Biochimica et Biophysica Acta 1852 (2015) 1124–1136

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

# Resveratrol and inflammation: Challenges in translating pre-clinical findings to improved patient outcomes☆

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ARTICLE INFO

*Article history:*
Received 3 September 2014
Received in revised form 16 December 2014
Accepted 21 December 2014
Available online 9 January 2015

*Keywords:*
Resveratrol
Inflammation
Metabolism
In vitro
In vivo
Clinical trial

ABSTRACT

Throughout the Western world obesity prevalence is steadily increasing, and associated metabolic co-morbidities are projected to rise during the years to come. As weight loss and weight maintenance remains a major problem, new strategies to protect against obesity-related morbidity are needed. There is a clear association between obesity, low-grade inflammation and obesity-associated diseases, thus, the development of new anti-inflammatory substances is urgently needed as these may ultimately pave the way for novel treatments of obesity and lifestyle-related diseases. A candidate molecule is the polyphenolic compound resveratrol, and in the present review, we provide an overview of the field, and discuss the future scientific perspectives. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.



## 1. Introduction

Throughout the Western world obesity is a rapidly increasing problem gradually reaching epidemic heights [1]. Associated co-morbidities such as type 2 diabetes are projected to rise steadily during the years to come [161]. On the individual as well as on a societal level this detrimental condition comprises a major problem, as it predisposes to increased overall morbidity and mortality [121,129].

The strong correlation between increasing adiposity and development of obesity-associated diseases is well-established [45]; consequently, the risk of death from various metabolic conditions comprising the metabolic syndrome increases dramatically with increasing fat mass, especially with increases in abdominal obesity [121,134,169,171]. Despite these clear-cut correlations, the pathophysiological background is not fully elucidated or agreed on. During the last decades, it has, however, become clear that the adipose tissue itself generates a systemic inflammatory process [75,99]. Traditional inflammatory responses are often transient and represent the organism's response to potential harmful stimuli and as such constitute a favorable homeostatic response. In general, however, prolonged inflammatory reactions are often deleterious. This seems to be the case in obesity-induced inflammation, which is considered a chronic metabolic low-grade inflammatory state sometimes referred to as "metaflammation" [75]. Following the general perception of the adipose tissue as a passive storage organ, it is today well-established that adipose tissue is a complex endocrine organ playing a pivotal role in metabolic homeostasis and immune regulation (Fig. 1). Some of the secreted factors, termed adipokines, are exclusively synthesized by and secreted from adipocytes, whereas numerous other unspecific cytokines, the adipocytokines, are also secreted from various other cell types within the adipose tissue.

For several reasons, great effort has in the recent years been put into discontinuing the progression of the obesity epidemic and the associated low-grade inflammation. However, so far none of the available strategies have managed to sufficiently curb the development. Consequently, as the conventional preventive and therapeutic options seem inadequate, physicians are instead obliged to resort to medical treatment of the obesity-associated conditions and complications, often at an advanced stage of the diseases.

As weight loss and weight maintenance remains a major problem, new strategies to protect against obesity-related morbidity are needed. There is a clear association between obesity, low-grade inflammation and obesity-associated diseases, thus, the development of new anti-inflammatory substances is urgently needed as these may ultimately pave the way for novel treatments of obesity and lifestyle-related diseases. A candidate molecule is the polyphenolic compound, resveratrol, which is already widely distributed as an over-the-counter nutritional

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http://dx.doi.org/10.1016/j.bbadis.2014.12.024
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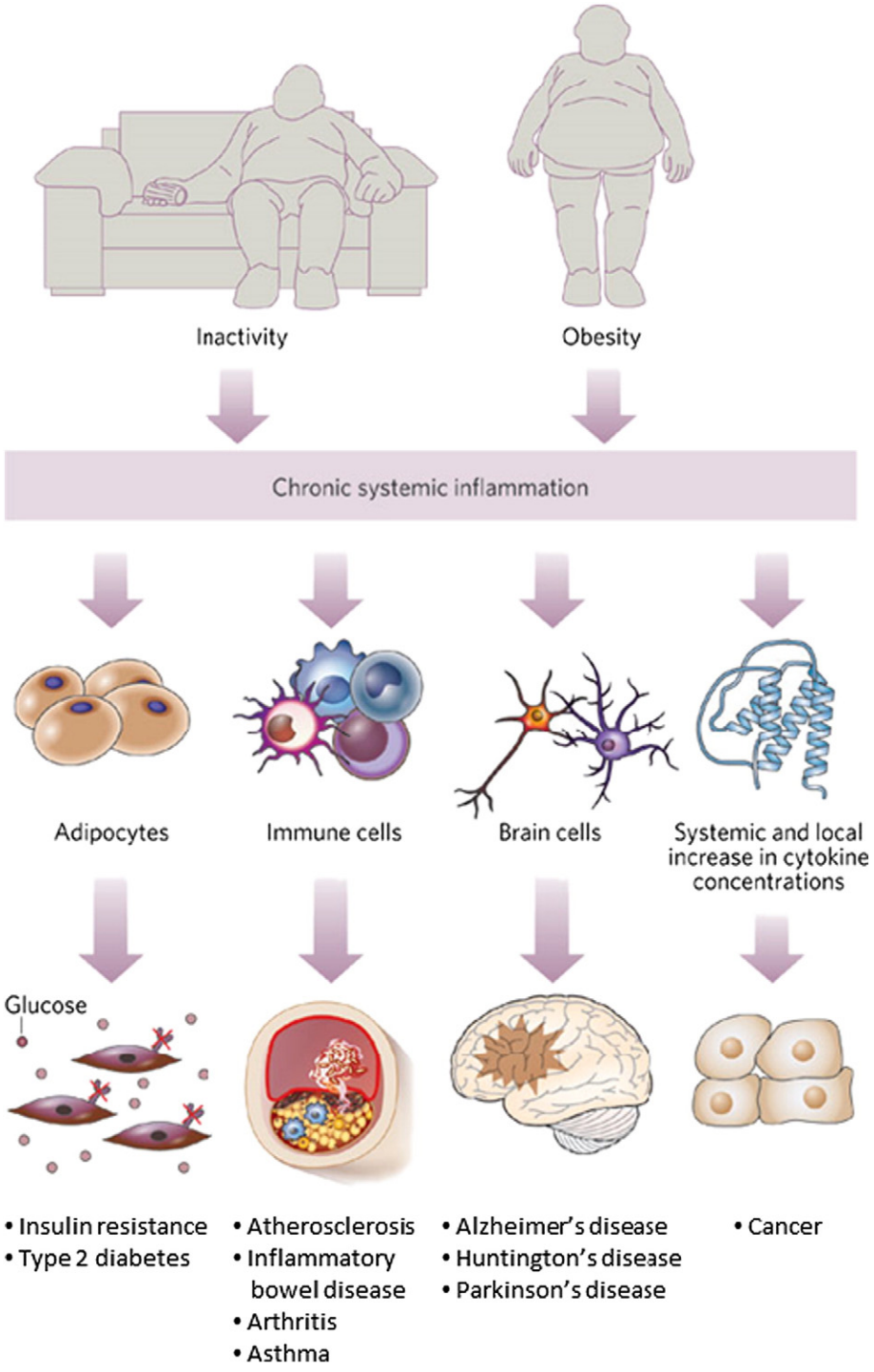


**Fig. 1.** Inflammation and chronic diseases. Inactivity and obesity trigger persistent, low-grade systemic inflammation. Moreover, inflammation in certain tissues is linked to the development of many chronic diseases. Examples of such tissues and the consequences of inflammation are shown. Inflammatory cytokines released from adipose tissue are linked to the development of insulin resistance and type 2 diabetes. Inflammatory responses by immune cells and glial cells are associated with atherosclerosis, inflammatory bowel disease, arthritis, asthma and neurodegenerative diseases, respectively. The systemic and local production of cytokines contribute to the etiology of certain cancers.
Adapted with permission from *Nature* (Spigelmann et al., vol 454, 463–469, 2008).

supplement with an array of alleged beneficial effects in relation to human health.

## 2. Resveratrol

During the last decades, resveratrol has gained steadily increased attention in relation to metabolic health. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a small polyphenolic compound chemically belonging to the stilbenoid class, and in the lay press, resveratrol is probably best known as a constituent of grapes and wine, albeit in minute amounts (in red wine on average 1.9 mg/L [139]). Triggered by this relation, in the early 1990's resveratrol gained great attention as the 'missing link' to explain 'the French paradox' [36,125], which is the epidemiological observation that French people appear to have relatively low incidence of cardiovascular disease, despite consuming a diet high on saturated fat. Even though this concept has scientifically been challenged since

then, the interest of resveratrol is progressively increasing. A major milestone appeared in 2006, as the Sinclair group demonstrated a resveratrol-mediated shift in the physiology of middle-aged mice kept on a high-calorie diet toward that of mice fed a standard diet, thereby significantly increasing their survival [11]. The first randomized clinical trial systematically examining metabolic effects in human subjects was published in late 2011 [142].

An exhaustive description of the purported molecular-biological targets and overall physiological effects of resveratrol action is beyond the scope of the present review, but one of the central elements in the action of resveratrol is the anti-inflammatory potential, which per se probably interconnects or directly affects other physiological outcomes, e.g. diabetes, cancer, cardiovascular disease and neurodegeneration.

## 3. The inflammatory cascade

Low grade inflammation is observed in various other tissues than the adipose tissue which is probably caused by different stimuli in specific cells within these tissues. The toll-like receptors (TLRs) belong to the transmembrane pattern recognition receptors (PRRs) which are key components of the innate immune system. They initiate a defense response when pathogen-associated molecular patterns (PAMPs), which derivate from cellular stress or microbial pathogens, or damage-associated molecular patterns (DAMPs), which derivate from cellular damage, bind to the specific PRRs. Endogenous compounds such as saturated fatty acids may also bind to the PRRs and trigger an inflammatory response [167]. Macrophages as well as adipocytes express TLRs and it has been suggested that the TLRs may have an important role in relation to the obesity-induced chronic low-grade inflammation. Particularly, the expression of TLR4 and TLR2 is elevated in obesity and metabolic diseases [4]. TLR4 binds LPS, an endotoxin which is found in the outer membrane of gram-negative bacteria, and activates the transcription factor NF-κB which triggers an inflammatory response. Certain endogenous free fatty acids can also activate TLR4 and induce a similar inflammatory response [100]. Moreover, high fat diet has been suggested to increase the intestinal permeability for LPS and thereby trigger the low-grade inflammation [25]. TLR2 binds lipoproteins from gram-positive bacteria; however, it also recognizes viral, fungal, and endogenous substances, which activate the NF-κB pathways. The activation of the TLRs triggers a downstream signaling pathway which consists of multiple paths. A family of IκB kinases (IKK) plays a central role in controlling the NF-κB activity. The IKK control the signaling of NF-κB by phosphorylating an inhibitor of NF-κB (IκBα), thus IκBα, sequesters NF-κB in the cytosol. Upon TLR activation the IKK is activated and catalyzes the phosphorylation of IκBα which releases NF-κB that translocates into the nucleus and up-regulates genes associated with inflammation e.g. IL-6, MCP-1, and TNF-α [67]. The c-Jun amino-terminal kinases (JNKs) are also activated by inflammatory cytokines and free fatty acids and increased JNK activity is associated with low-grade inflammation and insulin resistance [73] (Fig. 2).

A recent study by Ahmad et al. demonstrated an increased expression of both gene and protein levels of TLR2 and TLR4 in the subcutaneous adipose tissue and monocytes from obese subjects compared with lean subjects [4]. Accordingly, the TLRs may be important targets for therapeutic approaches reducing obesity and low-grade inflammation.

## 4. Low-grade inflammation in obesity

The first clear indication connecting obesity, low-grade inflammation, and development of obesity-related morbidity was the finding that TNF-α overexpression in adipose tissue of obese rodents contributed to insulin resistance [77]. This association was supported by studies demonstrating improved insulin sensitivity and glucose homeostasis in obese mice lacking the TNF-α function [150,151]. These pioneer studies were consolidated by similar findings in humans [76,86,93,138]. Taken together, the studies on TNF-α confirm that the inflammatory response induced by adiposity is critically involved in the insulin action in obesity.

It is today clear that an array of other adipocytokines/chemokines than TNFα is also increased in obesity, e.g. IL-6, IL-8, and MCP-1. More or less potent, these mediators in various ways contribute to the inflammatory state of obesity and the overall link connecting obesity and the inflammatory networks has recently been strengthened in a study using large scale genetic transcription analysis [49].

In order to develop novel therapeutically modalities it is important to understand how the obesity-induced low-grade inflammatory process is initiated and maintained. This is important since obesity is neither a necessity nor prerequisite for developing metabolic disease. In fact, up to 30% of the obese individuals appear metabolically healthy [83]. Conversely, in the general population the prevalence of normal weight individuals displaying a cluster of obesity-related abnormalities is approximately 20% [85]. Furthermore, no standardized criteria to categorize metabolically healthy but obese individuals exist. However, some characteristics recur such as a favorable lipid profile and low visceral fat content [83]. Based on a previous cohort study, it can be suggested that the inflammatory profile is a predictor of morbidity in obesity [84], and consequently it is important to study the biological mechanisms of low-grade inflammation.

Despite a positive correlation between the degree of obesity and the level of circulating of pro-inflammatory cytokines/chemokines like TNF-a, IL-6, MCP-1, IL-8, and acute phase reactants like C-reactive protein (CRP) [32,64,87,152,154] the increase in the absolute levels of these mediators is often only modestly elevated about 2-fold compared with the level in non-obese subjects [9,51]. The degree of low-grade inflammation is not only associated with the body weight but also an unhealthy fat distribution has a profound effect on the inflammatory status [85,92], thus, abdominal and especially visceral fat accumulation is associated with increased level of pro-inflammatory cytokines/chemokines [70,71].

Adiponectin and leptin, which are two adipokines, exclusively secreted by the adipocytes, have attracted great attention since both adipokines constitute central elements in appetite regulation, energy balance, and innate immunity [141]. Large population studies have shown that the concentration of adiponectin and leptin strongly correlates with the risk of diabetes and cardiovascular disease [78,104]. The level of adiponectin correlates inversely with BMI [141] and the obesity-associated decrease in adiponectin is, based on pre-clinical experience, considered a causal pathophysiological factor [3]. Overexpression of adiponectin in mice has a protective function by reducing the formation of atheromatous plaques and reducing the infarct size after myocardial infarction [116]. Conversely, high levels of IL-8 and MCP-1 are thought to be important for the development of atherosclerosis [42,43]. Furthermore, it is shown that the metabolic disturbances observed in lipo-atrophic transgenic mice can be rescued by treatment with leptin and adiponectin [163,164]. Thus, the low adiponectin level, which is seen in obese individuals, is suggested to cause insulin resistance, higher degree of inflammation, and to have negative effects on cardiovascular health.

The obesity-induced inflammation (metaflammation) is reflected in the adipose tissue by an overexpression of the inflammatory genes including MCP-1, PLAUR, CSF-3, and HIF-1alpha [7,21]. Furthermore, an increased number of macrophages infiltrate the adipose tissue in relation to chronic low-grade inflammation in obesity [39,159]. The fat distribution plays an important role in relation to the inflammatory state, thus, the visceral adipose tissue contains a higher number of macrophages than the subcutaneous adipose tissue [19,22,71] and accordingly have a higher degree of local inflammation. Traditionally, macrophage phenotypes are divided into pro-inflammatory (M1) and anti-inflammatory (M2) subpopulations. M1 or classical activated macrophages are induced by substances like LPS and TNFα and produce pro-inflammatory cytokines whereas M2 or alternative activated macrophages are induced by substances like glucocorticoids, adiponectin and Il-10 to produce anti-inflammatory cytokines [40].

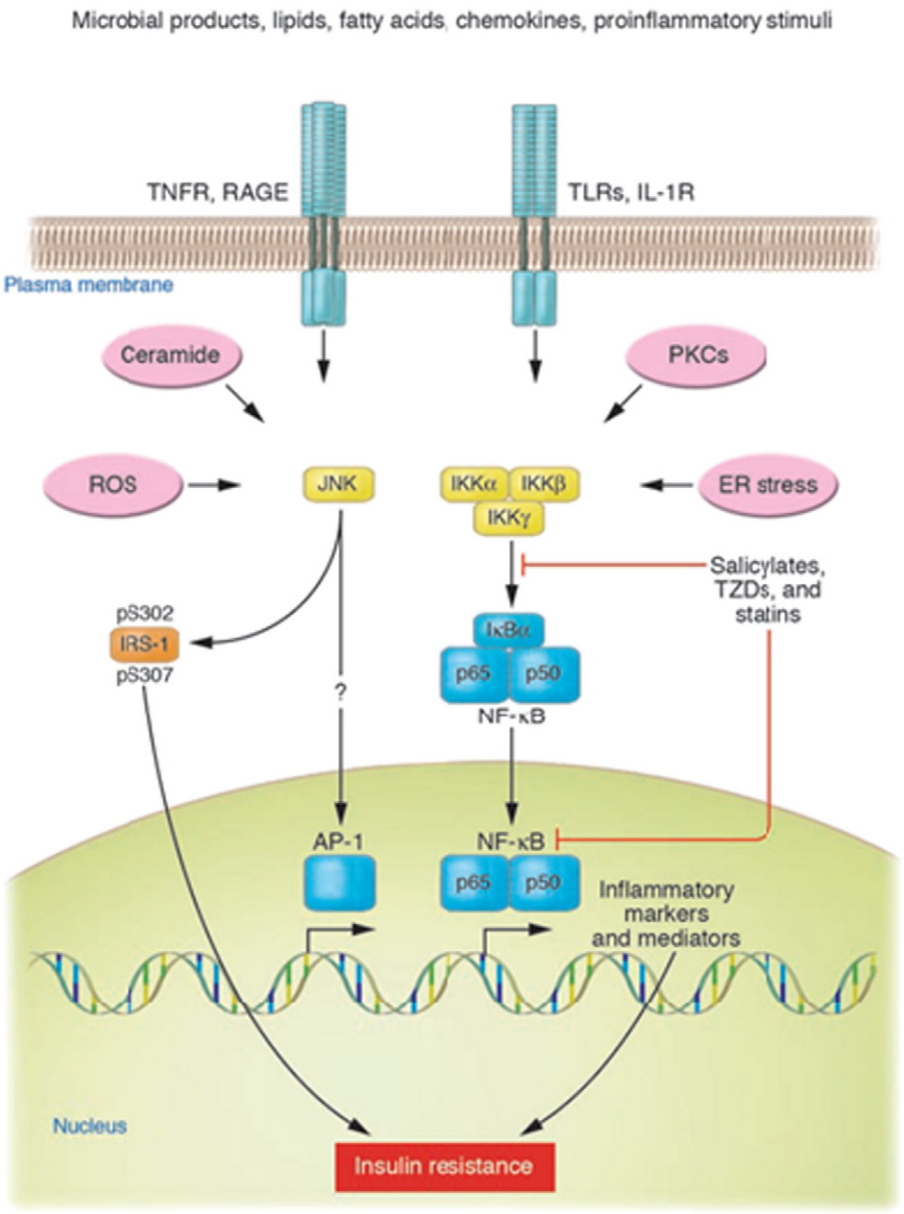


**Fig. 2.** Potential cellular mechanisms for activating inflammatory signaling. Obesity and high-fat diet activate IKKβ/NF-κB and JNK pathways in adipocytes, hepatocytes, and associated macrophages. Stimuli that have been shown to activate these pathways during metabolic dysregulation include ligands for TNF-α, IL-1, Toll, or AGE receptors (TNFR, IL-1R, TLR, or RAGE, respectively), intracellular stresses including ROS and ER stress, ceramide, and various PKC isoforms. Obesity-induced IKKβ activation leads to NF-κB translocation and the increased expression of numerous markers and potential mediators of inflammation that can cause insulin resistance. Obesity-induced JNK activation promotes the phosphorylation of IRS-1 at serine sites that negatively regulate normal signaling through the insulin receptor/IRS-1 axis. Examples include serine-302 (pS302) and serine-307 (pS307). By contrast, evidence has not been reported for obesity-induced effects on transcription factors such as AP-1 that are regulated by JNK. IKKβ and/or NF-κB are inhibited or repressed by the actions of salicylates, TZDs, and statins.
Reprinted with permission from *Journal of Clinical Investigation* (Shoelson et al., 116(7):1793–801, Jul 2006).

The adipose tissue macrophages are often arranged in so-called crown-like-structures (CLSs) surrounding dead or dying adipocytes and it has been suggested that they may have a scavenger function in response to the necrotic adipocytes [33]. The presence of CLSs in the adipose tissue is a strong indicator of local inflammation in the adipose tissue [160] (Fig. 3). The accumulating adipose tissue macrophages produce several pro-inflammatory cytokines and are suggested to be major contributors to the systemic low-grade inflammation. Recently, it was shown that the number of macrophages in human adipose tissue was increased in relation to obesity in subcutaneous adipose tissue and the expression of pro-inflammatory cytokines was elevated in adipose tissue from obese subjects, but interestingly, when normalized for the number of macrophages the expression profile indicated that the macrophages in obese subjects were changed toward a more anti-inflammatory profile (M2 phenotype) [54]. Besides macrophages, also the adipocytes play an important role in relation to the low-grade inflammation by their production of adipokines. Increased expression and secretion of adipokines are seen in relation to hypertrophic adipocytes [135], which occur due to excess fat accumulation in the adipose tissue. The fat depots differ in the production of adipokines and chemokines as the subcutaneous adipocytes have a higher production of leptin and adiponectin compared with the visceral adipocytes [68,149], and the visceral adipocytes have a higher production of e.g. IL-8, IL-6, and MCP-1 than the subcutaneous adipocytes [18,19,52].

Accumulation of lipid in the subcutaneous adipose depot corresponding to the gluteal and femoral area, is not associated with negative health consequences whereas accumulation of adipose tissue in the abdominal adipose depot and especially in the visceral adipose depot is

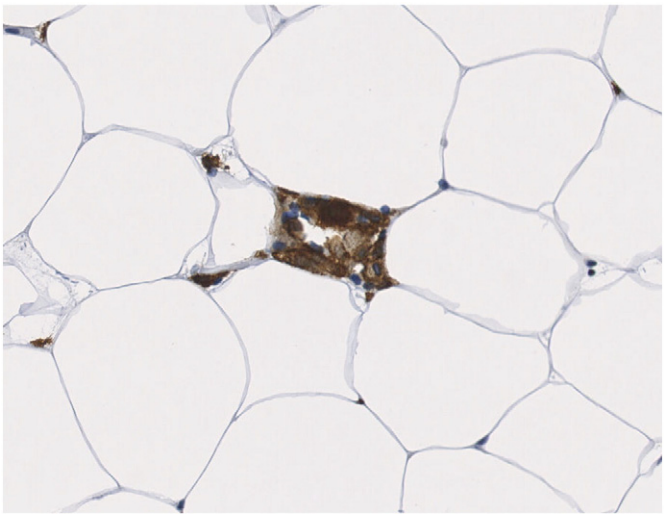

**Fig. 3.** CD68-positive macrophages arranged in crown-like structures in visceral adipose tissue from an obese subject (20×). Photo: Fjeldborg K.

associated with a marked risk of cardiovascular disease and type 2 diabetes [79]. It has been proposed that the adipose tissue has a defined individual capacity to expand and when this limit is exceeded the lipid will deposit ectopically in non-adipose tissues such as the liver, skeletal muscles, pancreas, and other organs in which it causes local inflammation and other toxic effects [153].

Several hypothetical links between obesity and low-grade inflammation exist. Prevailing hypotheses on how obesity-induced low-grade inflammation is initiated include macrophage infiltration, adipocyte hypertrophy, adipocyte cell death, nutrient-induced immune responses, endoplasmatic reticulum stress, oxidative stress, toll-like receptor activation, gut microbiota, and adipose tissue hypoxia [67,140,147,165].

Accumulation of excess lipid in the adipose tissue leads to adipocyte hypertrophy which may exceed the diffusion distance of oxygen and cause local hypoxia in the adipose tissue. The local hypoxia is consequently suggested to induce inflammation and increase the number of macrophages in the adipose tissue [147]. However, adipose tissue hyperoxia as a result of reduced oxygen extraction and mitochondrial dysfunction in the adipocytes has also been suggested to be associated with low-grade inflammation in obese subjects [65]. This theory is supported by the fact that most experimental studies on adipose tissue hypoxia have been performed under very low $PO_2$ levels (for normoxia, cells are incubated in the presence of the 21% $O_2$, whereas for hypoxia, 1–2% $O_2$ is generally used [146]) which may not reflect the physiology of the human adipose tissue. Another theory behind the low-grade inflammation is that the adipocyte hypertrophy leads to adipocyte necrosis. The necrotic adipocytes release cellular components which lead to an inflammatory response with activation of the macrophages that infiltrate the adipose tissue and aggregate around the necrotic adipocytes forming crown-like structures (CLS) [33]. Excess lipid accumulation and mechanical stress in relation to obesity are linked to endoplasmatic reticulum (ER) stress which is associated with activation of the inflammatory pathways [66,117]. When ER is challenged with excess nutrients the unfolded protein response (UPR) is activated. This process subsequently links to major inflammatory pathways, including the activation of JNK-AP-1 and IKB kinase nuclear factor κB (IKK-NFκB) [66]. Accumulation of excess lipid has also increased the systemic oxidative stress, thus, the elevated level of reactive oxygen species may lead to a dysregulated production of adipokines in the adipose tissue [57]. Elevated levels of free fatty acids released from the enlarged adipose tissue in obese subjects may induce inflammatory signaling by stimulating the toll-like receptors present on immune cells and adipocytes. Also nutritional free fatty acids can activate the toll-like receptors [133]. Furthermore, it has been suggested that a diet high on fat may change the gut microbiota and increase the intestinal permeability for lipopolysaccharides (LPS) [25] leading to higher circulating LPS levels which may induce inflammation via direct stimulation of the toll-like receptor in adipocytes, immune cells, and other important cells like the hepatic cells [58]. Based on animal studies the chronically increased plasma levels of LPS, termed metabolic endotoxemia, seem causally associated with obesity, insulin resistance and diabetes, as endotoxemia induced by continuous subcutaneous LPS infusion induces similar metabolic derangements as high fat diet. Consequently it is speculated that lowering plasma LPS concentrations could provide a novel approach in preventing metabolic diseases [24]. Finally, physical inactivity has also been associated with increased low-grade inflammation as seen by an increase in the level of hs-CRP [98]. The mechanisms behind this association are not completely settled but changes in the adipose tissue volume might be of importance. Moreover, a direct effect of physical activity has been proposed. Physical activity is known to activate AMPK which subsequently may regulate the inflammatory cascade via stimulation of PGC-1α and inhibition of NF-kB [113].

There are several mechanisms that may induce low-grade inflammation in relation to obesity; however, the precise underlying pathophysiological mechanism is not elucidated. The increased numbers of immune cells within the adipose tissue play an essential role and weight loss intervention studies have demonstrated a reduction in the number of adipose tissue macrophages and in the level of circulating pro-inflammatory cytokines in relation to weight loss [10,17,21,31,53,69] indicating that the inflammatory process is dynamically regulated and may therefore be a potential target for intervention.

As weight loss regimens tend to fail, various approaches have been explored in order to circumvent the low-grade inflammation associated with obesity. In addition to resveratrol and similar compounds (eg. Salsalate and Aspirin, see later) the intimate relation between gut microbiota alterations in relation to weight changes and metabolic morbidity serves as another field of future interest: In a recently published review it is suggested that modulation of intestinal permeability through interventions that modify the composition of the intestinal microbiota, or activation of the immune system and associated inflammatory responses, may constitute a key strategy to address obesity and obesity-related disease [34]. Another approach is modulation of the inflammasome by affecting central inflammatory mediators: By means of an IL-1 receptor antagonist or IL-1β antagonism systemic markers of inflammation are decreased and pertinent physiological markers of glucose homeostasis are improved [26,96,97,127,136]. As stated earlier TNFα seems crucially involved in low grade inflammation and development of insulin resistance, however, the effect of TNFα antagonists on insulin resistance in patients with metabolic syndrome or diabetes is only detected in some [138] but not all studies [46,114,119]. On the other hand insulin sensitivity was improved in non-diabetic patients with rheumatoid polyarthritis [90]. Other pharmaceutical targets being currently explored include IL6 antagonists, AMPK activators other than Metformin, mTOR inhibitors, CCR-2 antagonists and, finally, SIRT1 activators other than resveratrol [50].

## 5. Consequences of low-grade inflammation

The obesity-associated low-grade inflammation has been suggested to be the culprit for many serious diseases and conditions affecting millions of people throughout the world. Especially, the so-called lifestyle diseases have been related to low-grade inflammation which includes the development of insulin resistance, type 2 diabetes, cardiovascular disease, certain cancers, and neurodegenerative diseases [27,41,102,137] (Fig. 1). The elevated levels of circulating pro-inflammatory cytokines characterizing low-grade inflammation have been suggested to induce insulin resistance e.g. by inducing phosphorylation of serine residues of the insulin receptor substrate-1 (IRS-1) which impairs the normal insulin signaling pathway. Also high levels of free fatty acids can

promote insulin resistance by inducing phosphorylation of serine residues of IRS-1 [133].

The association between low-grade inflammation and metabolic consequences could be either a coincidence or causative. The causative link, in relation to insulin resistance, was established by a proof-of-concept study performed by Fleischman et al. which proved that treating young obese and insulin resistant subjects with the anti-inflammatory drug, Salsalate (prodrug of salicylate), not only improved the inflammatory state but also improved various metabolic variables including the insulin sensitivity and HbA1c [55]. Subsequently these findings were corroborated in a larger multicenter study (the TINSAL-T2D trial) [62] in which it was shown that Salsalate treatment reduced inflammatory mediators and improved glycemic control in patients with T2DM. Likewise, treating obese and insulin resistant rodents with the anti-inflammatory compound Aspirin demonstrated that inhibition of the inflammatory kinase IKKβ by Aspirin resulted in improved insulin sensitivity, and moreover, reduced triglyceride and free fatty acid levels [168] Salsalate and Aspirin are chemically related as both are built on salicylic acid which is originally a plant derived phenolic phytohormone which is produced by plants in response to pathogens. Also resveratrol is a phenolic phytohormone which is produced by plants in response to stress (Fig. 4).

Finally, targeting ER stress [118] and PPARγ [72] have demonstrated anti-inflammatory effects and beneficial outcomes on metabolic disturbances. Accordingly, some evidence exists that resveratrol in animal models, reduces ER stress [103] and induces PPARγ [56,156], hereby yielding beneficial effects in relation to retinal ER stress and atherogenesis, respectively.

Taken as a whole, modulation of the inflammatory status associated with obesity may likely affect metabolic variables in a positive way, and once again this underscores the need for novel therapeutic approaches.

## 6. Anti-inflammatory effects of resveratrol in vitro

Several biological targets of resveratrol have been reported, however the mechanisms by which resveratrol exerts its biological functions are still not fully elucidated (Fig. 5). Resveratrol exhibits its anti-inflammatory effects through various pathways that lower the NF-κB activity. Resveratrol inhibits the activity of especially cyclooxygenase-1 (COX1) [23] and the expression of COX1 and COX2, which are rate limiting enzymes involved in the production of pro-inflammatory mediators [6]. Moreover, the activity of microsomal prostaglandin E synthase-1 (mPGES-1), which is an essential enzyme responsible for the synthesis of the pro-inflammatory prostaglandin $E_2$ (PGE2), has also been shown to be attenuated by resveratrol [23].

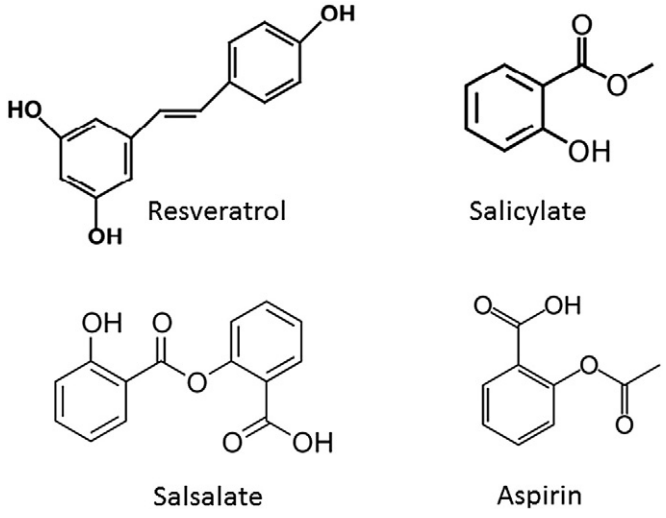


**Fig. 4.** Chemical structure of resveratrol, salicylate, salsalate and aspirin.

Hypoxia is a strong inducer of inflammation in the adipose tissue in vitro [146], and interestingly resveratrol attenuates the hypoxia induced inflammation in human adipose tissue explants [38]. A recent preclinical study has demonstrated that hypoxia-inducible factor 2α (HIF-2α) attenuates adipose tissue inflammation [29], thus, resveratrol may have an indirect anti-inflammatory effect since it is shown that SIRT1 is an inducer of HIF-2α in relation to hypoxia [44].

After binding of LPS to the toll like receptor (TLR) the cells respond by increasing the production of inflammatory cytokines which are inhibited by resveratrol. The study by Kim et al. dissected the involved pathways and reported that resveratrol suppressed the adaptor protein Toll Receptor-domain-containing-adaptor-inducing interferon-beta (TRIF) and the TANK-binding kinase (TBK) which resulted in lower activation of NF-kappaB, interferon regulatory factor 3 (IRF3) and activator protein 1 (AP-1) [89].

Another possible anti-inflammatory pathway utilized by resveratrol could be through the estrogen receptor. Estradiol possesses anti-inflammatory effects via estrogen receptor-alpha by controlling the intracellular localization of NF-kappaB [60] and resveratrol acts as a mixed agonist/antagonist for estrogen receptors [15]. However, at least in human adipose tissue fragments the anti-inflammatory effects of resveratrol are not mediated via estrogen receptors as an estrogen receptor-blocker did not affect the resveratrol effect [115].

Recently, death-associated protein kinase1 (DAPK1) has been proposed as a modulator of inflammation [111,112]. DAPK1 inhibits NF-kB activation and pro-inflammatory cytokine expression after stimulation with LPS and TNFa: however, other studies have reported a pro-inflammatory effect of DAPK1. The difference in pro- or anti-inflammatory effects of DAPK1 could be cell type dependent and/or depend upon the intra-cellular protein pool available as DAPK1 interacts via protein–protein binding; reviewed in [94]. This is interesting as resveratrol has increased the expression level of DAPK1 in human fibroblasts [30] raising the possibility that at least some of the anti-inflammatory effects of resveratrol might be caused by the regulation of DAPK1 which subsequently regulates the inflammatory status.

Numerous in vitro studies support the notion that resveratrol has strong anti-inflammatory effects in a variety of cell models, and the anti-inflammatory effect seems unrelated to the inflammatory stimulus. Thus, resveratrol attenuates inflammation and suppresses the activation of NF-κB in cells stimulated with e.g. LPS, TNF-α, or other well-known activators of inflammation [108,148]. The anti-inflammatory effects of resveratrol have been described in macrophages [148], T3T preadipocytes [172], endothelial cells [37], smooth muscle cells [91], chondrocytes [132], microglial cells [23], and adipose tissue [115]. Finally, in human adipocytes incubated with resveratrol, secretome analysis has indicated a less inflammatory phenotype resembling the outcome of calorie restricted adipocytes [126].

## 7. Anti-inflammatory effects of resveratrol in animal studies

Several animal studies have substantiated the anti-inflammatory effects of resveratrol found in vitro, and confirmed some of the proposed mechanisms of action. Among studies thoroughly exploring anti-inflammatory potential, Wang B. et al. fed C57BL/6 mice a high fat diet (HFD) and mice were designated as either diet-induced obese (DIO) mice or diet-resistant (DR) mice. A control group was fed a standard diet for comparison. DIO mice and DR mice were further subdivided into three groups receiving HFD alone, HFD with 0.03% resveratrol, or HFD with 0.06% resveratrol for 13 weeks. HFD alone increased TNF-α, IL-1, and IL-6, and decreased IL-10 in DIO mice compared to control mice. DIO mice supplemented with resveratrol exhibited decreased TNF-α, IL-1, and IL-6, and increased IL-10 compared to DIO mice fed HFD alone. The anti-inflammatory effects of resveratrol were dose-dependent [158]. Rivera L. et al. investigated the effects of resveratrol supplementation in obese Zucker rats. For eight weeks either vehicle

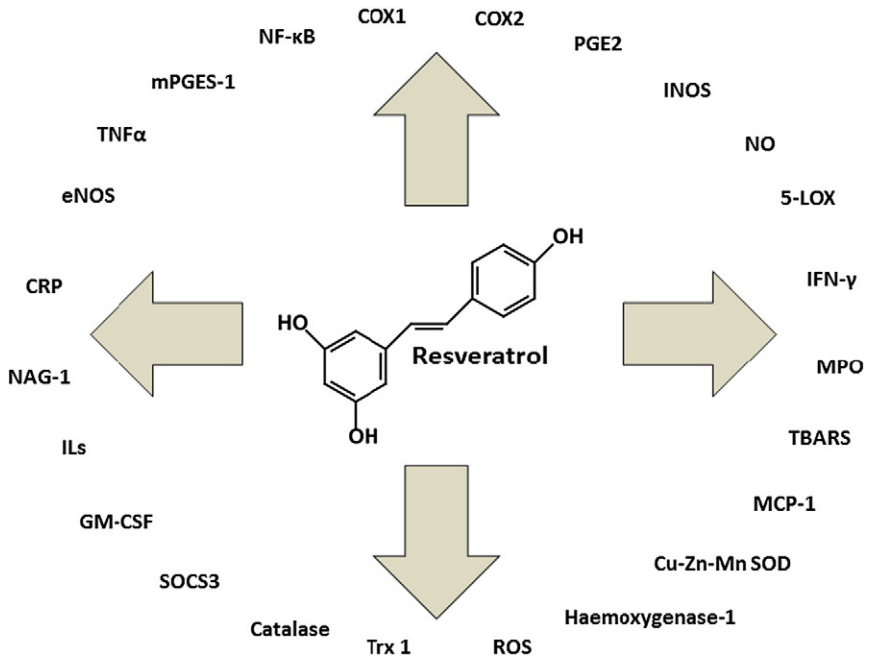


**Fig. 5.** Purported molecular biological targets of resveratrol in relation to anti-inflammatory and anti-oxidative processes.

or resveratrol (10 mg/kg body weight daily) was administered orally by gavage. Administration was stopped two days prior to termination of the study, in order to identify long-term effects rather than acute effects of resveratrol treatment. Resveratrol treatment increased adiponectin and decreased TNF-α production from the visceral adipose tissue compared to vehicle treatment. Additionally, resveratrol enhanced the eNOS expression in the visceral adipose tissue and aorta, and resulted in an improvement in the dyslipidemia, hyperinsulinemia, and hypertension normally characterizing the obese Zucker rats. The authors suggested that effects were mediated by AMPK activation [128]. Using SIRT1 knockout mice it was demonstrated that the activation of AMPK by resveratrol could be both mediated via SIRT1 dependent pathways (low resveratrol dose) and via SIRT1-independent pathways (high resveratrol dose) [124]. Another study using Zucker rats confirmed these anti-inflammatory effects of resveratrol (15 mg/kg body weight daily). Six weeks of resveratrol treatment reduced serum levels of TNF-α, MCP-1, and CRP compared to control animals. The modulation of plasma cytokine levels may result from decreased NF-κB activity and reduced macrophage infiltration in the adipose tissue [63]. Also, a study in C57BL/6 mice fed HFD for 20 weeks, found a reduction in adipose tissue macrophage infiltration and serum TNF-α levels in response to high-dose resveratrol treatment (200 mg/kg body weight daily) [80]. Likewise, in a model of colitis, resveratrol (10 mg/kg body weight daily) prevented the expected increase in TNF-α and reduced the expected overexpression of COX-2, in addition to a significant decrease in NF-κB [109]. Finally, in 2013 Jimenez-Gomez Y. et al. published interesting data from a quasi-randomized trial investigating the effects of long-term resveratrol treatment in adult rhesus monkeys. Animals were divided into three groups receiving high fat/high sugar diet (HFS) + resveratrol, HFS + placebo, or standard diet. The dose of resveratrol was 40 mg twice daily the first year, followed by 240 mg twice daily for another year. Resveratrol has been proven to increase the SIRT-1 expression, decrease the NF-κB activation, and decrease the mRNA expression for IL-6, TNF-α, IL-1β, and adiponectin in the visceral adipose tissue [81].

In addition, resveratrol has anti-inflammatory effects in a variety of other rodent disease models. In an arthritis model induced by intra-articular LPS injections showed that subsequent injection of resveratrol in the affected knees reduced inflammation and preserved cartilage [47]. Another model of arthritis revealed similar effects of resveratrol on protection of cartilage, whereas in this model resveratrol did not inhibit synovial inflammation [48]. In cell culture resveratrol also possesses positive effects on chondrocytes [88,106].

In a mice model of inflammatory bowel disease induced by infection with *Toxoplasma gondii* resveratrol could decrease inflammation and improve survival [12], and similar findings have been presented in another model using dextran sulfate sodium to induce colitis. In this model resveratrol protected mucosa and reduced systemic inflammation [95].

In the asthmatic mouse model induced by ovalbumin sensitization of resveratrol reduced inflammatory response, mucus hypersecretion and airway hyperresponsiveness [101], and in another study using the same model resveratrol similarly reduced inflammation and also airway remodeling [130].

From these animal studies it seems reasonable to conclude that resveratrol in the majority of models holds the potential to modulate inflammatory pathways. The effects are quite consistent across animal species, across wide dosing ranges, and across various treatment durations. Suggested mechanisms primarily evolve around decreased NF-κB activation and possibly reduced macrophage infiltration in the adipose tissue. SIRT-1, AMPK, and eNOS are other possible mediators. Nonetheless, anti-inflammatory action is not an essential prerequisite for mediating physiological effects of resveratrol [122].

## 8. Anti-inflammatory effects of resveratrol in human clinical trials

Based on in vitro studies and animal models the pre-clinical evidence demonstrating anti-inflammatory effects of resveratrol via Sirt1 activation is substantial. It has been demonstrated that human tissues (muscle [105] and adipose tissue [120]) express Sirt1 and that the expression is regulated similarly to what have been demonstrated in rodents. On this basis clinical studies on effects of resveratrol in humans were initiated, however, demonstration of a clinical relevant anti-inflammatory effect of resveratrol has been more challenging than anticipated and most positive findings remain modest, yet significant. Thus, the clinical results are not as promising as the pre-clinical data. A small number of long-term intervention studies have demonstrated modest reductions in the degree of inflammatory parameters based on direct measurement of the plasma levels of well-known pro-inflammatory markers [14,142–144] (see Table 1 for a complete list).

**Table 1**
Human clinical trials investigating anti-inflammatory potential of resveratrol. Arranged alphabetically. White background denotes anti-inflammatory and/or anti-oxidant effect, gray denotes absence of anti-inflammatory effect. White/gray does not differentiate between potential physiological effects [8,13,16,35,107,162,170].

| Study | Design | Outcome |
|---|---|---|
| Agarwal et al. [2] | Double–blind randomized study.<br>400 mg resveratrol vs. placebo daily for 30 days.<br>N = 44 healthy subjects. | Significantly reduction in plasma level of IFNγ.<br>No change in TNFα, IL–6 or leptin.<br>Improved fasting insulin. |
| Bakker et al. [8] | Double–blinded, placebo–controlled cross–over.<br>Dietary mix containing resveratrol<br>N = 36 healthy overweight men. | Modulation of inflammation and oxidative and metabolic stress |
| Bhatt et al. [13] | Randomized study.<br>250 mg resveratrol vs. no resveratrol daily for 3 months.<br>N = 62 type 2 diabetic patients. | Anti–inflammatory effect not examined.<br>(Improved HbA1c) |
| Bo et al. [14] | Randomized, double–blinded, cross–over study<br>500 mg resveratrol vs. placebo for 30 days<br>N = 50 healthy adult smokers | Decrease in CRP and Total Antioxidant Status (TAS) |
| Brasnyo et al. [16] | Double–blind study.<br>5 mg x 2 resveratrol vs. placebo daily for 4 weeks..<br>N = 19 type 2 diabetic patients | Decreased oxidative stress.<br>(Improved insulin sensitivity) |
| Chachay et al. [28] | Randomized, double–blinded, placebo–controlled.<br>3000 mg resveratrol vs placebo for 8 weeks.<br>N = 20 overweight or obese men with NAFLD. | No anti–inflammatory or metabolic effects. |
| Crandall et al. [35] | Open–label study.<br>1, 1.5, or 2 g resveratrol daily for 4 weeks.<br>N = 10 subjects with impaired glucose tolerance. | No change in hs–CRP or adiponectin.<br>(improved postprandial glycemia) |
| Ghanim et al. [59] | Randomized study.<br>40 mg resveratrol vs. placebo daily for 6 weeks.<br>N = 20 lean and healthy subjects. | Significantly decreased plasma level of TNF–α and CRP.<br>Suppression of ROS generation.<br>Suppressed intranuclear binding of NFκB, TNFα and IL–6 in isolated mononuclear cells. |
| Gliemann et al. [61] | Randomized, double–blinded, placebo–controlled.<br>250 mg resveratrol vs. placebo. Both groups with concomitant high intensity exercise training.<br>N = 27 inactive men. | Resveratrol blunts the positive effect of exercise training on cardiovascular health. |
| Magyar et al. [108] | Double–blind study.<br>10 mg resveratrol vs. placebo daily for 3 months.<br>N = 40 post–infarction subjects | No change in HbA1c, TNFα or CRP. |
| McAnulty et al. [111] | Double–blinded cross–over study.<br>Various resveratrol doses + quercetin vs. placebo.<br>N = 14. | IL–8 and CRP were unaffected by treatment (in relation to acute exercise induced stress). |
| Poulsen et al. [124] | Double–blinded, randomized, placebo–controlled study.<br>1.5 g resveratrol vs. placebo daily for 4 weeks.<br>N = 24 obese subjects. | No change in hs–CRP, IL–6, TNF–α, leukocytes or MCP–1.<br>(No change in HOMA–IR) |
| Semba et al. [132] | Prospective cohort study.<br>N = 783 community–dwelling men and women 65 years or older. | Total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, or cancer or predictive of all–cause mortality. |
| Timmers et al. [143] | Double blind cross over study..<br>150 mg resveratrol vs. placebo daily for 30 days.<br>N = 11 obese subject | TNF–a, Leptin, leukocytes significantly decreased.<br>Tendency towards a reduction in CRP and IL–6. No change in adiponectin and IL–8.<br>Improved HOMA–IR.<br>Microarray analysis. |
| Tome–Carneiro et al. [145] | Triple–blind randomized study.<br>8 mg resveratrol vs. grape extract without resveratrol vs. placebo daily for 12 months.<br>N = 75 male participants | Significantly increased plasma level of adiponectin, and decreased PAI–1.<br>(tendency towards decreased CRP, no change in TNFα or IL6) |
| Voduc et al. [156] | Randomized, double–blinded cross–over study.<br>500–1000 mg resveratrol vs placebo for 4 weeks.<br>N = 13 healthy sedentary adults. | Inflammatory parameters unaffected. |
| Witte et al. [163] | Randomized study.<br>200 mg resveratrol vs. placebo daily for 26 weeks.<br>N = 26 overweight subjects. | Significantly reduction in TNF–α and IL–6 both in resveratrol and placebo group.<br>(Improved HbA1c) |
| Yoshino et al. [167] | Double blind randomized study.<br>75 mg resveratrol vs placebo daily for 12 weeks.<br>N = 29 non–obese subjects. | No change in leptin, CRP, IL–6 or adiponectin.<br>(no change in HOMA–IR) |
| Zahedi et al. [171] | Randomized study.<br>40 mg resveratrol vs. placebo daily for 6 weeks.<br>N = 20 healthy, exercising subjects. | Significantly decreased levels of TNF–α and IL–6. |

The first randomized clinical trial systematically examining metabolic and anti-inflammatory effects in human subjects was published in late 2011 by Timmers et al. [142]. In this placebo controlled, double blinded cross over study 11 obese but otherwise healthy male participants were treated with resveratrol and placebo for four weeks with an intervening wash out period. Significant albeit moderate improvements were recorded in various metabolic parameters like HOMA-IR index, lipid profile and in the context of the present review a small reduction in TNFα and a tendency toward lower IL6 level. Other studies have revealed anti-inflammatory potential based on genetic expression of cytokines obtained from white blood cells [145].

However, the topic is highly complex as an additional number of randomized clinical trials fail to demonstrate any anti-inflammatory effect of resveratrol [28,123,131,166] (see Table 1 for a complete list). In the work by Yoshino et al., published in October 2012, 29 non-obese postmenopausal women were treated with resveratrol (N = 15) or placebo (N = 14) for 12 weeks [166]. Exhaustive metabolic examination did not reveal any physiological effect nor anti-inflammatory potential. This corresponds with the outcome of our own clinical, randomized, placebo controlled, parallel group trial in which 24 obese but otherwise healthy male participants were randomized to resveratrol (N = 12) or placebo treatment for four weeks [123]. It should be kept in mind, however, that none of the studies referenced above have explicitly been designed to evaluate the anti-inflammatory potential as the primary outcome.

In a study by Agarwal et al. [2] there was no significant change in the degree of inflammation measured in plasma, however, plasma from the resveratrol treated subjects had a significant anti-inflammatory effect on human coronary artery endothelial cells. Microarray analysis on skeletal muscle biopsies has demonstrated that several genes related to inflammation are down-regulated upon resveratrol supplementation [142]. Finally, supplementation with 40 mg resveratrol pr. day for 6 weeks has shown to reduce the expression of TNF-α and IL-6, decrease the nuclear binding of NF-κB, and suppress the generation of ROS in isolated mononuclear cells [59]. Taken as a whole, the majority of clinical studies have been designed and conducted in order to evaluate diverse metabolic outcomes, and as illustrated in Table 1, in both groups of studies (yielding positive and negative outcomes), doses and treatment duration vary considerably. This renders direct comparison nearly impossible and reviewing highly complex. However, among the published studies, approximately half of the studies find an anti-inflammatory effect (and among these some find an improvement of insulin sensitivity) whereas the other half of the studies find no effect of resveratrol in clinical trials (Table 1).

The acute effect of resveratrol on oxidative stress and inflammation in response to intensively exercise has also been examined in a double-blind randomized cross-over study [110]. The subjects were treated with resveratrol (120 mg daily) or placebo for 6 days and on the seventh day before exercise the subjects were treated with double dosage of resveratrol (240 mg) or placebo. Resveratrol attenuated post-exercise increases in oxidative stress, however, no difference in the plasma levels of IL-8 or hs-CRP was found. In another study, resveratrol blunted the positive effect of exercise training, but unfortunately no inflammatory parameters were measured [61]. Finally, in a third exercise study, neither aerobic capacity nor inflammatory markers were affected by resveratrol treatment [155].

The differences between the results in the clinical trials may be attributable to differences in the study populations. Gender, age, dosage of resveratrol, length of the study, and the health status of the participants have been suggested to be factors influencing the results. Especially, a large difference has been found in the concentration and dosage of resveratrol among the clinical studies. No consensus exists on which concentration of resveratrol may be ideal in relation to anti-inflammatory effects. Furthermore, when comparing in vitro studies with human studies it has become clear that the concentrations of resveratrol used in in vitro studies are unattainable in human clinical studies. Based on human studies it has been shown that the absorption of resveratrol is high, however the bioavailability is low since it is rapidly metabolized [5,157]. Accordingly, it has been suggested that resveratrol may possess biological effects despite low plasma levels, partly mediated by bioactive metabolites of resveratrol [20,74].

## 9. Future perspectives

Future studies on the anti-inflammatory effect of resveratrol in a clinical setting should address the limitations mentioned above which affect our present understanding of the effects. The studies should have enough power to detect differences, pure high-quality resveratrol should be used, a range of doses should be tried, long-term studies should be designed (at least 4 month) and the participants should be well characterized. Only by adhering to such strict methodology the anti-inflammatory effect of resveratrol can be defined in humans. In addition, more studies on the metabolism of resveratrol and the possible effect of resveratrol metabolites need attention. In addition, the combined effect of resveratrol and piperine needs further studies, as piperine enhances the bioavailability of resveratrol probably by inhibiting enzymes involved in the metabolism of resveratrol hereby increasing the plasma level of resveratrol considerably [82]. However, in elevating the plasma levels of resveratrol safety studies urgently need to focus on potential side effects, and besides, it remains unknown whether or not elevated plasma levels of resveratrol result in more robust physiological clinical outcomes.

## 10. Conclusion

As demonstrated above, at the pre-clinical level, the evidence of resveratrol-mediated anti-inflammatory effect, resulting in beneficial metabolic outcomes, is substantial. In humans, the evidence of anti-inflammatory effect is sparse, and substantial conflicting data exist. About half of the studies find a modest anti-inflammatory effect whereas the other half are unable to detect any anti-inflammatory effect. The disagreeing results might result from differences in study design, dose regimens, study population etc. In order to clarify the role of resveratrol in relation to anti-inflammatory potential in humans suffering from various conditions associated with low-grade inflammation, more large-scale randomized studies with the anti-inflammatory effect as the primary outcome are urgently needed in well-characterized patient populations and using both high and low resveratrol dosage regime.

## Acknowledgements

The study was supported by the Toyota Foundation, Elvira and Rasmus Riisfort Foundation, Ejnar Danielsens Foundation and the AP Møller Maersk Foundation. The study is part of the research program LIRMOI Research Center (www.LIRMOI.com), which is supported by the Danish Council for Strategic Research (Grant 10-093499).

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