mirjalili M, Dehghanian A, Vazin A. The effect of silymarin on liver enzymes and antioxidant status in trauma patients in the intensive care unit: a randomized double blinded placebo-controlled clinical trial. *Clin Exp Hepatol.* 2021 Jun;7(2):149-155. doi: 10.5114/ceh.2021.107067. Epub 2021 Jun 22. PMID: 34295981; PMCID: PMC8284169.
60. Al Zazour RH, Ahmad M, Asmawi MZ, Kaur G, Saeed MAA, Al-Mansoub MA, Saghir SAM, Usman NS, Al-Dulaimi DW, Yam MF. Phyllanthus Niruri Standardized Extract Alleviates the Progression of Non-Alcoholic Fatty Liver Disease and Decreases Atherosclerotic Risk in Sprague-Dawley Rats. *Nutrients.* 2017 Jul 18;9(7):766. doi: 10.3390/nu9070766. PMID: 28718838; PMCID: PMC5537880.
61. Ranilla LG, Kwon YI, Apostolidis E, Shetty K. Phenolic compounds, antioxidant activity and in vitro inhibitory potential against key enzymes relevant for hyperglycemia and hypertension of commonly used medicinal plants, herbs and spices in Latin America. *Bioresour Technol.* 2010 Jun;101(12):4676-89. doi: 10.1016/j.biortech.2010.01.093. Epub 2010 Feb 25. PMID: 20185303.
62. Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K, Zafrilla P. Effect of Ginger on Inflammatory Diseases. *Molecules.* 2022 Oct 25;27(21):7223. doi: 10.3390/molecules27217223. PMID: 36364048; PMCID: PMC9654013.

63. Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K, Zafrilla P. Effect of Ginger on Inflammatory Diseases. *Molecules*. 2022 Oct 25;27(21):7223. doi: 10.3390/molecules27217223. PMID: 36364048; PMCID: PMC9654013.
64. Bianca Fuhrman and others, Ginger Extract Consumption Reduces Plasma Cholesterol, Inhibits LDL Oxidation and Attenuates Development of Atherosclerosis in Atherosclerotic, Apolipoprotein E-Deficient Mice, *The Journal of Nutrition*, Volume 130, Issue 5, May 2000, Pages 1124–1131, <https://doi.org/10.1093/jn/130.5.1124>
65. Alizadeh-Navaei R, Roozbeh F, Saravi M, Pouramir M, Jalali F, Moghadamnia AA. Investigation of the effect of ginger on the lipid levels. A double blind controlled clinical trial. *Saudi Med J*. 2008 Sep;29(9):1280-4. PMID: 18813412.
66. Alsahli MA, Almatroodi SA, Almatroudi A, Khan AA, Anwar S, Almutary AG, Alrumaihi F, Rahmani AH. 6-Gingerol, a Major Ingredient of Ginger Attenuates *Diethylnitrosamine*-Induced Liver Injury in Rats through the Modulation of Oxidative Stress and Anti-Inflammatory Activity. *Mediators Inflamm*. 2021 Jan 19;2021:6661937. doi: 10.1155/2021/6661937. PMID: 33531877; PMCID: PMC7837795.
67. “Dandelion - Western New York Urology Associates, LLC.” WNY Urology Associates, <https://www.wnyurology.com/content.aspx?chunkiid=21667>. Accessed 16 May 2023.
68. Pflingstgraf IO, Taulescu M, Pop RM, Orăsan R, Vlase L, Uifalean A, Todea D, Alexescu T, Toma C, Pârnu AE. Protective Effects of *Taraxacum officinale* L. (Dandelion) Root Extract in Experimental Acute on Chronic Liver Failure. *Antioxidants (Basel)*. 2021 Mar 24;10(4):504. doi: 10.3390/antiox10040504. PMID: 33804908; PMCID: PMC8063808.
69. Cai L, Wan D, Yi F, Luan L. Purification, Preliminary Characterization and Hepatoprotective Effects of Polysaccharides from Dandelion Root. *Molecules*. 2017 Aug 25;22(9):1409. doi: 10.3390/molecules22091409. PMID: 28841174; PMCID: PMC6151742.
70. Davaatseren M, Hur HJ, Yang HJ, Hwang JT, Park JH, Kim HJ, Kim MJ, Kwon DY, Sung MJ. *Taraxacum officinale* (dandelion) leaf extract alleviates high-fat diet-induced nonalcoholic fatty liver. *Food Chem Toxicol*. 2013 Aug;58:30-6. doi: 10.1016/j.fct.2013.04.023. Epub 2013 Apr 18. PMID: 23603008.
71. Khoshbaten M, Aliasgarzadeh A, Masnadi K, Tarzamani MK, Farhang S, Babaei H, Kiani J, Zaare M, Najafipour F. N-acetylcysteine improves liver function in patients with non-alcoholic Fatty liver disease. *Hepat Mon*. 2010 Winter;10(1):12-6. Epub 2010 Mar 1. PMID: 22308119; PMCID: PMC3270338
72. Khoshbaten M, Aliasgarzadeh A, Masnadi K, Tarzamani MK, Farhang S, Babaei H, Kiani J, Zaare M, Najafipour F. N-acetylcysteine improves liver function in patients with non-alcoholic

Fatty liver disease. *Hepat Mon.* 2010 Winter;10(1):12-6. Epub 2010 Mar 1. PMID: 22308119; PMCID: PMC3270338.

73. Jain SK, Velusamy T, Croad JL, Rains JL, Bull R. L-cysteine supplementation lowers blood glucose, glycated hemoglobin, CRP, MCP-1, and oxidative stress and inhibits NF-kappaB activation in the livers of Zucker diabetic rats. *Free Radic Biol Med.* 2009 Jun 15;46(12):1633-8. doi: 10.1016/j.freeradbiomed.2009.03.014. Epub 2009 Mar 26. PMID: 19328229; PMCID: PMC3568688.

74. De Oliveira CP, Simplicio FI, de Lima VM, Yuahasi K, Lopasso FP, Alves VA, Abdalla DS, Carrilho FJ, Laurindo FR, de Oliveira MG. Oral administration of S-nitroso-N-acetylcysteine prevents the onset of non alcoholic fatty liver disease in rats. *World J Gastroenterol.* 2006 Mar 28;12(12):1905-11. doi: 10.3748/wjg.v12.i12.1905. PMID: 16609997; PMCID: PMC4087516.

75. Dłudla PV, Nkambule BB, Mazibuko-Mbeje SE, Nyambuya TM, Marcheggiani F, Cirilli I, Ziqubu K, Shabalala SC, Johnson R, Louw J, Damiani E, Tiano L. N-Acetyl Cysteine Targets Hepatic Lipid Accumulation to Curb Oxidative Stress and Inflammation in NAFLD: A Comprehensive Analysis of the Literature. *Antioxidants (Basel).* 2020 Dec 16;9(12):1283. doi: 10.3390/antiox9121283. PMID: 33339155; PMCID: PMC7765616.

76. Ardekani, A., Tabrizi, R., Maleki, E., Bagheri Lankarani, K., Heydari, S. T., Moradinazar, M., & Akbari, M. (2023). Effects of coenzyme Q10 supplementation on lipid profiles and liver enzymes of nonalcoholic fatty liver disease (NAFLD) patients: A systematic review and meta-analysis of randomized controlled trials. *Food Science & Nutrition*, 00, 1– 9. <https://doi.org/10.1002/fsn3.3315>

77. Jane L Tarry-Adkins and others, Coenzyme Q₁₀ prevents hepatic fibrosis, inflammation, and oxidative stress in a male rat model of poor maternal nutrition and accelerated postnatal growth, *The American Journal of Clinical Nutrition*, Volume 103, Issue 2, February 2016, Pages 579–588, <https://doi.org/10.3945/ajcn.115.119834>

78. Yoo JY, Yum KS. Effect of Coenzyme Q₁₀ on Insulin Resistance in Korean Patients with Prediabetes: A Pilot Single-Center, Randomized, Double-Blind, Placebo-Controlled Study. *Biomed Res Int.* 2018 Jul 29;2018:1613247. doi: 10.1155/2018/1613247. PMID: 30151373; PMCID: PMC6087610.

79. "How Does BioPerine® Increase Absorption of Nutrients?" Superfood Science Supplements, 8 June 2021, <https://www.superfoodscience.com/blogs/health-blog/bioperine-nutrient-absorption>. Accessed 16 May 2023.

80. Derosa G, Maffioli P, Sahebkar A. Piperine and Its Role in Chronic Diseases. *Adv Exp Med Biol.* 2016;928:173-184. doi: 10.1007/978-3-319-41334-1_8. PMID: 27671817.

