Weight Loss & Liver Support

Goal

This product aims to deliver isolated non-caloric nutrition in amounts uncommon in human diets that can support proper liver health and metabolism and subsequent body fat reduction through multiple mechanisms. The Weight Loss and Liver Support (WLLS) ingredient combination works to mobilize ectopic fat deposits in organs and attenuate related oxidative stress and inflammation to improve overall metabolism, especially the usage of dietary fats and carbohydrates to support efficient diet-induced body fat reduction and appetite control. By delivering clinically effective doses of African Mango (*Irvingia gabonensis)* to control appetite; choline, milk thistle (silymarin), N-acetylcysteine (NAC), and epigallocatechin gallate (EGCG) from green tea to mobilize unhealthful liver fat and subsequently attenuating runaway oxidation/inflammation, WLLS is designed to speed and ease the weight/bodyfat reduction journey while improving overall health. Users may discontinue use once the body composition goal is achieved unless instructed differently by a qualified health practitioner.

Rationale

Most adults' body fat rises throughout their life, often causing fatty deposits in liver cells, disturbing its ability to process incoming carbohydrates, protein, and fat, initiating a chain reaction starting with disturbed energy usage and oxidative stress that causes multiple negative health outcomes including the progression of unhealthy body composition.

The evolutionary design of the human liver allows it to store little energy that is predominately carbohydrate (CHO) in the form of glycogen, but not fat.[1] Storing excess energy as fat is the role of a healthy body's fat tissue (adipose tissue).[2] Therefore, a healthy human liver contains few or no fat droplets. When there are fat droplets in more than 5% of the liver cells, it is considered abnormal or pathological. Therefore, in people with fatty liver disorders, greater than 5% of their liver cells contain these fat droplets leading to flawed energy metabolism.[3] The energy storage function of the adipocytes is compromised by conditions such as steady body fat increases, lipid overflow, and alternative storage in the form of ectopic fat deposits that occur as visceral fat and in organs like the liver, heart, muscle, etc.[4]

More than 70% of the US adult population, as well as in many peer nation populations, are overweight and obese. This number **continues to rise,**[5] becoming a primary driver in the increase of nonalcoholic fatty liver disorders.[6] Most body fat is subcutaneous (below the skin). Hidden fat, or visceral adipose tissue (VAT), is stored deep inside the abdomen and surrounds many vital organs. Ectopic fat accumulates inside vital organs such as the liver, heart, pancreas, and muscles. Visceral and ectopic fat are known risk factors for cardiovascular disorders, insulin resistance (IR), and Type 2 diabetes. Further, IR impairs glycogen synthesis, postprandially diverting a substantial amount of carbohydrates to the liver and storing them as fat.[7] Ectopic fat accumulation in the liver causes nonalcoholic fatty liver disorders (NAFLD), now the most common cause of chronic liver disorders in Western nations.[3] The risk of NAFLD increases with increasing body fat and age, but it is also found in lean people.[6] The type of fat storage that is relevant to NAFLD is fat (mainly triglycerides) that is stored in droplets in the liver cells. Although these droplet sizes can vary, they are primarily large and consequently can fill up the entire inner part of the cell, pushing other parts to the cell border, a condition known as macrovesicular steatosis, which negatively affects liver cell functions, including fat and carbohydrate metabolism since the liver is the first point where nutrients (e.g. sugars, fats, proteins, etc.) are filtered and further processed.[8,9] The term "microvesicular steatosis of the liver," partially caused by a reduction in hepatic oxidation of fatty acids because of mitochondrial dysfunction, refers to a variant form of hepatic fat accumulation whose histologic features contrast with the much more common macrovesicular steatosis (microvesicular steatosis is characterized by the presence of numerous small vesicles of fat that do not displace the nucleus. Macrovesicular steatosis is characterized by the engorgement of the hepatocyte by a large fat globule that displaces the nucleus).[10,11,12] Since the liver is the primary nutrient depot, processor, and dispenser following absorption, these

lipid-related disturbances in liver cell functioning impairs many areas of overall metabolism, especially energy production, and usage.[3] In simple terms, when the liver gets "clogged" (from the imbalance between its fat input and fat output) from cellular fat deposits that do not belong there, its ability to convert food to energy and utilize fat and CHO is disturbed, causing a negative health and body composition chain reaction to occur.[3,13]

As mentioned, due to the population's continuing increase in unhealthy body fat, non-alcoholic fatty livers (NAFL) and non-alcoholic steatohepatitis (NASH) are increasingly common chronic liver conditions that have reached epidemic proportions in developed countries. In Western nations, the prevalence of NAFLD in the general population ranges from 30% to 40%, 60-70% in people with Type 2 Diabetes, and 50-90% of the obese population worldwide.[14,15] Further, there are no pharmaceutical options currently approved for its treatment, with lifestyle modifications such as exercise and dietary/nutrition intervention remaining the cornerstone of NAFLD treatment,[16] including the use of nutraceuticals (specific isolated natural bio-actives[17]) for protection.[16,18,19,20,21,22]

Along with diet-induced weight loss, exercise, and high protein meal replacement therapy, specific nutrition ingredients such as choline,[23] milk thistle (silymarin),[24] N-acetyl-cysteine (NAC) [25] vitamins E and D, and omega-3 fatty acids[26] are often incorporated by health professionals to help protect and manage fatty liver disorders.*[9,11,15,21,**Error! Bookmark not defined.**,26,27,28] Also commonly used in NAFLD is epigallocatechin gallate (EGCG) from green tea for its potential hepatic protection, including antioxidant properties.[28,29,30,31] In this particular formulation, *Irvingia gabonensis* has been included for its potential to help manage hormone levels (e.g., adiponectin, leptin, etc.) that affect appetite and lipid deposition and subsequently improve weight loss results and related metabolic outcomes.[32,33,34]

In summary, weight gain, poor eating habits, and to a lesser extent genetics, often lead to a fatty liver and subsequent oxidative stress on this vital nutrition processing organ, compromising its overall functioning, including inhibiting the body's ability to control proper utilization of CHO, protein, and fat, causing a cascade of negative health consequences.[2,3,4,6,7,9,9,16,15,18,35,36,37,38]

A complete Multivitamin and Mineral Formula (MVM) should always be the base recommendation so that dietary supplements such as the ingredients in WLLS can optimize their target activities since vitamins and minerals are the actuators of all human metabolism and are commonly under-consumed by the majority of the population and especially in overweight individuals.

WLLS Ingredients

Choline

Choline is a water-soluble (can also be found in specific foods as lipid soluble) nutrient that is an important component of cell membranes and is now classified as an essential nutrient because humans do not synthesize it in amounts sufficient to meet a healthy body's needs.[39,40] Further, choline is listed as an under-consumed nutrient of concern to public health in the Dietary Guidelines for Americans (DGA).[41] Choline is a precursor to acetylcholine, betaine, and the phospholipid backbone glycerophosphocholine. Through its metabolite, phosphatidylcholine (PTC), choline is essential for removing lipids from the liver[42,43] as it is needed for the membranes used in exporting triglycerides as very low-density lipid proteins (VLDLs). [44,45,46,47] Thus, choline acts as a lipotropic agent that has been shown to hasten the removal of fat from the liver.[47,48,49,50,51] Recently the Institute of Medicine (IOM) established the adequate intake (AI) of choline at 425-550 mg/day for women and men respectively, and that choline deficiency can have a negative impact on different aspects of health, especially related to fatty liver.[41,52,53,54,55,56] Along with most persons not meeting current choline recommendations, some evidence suggests that these recommendations may be suboptimal for a large percentage of populations.[57,58,59,60,61] Further, higher choline intakes are associated with a lower risk of NAFLD and related health disorders.[56,62,63,64,65] Therefore, this product contains ~400 mg of choline in a daily dose to complement shortages in normal synthesis and diet to reach daily levels shown to have a positive effect on managing liver health.

Trimethylamine N-oxide (TMAO) in Cardiovascular (CV) Events

TMAO is a dietary component that belongs to the class of amine oxides and is an oxidized form of trimethylamine (TMA).[66] A primary function of TMAO is its ability to affect the structure and activity of a large group of biologically important compounds as it acts a stabilizer of the protein folded state and nucleic acid. Thermodynamic studies on the effects of TMAO on proteins have shown that it prevents protein denaturization and counteracts the effects of pressure and heat.[67]

In certain less-healthy populations (existing cardiometabolic conditions), high choline dietary intake (foods high in carnitine, choline, or choline-containing compounds, such as red meat, fish, eggs, etc.) has been associated with elevated levels of TMAO, which has been suggested to be a risk factor in CV health in these cohorts.[68] This observation comes from the fact that excess dietary choline consumption can be metabolized to trimethylamine (TMA) by the gut microbiota. TMA can be oxidized to trimethylamine N-oxide (TMAO) in the liver. Although epidemiological studies have shown a positive correlation between plasma TMAO concentrations and cardiovascular events, it is debated whether increased TMAO concentrations are the cause or result of these health disorders. Overall, a recent meta-analysis consisting of a total of 184,010 participants with 18,076 incident CV events and 5,343 CV deaths suggested no significant associations of dietary choline or betaine intake with CV disorder risk or mortality[69] or have shown increases in plasma chronic TMAO concentrations in humans or animals.[70,71] Additionally, 400 mg per day of choline delivered by supplementation or three eggs daily increased plasma choline while decreasing inflammation in subjects with negative cardiometabolic conditions.[72] Moreover, it was demonstrated that compared to the baseline, plasma TMAO was not increased by eggs or 400 mg per day of choline supplementation in a healthy young population. This suggests that meeting recommendations would offer choline's natural health protective effects named above.[73]

Summary

Choline is an essential nutrient (i.e., food components humans cannot live without) that is grossly under-consumed but necessary for good health and especially needed for exporting fat from the liver, which accumulates in detrimental amounts in overweight individuals. Achieving proper choline levels can help manage better liver and related CV health and body fat reduction through choline's indispensable role in packaging and transporting fat that would otherwise disturb the body's usage of dietary fat and CHO exacerbating poor body composition.

Meeting choline recommendations (450-550 mg/d) demonstrates positive health effects, and slightly more may be temporarily necessary for specific populations (e.g., pregnancy, NAFLD, etc.) as described above. But like most other essential nutrients, although there may be a wide range of safety, too much can be harmful, especially in subpopulations with genetic abnormalities or other health issues diagnosed by a qualified health professional.

Milk Thistle

Milk Thistle (Silybum marianum) is the most recommended phyto-ingredient for multiple liver/hepatic disorders. It produces its effects from its makeup of flavonolignans through multiple mechanisms such as its antioxidant, anti-inflammatory and anti-fibrotic actions, making it a safe and effective liver health support compound in ameliorating common liver problems such as liver fibrosis, fatty liver disorders related to weight gain, and many other hepatic conditions.

Traditional Chinese herbs generally have both edible and medicinal value and are widely reorganized as alternative medications for the treatment of various disorders.[24,74,75,76,77] Milk thistle is derived from the milk thistle plant *Silybum marianum,* and silymarin is the active component in the seeds of the milk thistle plant.[78] Silymarin is a complex mixture of six major flavonolignans (silybins A and B, isosilybins A and B, silychristin, and silydianin), as well as other minor polyphenolic substances, among which, silybin is identified as the major biologically active component generally making up more than 50% of successful therapeutic extractions.[78,79,80] Milk thistle has been used safely for centuries in treating liver problems, including improving circulation, and maintaining the integrity of liver cell membranes while increasing the liver's regenerative ability and formation of new cells.[24,75,81,82,83,84,85]

Studies demonstrate that silymarin and silybin have four major mechanisms of action related to supporting liver health: 1) local antioxidant by neutralizing free radicals and regulating the cell's internal glutathione; 2) stabilizes cell membranes and regulates the permeability of the liver cells to prevent toxic chemicals from entering the cells; 3) stimulates ribosomal RNA synthesis and hepatic cell renewal; 4) antifibrotic properties, as it inhibits the deformation of star-shaped hepatocytes into myofibroblasts, a process that is responsible for the deposition of collagen fibers which leads to major liver disorders/cirrhosis (also inhibits the 5-lipoxygenase, NFKB [Nuclear factor kappa B] and JNK [c-Jun N-terminal kinases] pathways).[86,87,88,89] Further, milk thistle (silymarin/silybin) clinical studies demonstrating decreased hepatic serum enzyme levels, especially alanine aminotransferase (ALT), indicate that silymarin/silybin could partially restore the liver's function and mitigate NASH patients' symptoms.[24,88,90,91,92] These mechanisms are also responsible or related to studies demonstrating milk thistle's antiviral, anti-inflammatory, and immunomodulatory functions in human liver and immune cells.[24,76,77,78,91,93,94,95] Additionally, because silymarin is lipophilic, it tightly binds to plasma membrane compounds, subsequently increasing plasma membrane strength and helping prevent membranes from breaking and disintegrating.[96] Doses of 140-750 mg have been used safely and effectively in patients with NAFLD and have been shown to regenerate the liver and bring the hepatic markers, AST, ALT, and others, to normal levels.[24,74,77,88,91,94,97,98,99,100,101,102]

N-acetylcysteine (NAC)

The primary value of NAC in supporting liver health is its anti-inflammatory and antioxidant activities, including its ability to act as a precursor of the "master antioxidant" glutathione (GSH) to replenish the intracellular GSH pool when it has been depleted during conditions of oxidative stress, which is common in fatty liver disorders.

N-acetylcysteine (NAC), molecular formula: $C_5H_9NO_3S$, is an acetylated derivative of cysteine, a sulfur-containing amino acid, and as a drug, NAC is often used to mitigate potentially hepatotoxic doses of acetaminophen (intravenous administration), and shown to exert neurochemical effects in Substance Use Disorder (as the acetylated form of cysteine, it is readily absorbed and can cross the blood-brain barrier).[103,104] NAC is also sold as a dietary supplement in the US and other countries where it is often used to support liver health because of its known hepatoprotective, mucolytic (mucolytics can dissolve thick mucus and used to help relieve respiratory difficulties via breaking down chemical bonds between molecules in the mucus.[105]), antioxidant, and anti-inflammatory activities with the latter two actions related to supporting liver health.[104,106] Further, NAC is a derivative of the amino acid l-cysteine, an essential precursor in the formation of the antioxidant glutathione (GSH), and administration has been shown to replenish GSH stores (cysteine is the rate-limiting component in GSH production).[106,107,108]

GSH is the most abundant nonprotein thiol in the body and is considered one of the most (if not the most) important antioxidants responsible for maintaining cellular redox homeostasis, especially in the liver.[109,110] In addition to GSH reacting directly with reactive species, it serves as a cofactor or substrate for myriad antioxidant enzymes, which levels are overwhelmed/negatively compromised during liver injury related to fatty liver.[111,112] Since the hepatocellular synthesis of GSH through de novo or via the salvation pathways is required, intracellular GSH levels cannot be increased by administering isolated GSH supplements.[112,113] This fact explains the role of NAC as a precursor of cysteine and increasing intracellular GSH.[106,107,108,114] Consequently, the importance of NAC as a potent antioxidant is directly linked to its ability to increase levels of intracellular cysteine with subsequent increase in GSH. Further, because the NAC molecule is a known antioxidant, it acts directly and/or by increasing intracellular GSH, especially in hepatic tissue.[108,115,116] NAC has an ideal thiol redox state, making it highly valuable in optimizing the protective ability of the cell to counterbalance oxidative stress and inflammation.[107,116]

For more details on NAC's mechanisms of actions, readers are referred to the review article titled **"N-Acetylcysteine: A Review of Clinical Usefulness (an Old Drug with New Tricks)"** by Schwalfenberg et al., mindful that clinical drug dosages for NAC far exceed its common dietary supplement recommendations to support liver health.[104] Table 1 below is from Schwalfenberg et al.[104]

In NAFLD,

there is evidence that NAC in lower doses may inhibit hepatic lipid accumulation and provide protective benefits against the metabolic complications common in NAFLD described above, actions that are primarily due to NAC's antioxidant properties (including its ability to restore the master antioxidant GSH), and ability to attenuate lipid peroxidation, therefore the purpose for inclusion in this formulation.[117]

Table 1 from Schwalfenberg et al: N-acetylcysteine (NAC) potential mechanisms of action (**references numbers in actual article**).

1. Action on glutathione: NAC restores glutathione (cysteine is rate limiting) [5] as seen in cell and animal studies and clinically in acetaminophen overdose.
2. Stabilizes proteins/DNA: Protects proteins by crosslinking cysteine disulfide molecules [6]. Various mechanisms of DNA repair/protection [7] as seen in animal studies and human cell studies.
3. Scavenges free radicals: Scavenging property via the redox potential of thiols [8] as demonstrated in cell culture.
4. Anti-inflammatory property: Reduces proinflammatory cytokines [9] as seen in animal studies.
5. Antioxidant property: Reduces oxidative damage [10] as seen in cell cultures.
6. Mucolytic property: Splits disulfide bonds in mucoproteins lowering viscosity [11] demonstrated in purified mucus gels and tracheal explant systems and in vitro (in a pig tracheal pouch) models.
7. Mitochondrial resilience: Neurogenesis-inducing ability [12] reduces apoptosis of mitochondria [13] as demonstrated in human dental pulp cells.
8. Metal chelation: Thiol groups provide binding sites for metals [14] in animal studies.
9. Glutamate/dopamine homeostasis: Modulates glutamate and dopamine [15] extensive studies in humans.
10. Antiviral properties: Immune modulation, anti-NF-KB properties, and other unexplored mechanisms [16] observed in vitro and in vivo.
11. Vascular endothelial growth factor: Inhibition of vascular permeability [17] as seen in human keratinocytes.
12. Adenosine triphosphate (ATP) and nitric oxide (NO) production: Increased ATP production in some cells like fibroblasts in vitro [18]. Increased nitric oxide production [19] as demonstrated in human studies.

Moreover, according to Aldini et al. the *in vivo* antioxidant activity of NAC can be related to at least three different mechanisms:[111]

- A direct antioxidant effect on certain oxidant species.
- An indirect antioxidant effect based on the ability of NAC to act as a precursor of cysteine, which is a building block and the rate-limiting step in GSH synthesis. GSH is a well-known direct antioxidant and a substrate of various important antioxidant enzymes.
- A breaking effect on disulfides and the ability to restore thiol pools, which in turn regulate the redox state.

Figure 1 below depicts how environmental insults to the liver (e.g., poor diet, weight gain, drugs, etc.) can lead to a fatty liver and liver fibrosis (act of hepatic wound healing), with inflammation generally being the first phase, and developing to fibrosis after chronic oxidative stress, giving purpose for using agents, such as NAC, to help control runaway hepatic inflammation and subsequent free radical production to help restore or protect proper liver function and health.[108,112,113,116,117,118,119,120,121,122]

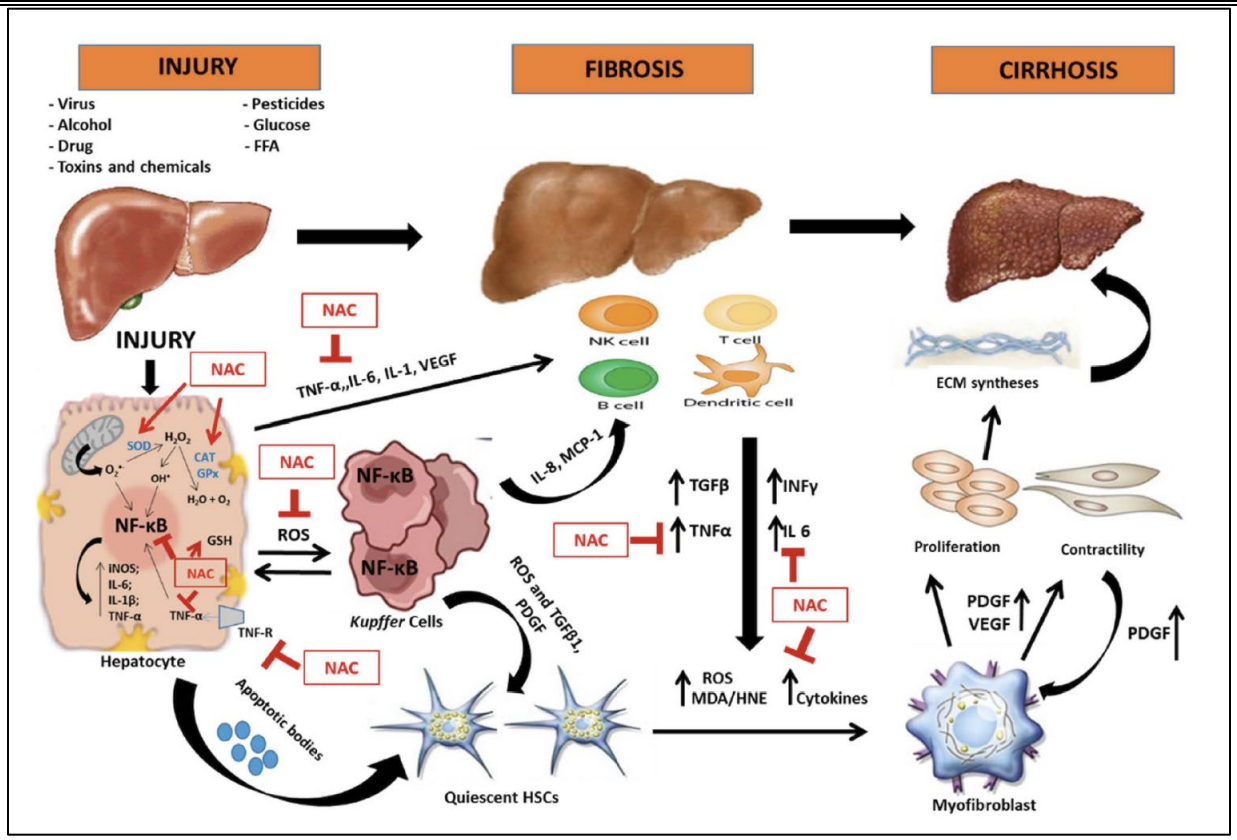


Figure 1 - (Adapted from Cohen-Naftaly; Scott L. Friedman, 2011) Proposed molecular mechanisms of action of NAC in attenuation of liver injury involving oxidative stress and inflammation. Legend: CAT: catalase; ECM: extracellular matrix; FFA: free fatty acids; GPx: glutathione peroxidase; HSCs: hepatic stellate cells; iNOS: inducible nitric oxide synthase; IL: interleukin; INF: interferon gamma; MCP-1: monocyte chemoattractant protein-1; MDA/HNE: malondialdehyde/4-hydroxynonenal; NF-kB: nuclear factor kappa-light-chain enhancer of activated B cells; PDGF: platelet-derived growth factor; ROS: reactive oxygen species; SOD: superoxide dismutase; TGFβ1: transforming growth factor β 1; TNF-α: tumor necrosis factor α; TNF-R: TNF- α receptor; VEGF: Vascular endothelial growth factor; ⊣ Inhibition; ➡ stimulation; ↑increase

In summary, fatty liver causes a negative metabolic chain reaction (including disordered fat utilization), starting with hepatic inflammation and runaway free radical damage, which NAC supplementation has been shown to ameliorate. The importance of NAC as a potent antioxidant is directly tied to its ability to increase levels of intracellular cysteine with subsequent increase in intracellular GSH, making NAC one of the major strategies to reduce the damage caused by hepatic oxidative stress. Further, clinical doses ranging from 200 mg to 5,000 mg/day have been found to be safe. The non-clinical application of this product uses a dose (150 mg/day) to complement the other ingredients in managing moderate fatty liver conditions. Higher doses of NAC (i.e., a clinical need) should require a separate prescription from a qualified physician.

Green Tea Extract Including 270 mg (3-tabs) of Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG) from green tea is included because it is one of the best documented plants that have been used in the prevention of liver disorders and associated with healthy effects on body composition.[22,28,29,30,31,84,123,124,125]

It is generally agreed that much of the positive health effects associated with green tea (GT) are from the actions of its polyphenols known as catechins.[28,126,127,128,129] The major catechins in green tea are EGCG, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epicatechin. EGCG accounts for 50% to 80% of GT catechins amounting to ~80 to 150 mg per

brewed (2.5 g tea leaves) cup of green tea and 20-50 mg of caffeine (tea processing results in wide variances).[130,131] In addition, green tea and its extracts also often include some polyphenols like caffeine, theanine, theaflavin, thearubigin, quarcetin, cholorogenic acid and gallic acid.[132,133]

EGCG in Fatty Liver

As described above, the underlying mechanisms facilitating the initiation and progression of NAFLD are insulin resistance leading to disordered triglycerides synthesis and transport resulting in free fatty acids (FFA) accumulation in the hepatocytes, which in turn impairs the β-oxidation in mitochondria, raising levels of cytochrome P450 4A (CYP4A), CYP2E1, and increases the formation of reactive oxygen species (ROS).[2,3,4,31] The subsequent oxidative stress then speeds the onset and accelerates progression of NAFLD.[2,134] Currently, other parallel and cascading events such as lipotoxicity, adipokine secretion by adipocytes, endotoxins (lipopolysaccharide, LPS) released from gut microbiota, and endoplasmic reticulum (ER) stress, have also been identified as culprits in the development NAFLD and progression from simple steatosis to more serious NASH, fibrosis and end-stage liver disorders.[1,2,31,134,135,136]

Of all these factors in the development of NAFLD, as noted previously, the resulting oxidative stress plays the major role as it responds to the hepatic and extrahepatic insults and the uncontrolled stress further promotes hepatic lipid accumulation, infiltrated inflammation, and interstitial fibrosis, during the progression of NAFLD.[134,137,138,139,140] Therefore, ameliorating oxidative stress and maintaining redox homeostasis in the liver has been a notable NAFLD protection and management strategy.[2,3,31,134,135,136,141]

Green tea demonstrates potent antioxidant activity from its many tea catechins named above, but especially EGCG, which is the most active and plentiful antioxidant catechin of green tea and often singled out as the primary ingredient in GT that is associated with protecting liver health.[18,28,29,30,31,129,130,131,132,133,142] The protective and liver health management effects of ingesting GT and EGCG are proposed to be from its unique properties in regulating metabolism, functioning as a local antioxidant, anti-inflammation and anti-fibrosis agent.[31,143,144,145]

Further, noting that the nuclear factor erythroid 2–related factor 2 (Nrf2) pathways are essential factors in limiting or controlling oxidative stress via transcriptional activities, regulating xenobiotic metabolism (foreign substances) and defensive antioxidant systems, EGCG has been shown to exert anti-inflammatory and hypolipidemic activities in both NRF2-dependent and NRF2-independent manner.[31,146,147] Other proposed mechanisms of EGCG in liver health protection and NAFLD management, as shown in Figure 2 from Tang et al., is its ability to upregulate AMP-activated protein kinase (AMPK), which plays an essential role in regulating de-novo lipogenesis in liver, and sirtuin 1 (SIRT1).[147,148,149,150,151] SIRT1 has a major role in the regulation of glucose and lipid homeostasis, management of mitochondrial biogenesis, and control of insulin sensitivity and oxidative stress.[31,152]

For readers interested in detailed descriptions, including related clinical trials, of EGCGs mechanisms of action in managing liver health, you are referred to the Tang et al. article, *Green Tea and Epigallocatechin Gallate (EGCG) for the Management of Nonalcoholic Fatty Liver Diseases (NAFLD): Insights into the Role of Oxidative Stress and Antioxidant Mechanism*.[31] Below is the authors summary:

"Abundant animal/human and cellular studies have demonstrated that green tea and EGCG may protect against NAFLD initiation and development by alleviating oxidative stress and the related metabolism dysfunction, inflammation, and fibrosis. The targeted signaling pathways may include, but are not limited to, NRF2, AMPK, SIRT1, NF-κB, TLR4/MYD88, TGF-β/SMAD, and PI3K/Akt/FoxO1, etc." The review thoroughly discusses the oxidative stress-related mechanisms involved in NAFLD development, as well as summarizing the protective effects and underlying mechanisms of green tea and EGCG against NAFLD.[31]

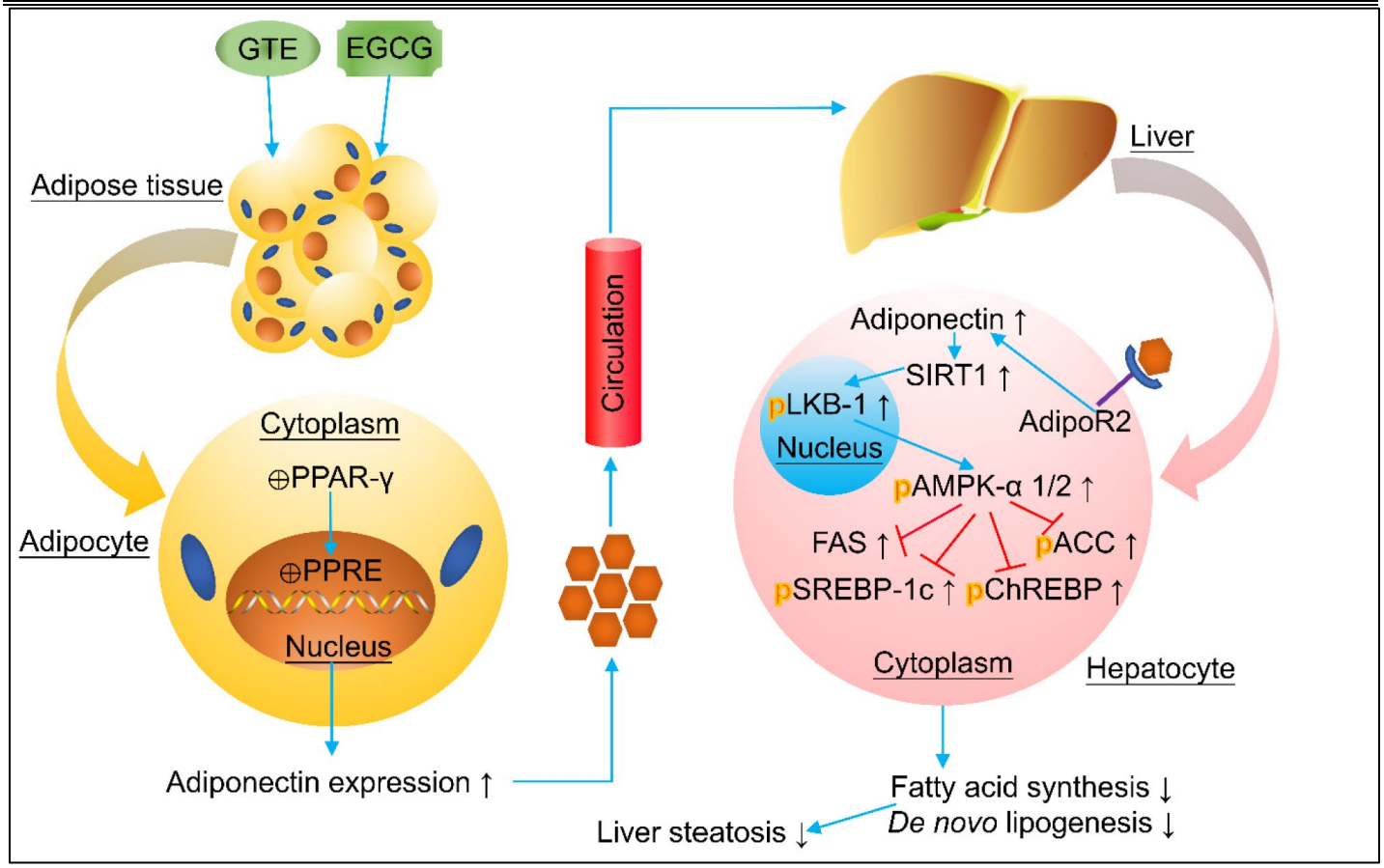


Figure 2 - Green tea extract (GTE) and epigallocatechin gallate (EGCG) may ameliorate liver steatosis in NAFLD by improving lipid metabolism via targeting SIRT1 and AMPK signaling pathways. Abbreviations: PPAR-, peroxisome proliferator-activated receptor ; PPRE, PPAR-responsive element; AdipoR2, adiponectin receptor 2; SIRT1, sirtuin 1; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; SREBP-1c, sterol element-binding protein 1c; and ChREBP, carbohydrate response element-binding protein.[31]

EGCG in Body Composition

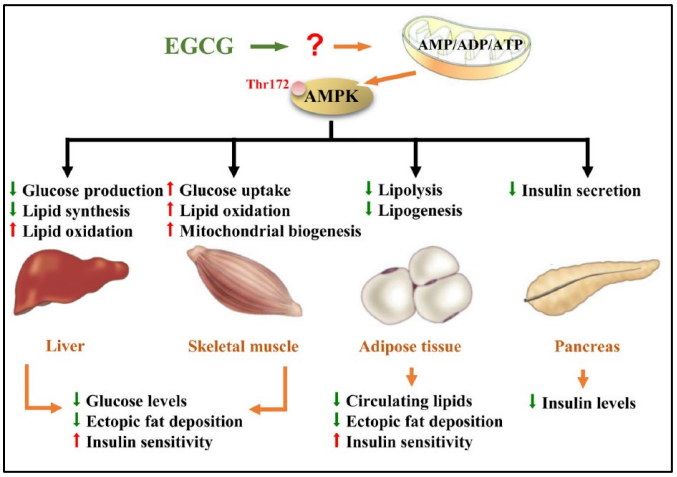
EGCG ingestion has been shown to improve lipid/fat metabolism, including reducing circulating triglycerides and LDL cholesterol;[31,126,133,153] enhance catabolism (breakdown) and oxidation (energy usage/partitioning); [154,155,156,157,158,159] increase energy expenditure;[154,155,158,160,161] and contribute a modest but favorable influence on weight control/body composition.[22,126,161,162,163]

Mechanisms of Action in Body Composition

Research offers many mechanisms in which EGCG (mindful that many EGCG extracts of GT contain some caffeine, albeit relatively low amounts[164,165]) may promote weight loss and/or improve body composition and thermogenesis including total daily energy expenditure and fat metabolism: 1) EGCG directly inhibits the enzyme catechol-O-methyl-transferase (COMT),[166,167] that degrades epinephrine (EPI) and norepinephrine (both hormones are stimulated by caffeine), fostering higher circulating concentration of sympathetic-induced catecholamines and enhancing beta-oxidation thus fat oxidation (FO); [132,154,155,156,157,158,168] 2) may suppress gluconeogenesis and lipogenesis and enhance lipolysis through activation of AMP-activated protein kinase (AMPK),[31,147,169,170,171,172] (possibly via upregulation of sirtuin 1[171,173]) which has been shown to take place in muscle, liver, adipose tissue and pancreas[171,172,174,175,176] with manifestations as depicted by Yang et al. in Figure 3;[169] 3) in the gastrointestinal tract (GI) EGCG may decrease digestion and absorption of macronutrients: lipids by interfering with the emulsification needed for absorption and

inhibiting pancreatic lipase (enzyme that breaks down fat),[177] and carbohydrates by inhibiting amylase and glucosidase;[162,178] 4) green tea constituents may enrich the probiotic population in the intestines, favoring a flora consistent with leaner humans;[31,162,179,180,181,182] in which part of this enhancement may be from an increase production of short-chain fatty acids (SCFA) caused by EGCG (SCFA generation has recently been found capable of signaling a cascade effect in the body, activating AMPK, and inducing weight-loss;[126,169,182,183,184] 5) EGCG also works as an antioxidant (and possibly an indirect antioxidant [prooxidant] stimulating other antioxidant systems) scavenging free radicals and preventing the formation of reactive oxygen species (ROS) by chelating metal ions (more apparent in subjects under high oxidative stress, e.g. overweight/obese);[31,126,141,143,144,145,169,185,186] 6) EGCG has demonstrated an ability to destroy fat cells;[177,187,188] and 7) EE and fat oxidation may also increase via an effect of catechins on the gene expression of proteins that play a role in thermogenesis and beta-oxidation.[164,167,186]

Figure 3 - Proposed EGCG AMPK Actions on Organs



Yang et al. hypothesis on the role of AMPK in metabolic regulation by EGCG.[169]

"EGCG is proposed to active AMPK through affecting the ratios of AMP/ADP/ATP. The activated (phosphorylated) AMPK regulates metabolism in different organs toward the direction of reducing (↓) gluconeogenesis, fatty acid synthesis, insulin secretion and ectopic fat deposition in muscle and liver. These are accompanied by increased (↑) insulin sensitively and the oxidation of glucose and fatty acids". The lower part of the figure was modified from Long et al.[170]

Study Endpoints

One or a combination of any of the proposed mechanisms have produced clinical trials demonstrating that regular ingestion of the green tea catechins (GTCs), primarily EGCG at ~250-300 mg/d, can increase overall EE,[29,157,169,189,190] and enhance fat oxidation,[160,169,186,190, 191,192,193,194,195,196] both conditions often leading to favorable changes in body composition.[126,154,164,165,169,190] Other GTC supplementation findings suggest that green tea catechin consumption enhances exercise-induced changes in abdominal fat and serum triglycerides in humans[197] and in animal models.[198] It should be noted that a study by Kumar et al. using 400 mg/d of a decaffeinated GTC (<1% caffeine) containing 50-75% EGCG, produced significant reductions in serum Prostate Specific Antigen (PSA) compared to placebo but at this dose (~200-300 mg EGCG) delivered no changes in body weight after 12 months of use suggesting at least some caffeine is important in EGCGs potential body composition benefits.[199] Other studies have found promising comparable results with decaffeinated GTC.[22,163,186,200,201]

EGCG with Naturally Occurring Caffeine

As noted above, most EGCG extracts of GT contain some natural caffeine, albeit in small amounts (generally <50 mg). However, the observation that EGCG from GT stimulates EE and fat oxidation cannot be completely attributed to its caffeine content because the thermogenic effect of GT extracts containing caffeine and catechin polyphenols is greater than that of an equivalent amount of caffeine alone (Figure 4).[154] According to Dulloo et al., fat oxidation accounted for approximately 42% of the total calories burned over the course of 24 hours in the EGCG group (270 mg) compared to the placebo (32%) and caffeine (34%) groups (Figure 5).[154] Moreover, respiratory quotient is lower in subjects who consumed decaffeinated EGCG compared to placebo during and after workloads which indicates greater

fat oxidation.[155,159] A study conducted by J.D. Roberts and M.G. Roberts et al., using 571 mg/day of a decaffeinated GT extract (providing 400 mg/day of EGCG) for four weeks in exercisers found a 24.9% increase in fat oxidation rates, a 1.63% decrease in body fat, and a 10.9% improvement in performance distance covered (20.23 km to 22.43 km), all compared to placebo.[202] This study strongly supports EGCG's ability alone (no caffeine) to increase fat oxidation. Readers are referred to Hursel R, Westerterp, et al. for a thorough review on EGCG influence on total EE and fat oxidation,[160] and The Nobari et al. article, *"An Overview on How Exercise with Green Tea Consumption Can Prevent the Production of Reactive Oxygen Species and Improve Sports Performance"* for more on GT/EGCG in energy partitioning.[186]

Figure 4 - Dullo et al. showed at least a 10% increase in 24-hour EE or equivalent to 157 more calories burned in the caffeine/EGCG group (Average subject's weight was 173 lbs).[154]

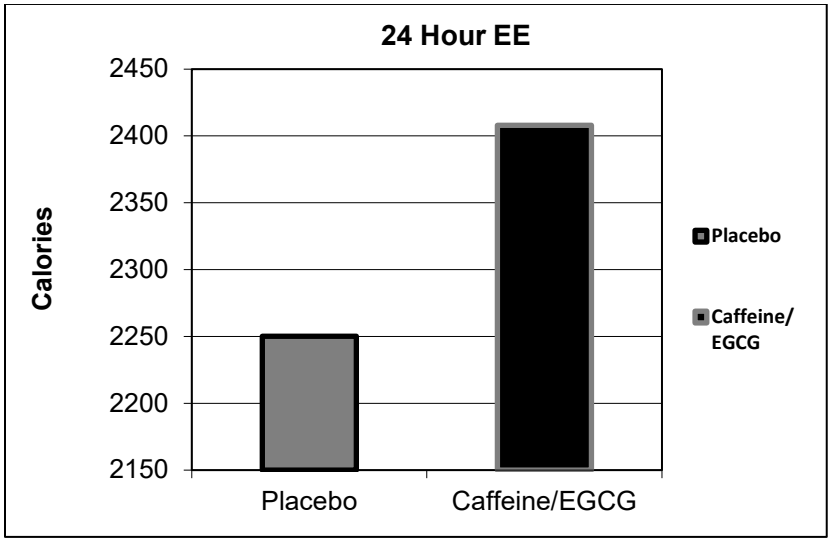
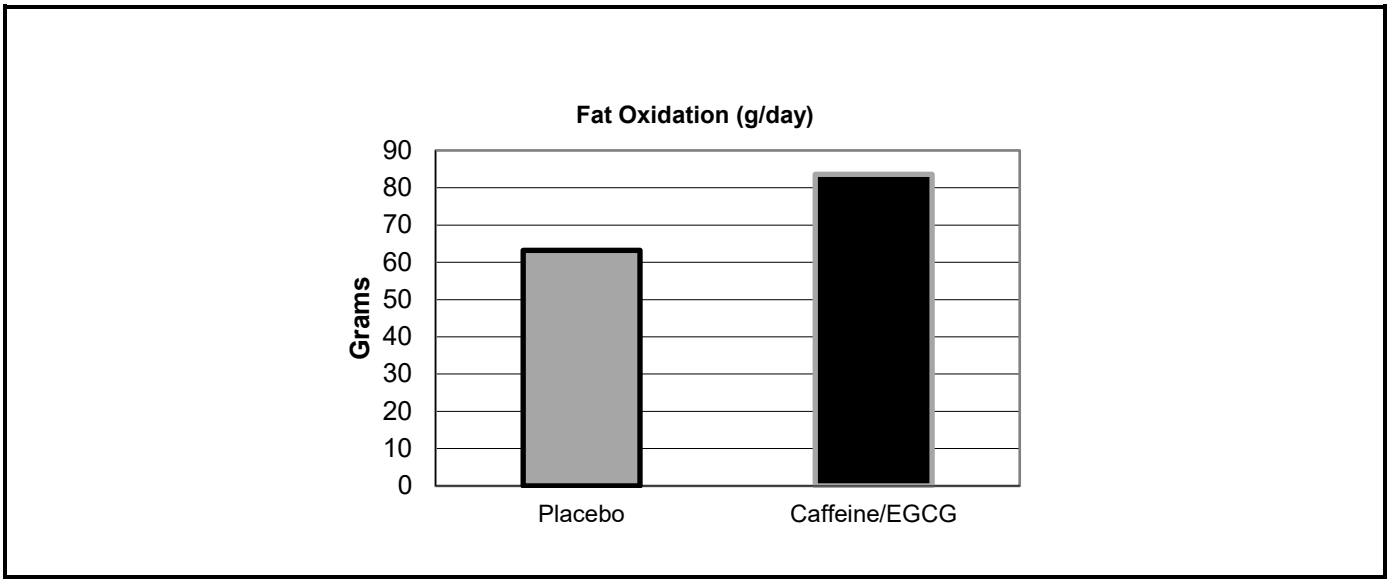


Figure 5 - In the same study, approximately 20 more grams of fat was oxidized daily by the supplemented group.[154]



EGCG Doses

A systematic review and meta-analysis of eight qualified RCTs by Kapoor et al. found that EGCG alone has the potential to increase metabolic rate, including respiratory quotient (RQ/FO) and EE at 300 mg/d dose, and collectively, the outcome supports the findings that EGCG influences metabolic parameters.[190] Similarly, Cisneros et al., in a systematic review of 15 qualified articles (out of 424 reviewed) on the effects of green tea and its EGCG content on body weight and fat mass, found that "daily consumption of green tea with doses of EGCG between 100 and 460 mg/day demonstrated the greatest effect on body fat and weight reduction in intervention periods of ≥12 weeks. However, the use of caffeine doses between 80 and 300 mg/day was shown to be a factor in studies with more positive results. Furthermore, results were greater in participants with lower habitual caffeine intakes (<300 mg/day) prior to the interventions.[161]

A meta-analysis and systematic review of clinical trials by Payab et al. found doses of catechins from 150-1,200 mg/day to be effective for improving body composition and cardiovascular/lipid markers.[22]

Roberts et al. found eight weeks of 400 mg/day of EGCG (along with alpha-lipoic-acid and quercetin) to be effective in improving maximal fat oxidation (154.4 ± 20.6 to 224.6 ± 23.2 mg·min−1) and FAT_{MIN} in healthy, overweight individuals. This corresponded with improved fat oxidation and usage (21% to 34.6%) during steady-state exercise and the reduced contribution of carbohydrates to total energy expenditure. The respiratory exchange ratio was reduced from 0.94 at week 4 to 0.89 at week 8.[203]

Safety

There have been reports of potential liver toxicity with regular ingestion of high-dose green tea extracts.[204,205] To address these accounts, The European Food Safety Association (EFSA) prepared an 89-page report concluding: "Based on the available data on the potential adverse effects of green tea catechins on the liver, the panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement statistically significantly increase serum transaminases in treated subjects compared to control."[205] Additionally, the EFSA also stated, "From the clinical studies reviewed, there is no evidence of hepatotoxicity below 800 mg EGCG/day up to 12 months." [205]

The Weight Loss and Liver Support (WLLS) full dosage (3 tabs per day) contains the known safe and in-range effective dose of 600 mg of green tea (camilla sinensis) leaf extract standardized to 98% polyphenols (588 mg), 80% catechins (480 mg), 45% EGCG (270 mg), 2% caffeine (4 mg naturally occurring), which is well below the EGCG/GT upper limit described by the EFSA.[205] dotFIT also states, as at the onset of this document: *use of any specialty dietary supplement, such as WLLS, as part of an overall weight loss plan is to speed and/or ease the journey contributing to enhanced motivation to complete the process,, at which time a specialty supplement, such as WLLS, should not be required to maintain the desired weight or body composition*. Therefore, long-term usage is not recommended or should be needed. That said, clinical trials using dosages ranging from 300-800 mg/d for up to one year have yielded no signs of liver damage.[126,157,163,169,199,206] It should be noted that regular higher doses (>800 mg) may yield a transient elevation in alanine aminotransferase (ALT), but in healthy subjects, levels should return to an individual's baseline upon cessation.[207] Anyone with a liver disorder should consult their doctor before considering the use at any dietary supplement, including products containing EGCG extracts. The dotFIT dosage and product duration recommendation would be considered safe and effective for supporting the majority of adult populations.

Irvingia Gabonensis (AKA African mango)

Excess body weight triggers disordered functioning in related hormones/adipokines like adiponectin (decreases with fat accumulation) and leptin (increases with fat accumulation). Irvingia gabonensis extract's primary proposed contribution to better weight management is the supplementation's effect on adipocytokines such as leptin and adiponectin, which regulate appetite and glucose levels as well as fatty acid breakdown respectively, potentially managing cascading complications from unhealthy weight gain.

Irvingia gabonensis, a fleshy West African fruit, is common in traditional Nigerian and Cameroonian cuisine, with the seed extract becoming a popular dietary supplement for weight loss.[34,208] Irvingia Gabonensis extract (IG) has been added to this formula for its potential in reducing specific complications brought on by unhealthy weight gain (adipose tissue disorders), including obesity-related outcomes from increases in inflammation/C-reactive protein (CRP), ROS, and resulting lipid, protein, and DNA structural damage as described in the opening section.[209] Further, excess weight-related adipose tissue dysfunction causes abnormal secretion/levels of adipokines, especially adiponectin and leptin (which play an important role in energy regulation/appetite,) negative conditions that IG supplementation has been shown to benefit.[210,211]

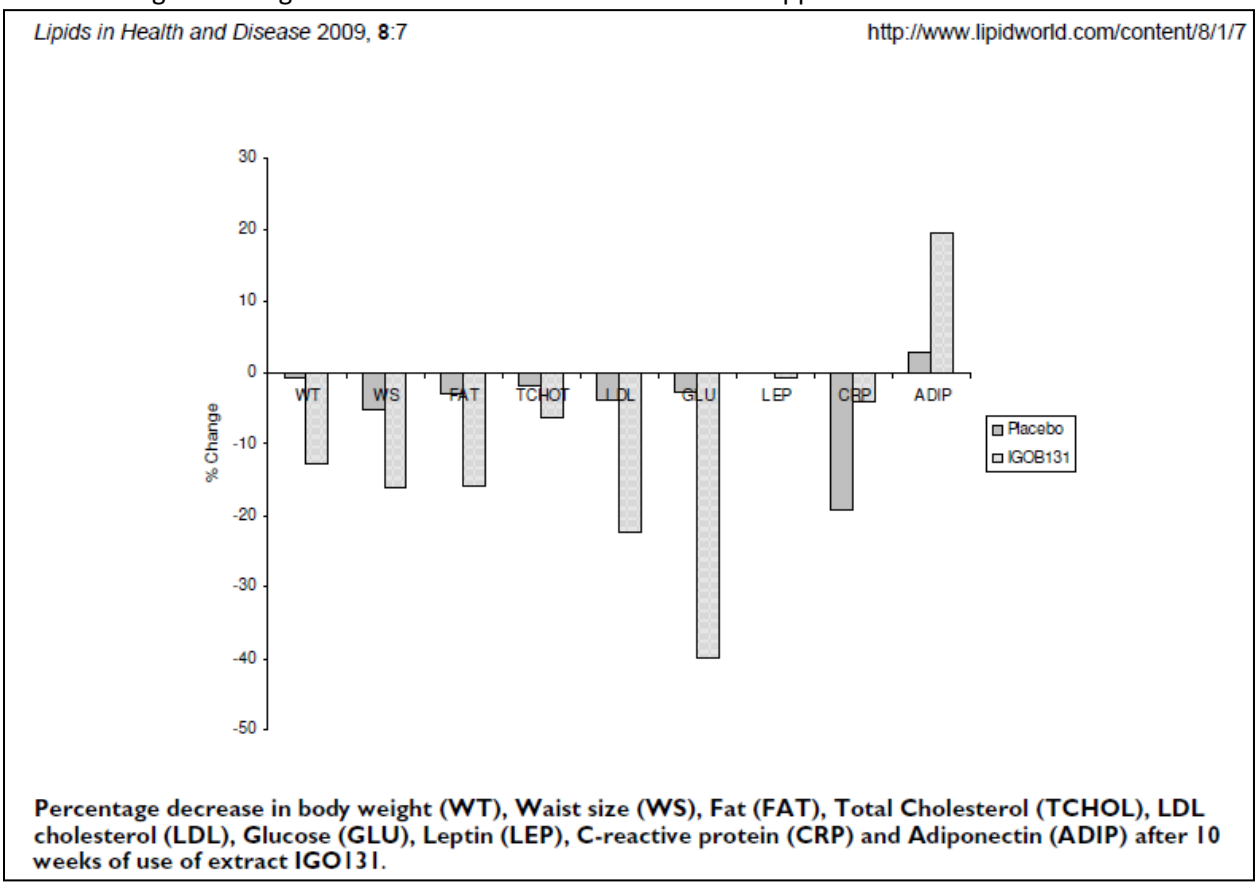
IG, like other water-soluble fibers (WSF), can delay stomach emptying, leading to a more gradual absorption of nutrients such as carbohydrates/sugars, thus reducing post absorptive elevation of blood sugar and offering appetite control.[212,213] Further, WSF, such as IG seed fiber, can bind to bile acids in the gut, causing removal thru feces, forcing the body to convert more cholesterol into bile acids resulting in the lowering of blood cholesterol and other blood lipids.[214]

Initial observations suggested beneficial changes in metabolic parameters (e.g., cholesterol, lipid profiles, insulin signaling, etc.) were associated with the high fiber content of IG.[32] Results of later analysis suggested that those beneficial observations of IG could not be from fiber content alone.[33,208,215] An *in vitro* study using a validated experimental model (murine 3T3-L1 adipocytes) to determine IG's potential mechanisms of actions, provided compelling data that IG may inhibit adipogenesis (activation/formation of fat cells) through modulation of peroxisome proliferator-activated receptor gamma (PPAR gamma), which regulates fatty acid storage and glucose metabolism (the genes activated by PPARG stimulate lipid uptake and adipogenesis by fat cells),[216] and modulation of glycerol-3 phosphate dehydrogenase (the enzyme which serves as a link between carbohydrate and lipid metabolism). Moreover, the bio-active component of IG, ellagic acid, has been shown to decrease adipogenesis thru the inhibition of cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding proteins (C/EBPs) expression (decreased C/EBP expression reduces adipogenesis).[217] These actions are in addition to IG's potential beneficial impact on leptin (appetite hormone) and adiponectin (involved in regulating glucose levels as well as fatty acid breakdown, and levels of the hormone are inversely correlated with body fat percentage in adults[218]).[211,219]

Preliminary clinical research showed that taking 1.05 grams of a crude seed extract three times daily combined with a low-fat, low-calorie diet of 1,800 kcal/day reduces weight by about 4 kg after four weeks, compared to no weight reduction in overweight patients taking a placebo.[32] Another preliminary clinical study (see Figure 6 below) demonstrated that a standardized seed extract (IGOB131) (also used in WLLS) taken at 150 mg twice daily for ten weeks reduced weight by 12.8 kg, compared to 0.7 kg in overweight patients taking a placebo.[33] In this study, overweight patients taking Irvingia gabonensis (IG) consumed an average of 2,767 kcal/day compared to 3,156 kcal/day in the placebo group, suggesting favorable effects on appetite. While the body weight results appear exaggerated, the IG group also decreased total and LDL cholesterol levels by 26% and 27%, respectively, compared with 2% and 5% with placebo.[33] Similar results also occurred in a study using a combination of standardized Irvingia gabonensis seed extract (IGOB131) and Cissus quadrangularis, for ten weeks in overweight adults.[220] Although systematic reviews of the direct effects of IG supplementation on weight loss have generally yielded significant positive outcomes, some trials suffer from poor reporting quality of the RCTs and short durations. At the same time, none demonstrated negative or nil results.[34,221] However, positive IG supplementation outcomes common to all trials was an improvement in specific weight-related comorbidities such as lipid profiles, adiponectin, and leptin levels (preventing decreases in levels).[22,32,33,34,219,220,**Error! Bookmark not defined.**] The latter two hormone levels were shown to be maintained versus placebo by Nonsa-ard et al., suggesting an IG's protective effect on obesity-related complications and long term use may offset weight loss driven appetite increases.[211] For these reasons, IG is hypothesized to offer a positive synergistic effect to the other ingredients described above that are all shown to have unique and complementary effects on body composition, weight control, and overall health (mitigating overweight/obesity-related complications), including supporting proper liver function to also help accelerate body fat reduction and maintenance.

In summary, IG supplementation alone demonstrates helpful weight management potential through primarily hormone level changes in adiponectin and leptin that are otherwise compromised by unhealthy weight gain and thus contribute to the weight gain cycle of disorders. Including IG in this formula, containing other distinctive weight control ingredients that target other weight gain related complications (e.g., NAFLD and subsequent runaway inflammation and oxidation, improper energy partitioning, etc.), adds another unique mechanism of action to help break or reverse the unhealthy cascading events from unwanted weight gain.

Figure 6 – Percentage of Change in Various Biomarkers with IGOB131 Supplementation vs. Placebo



Typical Use

- Non-stimulant body fat loss aid
- Recommended for overweight people to support a complete weight loss program, including related liver health.
- Take one tablet three times daily, generally 30 minutes before meals, with at least eight fl. oz of water, or spread three tablets evenly throughout your awake hours*
- Discontinue after reaching the body fat reduction goal or when the lifestyle is under control to continue to the desired body composition goal without assistance.

* The bottom line is that WLLS should be consumed three times daily and separated as evenly as possible to help maintain the desired levels of ingredients regardless of total daily meals or frequency. Taking it before a meal is one way of spreading it out and getting extra help in appetite support within 30 minutes. But it's unnecessary once you start using the product three times daily, as proper blood levels will be maintained to achieve the desired results.

Safety

Adverse events, precautions, or contraindications with any ingredients in WLLS are rare or unknown in the general population when supplementing the diet properly, as described above. The section below is a high-level summary related to specific subpopulations. Qualified practitioners needing more information related to these categories, including drug interactions, are referred to the TRC Natural Medicine Data Base (TRCNMD), which is continually updated with emerging evidence-based data.[222]

Precautions

Weight Loss & Liver Support (WLLS) is historically (a combination of ingredients have 13 years of widespread use) and generally considered a safe fat-loss aid. Theoretically, concomitant use of choline (much higher doses than found in this product) and atropine may decrease the effects and side effects of atropine.[223]
Diabetes: milk thistle constituents might lower blood glucose in patients with type 2 diabetes. People with diabetes using milk thistle products should closely monitor blood glucose levels. Dose adjustments to diabetes medications might be necessary.[224,225] People with liver disorders should consult their physician before using a product containing ECGC.[226] No IG studies reported more adverse events than the placebo groups[34,211,Error! Bookmark not defined.] Much higher doses than contained in WLLS of NAC (i.e., a clinical need) should require a separate prescription from a qualified physician.[104]

Contraindications (also see Precautions)

Weight Loss & Liver Support is contraindicated in pregnancy and lactation because of a lack of data for this population. Because of NAC, do not take if using anticoagulant drugs or nitroglycerine.
Clinical research shows that milk thistle extract, alone or with tree turmeric extract, can lower blood glucose levels and glycated hemoglobin (HbA1c) in patients with type 2 diabetes, including those already taking anti-diabetes drugs.[227]
TAMOXIFEN (Nolvadex): theoretically, the milk thistle constituent silibinin might increase tamoxifen levels and interfere with its conversion to an active metabolite. However, this has not been shown in humans.[228]

Adverse Reactions

Milk Thistle: Orally, milk thistle is usually well-tolerated and considered safe when used orally and appropriately.[101] A specific milk thistle extract standardized to contain 70% to 80% silymarin has been safely used in doses up to 420 mg daily for up to 4 years.[24,76,77,78,229] Uncommon events may include an occasional laxative effect, nausea, diarrhea, dyspepsia, flatulence, abdominal bloating, fullness or pain.[230]

EGCG: typical doses range from one to 10 cups of green tea daily without any adverse events.[231] A very high intake of green tea may cause nausea, abdominal bloating, pain, flatulence, and diarrhea. It can also cause central nervous system stimulation and adverse effects such as dizziness, insomnia, fatigue, agitation, tremors, restlessness, and confusion. These effects are more common with higher doses of green tea or green tea extract, equivalent to 5-6 liters of tea per day.[232] There have been reports of potential liver toxicity with regular ingestion of high-dose green tea extracts.[233,234] To address these accounts, The European Food Safety Association (EFSA) prepared an 89-page report concluding: "Based on the available data on the potential adverse effects of green tea catechins on the liver, the Panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement statistically significantly increases serum transaminases in treated subjects compared to control."[205,] the EFSA also stated, "From the clinical studies reviewed, there is no evidence of hepatotoxicity below 800 mg EGCG/day up to 12 months." [205] WLLS total dosage (3 tablets/d) contains the known safe and in-range effective dose of 600 mg of green tea (Camilla Sinensis) leaf extract standardized to 98% Polyphenols (588 mg), 80% Catechins (480 mg), 45% EGCG (270 mg), 2% Caffeine (naturally occurring 4 mg), which is well below the EGCG/GT upper limit described by the EFSA.[205] Anyone with liver disorders should consult their doctor before

considering EGCG use at any dosage. The dotFIT dosage and product duration recommendation would be considered safe and effective for the general population, including the overweight adult population.

Choline is not likely to cause side effects at doses up to 3,000 mg/day.[235] Amounts at very high levels (over 9 g daily) can include sweating, a fishy body odor, and gastrointestinal distress.[236]

Irvingia gabonensis: The only side effects reported using the specific standardized extract of Irvingia gabonensis (IGOB131) were flatulence, headaches, and difficulty sleeping, which were similar to the reports in the placebo group.[33,34,211]

Upper Limit/Toxicity

Choline: the IOM set the UL for choline is 3,500 mg/day, and the LOAEL is 7,500 mg/day.[57]

NAC: The LD50 for NAC in mice is 7,888 mg/kg, and in rats is 6,000 mg/kg. An AMES test performed on NAC was negative for mutagenicity.[83]

Milk Thistle: there is no established UL and is considered relatively safe for long-term use as directed.[237]

EGCG: High doses of green tea or green tea extract, equivalent to 21-25 cups of tea per day, can cause gastrointestinal distress.[238,239] The EFSA stated, "From the clinical studies reviewed, there is no evidence of hepatotoxicity below 800 mg EGCG/day up to 12 months." [205]

Irvingia gabonensis: There is no established UL or known toxicity data available at this time.

Natural Product Note

Based on the individual ingredients' unique and synergistic mechanisms of action, including multiple metabolic targets, this combination may allow the user to avoid or overcome typical plateaus related to early weight loss attempts. With weight loss prescription drugs being shown to have many negative side effects (including being pulled off the market[240]) with minimal results, [241] ***there is high interest in products like WLLS and other natural sources for assisting in weight management.*** [18,20,22,31,221,**Error! Bookmark not defined.**,242,243,244,245,246]

Note: while many of the positive weight control studies cited here were supplement usage without diet and exercise, dotFIT considers diet, exercise, and evidence-based supplementation all integral components of a weight/fat loss solution, where the role of supplementation is to accelerate, ease and allow a healthful journey, thus enhancing motivation to continue until the goal is reached. In other words, healthy weight/body composition management with less hardship, mindful that the small contributions that properly formulated supplements make, whether it be burning an extra 100-200 calories daily, controlling appetite, and/or preserving lean body mass (all compared to a non-supplemented state) can be a substantial contribution in the long-term big picture with little to no negative side-effects.

Summary

Purpose

Non-stimulant body fat loss aid in supporting liver health to improve overall metabolism leading to proper energy substrate (dietary fats/carbohydrates/proteins) usage/burning, and enhanced appetite management, thus easing and accelerating the desired body composition journey.

- When the body regularly stores fat, some is deposited in organs such as the liver, compromising its overall functioning, especially its ability to manage the usage and burning of carbs/sugar and fat.
- WLLS's natural ingredients (such as green tea extract, milk thistle, and choline) target mobilizing liver (belly) fat to improve sugar and overall fat metabolism/burning; also includes specialized antioxidants such as NAC and EGCG to reduce weight gain's related oxidative stress – i.e., break the negative chain reaction of unhealthy weight gain.
- The synergistic and unique contribution of African Mango can improve lipid profiles and support appetite control to make the individualized fitness journey easier and faster.
- Especially important for significantly overweight or obese people (females >32% body fat and males >22%) to support liver health to begin a healthy bodyfat reduction journey.
- May be discontinued when the goal is achieved.

Unique Features

- Unique and proprietary non-stimulant formulation that, when bodyfat reaches unhealthy amounts, works at many different and synergistic levels, such as removal of liver fat and attenuation of related inflammation and oxidative stress, subsequently improving overall health while accelerating achieving the desired body composition and offering appetite control.
- Can be used alone or as part of the dotFIT 90-Day Weight Loss Solution (aka LeanPak90)
- Manufactured in a regularly inspected NSF-certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC.

Supplement Facts Panel

Supplement Facts

Serving Size: 1 Tablet
Servings Per Container: 90

	Amount Per Serving	% DV
Green Tea (Camelia Sinensis) Leaf Extract [Standardized to 98% Polyphenols (196 mg), 80% Catechins (160 mg), 45% EGCG (90 mg), 2% Caffeine (naturally occuring 4 mg)]	200 mg	*
Choline (as Choline Bitartrate)	133 mg	*
N-Acetyl Cysteine	50 mg	*
Milk Thistle (Silybum Marianum L.) Seed Extract (Standardized to 80% Silymarin)	166 mg	*
Irvingia Gabonensis Seed Extract	150 mg	*

* Daily Value not estabilished

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