Resveratrol: A Pleiotropic Phytoconstituent

Prashant N. Amale\textsuperscript{1}, Manish P. Deshmukh\textsuperscript{2}, Ashish B. Budhrani\textsuperscript{3}, Shilpa A. Deshpande*\textsuperscript{1}

\textsuperscript{1}Department of Pharmacology, Priyadarshini J. L College of Pharmacy, MIDC, Electronic Zone Building, Hingna Road, Nagpur, Pin-440016, Maharashtra, India
\textsuperscript{2}Department of Pharmacology, Jawaharlal Nehru Medical College, Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (DU), Wardha, Pin-442001, Maharashtra, India
\textsuperscript{3}Department of Pharmaceutics, Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (DU), Wardha, Pin-442001, Maharashtra, India

\textbf{Article History:}
Received on: 31 Jul 2020
Revised on: 23 Aug 2020
Accepted on: 02 Sep 2020

\textbf{Keywords:}
Resveratrol, Pleiotropic, phytoconstituents, pain, inflammation

\textbf{ABSTRACT}
Resveratrol (RSV) is a plant polyphenol or phytoalexin phytoconstituent obtained from the grapes, berries, peanuts, and wine. RSV is obtained from natural source and regarded as safe, effective, and hepatoprotective drug with no other serious organ toxicities are reported yet. This property of RSV makes it advantageous over the allopathic medicine having symptomatic cure and plethora of adverse effects. It’s a cheap and widely available phytoconstituent approved in the global market in the active form as trans-resveratrol. It has multiple pharmacological actions including, analgesic, anti-inflammatory, anti-anxiety, anti-parkinsonian, anti-alzheimers, antioxidant, antidepressant, anti-cancer, anti-diabetic, anti-atherosclerotic effects. These effects are mediated via modulation of diverse underlying endogenous molecules like reactive oxygen species, nitric oxide, malonaldehyde, neutrophil, sirtulin, cyclo-oxygenase, inducible nitric oxide syntheses, superoxide dismutase, catalase, glutathione s-transferase, alpha-secretase, metalloproteinases, C-reactive protein, dopamine, nor-adrenaline, serotonin, cytokines (interleukins), nuclear factor kappa, signal transducer activator of transcription, brain derived neural nactor, neuropeptide, hypothalamo-pitutary axis, astroglia, mitochondrial dysfunction, glutamate, adrenergic, cholinergic, opioidergic, and purinergic receptors. Researchers are trying to explore its additional health benefits and preparing new analogues for better survival in the field. Present review will help to enlighten the multi-target pleiotropic pharmacological nature of a RSV in relation to the variety of the molecular targets modulation through extensive web science literature survey.

\*Corresponding Author
Name: Shilpa A. Deshpande
Phone: +91-9422443171
Email: Shilpa@hotmail.co.in

ISSN: 0975-7538
DOI: \url{https://doi.org/10.26452/ijrps.v11iSPL4.4325}

\textbf{INTRODUCTION}
Resveratrol (RSV) is a polyphenol, abundantly found in grape (skin and seeds), berries, peanuts and wine. This compound has many properties, including activity against glycation, immune response, oxidative stress, inflammation, neurodegeneration, several types of cancer, and aging (Kataria and Khatkar, 2019). RSV is well tolerated phytoconstituent and believed to be a promising compound in preventing many diseases, like depression, diabetes, asthma and other complications (Chen...
RSV is a pleiotropic agent having a variety of pharmacological effects like analgesic, anti-viral, anti-platelet, anti-inflammatory, anti-mutagenic, antioxidant, anti-psoriatic, immunosuppressive, neuroprotective, antidepressant, anti-anxiety, anti-parkinson's, anti-Alzheimer (Gu et al., 2019).

MATERIALS AND METHODS

Extensive literature survey was done using the PubMed online databases for the selected phrases like Resveratrol and pain, inflammation, anxiety, depression, Alzheimer, Parkinson which were individually feed into the database with time limit of past 10 years (2010-2020). Out of the total searched article (1862) the most related and suitable articles (215) were read thoroughly and about 96 were found to have relation with the present study and hence considered further. The selected literature out of yielded for the phrases specifically are as “resveratrol” and “pain”(34/145), Resveratrol and inflammation (16/1359), Resveratrol and anxiety (9/43), Resveratrol and “depression” (11/87), “Resveratrol” and “parkinsons” (11/53), “Resveratrol” and “Alzheimers” (15/175).

RESULTS AND DISCUSSION

Pleiotropic Role of Rsv In Management of Pathological Conditions

Pain

The RSV has revealed its therapeutic efficacy in the relief acute and chronic types of pain including peripheral, inflammatory, cancer, neuropathic, diabetic, post surgery, burn /tissue injury and constriction induced pain. It was found to act by modulation of cytokines, chemokines, neurotransmitters and enzymes involved in the pain pathology Figure 1. Plethora of evidences suggested that inhibition of pro-inflammatory cytokines, Cyclo-oxygenase (COX), and encouragement of the Interleukin (IL)-10 modulation of glutamatergic-Methyl-D-Aspartate (NMDA), purinergic P2X3, and serotonergic(5-Hydroxy tryptaminic) 5-HT3, and 5-HT7 receptors are the key targets of RSV (Zeng et al., 2017). RSV also helps in the recovery of spinal cord after injury by inhibition of COX-1, liperoxidation and by building theglutathione level model of pain. Modulation of spinal 5-HT7 and supraspinal 5-HT1A serotonergic receptor are involved in anti-hyperalgesic action of RSV in thermal stimuli induced algesia (Zhao et al., 2014).

RSV has been found to target Adenosine MonophosphateActivated Protein Kinase (AMPK) and inhibits the Extracellular Signal regulated Kinase (ERK) and Mammalian target of Rapamycin (mTOR) signalling in the incision triggered acute and chronic pain (Tillu et al., 2012). RSV found to alleviate chronic Neuropathic pain (NP) through inhibitionof ERK phosphorylation and P2X3 up-regulation, activation of Silent Information Regulator 1 (SIRT1) and up-regulation of miR-182 expression in Dorsal Root ganglia (DRG) to suppress Nav1.7 expression in NP induced rat (Jia et al., 2020). RSV reduce IL-1β, Malonaldehyde (MDA) while increase IL-10 and Superoxide Dismutase (SOD) level resulting inhibition of paclitaxel-induced mitochondrial damage by blockage of phosphatidylinositol 3-kinase (PI3K)/ Protein Kinase B (Akt) mediated pathway of NP (Li et al., 2019).

RSV is known to produce analgesia in bone cancer pain by modulation of the AMPK and direct allo-steric activation of SIRT1 (Kulkarni and Canto, 2015). RSV regulates the nociceptive markers by inhibiting the Tumour Necrosis Factor (TNF) Receptor Associated Factor TRAF6/Nuclear Factor Kappa B (NF-κB) communication pathway and reduction oﬁtri-nitrobenzene sulﬁdic acid (TNBS)-induced spinal GFAP, TRAF6, pNF-κB, TNF-α and IL-1β level. In addition, antinociceptive effect of RSV involves alteration of Ca2+/calmodulin-dependent signalling, TNF-α, Transient Receptor Potential channels, and NO levels at spinal level (Wang et al., 2017). Trans-RSV produces analgesia through an opioidergic mechanism similar to the morphine. Moreover, RSV also down-regulates NMDAR; NMDA Receptor (NR)-1 and NR2B subunit expression and alleviates morphine tolerance in experimental animals (Tsai et al., 2012).

Inflammation

Our body responds to various stimuli in various ways of self defence against chemical, mechanical, biological and radiation stimuli. Inflammation is one of protective response. Inflammation is caused by a series of markers contributes which includes cytokines viz. IL-1, IL-2, IL-6, IL-12, TNF-α, TNF-β, chemokines, NF-κB, signal transducer and activator of transcription (STAT)-3, pro-inflammatory enzymes COX-2, 5-lipoxygenase (LOX), 12-LOX, matrix metalloproteinases (MMPs), prostate-specific antigen (PSA), C-reactive protein, intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM)-1, endothelial-leukocyte adhesion molecule (ELAM)-1, vascular endothelial growth factor (VEGF) (Ahn and Aggarwal, 2005).

According to a research, inflammation is inhibited by Resveratrol (RSV). This is caused by the inhibition of contributory elements like COX2, ICAM-
Figure 1: Pleiotropic mechanism of resveratrol in pathological conditions

1, VCAM-1, neutrophil infiltration, oxidative stress, CRP, toll like receptor. It has also been found out that RSV suppresses mRNA, VEGF, and proteins expressions of IL-1β and MMP-3 by inhibiting the PI3K-AKT pathway in inflammatory conditions. RSV is a pleiotropic agents that suppresses TNF-α, IL-1β, NF-kB, IL-6, iNOS, MDA,ICAM-1, caspase-3 and myeloperoxidase and at the same time it was found that it considerably supported an increased secretion of SOD, catalase, and IL-10 level in inflammation induced rats (Tain et al., 2013).

Moreover, RSV prevents membrane translocation of the p47 subunit and blocks NADPH oxidase which in turn results in reduction of Reactive Oxygen Species (ROS) formation during the inflammation (Zhang et al., 2010). Interference of phosphorylation of ERK 1/2, p38 and JNK by RSV suppresses the inflammatory reaction (Jia et al., 2020).

Depression
Antidepressant potential of RSV is well explored in last two decades due to its capacity to cross blood brain barrier. Imbalance of basic brain monoamines level has major contribution in the pathophysiology of depression; however, administration of RSV restores the normal monoamine (5-HT, NA) function, reduced sucrose consumption and exhibited the antidepressant like effect in Forced Swim Test (FST), Tail Suspension Test (TST) model of depression. Gu et al. 2019 showed that RSV can significantly increase the levels of Dopamine (DA), 5-HT, Brain Derived Neural Factor (BDNF) and Neuropeptide Y (NPY) in the brain and acts as an antidepressant. RSV reversed the corticosterone elevated level of BDNFand serum corticosterone by modulating the Hypothalamo-Pituitary Axis (HPA) axis in mice (Xu et al., 2010).

RSV is known to protect the mitochondrial function. This is achieved by reduction in mitochondrial oxygen production, glutathione synthase (GSH) deletion, ROS production, Sestrin2, SIRT1, peroxisomeproliferator - activated receptor-γ co-activator (PGC-γ) - 1α and enhancement in antioxidant enzymes (Chen at al. 2017). RSV is not found to increase or decrease locomotor activity and hence the anti-depressant activity of this drug is not related with overall attenuation of psychomotor...
activity (Liu et al., 2016).

**Anxiety**

Anxiety is associated with diabetes and RSV treatment for 2week aggravatedanti-inflammatory-like effects in streptozotocin-induced diabetic mice. Pre-diabetic condition found to be associated with hyper-anxiety which is significantly ameliorated by RSV with modulation of sirtuins, which may be similar to metformin (Reddy et al., 2016).

Trans-RSV HPA (hypothalamic-pituitary-adrenal) axis/pCREB/BDNF pathway and improve the TDS-induced anxiety-like behaviours and fear memory deficits in rodent. Tran-RSV increased the percentage of centre zone time and time spent in open arm with entries in the open field test (OFT) and the elevated plus maze, while reduced freezing time in the contextual test (Li et al., 2018).

RSV treatment increased rearing and movement in the OFT, elevated sucrose preference index, and reduced immobility in the FST in subclinical hypothyroidism rats. This anxiolytic and antidepressant-like effect was thought to be due to down-regulation of hyperactivity of the HPA axis and regulation of HPT (hypothalamic-pituitary-thyroid) axis and the Wnt/β-catenin pathway ultimately balancing of the HPA and HPT (Ge et al., 2016).

**Parkinson’s Disease (PD)**

Activation of the AMPK-SIRT1 autophagy pathway involved in the neuroprotective effects of RSV in cellular model of PD. The RSV found to down-regulate the expression of metastasis-associated lung adenocarcinoma transcript (MALAT)-1, which acted as a negative regulator of miR-129. Alpha-synuclein (SNCA) gene, a target gene of miR-129 induces neuronal apoptosis and causes PD. MALAT1 is suppressor of the miR-129 and RSV down-regulates the expression of MALAT1 results in indirect inhibition of apoptosis and established anti-parkinssonianphytocconstituents (Xia et al., 2019).

COX-2 and TNF-α is a pro-inflammatory enzyme and cytokine involved in aetiology of PD. RSV treatment reduces 6-OHDA-increased expression of TNF-α mRNA, COX-2 protein, COX-2 enzyme level and corrected the behavioural impairment, damage of dopaminergic system of substantia nigra in rat model of PD. RSV attenuates 6-OHDA-induced apoptosis and motor dysfunction by promoting the PI3K/Akt signalling pathway thus delayed the progression and symptoms in 6-OHDA model of PD. In addition, RSV may ameliorate the behavioural, biochemical, and histo-pathological abnormalities caused due free radicals formation during PD (Huang et al., 2019).

Mitochondrial fission/fusion and biogenesis majorly regulates mitochondrial homeostasis, while its impairment may underlie the pathogenesis of PD. Oxidative stress and mitochondrial dysfunction causes loss of dopaminergic neurons in PD. RSV attenuates MPP+ induced mitochondrial dysfunction and cell apoptosis through AKT/GSK-3β pathway (Zeng et al., 2017).

Liu et al. showed that RSV attenuates MPTP-induced dopaminergic neuronal loss, astroglial activation, expression of α-synuclein, activation of caspase-3, IL-1β level, pro-apoptotic Bax molecule. On the contrary RSV increased levels of the anti-apoptotic Bcl-2, pAkt/Akt ratio and enhanced dopaminergic neuronal survival in the striatum. RSV reduced the dose of L-DOPA from alone 8mg/kg to 5mg/kg when given combination in MPTP-induced PD. All the biological, molecular, morphological changes behavioural dysfunction in parkinson’s enforces RSV as promising therapeutic agent for PD (Liu et al., 2019).

**Alzheimer’s disease (AD)**

RSV have been observed to reduce the neuroinflammation, and it induces adaptive immunity by reducing CSF MMP9 and elevates macrophage-derived chemokine (MDC), IL-4, and fibroblast growth factor (FGF)-2 (Moussa et al., 2017).

RSV facilitates clearance of neurotoxicamyloid beta (Aβ) peptides and breakdown of the amyloid precursor protein (APP). RSV also promotes SIRT1 expression, regulates cholesterol homeostasis and reduced the amyloidogenicplaque formation in AD (Braidy et al., 2016). RSV and oxy-RSV cause activation of α-secretase and MMP-9 to lower Aβ levels without causing cell death. RSV, metallorphyrins, and nicotinamideriboside synergistically reduced amyloid β protein leading to improvement of mitochondrial and cognitive function in AD (Dragicevic et al., 2017). Elevated concentration of RSV increased thigmotaxis response and slow β-amyloid toxicity progression for C. elegans strain c4176 in normal and diabetic conditions (glucose toxicity). In addition 5 mg RSV, 5g dextrose/glucose and malate in grape juice for 1 year reduced the progression of AD (Zhu et al., 2019).

RSV was also found to affirmatively modulate antioxidant and anti-aging factors by increasing the expression of genes of catalase, copper chaperone for SOD 1, glutathione S-transferase zeta 1, sirtuin 1 and 3 in AD, healthy, controlled and lymphoblastoid cell lines. According to a study, RSV is found to reduce oxidative stress, Aβ1–42-induced...
cell death with enhanced mitophagy and is also known to produce neuroprotective effects. RSV or Losartan at 10 mg/kg dose increases hippocampal BDNF level along with causing a decrease in blood pressure and nucleus tractussolitarius (NTS) ROS production in the Ang-II group. Hippocampal TauT231 phosphorylation activated AktS473 phosphorylation is inhibited by Losartan, and Ang-II-induced Aβ precursors, active caspase 3, and glycogen synthasekinase 3β (GSK-3β)Y216 expressions are significantly abolished. Losartan and RSV, both decrease the secretion level of NADPH oxidase 2 (NOX2) and elevate the level of SOD2, which in turn causes restoration of hippocampal-dependent contextual memory (Lin et al., 2018). Memory impairments, β-amylod plaques, tau protein hyperphosphorylation, and neuronal loss are caused by the elevated. RSV is found to reduce the formaldehyde-induced damages by promoting phosphoseryl/phosphothreonyl protein phosphatase-2A (PP2A) activity and suppressing glycogen synthasekinase (GSK-3β), calmodulin-dependent protein kinase II (CaMKII), hyperphosphorylation of tau protein and cytotoxicity in N2a Cells (He et al., 2017).

Intra-hippocampally administration of Ibotenic Acid (IBO) produces excitotoxicity, alteration of mRNA expression of NR2A and NR2B subunits of glutamate (NMDA) receptors. It is also reported to result in decreased in expression particularly α7-nAChR with increased m1AChR. Apart from this, RSV administration significantly yielded better results when it was administered to the IBO lesioned rat model of AD (Karthick et al., 2016).

CONCLUSIONS

RSV is plant constituent and a recommended phytoc constituent as supplemental for the well being. RSV being a single molecule possesses multi target modulation ability involved in the number of pathological conditions. Present study has shown the evidence based pleiotropic potential of the RSV in the management of the pain, inflammation, anxiety, depression, parkinson's and Alzheimer disease . It also provides future scope for the development of the most suitable congener of RSV with appropriate dose in treatment of number of clinical conditions. It also draws the attention of researchers to minimize number of molecule for single or multiple pathologies and reduces the patient suffering with greater therapeutic outcome.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

REFERENCES

Ahn, K. S., Aggarwal 2005. Transcription Factor NF-B: A Sensor for Smoke and Stress Signals. Annals of the New York Academy of Sciences, 1056(1):218–233.

Braidy, N., Jugder, B.-E., Poljak, A., Jayasena, T., Mansour, H., Nabavi, S. M., Sachdev, P., Grant, R. 2016. Resveratrol as a Potential Therapeutic Candidate for the Treatment and Management of Alzheimer's Disease. Current Topics in Medicinal Chemistry, 16(17):1951–1960.

Chen, W. J., Du, J. K., Hu, X., Yu, Q., Li, D. X., Wang, C. N., Zhu, X. Y., Liu, Y. J. 2017. Protective effects of resveratrol on mitochondrial function in the hippocampus improves inflammation-induced depressive-like behavior. Physiology & Behavior, 182:54–61.

Dragicevic, N., Zhang, P., Bradshaw, P. 2017. Synthetic Metalloporphyrins and Resveratrol act synergistically as enhancers of cognitive performance through reduction of deposited amyloid beta and improvement of mitochondrial function in Alzheimer's mice. Neurology, 88(16).

Ge, J.-F., Xu, Y.-Y., Qin, G., Cheng, J.-Q., Chen, F.-H. 2016. Resveratrol ameliorates the anxiety- and Depression-like Behavior of subclinical hypothyroidism rat: Possible involvement of the hPT axis, hPa axis, and Wnt/β-catenin Pathway. Front Endocrinol (Lausanne), 7.

Gu, Z., Chu, L., Han, Y. 2019. Therapeutic effect of resveratrol on mice with depression. Experimental and therapeutic medicine, 17:3061–3064.

He, X., Li, Z., Rizak, J. D., Wu, S., Wang, Z., He, R., Su, M., Qin, D., Wang, J., Hu, X. 2017. Resveratrol Attenuates Formaldehyde Induced Hyperphosphorylation of Tau Protein and Cytotoxicity in N2a Cells. Front Neurosci, 10:598–598.

Huang, N., Zhang, Y., Chen, M., Jin, H., Nie, J., Luo, Y., Zhou, S., Shi, J., Jin, F. 2019. Resveratrol delays 6-hydroxydopamine-induced apoptosis by activating the PI3K/Akt signaling pathway. Experimental Gerontology, 124:110653–110653.

Jia, Q., Dong, W., Zhang, L., Yang, X. 2020. Activating Sirt1 by resveratrol suppresses Nav1.7 expression in DRG through miR-182 and alleviates neuropathic pain in rats. Channels, 14(1):69–78.

Karthick, C., Periyasamy, S., Jayachandran, K. S.,
Anusuyadevi, M. 2016. Intrahippocampal Administration of Ibotenic Acid Induced Cholinergic Dysfunction via NR2A/NR2B Expression: Implications of Resveratrol against Alzheimer Disease Pathophysiology. *Frontiers in Molecular Neuroscience*, 9.

Kataria, R., Khatkar, A. 2019. Resveratrol in Various Pockets: A Review. *Current Topics in Medicinal Chemistry*, 19(2):1114–1122.

Kulkarni, S. S., Canto, C. 2015. The molecular targets of resveratrol. *Biochim Biophys Acta*, 1852(6):1114–1123.

Li, G., Wang, G., Shi, J., Xie, X., Fei, N., Chen, L., Liu, N., Yang, M., Pan, J., Huang, W., Xu, Y. 2018. Trans-Resveratrol ameliorates anxiety-like behaviors and fear memory deficits in a rat model of post-traumatic stress disorder. *Neuropharmacol*, 133:181–188.

Li, X., Yang, S., Wang, L., Liu, P., Zhao, S., Li, H., Jiang, Y., Guo, Y., Wang, Y. 2019. Resveratrol inhibits paclitaxel-induced neuroapathic pain by the activation of PI3K/Akt and SIRT1/PGC1α pathway. *J Pain Res*, 12:879–890.

Lin, Y. T., Wu, Y. C., Sun, G. C., Ho, C. Y., Wong, T. Y., Lin, C. H., Chen, H. H., Yeh, T. C., Li, C. J., Tseng, C. J., Cheng, P. W. 2018. Effect of Resveratrol on Reactive Oxygen Species-Induced Cognitive Impairment in Rats with Angiotensin II-Induced Early Alzheimer’s Disease. *J. Clin. Med*, 7(10):329–329.

Liu, L., Zhang, Q., Cai, Y., Sun, D., He, X., Wang, L., Yu, D., Li, X., Xiong, X., Xu, H., Yang, Q., Fan, X. 2016. Resveratrol counteracts lipopolysaccharide-induced depressive likebehaviors via enhanced hippocampal neurogenesis. *Oncotarget*, 7(35):56045–56059.

Liu, Q., Zhu, D., Jiang, P., Tang, X., Lang, Q., Yu, Q., Zhang, S., Che, Y., Feng, X. 2019. Resveratrol synergizes with low doses of L-DOPA to improve MPTP-induced Parkinson disease in mice. *Behav Brain Res*, 367:10–18.

Moussa, C., Hebron, M., Huang, X., Ahn, J., Rissman, R. A., Aisen, P. S., Turner, R. S. 2017. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer’s disease. *Journal of Neuroinflammation*, 14(1).

Reddy, B. R., Maitra, S., Jhelum, P., Kumar, K. P., Bagul, P. K., Kaur, G., Banerjee, S. K., Kumar, A., Chakravarty, S. 2016. Sirtuin 1 and 7 mediate resveratrol-induced recovery from hyper-anxiety in high-fructose-fed prediabetic rats. *Journal of Biosciences*, 41(3):407–417.

Tain, J., Chen, J. W., Gao, J. S., Li, L., Xie, X. 2013. Resveratrol inhibits TNF-α-induced IL-1β, MMP-3 production in human rheumatoid arthritis fibroblast-like synoviocytes via modulation of PI3K/Akt pathway. *Rheumatol. Int*, 33(7):1829–1835.

Tillu, D. V., Melemedjian, O. K., Asiedu, M. N., Qu, N., Felice, M. D., Dussor, G., Price, T. J. 2012. Resveratrol Engages AMPK to Attenuate ERK and mTOR Signaling in Sensory Neurons and Inhibits Incision-Induced Acute and Chronic Pain. *Molecular Pain*, 8.

Tsai, R. Y., Chou, K. Y., Shen, C. H., Chien, C. C., Tsai, W. Y., Huang, Y. N., Tao, P. L., Lin, Y. S., Wong, C. S. 2012. Resveratrol Regulates N-Methyl-D-Aspartate Receptor Expression and Suppresses Neuroinflammation in Morphine-Tolerant Rats. 115:944–952.

Wang, X. L., Li, T., Li, J. H., Miao, S. Y., Xiao, X. Z. 2017. The Effects of Resveratrol on Inflammation and Oxidative Stress in a Rat Model of Chronic Obstructive Pulmonary Disease. *Molecules*, 22(9):1529–1529.

Xia, D., Sui, R., Zhang, Z. 2019. Administration of resveratrol improved Parkinson’s disease-like phenotype by suppressing apoptosis of neurons via modulating the MALAT1/miR-129/SNCA signaling pathway. *Journal of Cellular Biochemistry*, 120(4):4942–4951.

Xu, Y., Wang, Z., You, W., Zhang, X., Li, S., Barish, P. A., Vernon, M. M., Du, X., Li, G., Pan, J. 2010. Antidepressant-like effect of transresveratrol: Involvement of serotonin and noradrenaline system. *European Neuropsychopharmacology*, 20(6):405–413.

Zeng, W., Zhang, W., Lu, F., Gao, L., Gao, G. 2017. Resveratrol attenuates MPP+-induced mitochondrial dysfunction and cell apoptosis via AKT/GSK-3β pathway in SN4741 cells. *Neuroscience Letters*, 637:50–56.

Zhang, F., Shi, J. S., Zhou, H., Wilson, B., Hong, J. S., Gao, H. M. 2010. Resveratrol Protects Dopamine Neurons Against Lipopolysaccharide-Induced Neurotoxicity through Its Anti-Inflammatory Actions. *Molecular Pharmacology*, 76(3):466–477.

Zhao, X., Yu, C., Wang, C., Zhang, J. F., Zhou, W. H., Cui, W. G., Ye, F., Xu, Y. 2014. Chronic resveratrol treatment exerts antihyperalgesic effect and corrects co-morbid depressive like behaviors in mice with mononeuropathy: Involvement of serotonergic system. *Neuropharmacol*, 85:131–145.
2019. PDE4D-mediated cAMP signaling plays an important role in resveratrol’s protective effects on stress-induced depression- and anxiety-like behavior. *Neuropharmacol*, 153:20–31.