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RESEARCH ARTICLE

RESVERATROL STABILIZES CYTOSOLIC ß-CATENIN THROUGH THE ACTIVATION OF THE THERMOGENIC CASCADE

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ABSTRACT

Purpose: Resveratrol is a polyphenolic compound that has been shown to stimulate fatty acid oxidation and increase the expression of genes associated with thermogenic processes. Therefore, it is important to investigate the effects of resveratrol beyond intracellular thermogenic pathways to determine side effects at the cellular level. The aim of this study was to evaluate the effect of resveratrol on intracellular ß-catenin, in addition to its thermogenic effect.
Materials and Methods: The effect of resveratrol on thermogenic genes such as SIRT1 gene, UCP1, PGC1α, PRDM16 and ß-catenin gene expression levels was analyzed by RT-PCR. The cytosolic ß-catenin level analyzed by western-blot.
Results: The effect of resveratrol on thermogenic genes such as SIRT1 gene, UCP1, PGC1α, PRDM16 and ß-catenin gene expression levels was analyzed by RT-PCR. The cytosolic ß-catenin level analyzed by western-blot. We found that the expression levels of UCP1, PPARγ, PRDM16 were increased by SIRT1 protein activated by resveratrol, but it had no effect on ß-catenin mRNA expression. While ß-catenin did not change at the mRNA level, we found that ß-catenin increased at the protein level in the cell independently of the canonical Wnt pathway.
Conclusion: Our results suggest that resveratrol, which is widely used as a supplement, may also act on different signaling pathways in the cell.

Keywords: Resveratrol, obesity, thermogenesis, β-Catenin

INTRODUCTION

Obesity is a metabolic disease that is defined by the abnormal accumulation of fat within the body, caused by a disruption in energy homeostasis. In recent years, novel alternative treatments have been introduced with the objective of controlling the global incidence of obesity (1). One such application is the stimulation of thermoregulation in adipose tissue. Thermogenesis is defined as the production of heat in warm-blooded animals. In thermogenesis, energy is distributed as heat in brown adipose tissue (2). In addition to the increase in physical activity for the purpose of energy expenditure in the context of obesity, thermogenesis represents a physiological process that exerts a profound effect on energy metabolism. The activation of thermogenic adipocytes has been demonstrated to exert a beneficial impact on metabolic health in murine models of obesity, diabetes, and atherosclerosis. Nevertheless, it has been demonstrated that the activity of thermogenic adipocytes is markedly

diminished in individuals with obesity and in the elderly (3).

Uncoupling protein 1 (UCP1), also known as thermogenin, is located in the inner mitochondrial membrane of brown adipose tissue. It dissipates the electrochemical proton gradient generated during oxidative phosphorylation, allowing heat to be released instead of ATP synthesis. This process is called thermogenesis (4). Although beige adipose tissue has a developmental origin similar to that of white adipose tissue, it has been observed that when induced, it can exhibit morphological features and functions specific to brown adipose tissue, accompanied by an increase in UCP1 activity (5). The aim of the studies conducted is to determine the factors that can be used to increase the thermogenic capacity of white adipose tissue, thereby initiating the transformation process into brown adipose tissue. One of the factors used in adipose tissue transformation is dietary bioactive compounds. Dietary bioactive compounds, which are secondary metabolites, influence plant growth and development. Epidemiological studies have shown that bioactive compounds have beneficial effects on chronic diseases such as obesity and cancer. Dietary bioactive compounds can be classified into the following broad categories: phenolics, alkaloids, nitrogen-containing compounds, phytosterols, and carotenoids. Of these phytochemical groups, phenolics have been the most extensively studied (6). Resveratrol, a natural polyphenolic compound, has been documented in the literature to exert an anti-obesity effect by stimulating fatty acid β-oxidation and decreasing the expression of adipogenic transcription factors while increasing the expression of thermogenic genes (7).

Animal studies have shown that resveratrol is able to mimic the effects of caloric restriction through the activation of the SIRT1 (Sirtuin 1) protein, which plays a pivotal role in the regulation of cellular homeostasis and mitochondrial biogenesis (8). SIRT1 is a nicotinamide adenine dinucleotide (NAD) dependent protein deacetylase and a major metabolic regulator in various metabolic tissues, including pancreas, liver, and adipose tissue (9). Resveratrol binds directly to the amino-terminal region of SIRT1, thereby allosterically activating it (10). SIRT1 has both physical and functional interactions with PPARγ (peroxisome proliferator-activated receptor-γ) and its cofactor peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). It serves as a master regulator of mitochondrial biogenesis and oxidative metabolism in brown fat and other cell types, including skeletal muscle. In muscle and brown adipose tissue, SIRT1-mediated deacetylation of PGC-1α has been shown to be associated with increased mitochondrial activity and thermogenesis (11). PGC-1α, a coactivator of PPARγ, primarily induces UCP1, thereby initiating conversion to beige adipocytes (12). Another protein associated with thermogenesis in beige adipose tissue is PR domain containing 16 (PRDM16). Activation of SIRT1/PGC-1α has been shown to increase the expression of PRDM16 as well as UCP1 (13). Furthermore, a substantial body of experimental evidence suggests that stimulation or stabilization of PRDM16 expression may be a promising avenue for the treatment of obesity (14). It has been proposed that the transcriptional complex involving PRDM16 may stimulate thermogenic activity independently of PGC-1α (15).

The Wnt/β-catenin signaling pathway plays a central role in the regulation of numerous genes that control cell differentiation and proliferation processes. Upon binding of Wnt ligands to their receptors, ß-catenin is rescued from degradation and translocated to the nucleus, where it interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to regulate the expression of target genes (16). The role of the Wnt/ß-catenin pathway in obesity and thermogenesis has been the subject of limited studies, although it has been reported to be effective in preadipocyte differentiation. Activation of the Wnt/ß-catenin pathway has been shown to inhibit adipogenesis by preventing the induction of C/EBPα and PPARγ, the key regulators of preadipocyte differentiation (6). The role of β-catenin in the inhibition of adipogenesis is significant. The intracellular changes in β catenin, a negative regulator of adipogenesis, in the presence of resveratrol, which has been reported to directly stimulate thermogenesis, remain poorly understood. Existing studies are primarily concerned with pain or cancer (17).

The present study aimed to examine the alterations in SIRT1 expression, thermogenic gene expressions, and β-catenin levels following the differentiation of preadipocytes into mature adipocytes in the presence/absence of resveratrol. Our objective was to elucidate the effect of resveratrol on β-catenin expression, which may affect various intracellular mechanisms while activating the thermogenic

pathway. Our findings will contribute to future studies in understanding the role of resveratrol in regulating β-catenin and its associated intracellular mechanisms.

MATERIALS AND METHODS

Cell Culture and Differentiation

The 3T3-L1 (RRID: CVCL_0123) cells were incubated in Dulbecco's modified Eagle's medium (DMEM) containing fetal bovine serum (10%) and penicillin/streptomycin (1%) at 37°C in a 5% CO_2 incubator. The Reed and Lane protocol was employed for the differentiation of preadipocytes (18). The cells were incubated for 48 hours in an adipogenic medium containing 10 µg/mL insulin, 0.5 µM dexamethasone, and 0.5 mM IBMX (3-isobutyl-methylxanthine). Subsequently, the medium was replaced every two days until the cells had differentiated into mature adipocytes, which was achieved by adding a medium containing 10 µg/ml insulin. Following differentiation, the cells were treated with resveratrol at concentrations of 20 µM and 50 µM for 48 hours. The control group was treated with dimethyl sulfoxide (DMSO).

Real-time Polymerase Chain Reaction

RNA isolation kit (New England Biolabs #T2010S) was used for total cell RNA extraction. For complementary DNA synthesis, a complementary DNA synthesis kit (Fermantas K1612) was used using 20µl reaction volume. Real-Time PCR reaction was performed on an RT-PCR instrument (QiaGen Rotor-GeneQ) using SYBR Green PCR mix (Luna 2X qPCR mix). The Real-Time PCR thermal profile was 95°C for 15 seconds for denaturation, 60°C for 30 seconds for primer binding and 72°C for the elongation step. During the reactions, β-actin gene was used as a control gene. The sequences of the primers of the genes used in the reactions;

- ß-Catenin- F: 5'GCTAGTGGTGGACCCCAAGC3'
- ß-Catenin-R: 5'GGAGACCTTCCATCCCTTCCTTCCTG3'
- UCP-1- F: 5'CCTGCCTCTCTCTCGGAAACAA3'
- UCP-1- R: 5'GTAGCGGGGGGTTTGATCCCAT3'
- SIRT1- F: 5'TCGTGGAGACATTTTTAATCAGG3'
- SIRT1- R: 5'CCACTTGCCATCATGAAGC3'
- PPARγ- F: 5'GGAAGACCACTCGCATTCCTT3'
- PPARγ- R: 5'GTAATCAGCAACCATTGGGTCA-3'
- PGC1α- F: 5'TGTTCCCGATCACCATATATTCC3'
- PGC1α- R: 5'GGTGTCTGTAGTGGCTTGATTC3'
- PRDM16- F: 5'CCCCACATTCCGCTGTGAT3'
- PRDM16- R 5'CTCGCAATCCTTGCACTCA3'
- ß-Actin- F: 5'CAAGAAGAAGAAGCCCCCCTGA3
- ß-Actin- R: 5'AAGTGGTGGCTGGCTGAGGTTGTC3'.

Dosage information

Resveratrol was purchased from Sigma-Aldrich (USA) and was dissolved in DMSO at room temperature. The final solutions were prepared at concentrations of 20 µM and 50 µM for the experimental groups. Resveratrol treatment was applied for 48 hours after the completion of the preadipocyte differentiation process. The selected concentrations were based on previous studies(19).

Oil Red O Staining

The lipid content of the adipocytes was determined using Oil Red O staining. The differentiated cells were removed from the incubator. The previous medium was removed from the system. The cells were then washed twice with PBS. The cells were fixed by incubating 1 ml of 10% formaldehyde for one hour at room temperature. One milliliter of 0.3% Oil Red O solution was added to the cells and then incubated at room temperature for 15 minutes. The Oil Red O solution was removed and washed four times with distilled water. For nuclear staining, hematoxylin was added and incubated for one minute. Then, the hematoxylin was removed and washed two to five times with ddH_2O. Observation was made under a light microscope.

Western Blot

Protein lysate was prepared from resveratrol-treated and control group adipocytes. Cells were washed with ice-cold Phosphate Buffered Saline (PBS). Cell lysis buffer consisted of PYLB buffer supplemented with 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.6), 50 mM NaF, 5 mM ethylenediaminetetraacetic acid (EDTA), 10 mM sodium pyrophosphate (NaPPi), 1% Triton X-100, 50 mM NaCl, protease and phosphatase inhibitors (Applichem, Germany). Extracted protein content was measured by Bradford assay according to the manufacturer's protocol (A6932, 0500, Applichem, Germany). β-actin was used as a loading control. 30 µg protein was loaded for SDSPAGE electrophoresis, transferred to PVDF membrane and blocked with Tris-Buffered Saline containing 0.1% Tween 20 and 5% non-fat dried milk powder for 1 h at room temperature.

Membranes were blotted with antibodies to β-actin (#4970, Cell Signaling, USA), β catenin (#9582, Cell Signaling, USA) in PBS containing 0.1% Tween 20 at 4 °C overnight. Anti-rabbit IgG, HRP-linked Antibody (#7074S, Cell Signaling, USA) was used as

secondary antibody. Protein bands were detected using Luminata Forte Western HRP Substrate (Millipore, USA) and densitometric analysis of protein bands was performed using ImageJ software.

Statistical Analysis

Statistical analysis of the data was obtained using IBM SPPS.22 program. Data were expressed as mean ± standard error of the mean. For statistical evaluation, oneway ANOVA followed by Dunnet and Bonferroni Tamhane and Games-Howell post hoc tests were used.

Ethics Approval

Ethics committee approval was obtained from Dokuz Eylul University, Non-International Research Ethics Committee (Date: 23.11.2020, Approval No: 2020/28–39).

RESULTS

The 3T3-L1 cell line is a morphologically fibroblastic mouse embryonic cell line that was isolated from 3T3 cells. The preadipocytes were differentiated into mature adipocytes using a combination of insulin, dexamethasone, and IBMX, as previously described by Reed and Lane (1980) (18)OilO red staining was used to visualize mature adipocytes following adipogenesis (Figure 1).

Following the resveratrol treatment of mature adipocyte cells at concentrations of 20 µM and 50 µM, the mRNA expression levels of the β-catenin, SIRT1, PPARγ, PGC-1α, and PRDM16 genes were evaluated using real-time PCR. There was a statistically significant increase in SIRT1 mRNA levels with increasing resveratrol doses ($p < 0.01$). The increase in mRNA expression levels of PPARγ, which plays a role in adipogenesis and thermogenesis processes, between the 20 µM and 50 µM resveratrol-treated group and the control group was found to be statistically significant ($p < 0.05$). No statistically significant change was observed in PGC-1α, the coactivator of PPARγ. In particular, the mRNA level of UCP1, which plays a central role in thermogenesis, was found to be significantly increased between the 20 µM and 50 µM resveratrol-treated groups compared to the control group ($P < 0.01$). The PRDM16 mRNA level was found to be significantly elevated in the 50 µM resveratrol-treated group in comparison to the control group ($P < 0.05$).

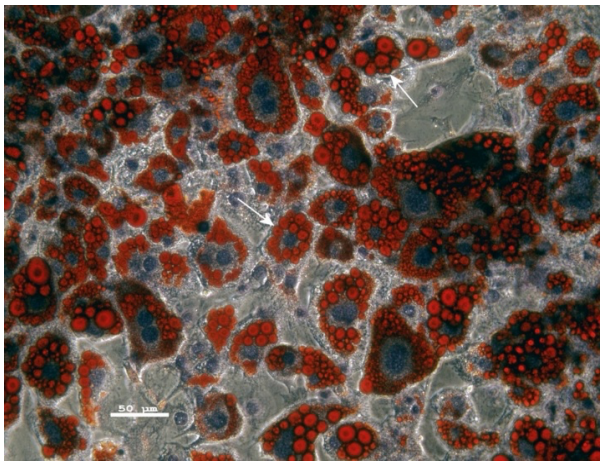


Figure 1. Image of differentiated adipocytes after Oil Red O staining. Scale bars indicate 50 µm.

Nevertheless, no notable alteration was observed in the expression of β-catenin mRNA (Figure 2). Western blotting revealed a notable increase in β-catenin protein expression following treatment of mature adipocyte cells with 20 µM and 50 µM resveratrol (Figure 3), indicating an escape from cytoplasmic degradation and accumulation within the cytosol.

DISCUSSION

The therapeutic targeting of mechanisms that activate brown or beige adipocytes represents a promising avenue for the development of novel approaches to the management of metabolic disorders such as obesity. In particular, the stimulation of brown adipocytes or the induction of white adipose tissue to acquire brown fat-like properties may prove an efficacious strategy for the reduction of body weight and fat mass. Resveratrol is a known activator of SIRT1. Activation of SIRT1 results in the deacetylation of PPARγ (20). It forms a complex with the PRDM16 transcription factor, thereby inducing the expression of thermogenesis-related genes, including PGC1α and UCP1 (21). The present study demonstrated a significant increase in SIRT1 gene expression at concentrations of resveratrol of 20 µM and 50 µM. In support of our data, a study conducted by Imamura et al. (2017), an increase in SIRT1 gene expression levels was observed in the 3T3-L1 cell line in a resveratrol concentration dependent manner (19). It has been proposed that SIRT1 may regulate the expression of UCP1, thereby exerting an indirect influence on thermogenesis (21).

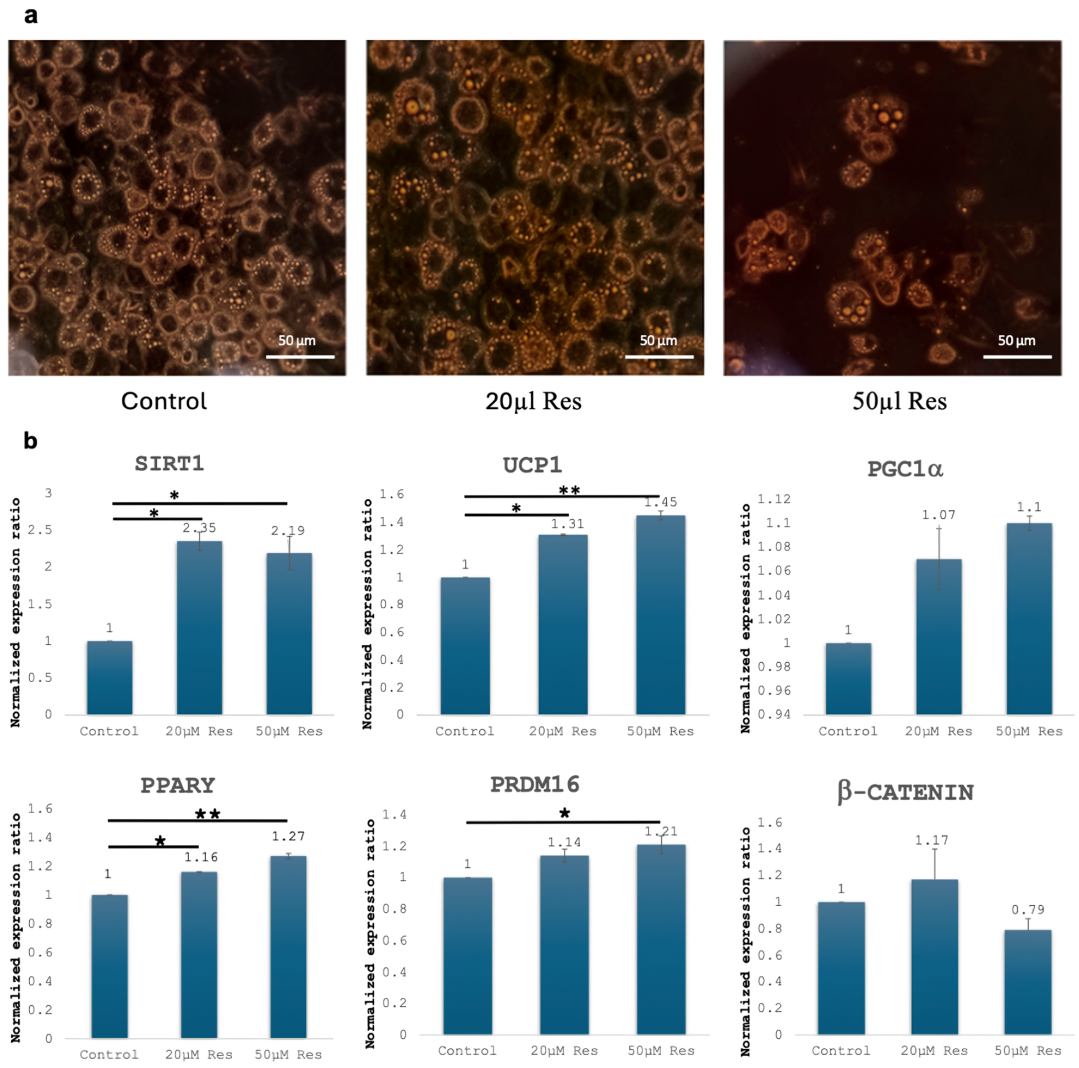


Figure 2. Phase-contrast images of control and 20, 50 µM resveratrol treated cells. Scale bars indicate 50 µm. **b.** PPARγ, UCP1, PGC-1α, PRDM16, ß-CATENIN, SIRT1 gene expression changes in control and experimental groups (20 µM and 50 µM Resveratrol). ß-ACTIN was used as the housekeeping gene for normalization. Data are shown as mean ± standard error of the mean. (ANOVA was used for statistical evaluation and Bonferroni test was used as post-hoc test. n=3, *: p<0.05,**:P<0.01)

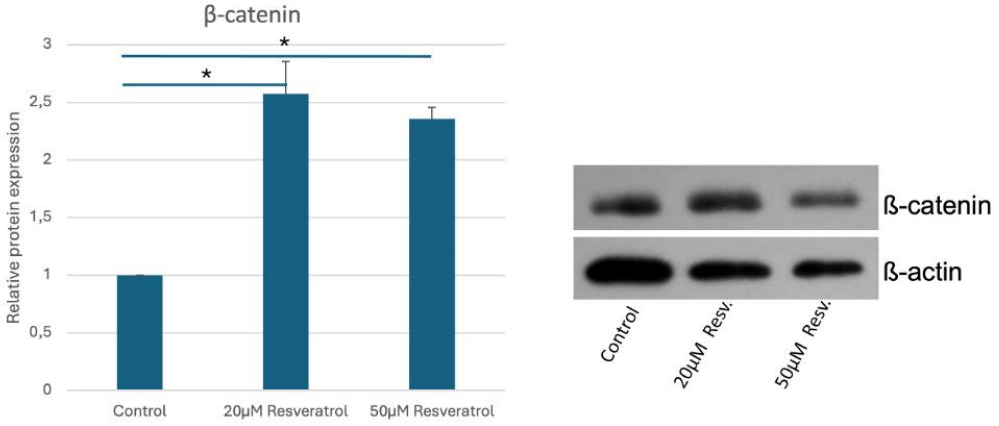


Figure 3. ß-catenin protein expression change in control and experimental groups (ANOVA was used for statistical evaluation and Bonferroni test was used as post-hoc test. n=3, *: p<0.05)

UCP1 is a key protein involved in the thermogenic process. The UCP1 protein is located in the inner mitochondrial membrane and distributes the proton gradient across the membrane, allowing energy to be released as heat instead of ATP and thus suppressing oxidative phosphorylation. Our results show a significant increase in UCP1 gene expression in cells treated with 20 µM and 50 µM resveratrol when compared with the control group. PPARγ, a primary regulator of adipogenesis, is a transcription factor involved in the differentiation mechanisms of brown and beige adipocytes (22). We show a notable elevation in PPARγ gene expression levels across the control, 20 µM, and 50 µM resveratrol groups. Qiang et al. reported results that align with our data, demonstrating that the expression of the PPARγ gene increased in adipocytes treated with resveratrol (23). PPARγ has been shown to play a role in both adipogenesis and the induction of the thermogenesis pathway (22). Nevertheless, its precise role in these two distinct mechanisms remains unclear and further detailed studies are required. PGC1α, a coactivator of PPARγ, plays a role in mitochondrial biogenesis and the control of oxidative respiration. PGC1α has been demonstrated to stimulate UCP1 in thermogenic pathway (24). In addition, Liu Z. et al., reported that the expression level of PGC1α increased in cells treated with resveratrol (25). In the present study, the addition of resveratrol did not result in a statistically significant change in the expression level of the PGC1α gene.

PRDM16, a key transcription factor in the activation of the thermogenic pathway, has been shown to stimulate the differentiation of beige adipocytes by transcriptionally activating PPARγ (14) The results of our study indicate a notable elevation in PRDM16 gene expression in the 50 µM resveratrol group compared to the control. This finding aligns with the results reported by Wang et al, who observed a similar increase in PRDM16 gene expression in resveratrol-treated mice (7). The present data indicates that resveratrol does not stimulate the expression of PGC1α, yet there is a notable elevation in PRDM16 gene expression. This suggests that the thermogenic activation induced by resveratrol is mediated by PRDM16, which acts through PPARγ. Further experimentation is required to corroborate this hypothesis. Upon evaluation of our data, it can be stated that resveratrol is an effective agent, a finding that is consistent with the existing literature.

The mRNA expression of β-catenin, a pivotal factor in the Wnt/β-catenin signaling pathway, which is involved in cellular processes such as differentiation, proliferation, and migration, remained unaltered following resveratrol treatment. However, an increase in the intracellular β-catenin protein level was observed, particularly in cells treated with resveratrol at a concentration of 50 µM, regarding the control group. This outcome can be attributed to the deacetylase effect of SIRT1, which has been demonstrated to inhibit β-catenin degradation in previous studies. The literature contains conflicting reports regarding the effect of resveratrol on β-catenin levels. For example, Mineda et al. (2019) and Liu et al. (2023) reported a reduction in the expression level of β-catenin in their studies (26, 27). Additionally, in the study by Chen et al. (2021) the combined treatment with resveratrol and titanium alloy particles led to an increase in β-catenin mRNA levels (28). Given the multiple factors involved in the regulation of β-catenin levels and the complexity of intracellular signaling pathways, differences observed at the mRNA level is expected. The results of our study indicate that there was no statistically significant change in the mRNA level of β-catenin. The disparate findings at the mRNA level in the existing literature proved instrumental in addressing the fundamental question posed by our study. However, an increase in the protein level was observed following resveratrol administration, as reported by Yang et al. (2021) (29). This finding is consistent with our own results. The currently available data do not permit a direct association between the increase in β-catenin protein levels following resveratrol treatment and thermogenic activation to be established. This result may be attributed to a distinct consequence of the deacetylase effect of

SIRT1, stimulated by resveratrol, independent of thermogenic activation in intracellular pathways. However, Zhou et al. (2016) have reported that SIRT1 suppresses adipogenesis by increasing βcatenin activation (30). To elucidate the role of β-catenin in the adipogenesis process, further experiments are required to directly assess the effect of β-catenin on this process, including experiments to suppress and intensely express β-catenin.

CONCLUSION

The increase in intracellular ß-catenin and especially the stimulation of proliferative genes suggest that

resveratrol may also affect different cellular pathways. The data obtained from the literature and our own study are insufficient to elucidate the mechanism by which resveratrol increases ß-catenin levels in the presence of SIRT1. The results of our study indicate that resveratrol may have proliferative effects on cells other than those involved in the thermogenic pathway, through activation of ß-catenin. Consequently, we believe the use of resveratrol should be monitored while further studies elucidate its effects on ß-catenin signaling.

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

1. Dos Santos TW, Pereira QC, Teixeira L, Gambero A, Villena JA, Ribeiro ML. Effects of Polyphenols on Thermogenesis and Mitochondrial Biogenesis. Int J Mol Sci 2018;19.
2. Park A, Kim WK, Bae K-H. Distinction of white, beige and brown adipocytes derived from mesenchymal stem cells. World J Stem Cells 2014;6:33.
3. Bartelt A, Widenmaier SB. Proteostasis in thermogenesis and obesity. Biol Chem 2020;401:1019–30.
4. Saely CH, Geiger K, Drexel H. Brown versus white adipose tissue: a mini-review. Gerontology 2012;58:15–23.
5. Kuryłowicz A, Puzianowska-Kuźnicka M. Induction of Adipose Tissue Browning as a Strategy to Combat Obesity. Int J Mol Sci 2020;21:1–28.
6. Liu RH. Dietary Bioactive Compounds and Their Health Implications. J Food Sci 2013;78:A18–25.
7. Wang S, Zhu MJ, Du M. Prevention of obesity by dietary resveratrol: how strong is the evidence? Expert Rev Endocrinol Metab 2015;10:561–4.
8. de Ligt M, Timmers S, Schrauwen P. Resveratrol and obesity: Can resveratrol relieve metabolic disturbances? Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2015;1852:1137–44.
9. Li X. SIRT1 and energy metabolism. Acta Biochim Biophys Sin (Shanghai) 2013;45:51–60.
10. Gut P, Verdin E. Rejuvenating SIRT1 activators. Cell Metab 2013;17:635–7.
11. Yamamoto H, Schoonjans K, Auwerx J. Sirtuin functions in health and disease. Mol Endocrinol 2007;21:1745–55.
12. Azhar Y, Parmar A, Miller CN, Samuels JS, Rayalam S. Phytochemicals as novel agents for the induction of browning in white adipose tissue. Nutr Metab (Lond) 2016;13.
13. Pan MH, Koh YC, Lee TL, Wang B, Chen WK, Nagabhushanam K, et al. Resveratrol and Oxyresveratrol Activate Thermogenesis via Different Transcriptional Coactivators in High-Fat Diet-Induced Obese Mice. J Agric Food Chem 2019;67:13605–16.
14. Jiang N, Yang M, Han Y, Zhao H, Sun L. PRDM16 Regulating Adipocyte Transformation and Thermogenesis: A Promising Therapeutic Target for Obesity and Diabetes. Front Pharmacol 2022;13.
15. Emont MP, Kim D il, Wu J. Development, activation, and therapeutic potential of thermogenic adipocytes. Biochim Biophys Acta Mol Cell Biol Lipids 2019;1864:13–9.
16. Prestwich TC, MacDougald OA. Wnt/β-catenin signaling in adipogenesis and metabolism. Curr Opin Cell Biol 2007;19:612.
17. Dai H, Deng HB, Wang YH, Guo JJ. Resveratrol inhibits the growth of gastric cancer via the Wnt/β-catenin pathway. Oncol Lett 2018;16:1579–83.
18. Reed BC, Lane MD. Insulin receptor synthesis and turnover in differentiating 3T3-L1 preadipocytes. Proc Natl Acad Sci U S A 1980;77:285–9.
19. Imamura H, Nagayama D, Ishihara N, Tanaka S, Watanabe R, Watanabe Y, et al. Resveratrol attenuates triglyceride accumulation associated with upregulation of Sirt1 and lipoprotein lipase in 3T3-L1 adipocytes. Mol Genet Metab Rep 2017;12:44–50.
20. Mayoral R, Osborn O, McNelis J, Johnson AM, Oh DY, Izquierdo CL, et al. Adipocyte SIRT1 knockout promotes PPARγ activity, adipogenesis

and insulin sensitivity in chronic-HFD and obesity. Mol Metab 2015;4:378.
21. Elibol B, Kilic U. High Levels of SIRT1 Expression as a Protective Mechanism Against Disease-Related Conditions. Front Endocrinol (Lausanne) 2018;9.
22. Lo KA, Sun L. Turning WAT into BAT: a review on regulators controlling the browning of white adipocytes. Biosci Rep 2013;33:711–9.
23. Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, et al. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Pparγ. Cell 2012;150:620–32.
24. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 1998;92:829–39.
25. Liu Z, Liao W, Yin X, Zheng X, Li Q, Zhang H, et al. Resveratrol-induced brown fat-like phenotype in 3T3-L1 adipocytes partly via mTOR pathway. Food Nutr Res 2020;64.
26. Mineda A, Nishimura M, Kagawa T, Takiguchi E, Kawakita T, Abe A, et al. Resveratrol suppresses proliferation and induces apoptosis of uterine sarcoma cells by inhibiting the Wnt signaling pathway. Exp Ther Med 2019;17.
27. Liu H, Zhang X, Fang C, Li S. Resveratrol induces the growth inhibition of CDX-deficient gastric cancer cells using CDX2 and RUNX3 via the β-catenin/TCF4 signaling pathway. Transl Oncol 2023;35.
28. Chen X, Sun S, Geng T, Fan X, Zhang S, Zhao S, et al. Resveratrol reduces the progression of titanium particle-induced osteolysis via the Wnt/β-catenin signaling pathway in vivo and in vitro. Exp Ther Med 2021;22.
29. Yang M, Li Z, Tao J, Hu H, Li Z, Zhang Z, et al. Resveratrol induces PD-L1 expression through snail-driven activation of Wnt pathway in lung cancer cells. J Cancer Res Clin Oncol 2021;147:1101–13.
30. Zhou Y, Song T, Peng J, Zhou Z, Wei H, Zhou R, et al. SIRT1 suppresses adipogenesis by activating Wnt/β-catenin signaling in vivo and in vitro. Oncotarget 2016;7:77707–20.