Naturally Occurring Nrf2 Activators in the Management of Diabetes

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Abstract

Nuclear factor erythroid-2 (NFE-2)-related factor-2 (Nrf2), a key leucine zipper transcription factor that regulate the expression of antioxidant enzymes, is an important target for mitigating the complications of diabetes. Several lines of evidences have concluded that targeted activation of Nrf2 using phytochemicals helps to protect insulin secreting pancreatic β-cells thereby reduce hyperglycemia induced changes such as retinopathy, nephropathy, cardiomyopathy, and many other complications. Mechanistically, Nrf2 activators promote the release of Nrf2 from Keap1 - Nrf2 complex by disrupting the protein - protein interactions or by promoting the degradation of Keap1 in cells.

Once released, the Nrf2 translocates into nucleus thereby trigger the transcription of genes such as NQO1, GST, H0 1, HIF1 α, and many more, which are involved in controlling oxidative stress. Therefore, identification of naturally occurring Nrf2 activators and the use of diets rich in these activators is a potential strategy to control diabetes. However, further studies are warranted to test the safety and efficacy of Nrf2 activators for treating diabetes in clinical trials. In this mini-review, we have summarized the recent findings of cell-based and preclinical studies evaluating the role of Nrf2 in preventing and treating diabetes. In addition, the details of preclinical studies that have tested the Nrf2 activators are tabulated. For additional and more detailed information the readers can refer the publications listed in the references section.

Keywords: Nrf2; Diabetes; Pancreatic β-cells; Nfr2 -activators; Sulforaphane; Curcumin

Introduction

Despite various cost-effective treatment strategies and public health campaigns highlighting the key risk factors, the incidence and burden due to diabetes is increasing at an alarming rate globally with an estimated 422 million individuals currently suffering from this disease. Recent predictions by IDF projected that the number of diabetics is likely to increase to 642 million by 2040 [1]. Etiologically, Type-1 and Type-2 diabetes have originated due to a significant decrease in the number of insulin-producing β-cells [2]. As a result, diabetics experience chronic hyperglycemia [3,4] and several secondary abnormalities that include loss of vision, malfunction of kidneys and ultimately coma and death [5].

Recent studies have identified that oxidative stress, caused by excess reactive oxygen species, is one of the most important causing factors for diabetes complications [6]. Moreover, since pancreatic β-cells express very low antioxidant defence enzymes, they are more susceptible to the damage caused by

A. Free radicals;
B. Misfolded proteins;
C. Endoplasmic reticulum hyperactivity [7,8].

Therefore, coordinated up-regulation of genes coding for detoxifying and antioxidant enzymes has been shown to be a potential therapeutic strategy against oxidative stress-induced pancreatic β-cell damage [9,10]. Use of naturally occurring photochemical is one such strategy to mitigate the toxic effects, and protect pancreatic β-cells [11]. Several recent clinical trials have also confirmed the advantages of using bioactive compounds derived from natural sources for diabetes management [12-14].

Among various phytochemicals, polyphenolic compounds had shown potent anti-diabetic properties [15]. Polyphenols can

A. Activate key transcription factors such as nuclear factor erythroid-2 (NFE-2)-related factor-2 (Nrf2), a known master regulator of the antioxidant response- and phase-II detoxifying enzymes; and

B. Reduce toxic reactive oxygen species in to less toxic hydroxyl radical and hydrogen peroxide [16].

Hence, in this review, we have summarized the key findings of various research studies demonstrating the anti-diabetic properties of naturally occurring Nrf2 activators. Interested readers can refer recent review articles published for more detailed information.

Role of Nrf2 in Diabetes

Several studies have demonstrated the role of Nrf2 in mitigating the complication of diabetes using cell-based and animal model systems [17,18]. In vitro studies using human and animal cells indicated that activation of Nrf2 depends on cell type and glucose concentration [19,20]. Moreover, many studies have also demonstrated that mice lacking Nrf2 (Nrf2-knockout mice) or Keap1 (Keap1- knockout mice) failed to reduce the complications of insulin resistance as they could not activate Nrf2 and its target genes, indicating a key role of Nrf2 in preventing diabetic complications [21].

Additionally, recent clinical findings have also shown that Nrf2 function has significantly decreased in subjects with diabetes [22]. Supporting this, analysis of peripheral blood mononuclear cells (PBMC) from prediabetic and diabetic subjects showed decreased Nrf2 and HO-1 levels [23]. Likewise, a separate study reported that diabetic skin tissue showed down regulation of Nrf2 and its target genes NQO1 and HO-1, at both the mRNA and protein levels compared with non-diabetic tissue. Many other studies similarly have shown changes in the expression of Nrf2 in diabetes compared to non-diabetic individuals highlighting its role as a key regulator in diabetes.

Nrf2 Modulates Metabolic Pathways to Control Hyperglycemia-induced Aberration in Diabetes

Hyperglycemia arising from uncontrolled glucose regulation causes tissue damage through increased polyol pathway producing excessive sorbitol by aldose reductase activity [24,25]. Elevated sorbitol induces TGFβ1 and inhibits Nrf2 expression resulting in elevated ROS levels [26]. Excessive cellular ROS in turn activate the TGFβ1 pathway in feed-forward mechanisms, leading to increased AR expression.

Therefore, restoring Nrf2 activity using naturally occurring Nrf2 activators helps to down-regulate sorbitol-mediated ROS induction. In support of this, a separate study recently showed that activation of Nrf2 inhibits the function of TGFβ1 [27]. Formation of toxic advanced glycation end (AGE) products methylglyoxal (MG), glyoxal and carboxymethyl lysine is another characteristic feature of diabetes [28]. AGEs that are produced as a result of non-enzymatic binding of reducing sugars with the amino groups in proteins, lipids or nucleic acids damage target cells by directly disrupting matrix-matrix and matrix-cell interactions through excessive cross-linking of proteins [29]. One way to overcome AGEs-mediated toxic effects is to increase the expression of glyoxalase-1 (Glo-1), a key enzyme which catalyzes the conversion of MG to lactic acid [30].

Interestingly, Glo-1 is a direct target of Nrf2 [31]. A study by Chang wc et al. [32] showed induction of hepatic glyoxalase mRNA and glutathione (GSH) by elevated Nrf2, which helped in reducing the serum and hepatic AGEs as well as inflammatory factors in MG-treated rats. In a separate study it has been demonstrated that Nrf2 activation prevented the AGEs-induced ROS formation in LX-2 and human stellate cells through up regulation of γ-glutamyl cysteine synthetase and glutathione synthesis [33,34].

Elevated diacylglycerol (DAG) levels are another characteristic feature of diabetes [35]. DAG is usually produced when the glycolytic intermediate dihydroxy acetone phosphate (DHAP) gets reduced in a series of reduction reactions first producing glycerol-3-phosphate followed by DAG [36]. DAG thus produced activates protein kinase C (PKC), a serine/threonine kinases responsible for various structural and functional changes that include

A. Cellular permeability;
B. Inflammation;
C. Cell growth;
D. Angiogenesis;
E. Extracellular matrix expansion; and
F. Apoptosis [37].

In addition, PKC regulate intracellular eNOS, NADPH oxidase, endothelin-1 (ET-1), phospholipase A2 (PLA2), VEGF, connective tissue growth factor (CTGF), vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), NF-kB, and TGF-α [38].

In summary, PKC is a key regulator of various processes that lead to the
Natuurlijk voorkomende Nrf2-activatoren in de behandeling van diabetes

Nrf2 speelt een belangrijke rol in het moduleren van deze metabole aberraties tijdens hyperglycemies door de regulatie van PKC en de enzymen betrokken in de glucose metabolisme [39]. Mechanisch, Nrf2 up-reguleert Slc2a1, Hk2 en Pkm2 expressie in lever, bruine vetweefsel, hersenen en nier, terwijl hij de nadruk legt op de glucose-metabolie door te moduleren. Daarom is het activeren van Nrf2 met phytokemische stoffen een betere strategie om diabetestriggerende complicaties te beïnvloeden.

Helaas hebben enkele onderzoekers ontwikkelde screenings- en validatiemethoden om potentieel Nrf2-activatoren te identificeren uit plant bronnen. Eén van de meest geweegde screeningsmethoden om Nrf2-activatoren te identificeren is de complementatieassay. Deze screeningssysteem werkt op basis van de natuurlijke producten die Nrf2 activeren door de expressie van luciferase te beïnvloeden door middel van een interferentie met de bindingsprocessen van Nrf2 aan Keap1-proteine [40]. Daarom is een lagere luciferase-signal een indicatie van een potentieel activerend agent van Nrf2. Tabel 1 toont verschillende plant producten die bekend zijn om Nrf2 te activeren [41-64].

Tabel 1: Natuurlijk voorkomende Nrf2-activatoren in experimenteel diabetes.

| S No | Common and IUPAC Names, and Structure | Source | Experimental Model Tested | Diabetes Condition | Mechanism(s) |
|------|--------------------------------------|--------|---------------------------|--------------------|--------------|
| 1    | 1-Isothiocyanato-4- (methylsulfinyl) butane | Armoracia rusticana (Common name: Horse radish, Fam.By: Brassicaceae) | Eight-week-old WT C57BL/6J (Nrf2+/+) and I29S1 (MT+/+) male mice | Diabetic nephropathy | Sulforaphane enhanced renal Nrf2 expression [41] |
|      | | | Induction of Type 2 diabetes by feeding HFD | SFN at 0.5 mg/kg for 4 months with HFD | |
|      | | | Male Sprague–Dawley Rats | Single dose of STZ at 60 mg/kg i.p. | Diabetic nephropathy | SFN-ameliorated renal damage through GSK3β/Fyn/Nrf2 signaling pathway [42] |
|      | | | SFN at 5.0 mg/kg daily for 12 weeks i.p. | | |
|      | | | C57BL/6j male HFD-fed for 3 months and single dose of STZ 100 mg/kg i.p. | Cardiomyopathy | Down-regulated diabetes-induced PAI-1, TNF-α, CTGF, TGF-β, 3-NT, and 4-HNE expression Inhibited LKB1/AMPK pathway Increased Nrf2, and target genes H0-1 and NQO-1 [43] |
|      | | | SFN 0.5 mg/kg for 5 days each week for 4 months , subcutaneously | | |
| No. | Resveratrol (RSV) | Vitis vinifera  
(Common name: Grape vine  
Family: Vitaceae) | Four-week-old male Balb/C mice  
Methylglyoxal 1% in water, daily for 12 weeks orally  
Resveratrol 10 mg/kg daily for 12 weeks orally | Pancreatic Damage  
Promoted Nrf2-phosphorylation [44] |
|-----|------------------|-----------------------------|---------------------------------|----------------------------------|
| 2   | 3,4',5-Trihydroxystilbene | H9C2 cells treated with palmitate 500 μM and curcumin (20 μM) for 1h | H9C2 cells treated with palmitate 500 μM and curcumin (20 μM) for 1h  
Eight-week-old male C57BL/6 mice fed with HFD for 8 weeks  
Curcumin - 50 mg/kg daily for 8 weeks, orally | Heart  
Increased the expression of Nrf2, but inhibited NF-κB [47] |
| 3   | Curcumin (CUR) | Curcuma longa  
(Common name: Turmeric Family: Zingiberaceae) | Five month old male Wistar rats fed with high fructose diet (60%)  
Curcumin in 200 mg/kg for 10 weeks, orally | Inflammation, oxidative stress and insulin resistance  
Lowered TNF-α, C reactive protein (CRP) levels and down-regulated COX-2 and PKC θ expression.  
Inhibited the activation of stress sensitive Kinases and inflammatory cascades [48] |
| 4   | Quercetin | Allium cepa  
(Common name: Onion Family: Amaryllidaceae) | High-carbohydrate, high-fat diet-fed Male Wistar Rats  
Quercetin - 0.8 g/kg for 8 weeks with diet | Cardiovascular and Hepatic complications  
Increased the expression of Nrf2, HO-1, and CPT1, but lowered the levels of NF-κB [49] |
|   | Naturally Occurring Nrf2 Activators in the Management of Diabetes. |   |
|---|---------------------------------------------------------------|---|
| 5 | Epigallocatechin-3-gallate (EGCG)                            |   |
|   | (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6- heptadiene-3,5-dione |   |
|   | Camellia sinensis (Common name: Green tea)                  |   |
|   | Family: Theaceae                                             |   |
|   | Male Wistar rats with single dose Cisplatin - 7 mg/kg i.p.   |   |
|   | EGCG 100 mg/kg for 12 days p.o.                             |   |
|   | Nephrotoxicity                                               |   |
|   | Increased the levels of Nrf-2 and HO-1, but inhibited NF-κB and HNE [50] |   |
| 6 | Diallyl sulfide (DAS)                                        |   |
|   | Allium sativum (Common name: Garlic Family: Amaryllidacea)  |   |
|   | Wistar male albino rats with Gentamicin (100 mg/kg) for six consecutive days i.p. |   |
|   | DAS (150 mg/kg) for 6 days, i.p.                            |   |
|   | Nephrotoxicity                                               |   |
|   | Activation of Nrf2 and the suppression of iNOS, TNF-α and NF-κB [51] |   |
| 7 | Naringenin                                                  |   |
|   | Mentha aquatica (Common name: Water mint Family: Lamiaceae) |   |
|   | H9C2 cells with H2O2 stress of 150 μM for 1 h               |   |
|   | Treated with 50μM of Naringenin for 24 h                     |   |
|   | Cardiomyoblast                                               |   |
|   | Increased Nrf2 and its target genes, upregulated Akt and downregulated NF-κB and caspase3 genes [52] |   |
| 8 | Pterostilbene (PTS)                                         |   |
|   | Cyanococcus (Common name: Blue berry Family: Ericaceae)     |   |
|   | INS 1-E cell PTs (0–16μM) treatment up to 48h, followed by STZ (10mM) for 1 h |   |
|   | Pancreatic β-cell damage                                     |   |
|   | Upregulation of Nrf2, HO-1, SOD, CAT, GPx, and Bcl-2, Down regulation of Bax and caspase-3 expression [54] |   |
| 9 | Caffeic Acid Phenethyl Ester (CAPE)                          |   |
|   | Pinophyta (Common name: Conifer Family: Pinaceae)           |   |
|   | Male wistar rats treated with single dose of STZ 50mg/kg 1p. |   |
|   | CAPE 30mg/kg/day administrated by oral gavage for 6 weeks   |   |
|   | Atherosclerosis                                              |   |
|   | Inhibition of TNF-α in the serum Induced the expression of Nrf2-target gene HO-1 in aorta [55] |   |
|   | Substance | Mechanism | Species | Plant Name | Dose | Mode of Administration | Disease | Effect |
|---|-----------|-----------|---------|------------|------|------------------------|---------|--------|
| 10 | Fisetin | Male Sprague-Dawley rats treated with single dose of STZ 55 mg/kg i.p. | Senegalia greggii (Common name: Cat claw Family name: Legumaceae) | 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4H-chromen-4-one | Fisetin (10 mg/kg/day) administered by p.o daily for 2 weeks | Diabetic neuropathy | Increased the expression of Nrf2 and NF-κB [56] |
| 11 | Lithospermate B (LAB) | Male Sprague-Dawley rats with single dose of STZ -55 mg/kg i.p LAB -50 mg/kg, for 15 days i.p | Salvia miltiorrhize (Common name: Red sage Family name: Lamiaceae) | (2S,3S)-4-{(E)-3-[(1R)-1-carboxy-2-(3,4-dihydroxyphenyl)ethoxy]-3-oxoprop-1-enyl}-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-3-carboxylic acid |  | Atherosclerosis | Activation of NQO1 via Nrf2-ARE pathway [57] |
| 12 | Ferulic acid | Rat hepatocytes and cardiomyocytes treated with high glucose (80 mmol/L glucose) Ferulic acid -1, 5, or 10 µg/mL | Brassica oleracea (Common name: Wild cabbage Family name: Brassicaceae) | (E)-3-{(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid |  | Diabetes | Promotes the expression of Nrf2 and its target genes HO-1 and glutathione S•transferase in a dose dependent manner [58] |
| 13 | Zerumbone | Male wistar rats treated with single dose of STZ 60mg/kg i.p. Zerumbone -20-40 mg/kg/day by oral gavage daily for 8 weeks | Zerumbone (Common name: South east Asian ginger Family name: Zingiberaceae) |  |  | Diabetic nephropathy | Decreased p38MAPK activation, and TNFα. A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [59] |
| 14 | Carnosol | Male wistar rats treated with single dose STZ 50mg/kg i.p. Carnosol – up to 100mg/kg by p.o daily for 15days | Rosmarinus officinalis (Common name: Rosemary Family name: Lamiaceae) | 1,3,4,9,10,10aS,hexahydro-5,6-dihydroxy-1,1-dimethyl-7-isopropyl-2H-9S,4aR-(epoxymethano) phenanthren-12-one |  | Diabetes | A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [60] |
### Naturally Occurring Nrf2 Activators in the Management of Diabetes

**Cafestol**  
(Coffee arabica)  
*INS1E- cells treated with cafestol (10µM - 1picM) for 72hr followed by 16 min stimulation with high glucose (16.7mM).*  
**Diabetes**  
A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation.  
Note: Insulin secretion is enhanced by this compound [61]

**Ellagic acid**  
(Quercus alba)  
*Male long Evans rats treated with a single injection of alloxan monohydrate (90 mg/kg i.p. Ellagic acid rich Momordica charantia provided as 5% of diet.*  
**Diabetes**  
Improved antioxidant potentials.  
A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [62]

**Eugenol**  
(Syzygium aromaticum)  
*Male Sprague Dawley rats treated with single dose of STZ (55 mg/kg) i.p. Eugenol - 5 and 10 mg/kg orally for 4 weeks.*  
**Diabetes**  
Decreasing TGF-β1 expression  
A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [63]

**Kaempferol**  
(Malus pumila, Camellia sinensis)  
*Male albino wistar rats treated with single dose of STZ 40 mg/kg i.p. Kaempferol - 50,100 and 200mg/kg administered p.o daily for 45days.*  
**Diabetes**  
Decreased lipoperoxidation markers and increased anti oxidant levels.  
A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [64]

### Future Direction

Even though several studies have demonstrated the vital role played by Nrf2 in controlling diabetes related complications, and identified potential activators of Nrf2, not many studies have evaluated Nrf2 activators in clinical trials. Therefore, future studies should investigate the potential of naturally occurring Nrf2 activators for preventing / treating diabetes in clinical trials. In addition, strategies such as use of nano-formulations should be adopted to deliver poorly bioavailable Nrf2 activators.
Schematic representation showing the mechanism of cytoprotection by Nrfl2 activators: Schematic representation demonstrating various signaling cascades modulated through Nrfl2 pathway in diabetes. Nrfl2- activators reduce diabetes by upregulating glycolytic enzymes hexokinase (HK), phosphofructokinase-1 (PFK1) and glyceraldehyde 3-phosphate dehydrogenase (G3PD), and enzymes of hexose monophosphate shunt pathway in particular glucose-6-phosphate dehydrogenase (G6PD). In addition, Nrfl2-activators inhibit the enzymes of gluconeogenesis Glucose 6 Phosphatase (G6P) and F1BPase. Furthermore, Nrfl2 target genes protect pancreatic β-cells from ROS induced damage by up regulating NQO1 and SOD levels. Additionally, Nrfl2 controls cell proliferation, apoptosis, autophagy and angiogenesis in diabetes (Figure 1).

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