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Study of Recent Advances on Various Pharmacological Targets in Vascular Endothelial Dysfunction

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Abstract

Vascular endothelial dysfunction (VED) is major cardiovascular disorder that distrupts the integrity and functioning of endothelial lining through enhance the markers of oxidative stress and decrease endothelial nitric oxide synthase (eNOS) expression which plays pathological role in hypertension, Ischemic heart disease, congestive heart failure. Beside these environmental factors that are involved in pathophysiology of VED such as cigarette smoking, alcohol consumption and exposure to arsenic. The pharmacological treatment of VED with various agents such as Rho-kinase inhibitor, statins, angiotensin converting enzyme inhibitor, calcium channel blocker, endothelin antagonist, anti-oxidants, L-arginine, insulin sensitizing agents, Poly (ADP ribose) polymerase (PARP), Peroxisome proliferator activated receptor gamma (PPAR-γ), Glucagon like peptide (GLP-1) agonist and Dipeptidylpeptidase-IV (DPP-IV) inhibitor targets. So we plan to study the entire drugs where they act in cell signaling which explore the recent targeted site and how they treat the vascular endothelial dysfunction.

Key Words: Vascular endothelial dysfunction, Hypertension, Diabetes, Atherosclerosis, Glucagon like peptide-1, Depeptidylpeptidase-IV

Introduction

Endothelium is a thin monolayer of specialized epithelium consisting of simple squamous cells that covers the inner surface of the vasculature,[1] and it lie in between the circulating blood and vascular smooth muscle cells (VSMC). A healthy endothelium posses anti-atherogenic, antiplatelet and anti-proliferative property to regulates the vascular tone and maintain free flow of blood in vessels.[2] Normal vascular endothelium releases various vasodilatory as shown in figure 1 and vasoconstrictory substances. Vasodilatory substances are nitric oxide (NO),[3] prostacyclin[4] and endothelium-derived hyperpolarizing factors.[5] Vasoconstrictory substances are endothelin-1 (ET-1), angiotensin II (Ang II),[6]thromboxane A2,[7] and reactive oxygen species (ROS). NO has been shown to play an important role in the maintenance of vascular tone of the blood vessels due to its vasodilatory property.[2] This NO is formed from enzyme endothelial nitric oxide synthase (eNOS), which converts the L-arginine to L-citrulline and NO with the help of various cofactors such as tetrahydrobiopterin (BH_4), Calcium calmodulin, nicotinamide- adenine- dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN).[8] After synthesized, NO diffuses across the endothelial cell into the smooth muscle where it causes the activation of soluble guanylyl cyclase enzyme (sGC).[9] The activated enzyme increases the rate of conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) which leads to decrease level of Ca^+ in smooth cell and causes relaxation. On the other hand prostacyclin (PGI2) are synthesized from arachidonic acid with help of cyclooxygenase-2 (COX-2) enzyme.[10] This PGI_2 binds to prostacyclin receptor9[11] which is present on both platelet and vascular smooth muscle cells[12] and activates the adenylate cyclase which induces the synthesis of cyclic adenosine monophosphate(cAMP),[13] leads to decrease the level of Ca^{2+} which causes the smooth muscle cell relaxation. Similarly EDHF is released from the endothelium during activation of endothelial cells by binding of agonist such as bradykinin and acetylcholine.[14][15] EDHF increases the intracellular calcium concentration in endothelium and activation of calcium dependent potassium channels that are present on vascular smooth muscle. This leads to increase the potassium efflux from the smooth muscle and leads to hyperpolarization.[16] Thus, healthy vascular endothelium is necessary to maintain the vascular tone and its functions. Thus, vascular endothelial dysfunction (VED) is a condition associated with partial impairment of vasodilatory substances,[17][18] thrombolysis,[19] and growth regulation.[20] Mainly, VED occurs due to decrease synthesis and

release of NO upon inactivation and uncoupling of eNOS, increases generation of reactive oxygen species (ROS), and up regulation of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of eNOS.[21][22] VED is major cardiovascular disorder associated its pathological role in hypertension,[23] Ischemic heart disease (IHD), congestive heart failure (CHF),[24] diabetes, hyperhomocystenemia,[25] atherosclerosis,[26] erectile dysfunction[27]

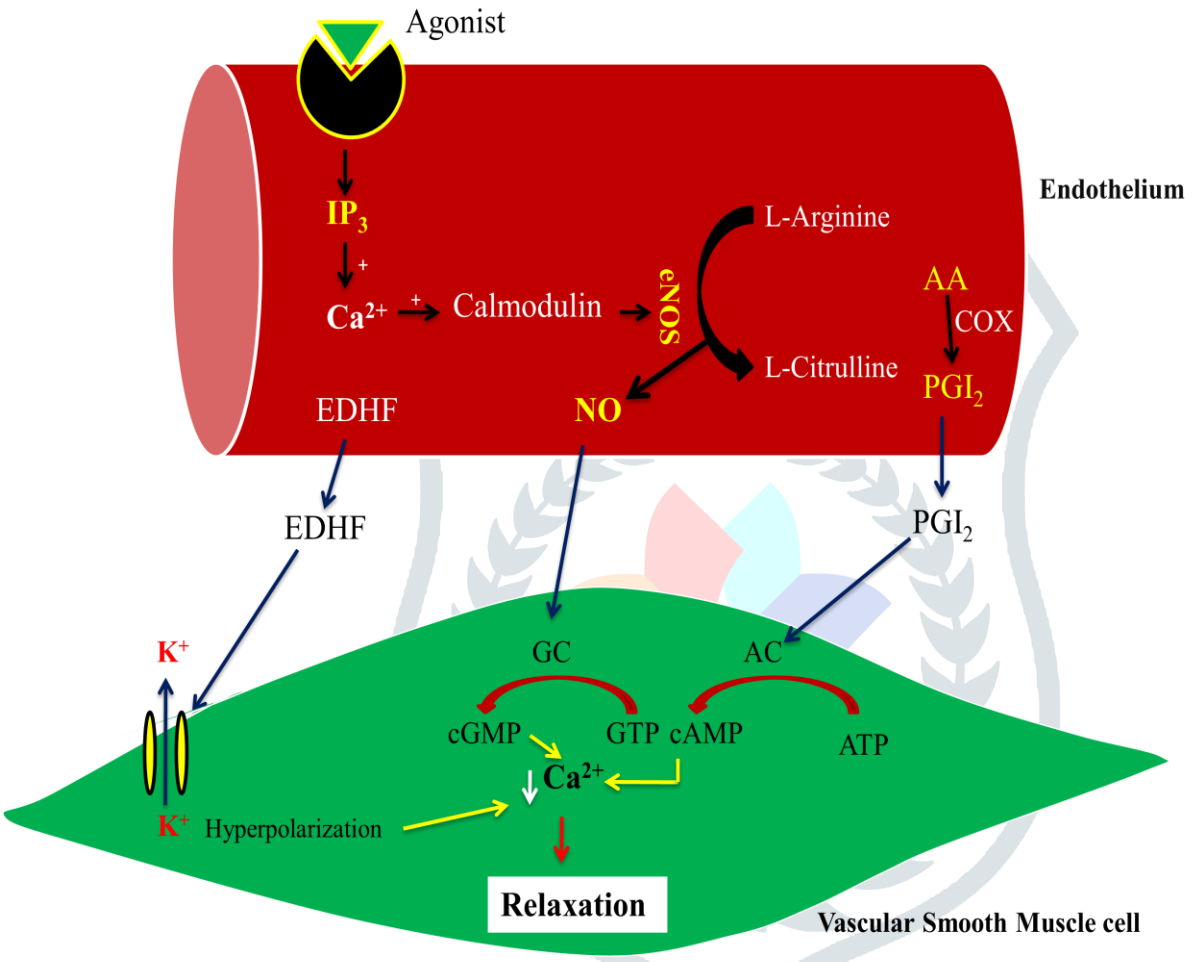

Figure 1: Mechanism of endothelium dependent vascular smooth muscle relaxation

VASCULAR ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is defined as changes to the endothelial properties, as a result of injury, that can lead to its abnormal function. Vascular endothelial dysfunction is characterized by reduced activation of endothelium nitric oxide synthase (eNOS) and increased production of reactive oxygen species (ROS), which account for reduced synthesis and bioavailability of NO. Reduced NO bioavailability is hallmark of vascular disease such as vascular endothelial dysfunction[28][29] is shown in figure 2. In VED, increases the upregulation of Procoagulants, Prothrombotics and proinflamatory mediators occur. It inhibits adhesion molecules by interfering with rolling of leukocytes and diminishing the cytokine induced expression of vascular cell adhesion

molecule -1 (VCAM-1), monocytes chemoattractant protein- 1(MCP-1)[30] and upregulation of asymmetrical dimethylarginine (ADMA). It has been suggested that decrease the dimethylarginine dimethylaminohydrolase (DDAH) activity is key factor for upregulation of ADMA which is an endogenous inhibitor of eNOS.

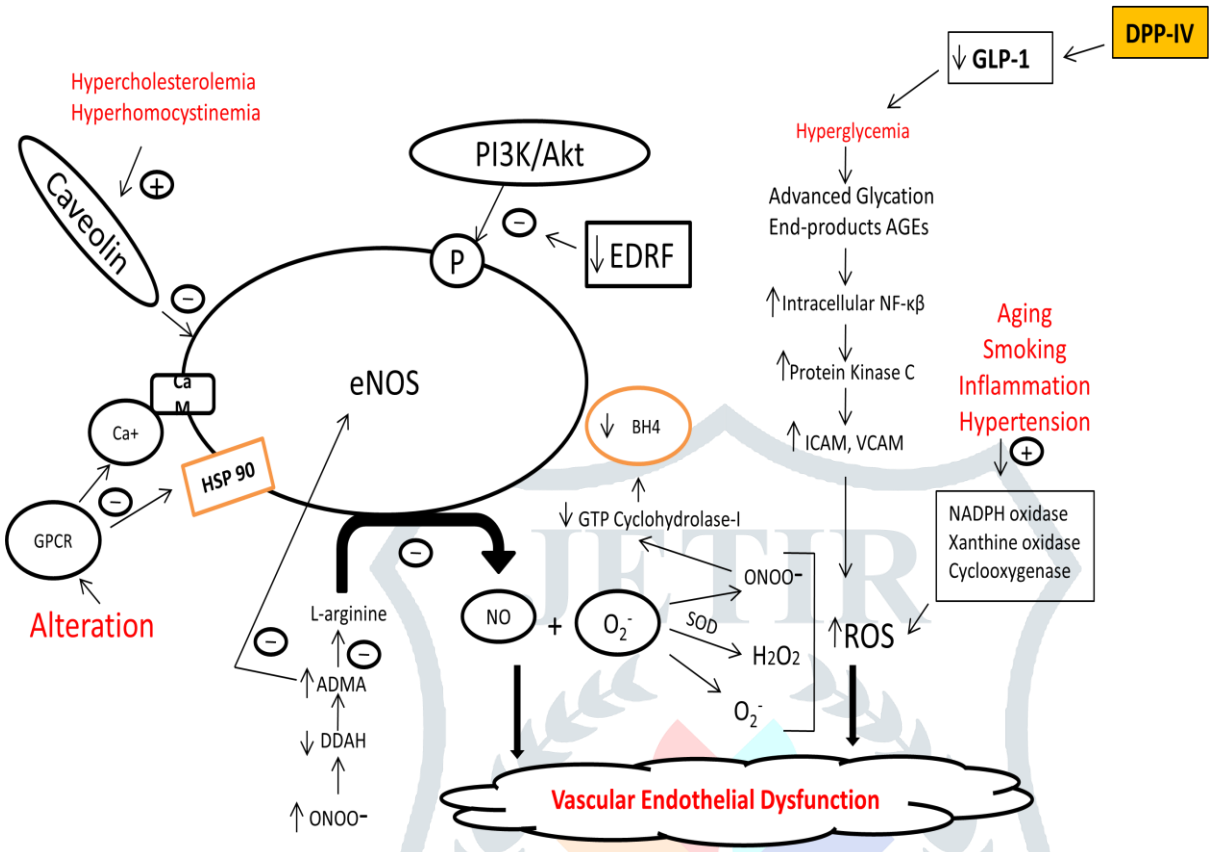

Figure 2: Pathophysiology changes and Pharmacological targets involved in vascular endothelial dysfunction

Oxidative stress plays important role in the development of VED[31]. In pathophysiology of cardiovascular disorder, upregulation of ROS sources, NADPH oxidase,[32][33] xanthine oxidase, cyclooxygenase plays role.[34] Harmful effect of oxidative stress include increasing vascular smooth muscle cell proliferation, endothelial cell apoptosis and increased expression of matrix metalloproteinases, which are involved in the establishment of an atherosclerotic plaque.[35] Oxidant stress comprises increased rates of oxidant production and decreased levels of antioxidant activity for example superoxide dismutase, vitamin C and vitamin E.[36] Peroxynitrite is implicated in the direct induction of VED by the decreasing the NO leading to the production of highly reactive and harmful reactive nitrogen species.[37] Inflammation is another common mechanism of VED.[38] In physiological condition, the endothelium regulates vascular inflammation including expression of adhesion molecules and leukocytes adhesion via the release of NO.[39] Inflammation is associated with overexpression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1). These inflammatory cytokines prompt the endothelial cells or macrophages to enhance adhesion molecule such as VCAM-1 and ICAM-1, MCP-1, IL-6 resulting in endothelial activation, which is precursor of VED.[40]

Tetrahydrobiopterin (BH_4) is an essential cofactor for 3 isoforms of NOS and is involved in the reduction of the heme iron of the NOS enzyme to form an iron-oxy species that hydroxylase L-arginine to produce NO. Reduced bioavailability of BH_4 due to increase in BH_4 oxidation and decrease in GTP cyclohydrolase-I activity, enhances uncoupling of eNOS.[41] BH_4 is itself causes auto-oxidation by reactive oxygen species and causes the eNOS uncoupling that contributes in endothelial dysfunction.[42] Thus, decrease in enzymatic production of nitric oxide, increase in production of superoxide anions and partial uncoupling of eNOS may lead to vascular endothelial dysfunction that collectively diminish the vasodilatory, anti-inflammatory and antithrombotic properties of endothelium.[8][27]

Mainly, VED is characterized by reduced endothelium-mediated vasorelaxation, hemodynamic desregulation,[43] impaired fibrinolytic ability, overproduction of growth factor, increased expression of adhesion molecule and inflammatory genes, excessive generation of reactive oxygen species (ROS), increased oxidative stress and enhanced permeability of the cell layer.[19][44][45][46] NADPH oxidase derived ROS such as superoxide anion, hydrogen peroxide, hydroxyl radical and peroxynitrite damage the endothelial cells by upregulating the pro-inflammatory mediators, adhesion molecules and induce apoptotic cell death.[47]

Thus Vascular endothelial dysfunction (VED) is major CVS disorder which plays pathological role in hypertension,[23] Ischemic heart disease, congestive heart failure,[24] diabetes and hyperhomocystenemia,[25] atherosclerosis,[26] erectile dysfunctions,[27] blackfoot disease,[48]2 hyperlipidemia and aging. There are several other environmental factors that are involved in pathophysiology of vascular endothelial dysfunction such as cigarette smoking, alcohol consumption and exposure to arsenic play a critical role in the development of endothelial dysfunction.

DRUG APPROACHES TO TREATMENT OF VASCULAR ENDOTHELIAL DYSFUNCTION

The pharmacological treatment of VED with agents such as Rho-kinase inhibitor,[49] statins,[50] angiotensin converting enzyme inhibitor,[51] calcium channel blocker,[52] endothelin antagonist,[53] anti-oxidants,[54] L-arginine,[55] insulin sensitizing agents,[56] BH_4,[57] Poly (ADP ribose) polymerase are studied in Table1. After these recent pharmacological targets involved in VED are PPAR-γ activator, Glucagon like peptide (GLP-1) agonist and Dipeptidyl peptidase-IV (DDP-IV) inhibitor.

S.NO	Pharmacological Intervention	Dose/ Route	Parameters/Results	Mechanism	Ref. No.
1.	Probucol	1% in diet	↓LDL level, ↑SOD level, ↓TBARS level	Restoration of EDRF action	[69]
2.	Atorvastatin Simavastatin	10µM 10 µM	↓LDL oxidation. Immunoblotting, gel electrophoresis, ↑eNOS activity,	Inhibition of cholesterol synthesis, decrease the LDL level	[70]
3.	L-arginine & BH_4	1µM 100µM	Histopathology study, Improves IARP	Improve NOS activity, increased serum nitrite/nitrate level	[71]
4.	Perindopril	2mg/kg,in drinking water	Improves IARP, mRNA expression, Biochemical estimation, infarct size, collagen content	Act as ACE inhibitor	[72]
5.	PJ34	10mg/kg, *p.o.*	Improves IARP, ↑plasma NO level,	Act as Anti-inflammatory, Antioxidant	[73]
6.	PJ34	10mg/kg, *p.o.*	Improves IARP, Histopathology	Anti-inflammatory effects	[74]
7.	Quinapril, GA-0113	10mg/kg, *p.o.* 0.3mg/kg, *p.o.*	Improves IARP, Immunohistochemical Analysis, Improves Hepatocyte growth factor level	↑ Hepatocyte growth factor	[75]
8.	Fenofibrate	30,100mg/kg *i.g.*	Improves IARP, ↑serum nitrite/ nitrate level, ↓TNF-α, creatinine level	Decrease ADMA production, Increase eNOS	[76]
9.	L-arginine	2.25% in drinking water	Improves IARP, VLDL, Alanine aminotarnsferase activity	Inhibit Xanthine oxidase activity	[77]
10.	Adenoviral vector	-	RT-PCR, Improves IARP, western blotting , ↑Akt activity	Activation of Akt , eNOS	[78]
11.	Curcumin	5µmol/l	Improves IARP, ↓ ROS Immunohistochemical analysis	As antioxidant	[79]
12.	Pravastatin	1mmol/l	Improves IARP, ↑serum NO level, DDAH level, ↓MDA level	Restoration of DDAH activity, Antioxidant property	[80]
13.	8-Br cAMP	5mg/kg, *i.p.*	Improves IARP, mRNA expression, ECM, ↑serum nitrite/nitrate level, ↑SOD level, ↓TBARS	Activation of PKA	[81]
14.	Captopril	3mg/kg/day for 3 weeks, *i.v.*	Improves IARP, ↑serum NO level SEM, ↓TBARS, superoxide anion level	Inhibiting the synthesis of Ang-II	[82]
15.	Fasudil	15mg/kg, *p.o.* 30mg/kg, *p.o.*	Improves IARP, ↑serum NO level SEM, ↓TBARS, superoxide anion level	Inhibition of Rho-kinase	[49]
16.	Vit.E, Vit. C & gliclazide	2%, 4%, 5mg/kg, *p.o.*	↓MDA level, ↑Vitamin level	Antioxidant property	[83]
17.	3aminobenzamide	40mg/kg, *i.p.*	Body weight, plasma blood glucose level, Improves IARP	Block proinflammatory pathway	[84]
18.	Demethylasterroquinone B1	5mg/kg, *p.o.*	Improves IARP, ↑serum NO level, ↑SOD level	Act through Akt Activation	[85]

19.	bis (maltolato) oxovanadium (BMOV)	0.2 mg/ml in drinking water	Improves IARP, ↑serum NO level SEM, ↓TBARS	Activation of ATP sensitive K+ channel	[86]
20.	Benfotiamine	70mg/kg, *p.o.*	Improves IARP, ↑serum NO, SEM, ↓TBARS, superoxide anion level	Activation of Akt/PKB/PI3K	[87]
21.	Amlodipine, Atorvastatin	5µmol/l, 3-6µmol/l	↑NO level, Western blot Analysis, Electron microscopy	Anti-oxidant property, ↑coupling of eNOS	[88]
22.	Curcumin	10^{-11} mol/l	Improves IARP, ↑HO level	↑ HomoOxygenase-1 activity, stimulation of Guanylyl Cyclase	[89]
23.	BQ123 BQ788	1µmol/l 100nmol/l	Improves IARP, ↓Hhcy level, ↑serum nitrite/nitrate level, RT-PCR, Autoradiography,	Act as Endothelin antagonist	[90]
24.	Benidipine	4mg/kg, *p.o.*	Improves IARP, calcium level	Act through membrane stabilization	[52]
25.	Niacin, chromium	100mg/kg+ 250µg/kg, *p.o.*	Improves TC, LDL,HDL, RT-PCR, western blot analysis, Immunohistochemical Analysis	Decrease ox-LDL/LOX-1 signaling pathway	[91]
26.	Tripterine	50-200nM	Endothelial monolayer permeability Assay, cell viability assay, western blot analysis, superoxide production, ↑Serum nitrite level	Act through Jak2-dependent induction of iNOS and Nox, inhibits peroxynitrite precursor synthesis	[92]
27.	Atorvastatin	10mg/kg, *p.o.*	BP measurement, Improves IARP, RT-PCR, mRNA expression	Elevation of iNOS level, improve NO	[93]
28.	Benfotiamine + fenofibrate	70mg/kg, *p.o.* 32mg/kg, *p.o.*	Improves IARP, ↑serum NO, ↓TBARS, SEM, ↓ superoxide anion level	Alternation of lipid level, antioxidant property	[94]
29.	1,5-isoquinolinediol	3mg/kg, *i.p.*	Improves IARP, Immunohistochemical Analysis	Inhibiting the PARP activation	[95]
30.	Crataegus Extract WS 1442	300µg/ml	Improves IARP, western blot, ↓ROS level	Phos.of Akt, eNOS	[96]
31.	Globular Adiponectin	2mg/ml, 4mg/ml	Improves IARP ,↑NO production, ↓ oxidative stress	AMPK activation	[97]
32.	Benfotiamine	25,50,100 mg/kg, *p.o.*	Improves IARP, ↑serum NO level SEM, ↓TBARS, ↓ superoxide anion level	Activation of Akt/PKB/PI3K	[98]
33.	Fenofibrate	30mg/kg, *p.o*	Improves IARP, mRNA expression, ECM, ↑serum nitrite/nitrate level, SOD level, ↓TBARS, Improves TC, TG, HDL	Activation of eNOS, generation of NO, lipid lowering property	[99]
34.	Astragaloside IV	5,10,50,100 µg/ml	Improves IARP, ↑ NO level, ↓ ROS production	As antioxidant	[100]
35.	Lysimachia clethroides Extract	30µg/ml	Improves IARP, ↑eNOS level, ↑Akt phosphorylation	Inhibition of NADPH oxidase activity, improve eNOS activity	[101]
36.	Chebulic acid	0,1,5,10, 25, 50,100, 250µM	↓ ROS production	Act through inhibition of Advanced Glycation End products	[102]

				(AGEs)	
37.	Palm Oil	1mg/ml	Improves IARP	Anti-oxidant property	[103]
38.	Amlodipine	10mg/kg	Improves IARP, ↓serum MDA, ↑NO level, superoxide production	Anti-oxidant property	[104]
39.	Ang (1-7)	82µg/kg, through osmotic minipumps	↓H_2O_2, ↑cGMP level, ↑renal NO level, Improves eNOS expression	Activation of MAS receptor	[105]
40.	5Aminoimidazole-4-carboxyamide ribonucleosie (AICAR)		Improves IARP, immune-Blotting, improves Akt phosphorylation, ↓ROS level	Activation of AMPK	[106]
41.	Doxycycline	30µmol/kg, intragastically	Improves IARP, Plasma insulin level, ↓MDA, GSH, Thiols, ↑serum nitrite level, western blot analysis	Antioxidant property	[107]
42.	Nicrorandil	15mg/kg in drinking water	Western blot analysis, ↑serum Nitrite level, cell culture study	Antioxidant Action, inhibition of NADPH oxidase	[108]
43.	Vit.B_6,folic acid,L-arginine	2mg/kg, *i.p.* 0.2mg/kg, *i.g.* 200mg/kg, *i.p.*	Improves IARP, systolic BP, diastolic BP, Coefficient of endothelial dysfunction	Improving eNOS activity	[55]
44.	Rhein lysinate	10µmol/l	RT-PCR, immunoblotting, galactosidase staining, mRNA expression, cell cycle Assay	Up regulation of Sirt1 expression, down regulation of p53, p16 expression	[109]
45.	Sesamin	10, 20mg/kg, *p.o.*	Improves IARP, ↓MDA level, ↑ SOD level	As anti-oxidant	[110]
46.	Fenofibrate	32mg/kg. *p.o.*	Improves IARP, mRNA expression, Extracellular Matrix, ↑serum nitrite/nitrate level, ↓ superoxide anion level	Activation of Akt, Activation of eNOS, generation of NO,	[111]
47.	Epicatehnin	2, 10 mg/kg, *p.o.*	Improves IARP, ↑ NO level, ↑ phos. of Akt,	↑expression of Nrf 2 and Nrf2 target genes in the vascular wall.	[112]
48.	Co Q	2.5-20µM	RT-PCR, ↓ SOD level, immunoblotting	Prevents ox LDL-induced ROS generation by activation of AMPK/PKC	[113]
49.	L-carnitine, Taurine, Pomegranate extract, Soy isoflavones	1µg/ml, 50µg/ml, 250µg/ml	↓ Proliferation, ↓Apoptosis	Antiapoptic & anti proliferative property	[114]
50.	Ligustrazine	40µg/ml	↑serum nitrite/nitrate level, Western blotting, RT-PCR, ↓ICAM-1 level, HSP-60	Downregulate the ICAM-1 , HSP-60, TNF-α	[115]
51.	Tribulus Terrestris	6% mixed with food	Improves IARP	↑ expression of eNOS	[116]
52.	Anandamide, Cannabidiol	1µM, 10µM 10µM	Body weight, blood glucose level , Improves IARP	Activation of CB1 receptor, improve NO bioavailability	[117]
53.	Lipoic Acid	20mg/kg, *p.o.*	↑Serum nitrite/nitrate level, histopathology, ↓oxidative stress, lipid profile	Activation of AMP activated protein kinase, Antioxidant,	[118]

				anti inflammatory	
54.	Sodium butyrate Amino guanidine	100mg/kg, *i.p.* 150mg/kg, *i.p.*	Improves IARP, ↑serum nitrite/ nitrate level, ↓TBARS, ↓superoxide anion level, ↓glutathione level, brain total protein	Inhibition of histone acetylation, decrease ROS, Apoptosis	[119]
55.	Allicin	6mg/kg (low dose)10mg/kg (High dose) *i.p.*	Homocystein assay, Endothelin-1 assay, ↑serum nitrate/nitrate level, ↑SOD level, ↓MDA level immunohistoanalysis, ↓total protein , triglycerides, total cholesterol	↑eNOS production , ↑SOD activity, ↓TNF-α, bFGF, ICAM -1	[120]
56.	Berberine	1.25-5.0 μmol/L	↑serum nitrite /nitrate level, ↓ ROS production,↑ eNOS expression, ↓ NOX4 protein expression	Activation of AMPK and eNOS	[121]
57.	Lindera obtusiloba extract, YJP-14,	100mg/kg, *p.o.*	Improves IARP, ↓ ROS, ↓ Ang	Act trough inhibiting the Ang	[122]
58.	Flaxseed	15g/100g in diet	↓TBARS, ↓ ROS, ↑GSH	As anti-oxidant	[123]
59.	Fish Oil	2ml/kg/day, *p.o.*	Improves IARP, Scanning Electron microscopy, ↓TBARS, ↓ ROS, ↓TC	Act through activation of PPAR-γ-eNOS pathway	[124]
60.	Low p53		Improves IARP, ↓ ROS Western blot Analysis, RT-PCR	Prevent circulating level of cholesterol	[125]
61.	Apigenine	20, 50 µmol/l	↑ Akt phos.	Reduction of TNF-α, Activation of PKB	[126]
62.	Resveratrol, N-PEP-12	20mg/kg, *p.o.* 60mg/kg, *p.o.*	Improves IARP	As anti-oxidant, increasing cGMP level	[127]
63.	Atorvastatin	10mg/kg, *p.o.*	Improves IARP, PCR, P-eNOS, Histopathology	Act through modulation of NO signal and inflammatory mediator	[50]
64.	Catechin	50 mg/kg/day, *p.o.*	Improves IARP, ↑serum NO level, ↓TBARS, ↓SOD level, GSH, Histopathology study	Activation of PI3K, eNOS, anti-oxidant,	[128]
65.	Ferulic acid + Astragaloside IV	50 mg/kg/day + 50mg/kg/day *p.o.*	Improves IARP, ↓ ROS Western blot Analysis, RT-PCR	As antioxidant	[129]
66.	Atorvastatin	30mg/kg, *p.o.*	Improves IARP, western blot, RT-PCR, insulin sensitivity, ↑serum NO level, plasma DDAH/ADMA level	Modulation of DDAH/ADMA level	[130]
67.	Rosuvastatin	10 mg/kg, *i.p.*	Improves IARP, endothelial lining, ↑serum nitrite/nitrate level, ↓ oxidative stress	Activation of PPAR-γ and eNOS signaling pathway	[131]
68.	Rosiglitazone	3mg/kg, *p.o.* 5mg/ kg, *p.o.*	Improves IARP, ↑serum NO level ↓TBARS, Histopathology	Activation of ATP sensitive K+ channel	[132]
69.	Exendin-4	2.5nM	Improves IARP, Immunohistochemistry, NO level, body wt., serum lipid profile	Stimulation of cAMP/AMPK pathway	[66]
70.	Exendin-4	1µg/kg, *i.p.*	Improves IARP,↑serum NO level ↓TBARS, Histopathology	Activation of Akt, GLP-1	[25]
71.	Linagliptin	3mg/kg/i.p 1.5mg/kg/i.p	↓TNF- α, ↓TBARS, ↓Superoxide anion, ↑glutathione, ↑serum nitrite/nitrate concentration	Reduces Oxidative stress and inflammation Activate the eNOS	[68]

Table 1: List of Pharmacological interventions acting on vascular endothelial dysfunction

Peroxisome proliferator activated receptor gamma (PPAR-γ)

PPAR-γ agonists are Insulin sensitizing agent and better therapeutic approach for improving endothelial dysfunction. They inhibit expression of TNF-α, IL-6, IL-1β, VCAM-1 and ICAM-1 and protect inflammation of vascular endothelium.[58] PPAR-γ activator, rosiglitazone, pioglitazone, triglitazone decreases the peripheral resistance[59] and increases the production of NO.[60] These drugs improve endothelial function, insulin resistance leads to improve the endothelial dysfunction.[61][62]

Glucagon like peptide -1 (GLP-1):

The incretin hormone to be discovered as gastric inhibitory polypeptide (GIP) and renamed Glucagon like peptide (GLP-1). So, GLP-1 or GIP define that an intestinal incretin hormone that stimulates insulin release in a glucose dependent manner. The physiological action of GLP-1 is stimulates the insulin secretion. GLP-1-mediated eNOS phosphorylation/NO production by protein kinase A (PKA).[63] Exendin-4 and liraglutide are two agonist of GLP-1. In 2010, it is reported that Exendin- 4 prevent vascular endothelial dysfunction in diabetic and homocystein induced VED by activation of PKA and inhibiting the reactive oxygen species[64][25]GLP-1 receptor agonist liraglutide improve vascular endothelial dysfunction in Apolipoprotein deficient mice[65]. Exendin – 4 also improve VED in obese rats by activation of cAMP/ eNOS pathway[66]

Dipeptidyl peptidase –IV (DPP-IV):

DPP-4 is an enzyme that rapidly degrades the incretin hormones mainly glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), the function of which are to release insulin from pancreatic beta cells in response to elevated blood glucose levels and reduce glucagon secretion from pancreatic alpha cells. DPP-IV inhibitor enhances the bioavailability of GLP-1 and GIP, resulting in stimulation of the release of insulin in a glucose-dependent manner and reduction of glucagon secretion[67]. This pharmacological event ultimately reduces the excessive circulating glucose levels, which would be beneficial to patients with T2DM. Linagliptin is a potent, long-acting DPP-IV inhibitor prevents sodium arsenite induced vascular endothelial dysfunction by inhibiting Reactive oxygen species and enhanced the generation and bioavailabitity of NO[68].

Conclusion:

This concludes that above review suggests that more studies are required in this target area to explore the mechanism for the treatment of vascular endothelial dysfunction. As we know, vascular endothelial dysfunction is treated by maintaining the integrity and functioning of endothelial Lining through enhanced production of nitric oxide, decreased the endothelium-derived hyperpolarizing factors and reduced oxidative stress. In last decades, we studies the various new pharmacological targets involved in the treatment of vascular endothelial dysfunction are PPAR-γ, GLP-1 and DPP-IV which results that cardiovascular disorder treatment drugs improves the vascular tone and its function by maintain the production of insulin and vasodilatory substances through activation of Protein kinase A and phosporylation of PI3k/Akt Pathway. Now, this becomes the new era of research in vascular endothelial dysfunction.

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