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Research Article

Nuclear Respiratory Factor-1 (NRF-1), A Versatile Therapeutic Target: Influence of Plant Metabolites

Ayeleso A.O[1,2], Adepoju A.E[2] and Mukwevho E[1]

[1]*Department of Biochemistry, Faculty of Natural and Agricultural Science, North West University, Mafikeng Campus, Private Bag X2046, Mmabatho 2735, South Africa*

[2]*Department of Biochemistry, Faculty of Science, Adeleke University, P.M.B. 250, Ede 232, Osun State, Nigeria*

ABSTRACT

Nuclear-encoded transcriptional regulatory proteins called transcription factors can potentially influence mitochondrial gene expression directly or indirectly. Mitochondria contain their own genome, which encodes 13 of the ~100 proteins that constitute the enzyme complexes of the respiratory chain. Mitochondria are the fuel stations of all eukaryotic cells and functions as central component of mammalian cellular survival through production of ATP and re-oxidized NAD. Nuclear respiratory factor-1 (NRF-1) coordinates the expression of nuclear and mitochondrial genes for mitochondrial biogenesis. It increases mitochondrial respiratory capacity and induces expression of a subset of genes governing mitochondrial activity. It has a major function in cellular adaptation to energy demands by translating physiological signals into an enhanced capacity for energy production. Oxidative stress has been implicated in the pathogenesis of many diseases such as diabetes, cardiovascular disease, cancer and neurodegenerative diseases. NRF proteins are also essential in the upregulation of antioxidant and xenobiotic-metabolizing enzymes during oxidative stress. NRF-1 plays a role in mediating activation of oxidative stress response genes through antioxidant response element and hence, confirms its potential roles in chronic diseases. This review has clearly revealed the versatility of NRF- 1 as a therapeutic target and showed that plants could exhibit their fight against diseases through activation of NRF-1.

Keywords: Nuclear respiratory factor-1, Plant metabolites, Mitochondria, Oxidative stress, Diseases

*Author for correspondence: *E-mail*: Emmanuel.Mukwevho@nwu.ac.za; Tel. +27 18 389 2854

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INTRODUCTION

NRF-1, a member of the cap'n'collar (CNC) family is an important transcription factor for functions in various types of cells (Hirotsu *et al.*, 2012; Kim *et al*., 2016) and is ubiquitously expressed in a wide range of tissues (Biswas and Chan 2010; Wang *et al*., 2019) . Other transcription factors in the CNC family of basic-leucine zippe (bZIP) transcription factors include NFE-2, NRF-2 and NRF-3 and they are involved in the regulation of genes with a broad range of functions in response to both physiological and exogenous signals (Williams *et al.*, 2013; Tonelli *et al*., 2018). NRF-1 is targeted to the endoplasmic reticulum (ER) under physiological conditions, which means that it translocates into the nucleus in response to an activating signal (Tsuchiya *et al.*, 2011; Chowdhury *et al*., 2017). Firstly, NRF-1 was discovered to be an activator of the cytochrome c gene and afterwards, was found to play a broader function in nuclear-mitochondrial interactions (Virbasius *et al.*, 2012; Niu *et al*., 2019). It is a transcriptional activator of nuclear genes that encode a range of mitochondrial proteins (Barr *et al.*, 2003; Cardamone *et al*., 2018).

Mitochondria play a key role in the synthesis of adenosine triphosphate (ATP) by oxidative phosphorylation in almost all eukaryotic cells (Satoh *et al.*, 2013; Hahn and Zuryn, 2019). Mitochondria biogenesis abnormalities are linked with mitochondrial function and mitochondrial number and size (Ren *et al.*, 2010; Santos and Kowluru, 2010; Srivastava, 2017). Mitochondrial dysfunction can be damaging to cell viability causing tissue malfunctioning and severe pathological disorders due to its role as key player in cellular homeostasis (Wenz, 2009, Huang *et al*., 2019). NRF-1 binds to and activates the promoters of many genes of the

mitochondrial electron transport system which include cytochrome c, NADH dehydrogenase subunit 8, some cytochrome oxidase subunits, some ATP synthase subunits, mitochondrial transcription factor A (Tfam) (Scarpulla, 2002; Cho *et al.,* 2005; Esteras *et al*., 2016). Tfam is a protein that is encoded by the Tfam gene and controls the transcription, replication, damage sensing, and repair of mitochondria DNA (Alvarez *et al.,* 2013; Kang *et al*., 2018). It encodes protein of 246 amino acids (25 kDa) with a mitochondrial targeting presequence of 42 amino acids (Fisher and Clayton, 1985; Choi *et al.,* 2004; Kukat *et al*., 2015). Peroxisome proliferator–activated receptor-γ coactivator-1 (PGC-1) stimulates the expression of NRF-1 and coactivates the transcription function of NRF-1 on the promoter of Tfam (Wu *et al.,* 1999; Choi *et al.,* 2014; Cheng *et al*., 2018).

NRF-1 induces the expression of Tfam, which, along with other nuclear-encoded mitochondrial proteins (NEMPS), is taken into mitochondria by the protein import machinery (Hood *et al.,* 2006; Suliman and Piantadosi, 2015). NRF-1 and NRF-2 are essential in the regulation of the expression of many antioxidant genes which include peroxiredoxin-1 (Prx-1), thioredoxin-1 (Txn-1), glutamate cysteine ligase catalytic subunit (GCLC), an enzyme responsible for catalyzing the formation of glutathione), glutathione peroxidase (GPX-1), drug metabolizing enzymes (cytochrome P-450s), and several ATP Binding Cassette (ABC) transporters that are responsible for drug efflux (Schultz *et al.,* 2010; Paramasivan *et al*., 2019).

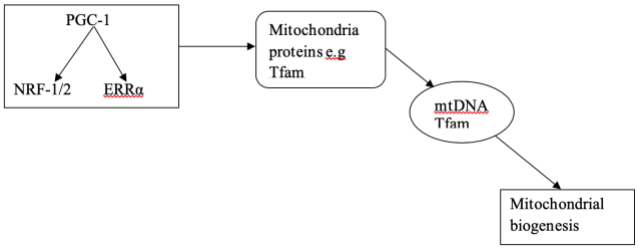

Figure 1:
This illustration indicates the involvement of PGC-1 coactivators, NRF-1/2 and TFAM in the regulation of mitochondrial biogenesis (Adapted from Dillion *et al.,* 2012).

NRF-1 and Oxidative stress

Oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and body antioxidant defences plays an important part in the pathogenesis of a variety of diseases. ROS can cause a serious damage to the cell through oxidation of proteins, DNA (including mitochondrial DNA), and nitrosylation of proteins (through generation of ROS), resulting to protein malfunction (Bugger and Abel, 2008). Cellular oxidative stress entails both cytosolic and mitochondrial oxidative stress and in addition, cytosolic oxidative stress contributes to mitochondrial dysfunction, mitochondrial oxidative stress and vice versa (Aroor *et al.,* 2012). Oxidative stress related diseases include type 2 diabetes (Chang and Chuang, 2010; Niemann *et al*., 2017), cancer (Reuter *et al.,* 2010; Sung *et al*., 2018), cardiovascular diseases (Dhalla *et al.,* 2000; Higashi *et al.,* 2009) and neurodegenerative diseases (Barnham *et al.,* 2004; Kim *et al*., 2015).

Oxidative stress activates transcription of a variety of antioxidant genes through cis-acting sequence known as antioxidant response element (ARE) (Biswas and Chan, 2010). Some antioxidant and detoxification enzymes are transcriptionally induced during oxidative or electrophilic stress through ARE (Nguyen *et al.,* 2003; Jyrkkänen *et al.,* 2011). Transcription factors can either transactivate or repress gene expression through binding to the ARE (Jyrkkänen *et al.,* 2011). NRF-1 binds to the antioxidant response elements (AREs) and regulates genes involved in protecting cells from oxidative damage. In a study conducted by Parola and Novo (2005), hepatocytes lacking NRF-1 confirmed oxidative stress and there was a decreased expression of various ARE-containing genes and up-regulation of CYP4A genes. It was further stated that NRF-1 had protective effects against oxidative stress and a potential role in lipid homeostasis in the liver. Chen *et al.* (2003) showed that defective GSH expression correlated with loss of NRF-1, suggesting its role in protecting fetal liver cells from oxidative stress. Loss of NRF-1 resulted to marked oxidative stress in cells, an indication of increased intracellular reactive oxygen species levels and cell death (Leung *et al.,* 2003). In another study, Hernandez-Montes *et al.* (2006) suggested that the protective effects of genistein, a flavonoid depend largely on the activation of glutathione peroxidase, an antioxidant enzyme and it is mediated by NRF-1 activation.

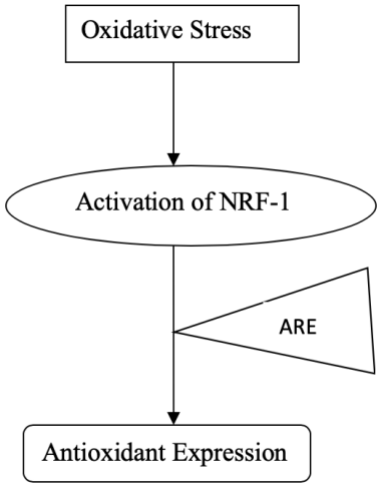

Figure 2:
Pathway showing primary cellular defences of NRF-1 against of oxidative damage

NRF-1 and Metabolic Syndrome

Metabolic syndrome is characterized by a coming together of risk factors for cardiovascular diseases and diabetes usually linked to insulin resistance and obesity (Duncan and Schimidt, 2001; Gepstein and Weiss, 2019). Cardiovascular disease is a class of diseases affecting the heart and/or blood vessels and its risk factors include smoking, elevated blood cholesterol levels, high blood pressure, physical inactivity, obesity, insulin resistance and type 2-diabetes (Oguntibeju *et al.,* 2009). Obesity, an energy imbalance due to excessive food

ingestion and insufficient physical activity is a chronic disease that serves as a triggering agent for the development of the metabolic syndrome (Gutiérrez-Salmeán *et al.,* 2012). The occurrence of type 2 diabetes and its related metabolic disorders including obesity and insulin resistance is rapidly increasing throughout the world (Lai *et al.,* 2009).

Type 2 diabetes mellitus is characterized by insulin resistance and dysfunction in pancreatic beta-cell (Patti *et al.,* 2003). Insulin resistance is generally referred as decline in the ability of insulin to stimulate the uptake of glucose from body peripheral tissues (Martins *et al.,* 2012). ROS may likely play an essential role in the impairment of mitochondrial energy metabolism by participating in mitochondrial uncoupling (in type 2 diabetes and cardiac efficiency) thus directly damaging mitochondrial proteins (Bugger and Abel, 2008). Wang *et al.* (2004) reported that mitochondrial dysfunction takes part in the pathophysiology of insulin insensitivity and the activation of mitochondrial biogenesis could be a helpful in the prevention or treatment of insulin resistance and type 2 diabetes. Many of the genes dysregulated in both diabetes and 'prediabetes' are regulated by NRF-1 and PGC-1 (Patti, 2004; Sergi *et al*., 2019). The mechanism of insulin resistance by decreased mitochondrial function could be due to decreased PGC1, a coactivator of NRF-1 and subsequently, transcription and translation of Mitochondria (Lee *et al.,* 2005). Cho *et al.* (2005) found out that the haplotypes of the NRF1 gene, the regulator of oxidative phosphorylation in mitochondria are associated with type 2 diabetes in the Korean population. In DM, expression of oxidative phosphorylation genes is decreased, perhaps as a result of decreased expression or transcriptional activity of NRF-1 (Patti *et al.,* 2003).

The reduced expression of NRF-dependent genes could be due decrease in PGC-1 expression which leads to metabolic disturbances characteristic of insulin resistance and DM (Uguccioni *et al.,* 2010). Choi *et al.* (2004) showed that *in vitro* exposure of L6 rat skeletal muscle cells to high glucose induced Tfam promoter expression and was mediated by NRF-1. They further stated that since, Tfam plays an essential role in the replication and transcription of mitochondrial DNA, the effect of glucose may explain the correlation between diabetes and dysfunctions of mitochondrial biogenesis and/or oxidative phosphorylation. The expression of GLUT4, a rate-limiting for glucose transport into muscle was indirectly regulated by NRF-1 because NRF-1 is not a transcriptional activator of the GLUT4 gene (Baar *et al.,* 2003). They found out that overexpression of NRF-1 resulted in increased expression of GLUT4 muscle and further stated that this could help to give an explanation on a mechanism that accounts for associated increase in the capacities for glucose transport and oxidative generation of ATP in skeletal muscle adapting to endurance exercise. Mitochondrial DNA copy number and mitochondrial gene expression are reduced in heart failure (Sano and Fukuda, 2008). From available literature, not much information has been documented on the influence of NRF-1 in cardiovascular diseases. However, a study conducted by Garnier *et al.* (2003) showed that the expression of PGC-1α, NRF-1, and Tfam in a failing heart was down regulated.

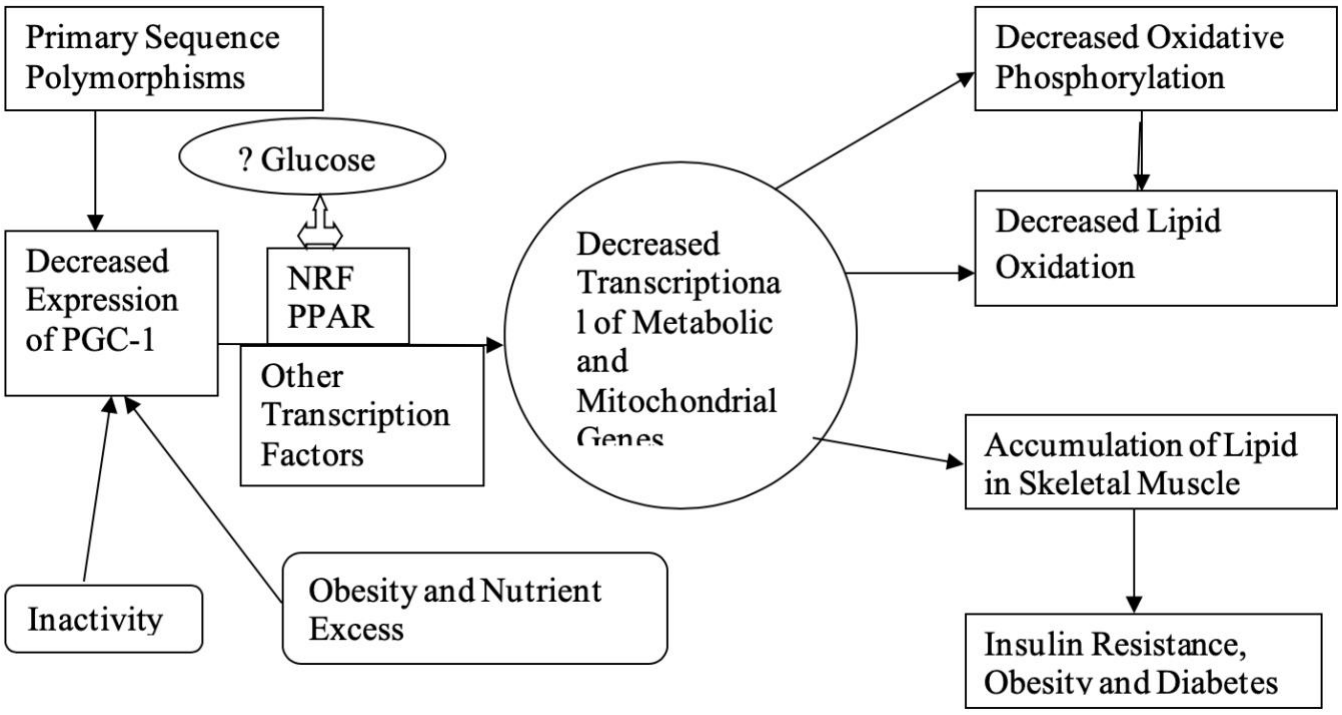

Figure 3:
Involvement of PGC-1 and NRF-dependent transcription to expression and metabolic phenotype of insulin resistance and type 2 diabetes as proposed by Patti *et al.* (2003).

NRF-1 and Carcinogenesis

Excessive production of ROS damage lipids, DNA, and proteins in the cell, disrupting cell function and it is detrimental to both normal and cancer cells (Schultz *et al.*, 2010; Pizzino *et al*., 2017). Cancer is a disease characterized and caused by dynamic genomic changes (Pikor *et al.,* 2013). Genomic instability comes as a result of mutations in DNA repair genes and steer the development of cancer (Negrini *et al.,* 2010). It is a transient or persistent state that increases the spontaneous mutation rate, leading to gross genetic alterations such as rearrangements and changes in chromosome number (Pikor *et al.*, 2013). NRF-1 is essential to the cellular response to oxidative stress (Schultz *et al*., 2010). A potential molecular link between NRF-1 and cancer has been reported. NRF-1 is the main transcription factor regulating the expression of TOMM34 (Blesa *et al.,* 2008).

TOMM34 is frequently upregulated in colorectal tumours and can be a potential target for novel anticancer drugs (Blesa *et al.*, 2008). Xu *et al.* (2005) showed that hepatocyte-specific deletion of NRF-1 in mice led to apoptosis, inflammation and liver tumor development. It was further reported that the fuction of NRF-1 as a tumor suppressor in hepatocytes cannot be ruled out. Oh *et al.* (2012) showed that genomic instability can be caused due to loss of NRF-1 function and suggested that the influence of NRF-1 in cellular homeostasis goes beyond oxidative and proteolytic stress response to include genomic integrity maintenance. Since genomic instability is often linked with cancer and can be suggestive of a poor diagnosis for some types of cancer, it is imperative to conclude that NRF-1 plays an important in the prevention of cancer. The X gene, a viral oncogenic factor of hepatitis B virus (HBV) is one of the majors in HBV-induced hepatocarcinogenesis (Tokusumi *et al.* 2004). NRF-1 has been reported to be involved in the regulation of the expression of the HBV X gene (Tokusumi *et al.* 2004; Jin *et al*., 2017).

Zhao *et al.* (2011) showed that the knockdown of NRF-1 increased inorganic arsenite (iAs^{3+}) induced cytotoxicity and apoptosis in human keratinocytes. They reported that long isoforms of NRF-1 contributed to arsenic-induced antioxidant response in human keratinocytes and protected the cells from acute arsenic cytotoxicity. Similarly, a somatic inactivation of NRF-1 in the liver of mice resulted in hepatic cancer (Parola and Novo, 2005). Degradation of proteins by the proteasome plays a vital role in all major cellular pathways while an abnormal proteasome activity is linked with cancer (Xu *et al*., 2012). According to a study by Radhakrishnan *et al.* (2010), the antioxidant response elements in NRF-1-mediated the upregulation of proteasome subunit genes. It was further stated that NRF-1-mediated proteasome homeostasis could be an attractive target for therapeutic intervention in cancer.

NRF-1 and Neurodegenerative Diseases

Neurodegenerative diseases which include Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis are caused by gradual loss of neurons (Lee *et al.,* 2009). Alzheimer's disease is a progressive neurological disorder that causes death of brain cells and leads to disorientation, with impaired memory, thinking, and judgment. Parkinson disease (PD) is linked with progressive loss of dopaminergic neurons in the substantia nigra and widespread neuronal changes that cause complex and variable motor and nonmotor symptoms (Henchcliffe and Beal, 2008). Oxidative stress has been implicated in the pathophysiology of many neurological, especially neurodegenerative diseases (Gilgun-Sherki *et al.,* 2001; Kim *et al*., 2015). The brain is exposed throughout life to excitatory amino acids, whose metabolism is a factory of ROS, a source of oxidative stress (Gilgun-Sherki *et al.,* 2001; Uttara *et al*., 2009).

Malfunctioning in physiology of mitochondrial plays a crucial role in the pathogenesis of the neurodegenerative disease (Satoh *et al.*, 2013). Mitochondrial dysfunction is a prominent feature of Alzheimer's and Parkinson`s disease s which may be of vital importance in the genesis and increase of reactive oxygen species and the pathophysiology of the diseases (Yah *et al.,* 2013). Piao *et al.* (2010) showed that mitochondrial activation by TFAM, NRF-1, and myr-AKT abrogated 1-methyl-4-phenyl-2, 3-dihydropyridinium ion (MPP^{+}) -mediated the impairment on mitochondria and insulin signalling, resulting in the recovery of nigrostriatal neurodegeneration and hence, could be the critical points of therapeutic intervention for Parkinson's diseases. Huntington disease (HD), another neurodegenerative disease is inherited and caused by an abnormal expansion of a CAG repeat in the huntingtin HTT (HD) gene and impaired mitochondrial biogenesis in response to energetic stress plays a significant role in its pathogenesis (Taherzadeh-Fard *et al.,* 2011). They further stated that upregulation of transcriptional activators of PGC-1alpha which enhances the expression and activity of NRF-1 may be useful targets in the treatment of HD (Taherzadeh-Fard *et al.*, 2011).

NRF-1 is a key transcription factor in the human genome and it is involved in neurite outgrowth in neuroblastoma cells (Wang *et al*., 2013; Jin *et al*., 2017). a-Pal/ NRF-1 is a critical transcriptional regulator of the human IAP (or CD47) gene, a memory-related gene that is up-regulated in hippocampus during the process of memory formation (Chang and Huang, 2004; Huang *et al.*, 1998). Due to the activation caused by a-Pal/ NRF-1, an increase in IAP mRNA (neurtite outgrowth) was observed and this explains its role in memory formation (Chang *et al.*, 2005). Lee *et al*., (2011) showed a new function of NRF-1 in maintaining proteasome homeostasis and protection against neuronal apoptosis. Proteasome is a large intracellular protease found in all cells of the central nervous system (CNS) and it is accountable for the majority of intracellular protein degradation (Keller *et al.,* 2002). Lee *et al.,* (2011) revealed NRF-1 as a key transcriptional regulator required for the expression of proteasomal genes in neurons and suggested that the knockout of NRF-1 in the brain of mice may offer a model to study mechanisms of neurodegenerative diseases. The impairment of mitochondrial function plays a critical role in the pathogenesis of HD and that upstream transcriptional activators of PGC-1alpha may be useful targets in the treatment of HD (Lee *et al.,* 2011).

Activation of NRF-1 by plant metabolites

Hernandez-Montes *et al.* (2006) suggested that the protective effects of genistein, a flavonoid depend largely on the activation of glutathione peroxidase, an antioxidant enzyme

which is mediated by NRF-1 activation. In another study, icariin, an active ingredient of plant herb *Epimedium*, increased the expression of PGC-1α, PPARα, and NRF-1 during cardiomyocyte differentiation of murine ES cells *in vitro* in a dose-dependent manner (Ding *et al.,* 2007). Epigallocatechin-3-gallate (EGCG) increased mRNA levels of nuclear respiratory factor NRF-1, medium chain acyl coA decarboxylase (MCAD), uncoupling protein+(UCP)3, and PPARα by 1.4 – 1.9-fold in the skeletal muscle of high fat-fed mice when compared to high fat-fed controls (Sae-tan *et al.,* 2011). The expression of these genes which are all related to mitochondrial fatty acid oxidation suggest that EGCG could be helpful in alleviating obesity and type 2 diabetes. Kuo *et al*. (2012) showed that curcumin protected hepatocytes from high free fatty acid -induced lipoapoptosis and mitochondrial dysfunction due to mechanism of action related to improvements in mitochondrial function and biogenesis. NAFLD is associated with the metabolic syndrome, especially obesity, hyperlipidaemia and diabetes (Hiramitsu *et al.,* 2014). Insulin resistance occurs in almost all patients with non-alcoholic fatty liver disease (NAFLD, characterized by high serum concentration of free fatty acids, liver steatosis and hepatocyte apoptosis) and mitochondrial dysfunction likely plays a pivotal role in the progression of fatty liver into non-alcoholic steatohepatitis (NASH) (Kuo *et al*., 2012). In the study, curcumin increased the levels of transcriptional factors that regulate mitochondrial biogenesis such as PGC1α, NRF1 and Tfam.

The effect of combined bioactive dietary constituents (resveratrol and equol) on mitochondrial function was conducted (Davinelli *et al.,* 2013). It was shown that the co-administration of both compounds on HUVEC cells induced mitochondrial biogenesis factors such as PGC1-α, TFAM and NRF-1. They suggested that the co-administration of these agents may be a possible nutraceutical and/or anti-ageing strategy. Quercetin treatment has been found to induce expression of mitochondrial biogenesis activators (PGC-1α, NRF-1, TFAM) in HepG2 cells (Rayamajhi *et al*., 2013). It was demonstrated that quercetin enhances cell survival against oxidative stress through heme oxygenase (HO-1)/carbon monoxide (CO) (an inducible cytoprotective mechanism in mammalian cell) dependent increase in mitochondrial biogenesis. Another study conducted by Hiramitsu *et al*. (2014) using a zebrafish model of diet-induced obesity, eriocitrin, a powerful antioxidative flavonoid in lemon ameliorated hepatic steatosis with activation of mitochondrial biogenesis by increasing NRF-1 and TFAM. The liver-specific inactivation of NRF-1 leads to hepatic steatosis and neoplasia and this indicates that the therapeutic action of eriocitrin is through NRF1 induction. People with DS are known to show early aging associated with a decline in intellectual abilities, with a high tendency to develop neuropathological features associated with Alzheimer's disease (Valenti *et al.,* 2013). Epigallocatechin-3-gallate has also been shown to promote mitochondrial biogenesis in human cells from subjects with Down's syndrome (DS) by increasing NRF-1 and T-FAM protein levels (Valenti *et al.,* 2013). It was reported from the study that EGCG treatment promises to be a therapeutic approach to counteract mitochondrial energy shortage in DS.

Song *et al*. (2015) reported that the roots of *Atractylodes macrocephala* Koidzumi (*Atractylodis Rhizoma* Alba, ARA) enhanced glucose and lipid metabolism in C2C12 myotubes via mitochondrial regulation. The root extract was found to stimulate mitochondria biogenesis markers such as PGC1α, NRF1, and TFAM with increase of ATP content. It was suggested that ARA extract and its active constituents possess therapeutic potential for the treatment of insulin resistance, obesity, and T2 diabetes. *Boesenbergia pandurata* has been found to stimulate exercise endurance through elevation of mRNA expression of key factors of mitochondria biogenesis and function such as NRF-1 (Kim *et al*., 2016). It was concluded that *Boesenbergia pandurata* could be a potential nutraceutical candidate for the enhancement of exercise endurance due on its mitochondrial biogenesis and exercise-mimicking effects. The extract of orange-fleshed sweet potato has been shown to improve the expression of *nrf-1* gene in palmitate-induced insulin resistant C2C12 cells (Ayeleso *et al.,* 2018). In another study, it was shown that the neonatal administration of oleanolic acid, a a pentacyclic triterpenoid in plant could help to increase the expression of *glut-4*, *cpt-1* and *nrf-1* in fructose-induced metabolic dysfunction in both young and adult rats (Molepo *et al*., 2018).

Conclusion

Nuclear respiratory factor-1 helps in the stimulation of the transcription of nuclear-encoded genes involved in regulating mitochondrial genome transcription and biogenesis. Oxidative stress which is thought to be involved in the development of many diseases activates transcription of a variety of antioxidant genes through cis-acting sequence known as antioxidant response element. NRF-1 has been implicated to play a role in mediating activation of oxidative stress response genes through antioxidant response element and hence, confirms its potential roles in chronic diseases. It can therefore be concluded that a mechanism by which medicinal plants and their bioactive compounds exert their pharmacological potentials could be through NRF- 1 as the therapeutic target in managing several chronic diseases.

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