

Neuroprotective effects of resveratrol in Alzheimer's disease

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1. ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder, which is commonly seen in older individuals. This is characterized by cognitive dysfunction, which leads to dementia. Pharmacological treatments for AD are mainly targeted on its symptoms like memory loss and cognitive impairment. The pathophysiology involved in AD is intra-neuronal accumulation of hyperphosphorylated tau protein as neurofibrillary tangle and extra cellular beta amyloid plaque deposition, which is due to oxidative stress. Here we review the neuro-protective effects of Resveratrol (RSV) and its treatment efficacy in AD. RSV is a naturally available polyphenolic compound, which has antioxidant, anti-cancerous, anti-inflammatory and anti-aging properties. RSV crosses blood brain barrier and

exerts its antioxidant effect by enhancing the antioxidant enzymes. RSV is involved in Sirtuin (SIRT1) mediated lifespan extension activity. RSV has reduced glial activation and helped in increasing the hippocampal neurogenesis. RSV was able to decrease the expression of amyloid precursor protein, along with improvement of spatial working memory. Since RSV acts as an antioxidant, it can be safely used as oral drug.

2. ALZHEIMER'S DISEASE (AD)

AD is a neurodegenerative disorder, which is characterized by cognitive dysfunction leading to dementia. On an average, AD is leading to death, three to ten years after its initial diagnosis (1).

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According to World Health Organization (WHO), there are about 35.6 million people who are diagnosed with AD and this number may increase to 65.7 million by 2030. This increase in number will affect developing countries like India and will be due to increased aging population. The pathophysiology involved in AD is intra-neuronal accumulation of hyper-phosphorylated tau protein as neurofibrillary tangle and extra cellular beta amyloid plaque deposition, which is due to oxidative stress (2). Normal tau is an unfolded and highly soluble protein, which is accumulated in axons and dendrites of neurons (3). These tau proteins when associated with microtubules, help in maintaining the neuronal structure and neuronal transport (4). Though tau protein helps in stabilizing the microtubules, its phosphorylated form becomes cytotoxic (5). Hence the function of tau protein is dependent on its phosphorylation state. Tau conformation and balance between the phosphate and kinase will determine the binding of phosphate group into the tau protein. Altered tau conformation will lead to hyper-phosphorylation. In addition, the binding capacity of tau proteins into the microtubules is reduced. These are the two phenomenon which play crucial role in the process of neuro-degeneration (3). The hyper activated phosphatases will lead to paired helices filament and neurofibrillary tangle formation (4). Hyperphosphorylation of tau reduces the stability of microtubules, which leads to disruption of microtubules, aggregation of oligomers and paired helices filaments (6). Several studies propose, oxidative stress as a pathogenic mechanism in AD. In AD, the evidences of oxidative stress in brain are increased iron, alteration in protective enzymes and markers of oxidative damage to proteins and lipids.

3. TREATMENTS FOR AD

Pharmacological treatments for AD are mainly targeted on its symptoms like memory loss and cognitive impairment. There are two therapeutic strategies in the treatment of AD. One is to inhibit the acetylcholine esterase, which helps to keep the acetylcholine in synapse. Another strategy is to use antagonists to the *N*-methyl-D-aspartate (NMDA) receptors. Commonly used cholinesterase inhibitors are donepezil, rivastigmine, galantamine and tacrine, whereas memantine is non-competitive antagonists

for NMDA. In mild to moderate AD, cholinesterase inhibitors are used, and in case of moderate to severe AD, memantine is used. Amongst these drugs, donepezil was first to be approved by US Food and Drug Administration (FDA) (7). Besides there are many investigations are working on the molecules to act on the pathophysiology of AD.

Since AD is a multifactorial syndrome, multi-target drugs would show more therapeutic potency. Zhang *et al.* (8), in their review, have highlighted on nine major targets associated with AD, which are acetylcholine esterase (AChE), beta-site amyloid precursor protein cleaving enzyme 1 (β -secretase, BACE-1), glycogen synthase kinase 3 beta (GSK-3 β), monoamine oxidases (MAOs), metal ions in the brain, NMDA receptor, 5-hydroxytryptamine (5-HT) receptors, the third subtype of histamine receptor (H₃ receptor), and phosphodiesterases (PDEs). Sahoo *et al.* (9) has also opined that one-molecule-one-target strategy is failed to treat the AD. They reported that "combinations-drugs-multiple-targets" (CDMT) should be considered in treatment of AD.

Since these therapies have failed to become a promising remedy for AD (10), there is a significant gap in improving the therapeutic modules. Oxidative stress, being major pathophysiology in AD, antioxidant components have shown their efficacy in various studies and clinical trials (11-13). Polyphenol compounds found in plants which reduce the oxidative stress in them, would provide antioxidant support in human brain also. RSV is a naturally occurring polyphenolic compound found majorly in grapes. RSV has gained attention in pharmacology field due to its antioxidant, anti-inflammatory, anti-cancerous and anti-aging properties (14-15).

4. RESVERATROL (RSV)

RSV is a phytoalexin found in many plants like white hellebore, mulberry, skin of grapes, red wine extracts and peanuts. RSV belongs to a family polyphenolic compounds called stilbenes (16). RSV was isolated for the first time, from the root of white hellebore (*Veratum grandiflorum*) in 1940 (17). Later RSV was extracted from root of polygonum cupsidatum in 1963. These plants were used in

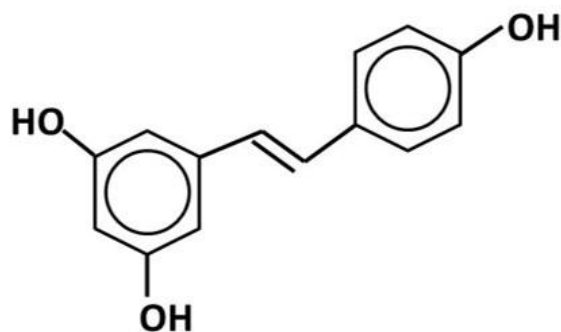


Figure 1. showing the chemical structure of trans-RSV.

traditional Chinese and Japanese medicine (17). RSV gained its popularity in pharmacology, when an *in vivo* study showed its anti-carcinogenic activity during 1997. Far ahead, several reports confirmed the advantageous properties of RSV due to its antioxidant, anti-inflammatory, anti-diabetic and anti-obesity effects (17-19). It is also observed that RSV reduces the incidence of cardiovascular diseases (20).

4.1. Chemical structure of RSV

The chemical structure of RSV is: P-hydroxyl group in ring A and conjugated double bond system, which is responsible for its antioxidant property. Chemical structure of RSV is similar to oestrogen diethylstilbestrol (21) (Figure 1). RSV presents as two geometric isomers: cis-RSV and trans-RSV. Trans-RSV is synthesized in plants as the end product of phenylpropanoid pathway. When trans-RSV is exposed to ultra-violet rays, it can get isomerized into cis-RSV (22). It is readily soluble in fat and stable in powder form. Other compounds which belong to stilbene group are Combrestatin A-4 and Pterostilbene *etc.* (23).

4.2. Sources of RSV

RSV was found in more than 70 plant species (24). RSV was used in traditional Japanese and Chinese medicine especially in cancer treatments. The major dietary source of RSV is red wine. In India also, the Ayurvedic preparation Drakshasava contains RSV (20). Though RSV is present in many plants, red wine is the important dietary source of RSV. Many review articles on RSV

mention about the "French Paradox". In France, the incidence of cardiovascular diseases are less in spite of consuming high fatty diets. This is believed to be due to the consumption of red wine, which contains RSV (17).

Reinisalo *et al.* (25), have mentioned the sources of stilbene compounds. Their list contains many sources of RSV and some of the plants also contain other stilbenes. The sources of RSV according to Reinisalo *et al.* (25) are represented in Table 1.

4.3. Neuroprotective effects of RSV

Several *in-vitro* and *in-vivo* studies have revealed the neuroprotective effect of RSV. RSV crosses blood brain barrier and exerts its antioxidant effect by enhancing the anti-oxidant enzymes (26). RSV was stated to be beneficial against cell death of neurons (Table 2) and cell dysfunction and was found to be beneficial against ailments like AD, Huntington's disease and epilepsy (27-28). It is well known that RSV is neuroprotective and helps in diseases like diabetes mellitus and cerebral ischemia as well. RSV is also known to reverse the motor as well as cognitive impairment induced by 3-intropropionic acid in Huntington's model (29) and intra cerebro-ventricular colchicine induced cognitive impairment in Alzheimer's model (30).

4.3.1. Activation of SIRT1

RSV shows its neuroprotective activity by activating SIRT1 which is NAD⁺-dependent class III deacetylases (28, 31-32). SIRT1 up regulation is one of the major features of calorie restriction and it is a well-known fact that calorie restriction will prevent the neuronal degeneration. Howitz *et al.* (19) explained that RSV can increase the life of *Saccharomyces cerevisiae*, a yeast. This action of RSV appears to imitate the limiting of calories in diet and activates the sirtuin proteins. RSV is involved in SIRT1 mediated lifespan extension activity (19, 32-33).

Albani *et al.* (34) found that RSV reduces the oxidative stress (Table 2) and protein aggregation in *in-vitro* model using neuro-blastoma cell line SK-N-BE. RSV also shown its capacity to increase the expression of peroxisome proliferator-activated

Table 1. Sources of RSV and other stilbenes

Plant	Stilbene compounds
Cocoa (<i>Theobroma cacao</i> L.)	RSV
Grape (<i>Vitis vinifera</i> L.)	RSV
Hop (<i>Humulus lupulus</i> L.)	RSV
Peanut (<i>Arachis hypogaea</i> L.)	RSV
Rhubarbs (<i>Rheum</i> L.)	RSV, Piceatannol, Rhapontigenin,
Strawberry (<i>Fragaria x ananassa</i> Duch.)	RSV
Sugar cane (<i>Saccharum</i> spp.)	RSV, Piceatannol
Bilberry (<i>V. myrtillus</i>)	RSV
Cranberry (<i>V. macrocarpon</i>)	RSV
Tomato (<i>Lycopersicon esculentum</i> Mill.)	RSV
Highbush blueberry (<i>V. corymbosum</i>)	RSV, Piceatanno, Pterostilbene
Red wine	RSV, Piceatannol
White wine	RSV
RSV - Resveratrol	

receptor gamma co-activator 1 alpha (PGC-1 α), nuclear respiratory factor 1 (NRF1) and T fam, COX 1 level, thereby increasing the mitochondrial biogenesis in CA3 region of hippocampus in rat model of status epilepticus (28). In their study they observed changes in the mitochondrial biogenesis machinery, which up regulated the PGC-1 α expression. RSV which is a known activator of PGC-1 α , along with increased PGC-1 α expression promoted the mitochondrial biogenesis. They also observed that RSV has the capacity to decrease the activity of caspase -3 activity thereby decreasing the hippocampal damage. These observations state that RSV can show endogenous protective mechanism against hippocampal damage. Supporting the above study, Wang *et al.* (35) also confirmed the enhanced expression and activity of SIRT1 in hippocampus in status epilepticus rat model treated with RSV. In addition there was increase in PGC-1 α expression, mitochondrial antioxidant enzymes including SOD2 and uncoupling protein 2 (UCP2). They also observed the enhanced mitochondrial electron transport chain complex 1 activity with increased adenosine triphosphate (ATP). These studies conclude that RSV can minimize the oxidative stress by activating the SIRT1 in hippocampus.

Evidence suggesting the effect of RSV to mitigate the brain tissue damage and reestablish

normal activity of the mitochondria (Table 2) is partly credited to its effect on SIRT1-dependent deacetylation of PGC-1 α , a protein factor necessary for biogenesis of mitochondria and activation of peroxisome proliferator-activated receptor- γ (PPAR- γ) (36). This ability of RSV to intensify the action of SIRT1 and related enzyme activities could result in alteration in transcription profiles of the neurons and improved anti-apoptotic activities (Table 2). Altogether, these studies strongly specify that along with the anti-inflammatory and antioxidant property, RSV shows neuroprotective activity by initiation of SIRT1. By these evidences we can consider RSV as a therapeutic agent for neurodegenerative disorders.

4.3.2. Effect of RSV on microglia

Microglia are the chief immune cells found in the central nervous system. Microglia are known to show their inflammatory reactions by releasing pro-inflammatory mediators like tumour necrosis factor α (TNF- α), interleukin - β , nitric oxide (NO) and reactive oxygen species (ROS) with response to pathogen invasion and cell debris. In neurodegenerative disorders like AD, Parkinson's disorder and Multiple sclerosis, the activated microglia are accumulated around the lesion. Though the role of activated microglia is to remove the necrotic neurons, over activated microglia may damage the neurons (37- 39). Microglia have two phenotypes, pro-

Table 2. Mechanisms of action of RSV

Action	Mechanism	References
Inhibition of A β plaque	Remodelling soluble oligomers and fibrillary β -amyloids into non-toxic form	Ahmed <i>et al</i> , (22)
Reducing the microglial activation	Supressing pro-inflammatory mediators	Yao <i>et al</i> , (37)
	Supression of M1 polarization and activation of M2 polarization	Yang, (39)
Prevention of oxidative stress	Activation of SIRT1	Albani <i>et al</i> , (34)
Mitochondrial biogenesis	Promotion of PGC-1 α expression	Chuang <i>et al</i> ,(28)
	AMPK Activation	Dasgupta and Milbrandt (36)
Prevention of cell death	Prevention in increase in ROS	Albani <i>et al</i> , (34)
Prevention of apoptotic cell death in hippocampus	Increased mitochondrial UCP2 expression, through activation of PPAR γ	Chuang <i>et al</i> (28), Lin <i>et al</i> , (16)

inflammatory M1 and anti-inflammatory M2. RSV has shown its anti-inflammatory potential by supressing M1 polarization and activating M2 polarization both *in-vitro* and *in vivo* (39). The previous study by Yao *et al*. (37), also proved that, RSV has the potential to inhibit the A β -induced BV-2 microglial cells (Table 2).

Another study by Kodali *et al*. (40) showed that RSV has reduced glial activation and helped in increasing the hippocampal neurogenesis along with the prevention of age related memory and mood dysfunction. The study was conducted on 21 month old F344 rats. The immuno-histochemical characterization using OX-42 (CD11b) antibody showed ramified (resting) microglia in hippocampus of RSV treated old aged rat models. However in old aged rats without RSV treatment, there was increased number of activated microglia (41).

4.3.3. Effect of RSV on amyloid plaque formation

Accumulation of amyloid plaques in the brain is one of the characteristic features of neuro degenerative disorders like AD. Accumulation of A β in brain leads to release of iNOS, which increases production of NO which causes neurodegeneration. In AD brain, high level of NO is seen. In A β induced AD rat model, intra-cerebro-vascular injection of RSV has reduced the accumulation of A β (Table 2) in hippocampus (41).

Chen *et al*. (42) have observed the beneficial effect of RSV in Tg6799 mice, a transgenic model of AD. Their study showed RSV was able to

decrease the expression of amyloid precursor protein, along with improvement of spatial working memory. RSV can bind directly to monomeric and fibrillary β - amyloids. The binding capacity of RSV is higher with fibril β - amyloids than that of monomers. RSV selectively remodels the soluble oligomers and fibrillary β -amyloids into non-toxic form. And it is also witnessed that incubation of A β 1-40 and 1-42 fragments when incubated with RSV, the length as well as number of these fibrils were reduced (22, 43-44). These observations clearly suggest the usage of RSV in preventing the progression of AD. The binding capacity of RSV may also help in the diagnosis of AD (22, 45).

4.4. Bio-availability of RSV

Though RSV shows good oral absorption, its bio availability is less due to poor water solubility. This poor bioavailability results in shorter biological half-life further leading to rapid metabolism and rapid clearance, thereby limiting the capacity to accumulate in the target tissue (46). The stability and biotransformation may influence the antioxidant property of RSV (47). The oral dose of 25mg of RSV results in less than 5 μ g/ml in the serum and intravenous dose of 0.2 mg results in 16.4- 30.7 ng/ml in serum (48). Modification in the chemical structure and metabolism can increase the efficacy by changing the cellular and metabolic targets. Hence many experiments have been working on modifying the chemical structure of RSV in order to increase its bioavailability and potency (47).

The molecular structure of trans-RSV is a stilbene core with two phenyl rings which is linked by a double bond. Three hydroxy groups are present in both phenyl rings in position 3, 4 and 5. Trans-RSV can be easily converted into its bio active form, isomer E RSV by isomerization of double bond (49). Many researchers have worked on modifying the chemical structure of RSV to increase its bioavailability. Most commonly used RSV analogue is its methylated derivative, 3,4,5,4'-tetramethoxy-stilbene, which has shown high accumulation in intestinal mucosa (48, 50). RSV when administered with bio-enhancers like piperine has showed better bio efficacy without showing its increase in bioavailability (51). Recent studies have showed that, nano-formulations of RSV can exhibit improved drug release and stability (52).

4.5. Adverse effects of RSV

In animal models RSV dose ranges from 0.1mg/kg to 1000 mg/kg body weight. Low dose RSV (5mg/kg/day) has caused weight gain in mice, whereas high dose (400mg/kg/day) has resulted in weight loss (17). Johnson *et al.* (53) reported that, administration of high dose of RSV in rats has shown hepatomegaly, but there was no histological evidences for hepatotoxicity. Chow *et al.* (54) reported from their human study, the events of adverse effects like diarrhea, heart burn, increased appetite, mood alteration and menstrual changes in females, which are possibly or probably caused by RSV. It has been opined that 1gm/day dose of RSV is well tolerated in human trials (53, 55). Since RSV is an antioxidant, it can be safely used as an oral drug.

4.6. Drug interaction and safety of RSV

Though there are several reports (17, 53-54) available about the pharmacological benefits of RSV, there are no significant evidence of drug interaction with RSV. Sahoo *et al.* (56) has reported that RSV can reverse the cognitive impairment in prenatal stress induced rats. This suggests that RSV is safe in pregnant rats and it has neuroprotective effects. RSV has been used with curcumine (57) and piperine (53) in order to increase its bioavailability and RSV shown its efficacy without any drug

interaction. However adverse effects have been reported with other phenolic compounds (58), hence further studies are required to prove that RSV is safe.

5. CONCLUSION

RSV has antioxidant, anti-aging and neuroprotective properties. RSV crosses blood brain barrier and exerts its antioxidant effect by enhancing the anti-oxidant enzymes. RSV has reduced glial activation and helped in increasing the hippocampal neurogenesis. It prevents age related mood dysfunction and memory loss. Though the bioavailability of RSV is less, it can be improved by modifying its chemical structure. The combinations-drugs-multiple-targets should be considered in treatment of AD. RSV if given along with other acetyl choline esterase inhibitors, can give better results in AD. There are no significant evidences to show the adverse effects of RSV. However adverse effects have been reported with other phenolic compounds, hence further studies are required to prove that RSV is safe.

6. REFERENCES

1. Zanetti, O., Solerte, S.B., and F. Cantoni: Life expectancy in Alzheimer's disease (AD). Arch Gerontol Geriatr 49, 237-243 (2009)
DOI: 10.1016/j.archger.2009.09.035
2. Huang, W.J., Zhang, X. and W.W. Chen: Role of oxidative stress in Alzheimer's disease. Biomed Rep 4, 519-522 (2016)
DOI: 10.3892/br.2016.630
3. Mietelska-Porowska, A., Wasik, U., Goras, M., Filipek, A., and G. Niewiadomska: Tau protein modifications and interactions: their role in function and dysfunction. Int J Mol Sci 15, 4671-4713 (2014)
DOI: 10.3390/ijms15034671
4. Pradeepkiran, J.A., and P.H. Reddy: Structure based design and molecular

- docking studies for phosphorylated tau inhibitors in Alzheimer's disease. *Cells* 8, 260 (2019)
DOI: 10.3390/cells8030260
5. Ballatore, C., Lee, V.M., and J.Q. Trojanowski: Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci* 8, 663-672 (2007)
DOI: 10.1038/nrn2194
 6. Yu, K.C., Kwan, P., Cheung, S.K. K., Ho, A., and L. Baum: Effects of resveratrol and morin on insoluble tau in tau transgenic mice. *Transl Neurosci* 9, 54-60 (2018)
DOI: 10.1515/tnsci-2018-0010
 7. Morrison, A.S. and C. Lyketsos: The pathophysiology of Alzheimer's disease and directions in treatment. *Advanced study in Nursing* 3, 256-270 (2005)
 8. Zhang, P., Xu, S., Zhu, Z., and J. Xu: Multi-target design strategies for the improved treatment of Alzheimer's disease. *Eur J Med Chem* 176, 228-247 (2019)
DOI: 10.1016/j.ejmech.2019.05.020
 9. Sahoo, A.K., Dandapat, J., Dash, U.C., and S. Kanhar: Features and outcomes of drugs for combination therapy as multi-targets strategy to combat Alzheimer's disease. *J Ethnopharmacol* 215, 42-73 (2018)
DOI: 10.1016/j.jep.2017.12.015
 10. Kamat, P.K., Kalani, A., Rai, S., Swarnkar, S., Tota, S., Nath, C., and N. Tyagi: Mechanism of oxidative stress and synapse dysfunction in the pathogenesis of Alzheimer's disease: understanding the therapeutics strategies. *Mol Neurobiol* 53, 648-661 (2016)
DOI: 10.1007/s12035-014-9053-6
 11. Joy, T., Rao, M.S. and S. Madhyastha: N-acetyl cysteine supplement minimize tau expression and neuronal loss in animal model of Alzheimer's disease. *Brain Sci* 8, pii: E185 (2018)
DOI: 10.3390/brainsci8100185
 12. Cente, M., Filipcik, P., Mandakova, S., Zilka, N., Krajciova, G. and M. Novak: Expression of a truncated human tau protein induces aqueous-phase free radicals in a rat model of tauopathy: implications for targeted antioxidative therapy. *J Alzheimers Dis* 17, 913-920 (2019)
DOI: 10.3233/JAD-2009-1107
 13. Park, S.Y., Kim, H.S., Cho, E.K., Kwon, B.Y., Phark, S., Hwang, K.W., and D. Sul: Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation. *Food Chem Toxicol* 46, 2881-2887 (2008)
DOI: 10.1016/j.fct.2008.05.030
 14. Mohan, S., Gobinath, T., Salomy, A., Nisha, M., Kandasamy, M., Essa, M.M., Jayachandran, K.S., and M. Anusuyadevi: Biophysical interaction of resveratrol with sirtuin pathway: Significance in Alzheimer's disease. *Front Biosci (Landmark Ed)* 23, 1380-1390 (2018)
DOI: 10.2741/4650
 15. Gomes, B.A.Q., Silva, J.P.B., Romeiro, C.F.R., Dos Santos, S.M., Rodrigues, C.A., Gonçalves, P.R., Sakai, J.T., Mendes, P.F.S., Varela, E.L.P., and M.C. Monteiro: Neuroprotective Mechanisms of Resveratrol in Alzheimer's Disease: Role of SIRT1. *Oxid Med Cell Longev*, Article ID 8152373, 15 pages (2018)

- DOI: 10.1155/2018/8152373
16. Li, H., Xia, N., Hasselwander, S., and A. Daiber: Resveratrol and vascular function. *Int J Mol Sci* 20, pii: E2155 (2019)
DOI: 10.3390/ijms20092155
 17. Timmers, S., Auwerx J., and P. Schrauwen: The journey of resveratrol from yeast to human. *Aging (Albany NY)* 4, 146-158 (2012)
DOI: 10.18632/aging.100445
 18. Vang, O., Ahmad, N., Baile, C.A., Baur, J.A., Brown, K., Csiszar, A., Das, D.K., Delmas, D., Gottfried, C., Lin, H.Y., Ma, Q.Y., Mukhopadhyay, P., Nalini, N., Pezzuto, J.M., Richard, T., Shukla, Y., Surh, Y.J, Szekeres, T., Szkudelski, T., Walle, T., and J.M. Wu: What is new for an old molecule? Systematic review and recommendations on the use of resveratrol. *PLoS One* 6, e19881 (2011)
DOI: 10.1371/journal.pone.0019881
 19. Howitz, K.T., Bitterman, K.J., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, J.G., Zipkin, R.E., Chung, P., Kisielewski, A., Zhang, L.L., Scherer, B., and D.A. Sinclair: Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425, 191-196 (2003)
DOI: 10.1038/nature01960
 20. Smoliga, J.M., Baur, J.A. and H.A. Hausenblas: Resveratrol and health-a comprehensive review of human clinical trials. *Mol Nutr Food Res* 55, 1129-1141 (2011)
DOI: 10.1002/mnfr.201100143
 21. Kong, D., Yan, Y. and X. He: Effects of resveratrol on the mechanisms of antioxidants and estrogen in Alzheimer's disease. *BioMed Research International* Article ID 8983752, 8 pages (2019)
DOI: 10.1155/2019/8983752
 22. Ahmed, T., Javed, S., Javed, S., Tariq, A., Šamec, D., Tejada, S., Nabavi, S.F., Braidy, N. and S.M. Nabavi: Resveratrol and Alzheimer's disease: mechanistic insights. *Mol Neurobiol* 54, 2622-2635 (2017)
DOI: 10.1007/s12035-016-9839-9
 23. Giacomini, E., Rupiani, S., Guidotti, L., Recanatini, M., and M. Roberti: The use of stilbene scaffold in medicinal chemistry and multi-target drug design. *Curr Med Chem* 23, 2439-2489 (2016)
DOI: 10.2174/0929867323666160517-121629
 24. Singh, C.K., George, J. and N. Ahmad: Resveratrol-based combinatorial strategies for cancer management. *Ann N Y Acad Sci* 1290, 113-121 (2013)
DOI: 10.1111/nyas.12160
 25. Reinisalo, M., Kärllund, A., Koskela, A., Kaarniranta, K. and R.O. Karjalainen: Polyphenol stilbenes: molecular mechanisms of defence against oxidative stress and aging-related diseases. *Oxid Med Cell Longev* 340520 (2015)
DOI: 10.1155/2015/340520
 26. Palle, S. and P. Neerati: Improved neuroprotective effect of resveratrol nanoparticles as evinced by abrogation of rotenone-induced behavioural deficits and oxidative and mitochondrial dysfunctions in rat model of Parkinson's disease. *Naunyn Schmiedebergs Arch Pharmacol* 391, 445-453 (2018)
DOI: 10.1007/s00210-018-1474-8
 27. Wan, D., Zhou, Y., Wang, K., Hou, Y., Hou, R. and X. Ye: Resveratrol provides

- neuroprotection by inhibiting phosphodiesterases and regulating the cAMP/AMPK/SIRT1 pathway after stroke in rats. *Brain Res Bull* 121, 255-262 (2016)
DOI: 10.1016/j.brainresbull.2016.02.011
28. Chuang, Y.C., Chen, S.D., Hsu, C.Y., Chen, S.F., Chen, N.C. and S.B. Jou: Resveratrol promotes mitochondrial biogenesis and protects against seizure-induced neuronal cell damage in the hippocampus following status epilepticus by activation of the PGC-1A signalling pathway. *Int J Mol Sci* 20, pii: E998 (2019)
DOI: 10.3390/ijms20040998
29. Kumar, P., Padi, S.S., Naidu, P.S., and A. Kumar: Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: possible neuroprotective mechanisms. *Behav Pharmacol* 17, 485-492 (2006)
DOI: 10.1097/00008877-200609000-00014
30. Kumar, A., Naidu, P.S., Seghal, N. and S.S. Padi: Neuroprotective effects of resveratrol against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress in rats. *Pharmacology* 79, 17-26 (2007)
DOI: 10.1159/000097511
31. Sinclair, D.A: Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev* 126, 987-1002 (2005)
DOI: 10.1016/j.mad.2005.03.019
32. Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., and D.A. Sinclair: Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 444, 337-342 (2006)
DOI: 10.1038/nature05354
33. Lamming, D.W., Wood, J.G., and A. Sinclair: Small molecules that regulate lifespan: evidence for xenohormesis. *Mol Microbiol* 53, 1003-1009 (2004)
DOI: 10.1111/j.1365-2958.2004.04209.x
34. Albani, D., Polito, L., Batelli, S., De Mauro, S., Fracasso, C., Martelli, G., Colombo, L., Manzoni, C., Salmona, M., Caccia, S., Negro, A., and G. Forloni: The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by alpha-synuclein or amyloid-beta (1-42) peptide. *J Neurochem* 110, 1445-1456 (2009)
DOI: 10.1111/j.1471-4159.2009.06228.x
35. Wang, S.J., Zhao, X.H., Chen, W., Bo, N., Wang, X.J., Chi, Z.F. and W. Wu: Sirtuin 1 activation enhances the PGC-1 α /mitochondrial antioxidant system pathway in status epilepticus. *Mol Med Rep* 11, 521-526 (2015)
DOI: 10.3892/mmr.2014.2724
36. Dasgupta, B. and J. Milbrandt: Resveratrol stimulates AMP kinase activity in neurons. *Proc Natl Acad Sci U S A* 104, 7217-7222 (2007)
DOI: 10.1073/pnas.0610068104
37. Yao, Y., Li, J., Niu, Y., Yu, J.Q., Yan, L., Miao, Z.H., Zhao, X.X., Li, Y.J., Yao, W.X., Zheng, P. and W.Q. Li: Resveratrol inhibits oligomeric A β -induced microglial activation via NADPH oxidase. *Mol Med*

- Rep 12, :6133-6139 (2015)
DOI: 10.3892/mmr.2015.4199
38. Xu, L., He, D. and Y. Bai: Microglia-mediated inflammation and neurodegenerative disease. *Mol Neurobiol* 53, 6709-6715 (2016)
DOI: 10.1007/s12035-015-9593-4
39. Yang, X., Xu, S., Qian, Y. and Q. Xiao: Resveratrol regulates microglia M1/M2 polarization via PGC-1 α in conditions of neuroinflammatory injury. *Brain Behav Immun* 64, 162-172 (2017)
DOI: 10.1016/j.bbi.2017.03.003
40. Kodali, M., Parihar, V.K, Hattiangady, B., Mishra, V., Shuai, B. and A.K. Shetty: Resveratrol prevents age-related memory and mood dysfunction with increased hippocampal neurogenesis and microvasculature, and reduced glial activation. *Sci Rep* 5, 8075 (2015)
DOI: 10.1038/srep08075
41. Huang, T.C., Lu, K.T., Wo, Y.Y., Wu, Y.J. and Y.L. Yang: Resveratrol protects rats from A β -induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation. *PLoS One* 6, e29102 (2011)
DOI: 10.1371/journal.pone.0029102
42. Chen, Y., Shi, G.W., Liang, Z.M., Sheng, S.Y., Shi, Y.S., Peng, L., Wang, Y.P., Wang, F. and X.M. Zhang: Resveratrol improves cognition and decreases amyloid plaque formation in Tg6799 mice. *Mol Med Rep* 19, 3783-3790 (2019)
DOI: 10.3892/mmr.2019.10010
43. Ge, J.F., Qiao, J.P., Qi, C.C., Wang, C.W. and J.N. Zhou: The binding of resveratrol to monomer and fibril amyloid beta. *Neurochem Int* 61, 1192-201 (2012)
DOI: 10.1016/j.neuint.2012.08.012
44. Ladiwala, A.R., Lin, J.C., Bale, S.S., Marcelino-Cruz, A.M., Bhattacharya, M., Dordick, J.S. and P.M. Tessier: Resveratrol selectively remodels soluble oligomers and fibrils of amyloid Abeta into off-pathway conformers. *J Biol Chem* 285, 24228-24237 (2010)
DOI: 10.1074/jbc.M110.133108
45. Guo, J.P., Yu, S. and P.L. McGeer: Simple in vitro assays to identify amyloid-beta aggregation blockers for Alzheimer's disease therapy. *J Alzheimers Dis* 19, 1359-1370 (2010)
DOI: 10.3233/JAD-2010-1331
46. Rege, S.D., Geetha, T., Griffin, G.D., Broderick, T.L. and J.R. Babu: Neuroprotective effects of resveratrol in Alzheimer disease pathology. *Front Aging Neurosci* 6:218 (2014)
DOI: 10.3389/fnagi.2014.00218
47. Delmas, D., Aires, V., Limagne, E., Dutartre, P., Mazué, F., Ghiringhelli, F. and N. Latruffe: Transport, stability, and biological activity of resveratrol. *Ann N Y Acad Sci* 1215, 48-59 (2011)
DOI: 10.1111/j.1749-6632.2010.05871.x
48. Walle, T: Bioavailability of resveratrol. *Ann N Y Acad Sci* 1215, 9-15 (2011)
DOI: 10.1111/j.1749-6632.2010.05842.x
49. Latruffe, N. and D. Vervandier-Fasseur: Strategic syntheses of vine and wine resveratrol derivatives to explore their effects on cell functions and dysfunctions. *Diseases* 6, 4 (2018)
DOI: 10.3390/diseases6040110
50. Sale, S., Verschoyle, R.D., Boocock, D., Jones, D.J., Wilsher, N., Ruparelia, K.C., Potter, G.A., Farmer, P.B., Steward, W.P. and A.J. Gescher: Pharmacokinetics in mice and growth-inhibitory properties of

- the putative cancer chemopreventive agent resveratrol and the synthetic analogue trans 3,4,5,4'-tetramethoxystilbene. *Br J Cancer* 90, 736-44 (2004)
DOI: 10.1038/sj.bjc.6601568
51. Wightman, E.L., Reay, J.L., Haskell, C.F., Williamson, G., Dew, T.P. and D.O. Kennedy: Effects of resveratrol alone or in combination with piperine on cerebral blood flow parameters and cognitive performance in human subjects: a randomised, double-blind, placebo-controlled, cross-over investigation. *Br J Nutr* 112, 203-213 (2014)
DOI: 10.1017/S0007114514000737
52. Soo, E., Thakur, S., Qu, Z., Jambhrunkar, S., Parekh, H.S. and A. Popat: Enhancing delivery and cytotoxicity of resveratrol through a dual nanoencapsulation approach. *J Colloid Interface Sci* 462, 368-374 (2016)
DOI: 10.1016/j.jcis.2015.10.022
53. Johnson, J.J., Nihal, M., Siddiqui, I.A., Scarlett, C.O., Bailey, H.H., Mukhtar, H. and N. Ahmad: Enhancing the bioavailability of resveratrol by combining it with piperine. *Mol Nutr Food Res* 55, 1169-76 (2011)
DOI: 10.1002/mnfr.201100117
54. Chow, H.H., Garland, L.L., Hsu, C.H., Vining, D.R., Chew, W.M., Miller, J.A., Perloff, M., Crowell, J.A. and D.S. Alberts: Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res (Phila)* 3, 1168-1175 (2010)
DOI: 10.1158/1940-6207.CAPR-09-0155
55. Goldberg, D.M., Yan, J. and G.J. Soleas: Absorption of three wine-related polyphenols in three different matrices by healthy subjects, *Clin Biochem* 36, 79-87 (2003)
DOI: 10.1016/S0009-9120(02)00397-1
56. Sahu, S.S., Madhyastha, S., and G.M. Rao: Neuroprotective effect of resveratrol against prenatal stress induced cognitive impairment and possible involvement of Na(+), K(+)-ATPase activity. *Pharmacol Biochem Behav* 103, 520-525 (2013)
DOI: 10.1016/j.pbb.2012.09.012
57. Gumireddy, A., Christman, R., Kumari, D., Tiwari, A., North, E.J. and H. Chauhan: Preparation, characterization, and in vitro evaluation of curcumin- and resveratrol-loaded solid lipid nanoparticles. *AAPS PharmSciTech* 20, 145 (2019)
DOI: 10.1208/s12249-019-1349-4
58. Tomé-Carneiro, J., Larrosa, M., González-Sarrías, A., Tomás-Barberán, F.A., García-Conesa, M.T. and J.C. Espín: Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. *Curr Pharm Des* 19, 6064-6093 (2013)
DOI: 10.2174/13816128113199990407

Abbreviations: AD, Alzheimer's disease; RSV, Resveratrol; SIRT1, Sirtuin; NMDA, *N*-methyl-D-aspartate; AChE, acetylcholine esterase; NAD, nicotinamide adenine dinucleotide; PGC-1 α , peroxisome proliferator-activated receptor gamma co-activator 1 alpha; COX 1, cyclooxygenase 1; CA 3, cornu ammonis 3; NO, nitric oxide; ROS, reactive oxygen species; NOS, nitric oxide synthase;

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