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Review article

Calcium Dobesilate and Micro-vascular diseases

Jie Liu[a,b], Shulin Li[a], Dong Sun[a,c,*]

[a] Department of Nephrology, Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China
[b] Department of Nephrology, Second Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China
[c] Department of Internal Medicine and Diagnostics, Xuzhou Medical University, Xuzhou 221002, China

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ABSTRACT

Micro-vascular diseases and its associated complications continue to be a significant health problem worldwide. Vascular lesions from microvascular involvement lead to impaired blood flow and contribute to damage and dysfunction of one or more target organs, that is, the heart, kidneys, eyes, and nervous system. Calcium Dobesilate Drug (CAD) is an established vasoactive and angioprotective drug that has shown a unique, multi-target mode of action in several experimental studies and in different animal models of diabetic microvascular complications. CAD has been widely used as an antioxidant and a vascular protective agent. At present, the application of Calcium Dobesilate is mainly related to Micro-vascular damage-related diseases, such as diabetic retinopathy (DR) and diabetic nephropathy (DN), and it is found to significantly improve the related symptoms. Its beneficial effects make it an attractive therapeutic compound especially in the early stages of these diseases. Scholars at home and abroad have studied the effectiveness, safety, and mechanisms of the related diseases, furthermore, the subjects involved patients and animal models, they have found some new clinical effects of this medicine. This paper makes a brief summary of a research progress of clinical application about Vascular injury related diseases and other aspects.

CAD (calcium 2,5-dihydroxybenzenesulfonate) is a vascular protective drug that has been used in some countries for the treatment of DR and chronic venous insufficiency in the past few decades [1,2]. The drug was recorded in the European pharmacopoeia in 1997 and the British Pharmacopoeia in 1998. It was put on the market in June 2001 and has been currently used mainly in the treatment of Micro-vascular related diseases such as DR and chronic kidney disease (CKD). Calcium dobesilate is considered an angioprotective drug that can reduce blood viscosity, platelet activity and capillary permeability, as well as alleviate microcirculatory and hemorheologic abnormalities [2]. In addition, recent studies have demonstrated that CAD exerts protective effects against diabetic nephropathy [3] and gentamicin-induced acute kidney injury [4]. However, some side effects of the drug have also been found as it has been widely used in clinical applications, which we will describe in detail below. At present, it has been found that the drug has significant effects on diabetic retinopathy, diabetic nephropathy and diabetic peripheral neuropathy [5–7] (Table 1).Studies on this drug were also increasingly in-depth, including drug efficacy, drug safety, and drug action mechanism. At the same time, some new clinical applications of CAD have been gradually discovered, and the progress of research and application is summarized briefly (Table 2).

1. Calcium Dobesilate and Micro-vascular injury

Micro-vascular injuries are mainly seen in the retina, kidney, nerves and myocardial tissue, especially DN and DR. DR and DN, which belong to diabetic Microangiopathy have a similar patho-physiological basis. The antioxidant and vascular protective effects of CAD have been demonstrated both in vivo and vitro experiments. For example, peritoneal permeability induced by oxidant stress was reduced after CAD treatment. CAD lowered the permeability of the blood vessels in ischemia-reperfusion injury models [8–11]. Experiments in vitro strongly demonstrated that the antioxidant properties of CAD play an important role in Micro-vascular injuries via its direct scavenging action, especially by eliminating the reactive oxygen species (ROS) [12,13].In addition to its antioxidant effects, CAD can inhibit the proliferation of blood vessels at a certain concentration, but its anti-angiogenic effect is dose-dependent [14,15].Despite increasing antiangiogenic efficacy with dose escalation, the only significant antiangiogenic scores obtained were 10–5 and 10–4 M concentrations of CaD [9]. In contrast, Larsen and Rasch et al. failed to demonstrate the beneficial effect of CAD on capillary resistance and its role in delaying the progression of DR [16,17].

* Corresponding author at: Department of Nephrology, Affiliated Hospital of Xuzhou Medical University, 99 West Huai-hai Road, Xuzhou 221002, Jiangsu, China.
E-mail address: sundong126@yahoo.com (D. Sun).

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Table 1
Effects of calcium dobesilate on diabetic retinopathy, diabetic nephropathy and diabetic peripheral neuropathy.

Type	Doses	Period of treatment	Effects
Diabetic retinopathy	0.5 g daily	3 months	The serum levels of endothelin-1 and hsCRP were reduced [5].
Diabetic nephropathy	0.5 g, 3 times daily	3 months	The 24 h urinary albumin and 24 h urinary protein levels significantly decreased, but the cystatin C-based glomerular filtration rate (GFR) remained unchanged [6].
Diabetic peripheral neuropathy	0.5 g, 3 times daily	2 weeks	It showed good clinical efficacy and an improved curative effect than single alprostadil treatment [7].

Table 2
Clinical applications of Calcium Dobesilate.

Type	Application
Microvascular diseases	Diabetic retinopathy, renal microvascular damage, diabetic peripheral neuropathy, microvascular lesions of the heart.
Other vascular diseases	Pregnancy-associated hypertension, erectile dysfunction in men, chronic venous insufficiency.
Other diseases	Rosacea, galactose cataract, reducing the levels of serum endothelin-1, hsCRP, total cholesterol, triglyceride and serum AST in patients with diabetic retinopathy.

1.1. The mechanisms of CAD improving microcirculation and reducing Micro-vascular injury

We summarized the mechanisms as follows (Table 3):

1.1.1. Reducing platelet aggregation caused by thrombin or collagen [18].
1.1.2. Significantly protecting peritoneal vascular from ROS effects of penetration [8].
1.1.3. Calcium dobesilate could inhibit capillary permeability, which is induced by vaso-active substances such as serotonin, bradykinin, and histamine [19].
1.1.4. Reducing endothelial shedding by the synthesis and release of nitric oxide [19].
1.1.5. Reducing platelet aggregation by inhibiting prostaglandin and reduce erythrocyte aggregation and viscosity of suspension [19].
1.1.6. Down-regulating the expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) to inhibit vascular endothelial cell proliferation [20–22].

1.2. Calcium Dobesilate and Diabetic Retinopathy

DR is an important cause of blindness in the working age population and is a major socio-economic problem [23,24]. The development of diabetic retinopathy is a multi-factors process, and many of the damages are due to retinal vascular extravasations and retinal hypoperfusion [25]. CAD which is, one of the few vascular protective agents that can slow the progression of this disease, was discovered more than 40 years ago and has have been registered as a treatment for DR in more than 20 countries. A systematic review and meta-analysis supported the effectiveness of CAD in diabetic retinopathy at both the systemic and local levels of the eye [26]. The clinical efficacy of CAD for DR is achieved by alleviating the high permeability of retinal vessels [27,28] and reducing the leakage of retinal albumin in diabetic animals, which also supports its beneficial effect on the permeability of the blood-retinal barrier [29]. It has also been suggested that CAD can stabilize the blood-retinal barrier in diabetic rats because of its antioxidant effects [30]. Moreover, CAD could relieve retinal edema through protecting the injured retina from oxidative stress induced by ischemia-reperfusion.

Ermelindo C. Leal et al. confirmed that CAD could reduce ROS generation and nitrosation stress because it completely blocks the increases in the Carbonyl-Oxide (CH_2O_2) and protein tyrosine residue caused by diabetes. The inflammatory changes that result from oxidative stress can lead to the breakdown of the blood-retinal barrier, their findings further support the view that CAD's vascular protection may be largely due to its antioxidant properties [31]. Ermelindo C. Leal et al. first clearly showed that CAD could inhibit the changes in tight junction protein, ICAM-1, and adhesion of white blood cells, which play an important role in increased retinal vascular permeability. Their study showed that the protective effect of CAD on intercellular permeability may be due to the inhibition of oxidative stress through inhibiting the activation of p38 MAPK and NF-κB pathways, which mediated the permeability of the blood retinal barrier [32,33]. This study revealed the molecular and cellular mechanisms of CAD's protective effects on diabetic retinal vascular disease and stressed the CAD's role in the treatment of DR, especially in the early stages of the disease [31].

The possible protective mechanisms of CAD on DR are summarized as follows (Table 4):

1.2.1. It can reduce the uneven distribution of ion content in the retina caused by ischemia-reperfusion by reducing the inhibition of Na+-K+-ATPase and Ca2+-Mg2+-ATPase's activity, resist the changes of ATP in the retina, prevent the loss of glutathione (GSH) in cells.
1.2.2. Inhibition of aldose reductase [34].
1.2.3. CAD can recover the vascular responses induced by acetylcholine, noradrenalin, and caffeine. It can also reduce the changes in vascular reactivity [9].
1.2.4. It can Inhibit leukocyte adhering to retinal blood vessels and suppress oxidative stress through p38 MAPK and NF-κB pathways [31].

Table 3
The mechanisms of CAD improving microcirculation and reducing Micro-vascular injury.

Type	Mechanisms
Improving microcirculation and reducing Micro-vascular injury	Reducing platelet aggregation [18]. Protecting peritoneal vascular from ROS effects of penetration [8]. Inhibiting capillary permeability [19]. Reducing endothelial shedding [19]. Reducing erythrocyte aggregation and viscosity of suspension [19]. Inhibiting vascular endothelial cell proliferation [20–22].

Table 4
The possible protective mechanisms of CAD on DR.

Type	Mechanisms
Calcium Dobesilate and Diabetic Retinopathy	Reducing the uneven distribution of ion content in the retina, resisting the changes of ATP in the retina and preventing the loss of glutathione (GSH) in cells. Inhibiting aldose reductase [34]. Recovering the vascular responses induced by acetylcholine, noradrenalin, and caffeine. It can also reduce the changes in vascular reactivity [9]. Inhibiting leukocyte adhering to retinal blood vessels and suppress oxidative stress [31]. Reducing retinal albumin leakage. Reducing the level of retinal AGEs and VEGF and reversing retinal high permeability [30].

1.2.5. It can reduce retinal albumin leakage.
1.2.6. It can significantly reduce the level of retinal AGEs (advanced Glycation end products) and VEGF and reverse retinal high permeability [30]. In addition, VEGF is overexpressed in the retina of diabetic rats, and is involved in the leakage of blood retinal barrier as well as the process of leukocyte adhesion [35,36].

However, in a five-year follow-up study of 635 patients with type 2 diabetes (mild to moderate no-proliferative DR). Christos Haritoglou et al. found that CAD could not prevent clinical significant macular edema (CSME) occurrence nor development. It is worth noting that they found no effect of the drug in patients who are in good control of blood glucose and blood pressure in the normal range, and in specific subgroups of patients, the placebo group was significantly better than that of CAD group. Their data showed that women with risk factors for the vascular disease might benefit from CAD treatment, although this explanation still needs further reasoning [37].

A study on laser treatment for diabetic macular edema with calcium dobesilate, found out the difference between the treatment group and the control group had no statistical significance [38]. There are also some studies found no beneficial effects of this drug for DR patients who were treated with the lower dose and shorter time (6–12 months) [30,39].

1.3. Calcium Dobesilate and Renal Micro-vascular damage

We studied a number of animal models with kidney diseases showed that the progressive fibrosis of kidney is closely related with the impairment and reduction extent of peritubular capillaries [40–42]. The damage and loss of Renal Micro-vascular can cause local tissue ischemia and hypoxia, which could lead to oxidative stress as well as aggravation of renal damage. Maintenance of the Renal Micro-vascular function and number can reduce renal histological damage as well as the deterioration of renal function, thereby delaying the process of the renal fibration [43].

As an antioxidant and Micro-vascular protective agent, CAD has been used clinically in patients with CKD. In clinical trials, CAD can significantly improve the renal dysfunction of CKD [44]. Our animal experiments found that CAD could reduce the urinary protein excretion of rats with Adriamycin Nephropathy which showed its protective effect on kidney. Nevertheless, the role of CAD improving renal function is unknown and needs further study.

Studies on the mechanisms of CAD's protective effect on Renal Micro-vascular (Table 5):

1.3.1. Reducing the level of Plasma Endothelin. The plasma endothelin (ET) level was decreased compared with the baseline which secretion could be reduced in the renal cortex of animal models [3,45]. In addition, calcium dobesilate can also alleviate vascular injury and protect the early DN vascular endothelium [46].
1.3.2. Inhibiting the activity of PAI-1 and increase the activity of t-PA: The role of calcium dobesilate inhibiting the activity of plasma plasminogen activator inhibitor 1 (PAI-1), increasing the activity of tissue-type plasminogen activator (t-PA) could be a mechanism of anti-thrombosis and improve Micro-circulation, delaying the renal fibrosis and reducing serum creatinine.
1.3.3. CAD had antioxidant effects: (Mostafa Jafarey et al.) first studied the protective effects of CAD on renal toxicity induced by Gentamicin whose results showed that CAD could reduce the renal toxicity induced by Gentamicin. The reason may be that CAD has antioxidant properties which could enhance the antioxidant system. These findings demonstrated that CAD was a novel kidney protector against renal toxicity induced by aminoglycosides and had medical effects. Furthermore, compared with the Gentamicin group, they found that CAD could reduce tissue malondialdehyde and increase tissue iron antioxidant capacity [4].
1.3.4. Maintaining the integrity of the glomerular filtration barrier: CAD could inhibit the synthesis of collagen in glomerular basement membrane [47]. CAD could significantly improve the morphology of renal tissue in CRF rats. After studying the ultrastructure of the glomerulus, Dong J et al. found that CAD had the following effects on the glomerular capillary filtration barrier: First, it prevented the thickening of glomerular capillary basement membrane (or decreased its thickening). Second, it allowed the gap between endothelial cells and podocytes to be more uniform, preventing disruption of podocyte-processes. The histological features and the expression of type IV collagen changes showed that CAD could reduce the deposition of collagen type IV in diabetic glomerular basement membrane as well as maintain the integrity of glomerular basement membrane, and then protect the glomerular filtration barrier from further destruction in DN and improve the glomerular filtration function of end-stage DN [48].
Experiments in vivo confirmed that glomerular basement membrane thickening and collagen IV deposition were associated with an increased expression of matrix metalloproteinase inhibitor-1 (TIMP1) in diabetic rats [49]. Studies by Dong J et al. showed that CAD could inhibit the deposition of collagen IV in the glomerular basement membrane, reducing the deposition of extracellular matrix and protect the glomerular filtration barrier, which may be related to the decreased expression of TIMP1 [48]. Whether CAD can also affect the activity of TIMP1, needs some further study.
1.3.5. Improving the micro-inflammatory state of the patients: Studies have shown that CAD may lower plasma levels of the hypersensitive C reactive protein (hsCRP) and ameliorate the state of micro-inflammation in maintaining hemodialysis patients. The inflammatory and atherosclerotic effects of CRP may lead to an increase in reactive oxygen species and the proliferation of vascular smooth muscle cells [50,51]. Uremic patients do have a state of micro inflammation. Xia Y et al. observed that CAD could significantly reduce the concentration of blood hs-CRP and IL-6 in maintenance hemodialysis patients, albumin, prealbumin, and transferrin concentrations were also significantly elevated.

Table 5
The mechanisms of CAD's protective effect on Renal Micro-vascular.

Type	Mechanisms
Calcium Dobesilate and Renal Micro-Vascular damage	Reducing the level of Plasma Endothelin [3,45]. Inhibiting the activity of PAI-1 and increase the activity of t-PA. Having antioxidant effects [4]. Maintaining the integrity of the glomerular filtration barrier [48]. Improving the micro-inflammatory state of the patients [50,51]. Down-regulating the over expression of BIM [52].

Furthermore, CAD could improve the micro-inflammation and nutritional status of the patients, and the effect was more obvious with the prolongation of time.

1.3.6. Down regulating the over expression of BIM: Calcium dobesilate protected against the apoptosis of proximal tubular epithelial cells induced by high glucose, in addition to the antioxidant effects, its possible mechanism was by down regulating the over expression of BIM, which was a key factor expressing apoptosis only in renal tubular epithelial cells [52].

Calcium dobesilate was confirmed to negatively interfere with 8 sarcosine oxidase-based methods as determined by experiments both in vitro and in vivo, albeit to different degrees. However the mechanism of this interference is not known, so we recommend using CysC to assess renal function in patients taking CAD [53].

1.4. Calcium Dobesilate and diabetic peripheral neuropathy

The pathogenesis of diabetic neuropathy involving Micro-vascular lesions has not yet been fully elucidated. Studies have found that CAD could improve the symptoms of the patients with diabetic peripheral neuropathy and their nerve conduction velocity. It is believed that the drug has a good therapeutic effect in the clinic through the following pharmacological actions (Table 6):

1.4.1. Correcting the albumin/globulin ratio, reducing plasma viscosity. The reduction of platelet clustering was good to prevent thrombus formation, besides the deformability and flexibility of erythrocyte was improved.

1.4.2. Blocking the channel of sugar to sorbitol, reducing the content of sorbitol, and inhibiting the dysfunction caused by the increase of sorbitol in the blood cells.

1.4.3. Improving the high permeability of capillaries, reducing the intimal damage and improving the collagen synthesis of the basement membrane. Besides, CAD could also inhibit vasoactive substances, improve lymph circulation and reduce edema.

1.4.4. Inhibiting the quantity and activity of bradykinin, prostaglandin, increasing the production of nitric oxide, relaxing the Micro-vascular, inhibiting the proliferation of vascular smooth muscle, and improving the ischemia and hypoxia state of nerve.

1.5. Calcium Dobesilate and cardiac function

Micro-vascular lesions can be manifested in the myocardium, Micro-vascular lesions of the heart and disturbance of myocardial metabolism can cause widespread focal necrosis of the myocardium. Studies have found that CAD could increase the perfusion pressure of the coronary arteries, which seemed to be mediated by the endothelium-derived relaxing factor EDRF, furthermore, the antioxidant properties of EDRF seemed to be achieved by reducing endothelial dysfunction in reperfusion injury. They believed that CAD reduced myocardial cell damage and mechanical dysfunction by preventing endothelial dysfunction [54]. In addition, calcium dobesilate could improve the blood rheology of patients undergoing coronary artery bypass grafting, which could improve the flexibility of red blood cells [55].

2. Other clinical applications of Calcium Dobesilate

In a randomized placebo-controlled clinical trial of 3 months in men with mild obesity, CAD was found to have no effects on blood pressure, markers of oxidative response, and endothelial function [56]. Indeed, animal experiments and in vitro experiments have shown that CAD had an effect on vascular function [57–60]. Studies have also shown that two or more antioxidants were crucial for oxidative stress, which may explain why CAD has not been shown to affect oxidative reactions in smokers [61].

A study in 1999 found that in women with pregnancy-associated hypertension, daily administration of 2 g of CAD resulted in a marked reduction in mean arterial pressure, their data suggested that higher doses of CAD may have an impact on vascular endothelium and blood pressure [62].

Alireza Javadzadeh et al. found that patients with DR could lower their serum levels of endothelin-1, hsCRP, total cholesterol, triglyceride, and serum AST by taking CAD [5].

In the human penile artery, CAD could reverse endothelial dysfunction caused by diabetes via specifically enhancing the hyperpolarizing factor derived from the endothelium, thereby being used to treat erectile dysfunction in men [63].

CAD is considered as a drug for the treatment of rosacea, while in another study, Cuevas et al. found that the drug could reduce the pathological angiogenesis in women [64].

In a randomized, double-blind, placebo-controlled clinical trial of chronic venous insufficiency, the calcium dobesilate group was found significantly reduce the volume of diseased legs [65]. But, overall, many studies have shown that CAD may have beneficial effects in chronic venous disease but that further studies are needed to establish a definitive role for this treatment [66].

Different doses of calcium dobesilate could delay and prevent the occurrence and development of galactose cataract, and there was no

Table 6
The mechanisms of CAD's protective effect on diabetic peripheral neuropathy.

Type	Mechanisms
Calcium Dobesilate and diabetic peripheral neuropathy	Correcting the albumin/globulin ratio, reducing plasma viscosity. Blocking the channel of sugar to sorbitol, reducing the content of sorbitol, and inhibiting the dysfunction caused by the increase of sorbitol in the blood cells. Improving the high permeability of capillaries, reducing the intimal damage and improving the collagen synthesis of the basement membrane. Inhibiting the quantity and activity of bradykinin, prostaglandin, increasing the production of nitric oxide.

significant difference between different doses of calcium dobesilate on galactose cataract [67].

Saphenectomy results in ipsilateral leg venous dysfunction, which could be prevented when CAD is added to usual precautions like varice socks [68].

3. Drug safety of Calcium Dobesilate

The application of CAD seemed to be safe, a meta-analysis of the effectiveness and safety about CAD treatment for chronic venous dysfunction confirmed the safety of this drug [69]. The most frequently reported side effects were fever (26%), other rare complications included: gastrointestinal disorders, skin reactions, joint pain, and very rare agranulocytosis (0.32 cases per million) [19].

4. Conclusion

The clinical application of CAD is becoming more and more extensive, but researches on improving microcirculation were focused on DR at home and abroad. Studies of CAD used in other Micro-vascular damage diseases are rare, mainly seen in the domestic reports, there are fewer researches on this topic in the world. In addition, the subjects of the CAD study were mainly animal models, lacking clinical multicenter follow-up studies. In particular, there are fewer clinical researches on other Micro-vascular diseases other than DR, and there is a lack of records about the side effects of Calcium Dobesilate in these clinical studies. The content of the research mechanism is relatively simple, mainly focused on the antioxidant effect [8]. The related mechanisms and efficacy are not yet fully understood, it is worthwhile for us to further improve the related studies and look forward to more large-scale and multicenter clinical follow-up studies.

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Conflict of interest

Authors declared no conflict of interest.

References

[1] P. Berthet, J.C. Farine, J.P. Barras, Calcium dobesilate: pharmacological profile related to its use in diabetic retinopathy, Int. J. Clin. Pract. 53 (1999) 631–636.
[2] T. Tejerina, E. Ruiz, Calcium dobesilate: pharmacology and future approaches, Gen. Pharmacol. 31 (1998) 357–360.
[3] X. Zhang, Therapeutic effects of calcium dobesilate on diabetic nephropathy mediated through reduction of expression of PAI-1, Exp. Ther. Med. 5 (2013) 295–299.
[4] M. Jafarey, S. Changizi Ashtiyani, H. Najafi, Calcium dobesilate for prevention of gentamicin-induced nephrotoxicity in rats, Iran. J. Kidney Dis. 8 (2014) 46–52.
[5] A. Javadzadeh, A. Ghorbanihaghjo, F.H. Adl, D. Andalib, H. Khojasteh-Jafari, K. Ghabili, Calcium dobesilate reduces endothelin-1 and high-sensitivity C-reactive protein serum levels in patients with diabetic retinopathy, Mol. Vis. 19 (2013) 62–68.
[6] Y. Zhou, C. Qi, S. Li, X. Shao, S. Mou, Z. Ni, Diabetic nephropathy can be treated with calcium dobesilate by alleviating the chronic inflammatory state and improving endothelial cell function, Cell. Physiol. Biochem. 51 (2018) 1119–1133.
[7] K. Han, C. Liu, X. Shi, X. Rao, Effects of alprostadil combined with calcium dobesilate in patients with diabetic peripheral neuropathy, Neuroendocrinol. Lett. 39 (2018) 143–147.
[8] J. Brunet, J.C. Farine, R.P. Garay, P. Hannaert, Angioprotective action of calcium dobesilate against reactive oxygen species-induced capillary permeability in the rat, Eur. J. Pharmacol. 358 (1998) 213–220.
[9] E. Padilla, P. Ganado, M. Sanz, M. Zeini, E. Ruiz, A. Trivino, et al., Calcium dobesilate attenuates vascular injury and the progression of diabetic retinopathy in streptozotocin-induced diabetic rats, Diabetes Metab. Res. Rev. 21 (2005) 132–142.
[10] J. Brunet, J.C. Farine, R.P. Garay, P. Hannaert, In vitro antioxidant properties of calcium dobesilate, Fundam. Clin. Pharmacol. 12 (1998) 205–212.
[11] M.E. Szabo, D. Haines, E. Garay, C. Chiavaroli, J.C. Farine, P. Hannaert, et al., Antioxidant properties of calcium dobesilate in ischemic/reperfused diabetic rat retina, Eur. J. Pharmacol. 428 (2001) 277–286.
[12] E. Ruiz, R. Lorente, T. Tejerina, Effects of calcium dobesilate on the synthesis of endothelium-dependent relaxing factors in rabbit isolated aorta, Br. J. Pharmacol. 121 (1997) 711–716.
[13] E.L. Lozovskaia, G.D. Kaplunskii, I.I. Sapezhinskii, Superoxide dismutase activity and photosensitizing properties of 2,5-dihydroxybenzolsulfonate, Biofizika 35 (1990) 912–916.
[14] S. Demirtas, A. Caliskan, O. Guclu, S. Yazici, O. Karahan, C. Yavuz, et al., Can calcium dobesilate be used safely for peripheral microvasculopathies that require neoangiogenesis? Med Sci. Monit. Basic Res. 19 (2013) 253–257.
[15] R.P. Garay, P. Hannaert, C. Chiavaroli, Calcium dobesilate in the treatment of diabetic retinopathy, Treat. Endocrinol. 4 (2005) 221–232.
[16] H.W. Larsen, E. Sander, R. Hoppe, The value of calcium dobesilate in the treatment of diabetic retinopathy. A controlled clinical trial, Diabetologia 13 (1977) 105–109.
[17] R. Rasch, Capillary fragility and doxium. A controlled clinical trial, Diabetologia 9 (1973) 483–485.
[18] M. Michal, C. Gotti, Effect of calcium dobesilate on platelet function, Thromb. Res. 51 (1988) 593–605.
[19] H. Allain, A.A. Ramelet, E. Polard, D. Bentue-Ferrer, Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids, Drug Saf. 27 (2004) 649–660.
[20] J. Angulo, C. Peiro, T. Romacho, A. Fernandez, B. Cuevas, R. Gonzalez-Corrochano, et al., Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial proliferation, arterial relaxation, vascular permeability and angiogenesis by dobesilate, Eur. J. Pharmacol. 667 (2011) 153–159.
[21] S. Lameynardie, C. Chiavaroli, P. Travo, R.P. Garay, N. Pares-Herbute, Inhibition of choroidal angiogenesis by calcium dobesilate in normal Wistar and diabetic GK rats, Eur. J. Pharmacol. 510 (2005) 149–156.
[22] P. Cuevas, I. Sanchez, R.M. Lozano, G. Gimenez-Gallego, Dobesilate is an angiogenesis inhibitor, Eur. J. Med. Res. 10 (2005) 369–372.
[23] M.I. Harris, Diabetes in America: epidemiology and scope of the problem, Diabetes Care 21 (Suppl. 3) (1998) C11–C14.
[24] Diabetes C, Complications Trial/Epidemiology of diabetes I, Complications Research G, J.M. Lachin, S. Genuth, P. Cleary, et al., Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy, N. Engl. J. Med. 342 (2000) 381–389.
[25] A.M. Joussen, V. Poulaki, M.L. Le, K. Koizumi, C. Esser, H. Janicki, et al., A central role for inflammation in the pathogenesis of diabetic retinopathy, FASEB J. 18 (2004) 1450–1452.
[26] X. Zhang, W. Liu, S. Wu, J. Jin, W. Li, N. Wang, Calcium dobesilate for diabetic retinopathy: a systematic review and meta-analysis, Sci. China Life Sci. 58 (2015) 101–107.
[27] E.B. Leite, M.C. Mota, J.R. de Abreu, J.G. Cunha-Vaz, Effect of calcium dobesilate on the blood-retinal barrier in early diabetic retinopathy, Int. Ophthalmol. 14 (1990) 81–88.
[28] M.L. Ribeiro, A.I. Seres, A.M. Carneiro, M. Stur, A. Zourdani, P. Caillon, et al., Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomised double-blind study, Graefes Arch. Clin. Exp. Ophthalmol. = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 244 (2006) 1591–1600.
[29] R. Rota, C. Chiavaroli, R.P. Garay, P. Hannaert, Reduction of retinal albumin leakage by the antioxidant calcium dobesilate in streptozotocin-diabetic rats, Eur. J. Pharmacol. 495 (2004) 217–224.
[30] J.C. Daubresse, R. Meunier, P. Dumont, A controlled clinical trial of calcium dobesylate in the treatment of diabetic retinopathy, Diabetes Metab. 3 (1977) 27–30.
[31] E.C. Leal, J. Martins, P. Voabil, J. Liberal, C. Chiavaroli, J. Bauer, et al., Calcium dobesilate inhibits the alterations in tight junction proteins and leukocyte adhesion to retinal endothelial cells induced by diabetes, Diabetes 59 (2010) 2637–2645.
[32] A.M. Joussen, V. Poulaki, N. Mitsiades, B. Kirchhof, K. Koizumi, S. Dohmen, et al., Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-alpha suppression, FASEB J. 16 (2002) 438–440.
[33] A.B. El-Remessy, M. Al-Shabrawey, Y. Khalifa, N.T. Tsai, R.B. Caldwell, G.I. Liou, Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes, Am. J. Pathol. 168 (2006) 235–244.
[34] T. Velpandian, J. Nirmal, P. Gupta, A.R. Vijayakumar, S. Ghose, Evaluation of calcium dobesilate for its anti-cataract potential in experimental animal models, Methods Find. Exp. Clin. Pharmacol. 32 (2010) 171–179.
[35] A.M. Joussen, V. Poulaki, W. Qin, B. Kirchhof, N. Mitsiades, S.J. Wiegand, et al., Retinal vascular endothelial growth factor induces intercellular adhesion molecule-

1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion in vivo, Am. J. Pathol. 160 (2002) 501–509.
[36] T. Qaum, Q. Xu, A.M. Joussen, M.W. Clemens, W. Qin, K. Miyamoto, et al., VEGF-initiated blood-retinal barrier breakdown in early diabetes, Invest. Ophthalmol. Vis. Sci. 42 (2001) 2408–2413.
[37] C. Haritoglou, J. Gerss, C. Sauerland, A. Kampik, M.W. Ulbig, group Cs, Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial, Lancet 373 (2009) 1364–1371.
[38] M. Feghhi, F. Farrahi, M. Abbaspour, A. Takhtaeian, Effect of adding oral calcium dobesilate to laser photocoagulation on the macular thickness in patients with diabetic macular edema: a randomized clinical trial, Adv. Pharm. Bull. 4 (2014) 375–378.
[39] R.L. Stamper, M.E. Smith, S.B. Aronson, J.C. Cavender, G.W. Cleasby, W.E. Fung, et al., The effect of calcium dobesilate on nonproliferative diabetic retinopathy: a controlled study, Ophthalmology 85 (1978) 594–606.
[40] D. Sun, J. Feng, C. Dai, L. Sun, T. Jin, J. Ma, et al., Role of peritubular capillary loss and hypoxia in progressive tubulointerstitial fibrosis in a rat model of aristolochic acid nephropathy, Am. J. Nephrol. 26 (2006) 363–371.
[41] D. Sun, C.X. Liu, Y.Y. Ma, L. Zhang, Protective effect of prostaglandin E1 on renal microvascular injury in rats of acute aristolochic acid nephropathy, Ren. Fail. 33 (2011) 225–232.
[42] D. Sun, Y. Ma, H. Han, Z. Yin, C. Liu, J. Feng, et al., Thrombospondin-1 short hairpin RNA suppresses tubulointerstitial fibrosis in the kidney of ureteral obstruction by ameliorating peritubular capillary injury, Kidney Blood Press. Res. 35 (2012) 35–47.
[43] T. Hirose, K. Totsune, N. Mori, T. Mori, R. Morimoto, H. Metoki, et al., Expression of adrenomedullin 2/intermedin, a possible reno-protective peptide, is decreased in the kidneys of rats with hypertension or renal failure, Am. J. Physiol. Ren. Physiol. 299 (2010) F128–F134.
[44] X.C. Liu, Y.M. Lu, X.B. Jin, H.B. Zeng, H.Y. Gao, Dobesilate calcium in the treatment of chronic kidney failure, Zhonghua Yi Xue Za Zhi 84 (2004) 1892–1893.
[45] H. Zhong, L. Guo, The plasma levels of endothelin in diabetic retinopathy and their changes after treatment with doxium, Hunan Yi Ke Da Xue Xue Bao = Hunan Yike Daxue Xuebao = Bulletin of Hunan Medical University 22 (1997) 56–58.
[46] M.J. Gao, M. Liu, B. Li, M.L. Li, L.X. Bian, G.N. Yu, Protective effect of calcium dobesilate against early diabetic nephropathy of rat kidney, Yao xue xue bao = Acta Pharm. Sin. 44 (2009) 126–133.
[47] C. Hasslacher, E. Burklin, H.G. Kopischke, Influence of calcium dobesilate on the raised synthesis of basement membrane collagen in diabetic rats, Res. Exp. Med. Zeitschrift fur die gesamte experimentelle Medizin einschliesslich experimenteller Chirurgie 178 (1980) 75–78.
[48] J. Dong, X. Liu, S. Liu, M. Li, Y. Xu, B. Cui, Effects of calcium dobesilate on glomerulus TIMP1 and collagen IV of diabetic rats, J. Huazhong Univ. Sci. Technolog. Med. Sci. = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban 25 (2005) 416–418 (26).
[49] S.V. McLennan, D.J. Kelly, A.J. Cox, Z. Cao, J.G. Lyons, D.K. Yue, et al., Decreased matrix degradation in diabetic nephropathy: effects of ACE inhibition on the expression and activities of matrix metalloproteinases, Diabetologia 45 (2002) 268–275.
[50] C.G. Schalkwijk, C.D. Stehouwer, Vascular complications in diabetes mellitus: the role of endothelial dysfunction, Clin. Sci. 109 (2005) 143–159.
[51] S.K. Venugopal, S. Devaraj, I. Jialal, Effect of C-reactive protein on vascular cells: evidence for a proinflammatory, proatherogenic role, Curr. Opin. Nephrol. Hypertens. 14 (2005) 33–37.
[52] T. Cai, X.Y. Wu, X.Q. Zhang, H.X. Shang, Z.W. Zhang, L. Liao, et al., Calcium Dobesilate prevents diabetic kidney disease by decreasing bim and inhibiting apoptosis of renal proximal tubular epithelial cells, DNA Cell Biol. 36 (2017) 249–255.
[53] X. Guo, L. Hou, X. Cheng, T. Zhang, S. Yu, H. Fang, et al., Strong negative interference by calcium dobesilate in sarcosine oxidase assays for serum creatinine involving the Trinder reaction, Medicine 94 (2015) e905.
[54] I. Cihan Ozbek, C. Arslan, E. Canturk, O. Suzer, The effects of calcium dobesilate on the mechanical function of rat hearts, J. Cardiovasc. Surg. 50 (2009) 395–401.
[55] K. Besirli, B. Aydemir, C. Arslan, A.R. Kiziler, E. Canturk, B. Kayhan, Calcium dobesilate may improve hemorheology in patients undergoing coronary artery bypass grafting, Rev. Bras. Cir. Cardiovasc.: orgao oficial da Sociedade Brasileira de Cirurgia Cardiovascular 27 (2012) 260–266.
[56] M.T. Schram, F. Stam, R.T. de Jongh, G. de Vries, R.A. van Dijk, E.H. Serne, et al., The effect of calcium dobesilate on vascular endothelial function, blood pressure, and markers of oxidation in obese male smokers: a placebo-controlled randomised clinical trial, Atherosclerosis 170 (2003) 59–72.
[57] C. Suschek, H. Kolb, V. Kolb-Bachofen, Dobesilate enhances endothelial nitric oxide synthase-activity in macro- and microvascular endothelial cells, Br. J. Pharmacol. 122 (1997) 1502–1508.
[58] E. Ruiz, T. Tejerina, Calcium dobesilate increases endothelium-dependent relaxation in endothelium-injured rabbit aorta, Pharmacol. Res. 38 (1998) 361–366.
[59] E. Ruiz, T. Tejerina, Calcium dobesilate increased endothelium-dependent relaxation in isolated rabbit aorta, Gen. Pharmacol. 30 (1998) 713–718.
[60] M. Sanz, E. Ruiz, P. Ganado, T. Tejerina, In vitro effects of calcium dobesilate on the responsiveness of spontaneously diabetic rat aorta, Jpn. J. Pharmacol. 78 (1998) 391–394.
[61] A.C. Carr, B.Z. Zhu, B. Frei, Potential antiatherogenic mechanisms of ascorbate (vitamin C) and alpha-tocopherol (vitamin E), Circ. Res. 87 (2000) 349–354.
[62] P. Tamas, T. Csermely, T. Ertl, M. Vizer, I. Szabo, F.T. Prievara, Calcium dobesilate lowers the blood pressure in mild to moderate midtrimester hypertension: a pilot study, Gynecol. Obstet. Investig. 47 (1999) 210–213.
[63] J. Angulo, P. Cuevas, A. Fernandez, S. Gabancho, A. Allona, A. Martin-Morales, et al., Diabetes impairs endothelium-dependent relaxation of human penile vascular tissues mediated by NO and EDHF, Biochem. Biophys. Res. Commun. 312 (2003) 1202–1208.
[64] P. Cuevas, J.M. Arrazola, Therapeutic response of rosacea to dobesilate, Eur. J. Med. Res. 10 (2005) 454–456.
[65] E. Rabe, S. Ballarini, L. Lehr, E.D.X.S.G. Doxium, A randomized, double-blind, placebo-controlled, clinical study on the efficacy and safety of calcium dobesilate in the treatment of chronic venous insufficiency, Phlebology 31 (2016) 264–274.
[66] A. Mansilha, J. Sousa, Pathophysiological mechanisms of chronic venous disease and implications for venoactive drug therapy, Int. J. Mol. Sci. 19 (2018).
[67] G.Y. Zheng, Y. Jiang, R.N. Wang, L.L. Hao, D. Xu, Evaluation of calcium dobesilate for its anti-cataract potential in experimental rat models, Zhonghua Yan Ke Za Zhi [Chin. J. Ophthalmol.] 49 (2013) 927–933.
[68] K. Cagli, K. Ozisik, M. Emir, O. Yurdakok, S. Gurkahraman, V. Bakuy, et al., The effect of calcium dobesilate on venous function following saphenectomy in coronary artery bypass grafting, Cardiovasc. Revasc. Med.: including molecular interventions 7 (2006) 212–216.
[69] A. Ciapponi, E. Laffaire, M. Roque, Calcium dobesilate for chronic venous insufficiency: a systematic review, Angiology 55 (2004) 147–154.