Thiamine, known as vitamin B\textsubscript{1}, plays an essential role in energy metabolism. Benfotiamine (S-benzoylthiamine O-monophosphate) is a synthetic S-acyl derivative of thiamine. Once absorbed, benfotiamine is dephosphorylated by ecto-alkaline phosphatase to lipid-soluble S-benzoylthiamine. Transketolase is an enzyme that directs the precursors of advanced glycation end products (AGEs) to pentose phosphate pathway. Benfotiamine administration increases the levels of intracellular thiamine diphosphate, a cofactor necessary for the activation transketolase, resulting in the reduction of tissue level of AGEs. The elevated level of AGEs has been implicated in the induction and progression of diabetes-associated complications. Chronic hyperglycemia accelerates the reaction between glucose and proteins leading to the formation of AGEs, which form irreversible cross-links with many macromolecules such as collagen. In diabetes, AGEs accumulate in tissues at an accelerated rate. Experimental studies have elucidated that binding of AGEs to their specific receptors (RAGE) activates mainly monocytes and endothelial cells and consequently induces various inflammatory events. Moreover, AGEs exaggerate the status of oxidative stress in diabetes that may additionally contribute to functional changes in vascular tone control observed in diabetes. The anti-AGE property of benfotiamine certainly makes it effective for the treatment of diabetic neuropathy, nephropathy and retinopathy. Interestingly, few recent studies demonstrated additional non-AGE-dependent pharmacological actions of benfotiamine. The present review critically analyzed the multifaceted therapeutic potential of benfotiamine.
complications such as neuropathy, nephropathy and retinopathy by inhibiting the formation of advanced glycation end products (AGEs) [3,5,6]. Benfotiamine prevents the progression of diabetic complications by increasing tissue levels of thiamine diphosphate, which enhances the transketolase activity that directs the precursors of AGEs to pentose phosphate pathway, resulting in the reduction of tissue levels of AGEs [7–10]. Other beneficial effects of benfotiamine include improvement in cardiomycocyte contractile dysfunction in experimental diabetes mellitus [11], reduction in neuropathic pain [12–14] and improvement in experimental post-ischaemic healing [15]. Moreover, benfotiamine has been shown to reduce oxidative stress in a mechanism unrelated to its anti-AGE property [4]. In addition to its beneficial effects in preventing the progression of diabetic complications, benfotiamine has been demonstrated to prevent the induction of vascular endothelial dysfunction [9,16–19], which suggests the novel role of benfotiamine in improving the vascular functional regulation. Benfotiamine is absorbed in the body better than thiamine and in fact benfotiamine has better bioavailability than thiamine. Although benfotiamine has been shown to be similar to thiamine in correcting endothelial cell defects induced by high glucose [16], thiamine is needed to be administered at high dose as compared to benfotiamine to prevent the diabetic complications [8]. The present review critically discussed the wide array of recently revealed therapeutic potential of benfotiamine.

2. Pharmacology of benfotiamine

Thiamine-derived compounds were discovered from the plants of Allium genus such as onions, shallots and leeks and named as allithiamines [20]. The most effective compound of allithiamine family having the anti-AGEs property was subsequently identified and named as benfotiamine. The benfotiamine is a lipid-soluble analogue after its oral administration is superior as compared to S-benzoylthiamine by the ecto-alkaline phosphatase present in the brush borders of intestinal mucosal cells. The lipophilic S-benzoylthiamine is absorbed and then diffuses by passive diffusion through the membranes of intestinal and endothelial cells and subsequently appears in circulation. In fact, a significant part of S-benzoylthiamine is captured by erythrocytes and is converted to free thiamine. In the liver, the leftovers can be enzymatically hydrolyzed to thiamine and benzoic acid by thioesterases [24,25]. The absorption and bioavailability of this lipid-soluble thiamine analogue after its oral administration is superior as compared to water-soluble thiamine [22,26,27]. Benfotiamine is more easily absorbed in the body and its oral administration results in the availability of at least five times greater plasma concentration of thiamine than an equivalent dose of thiamine [27–29]. Benfotiamine is practically insoluble in organic solvents and differs from truly lipid-soluble thiamine disulfide derivatives such as allithiamine and the synthetic sulbutiamine and fursultiamine with a different mechanism of absorption and different pharmacological properties [10]. Oral administration of benfotiamine leads to significant increases in thiamine, thiamine monophosphate and thiamine diphosphate levels in blood and liver but not in the brain. This difference is with the known pharmacological profile of benfotiamine, i.e., the beneficial effects of the drug concern with peripheral tissues but not the central nervous system. Benfotiamine was developed in Japan to treat alcoholic neuropathy and other neuropathic neurological complications. Growing body of evidence suggests that benfotiamine is an effective and safe compound with good safety profile. Benfotiamine may be useful for the treatment of acute peripheral syndromes of thiamine deficiency because of its better absorption capacity [10]. Due to its fine pharmacological profile, benfotiamine may be preferred in the treatment of relevant indications.

3. Formation of AGE products and their pathological implications: a fleeting look

Nonenzymatic protein glycation by glucose is a complex cascade of reactions yielding a heterogeneous class of compounds, collectively termed as AGEs. The AGEs are formed by nonenzymatic reaction between reducing sugars and amino acids on proteins, lipids and nucleic acids (Fig. 2). There are two major pathways in which AGEs can be formed in the biological system. One way is through a simple series of chemical reactions known as Maillard pathway (Fig. 3). The Maillard reaction begins with the reaction of the carbonyl group (aldehyde or ketone) of the reducing sugar to form a reversible Schiff base with the amino group of the membrane protein. The Schiff base can undergo an intramolecular rearrangement to form amadori products, which further undergo a series of rearrangements, dehydration and condensation to form AGEs [30]. In addition, aldose reductase reduces glucose to sorbitol, which is converted into fructose by sorbitol dehydrogenase. Fructose thus formed is further metabolized into fructose-3-phosphate and 3-deoxyglucosone that result in the formation of AGEs [64]. In the second pathway, the high sugar levels within the cells disrupt the normal cellular metabolism of glucose resulting in the accumulation of super-reactive glucose-metabolic intermediates such as triosephosphates within the cell. The excess triosephosphates attack the surrounding reactive glucose-metabolic intermediates such as triosephosphates and causing AGE damage in the cell [1,31]. The AGE products include pentosidine, bis[lysyl]imidazolyl cross-links such as glyoxal-derived lysine dimmer (GOLD), methylglyoxal-derived lysine dimmer (MOLD), 3-deoxyglucosone-derived lysine dimmer (DOLD), and hydroxymidazolones such as glyoxal-derived hydroxymidazolone (G-H), methylglyoxal hydroxymidazolone (MG-
Fig. 2. Diagram depicting the formation of AGE products and their implication in diabetic complications. Sugar molecule reacts with proteins resulting in the formation of Schiff's base that rearranges to form amadori products. In addition, aldose reductase (AR) reduces glucose to sorbitol, which is converted into fructose by sorbitol dehydrogenase (SDH). Fructose is further metabolized into fructose-3-phosphate (F-3-P) and 3-deoxyglucosone (3-DG) that result in the formation of AGEs. The high sugar levels within the cells cause an accumulation of triosephosphates, which attack the surrounding proteins, lipids and DNA resulting in the formation of oxoaldehydes and causing AGE damage in the cell. Moreover, sugars with lipids go on to form dicarbonyl intermediates, that collectively results in AGes formation, which by activating RAGEs induce inflammatory pathways and high oxidative stress that ultimately lead to diabetic vascular complications (ox indicates oxidation).

Indeed, AGES disrupt the function of blood vessels, neurons and kidney by acting on cell surface specific receptors named RAGEs [35]. AGES have been implicated in the induction and progression of various vascular diseases [37,38], diabetic neuropathy [39,40], diabetic nephropathy [41,42] and diabetic retinopathy [43,44]. AGES activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitogen-activated protein kinases (MAPK), cell division control protein 47 (cdc47), and protein having GTPase activity (p21 RAS) that further activate various transcriptional factors like nuclear factor-kappa B (NF-kB) to induce local inflammatory cascades, which execute diabetic vascular complications [35,45–47].

Fig. 3. Depicted here the formation of AGE products by Maillard pathway. GOLD, glyoxal-derived lysine dimmer; MOLD, methylglyoxal-derived lysine dimmer; DOLD, 3-deoxyglucosone-derived lysine dimmer; G-H, glyoxal-derived hydroimidazolone; MG-H, methylglyoxal hydroimidazolone; 3DG-H, 3-deoxyglucosone hydroimidazolone; CML, N-carboxymethyl-lysine; CEL, N-carboxyethyl-lysine.
The mechanisms involved in AGEs-mediated development of diabetic complications have been depicted in Fig. 4.

4. AGE-dependent and -independent pharmacological actions of benfotiamine

Benfotiamine, an inhibitor of the formation of AGEs, exerts its beneficial effects through a diverse mechanism. In diabetes, benfotiamine blocks three major biochemical pathways implicated in the pathogenesis of chronic hyperglycemia-induced vascular damage, i.e., hexosamine pathway, AGE formation pathway and diacylglycerol (DAG)–protein kinase C (PKC) pathway, which are activated by the high availability of the glycolytic metabolites such as glyceraldehyde-3-phosphate and fructose-6-phosphate [3]. Benfotiamine has been reported to prevent the progression of diabetic complications by increasing tissue levels of thiamine diphosphate and subsequently enhancing transketolase activity, which converts glyceraldehyde-3-phosphate and fructose-6-phosphate into xylulose-5-phosphate and erythrose-4-phosphate, respectively, and thus blocks the aforementioned three major biochemical pathways especially the formation of AGEs [3,10]. 

Benfotiamine prevented the development of diabetic neuropathy that was demonstrated by the fact that a marked improvement in nerve conduction velocity was observed in the treatment group as compared to placebo [48]. The most significant effect in reducing the neuropathic pain was noted in patients receiving high-dose benfotiamine [13]. In addition, benfotiamine prevented motor nerve conduction velocity as well as the formation of AGEs in peripheral nerve tissue in experimental diabetic neuropathy [5]. A 3-week randomized, controlled pilot study demonstrated the therapeutic efficacy of benfotiamine in the treatment of diabetic polyneuropathy [14]. Benfotiamine is considered to be a transketolase activator that directs the elevated levels of hexose and triose phosphates to the pentose phosphate pathway leading to a reduction in tissue AGEs in experimental diabetic neuropathy [14,49]. The combination of benfotiamine and cyanocobalamin prevented diabetic neuropathy by improving sensory symptoms and vibration perception thresholds in diabetic patients [50,51]. Lipid-soluble benfotiamine has been documented to be superior than water-soluble thiamine in preventing functional nerve damage and reducing AGEs formation in experimental diabetic neuropathy [5,52]. Administration of benfotiamine in diabetic patients having thiamine deficiency markedly ameliorated neuropathic symptoms by neutralizing the damaging effects of hyperglycaemia on neuronal vascular cells [53]. Benfotiamine has been recently suggested to be considered as a first choice nutritional supplement in preventing the progression of diabetic neuropathy based on its efficacy and safety data [54].

Diabetic neuropathy is a major cause of end-stage renal failure and the mortality rate due to this threatening complication is continuously progressing worldwide [55]. Diabetic neuropathy is characterized by marked structural changes in the kidney such as thickening of the glomerular basement membrane, glomerular hypertrophy, glomerulosclerosis, mesangial cell expansion, tubulointerstitial fibrosis and renal inflammation [56,57]. Hyperglycemia results in accumulation of triosephosphates arising from high cytosolic glucose concentrations that trigger biochemical dysfunction in the renal cells ultimately leading to the development of diabetic nephropathy [8]. Benfotiamine in high dose prevented the development of diabetic nephropathy by increasing transketolase expression in renal glomeruli, triggering the conversion of triosephosphates to ribose-5-phosphate, and inhibiting the incidence of microalbuminuria, which is associated with decreased activation of PKC and reduced occurrences of protein glycation and oxidative stress [8]. The major effects attributable to benfotiamine on renal functional improvement during diabetes are the normalization of glucose levels and prevention of AGEs formation in the endothelial cells of the kidney by selectively stimulating renal transketolase activity [58,59]. Supplementation of benfotiamine in patients with diabetic nephropathy ameliorated the incidence of albuminuria/proteinuria, high oxidative stress and AGEs accumulation in renal tissue and thereby decreased the inflammatory and fibrotic responses to reduce the progression of diabetic nephropathy [58–60]. We have recently demonstrated that the concurrent administration of benfotiamine and fenofibrate may provide synergistic benefits in preventing the development of diabetes-induced nephropathy by reducing the oxidative stress and renal pathological changes, and subsequently improving the renal function [19]. Taken together, these studies suggest the beneficial effects of benfotiamine in preventing the induction and progression of diabetic nephropathy.

Diabetic retinopathy is a major cause of blindness and its prevalence is continuously increasing worldwide [61]. Early and selective loss of pericytes and thickening of the basement membrane have been reported to be hallmark of diabetic retinopathy [62]. The administration of high-dose benfotiamine in diabetic rats prevented the development of retinopathy by halting AGEs formation [63]. Benfotiamine decreased the retinal capillary changes in streptozotocin-induced diabetic rats [3]. The high-dose benfotiamine therapy increased the activity of transketolase in the retina of diabetic rats to prevent the development of retinopathy [3]. In addition, benfotiamine was shown to block three major pathways of hyperglycemic damage including AGEs, PKC and hexosamine pathways to prevent the progression of diabetic retinopathy [3]. Glycemic fluctuations play a vital role in the development of diabetic retinopathy. Interestingly, benfotiamine has been shown to prevent diabetic retinopathy by reducing the aldose reductase mRNA expression and intracellular glucose, and consequently increasing the expression and activity of transketolase in human endothelial cells and bovine retinal pericytes exposed to high glucose [65]. Moreover, benfotiamine prevents human pericyte apoptosis, which reveals its additional role in preventing diabetic complications [66]. Furthermore, benfotiamine has been recently
shown to prevent experimental diabetic retinopathy by increasing extracellular matrix turnover [67]. These studies enlighten the novel pharmacological mechanisms of benfotiamine in halting the development of diabetic microvascular complications.

In addition to aforementioned studies of AGE-dependent inhibitory actions of benfotiamine, few studies also demonstrated AGE-independent actions of benfotiamine. It has been reported that benfotiamine reduced diabetes-induced increase in oxidized glutathione (GSSG) levels and oxidative stress independent of AGE-inhibitory mechanism [4]. In addition, benfotiamine treatment antagonized impaired cardiomyocyte contractile function in the streptozotocin-induced diabetic mouse by altering glucose metabolism and protein kinase C activation independent of its AGE-inhibitory mechanism [11]. Moreover, we have recently demonstrated the novel non-AGE-dependent role of benfotiamine in reducing the oxidative stress and improving the function of vascular endothelium in rats administered nicotine and sodium arsenite [18,69].

5. Novel therapeutic role of benfotiamine

Benfotiamine possesses much higher bioavailability than genuine thiamine that may uplift the preference of benfotiamine instead of thiamine for related therapeutic applications. Benfotiamine counteracts the damaging effects of hyperglycaemia on vascular cells that accounts for its beneficial defensive role in preventing diabetic complications [53]. As stated in previous section, benfotiamine has a therapeutic potential to halt the development of diabetes-induced neuropathy, nephropathy and retinopathy. In addition, benfotiamine has been noted to accelerate the healing of ischemic diabetic limbs in mice through protein kinase B/Akt-mediated potentiation of angiogenesis and subsequent inhibition of apoptosis [15]. It is worthwhile to note that high-dose benfotiamine prevented cardiomyocyte contractile dysfunction in streptozotocin-induced experimental diabetes mellitus [11]. Benfotiamine significantly attenuated diabetes-induced elevation in AGEs and collagen cross-linking in the rat heart providing its additional role in diabetic cardiomyopathy [70]. Numerous studies revealed few more additional therapeutic benefits of benfotiamine. Administration of benfotiamine reduced vibration perception, motor function and overall scores of alcoholic polyneuropathy that were significantly improved in an 8-week randomized controlled study [12]. Benfotiamine administration for 8 weeks showed improvement in alcoholic peripheral neuropathy by improving vibration perception threshold [71]. Treatment with benfotiamine significantly reduced peripheral neuropathy-induced mortality and morbidity [72]. Benfotiamine has been noted to prevent endotoxin-induced uveitis in rats by suppressing oxidative stress-induced NF-κB-dependent inflammatory signaling [23].

Endothelium is an innermost lining of the blood vessel that regulates the vascular tone. The dysfunction of vascular endothelium often leads to diminished vasodilation, proinflammatory and prothrombotic environments in the vessel wall. The reduction in nitric oxide production and increase in oxidative stress often lead to vascular endothelial dysfunction [68]. The risk factors like cigarette smoking, alcohol consumption and exposure to environmental arsenic play a critical role in the development of vascular endothelial dysfunction. The dysfunction of vascular endothelium is considered to be a hallmark for various cardiovascular disorders such as hypertension, atherosclerosis, heart failure, myocardial infarction, diabetic nephropathy and stroke [19,56,68]. Benfotiamine has been shown to prevent macro/microvascular endothelial dysfunction and oxidative stress following a meal rich in AGEs in individuals with type 2 diabetes [9]. We previously reported that benfotiamine prevented nicotine and uric acid-induced vascular endothelial dysfunction in rats by reducing the oxidative stress and consequently improving the integrity of vascular endothelium and enhancing the generation and bioavailability of nitric oxide [18]. The vascular protective potential of benfotiamine was confirmed in our recent study in which benfotiamine was noted to reduce oxidative stress and activate endothelial nitric oxide synthase to enhance the generation and bioavailability of nitric oxide, and subsequently improve the integrity of vascular endothelium to prevent sodium arsenite-induced vascular endothelial dysfunc-

tion in the rat [69]. Our study reveals the non-AGE-dependent therapeutic potential of benfotiamine in improving the function of vascular endothelium and preventing the development of vascular endothelial dysfunction in non-diabetic animals. It may be important findings that open a vista of further investigations to explore the novel therapeutic potentials of benfotiamine in treating cardiovascular disorders associated to vascular endothelial dysfunction. Therefore further studies are certainly warranted to determine the therapeutic efficacy of benfotiamine on cardiovascular complications in diabetic and non-diabetic conditions. The multifaceted therapeutic potentials of benfotiamine in preventing the progression of diabetes/non-diabetes-associated pathological conditions have been shown in Fig. 5.

6. Concluding remarks

Benfotiamine has ability to halt the progression of many serious complications of prolonged hyperglycemia that certainly supports its therapeutic applications in diabetic patients. In fact, any bodily function improved by a therapeutic level of thiamine would most likely be enhanced by benfotiamine. The exaggerated benfotiamine consumption as a dietary supplement could over-stimulate the enzyme transketolase, which may account for some serious adverse drug reactions; however, the clear scientific data are missing in this regard. Growing body of evidence suggests that benfotiamine alleviates diabetes-associated neuropathy, kidney diseases, cardiac impairment, peripheral vascular diseases and retinopathy. Hence, benfotiamine may be considered as an adjuvant nutritional therapeutic agent against the devastating consequences of hyperglycemia due to its inherent ability to confer functional support for blood vessel, nerve, kidney, eye and the heart. In addition, the non-AGE-dependent therapeutic potential of benfotiamine in preventing the development of vascular endothelial dysfunction has been explored in non-diabetic animals that may further accelerate its investigations in the management of cardiovascular disorders associated with vascular endothelial dysfunction. Most of the effects attributed to benfotiamine are extrapolated from in vitro and animal studies. Unfortunately apparent evidences from human studies are scarce and especially end point studies are missing. Therefore the therapeutic potential of benfotiamine in both diabetic and non-diabetic pathological conditions.

Conflict of interest

The authors declared no conflict of interest.

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