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**Effects of resveratrol in experimental and clinical non-alcoholic fatty liver disease**

Heebøll S *et al*. Resveratrol in non-alcoholic fatty liver disease

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**Abstract**

The prevalence of obesity and related conditions like non-alcoholic fatty liver disease (NAFLD) is increasing worldwide and therapeutic options are limited. Alternative treatment options are therefore intensively sought after. An interesting candidate is the natural polyphenol resveratrol (RSV) that activates AMP-activated protein kinase (AMPK) and silent information regulation-2 homolog 1 (SIRT1). In addition, RSV has known anti-oxidant and anti-inflammatory effects. Here, we review the current evidence for RSV-mediated effects on NAFLD and address the different aspects of NAFLD and non-alcoholic steatohepatitis (NASH) pathogenesis with respect to free fatty acid (FFA) flux from adipose tissue, hepatic *de novo* lipogenesis, inadequate FFA β-oxidation and additional intra- and extrahepatic inflammatory and oxidant hits. We review the *in vivo* evidence from animal studies and clinical trials. The abundance of animal studies reports a decrease in hepatic TG accumulation, liver weight and a general improvement in histological fatty liver changes along with a reduction in circulating insulin, glucose and lipid levels. Some studies document AMPK or SIRT1 activation, and modulation of relevant markers of hepatic lipogenesis, inflammation and oxidation status. However AMPK/SIRT1-independent actions are also likely. Clinical trials are scarce and have primarily been performed with focus on overweight/obese participants without a focus on NAFLD/NASH and histological liver changes. Future clinical studies with appropriate design are needed to clarify the true impact of RSV treatment in NAFLD/NASH patients.

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**Core tip:** The prevalence of obesity and related conditions like non-alcoholic fatty liver disease (NAFLD) is increasing. Therapeutic options are limited and alternative treatment options are sought after. An interesting candidate is resveratrol (RSV), a known AMP-activated protein kinase and silent information regulation-2 homolog 1 activator with anti-oxidant and anti-inflammatory properties. Here, we review the current evidence for RSV-mediated effects and address the different aspects of NAFLD and non-alcoholic steatohepatitis pathogenesis. We review the *in vivo* evidence from animal studies and clinical trials. Uniformly, animal studies report a decrease in hepatic triglyceride accumulation and improvements in histological fatty liver changes whereas results from the few clinical trials are equivocal.

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**INTRODUCTION**

The prevalence of obesity is increasing worldwide and consequently, related conditions like non-alcoholic fatty liver disease (NAFLD) have increased. NAFLD now affects up to one-third of adults and a growing number of children in developed countries[[1-3](#_ENREF_1)]. Early stages of NAFLD involve pathologic accumulation of triglyceride (TG) in the liver, a fairly benign condition, however some individuals elicit an inflammatory response that can progress to cirrhosis, cirrhosis complications and an increased risk of liver cancer[[4](#_ENREF_4)]. NAFLD is now the third leading cause of liver transplantation in the United States[[5](#_ENREF_5)]. Thus, NAFLD and especially the subtype non-alcoholic steatohepatitis (NASH) are thought to become a major health issue in the United States and throughout the world[[6](#_ENREF_6)].

Therapeutic options are limited and include weight loss, which is hard to obtain and sustain[[7](#_ENREF_7)], bariatric surgery, Vitamin E and glitazone treatment, especially the latter with a risk of significant side effects[[8-11](#_ENREF_8)]. Alternative treatment options are therefore warranted and intensively sought after[[12-15](#_ENREF_12)].

A potential new therapeutic option is the polyphenol Resveratrol (RSV). RSV is found in a number of plants, although in low concentrations. It is known as an activator of AMP-activated protein kinase (AMPK) and silent information regulation 2 homolog 1 (SIRT1), thereby mimicking a condition of caloric restriction *in vivo*. In addition, RSV has anti-oxidant and anti-inflammatory properties. All of these effects could in theory be beneficial for the treatment of NAFLD, and a number of experimental and clinical studies have been performed.

The aim of the present review is to provide a comprehensive description of the rationale for RSV treatment for NAFLD, and to review the present evidence from RSV intervention in experimental and clinical NAFLD studies.

**RSV ACTIONS**

RSV is primarily recognized as an AMPK and SIRT1 activator[[16-18](#_ENREF_16)]. AMPK and SIRT1 are both central in the metabolism of many different cell types, rendering RSV with pleotropic effects in various tissues. To date, studies have been unable to determine if RSV activates AMPK, SIRT1 or both, directly or indirectly[[19](#_ENREF_19)], a matter of ongoing debate[[20](#_ENREF_20)]. Regardless, the effects of the enzymes are closely interdependent. Recently, Park et al. proposed a mechanism involving a direct RSV-mediated inhibition of cAMP-specific phosphodiesterases and identified the cAMP effector protein Epac1 as a key mediator, which may lead to activation of first AMPK[[21](#_ENREF_21)] and then SIRT1 through the up-regulation of NAD+[[20](#_ENREF_20)]. Further, RSV may also act independently of AMPK/SIRT1, however the mechanisms are not clarified.

Through the activation of AMPK, SIRT1, and alternative routes including anti-inflammatory and anti-oxidant actions, RSV may inhibit the development or progression of steatosis and steatohepatitis. Former attempts to use the AMPK activator metformin in the treatment of NAFLD have largely been abandoned, because clinical studies showed no effect on histological NASH changes, despite a general decrease in hepatic steatosis and transaminase levels[[22-24](#_ENREF_22)].

**AMPK**

The AMPK pathway regulates energy homeostasis, both intracellularly and at the whole-body level. Through the action of upstream kinases, AMPK responds to changes in the AMP/ATP ratio, and thus serves as an intracellular sensor of energy levels, *e.g.*, in the situation of fasting, calorie restriction or accelerated ATP consumption[[25](#_ENREF_25)].

AMPK activation in the liver shuts down anabolic processes like cholesterol and TG biosynthesis by reducing the activities of, *e.g.*, sterol regulatory element-binding protein-1c (SREBP-1c) and fatty acid synthase (FAS). AMPK activation also promotes catabolic processes, *e.g.*, fatty acid (FA) β-oxidation by inactivation of acetyl-CoA carboxylase (ACC) and promotion of carnitine palmitoyl transferase-1 (CPT-1) activity[[26-28](#_ENREF_26)]. *In vivo*, it has been shown that chronic AMPK activation limits TG accumulation in both high-fat and control diet fed rats[[29](#_ENREF_29)]. These AMPK-mediated effects have been shown in *in vitro* and *in vivo* studies, using RSV as an AMPK activator[[28](#_ENREF_28)]. As an example, RSV treatment of HepG2 cells in high glucose media dose-dependently attenuated enhanced FAS expression, increased ACC activity and elevated TG accumulation[[30](#_ENREF_30)].

In adipose tissue the AMPK effects are similar, impairing lipolysis and promoting mitochondrial β-oxidation, thereby decreasing the level of circulating FFAs and the FFA load on the liver[[26](#_ENREF_26)]. Both hepatic and peripheral insulin sensitivity is augmented.

**SIRT1**

SIRT1 is a member of the sirtuin family and a NAD+-dependent deacetylase that acts as a master metabolic sensor of NAD+. Thus, it adapts gene expression and metabolic activity in response to the intracellular energy state. SIRT1 is mainly found in the nucleus, where it functions as a transcriptional repressor through histone, transcription factor, co-factor, and enzyme deacetylation[[31](#_ENREF_31)]. Following the SIRT1 metabolic effects, the molecule is thought to link calorie restriction and healthy aging and/or longevity. A number of studies have confirmed this *in vivo* and *in vitro*[[32-34](#_ENREF_32)], while few have disputed it[[35](#_ENREF_35)].

In the liver, SIRT1 is implicated in the control of energy metabolism through deacetylation and activation of especially peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and the lipid-sensing transcription factor peroxisome proliferator-activated receptor (PPARα), resulting in increased FA β-oxidation[[36](#_ENREF_36)]. PGC-1α stimulates mitochondrial biogenesis, thereby increasing the mitochondrial content in hepatocytes[[37](#_ENREF_37)]. In unison with AMPK, SIRT1 deacetylates and regulates SREBP-1c and liver X receptor (LXR), which govern [lipid](http://en.wikipedia.org/wiki/Lipid) and [cholesterol](http://en.wikipedia.org/wiki/Cholesterol) [metabolism](http://en.wikipedia.org/wiki/Metabolism)[[38-41](#_ENREF_38)]. Adenovirus-mediated overexpression of SIRT1 specifically in mouse liver has been shown to reduce liver fat by down-regulation of SREBP-1c and FAS and up-regulation of expression of genes that control FA β-oxidation[[42](#_ENREF_42)].

SIRT1 is an inhibitor of inflammation, repressing especially NF-κB transcription and activation as shown in liver and adipose tissue[[31](#_ENREF_31),[36](#_ENREF_36),[43](#_ENREF_43)]. Anti-inflammatory effects of RSV have also been demonstrated in *in vitro* and *in vivo* studies, however better documented in adipose tissue[[44-48](#_ENREF_44)], than in hepatic cells or tissue[[18](#_ENREF_18),[49-52](#_ENREF_49)].

Targeting SIRT1 activation for treatment of NAFLD has been suggested[[53](#_ENREF_53)], as SIRT1 expression is decreased in dietary NAFLD models and NAFLD patients[[54-56](#_ENREF_54)] and moderate SIRT1 overexpression protects mice from developing NAFLD[[57](#_ENREF_57)].

**NAFLD PATHOGENESIS**

The pathogenesis of NAFLD and NASH is far from clarified, and especially the factors that drive disease progression towards a more progressive, inflammatory phenotype are not fully characterized. Recently, a “multiple parallel hit hypothesis” has been proposed by Tilg and Moschen. Here, TG accumulation is viewed as an “innocent bystander”, while a number of different parallel hits lead to NASH development[[58](#_ENREF_58)]. Thus, it appears that there are 3 types of NAFLD patients; the “Good Fat Storer” (the NAFLD patient with a benign course), “the Bad Fat Storer” (the patient who develops immediate NASH), and the “Unfortunate Good Fat Storer” (the NAFLD patient that experiences additional hits and becomes a NASH patient)[[59](#_ENREF_59)]. Only the latter two may require pharmacological treatment, however bearing in mind that NAFLD may be an independent risk factor for type 2 diabetes[[60](#_ENREF_60),[61](#_ENREF_61)].

**STEATOSIS**

Hepatic steatosis occurs most often in the setting of obesity and metabolic syndrome, and is the result of lipid overload, primarily with increased free fatty acid (FFA) flux and TG accumulation. Several mechanisms are involved[[58](#_ENREF_58),[62](#_ENREF_62)], and some may be targeted directly or indirectly by RSV treatment. An illustration of the proposed RVS effects on NAFLD pathologenesis is shown in Figure 1.

***Increased FFA supply due to increased lipolysis from adipose tissue***

Insulin resistance (IR) results in increased lipolysis of TG in adipose tissue, resulting in elevated levels of circulating FFAs. Hepatic uptake of both diet- and lipolysis-derived FFAs is unregulated with limitless hepatocyte uptake *via* fatty acid transporters (*e.g.*, CD36). The bulk of hepatic TG (two-thirds) is derived from circulating FFA from lipolysis[[62](#_ENREF_62)]. RSV may decrease lipolysis in adipose tissue through improvement of peripheral insulin sensitivity, as documented in several studies[[63](#_ENREF_63),[64](#_ENREF_64)]. Further, RSV may favorably modulate the expression of fatty acid transporters[[65-67](#_ENREF_65)].

***Overnutrition***

Dietary fat contributes approximately 15% to the overall FFA load on the liver[[62](#_ENREF_62)]. Increased fat intake increases circulating FFA whereas elevated carbohydrate intake, especially in the form of fructose, increases *de novo* lipogenesis[[68](#_ENREF_68)].

***Increased de novo hepatic lipogenesis from dietary carbohydrates and amino acids***

Normally, *de novo* synthesis accounts for 5% of hepatic fat content, however, in subjects with NASH, up to 25% of the hepatic fat content may be caused by *de novo* lipogenesis[[62](#_ENREF_62)]. The process is regulated independently by insulin and glucose. In the postprandial and in the IR state, insulin stimulates the transcription factor SREBP-1c that promotes transcription of all genes involved in lipogenesis, among them ACC, FAS and peroxisome proliferator-activated receptor (PPARγ)[[69](#_ENREF_69),[70](#_ENREF_70)]. Glucose stimulates lipogenesis through stimulation of the transcription factor carbohydrate response element binding protein (ChREBP)[[71](#_ENREF_71)]. An upstream activator of both SREBP-1c and ChREBP is LXR, which is a transcription factor, governing [lipid](http://en.wikipedia.org/wiki/Lipid) and [cholesterol](http://en.wikipedia.org/wiki/Cholesterol) [metabolism](http://en.wikipedia.org/wiki/Metabolism)[[72](#_ENREF_72),[73](#_ENREF_73)].

Results from *in vitro* and *in vivo* studies show that RSV inhibits hepatic lipogenesis by AMPK/SIRT1-mediated inhibition of SREBP-1c, ACC and FAS activity[[27](#_ENREF_27),[28](#_ENREF_28),[37](#_ENREF_37),[44](#_ENREF_44),[74](#_ENREF_74)].

***Inadequate fatty acid oxidation***

Under normal physiological conditions, the mitochondria handle FFA by β-oxidation. Inadequate β-oxidation may be involved in NAFLD development due to the increased FFA flux through the liver[[62](#_ENREF_62),[68](#_ENREF_68)], and both de- and increased β-oxidation are reported[[75](#_ENREF_75)]. Regardless, SREBP-1c inhibits FA oxidation by indirect inhibition of CPT-1.

RSV may increase FA β-oxidation by stimulating mitochondrial biogenesis through PGC-1α activation[[37](#_ENREF_37)], increasing mitochondrial number[[37](#_ENREF_37),[76](#_ENREF_76)], increasing UCP2 expression[[76](#_ENREF_76)] and by increasing CPT-1 expression and activity[[27](#_ENREF_27),[77](#_ENREF_77)].

**STEATOHEPATITIS**

Hepatic inflammation is the hallmark of NASH, and the inflammation is driven by several inflammatory hits that may include both intra- and extrahepatic factors[[58](#_ENREF_58)].

Among the intrahepatic factors are the excess cholesterol, FFA, and lipotoxic intermediates, which elicit a number of damaging effects, collectively named “lipotoxicity”[[78](#_ENREF_78)]. This is recently reviewed in comprehensive reviews[[78](#_ENREF_78),[79](#_ENREF_79)]. Converging the harmful factors is the NF-κB pathway in immune cells, hepatocytes and hepatic stellate cells (HSC), resulting in an inflammatory, pro-fibrogenetic, and pro-apoptotic hepatic environment. NF-κB activation enhances transcription of pro-inflammatory cytokines[[80](#_ENREF_80),[81](#_ENREF_81)], with increased hepatic transcription of interleukin 6 (IL-6), tumor necrosis factor-α (TNFα) and the TNFα receptor as shown in NASH patients[[82](#_ENREF_82)]. Kupffer cells and damaged hepatocytes release, *e.g.*, transforming growth factor 1β(TGF-1β) that acts on quiescent HSC, inducing an activated state and thereby fibrosis. In addition, extracellular molecules, endotoxin such as lipopolysaccharide (LPS) (*via* toll-like receptor 4), TNFα, IL-1, IL-6, and reactive oxygen species, can induce NF-κB-mediated activation of the HSCs.

The anti-inflammatory effects of RSV are also documented in the liver. Animal studies have shown reduced hepatic macrophage infiltration[[51](#_ENREF_51)] and TNFα levels[[49](#_ENREF_49),[52](#_ENREF_52),[83](#_ENREF_83)] as well as inhibition of the NF-κB pathway[[50](#_ENREF_50),[52](#_ENREF_52),[83](#_ENREF_83)]. Only one study has focused on NASH-like fibrosis[[52](#_ENREF_52)], probably due to the lack of appropriate animal models, however other hepatic fibrosis models have shown RSV-mediated mitigating effects on markers of hepatic fibrosis[[84-87](#_ENREF_84)] and HSC activation[[86](#_ENREF_86),[88](#_ENREF_88),[89](#_ENREF_89)].

A number of studies report endoplasmatic reticulum stress, lipid peroxidation and oxidative stress as causative or early events in NASH pathogenesis[[90-93](#_ENREF_90)]. RSV is a known anti-oxidant compound and has been shown to lower hepatic oxidative stress in rodent diabetes and NAFLD models[[49](#_ENREF_49),[51](#_ENREF_51),[94-98](#_ENREF_94)]. One potential mechanism is interference in the keap1/Nrf2 pathway, leading to up-regulation of anti-oxidant enzymes[[99](#_ENREF_99),[100](#_ENREF_100)].

The extrahepatic inflammatory factors include dietary factors (*e.g.*, trans-fatty acids and fructose), gut-derived factors (*e.g.*, microbiota composition and bacterial byproducts), and adipose tissue-derived factors (*e.g.*, hypoadiponectinemia, adipo- and cytokines, namely leptin, resistin, IL-6, TNFα and monocyte chemotactic protein-1 (MCP-1)), that induce a state of whole-body low-grade inflammation in obesity[[101](#_ENREF_101)]. Several lines of evidence document the anti-inflammatory effects of RSV in adipose tissue, especially by inhibiting NF-κB activation[[46](#_ENREF_46),[102](#_ENREF_102),[103](#_ENREF_103)], lowering IL-6 levels[[47](#_ENREF_47),[104](#_ENREF_104)] and macrophage infiltration[[103](#_ENREF_103)], and modulating circulating cytokines and adipokines[[45](#_ENREF_45),[50](#_ENREF_50),[103](#_ENREF_103),[105](#_ENREF_105)]. RSV-mediated reduction of LPS-induced liver pathology and oxidative stress has also been reported[[106](#_ENREF_106),[107](#_ENREF_107)].

In summary, RSV has AMPK/SIRT1 activating, anti-inflammatory and anti-oxidant effects that may act in unison, combating the different hits in the pathogenesis of NAFLD and NASH development.

**RESVERATROL *IN VIVO***

Animal studies of RSV effects on NAFLD are numerous, and span a wide variety of models, intervention periods and RSV doses. The studies can be divided into low-dose [RSV doses 7-45 mg/kg bodyweight (BW) daily] and high-dose studies (RSV 45-300 mg/kg BW daily). Some of the studies have hepatic steatosis as the primary endpoint, others as secondary. The RSV treatment is generally started from the beginning of the study, and therefore, most of the studies concentrate on the preventive effect of RSV, and not the therapeutic effect. Almost uniformly, the studies report beneficial effects of RSV treatment on NAFLD pathology. In addition, RSV treatment in experimental models generally reduce circulating insulin and glucose levels[[18](#_ENREF_18),[37](#_ENREF_37),[45](#_ENREF_45),[46](#_ENREF_46),[50-52](#_ENREF_50),[63](#_ENREF_63),[105](#_ENREF_105),[108-110](#_ENREF_108)], and in some instances weight[[50](#_ENREF_50),[52](#_ENREF_52),[110-113](#_ENREF_110)], circulating transaminases[[44](#_ENREF_44),[52](#_ENREF_52),[77](#_ENREF_77),[110](#_ENREF_110)], and lipids[[45](#_ENREF_45),[50](#_ENREF_50),[65](#_ENREF_65),[96](#_ENREF_96),[108](#_ENREF_108),[111](#_ENREF_111),[112](#_ENREF_112)].

In Table 1 we present a list of published RSV animal studies with hepatic histological NAFLD/NASH data presented.

**MOUSE STUDIES**

In 2006, Baur *et al*[[37](#_ENREF_37)] published a much-cited study on the effect of RSV on the health and survival of mice on a high-fat diet (HFD). HFD and low-dose RSV (10 mg/d) were fed to the mice from senescence to death. Besides increased survival and a number of beneficial metabolic effects, the study showedRSV-mediated hepatic AMPK activation, ACC inhibition, decreased FAS transcription and increased mitochondrial number. RSV also decreased liver weight and the degree of steatosis. This study triggered a number of other mouse studies, often using C57BL/6J diet-induced obese (DIO) mice.

Regarding NAFLD data, the studies report a decrease in hepatic TG [[45](#_ENREF_45),[50](#_ENREF_50),[65](#_ENREF_65),[96](#_ENREF_96),[111](#_ENREF_111),[114](#_ENREF_114)] and/or cholesterol accumulation[[45](#_ENREF_45),[108](#_ENREF_108),[111-113](#_ENREF_111)] and liver weight[[37](#_ENREF_37),[65](#_ENREF_65),[112](#_ENREF_112)] along with improvement in histological fatty liver changes[[37](#_ENREF_37),[46](#_ENREF_46),[51](#_ENREF_51),[52](#_ENREF_52),[65](#_ENREF_65),[96](#_ENREF_96),[108](#_ENREF_108),[111](#_ENREF_111),[113-115](#_ENREF_113)]. Only few studies report NASH changes in the histological specimens. Ahn *et al*[[52](#_ENREF_52)] and Li *et al*[[65](#_ENREF_65)] find that RSV supplementation represses development of histological steatosis and steatohepatitis, in the latter study also fibrosis. Tauriainen *et al*[[115](#_ENREF_115)] find that high-dose RSV repress steatosis and hepatocyte ballooning in a model with minimal hepatic inflammation.

Although tested in a few studies, only two mouse studies are able to verify RSV-mediated AMPK activation in liver tissue[[105](#_ENREF_105),[114](#_ENREF_114)]. Also, no subsequent mouse studies have investigated hepatic PGC-1α deacetylation as a marker of SIRT1 activation. However, other markers of AMPK/SIRT1 activation have been documented in several mouse studies, among them inhibition of FAS expression and activation[[65](#_ENREF_65),[109](#_ENREF_109),[111](#_ENREF_111)], inhibition of ACC activation[[97](#_ENREF_97),[114](#_ENREF_114)], augmentation of FA β-oxidation[[111](#_ENREF_111)], inhibition of PPARγ and SREBP-1c expression and stimulation of PPARα expression[[52](#_ENREF_52),[65](#_ENREF_65)]. In mouse models RSV treatment inhibits NF-κB activation[[50](#_ENREF_50),[52](#_ENREF_52)] and lower hepatic expression of inflammation markers[[52](#_ENREF_52)]. Further, oxidative stress is alleviated by RSV treatment in a number of mouse models[[51](#_ENREF_51),[52](#_ENREF_52),[97](#_ENREF_97)].

In a long-term study of high-dose RSV treatment alone and in combination with another polyphenolic compound, namely quercetin, transcriptomic and metabonomic data demonstrated that combination therapy results in a significant restoration of gene sets in functional pathways of glucose and lipid metabolism (glycolysis and FA β-oxidation), inflammation/immunity, liver function, and the cardiovascular system, which were altered by HFD feeding[[108](#_ENREF_108)].

Also, in mutant Werner syndrome mice (showing premature signs of aging, *e.g.*, fatty liver) RSV treatment reversed liver steatosis and lipid peroxidation[[109](#_ENREF_109)]. Microarray and biologic enrichment analyses on liver tissues suggested that RSV mainly decrease lipogenesis and increase genes involved in the insulin signaling pathway and glutathione metabolism. The authors also observed a lower prevalence of hepatocellular carcinoma, however an increase in lymphomas and other solid tumors were observed.

**RAT AND HAMSTER STUDIES**

Numerous different rat models of NAFLD report on RSV effects on NAFLD relevant endpoints, along with a single hamster study. Similar to the mouse studies, the conclusions are overall positive. The studies show a decrease in liver weight[[67](#_ENREF_67),[74](#_ENREF_74),[77](#_ENREF_77)], hepatic TG[[27](#_ENREF_27),[44](#_ENREF_44),[66](#_ENREF_66),[67](#_ENREF_67),[74](#_ENREF_74),[76](#_ENREF_76),[77](#_ENREF_77)] and/or cholesterol accumulation[[66](#_ENREF_66),[67](#_ENREF_67)], and histological fatty liver[[49](#_ENREF_49),[66](#_ENREF_66),[67](#_ENREF_67),[74](#_ENREF_74)[76](#_ENREF_76),[77](#_ENREF_77)].

The first to describe RSV effects on NAFLD in rats was Shang *et al*[[74](#_ENREF_74)], using a HFD rat model in which the HFD was started 6 wk prior to the high-dose RSV treatment (100 mg/kg BW daily). This study therefore focused on the therapeutic effects of RSV. Besides alleviating NAFLD changes, it demonstrated that high-dose RSV treatment promotes phosphorylation and activation of AMPK and suppresses expression of FAS and SREBP-1c. This is backed by a recent study, in which the HFD was added a high amount of sucrose. Alberdi *et al*[[27](#_ENREF_27)] found that low-dose RSV treatment for 6 wk activates AMPK and PGC-1α, increases CPT-1 and decreases ACC activities with no change in the mRNA expression of SREBP-1c, PPARα, SIRT1, PGC-1α. Yet, not all rat studies find AMPK activation either. At variance, our group found no increase in AMPK phosphorylation or expression of related genes in spite of improvement in fatty liver changes, along with an increase in the hepatic mitochondrial content[[76](#_ENREF_76)].

Obese Zucker rats have been used in low-dose RSV studies[[44](#_ENREF_44),[77](#_ENREF_77)], with a reduction in hepatic lipid content and alanine aminotransferase levels, along with activation of AMPK and increased CPT-1 activity, which is important for the rate of FA β-oxidation. Resveratrol treatment also improved the inflammatory status of visceral adipose tissue[[44](#_ENREF_44)] and reduced liver oxidative stress[[77](#_ENREF_77)]. Here, the effect on lipogenetic enzyme activity was equivocal.

Similar results on inflammatory and oxidative status was found by Bujanda *et al*[[49](#_ENREF_49)], in a model in which cycles of fasting and feeding with a high carbohydrate-fat free diet induced steatosis. Low dose RSV for 4 wk lowered hepatic TNFα levels and reduced markers of lipid peroxidation and hepatic oxidative stress.

To our knowledge, only one study reports no RSV effect on hepatic lipid levels. Andersen *et al*[[116](#_ENREF_116)] used a dietary rat model and high-dose RSV treatment for 8 wk, yet, found no decrease in liver TG, FFA or cholesterol content. Also, they found no effect on liver SIRT1 protein expression.

Taken together, the current evidence shows that RSV prevents NAFLD-like hepatic steatosis in rodent NAFLD models. This may be caused by inhibition of adipose tissue lipolysis, inhibition of hepatic *de novo* lipogenesis and an increase in FA β-oxidation. A graphic illustration of the proposed RVS effects on NAFLD pathology is shown in Figure 1. Development of steatohepatitis may be attenuated by an inhibition of adipose tissue and hepatic inflammation and reduction of oxidative stress, however few studies have used appropriate animal NASH models and there is only one study documenting an alleviating effect on NASH fibrosis. RSV could exert some of these effects through AMPK activation, however AMPK activation is not found in all studies. Also, hepatic SIRT1 activation has not been verified in an experimental NAFLD model. Studies focusing on the therapeutic effect as opposed to the preventive effect of RSV on NAFLD and especially NASH are few but warranted.

**OTHER ANIMAL MODELS**

In a porcine model of metabolic syndrome Burgess *et al*[[110](#_ENREF_110)] found that high-dose RSV treatment had mitigating effects on insulin resistance and transaminase levels. Oil red O staining showed a decrease in hepatic lipid accumulation, however, a HE stain found no difference in histology in between the control, HFD and HFD with RSV groups, signifying that steatosis was not sufficiently induced in this model.

**CLINICAL TRIALS**

So far, only a few clinical RSV trials on efficacy outcomes have been concluded, and none of these studies have focused on fatty liver disease *per se*. Two studies on obese but otherwise healthy male participants report liver data. In the study by Timmers *et al*[[117](#_ENREF_117)], 11 participants received a daily dose of 150 mg RSV or placebo for 30 d in a double-blind, cross-over design. Results suggest a number of beneficial metabolic effects, among these a reduction of liver transaminases and liver fat by magnetic resonance (MR) spectroscopy. In another study, 24 participants received a dose of 1.5 g RSV or placebo daily for 4 wk[[118](#_ENREF_118)] and there was no effect on liver fat content (MR spectroscopy) or transaminase levels. This is consistent with another study in 45 non-obese postmenopausal women receiving a dose of 75 mg for 12 wk, where no effect on liver fat (MR spectroscopy) or any other physiological parameter could be demonstrated[[119](#_ENREF_119)].

Future clinical studies should focus on patients with biopsy verified NAFLD and NASH to determine any efficacy of RSV treatment in this setting

**CONCLUSION**

So far, clinical studies of RSV effects on steatosis are scarce and the overall positive effects seen in rodent studies are still missing. None of the studies have included verified NAFLD patients or histological data, and the studies differ significantly in the RSV dose used. New clinical studies should focus on the RSV effects in patients rather than healthy or near-healthy individuals[[120](#_ENREF_120)], in our case histologically verified NAFLD/NASH patients. In this setting the focus should be on the therapeutic effects of RSV, not its preventive effects, as reported in the majority of animal studies.

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**Figure 1 Proposed Rodent resveratrol effects on nonalcoholic fatty liver disease pathogenesis, AMP-activated protein kinase and silent information regulation-2 homolog 1 dependent and non-dependent mechanisms.** Evidence of *in vivo* effect demonstrated especially a RSV-mediated inhibition of adipose tissue lipolysis, inhibition of hepatic *de novo* lipogenesis and an increase in FA β-oxidation.ACC: Acetyl-CoA carboxylase; CPT-1: Carnitine palmitoyl transferase-1; FAS: Fatty acid synthase; FFA: Free fatty acids; NAFLD: Nonalcoholic fatty liver disease; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1 α; PPARγ/α: Peroxisome proliferator-activated receptor γ/α; ROS: Reactive oxygen species; SREBP-1c: Sterol regulatory element-binding protein-1c; TG: Triglyceride; TGF-1β: Tumor growth factor 1β.