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# Clinical Research Progress of NRF2 Activators in the Treatment of Age-related Diseases

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***Abstract:*** *Oxidation is closely related to the occurrence and development of aging and age-related diseases. NRF2 (Nuclear factor erythroid 2 related factor 2) is a key regulator of oxidative stress, which regulates the expression of antioxidant proteins, detoxification enzymes and various cytoprotective proteins. NRF2 maintains organism redox balance and genome stability, delaying the aging process and the occurrence and development of aging-related diseases. Pharmacological activators of NRF2 has been widely reported in basic research, and has performed well in clinical application research. In this article, we will focus on the latest news in basic and clinical research of NRF2 activators in age related diseases.*

***Keywords:*** *NRF2, aging, oxidative stress, age-related diseases, NRF2 activators*

## 1. Introduction

Aging refers to a series of impaired functions, occuring with the increase of age, which is a universal biological phenomenon. At the molecular level, aging can lead to obvious DNA damage, telomere wear, protein homeostasis, nutrient imbalance, and epigenetic changes. And it is associated with cellular senescence, stem cell failure, mitochondrial dysfunction, and oxidative stress at the cellular level. Besides, aging makes physiological functions and cognitive abilities decline [1]. Especially for the elderly, aging greatly increases the incidence of various chronic diseases [2, 3] (figure 1). The free radical theory proposed by Tanem Harman believes that the accumulation of reactive oxygen species (ROS) is the primary cause of biomolecular damage, and it is also an important explanation for orgnism dysfunction during the aging process. The accumulation of excessive ROS stimulates oxidative stress, induces serious damage of lipids, proteins and DNA, as well as persistent chronic inflammation, which can induce various chronic diseases [4].

Nuclear factor erythrocyte-like 2 related factor 2 (NFE2L2) is a member of the cap'n' collar (CNC) subfamily of the basic region leucine zipper (bZip) transcription factor [5]. Its structure is shown in Figure 2. The cell defense mechanism plays an important role in resisting acute and chronic damage from the environment [6, 7].

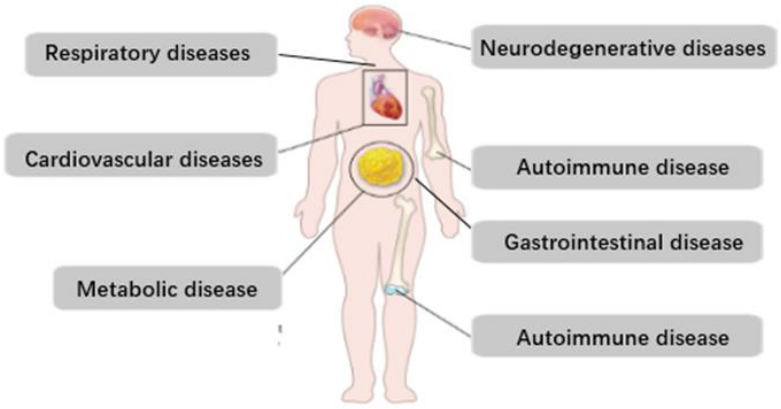


*Figure 1: Age-related diseases.*

Under physiological conditions, in the cytoplasm, Kelch-like ECH-related protein 1 (KEAP1), whose structure is shown in Figure 2, binds to NRF2 to form a KEAP1/NRF2 protein complex, and promotes the degradation of NRF2 by the 26S proteasome. However, under high oxidative pressure, the activity of

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KEAP1 to target NRF2 for ubiquitination and degradation decreases. NRF2 accumulates in large quantities and is transported to the nucleus to combine with the antioxidant response element (ARE) to promote the expression of a variety of detoxification enzymes, antioxidant enzymes and cytoprotective proteins [8] (Figure 3). Studies have shown that NRF2 knockout experimental animals have an increased prevalence of a series of aging-related diseases such as heart disease, atherosclerosis, liver damage, and premature aging and even shortened lifespan [9-11]. Most chronic diseases occur in the elderly, and these diseases have neither a unique etiology nor a single pathological feature. Therefore, the most effective treatment is to stimulate the extensive cellular defenses by activating NRF2 drugs [12].

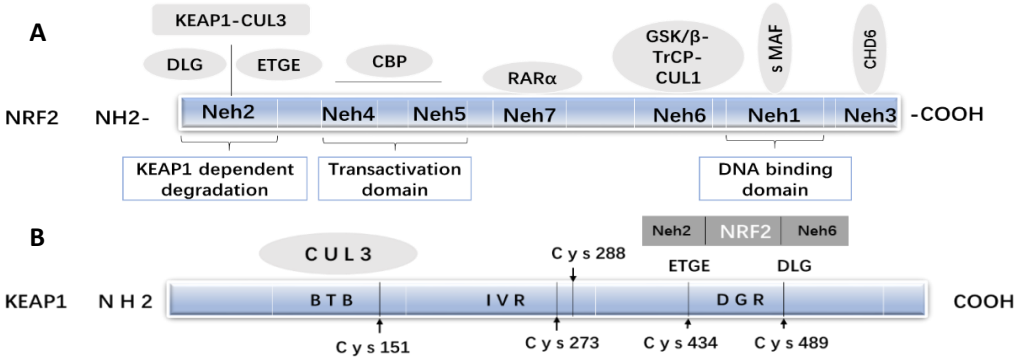


*Figure 2: Domain structure of NRF2 and KEAP1.*

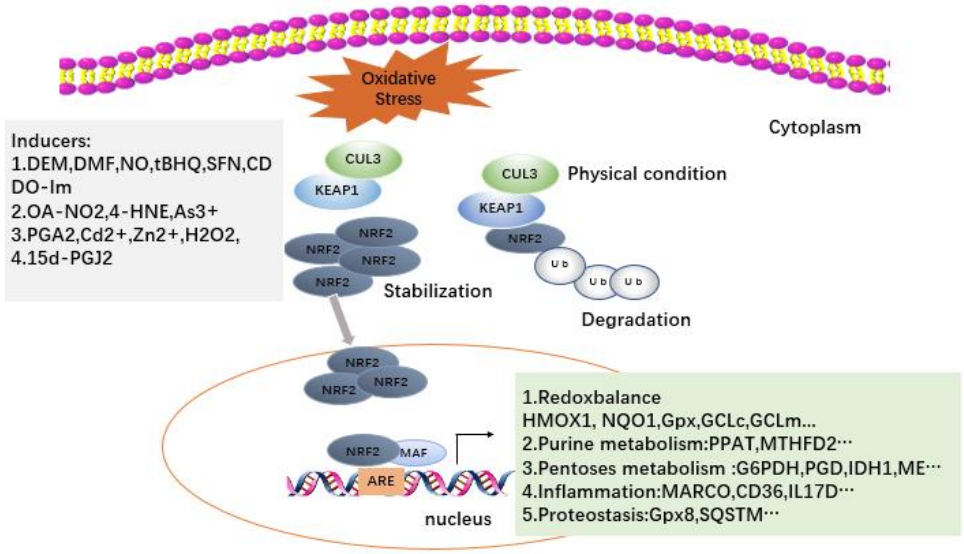


*Figure 3: NRF2/ARE signal pathway*

At present, the NRF2 agonists that have been widely studied and recognized include natural products such as resveratrol, curcumin, sulforaphane, cinnamaldehyde, quercetin, andrographolide, as well as DMF, CDDO-Me, RTA-408, etc. The activation mechanism of these compounds mainly includes modification of KEAP1 cysteine residues to destroy the NRF2-KEAP1 complex and promote the dissociation of NRF2; activation of upstream protein kinase B (Akt), extracellular signal-regulated kinase (Erk) and other protein kinase activities; inhibit proteasome degradation and NRF2 ubiquitination process. These mechanisms all lead to the accumulation of NRF2 in the cytoplasm and further translocate into the nucleus and activate the antioxidant cascade [13].

This article will mainly introduce the development and research progress of transcription factor NRF2 agonists as clinical drugs for the treatment of neurodegenerative diseases, metabolic diseases, cardiovascular diseases and other diseases.

## 2. Neurodegenerative diseases

Neurodegenerative diseases are caused by the loss of central nervous system (CNS) neurons or their myelin sheaths, which can lead to a series of chronic progressive dysfunctions, such as motor dysfunction,

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memory loss, and cognitive dysfunction. Studies have shown that neurodegenerative diseases mostly occur in the elderly, and aging is considered to be an important risk factor for their development. With the rapid aging of the global population, the incidence of neurodegenerative diseases is also rising sharply. The pathogenesis of neurodegenerative diseases is complex, but oxidative stress is considered to be a key factor in the research of multiple pathogenic mechanisms. The accumulation of oxidants such as glutamate and ROS in cells can cause damage to important cellular macromolecules and trigger a series of neurodegeneration and neuroinflammatory reactions [14]. The up-regulation of NRF2 and its target genes HO-1, NQO1, GCLM, Gpx, p62/SQSTM1, etc. can activate learning and memory in AD mouse models. Specific induction of NRF2-dependent antioxidant activity can activate cell defense, inhibit neuroinflammation, improve mitochondrial function and maintain protein homeostasis, so as to alleviate pathological features. Searching for effective activators to activate NRF2 in neurons and astrocytes is an important strategy for treating neurodegenerative diseases.

Abnormal phosphorylation and aggregation of Tau-like proteins are the important pathogenesis of neurodegenerative diseases. A large amount of phosphorylated Tau-like protein accumulation was found in the brains of NRF2 knockout mice. Sulforaphane (SFN), curcumin, and α-zinc sulfate can activate NRF2 and up-regulate the expression of NDP52 to eliminate phosphorylated Tau-like proteins [15]. Methylene blue can inhibit the abnormal accumulation of Tau protein. Research on the effectiveness and safety of methylene blue in the treatment of AD is in the phase 2 clinical trial phase, and its modified product TRx0237 is in the phase 3 clinical phase of AD treatment. After receiving treatment, the cognitive ability of moderate subjects improved significantly [16].

The gradual loss of synaptic function, the continuous damage of neuronal cells and the activation of microglia are important characteristics of the pathogenesis of neurodegenerative diseases. Curcumin can penetrate the blood-brain barrier, reduce inflammation in the brain, and affect synaptic plasticity. In wild-type mice, curcumin treatment can reduce ipsilateral cortical damage, neutrophil infiltration and microglia activation, increase the activity the expression of NRF2 and its downstream antioxidant enzymes [17]. In Wistar rat brain ischemia/reperfusion injury model, curcumin can improve rat brain oxidative damage and inflammation by up-regulating NRF2 and down-regulating NF-κB, and reduce infarct size [18]. The clinical trials of curcumin and its related preparations for the treatment of AD are currently mainly in the phase 1/2, which mainly focus on confirming the safety and effectiveness of curcumin as a treatment for AD. A large number of animal experiments have proved that resveratrol can reduce neuro-inflammation and protect nerve function, especially for AD model rats, it can well reduce the neuropathological characteristics of β-amyloid AD in rats, and improve the effect of β-amyloid AD. Memory loss caused by lesions [19]. In a phase 2 clinical trial of resveratrol in the treatment of AD, patients with AD received resveratrol or placebo for 12 months to determine whether daily resveratrol treatment is beneficial to delay or change memory and daily function. Some patients (15) were required to participate in a 24-hour pharmacokinetic (PK) sub-study, which will measure the level of resveratrol within 24 hours. The results show that resveratrol can maintain the integrity of the blood-brain barrier and alleviate the problem of cognitive decline in patients [20]. In addition to the treatment of AD, these activators can also be used to treat Parkinson's disease (PD).Potential for diseases such as amyotrophic lateral sclerosis (ALS). Among them, DMF was approved by FDA in 2013 for the treatment of MS.

## 3. Metabolic diseases

The incidence of diabetes has been increasing year by year around the world. At present, the prevalence of diabetes in China has reached 10.4%, ranking first in the world [21]. Studies have shown that diabetic patients are susceptible to aging-related complications, which indicates that diabetes may represent a state of aging. Senescent cells can induce insulin resistance and promote the development of diabetes by secreting senescence-related secretory phenotypes (SASP) such as TNFα and IL-6 [22]. The main characteristics of T2MD are chronic hyperglycemia, insulin secretion dysfunction and inflammation. In diabetic patients, the level of ROS is abnormally increased, and the expression of a variety of antioxidant enzymes is reduced. Obvious DNA damage can be observed, and free fatty acids, leptin and other circulating factors are increased [23]. Studies have shown that in NRF2 knockout mice and rats, ROS levels increase significantly, leading to increased blood glucose level and impaired insulin signaling pathways, indicating that the lack of NRF2 can aggravate type 1 diabetes and type 2 diabetes [24, 25].

Insulin secretion and insulin sensitivity can be significantly improved as the increasing level of NRF2. When KEAP1 knockout mice are crossed with diabetic db/db mice, the symptoms of insulin resistance and decreased insulin secretion can be improved. In addition, oral CDDO-Me can also reduce blood

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glucose levels in db/db mice [26]. CDDO-Me can prevent the further development of insulin resistance, it can also reverse the changes in protein tyrosine phosphatase 1B, insulin receptor substrate or insulin receptor expression, and prevent hepatic macrophage infiltration and inflammation [27]. A number of studies on the safety and effectiveness of CDDO-Me in the treatment of type 1 and type 2 diabetes and chronic kidney disease have entered the phase 2/3 clinical trial phase. Resveratrol can reduce the blood glucose level of high-glycemic rodents and can also regulate insulin levels. Continuous feeding resveratrol for 6 weeks in diabetic db/db mice can significantly reduce blood sugar, plasma free fatty acids, triglycerides and apolipoprotein B/apolipoprotein AI levels, and increase plasma adiponectin levels [28]. In rat experiments, resveratrol can inhibit impaired glucose tolerance and insulin resistance induced by high-fat diet in ovariectomized rats [29]. In the clinical research of resveratrol for the treatment of diabetes, a total of 18 items have been completed. In a phase II and phase III clinical trial on the effects of resveratrol on human age-related insulin resistance and inflammation, giving subjects 1000 mg/d resveratrol capsules for 28 days can reduce the patient's platelet activation and oxidized protein modification of high-density lipoprotein (HDL). Pentraxin3 concentration and total antioxidant level (TAS) can reflect the changes in inflammation levels in patients with type 2 diabetes after taking resveratrol. After giving subjects high and low doses (200mg/d and 40mg/d) of resveratrol for six months, the evaluation results show that resveratrol can dose-dependently enhance the levels of Pentraxin3 and TAS in patients [30]. In the Sprague-Dawley rat pancreatic islet test, SFN can improve the damage of pancreatic B cells and restore their insulin secretion function [31]. In addition, the study on the effect of curcumin on the efficacy of glimepiride in patients with T2DM, conducted by Tanta University in Egypt, will enter Phase IV clinical trials in September this year. The results of their previous studies show that curcumin can significantly improve the dyslipidemia of diabetic patients [32].

## 4. Cardiovascular disease

Hypoxia, blood flow disturbance and oxidative stress caused vascular endothelial dysfunction, which are the key risk factors for cardiovascular disease [33]. The analysis of a variety of cytoprotective genes regulated by NRF2 shows that NRF2 plays a key role in protecting cardiomyocytes and endothelial cells from dysfunction induced by oxidative stress [34]. NRF2 knockout mice are more susceptible to cardiac structure and function damage, as well as myocardial infarction and heart failure. In a variety of animal experimental models of cardiovascular-related diseases, it has been proved that NRF2 activators can reduce the severity of cardiovascular diseases related to ROS. For example, fumarate and hydrogen sulfide have obvious protective effects on myocardial ischemia-reperfusion injury and heart failure [35, 36]. Resveratrol [37-39] has the effects of protecting endothelial cell damage induced by high glucose, improving vascular calcification and vascular inflammation. MG132 can prevent aortic damage and myocardial damage [40].

The clinical trials of NRF2 agonists for the treatment of hypertension are still in the initial stage, mainly to confirm their safety and effectiveness in the treatment process. The results of the Phase I clinical trial on the safety and efficacy of DMF for the treatment of pulmonary hypertension prove that it does improve the clinical efficacy of patients with six-minute walking distance (6MWD). There are 5 clinical studies of resveratrol for the treatment of hypertension, which mainly illustrate the acute effect of resveratrol on vascular endothelial function in patients with hypertension. In addition, the results of the RESTORE randomized clinical trial on the effect of resveratrol on improving the 6MWD of patients with peripheral arterial disease (PAD) proved that the doses of 125mg/d and 500mg/d achieved significant differences in the improvement of patients' 6MWD compared with placebo, but there was no clinical significance. Curcumin's regulation of HDL particles is one of its mechanisms for improving cardiovascular diseases. Curcumin and polyphenol supplements on the anti-inflammatory properties of HDL entered a phase 2 clinical study to explore the effect of curcumin on the inflammation of patients' overall plasma levels, as well as the anti-inflammatory and cholesterol efflux properties of HDL particles.

## 5. Others

In view of the involvement of oxidative stress in the pathogenesis of many diseases, NRF2 is clearly an important target for the treatment of these diseases. In addition to studies on neurodegeneration, metabolic diseases and cardiovascular diseases, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD) ), the application research of NRF2 activator in the treatment strategy of other diseases is also gradually deepening. The efficacy and safety study of BG00012 (DMF) and methotrexate in the treatment of active

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rheumatoid arthritis is in the phase 2 clinical trial phase. A total of 153 subjects participated in the experiment. Oral 480mg and 720mg of BG00012 were taken orally every day and observed after 12 weeks. The proportion of subjects still with RA symptoms. The University of California in the United States has launched a phase 2 clinical study on curcumin's therapeutic effect on SLE. In addition, the results of a phase 2 clinical trial of fumarate in the treatment of SLE showed that giving patients one piece of fumarate a day for 24 weeks, the total RCLASI activity of skin lesions was reduced by 50%. The absence of NRF2 will aggravate the course of lung diseases such as IFP-like pulmonary fibrosis and COPD. Pirfenidone (PFD) is a drug currently approved for the treatment of IPF. It restores the balance of NRF2/Bach1 by inhibiting Bach1 and activating NRF2, thereby enhancing the anti-fibrotic activity of fibroblasts generated by TGF-β stimulation [41].

## 6. Conclusion

There are still many challenges in pushing NRF2 agonists into clinical applications, such as poor drug solubility and low bioavailability, which have become a major challenge in their clinical application. In addition, side effects such as reductive stress caused by NRF2 over expression have caused widespread safety concerns. Nevertheless, targeting KEAP1 to stabilize NRF2 protein to activate cell protection is still the most effective treatment so far. The research of NRF2 agonists is still a popular direction for the development of new drugs for the treatment of aging-related diseases, but there are only a handful of them that have successfully passed clinical research and have been approved for marketing, and there is a huge market for development.

## References

*[1] R. M, Evolutionary perspectives on ageing, Seminars in cell & developmental biology, 2017, 70, 99-107.*
*[2] M. D, P. LC and F. L, The genetics of human ageing, Nature reviews. Genetics, 2020, 21, 88-101.*
*[3] P. L, D. J and S. PE, Facing up to the global challenges of ageing, Nature, 2018, 561, 45-56.*
*[4] C. A, M. G, H. A, A. MJ, B. C, D. A, G. P, L. R, L. MG, O. B, P. M, R. AI, R.-A. N, V. AM, G. E and S. HHHW, Transcription Factor NRF2 as a Therapeutic Target for Chronic Diseases: A Systems Medicine Approach, Pharmacological reviews, 2018, 70, 348-383.*
*[5] Q. Ma, Role of nrf2 in oxidative stress and toxicity, Annu Rev Pharmacol Toxicol, 2013, 53, 401-426.*
*[6] K. TW, W. N and B. S, Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway, Annual review of pharmacology and toxicology, 2007, 47, 89-116.*
*[7] T. W, W. H, L. S, L. Q and S. H, The Anti-Inflammatory and Anti-Oxidant Mechanisms of the Keap1/Nrf2/ARE Signaling Pathway in Chronic Diseases, Aging and disease, 2019, 10, 637-651.*
*[8] Q. Liu, Y. Gao and X. Ci, Role of Nrf2 and Its Activators in Respiratory Diseases, Oxid Med Cell Longev, 2019, 2019, 7090534.*
*[9] C. A, R. AI, W. G, H. JD, C. SP, R. WL, A. OC, F. S, L. AL, K. TW and D.-K. AT, Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases, Nature reviews. Drug discovery, 2019, 18, 295-317.*
*[10] C. AR, G. AA, J. R, R. MR, M. LJ, L. JZ, A. M, R. Y, D. T, W. J, L. CJ and H. WA, Myeloid deletion of nuclear factor erythroid 2-related factor 2 increases atherosclerosis and liver injury, Arteriosclerosis, thrombosis, and vascular biology, 2012, 32, 2839-2846.*
*[11] V. D, L. Z, M. PM, S. E, W. N, D. YP, L. MP, K. TW and G. F, Inhibition of nuclear factor-erythroid 2-related factor (Nrf2) by caveolin-1 promotes stress-induced premature senescence, Molecular biology of the cell, 2013, 24, 1852-1862.*
*[12] G. Shanmugam, M. Narasimhan, R. L. Conley, T. Sairam, A. Kumar, R. P. Mason, R. Sankaran, J. R. Hoidal and N. S. Rajasekaran, Chronic Endurance Exercise Impairs Cardiac Structure and Function in Middle-Aged Mice with Impaired Nrf2 Signaling, Front Physiol, 2017, 8, 268.*
*[13] Y. M, K. TW and M. H, The KEAP1-NRF2 System: a Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis, Physiological reviews, 2018, 98, 1169-1203.*
*[14] L. Q, X. S, C. Y, L. Q, L. Q, L. Y, H. S, F. F, C. Y, Z. J, L. W, G. Q, S. Y and S. H, Reasonably activating Nrf2: A long-term, effective and controllable strategy for neurodegenerative diseases, European journal of medicinal chemistry, 2020, 185, 111862.*
*[15] C. Jo, S. Gundemir, S. Pritchard, Y. N. Jin, I. Rahman and G. V. Johnson, Nrf2 reduces levels of phosphorylated tau protein by inducing autophagy adaptor protein NDP52, Nat Commun, 2014, 5, 3496.*
*[16] L. Bakota and R. Brandt, Tau Biology and Tau-Directed Therapies for Alzheimer's Disease, Drugs, 2016, 76, 301-313.*

ISSN 2618-1584 Vol. 3, Issue 2: 10-16, DOI: 10.25236/FMSR.2021.030204

*[17] D. W, Y. B, W. L, L. B, G. X, Z. M, J. Z, F. J, P. J, G. D and Z. R, Curcumin plays neuroprotective roles against traumatic brain injury partly via Nrf2 signaling, Toxicology and applied pharmacology, 2018, 346, 28-36.*

*[18] L. W, S. NC and P. S, Curcumin by down-regulating NF-kB and elevating Nrf2, reduces brain edema and neurological dysfunction after cerebral I/R, Microvascular research, 2016, 106, 117-127.*

*[19] M. H. Rahman, R. Akter, T. Bhattacharya, M. M. Abdel-Daim, S. Alkahtani, M. W. Arafah, N. S. Al-Johani, N. M. Alhoshani, N. Alkeraishan, A. Alhenaky, O. H. Abd-Elkader, H. R. El-Seedi, D. Kaushik and V. Mittal, Resveratrol and Neuroprotection: Impact and Its Therapeutic Potential in Alzheimer's Disease, Front Pharmacol, 2020, 11, 619024.*

*[20] C. Moussa, M. Hebron, X. Huang, J. Ahn, R. A. Rissman, P. S. Aisen and R. S. Turner, Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease, J Neuroinflammation, 2017, 14, 1.*

*[21] W. Rathmann and G. Giani, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes care, 2004, 27, 2568-2569; author reply 2569.*

*[22] A. K. Palmer, B. Gustafson, J. L. Kirkland and U. Smith, Cellular senescence: at the nexus between ageing and diabetes, Diabetologia, 2019, 62, 1835-1841.*

*[23] 23. M. M, F. K and H. EH, Activation of Nrf2 signaling by natural products-can it alleviate diabetes?, Biotechnology advances, 2018, 36, 1738-1767.*

*[24] L. M. Aleksunes, S. A. Reisman, R. L. Yeager, M. J. Goedken and C. D. Klaassen, Nuclear factor erythroid 2-related factor 2 deletion impairs glucose tolerance and exacerbates hyperglycemia in type 1 diabetic mice, The Journal of pharmacology and experimental therapeutics, 2010, 333, 140-151.*

*[25] M. S. Bitar and F. Al-Mulla, A defect in Nrf2 signaling constitutes a mechanism for cellular stress hypersensitivity in a genetic rat model of type 2 diabetes, Am J Physiol Endocrinol Metab, 2011, 301, E1119-1129.*

*[26] U. A, F. Y, Y. Y, F. T, M. H, N. T, S. A, K. TW and Y. M, The Keap1-Nrf2 system prevents onset of diabetes mellitus, Molecular and cellular biology, 2013, 33, 2996-3010.*

*[27] C. D, Y. Y, S. A, D. CH, W. H, C. L and H. XF, Bardoxolone methyl prevents insulin resistance and the development of hepatic steatosis in mice fed a high-fat diet, Molecular and cellular endocrinology, 2015, 412, 36-43.*

*[28] D. GM, J. UJ, P. HJ, K. EY, J. SM, M. RA and C. MS, Resveratrol ameliorates diabetes-related metabolic changes via activation of AMP-activated protein kinase and its downstream targets in db/db mice, Molecular nutrition & food research, 2012, 56, 1282-1291.*

*[29] T. Z, Z. LJ, M. PW, L. SP, C. SJ, F. XD and W. TH, Caveolin-3 is involved in the protection of resveratrol against high-fat-diet-induced insulin resistance by promoting GLUT4 translocation to the plasma membrane in skeletal muscle of ovariectomized rats, The Journal of nutritional biochemistry, 2012, 23, 1716-1724.*

*[30] S. Bo, V. Ponzo, A. Evangelista, G. Ciccone, I. Goitre, F. Saba, M. Procopio, M. Cassader and R. Gambino, Effects of 6 months of resveratrol versus placebo on pentraxin 3 in patients with type 2 diabetes mellitus: a double-blind randomized controlled trial, Acta diabetologica, 2017, 54, 499-507.*

*[31] S. MY, K. EK, M. WS, P. JW, K. HJ, S. HS, P. R, K. KB and P. BH, Sulforaphane protects against cytokine- and streptozotocin-induced beta-cell damage by suppressing the NF-kappaB pathway, Toxicology and applied pharmacology, 2009, 235, 57-67.*

*[32] Y. Panahi, N. Khalili, E. Sahebi, S. Namazi, Z. Reiner, M. Majeed and A. Sahebkar, Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial, Complement Ther Med, 2017, 33, 1-5.*

*[33] C. PR, C. G, H. G, G. M, V. MA and G. JR, Age-associated stresses induce an anti-inflammatory senescent phenotype in endothelial cells, Aging, 2013, 5, 913-924.*

*[34] S. Satta, A. M. Mahmoud, F. L. Wilkinson, M. Yvonne Alexander and S. J. White, The Role of Nrf2 in Cardiovascular Function and Disease, Oxid Med Cell Longev, 2017, 2017, 9237263.*

*[35] A. H, C. G, B. M, A. D, S. AC, M. SJ, D. MS, K. J, B. JJ, L. C, I. H, Y. A, S. NB, C. H, C. TJ, S. N, B. DR, B. RI, H. I, T. DA, L. J, L. CA, J. M, K. RK, N. S, R. C, d. C. R, A. I, T. M, G. UL, R. AJ, V. MR, P. PJ, T. DJ and W. H, Fumarate is cardioprotective via activation of the Nrf2 antioxidant pathway, Cell metabolism, 2012, 15, 361-371.*

*[36] C. JW, E. M, N. CK, G. S, J. S, E. JW, R. A and L. DJ, Genetic and pharmacologic hydrogen sulfide therapy attenuates ischemia-induced heart failure in mice, Circulation, 2010, 122, 11-19.*

*[37] G. R, L. B, W. K, Z. S, L. W and X. Y, Resveratrol ameliorates diabetic vascular inflammation and macrophage infiltration in db/db mice by inhibiting the NF-κB pathway, Diabetes & vascular disease research, 2014, 11, 92-102.*

*[38] Z. X, Z. S, C. S, C. Y, D. J, L. J, L. R and Z. Y, Protective effects of chronic resveratrol treatment on vascular inflammatory injury in streptozotocin-induced type 2 diabetic rats: Role of NF-kappa B*

ISSN 2618-1584 Vol. 3, Issue 2: 10-16, DOI: 10.25236/FMSR.2021.030204

*signaling, European journal of pharmacology, 2013, DOI: 10.1016/j.ejphar.2013.10.034.*
*[39] U. Z, B. Z, F. A, R. FA, S. WE, P. K, d. C. R and C. A, Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2, American journal of physiology. Heart and circulatory physiology, 2010, 299, H18-24.*
*[40] M. X, C. W, S. W, X. Y, W. B, T. Y, C. L, M. L, F. Y, S. G and W. Y, Therapeutic effect of MG132 on the aortic oxidative damage and inflammatory response in OVE26 type 1 diabetic mice, Oxidative medicine and cellular longevity, 2013, 2013, 879516.*
*[41] A.-M. E, G. D, B. S, H. A, B. V, M.-S. J, A. ZE, C. B, K.-R. S, B. A and B. M, Nuclear factor erythroid 2-related factor 2 nuclear translocation induces myofibroblastic dedifferentiation in idiopathic pulmonary fibrosis, Antioxidants & redox signaling, 2013, 18, 66-79.*