



# 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  $\beta$ -cells thereby reduce hyperglycemia induced changes such as retinopathy, neuropathy, 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 in to nucleus thereby trigger the transcription of genes such as NQO1, GST, HO1, HIF1  $\alpha$ , 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  $\beta$ -cells; Nrf2 -activators; Sulforaphane; Curcumin

**Abbreviations:** AGEs: Advanced Glycation End-products; AR: Aldose Reductase; CREB: cAMP Response Element Binding Protein; CUR: Curcumin; DAG: Diacylglycerol; DM: Diabetes Mellitus; eNOS: Endothelial NOS; ET1: Endothelin-1; G6pc: Glucose-6-Phosphatase Catalytic-subunit; GCL: Glutamine Cysteine Ligase; GCS: Gamma-glutamine Cysteine Synthase; Glo-1: Glyoxalase-1; GSH: Glutathione; GST:  $\gamma$ - Glutamyl Cysteine Synthetase; Hk2: Hexokinase 2; HO-1: Heme Oxygenase 1; ICAM1: Intracellular Adhesion Molecule-1; IDF : International Diabetes Federation; LB: Magnesium Lithospermate B; MG: Methylglyoxal; NF-  $\kappa$ B: Nuclear Factor Kappa B; NQO1: NAD(P)H:quinone Oxidoreductase 1; Nrf2: Nuclear factor E2-related factor 2; PKC: Protein kinase C; Pkm2: Pyruvate kinase; PLA2: Phospholipase A2; ROS: Reactive Oxygen Species; RSV: Resveratrol; SFN: Sulforaphane; Slc2a1: Solute carrier family 2 member 1; TGF- $\alpha$ : Transforming growth factor-  $\alpha$ ; TGF- $\beta$ 1: Transforming Growth Factor Beta 1; VCAM 1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor

## 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  $\beta$ -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  $\beta$ -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  $\beta$ -cell damage [9,10]. Use of naturally occurring photochemical is one such strategy to mitigate the toxic effects, and protect pancreatic  $\beta$ -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 TGF $\beta$ 1 and inhibits Nrf2 expression resulting in elevated ROS levels [26]. Excessive cellular ROS in turn activate the TGF $\beta$ 1 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 TGF $\beta$ 1 [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  $\gamma$ -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- $\alpha$  [38].

In summary, PKC is a key regulator of various processes that lead to the

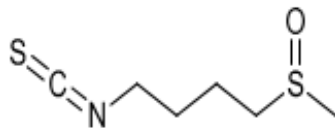
- a) Overproduction of ROS;
- b) Development of insulin resistance;
- c) Impaired glucose tolerance and
- d)  $\beta$ -cell dysfunction [38].

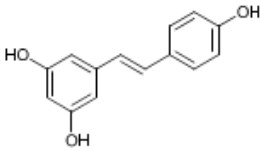
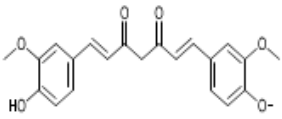
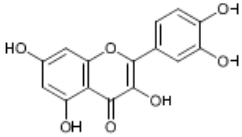
Nrf2 plays an important role in modulating these metabolic aberrations during hyperglycemias by regulating PKC and the enzymes involved in glucose metabolism [39]. Mechanistically, Nrf2 up regulate Slc2a1, Hk2 and Pkm2 expression in liver, brown adipose tissue, brain and kidney, while down-modulating G6p expression, cAMP- CREB signalling pathways. Therefore,

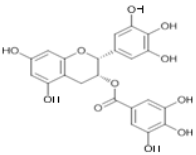
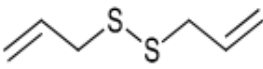
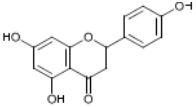
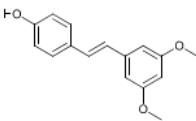
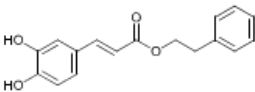
activation of Nrf2 using phytochemicals is a better strategy to inhibit diabetes-related complications.

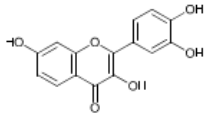
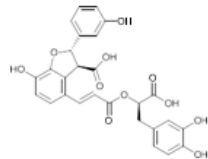
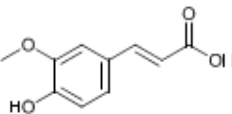
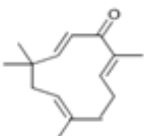
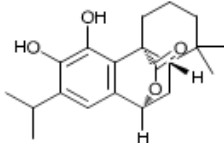
Hence, several researchers have developed screening and validation methods to identify potent Nrf2 activators from plant sources. One widely used screening method for identifying Nrf2 activators is complementation assay. Complementation screening system works on the principle that natural products activating Nrf2 prevents the expression of luciferase by interfering with Nrf2 binding to Keap1 protein [40]. Therefore, a decrease in luciferase signal is an indicator of potent activator of Nrf2. Table 1 shows various plant products known to activate Nrf2 [41-64].

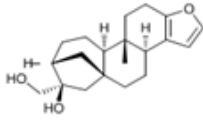
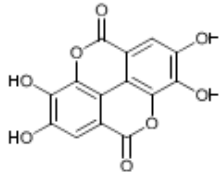
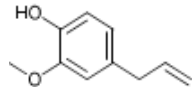
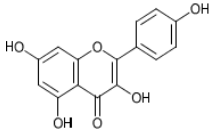
**Table 1:** Naturally occurring Nrf2 activators evaluated in experimental diabetes.

Naturally occurring Nrf2 activators evaluated in experimental Diabetes					
S No:	Common and IUPAC Names, and Structure	Source	Experimental Model Tested	Diabetes Condition	Mechanism(s)
1	<p>Sulforaphane (SFN)</p>  <p>1-Isothiocyanato-4- (methylsulfinyl) butane</p>	<p><i>Armoracia rusticana</i> (Common name: Horse radish, Family: Brassicaceae)</p>	<p>Eight-week-old WT C57BL/6J (Nrf2+/+) and 129S1 (MT+/+) male mice</p> <p>Induction of Type 2 diabetes by feeding HFD</p> <p>SFN at 0.5 mg/kg for 4 months with HFD</p>	Diabetic nephropathy	Sulforaphane enhanced renal Nrf2 expression [41]
			<p>Male Sprague–Dawley Rats</p> <p>Single dose of STZ at 60 mg/kg i.p.</p> <p>SFN at 5.0mg/kg daily for 12 weeks i.p.</p>	Diabetic nephropathy	SFN-ameliorated renal damage through GSK3 $\beta$ /Fyn/Nrf2 signaling pathway [42]
			<p>C57BL/6J male</p> <p>HFD-fed for 3 months and single dose of STZ 100 mg/kg i.p.</p> <p>SFN 0.5 mg/kg for 5 days each week for 4 months, subcutaneously</p>	Cardiomyopathy	<p>Down-regulated diabetes-induced PAI-1, TNF-<math>\alpha</math>, CTGE, TGF-<math>\beta</math>, 3-NT, and 4-HNE</p> <p>expression Inhibited LKB1/AMPK pathway</p> <p>Increased Nrf2, and target genes HO-1 and NQO-1 [43]</p>

2	<p>Resveratrol (RSV)</p>  <p>3,4',5-Trihydroxystilbene</p>	<p><i>Vitis vinifera</i> (Common name: Grape vine Family: <i>Vitaceae</i>)</p>	<p>Four-week-old male Balb/C mice Methylglyoxal 1% in water; daily for 12 weeks orally</p> <p>Resveratrol 10 mg/kg daily for 12 weeks orally</p> <p>Six-week-old male Wistar rats Single dose of STZ 50 mg/kg i.p. after administration of nicotinamide 110mg/kg i.p.</p> <p>Resveratrol 5 mg/kg for 30 days orally</p> <p>HepG2 Cells with MG (500 μM) and Resveratrol (50 μM) for 24h</p>	<p>Pancreatic Damage</p> <p>Diabetic nephropathy</p> <p>Insulin Resistance</p>	<p>Promoted Nrf2-phosphorylation [44]</p> <p>Increased the expression of Nrf2 and target genes γ-GCL, μ-GST and HO-1 in renal tissues [45]</p> <p>Enhanced Nrf2 nuclear translocation and its activation via ERK phosphorylation. Promoted Nrf2 target gene HO-1 levels [46]</p>
3	<p>Curcumin (CUR)</p>  <p>(1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6- heptadiene-3,5-dione</p>	<p><i>Curcuma longa</i> (Common name: Turmeric Family: <i>Zingiberaceae</i>)</p>	<p>H9C2 cells treated with palmitate 500 μM and curcumin (20 μM) for 1h</p> <p>Eight -week-old Male C57BL/6 mice fed with HFD for 8 weeks</p> <p>Curcumin - 50 mg/kg daily for 8 weeks, orally</p> <p>Five month old male Wistar rats fed with high fructose diet (60%)</p> <p>Curcumin 200 mg/kg for 10 weeks, orally</p>	<p>Heart</p> <p>Inflammation, oxidative stress and insulin resistance</p>	<p>Increased the expression of Nrf2, but inhibited NF-κB [47]</p> <p>Lowered TNF-α, C reactive protein (CRP) levels and down-regulated COX-2 and PKC θ expression.</p> <p>Inhibited the activation of stress sensitive Kinases and inflammatory cascades [48]</p>
4	<p>Quercetin</p>  <p>2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4- one</p>	<p><i>Allium cepa</i> (Common name: Onion Family: <i>Amaryllidaceae</i>)</p>	<p>High-carbohydrate, high-fat diet-fed Male Wistar Rats</p> <p>Quercetin - 0.8 g/kg for 8 weeks with diet</p>	<p>Cardiovascular and Hepatic complications</p>	<p>Increased the expression of Nrf2, HO-1, and CPT1, but lowered the levels of NF-κB [49]</p>

5	<p>Epigallocatechin-3-gallate (EGCG)</p>  <p>(1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6- heptadiene-3,5-dione</p>	<p><i>Camellia sinensis</i> (Common name: Green tea Family: <i>Theaceae</i>)</p>	<p>Male Wistar rats with single dose Cisplatin - 7 mg/kg i.p. EGCG 100 mg/kg for 12 days p.o.</p>	Nephrotoxicity	Increased the levels of Nrf-2 and HO-1, but inhibited NF-κB and HNE [50]
6	<p>Diallyl sulfide (DAS)</p>  <p>3-[[Prop-2-en-1-yl]disulfanyl]prop-1-ene</p>	<p><i>Allium sativum</i> (Common name: Garlic Family: <i>Amaryllidaceae</i>)</p>	<p>Wistar male albino rats with Gentamicin (100 mg/kg) for six consecutive days i.p. DAS (150 mg/kg) for 6 days, i.p.</p>	Nephrotoxicity	Activation of Nrf2 and the suppression of iNOS, TNF-α and NF-κB [51]
7	<p>Naringenin</p>  <p>5,7-Dihydroxy-2-(4-</p>	<p><i>Mentha aquatica</i> (Common name: Water mint Family: <i>Lamiaceae</i>)</p>	<p>H9C2 cells with H2O2 stress of 150 μM for 1 h Treated with 50μM of Naringenin for 24h</p>	Cardiomyoblast	Upregulated Nrf2 and its target genes, Upregulated Akt and downregulated NF-κB and caspase3 genes [52]
			<p>Male Sprague - Dawley rats with CCl4 10 ml/kg for 5 days i.p. Naringenin (50 mg/kg) for 7 days orally</p>	Hepatocytes	Increased Nrf2 and HO-1 expression Down-regulated TNF-α, iNOS, COX-2 [53]
8	<p>Pterostilbene (PTS)</p>  <p>4-[[E]-2-(3,5-Dimethoxyphenyl)ethenyl]phenol</p>	<p><i>Cyanococcus</i> (Common name: Blue berry Family: <i>Ericaceae</i>)</p>	<p>INS 1-E cell PTS (0–16μM) treatment up to 48h, followed by STZ (10mM) for 1 h</p>	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	<p>Caffeic Acid Phenethyl Ester (CAPE)</p>  <p>Phenethyl 3-(3,4- dihydroxyphenyl) acrylate</p>	<p><i>Pinophyta</i> (Common name: Conifer Family name: <i>Pinaceae</i>)</p>	<p>Male wistar rats treated with single dose of STZ 50mg/kg i.p. CAPE 30mg/kg/day administered by oral gavage for 6 weeks</p>	Atherosclerosis	Inhibition of TNF-α in the serum Induced the expression of Nrf2-target gene HO-1 in aorta [55]

10	<p>Fisetin</p>  <p>2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4H-chromen-4-one</p>	<p><i>Senegalia greggii</i> (Common name: Cat claw)</p> <p>Family name: <i>Legumaceae</i></p>	<p>Male Sprague-Dawley rats treated with single dose of STZ- 55 mg/kg i.p.</p> <p>Fisetin (10 mg/kg/day) administrated by p.o daily for 2 weeks</p>	Diabetic neuropathy	Increased the expression of Nrf2 and NF-κB [56]
11	<p>Lithospermate B (LAB)</p>  <p>(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</p>	<p><i>Salvia miltiorrhizae</i> (Common name: Red sage)</p> <p>Family name: <i>Lamiaceae</i></p>	<p>Male Sprague-Dawley rats with single dose of STZ -55 mg/kg i.p</p> <p>LAB -50 mg/kg. for 15 days i.p</p>	Atherosclerosis	Activation of NQO1 via Nrf2-ARE pathway [57]
12	<p>Ferulic acid</p>  <p>(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid</p>	<p><i>Brassica oleracea</i> (Common name: Wild cabbage Family name: Brassicaceae)</p>	<p>Rat hepatocytes and cardiomyocytes treated with high glucose (80 mmol/ L glucose)</p> <p>Ferulic acid- 1, 5, or 10 µg/mL</p>	Diabetes	Promotes the expression of Nrf2 and its target genes HO-1 and glutathione S-transferase in a dose dependent manner [58]
13	<p>Zerumbone</p> 	<p><i>Zerumbone</i> (Common name: South east Asian ginger Family name: <i>Zingiberaceae</i>)</p>	<p>Male wistar rats treated with single dose of STZ 60mg/kg i.p.</p> <p>Zerumbone - 20-40 mg/kg/day by oral gavage daily for 8 weeks</p>	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	<p>Carnosol</p>  <p>1,3,4,9,10,10aS-hexahydro-5,6-dihydroxy-1,1-dimethyl-7-isopropyl-2H-9S,4aR-(epoxymethano) phenanthren-12-one</p>	<p><i>Rosmarinus officinalis</i> (Common name: Rosemary Family name: <i>Lamiaceae</i>)</p>	<p>Male wistar rats treated with single dose STZ 50mg/kg i.p.</p> <p>Carnosol – up to 100mg/kg by p.o daily for 15days</p>	Diabetes	A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [60]

15	<p>Cafestol</p>  <p>(3bS,5aS,7R,8R,10aR,10bS)-3b,4,5,6,7,8,9,10,10a,10b,11,12-Dodecahydro-7-hydroxy-10b-methyl-5a,8-methano-5aH-</p>	<p><i>Coffea arabica</i> (Common name: Arabica coffee Family name: <i>Rubiaceae</i>)</p>	<p>INS1E- cells treated with cafestol (10µM - 1picM) for 72hr followed by 16 min stimulation with high glucose (16.7mM).</p>	<p>Diabetes</p>	<p>A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation.</p> <p>Note: Insulin secretion is enhanced by this compound [61]</p>
16	<p>Ellagic acid</p>  <p>2,3,7,8-Tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione</p>	<p><i>Quercus alba</i> (Common name: White oak Family name: <i>Fagaceae</i>)</p>	<p>Male long Evans rats treated with a single injection of alloxan monohydrate (90 mg/kg) i.p.</p> <p>Ellagic acid rich Momordica charantia provided as 5% of diet</p>	<p>Diabetes</p>	<p>Improved antioxidant potentials.</p> <p>A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [62]</p>
17	<p>Eugenol</p>  <p>4-Allyl-2-methoxyphenol</p>	<p><i>Syzygium aromaticum</i> (Common name: Clove Family name: Myrtaceae)</p>	<p>Male Sprague Dawley rats treated with single dose of STZ (55 mg/kg) i.p.</p> <p>Eugenol - 5 and 10 mg/kg orally for 4 weeks</p>	<p>Diabetes</p>	<p>Decreasing TGF-β1 expression</p> <p>A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [63]</p>
18	<p>Kaempferol</p>  <p>3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one Malus pumila, Camellia sinensis</p>	<p><i>Malus pumila, Camellia sinensis</i></p>	<p>Male albino wistar rats treated with single dose of STZ 40 mg/kg i.p.</p> <p>Kaempferol - 50,100 and 200mg/kg administrated p.o daily for 45days</p>	<p>Diabetes</p>	<p>Decreased lipoperoxidation markers and increased anti oxidant levels.</p> <p>A known activator of Nrf2. But it is currently unknown whether the anti-diabetic properties are mediated through Nrf2 activation [64]</p>

### 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.

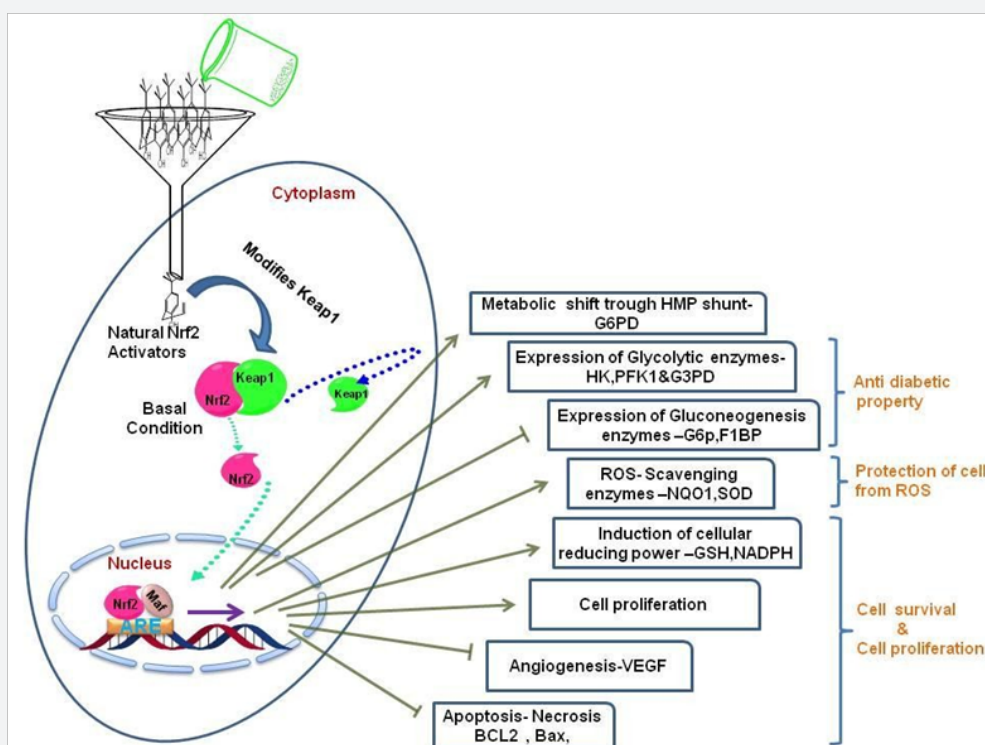


Figure 1: Schematic representation showing the mechanism of cytoprotection by Nrf2 activators.

Schematic representation showing the mechanism of cytoprotection by Nrf2 activators: Schematic representation demonstrating various signaling cascades modulated through Nrf2 pathway in diabetes. Nrf2- 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, Nrf2-activators inhibit the enzymes of gluconeogenesis Glucose 6 Phosphatase (G6P) and F1BPase. Furthermore, Nrf2 target genes protect pancreatic  $\beta$ -cells from ROS induced damage by up regulating NQO1 and SOD levels. Additionally, Nrf2 controls cell proliferation, apoptosis, autophagy and angiogenesis in diabetes (Figure 1).

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