Chapter 2
Berberine and Its Role in Chronic Disease

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Abstract Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is found in such plants as Berberis [e.g. Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), Berberis aristata (tree turmeric)], Hydrastis canadensis (goldenseal), Xanthorhiza simplicissima (yellowroot), Phellodendron amurense [2] (Amur corktree), Coptis chinensis (Chinese goldthread), Tinospora cordifolia, Argemone mexicana (prickly poppy) and Eschscholzia californica (Californian poppy). In vitro it exerts significant anti-inflammatory and antioxidant activities. In animal models berberine has neuroprotective and cardiovascular protective effects. In humans, its lipid-lowering and insulin-resistance improving actions have clearly been demonstrated in numerous randomized clinical trials. Moreover, preliminary clinical evidence suggest the ability of berberine to reduce endothelial inflammation improving vascular health, even in patients already affected by cardiovascular diseases. Altogether the available evidences suggest a possible application of berberine use in the management of chronic cardiometabolic disorders.

Keywords Berberine · Antioxidant · Anti-inflammatory · Type 2 diabetes · Cardiovascular disease · Depression

2.1 Introduction

Cardiovascular diseases are yet the most common causes of death and one of the first causes of disability in industrialized countries and despite the efforts towards primary prevention of cardiovascular disease, many patients still remain at risk [1]. Lifestyle interventions such as diet and/or physical activity are the most
cost-effective approach in delaying or preventing the onset of cardiovascular disease [2]. Moreover, people without a history of cardiovascular disease who lack common risk factors have a significantly greater risk of cardiovascular and all-cause mortality if they do not adhere to a healthy lifestyle [3]. However, lifestyle programs are often difficult to follow for long periods and some risk parameters, such as cholesterolemia, are relatively resistant to changes in dietary habits and physical activity [4]. On the other hand, a relatively large number of dietary supplements and nutraceuticals have been studied for their supposed or demonstrated ability to reduce cholesterolemia in humans [5]. The third National Cholesterol Educational Program suggested to integrate dietary supplements such as soluble fibres, omega-3 polyunsaturated fatty acids (PUFA), plant sterols and soy protein in the diet in order to achieve an optimal LDL-cholesterolemia [6]. These suggestions have been supported also by the recent new European guidelines of the management of dyslipidemias [7] that also cite some other nutraceuticals as potentially useful lipid-lowering substances. Since cardiovascular disease prevention needs a life course approach, both the tolerability and safety of dietary supplements/nutraceuticals used to control plasma cholesterol levels has to be adequately defined as well as the risk/benefit ratio of their assumption. A relatively large number of recent reviews already described the mechanism of action and the efficacy of the different nutraceuticals and botanicals with lipid-lowering effects [8–10]. In particular, Berberine (BBR) exhibits many different biological activities; among them, the best characterized are antioxidant, anti-inflammatory, cholesterol-lowering and anti-hyperglycemic effects.

2.1.1 Physico-Chemical and Pharmacological Properties of Berberine

Berberine is a quaternary ammonium salt from the group of isoquinoline alkaloids (2,3–methylenedioxy-9,10-dimethoxyprotoberberine chloride; C_{20}H_{18}NO_{4}^{+}) with a molar mass of 336.36122 g/mol [11]. It is highly concentrated in the roots, rhizomes and stem bark of various plants including Coptis chinensis, Rhizoma cop-tidis, Hydrastis canadensis, Berberis aquifolium, Berberis vulgaris, Berberis aristata, Tinospora cordifolia, Arcangelisia flava and Cortex rhellodendri [12]. Berberine is strongly yellow coloured, which explains the fact that in the past berberis species were used to dye wool, leather and wood. Under ultraviolet light, berberine shows a strong yellow fluorescence with a Colour Index of 75,160 [13].

*Berberis vulgaris* as well as other berberine-containing plants [14] are used medicinally in virtually all-traditional medical systems, and have a history of usage in Ayurvedic, Iranian and Chinese medicine dating back at least 3000 years [16]. Ancient Egyptians used barberry fruit with fennel seeds to ward off pestilent fevers [15]. Indian Ayurvedic physicians used barberry in the treatment of dysentery and traditional Iranian medicine uses its fruit as a sedative [15, 17]. In northern Europe,
barberry was used to treat gall bladder and liver problems, while it was used in the
treatment of abnormal uterine bleeds and rheumatism in Russia and Bulgaria [18,
19]. In North America, the Eclectics used barberry for treatment of malaria and as a
general tonic [20]. Also, the American Indians found it effective in improving
appetite and used its dried fruit as a gargle [21, 22].
Medicinal properties for all parts of the plant have been reported, including tonic,
antimicrobial, antiemetic, antipyretic, antipruritic, antioxidant, anti-inflammatory,
hypotensive, antiarrhythmic, sedative, antinociceptive, anticholinergic and cholagogue
actions, and it has been used in some cases like cholecystitis, cholelithiasis, jaundice,
dysentery, leishmaniasis, malaria and gall stones [23]. Furthermore, berberine has been used for treating diarrhoea and gastrointestinal disorders for a long
time [24, 25]. It has multiple pharmacological effects including: antimicrobial activity
against 54 microorganisms [26], inhibition of intestinal ion secretion and smooth
muscle contraction, inhibition of ventricular tachyarrhythmia, reduction of inflamma-
tion, stimulation of bile secretion and bilirubin discharge [27].
Berberine has low bioavailability and poor absorption through the gut wall
(<5 %) and bowel P-glycoprotein contributes to that, actively expelling the alkaloid
from the lumen mucosal cells [28].
In a rat noncompartmental model [29], unbound berberine is transported to bile
through active transportation and it is metabolized by P450 enzyme system in liver,
with phase I demethylation and phase II glucuronidation. Berberine has four main
metabolites identified in rats: berberrubine, thalifendine, demethyleneberberine and
jatrorrhizine, and all of them have glucuronide conjugates [30]. Intestinal bacterial
flora takes role in enterohepatic circulation of berberine and its conjugated
metabolites [28]. On the other hand, very small amount of unchanged berberine is
eliminated in urines [31].
As other alkaloids are present in H. canadensis extracts (i.e. hydrastine and
canadine), berberine may inhibit cytochrome P450 2E1 (CYP2E1) [32] and 1A2
(CYP1A2) [33]. This inhibition is not related to a significant increase in pharma-
cological interactions since the largest part of the available drugs is not metabolized
by these enzymatic systems.

2.1.2 Berberine Modulation of Cell Signalling Pathways

Berberine is a potent antioxidant and anti-inflammatory agent: these properties
could be particularly relevant in the management of type 2 diabetes and cardio-
vascular diseases.
In metabolic disorders, as obesity and type 2 diabetes, increased oxidative stress
is a common feature [34, 35]. It could induce or deteriorate insulin resistance and
diabetes through multiple mechanisms. In the process of oxidative stress, excessive
reactive oxygen species (ROS) are produced, mainly by mitochondria [36, 37].
They could cause damage and apoptosis of pancreatic islet β-cells and reduction of
insulin secretion [38]. ROS also activate c-Jun N-terminal kinase (JNK), protein
kinase C (PKC) and nuclear factor-κB (NF-κB), interfering with the insulin signalling pathway and causing insulin resistance [39–41]. In addition, oxidative stress also contributes to the development of chronic complications of diabetes, such as diabetic nephropathy, retinopathy and neuropathy [37].

Molecular mechanisms of berberine in reducing oxidative stress seem to be related with multiple cellular pathways (Fig. 2.1).

The NOX family of ROS-generating NADPH oxidases, a family of membrane-associated enzymatic complexes, is one of the major sources of ROS production in cells [42]; its activation is often associated to high levels of fatty acids, cholesterol, glucose or advanced glycation end products (AGEs) [43–45]. Among various NOX isoforms, berberine was reported to suppress the overexpression of NOX 2,4 and to decrease ROS production in macrophages and endothelial cells upon stimulation with inflammatory stimuli [46, 47]. In endothelial cells, berberine attenuated LDL oxidation induced by ROS and reduces the collapse of mitochondrial membrane potential, the chromosome condensation, the cytochrome C release and the caspase-3 activation [48]. Circulating endothelial
microparticles, vesicular structures found in plasma from patients with vascular diseases so utilized as a surrogate marker of endothelial dysfunction, are oxidative stress inducers; they promote upregulation of NOX4 expression and ROS production. It has been reported that berberine reversed NOX4-derived ROS production in human umbilical vein endothelial cells (HUVECs) [46].

NOX could be negatively regulated by adenosine monophosphate-activated protein kinase (AMPK) activation [49, 50]; in fact AMPK activators, such as metformin, may exert their cardiovascular protective function through NOX inhibition [51]. AMPK pathway is activated by berberine [52] and it seems to play a pivotal role in mediating its antioxidant activity [53, 54].

The AMPK is a ubiquitously expressed cellular energy sensor and an essential component of the adaptive response to cardiomyocyte stress that occurs during ischemia. AMPK plays also an important role in regulating function of NO synthesis in endothelial cells. In fact, AMPK is an upstream kinase of endothelial nitric oxide synthase (eNOS) which promotes the phosphorylation of eNOS at Ser1177 site as well as the formation of eNOS and HSP90 complex and NO production [55]. Zhang et al. [56] observed that in HUVECs berberine ameliorated palmitate-induced endothelial dysfunction by upregulating eNOS and downregulating of NOX4 through the activation of AMPK. In both cultured endothelial cells and blood vessels isolated from rat aorta berberine enhanced eNOS phosphorylation and attenuated high glucose-induced generation of ROS, cellular apoptosis, NF-κB activation and expression of adhesion molecules through AMPK signalling cascade activation, a key event in preventing oxidative and inflammatory signalling [57].

Besides NADPH oxidase downregulation and NO production, AMPK activation has been linked to upregulation of the antioxidant enzyme superoxide dismutase (SOD) [58, 59], which is dismutated to hydrogen peroxide. It was observed an increased SOD expression in berberine treated diabetic mice [60, 61]. Glutathione (GSH) is another antioxidant molecule which helps to maintain the balance of redox state in organisms and acting asco-substrate of glutathione peroxidase (GSH-Px) in the clearance of peroxides [62]. Berberine treatment promoted a GSH-Px and SOD hyperactivation in the liver of mice [63], attenuated ROS production and increased detoxifying enzymes GSH-Px and SOD in NSC34 motor neuron-like cells [64].

Recent studies revealed that berberine suppressed oxidative stress through induction of the nuclear factor erythroid-2-related factor-2 (Nrf2) pathway [65–67]. Nrf2 is a transcription factor which binds to antioxidative response elements (ARE) in DNA, leading to transcription of phase II enzymes and cytoprotective proteins genes such as NAD(P)H quinone oxidoreductase-1 (NQO-1) and heme oxygenase-1 (HO-1) with a wide range of activities in regulating redox state and energy metabolism in cells [68]. Now, Nrf2 is recognized as an important mediator of berberine in reducing oxidative stress, as blocking Nrf2 abolishes the antioxidant activity of berberine in macrophages and nerve cells [65–67]. The activation of AMPK, phosphatidylinositol 3-kinase (PI3K)/Akt and p38 kinase cellular pathways is involved in the effect of berberine on Nrf2, since the block of these pathways diminishes the stimulating effect of berberine on Nrf2 [65–67].
The anti-inflammatory activity of berberine was observed both in vitro and in vivo and was noted by the reduction of proinflammatory cytokines as well as acute phase proteins [69–78].

In cultured metabolically active cells (adipocytes and liver cells), immunocytes (macrophages and splenocytes) or pancreatic β-cells, berberine treatment reduced the production of TNF-α, IL-6, IL-1β, matrix metalloprotease 9 (MMP9), cyclooxygenase-2 (COX2), inducible NOS (iNOS), monocyte chemoattractant protein 1 (MCP-1) and C-reactive protein (CRP) and haptoglobin (HP) [70–100]. In insulin-resistant HepG2 cells, the anti-inflammatory activity of berberine was associated with its insulin-sensitizing effect. Berberine administration significantly decreased cytokine production, and reduced serine phosphorylation but increased insulin-mediated tyrosine phosphorylation of IRS in HepG2 cells treated with palmitate [71].

Berberine could reduce proinflammatory cytokines, acute phase protein and infiltration of inflammatory cells in animals with diabetes mellitus or insulin resistance, either induced by streptozocin injection/high-fat diet (HFD) feeding or spontaneously happened [69, 72, 74–76]. In these animal models, the anti-inflammatory activity of berberine was observed in different tissues like serum, liver, adipose tissue, and kidney and was associated with its effect against insulin resistance or diabetes mellitus [69, 72, 74–76]. Besides evidences from cultured cells and diabetic animal models, the anti-inflammatory effect of berberine was also observed in humans: the berberine dose of 1g/day for 3 months significantly reduced the serum hsCRP and IL-6 level in patients with acute coronary syndrome following percutaneous coronary intervention [80].

Berberine suppresses inflammation through complex mechanisms. In addition to antioxidant activity, the AMPK pathway was also crucial for the anti-inflammatory efficacy of berberine [72]. Blocking AMPK could abolish the inhibitory effect of berberine on the production of proinflammatory cytokines, like inducible nitric oxide synthase (iNOS) and COX2 in macrophages [72]. Excessive iNOS in cells could cause overproduction of NO and had close relationship with the development of insulin resistance [82]. COX2 is a key enzyme for the synthesis of prostaglandins [81], which are important mediators for the pathogenesis of diabetes mellitus and diabetic nephropathy [82].

The anti-inflammatory activity of berberine was also associated with its inhibitory effect on the mitogen-activated protein kinase (MAPK) signalling pathways, which were activated by inflammatory stimuli [72, 83, 84]. The inhibitory effect of berberine on MAPKs was dependent on AMPK activation in macrophages [72]. It seems that conflicting results exist concerning the regulatory effect of berberine on MAPK signalling. Although some results suggested that berberine suppressed the inflammation through inhibiting MAPKs [72, 83, 84], others indicated that p38 kinase was activated by berberine which was considered important for berberine’s efficacy against oxidative stress and inflammation [65–67].

The NF-κB pathway plays a key role in controlling inflammation [85]. In NF-κB signalling pathway, IkB kinase-β (IKK-β) could be activated by inflammatory stimuli like TNF-α, as well as nutritional factors like glucose and FFA [86]. The activation of IKK-β required phosphorylation of the serine residue at position 181
[87, 88]. In insulin-resistant 3T3-L1 adipocytes [89] and liver/adipose tissues from obese mice fed with HFD [74], berberine administration greatly reduced phosphorylation of ser181 and activation of IKK-β. In addition, the inhibitory effect of berberine on IKK-β required a cysteine residue at position 179 of IKK-β [89].

Recent studies proved that berberine could reduce renal inflammation in diabetic rats through inhibiting the Rho GTPase signalling pathway [69]. Rho GTPase is a member of the superfamily of small GTP binding proteins with multiple biological functions [90]; it was proven to positively regulate the NF-κB signalling pathway in diabetic rats [91]. Therefore, in addition to regulation of the classic NF-κB signalling pathway, berberine could inhibit NF-κB by suppressing Rho GTPase [69, 92]. Furthermore, the inhibitory effect of berberine on Rho GTPase relied on its antioxidant activity [69].

In addition to NF-κB, transcription factor activator protein 1 (AP-1) also played a role in the anti-inflammatory activity of berberine [93, 94]. Administration of berberine to macrophages or epithelial cells greatly attenuated the DNA binding activity of AP-1 and reduced the production of cytokines like MCP-1 and COX2 [93]. There were reports that the transcription stimulating activity of AP-1 and NF-κB could be inhibited by activation of peroxisome proliferator-activated receptor γ (PPARγ) [95–99].

2.1.2.1 Berberine Effects on Glucose Metabolism

In general, there are two distinct pathways to activate glucose uptake in peripheral tissues; one stimulated by insulin through the IRS-1/PI 3-kinase and the other by exercise or hypoxia via activation of AMP activated protein kinase (AMPK). In muscle, which is the major tissue responsible for whole body glucose disposal after liver, both pathways stimulate the translocation of glucose transporter-4 (GLUT4) to the cell membrane which accounts for the enhanced glucose uptake [100].

Current data suggest that the berberine effects are complex and may activate portions of both the insulin and the exercise-induced glucose uptake pathways [101]. In addition, berberine inhibits intestinal absorption of glucose, which also contributes to berberine glucose-lowering effect [102].

There is increasing evidence that the most widely expressed GLUT1, initially thought to be responsible only for basal glucose uptake, can be acutely activated by cell stressors such as azide [103, 104], osmotic stress [105, 106], methylene blue [107] and glucose deprivation [108, 109]. In particular, the acute activation of GLUT1 by hypoxia or azide has been attributed to activation of AMPK [110, 111]. In addition, it has been recently shown that peptide C activates GLUT1 transport activity in erythrocytes, establishing a potential link between GLUT1 activity and diabetes [112].

In cultured human liver cells and rat skeletal muscle, berberine increases insulin receptor mRNA expression through Protein kinase C-dependent activation of its promoter [113].

Since berberine was observed to act as an insulin-sensitizing agent in cultured cells [114], its activity has been compared with that of metformin in different animal
models. In rat models of type 2 diabetes (T2DM), berberine shows to have equal or better fasting plasma glucose (FPG), insulin-resistance and low-density lipoprotein cholesterol (LDL-C) lowering activity than metformin by a mechanism involving retinol binding protein-4 (RBP-4) and (GLUT-4) [115, 116].

Berberine exhibited a high hypoglycemic potential; it has been shown that berberine activates AMPK with subsequent induction of glycolysis [117]. AMPK, as an intracellular energy receptor, has attracted more attention and become a new target for the treatment of diabetes and its cardiovascular complications due to its regulatory effect on endothelial cell function and energy homeostasis. In H9c2 myoblast cell line treated with insulin to induce insulin resistance, berberine attenuated the reduction in glucose consumption and glucose uptake at least in part via stimulation of AMPK activity [118]. berberine enhanced acute insulin-mediated GLUT4 translocation and glucose transport in insulin-resistant myotubes through activation of AMPK and PI3K pathway [119] (Fig. 2.2).

Fig. 2.2 Main glucose-lowering effects of berberine in the human cells. Berberine administration could decrease glycemia through the GLP-1 receptor activation in pancreas beta cells, the increase of Insulin Receptor expression and the AMPK-modulated Glut-4 translocation in peripheral cells.
In a clinical study, the same group observed that berberine significantly lowered FPG, hemoglobin A1c, triglycerides and insulin levels in patients with T2DM as well as metformin and rosiglitazone (a combination commonly used for the T2DM therapy); the percentages of peripheral blood lymphocytes expressing InsR were significantly elevated after therapy [120].

In a recent meta-analysis of randomized clinical trials, berberine resulted to be safe and effective in the treatment of patients with T2DM [121].

### 2.1.2.2 Berberine Effects on Lipid Metabolism and Vascular Health

The cholesterol and triglycerides lowering effect of berberine has been clearly demonstrated by a recent meta-analysis of randomized clinical trials [122]. The lipid-lowering activity of berberine, in association with other nutraceuticals, has been also clearly confirmed in a relatively large number of randomized clinical trials [123, 124].

The supposed mechanism of action is the increased expression of the liver receptor for LDL mediated by the inhibition of the Pro-protein-converting subtilisin-kexin-9 (PCSK9) activity [125]. Besides its upregulation effect on the LDL receptor, berberine could also reduce triglycerides by AMP kinase activation and MAPK/ERK pathway blocking [126] (Fig. 2.3).

High levels of LDL and their oxidized counterpart, oxidized LDL (oxLDL), in the blood vessels represent a major risk factor for endothelial dysfunction and atherosclerosis [127]. Inactivity of LDL receptor (LDLR) or its low-level expression initiates accumulation of LDL in blood vessels [128]. On the other hand, the receptor of oxLDL, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) identified as the main endothelial receptor for oxLDL also present in macrophages and smooth muscle cells (SMC), activates a proatherogenic cascade by inducing endothelial dysfunction, SMC proliferation, apoptosis and the transformation of macrophages into foam cells and platelet activation via NF-κB activation [129].

LOX-1 contains a lectin-like extracellular C-terminal domain which interacts with oxLDL, proteolytically cleaved and released as a soluble circulating form (sLOX-1) that reflects the increased expression of membrane-bound receptors and disease activities [130].

In human macrophage-derived foam cells treated with oxLDL, berberine inhibits the expression of LOX-1 [131] as well as the oxLDL uptake of macrophages and reduces foam cell formation in a dose-dependent manner [132] by activating the AMPK-SIRT1-PPARγ pathway [133]. Chi and colleagues demonstrated that berberine combined with atorvastatin is more effective in diminishing LOX-1 expression than atorvastatin alone in monocyte-derived macrophages both in vitro and in rats through modulation of endothelin-1 receptor [134].

Berberine improves also the survival of TNF-α-treated endothelial progenitor cells (EPCs) via the activation of PI3K/AKT/eNOS transcription factor [135] possibly through AMPK activation. Wu and colleagues showed, both in vitro and in vivo that berberine reduces the leukocyte-endothelium adhesion and vascular cell
adhesion molecule-1 (VCAM-1) expression induced by LPS. Berberine was further confirmed to inhibit the nuclear translocation and DNA binding activity of LPS-activated NF-κB signalling pathway [136].

2.1.2.3 Berberine and Central Nervous System Disorders

A large number of preclinical evidence support a possible role of berberine in the management of Alzheimer’s disease, cerebral ischemia, mental depression, schizophrenia and anxiety, however the most part of these data have been obtained in purely experimental models [137]. Of particular interest is the potential antidepressant effect of berberine. Berberine inhibited the immobility period in mice in both forced swim and tail-suspension test, two animal models of depression, in a dose independent manner [138, 139]. Among the reported bioactivities of berberine, there is the inhibition of monoamino oxidase (MAO)-A activity, [140] an enzyme catalyzing the oxidative deamination of catecholamines, and thus inhibiting degradation of these neurotransmitters. In fact acute and chronic administration of berberine in
mice resulted in increased levels of norepinephrine, serotonin and dopamine, neurotransmitters induced by MAO-A enzyme [140]. In accordance with Kulkarni and colleagues data, Arora and Chopra [138] showed the protective antidepressant-like effect of berberine against the reserpine-induced biogenic amine depletion (a monoamine depletor commonly used to induce depression in animals. However, at the best of our knowledge, there are no available data on the evaluation of the potential antidepressant effects of berberine in humans [141].

### 2.1.2.4 Tolerability and Safety

Highly purified and concentrated berberine is safe, in fact, its Lethal Dose 50 (LD50) in mice is 25 mg/kg in mice [131].

Standard doses of berberine are usually well tolerated and adverse events are rare and mild. The most studied side effects are those on the gastrointestinal system. In fact, berberine and its derivatives can produce gastric lesions in animal models [142]. As shown by the determination of small intestinal transit time measurements by sorbitol and breath hydrogen test, berberine delays small intestinal transit time, and this may account for a part of its gastrointestinal side effects (but also of its antidiarrhoeal one) [143].

The main safety issue of berberine involves the risk of pharmacological interactions. In fact, berberine displaces bilirubin from albumin about tenfold more than phenylbutazone, thus any herb containing large amounts of berberine should be avoided in jaundiced infants and pregnant women [144]. Berberine also displaces warfarin, thiopental and tolbutamide from their protein binding sites, increasing their plasma levels [145].

Then, berberine can markedly increase blood levels of cyclosporine A because of CYP3A4 and P-glycoprotein inhibition in liver and gut wall, respectively, and because of the increase in gastric emptying time, thus causing increased cyclosporine A bioavailability and reduced metabolism [146]. In renal transplant recipients who take cyclosporine 3 mg/kg twice daily, the coadministration of berberine (0.2 g/day for three times a day for 3 months) increased the mean cyclosporine A AUC of 34.5 % and its mean half-life of 2.7 h [147].

Even if the main mechanism of berberine pharmacological interaction involves CYP3A4 and intestinal P-glycoprotein, it also inhibits CYP1A1, potentially interacting with drugs metabolized by this cytochrome isoporphm as well. The impact of this observation in clinical practise has yet to be evaluated since the CYP1A1 metabolized drugs are relatively rare [148].

Overall, the assumption of berberine in dosages of 500–1000 mg/day has to be considered safe for the most part of subjects and the risk of clinically relevant pharmacological interaction is limited to cyclosporine and warfarin.
2.2 Conclusion

Berberine is a natural alkaloid with proven antioxidant, anti-inflammatory, glucose-lowering and lipid-lowering actions, both in animal models and in humans. Altogether, these effects support the need to study the effects of the long-term exposition to berberine for the management and prevention of numerous chronic diseases such as type 2 diabetes and atherosclerosis.

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