Review

The anti-obesity effects of resveratrol on the 3T3-L1 adipocytes

A systematic review

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Abstract: Obesity is a severe health problem worldwide due to its association with various adverse health consequences. The present study aims to evaluate the anti-obesity effects of resveratrol, as a natural polyphenol, on the 3T3-L1 adipocytes. PubMed, Scopus, ScienceDirect, Web of Sciences, and Google Scholar databases were searched up to March 2022 using relevant keywords. All original articles, written in English, evaluating the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes were eligible for this review. Initially, 4361 records were found in the electronic search databases. After removing duplicates and irrelevant studies according to the title and abstract, the full text of the 51 articles was critically screened and 38 in vitro studies were included in this review. Except for one case, all of these studies reported that different doses (ranged 1–200 μM) of resveratrol treatment have anti-obesity effects on 3T3L1 adipocytes through various mechanisms such as induction of apoptosis, a decrease of fat accumulation and adipogenesis, promotion of white adipocytes browning, inhibition of preadipocyte proliferation and consequent differentiation, and up-regulation of miRNA that involved in the antiadipogenic and triacylglycerol metabolism in white adipose tissue. The findings indicate that resveratrol has anti-obesity effects. Therefore, resveratrol treatment could be used to prevent and treat obesity and its related disorders. Well-designed randomized clinical trials with different doses of resveratrol are recommended to be performed on obese subjects.

Keywords: obesity, resveratrol, 3T3-L1, adipocytes

Introduction

Obesity is a severe health problem worldwide due to its association with various adverse health consequences [1]. The prevalence of obesity is increasing year by year. Based on the World Health Organization (WHO) report, more than 1.9 billion adults aged above 18 years were overweight, and 650 million of them were obese in 2016 [2, 3]. It contributes to various chronic diseases including hypertension, atherosclerosis, metabolic syndrome, stroke, impaired glucose tolerance, and specific forms of cancer [4, 5, 6].

Environment, genetic, and lifestyle susceptibility are involved in the increased risk of obesity [4] and lifestyle factors such as low physical activity and an unhealthy diet are important risk factors [7]. The imbalance between energy intake and expenditure leads to abnormal body fat accumulation or obesity [8]. At a cellular level, obesity is characterized by the increase in the number and size of adipocytes, which are differentiated from fibroblastic preadipocytes in adipose tissue [9]. 3T3-L1 adipocytes are a widely used in vitro model of white adipocytes that display features of multiple adipocyte lineages such as white and brown adipocytes [10]. Adipocytes play an important role in maintaining metabolic health through functioning not only as energy storage but also as an active endocrine organ, regulating whole-body metabolic homeostasis, energy consumption, and appetite via secreting beneficial adipokines such as leptin and adiponectin under normal conditions [11, 12]. Adipogenesis is a complex process that includes adipocyte maturation and preadipocyte proliferation in response to different stimuli and conditions [13]. An increase in adipocyte size or hypertrophy is the early stage of obesity and an increase in the number of adipocytes or hyperplasia is the later stage [14, 15]. Hypertrophy and hyperplasia lead to an abnormal increase in the levels of cytokines and hormones secreted from adipose tissue that result in pathological conditions [16, 17].

Uncontrolled adipogenesis and lipogenesis that lead to obesity may provide a potential target in the prevention and treatment of obesity and its related disorders [18, 19].

The therapeutic benefits of plant polyphenols have raised great interest in preventing and treating obesity. Resveratrol (3,5,40-trihydroxy-trans-stilbene), a natural polyphenol found in the skin of grapes, polygonum cuspidatum, and other plants, has anti-adipogenic activity and significant beneficial effects on energy metabolism and related metabolic diseases [20]. It has been widely studied for its bioactive properties, such as its antioxidative, anti-inflammatory, cardioprotective, neuroprotective, and anticancer effects [21, 22, 23]. It is suggested that resveratrol combats obesity in mice [24], and provides beneficial effects on obese persons [25]. Some recent studies indicated that resveratrol through effects on the expression of peroxisome proliferator-activated receptor γ (PPARγ) and sirtuin 1 inhibits adipogenesis and prevents the accumulation of triglycerides, respectively [26, 27]. Other cases reported that resveratrol induces apoptosis in the adipocytes [28]. However, no study comprehensively studied all the anti-obesity effects of resveratrol. To our best knowledge, there is no systematic review that evaluates the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes. Therefore, this study was carried out to summarize the present evidence of the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes.

Materials and methods

The protocol of this study was registered and approved by the Research Vice Chancellor and the Nutrition Research Center of Tabriz University of Medical Sciences (ethical code: IR.TBZMED.VCR.REC.1400.581). Moreover, the protocol of the study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the identification number CRD42022297169.

Data sources and search strategy

The present systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29] by focusing on the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes. This study was performed using the MeSH terms and other related keywords ("obesity" OR "overweight" OR "body weight" OR "adipose tissue" OR "fat body" OR "body fat" OR "adipocyte" OR "adipogenesis" OR "3T3-L1" OR "anti-obesity" AND "resveratrol") on the electronic databases including PubMed, ScienceDirect, Scopus, Web of Sciences, and Google Scholar (Search strategy is shown in the Electronic Supplementary Material [ESM] 1). Moreover, to ensure the inclusion of all eligible studies, the forward and backward citation was tracked for all of the included studies. The search was limited until March 2022.

Eligibility criteria and screening method

Articles published in the English language that examined the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes were included in the present study. The exclusion criteria were book chapters, conference abstracts, letters, posters, editorials, commentary, thesis, animal and human studies, and review articles. Moreover, articles that studied the effects of resveratrol combination with other components or on other functions of 3T3L1 adipocytes, and studies which their full-text was not available were excluded from this review.

After removing the duplicate studies using the EndNote software (Version X9; Thomson Reuters, Philadelphia, PA, USA), two independent investigators initially screened titles and abstracts of the searched studies based on the inclusion and exclusion criteria. In the second step, the full text of papers that were eligible was assessed and studies that had sufficient information or could meet the predefined criteria were included in this review.

Data extraction

The following data were extracted from selected studies: the first author's name, year of publication, type and dose of treatment, treatment duration, and findings concerning the anti-obesity effects of resveratrol on 3T3L1 adipocytes.

Assessment of articles' quality and risk of bias

The quality of the selected articles was assessed by the two independent authors using the guideline for assessing the quality of in vitro studies as suggested by Samuel et al. [30]. This guideline has 11 items including descriptions of scientific background, study purpose, study model justification, study design, cell culture condition, endpoint measurement, endpoint outcome, statistical method, dose- or concentration-response consideration, results interpreted and discussed, and study funding. Each item scored 1 and the overall score was 11. Studies were graded as poor, fair, and good quality if they met $\leq$4, 5 to 8, and $\geq$9 items, respectively [30, 31].

Results

Selection of studies

In the initial search, 4361 records were found in electronic search databases including PubMed (n=868), Scopus (n=2627), ScienceDirect (n=505), Web of Sciences (n=65),

and Google Scholar (n=296). After removing duplicates, 2786 articles remained for further screening. Firstly, articles were screened according to the title and abstract of those 2736 studies were excluded because did not reach the eligibility criteria. Finally, the full text of the 51 remained articles were critically screened of which 13 articles were excluded because studied the effects of resveratrol in combined with other components (n=1), studied the effects of resveratrol on the other functions of 3T3L1 adipocytes (n=11), and studied the effects of resveratrol in human subjects (n=1). No additional articles were found through forward and backward citation tracking of the eligible studies. Therefore, 38 studies were included in this review (Table 1). PRISMA diagram for the process of the search and selection of this review is presented in Figure 1.

Quality of the articles

All of the included studies had good quality ratings and overall score of 22, 12, and 4 studies was 11, 10, and 9, respectively. The quality assessment result was shown in ESM 2.

Characteristics of the included studies

As shown in Table 1, of 38 included studies 26 cases used resveratrol as treatment, and others used resveratrol derivatives such as trans-resveratrol, trans-resveratrol-3-O-sulfate, trans-resveratrol-3'-O-glucuronide, trans-resveratrol-4'-O-glucuronide, resveratrol encapsulated lipid nanocarriers, resveratrol encapsulated liposomes, trans-resveratrol-4 -O-glucuronide, trans-resveratrol-3-O-sulfate, pinostilbene hydrate (a methylated resveratrol derivative), resveratrol-amplified grape skin extracts, red grape, Vitisin A (a resveratrol tetramer), 3,5-dimethoxy (4-methoxyphenyl) benzamide, 4-[2-(3,5-dimethoxy phenyl) vinyl] pyridine (DPVP), resveratrol analog ((E)-1,2-di (3,5-dimethoxy phenyl) ethene), and resveratrol in dimethyl sulfoxide. Doses of resveratrol that were used in included studies ranged from 1 to 200 μM and treatment duration ranged from 15 hours to 8 days.

Ninety-seven percent of our included studies revealed that resveratrol has anti-obesity effects through various mechanisms mentioned following. Seven cases evaluated the effects of resveratrol treatment on apoptosis of 3T3L1 adipocytes except for one study, all of them demonstrated that resveratrol treatment induced apoptosis. One study that reported resveratrol does not cause apoptosis but showed resveratrol decreased lipid accumulation in 3T3L1 adipocytes. Twelve studies assessed the effects of resveratrol on adipocyte differentiation 11 cases of them revealed that resveratrol inhibited 3T3L1 adipocyte differentiation. All five studies that evaluated the effects of resveratrol treatment on the browning of 3T3L1 adipocytes indicated that resveratrol enhanced the browning of white adipocytes. Two studies investigated the effects of resveratrol treatment on microRNA (miR) that involved in the antiadipogenic and demonstrated that resveratrol has an inhibitory effect on adipogenesis through miR-155 up-regulation and expression of miR-129, miR-328-5p, and miR-539-5p increased after resveratrol treatment that is relevant for triacylglycerol metabolism in white adipose tissue. Eleven studies showed that resveratrol treatment prevents lipid accumulation and adipogenesis and one study reported that resveratrol inhibits lipolysis in 3T3L1 adipocytes. Noriega-González et al. also indicated that resveratrol treatment decreased lipid content consequently declination of mitochondrial activity (Table 1).

Discussion

All the included studies revealed that different doses (1-200 μM) of resveratrol have anti-obesity effects on 3T3L1 adipocytes through induction of apoptosis, inhibition of preadipocytes proliferation and differentiation, promotion of browning of white adipocytes, up-regulation of miRNA that involved in the antiadipogenic and triacylglycerol metabolism in white adipose tissue, prevention of fat accumulation and adipogenesis, and inhibition of lipolysis, except for one case. The previous meta-analysis evaluated the effects of resveratrol on weight loss and reported that its administration significantly reduced body weight, waist circumference, body mass index, and fat mass [32]. Recent experiments in animal models also showed that resveratrol significantly decreased body weight [33]. The effect of resveratrol in these models was similar to that of a calorie restriction regimen. Moreover, it also improved mitochondrial function which is compromised in several metabolic diseases [34]. Resveratrol concentrations applied in the cellular experiments ranged between 5 μM and 100 μM; the most common concentration was 50 μM [35, 36]. These concentrations in the in vivo setting were potentially unachievable. Pharmacokinetic studies showed that after repeated dosing of 0.5–5.0 g/day for 28 days, the mean plasma concentration of resveratrol across the four dose levels ranged from 0.04 to 0.55 nmol/mL (0.04–0.55 μM) [37]. Human studies assessing the efficacy of resveratrol are emerging and the optimal dose of resveratrol in clinical practice is an unresolved issue [35].

Several studies showed that resveratrol treatment induced apoptosis in 3T3L1 adipocytes. Chen et al. revealed that resveratrol treatment could affect the checkpoints in S-phase (when the DNA synthesis occurs), resulting in decelerated cell cycle progression [28]. They also found that resveratrol treatment increased the dose-dependent loss

Table 1. Characteristics of the studies that examined the anti-obesity effects of resveratrol on the 3T3-L1 adipocytes

Study ID	Type of resveratrol	Dose of resveratrol	Treatment duration (hour/day)	Findings*	Mechanism
Aranaz et al. 2019 [52]	Resveratrol	50 μM	24 and 48 h	Resveratrol inhibited lipid accumulation along the whole process of differentiation.	Resveratrol would interact with specific residues of the receptor, which could determine their potential anti-adipogenic activity during the early stages of the differentiation.
Ahmed et al. 2016 [53]	Red grape	30 μM	72 h	Resveratrol had no antiadipogenic effect.	–
Bruckbauer et al. 2012 [54]	Resveratrol	200 nM	4–24 h	Does not effect on fatty acid oxidation only had a weak effect on Sirt1 and Sirt3 activity.	–
Chung et al. 2021 [55]	Pinostilbene hydrate (PH), a methylated resveratrol derivative	12.5, 25, 50, and 100 μM	48 h	Inhibited lipid and TG accumulation without cytotoxicity.	PH decreased the expression of adipogenesis-related transcription factors, such as PPAR, C/EBP, SREBP-1c, CREB, and FABP4, and phosphorylation of MAPK and AKT, and increasing the phosphorylation of AMPK and ACC, and decreasing the expression of FAS and FABP4.
Chen et al. 2012 [28]	Resveratrol in dimethyl sulfoxide	20, 40, 80 mM	24, 48, 72, 96 h	Resveratrol induced apoptosis.	Resveratrol caused S-phase arrest to inhibit cell proliferation, increased the LDH leaking ratio, activated the mitochondrial signaling with decreases in the MMP, Cyt C release, the activation of caspase 9 and caspase 3, and increased the protein level of SIRT1.
Chen et al. 2015 [56]	Resveratrol	25, 50, 100 μM	24 h	Resveratrol induced apoptosis.	Resveratrol activated the mitochondrial apoptotic signaling pathway with the decrease in the MMP, and the activation of caspase 3, elevated phosphorylation level of AMPKa, and reduced level of phosphorylation of AKT.
Chang et al. 2015 [19]	Resveratrol	Ranged from 0.03 to 100 μM	24 and 72 h	Resveratrol treatment (1 to 10 μM) inhibited the capacity of 3T3-L1 cells differentiated into mature adipocytes.	Resveratrol treatment (1 to 10 μM) downregulated PPARγ and perilipin protein expressions in differentiated adipocytes and inhibited TNFα-induced lipolysis in mature adipocytes.
Chen et al. 2011 [57]	Resveratrol	10, 20, 40, 80 μmol/L	During the differentiation process.	Resveratrol inhibits cell differentiation.	Resveratrol increased the phosphorylation and activation of AMPKa in a dose-dependent manner,
Eseberri et al. 2017 [58]	Trans-resveratrol, trans-resveratrol-3-O-sulfate, trans-resveratrol-3'-O-glucuronide, and trans-resveratrol-4'-O-glucuronide.	25 μM	During differentiation	Prevented lipid accumulation and adipogenesis.	Modified miR-155 and decreased gene expression of CREB1 and SREBf1.

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Table 1. (Continued)

Study ID	Type of resveratrol	Dose of resveratrol	Treatment duration (hour/day)	Findings*	Mechanism
Gracia et al. 2016 [59]	Resveratrol	30 mg kg^{-1} d^{-1}	6 weeks	Inhibited de novo lipogenesis in WAT.	Increased miR-129, miR-328-5p, and miR-539-5p, modulated target genes relevant for TG metabolism in WAT (PPARγ and HSL), reduced the SREBP1 protein expression, and FASN gene expression.
Hu et al. 2014 [60]	Resveratrol	1 and 10 μM	7 days	Resveratrol enhanced 3T3-L1 adipocyte differentiation.	Resveratrol activated GR and induced cell death when used at doses above 10 μM in differentiating cells.
Hwang et al. 2010 [61]	Resveratrol analogue ((E)-1,2-di (3,5-dimethoxyphenyl) ethene)	12.5 and 25 μM	48 h	The tested analogue potently inhibits the differentiation of 3T3-L1 adipocyte to a greater degree.	Downregulated the expression of fatty acid metabolism-related proteins such as FAS and ACC.
Hwang et al. 2012 [62]	Derivative of resveratrol (4-[2-(3,5-dimethoxyphenyl) vinyl] pyridine)	12.5, 25, 50 μM	48 h	Exerted inhibitory effects against 3T3-L1 adipocyte differentiation.	–
Hwang et al. 2014 [63]	3,5-dimethoxy (4-methoxyphenyl) benzamide	12.5, 25, 50 μM	8 days		Suppressed the hormone-induced differentiation of 3T3-L1 cells, reduced the protein expression of FAS and ACC, and decrease the PPAR-γ transcription activity.
Hsu et al. 2006 [64]	Resveratrol	100 μM	72 h	Resveratrol inhibited the cell population growth.	–
Imamura et al. 2017 [12]	Resveratrol	0, 25 or 50 μM	3 days	Resveratrol dose dependently enhanced Sirt1 expression and reduced TG accumulation.	Enhanced expressions of genes involved in FFA uptake (PPARγ and LPL) and in β-oxidation regulation (PGC1-α and CPT1a).
Kwon et al. 2012 [65]	Resveratrol	20–100 μM	16, 24 h	Resveratrol impaired the progression of MCE.	By suppressing the cell cycle entry of preadipocytes to G2/M phase and expression of cell cycle regulators cyclin A and cyclin dependent kinase 2. Inhibited insulin signaling pathway in the early phase of adipogenesis and IR activity that this is likely through a direct physical interaction between resveratrol and IR.
Kang et al. 2012 [17]	Resveratrol	0, 10, 20, and 40 μmol/L	6 days	Inhibited the cell proliferation and lipid accumulation in adipocyte	Decreased GPDH activity, the protein expression of C/EBPα and β, PPARγ, and FABP4, and the activity of MMP-2, and-9.
Kang et al. 2018 [66]	Resveratrol	40 mM	After 7 days of differentiation	Increased expression of browning markers.	Elevated expression of browning markers PGC-1a, PRDM16, and UCP1 as well as SIRT1-mediated activation of AMPK to pAMPK.

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Table 1. (Continued)

Study ID	Type of resveratrol	Dose of resveratrol	Treatment duration (hour/day)	Findings*	Mechanism
Kim et al. 2008 [67]	Vitisin A, a resveratrol tetramer	1, 5, 10, 25, 50 μM	15 h	Inhibited adipocyte differentiation.	Vitisin A decreased fat accumulation and PPARγ expression, inhibited preadipocyte proliferation and consequent differentiation, blocked the cell cycle at the G1-S phase transition, causing cells to remain in the preadipocyte state, increased p21 expression, and reduced the Rb phosphorylation level.
Lasa et al. 2012 [68]	Resveratrol, trans-resveratrol-4′-O-glucuronide and trans-resveratrol-3-O-sulfate.	1, 10, or 25 μM	Pre-adipocytes: 0 to day 8 Mature adipocytes: 24 h on day 12	Reduced TG content in maturing pre-adipocytes at 25 μM.	Reduced C/EBPβ mRNA levels, C/EBP-α, PPAR-γ, and LPL expression. In mature adipocytes increased ATGL, CPT-1, SIRT-1, and PGC1-α expression. Trans-resveratrol-3-O-glucuronide reduced mRNA levels of FASN and increased HSL and Sirt1 mRNA levels.
Li et al. 2016 [69]	Resveratrol	50, 100 μM	0–10 days	Resveratrol inhibited lipogenesis in differentiating adipocytes.	Inhibited ACC and insulin-induced signaling via Akt, and maintained signaling via AMPK.
Li et al. 2020 [2]	Resveratrol	5, 10, 20 μM	24, 48 h	Reduced fat content in adipocytes in a dose-dependent manner.	Decreased gene expressions related to lipogenesis (PPARγ, C/EBPα, and SREBP1c), increased genes expression related to lipolysis (ATGL, HSL, and LPL) and increased mRNA and protein levels of Sirt1.
Liu et al. 2020 [70]	Resveratrol	10, 20, 40 μM	6–8 days	Resveratrol induced the brown fat-like phenotype.	Activated protein expressions of brown adipocyte-specific markers, such as PPAR-γ, PGC-1α, and UCP1, and mTOR.
Mercader et al. 2011 [71]	Resveratrol	5, 10, 25, 50, 100 μM	24 h	Increased oxidative capacity and reduced lipogenesis, while down-regulating two putative insulin resistance factors.	–
Mosqueda-Solís et al. 2017 [72]	Resveratrol	1, 10, 25 μM	8 days	At 25 μM lipid accumulation was reduced.	–
Mitterberger et al. 2013 [73]	Resveratrol	100 μM	0, 1, 2, 4 days	Resveratrol prevents clonal expansion and terminal adipogenesis in 3T3-L1 preadipocytes.	Inhibited the AKT and MAPK signaling, downregulation of cyclin D1 expression, abrogation of Rb hyperphosphorylation, and subsequent inhibition of cell cycle reentry and clonal expansion, inhibited terminal adipogenesis at the level of PPAR-γ2 expression and activity.
Noriega-González et al. 2015 [74]	Resveratrol	25, 50 μM	48 h	Decreased lipid content.	Declined the mitochondrial activity.

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Table 1. (Continued)

Study ID	Type of resveratrol	Dose of resveratrol	Treatment duration (hour/day)	Findings*	Mechanism
Park et al. 2008 [75]	Resveratrol	100 μM	3 days	Resveratrol does not cause apoptosis but decreased lipid accumulation.	–
Patel et al. 2013 [46]	Resveratrol	25 μM	2–8 days	Resveratrol increases apoptosis and inhibits adipogenesis.	With disruption of PKCδ alternative splicing during 3T3L1 differentiation.
Rayalam et al. 2008 [76]	Resveratrol	25, 50, 100, 200 μM	48 h	Resveratrol induced apoptosis, decreased lipid accumulation in maturing preadipocytes, and decreased cell viability.	Resveratrol down-regulated the expression of PPARγ, C/EBPα, SREBP-1c, FAS, LPL and up-regulated the expression of genes regulating mitochondrial activity (SIRT3 and UCP1) and HSL.
Santos et al. 2014 [77]	Resveratrol	10, 20 or 30 μg/mL	–	Prevented lipid accumulation and adipogenesis.	Modulated the expression of C/EBPα, FAS, LPL, and PPARγ2 and induced the expression of UCP1.
Serrano et al. 2020 [78]	Resveratrol	5, 10, 25 μM	24 h	Direct effects on the DNA methylation machinery and favoring browning features.	Induced the TFAM and Ucp1 gene expression, increased the mitochondrial to nuclear DNA ratio, and increased mitochondrial oxidative metabolism.
Yang et al. 2008 [79]	Resveratrol	50, 100 μM	24 and 48 h	Resveratrol suppressed intracellular lipid accumulation, decreased viability, and increased apoptosis.	–
Zu et al. 2018 [80]	Resveratrol encapsulated lipid nanocarriers, and resveratrol encapsulated liposomes.	5, 10, 20 μM	15 h	Enhanced browning of white adipocytes.	Induced UCP1 mRNA and decreased white specific marker insulin growth factor binding protein 3 expression.
Zhao et al. 2016 [81]	Resveratrol	10 μmol/L	16 h	Inhibited lipolysis and reduced FFAs influx and DAG Accumulation.	Prevented the PKA/HSL activation by decreasing the accumulation of cAMP.
Zhang et al. 2012 [82]	Resveratrol-amplified grape skin extracts	0, 30, 60, 120, 250, 500, and 1000 μg/ml	24 and 48 h	Decreased lipid accumulation and glycerol-3-phosphate dehydrogenase activity without affecting 3T3-L1 cell viability.	Attenuated expression of key adipogenic transcription factors including PPAR, C/EBP, and their target genes (FAS and LPL).

ACC: Acetyl-CoA carboxylase; AMPKa: Adenosine monophosphate-activated protein kinase a; ATGL: Adipose triglyceride lipase; AKT: Protein kinase B; Cyt C: Cytochrome C; C/EBPα: CCAAT/enhancer-binding protein alpha; CREB: cAMP-response element binding protein; CPT1a: Carnitine palmitoyl-transferase 1a; DAG: Diacylglycerol; FAS: Fatty acid synthase; FABP4: Fatty acid binding protein; FFA: Free fatty acid; HSL: Hormone sensitive lipase; IR: Insulin receptor; GR: glucocorticoid receptor; LPL: Lipoprotein lipase; LDH: lactate dehydrogenase; MMP: mitochondrial membrane potential; MCE: Mitotic clonal expansion; mTOR: Mammalian target of rapamycin; MAPK: Mitogen-activated protein kinase; PGC1-α: Peroxisome proliferator–activated receptor gamma coactivator-1 alpha; PPARγ: peroxisome proliferator-activated receptor γ; PKCδ: Protein kinase C δ; Rb: Retinoblastoma protein; SIRT1: Silent information regulator sirtuin 1; SREBP-1c: Sterol regulatory element-binding transcription factor 1; TG: Triglyceride; TFAM: Mitochondrial transcription factor A; UCP1: Uncoupling protein 1. *All of findings are significant.

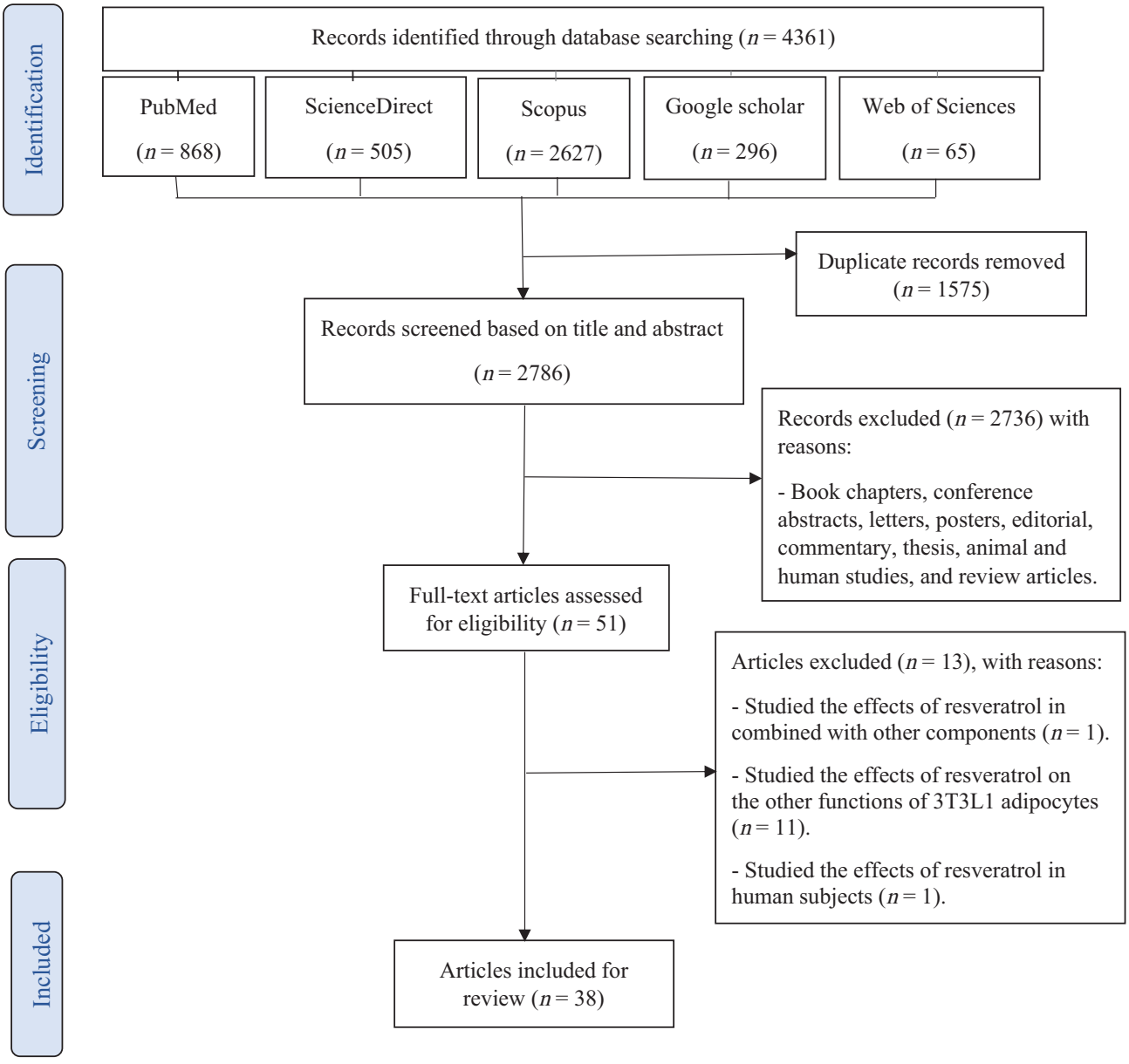

Figure 1. PRISMA diagram for the process of the search and study selection.

of mitochondrial membrane potential (MMP) indicating the initiation of cellular apoptosis. These results suggest that resveratrol has novel effects on the proliferation and apoptosis of murine 3T3-L1 preadipocytes [28]. Silent information regulator sirtuin 1 (SIRT1) protein operates as a nicotinamide adenine nucleotide (NAD+)-dependent histone deacetylase that is partially localized in the cytoplasm in certain cell lines [38], with cytoplasm-localized SIRT1 leading to increased sensitivity to apoptosis. The apoptosis enhanced by cytoplasm-localized SIRT1 is dependent on caspases [39]. Activating caspases such as types 9 and 3 leads to promoting apoptosis [40]. Chen et al. showed that the protein level of SIRT1 was increased in resveratrol-induced apoptotic cells. In addition, the protein levels of cytochrome C (Cyt C) (During cell apoptosis Cyt C is released into the cytoplasm) and cleaved caspases (caspase-9 and caspase-3) were suppressed with SIRT1 siRNA, indicating that enhanced apoptosis by SIRT1 may be dependent on the regulation of caspases activity [28].

Adenosine monophosphate-activated protein kinase (AMPK) is a eukaryotic heterotrimeric serine/threonine kinase and a central sensor of cellular energy. AMPK activation has been shown to induce apoptosis in human cancer cells [41, 42] and it can also enhance oxidative-stress-induced apoptosis in mouse neuroblastoma cells [43]. These findings indicated that resveratrol also induced

apoptosis in 3T3-L1 adipocytes by increasing the expression of SIRT1, which could activate AMPK and suppress protein kinase B (AKT) activity and further decrease the expression of survivin [28]. Survivin protein inhibits cell apoptosis by blocking the activation of caspases [44]. The AMPK activation reduces cell survival by inhibiting survivin expression [45] and the AKT-survivin pathway also may mediate resveratrol-induced apoptosis in preadipocytes [28]. AKT and AMPK pathways promote the release of Cyt C from mitochondria and the activation of caspase-9 and caspase-3, which would finally induce apoptosis in 3T3-L1 preadipocytes [28]. Patel et al. [46] reported that resveratrol increased apoptosis and affected adipogenesis in 3T3L1 cells along with modulating protein kinase C delta (PKCδ) splice variant expression which as a serine/threonine kinase, plays a central role in apoptosis. PKCδI promotes apoptosis while PKCδII has an anti-apoptosis effect [47]. Also, the lactate dehydrogenase (LDH) leaking ratio, a marker for apoptotic cells, increased in resveratrol treatment adipocytes. Therefore, resveratrol induced apoptosis through S-phase arrest to inhibit cell proliferation, increasing the LDH leaking ratio, activating the mitochondrial apoptotic signaling pathway with decreases the MMP, increasing the expression of SIRT1, Cyt C release, the activation of caspases 3 and 9, elevating phosphorylation and activation of AMPKa, reducing the phosphorylation level of AKT, and disruption of PKCδ alternative splicing during 3T3L1 differentiation.

Adipose tissue is classified into white, beige, and brown based on their distinct origins, metabolic functions, and anatomical distributions [48, 49]. Brown adipocytes can occur after thermogenesis stimulation at specific anatomical sites of white adipose tissue (WAT), defined as WAT browning [50]. Brown adipose tissue (BAT) can disperse stored energy as heat through the activation of brown-fat-specific uncoupling protein 1 (UCP1), which can uncouple adenosine triphosphate (ATP) production from mitochondrial respiration [51]. It has been reported that enhancement of BAT formation and function in WAT is a promising therapeutic approach to combat obesity and reduce associated comorbidity [2, 51]. Therefore, exploring new molecules for promoting browning is essential, as then developing novel treatments for severe obesity [2]. All of our included studies that evaluated the effects of resveratrol on 3T3L1 browning indicated that resveratrol treatment promoted WAT browning. Findings demonstrated that resveratrol treatment caused elevating expression of browning markers such as peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a), PR domain containing 16 (PRDM16), and UCP1 as well as SIRT1-mediated activation of AMPK to pAMPK, reduction of gene expressions related to lipogenesis PPARγ, CCAAT/enhancer-binding protein alpha (C/EBPα), and sterol regulatory element-binding transcription factor 1 (SREBP-1c)), enhancement of genes related to lipolysis (adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL)), activation of mammalian target of rapamycin (mTOR), induction of mitochondrial transcription factor A (TFAM) gene expression, the increase in the mitochondrial to nuclear DNA ratio, and increased mitochondrial oxidative metabolism.

The studies also showed that resveratrol treatment has anti-obesity effects through various other mechanisms as follows: inhibiting the 3T3-L1 adipocyte differentiation, attenuating triglyceride accumulation associated with upregulation of carnitine palmitoyl-transferase 1a (CPT1a), inhibiting tumour necrosis factor α (TNFα)-induced lipolysis in mature adipocytes, inhibiting the insulin signaling pathway in the early phase of adipogenesis and the insulin receptor (IR) activity (this is likely through a direct physical interaction between resveratrol and IR), activating glucocorticoid receptor and PPARγ, downregulation of the expression of fatty acid metabolism-related proteins such as fatty acid synthase (FAS), lipoprotein lipase (LPL), acetyl-CoA carboxylase (ACC), SREBP1, and PPAR γ and perilipin protein in differentiated adipocytes, decreasing glycerol-3-phosphate dehydrogenase (GPDH) and MMP-2 and -9 activity, reducing the protein expression of C/EBP and fatty acid binding protein (FABP4), blocking the cell cycle at the G1-S phase transition, causing to remain cells in the preadipocyte state, increasing p21 expression and the Rb phosphorylation level, downregulation of cyclin D1 expression, attenuating the expression of cAMP-response element binding protein (CREB), and increasing miR-129, miR-328-5p, and miR-539-5p (target genes relevant for triacylglycerol metabolism in WAT) (Table 1).

The most notable limitation of the present systematic review was the considerable heterogeneity between the included studies regarding resveratrol dose, duration of investigations, and treatment types. Thus, using a different dose and intervention duration could be a possible explanation for the non-significant results of one included study [54]. Moreover, different bioavailability of used resveratrol might impact their results. Nevertheless, this study has almost comprehensively summarized all the mechanisms associated with the anti-obesity effects of resveratrol in 3T3L1 adipocytes.

In conclusion, except for one case, all studies included in this systematic review revealed that resveratrol has anti-obesity effects on 3T3L1 adipocytes through induction of apoptosis of 3T3L1 adipocytes, inhibition of 3T3L1 preadipocytes proliferation and consequent differentiation, promotion of browning of white adipocytes, up-regulation of miRNA involved in the antiadipogenic and triacylglycerol metabolism in white adipose tissue, prevention of fat accumulation and adipogenesis, and inhibit lipolysis in 3T3L1

adipocytes. Therefore, the current study indicates that resveratrol could prevent obesity and its related disorders. It is recommended that well-designed randomized clinical trials with different doses of resveratrol and various treatment duration be performed on obese subjects to determine the effects of resveratrol in treating obesity.

Electronic Supplementary Material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000784

ESM 1. The anti-obesity effects of resveratrol on 3T3-L1 adipocytes: A systematic review: Method of the database search strategy using PubMed, Scopus, ScienceDirect, Google Scholar, and Web of Sciences (PDF).

ESM 2. Quality assessment of included studies (PDF).

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Conflict of interest
The authors declare that there are no conflicts of interest.

Authors' contributions
Both authors have made substantial contributions to the conception and design of this study. RMG and Dr. MR conducted the search and data extraction and the first draft of the manuscript was written by RMG, and Dr. MR commented on previous versions of the manuscript. Both authors read and approved the final content.

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