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EFFECTS OF OMENTIN ON ENDOTHELIAL DISRUPTION AND HYDROGEN PEROXIDE-INDUCED INFLAMMATION IN VASCULAR ENDOTHELIAL CELL MONOLAYER

NUR AQILAH BINTI KAMARUDDIN

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By

NUR AQILAH BINTI KAMARUDDIN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Chairman: Yong Yoke Keong, PhD
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The endothelial barrier plays important roles in maintaining vascular homeostasis. In response to oxidative stress, the endothelial barrier breaks down and results in an increase in endothelial permeability, which is followed by cell injury. Vascular damage is characterized by the breakdown of the endothelial barrier and the associated hyperpermeability. An increase in generation of reactive oxygen species (ROS) and the disruption of endothelial intercellular junctions are critical events in oxidative stress-induced endothelial cell injury. Omentin is an adipocytokine abundantly secreted in visceral adipose tissue and has anti-diabetic and anti-inflammatory properties. Withal, it has not been explored whether omentin can ameliorate endothelial injury and barrier dysfunction induced by oxidative stress. Both cytotoxic and cytoprotective effects of omentin were determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The apoptotic activity of human umbilical vein endothelial cells (HUVECs) was investigated using Annexin-V/PI and Hoechst 33258 staining. Omentin antioxidant activity was evaluated by measuring both ROS levels and glutathione peroxidase (GPx) activity. Conducive to understanding the role of omentin in preserving the endothelial barrier, the effect of omentin on endothelial hyperpermeability induced by hydrogen peroxide (H_2O_2) using sodium fluorescein (NaF), evans blue albumin (EBA) and transendothelial electrical resistance (TEER) has been assessed. Distribution of filamentous (F)-actin, adherens junctions (AJs) and tight junctions (TJs) in cells were investigated using immunocytochemistry and confocal imaging. Total protein expression of F-actin, vascular endothelial (VE)-cadherin, β-catenin, occludin, zona occludens (ZO)-1, Rho and ROCK2 was determined using Western blot analysis. This study indicated that there is no cytotoxic effect observed in HUVECs treated with omentin alone at concentrations of 150 to 450 ng/mL. The result of the MTT assay showed that omentin significantly blocked cell death induced by H_2O_2 ($p<0.001$). Hoechst staining and flow cytometry also revealed that omentin notably halted H_2O_2-induced apoptosis. In addition, omentin significantly inhibited ROS production ($p<0.01$) and also significantly ($p<0.01$) increased GPx activity in HUVECs, resulting in protection against oxidative stress-induced cell damage in HUVECs. Besides, pretreatment of omentin also

significantly (p<0.001) reduced endothelial hyperpermeability, as demonstrated by increased TEER value and decreased passage of NaF and EBA through the monolayer of the cells. Immunostaining data demonstrated that omentin reversed rearrangement of the cytoskeletal protein, F-actin, enhanced the distribution of AJs and TJs protein such as VE-cadherin, β-catenin, occludin, and ZO-1. In addition, omentin also significantly suppressed increased F-actin levels and prevented the reduced expression level of junctional proteins (p<0.01). Interestingly, omentin abolished the activation of RhoA/ROCK induced by H_2O_2 (p<0.01), an effect which was similar with the action of a ROCK inhibitor. These *in vitro* findings demonstrated that the antioxidant and anti-inflammatory actions of omentin involve a reduction in production of ROS, reduced endothelial hyperpermeability, the actin cytoskeleton stabilization and increased junction proteins by regulating the localization and protein expression of occludin, ZO-1, VE-cadherin and β-catenin. This study also implies that omentin prevents endothelial disruption and inhibits H_2O_2-induced inflammation in vascular endothelial cell monolayer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN OMENTIN TERHADAP GANGGUAN ENDOTELIAL DAN INFLAMASI YANG DISEBABKAN OLEH HIDROGEN PEROKSIDA PADA LAPISAN MONO SEL ENDOTELIAL VASKULAR

Oleh

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Sekatan endotelial memainkan peranan penting dalam mengekalkan homeostasis vaskular. Tindak balas kepada stres oksidatif telah menyebabkan gangguan fungsi sekatan endotelial, kebolehtelapan hiper endotelial dan diikuti oleh kecederaan sel. Kerosakan vaskular dicirikan oleh gangguan fungsi sekatan dan kebolehtelapan hiper endotelial yang berkaitan. Peningkatan spesies oksigen reaktif (ROS) dan gangguan persimpangan antara endotelial adalah titik genting dalam kecederaan sel endotelial yang diaruhkan oleh stres oksidatif. Omentin adalah sitokin lemak yang banyak dihasilkan dalam tisu lemak visera yang mempunyai ciri-ciri anti-radang dan anti-diabetes. Walau bagaimanapun, ia belum diterokai sama ada omentin boleh memperbaiki kecederaan endotelial dan kegagalan fungsi sekatan yang diaruhkan oleh stres oksidatif. Analisis sitotoksik dan sitoprotektif omentin ditentukan dengan menggunakan ujian 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). Aktiviti apoptosis di sel endotelial vena umbilikal manusia (HUVECs) dikaji dengan menggunakan kaedah pewarnaan Annexin-V/PI dan Hoechst 33258. Aktiviti antioksidan omentin ditentukan dengan mengukur tahap ROS dan aktiviti glutation peroksidase (GPx). Kesan omentin terhadap kebolehtelapan hiper endotelial yang diaruh oleh H_2O_2 dikenalpasti dengan menggunakan natrium fluorescein (NaF), albumin biru evans (EBA) dan rintangan elektrik transendotelial (TEER) untuk memahami peranan omentin dalam mengekalkan sekatan endotelial. Penempatan filamen (F)-aktin, simpang adherens (AJs) dan simpang ketat (TJs) dalam sel dinilai menggunakan analisis imunositokimia dan mikroskop konfokal. Pengekspresan jumlah protein F-aktin, endotelial vaskular (VE)-cadherin, β-catenin, occludin, zona occludens (ZO)-1, RhoA dan ROCK2 ditentukan menggunakan analisis pemendapan Western. Keputusan kajian ini menunjukkan bahawa tiada ciri-ciri sitotoksik diperhatikan terhadap HUVEC yang dirawat dengan omentin sahaja pada kepekatan 150 hingga 450 ng/mL. Keputusan ujian MTT menunjukkan bahawa omentin secara ketara menghalang kematian sel yang disebabkan oleh H_2O_2 (p<0.001). Pewarnaan Hoechst dan sitometri aliran juga mendedahkan bahawa omentin dengan ketara menghalang apoptosis yang disebabkan oleh H_2O_2. Selain itu, omentin bukan

sahaja menghalang pengeluaran ROS dengan ketara (p<0.01) tetapi juga (p<0.01) meningkatkan aktiviti GPx dalam HUVECs, di mana menghasilkan perlindungan terhadap kecederaan sel akibat stres oksidatif dalam HUVECs. Selain itu, omentin juga dengan ketara (p<0.001) mengurangkan kebolehtelapan hiper endotelial seperti yang ditunjukkan oleh peningkatan nilai TEER dan penurunan laluan NaF dan EBA merentas lapisan mono sel. Data imunositokimia menunjukkan bahawa omentin menstabilkan filamen, F-aktin, meningkatkan pengagihan protein simpang ketat dan adherens seperti occludin, ZO-1, VE-cadherin, dan β-catenin. Di samping itu, omentin juga secara ketara mengurangkan peningkatan tahap F-aktin dan meningkatkan tahap pengekspresan protein simpang (p<0.01). Menariknya, omentin menghalang pengaktifan RhoA / ROCK yang diaruhkan oleh H_2O_2 (p<0.01), dimana menghasilkan kesan yang sama dengan tindakan perencat ROCK. Penemuan *in vitro* ini menunjukkan bahawa tindakan anti-oksidan dan anti-radang omentin melibatkan penurunan pengeluaran ROS, mengurangkan kebolehtelapan hiper endotelial, menstabilkan sitoskeleton iaitu F-aktin dan meningkatkan protein simpang dengan mengawal penempatan dan pengekspresan protein occludin ZO-1, VE-cadherin dan β-catenin. Kajian ini menunjukkan bahawa omentin boleh mencegah gangguan dan menghalang inflamasi yang diaruhkan oleh H_2O_2 pada lapisan mono sel endotelial.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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4-HNE	4-hydroxy-2-nonenals
ADP	Adenosine diphosphate
AJ	Adherens junction
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BCA	Bicinchoninic acid
BSA	Bovine serum albumin
Ca^{2+}	Calcium ions
cAMP	Cyclic adenosine monophosphate
CAT	Catalase
COX-2	Cyclooxygenase 2
CS1	Catalytic subunit
DAPI	4',6-diamidino-2-phenylindole
DCF	2′-7′-dichlorofluorescin
DCFDA	2′,7′-dichlorofluorescin diacetate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EBA	Evans blue albumin
EGF	Epidermal growth factor
ELISA	Enzyme linked immuno-sorbent assay
eNOS	Endothelial nitric oxide synthase
FA	Focal adhesion
F-actin	Filamentous actin

FITC	Fluorescein
GDP	Guanosine diphosphate
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GSSG	Oxidised glutathione
GTP	Guanosine triphosphate
H_2O	Water
H_2O_2	Hydrogen peroxide
HBSS	Hank's balanced salt solution
HMGB1	High mobility group box 1
HOCL	Hypochlorous acid
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule-1
JNK	c-Jun N-terminal kinases
LDL	Low-density lipoprotein
M20	MYPT1-linked subunit
MAP kinase	Mitogen-activated protein kinase
MDA	Malondialdehyde
MLC	Myosin light chain
MLCK	Myosin light chain kinase
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MYPT1	Myosin phosphatase target subunit 1
NADPH	Nicotinamide adenine dinucleotide phosphate
NaF	Sodium fluorescein
NF-κB	Nuclear factor-κB
NO	Nitric oxide

O^{2-}	Oxide
O2 ·-	Superoxide anion radical
OH-	Hydroxide
OH·	Hydroxyl radical
PAH	Pulmonary arterial hypertension
PBS	Phosphate buffered saline
PDGF	Platelet-derived growth factor
PGI_2	Prostacyclin
PKC	Protein kinase C
PMSF	Phenylmethylsulfonyl fluoride
PS	Phosphatidylserine
ROCK	Rho-kinase
ROS	Reactive oxygen species
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
sGC	Soluble guanylate cyclase
SOD	Superoxide dismutase
SP-1	Sphingosine-1-phosphate
TEER	Transendothelial electrical resistance
TJ	Tight junction
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
VCAM-1	Vascular cell adhesion molecule-1
VE-Cadherin	Vascular endothelial-cadherin
VEGF	Vascular endothelial development factor
VSMC	Vascular smooth muscle cells
VVOs	Vesiculo-vacuolar organelles

ZO-1	Zona occludens-1
α-catenin	Alpha-catenin
β-catenin	Beta-catenin
γ-catenin	Gamma-catenin

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CHAPTER 1

INTRODUCTION

1.1 Research Background

The three-layer vessel wall is composed of continuous monolayer endothelial cells, which play pivotal roles in hemostasis, vasodilatation, angiogenesis, vascular permeability, and also response to various physiological and pathological stimuli. Endothelial cells contain metabolic and synthetic functions, as well as acting as a physical barrier between the flowing blood and vascular smooth muscle cells. Endothelial cells controls an array of cellular functions throughout the body by emitting a wide range of mediators such as anti-thrombotic factors, growth factors, inflammatory mediators, and others (Daiber et al., 2017). In pathological conditions such as atherosclerosis, disruption of the endothelial barrier results in an influx of plasma proteins into the extravascular space, leading to tissue edema which is accompanied by enhanced inflammatory responses. Endothelial cell injury is one of the early events in the development of atherosclerosis (Kattoor et al., 2017) and oxidative stress is considered a hallmark of endothelial cell injury (Steven et al., 2019).

Oxidative stress is caused by an imbalance between the pro-oxidant and the antioxidant defense mechanisms in the body. Uncontrolled reactive oxygen species (ROS) damages cellular and components including lipids, nucleic acids, and proteins, thereby leading to cell death (Incalza et al., 2018). Extensive ROS has also been notified to be one of the primary causes of endothelial cell injury and apoptosis (Han et al., 2017; Redza-Dutordoir & Averill-Bates, 2016). Amid ROS, hydrogen peroxide (H_2O_2) freely perforates the plasma membrane, causing damage to neighbouring cells along with H_2O_2-producing cells. Previous research reported that after being exposed to H_2O_2, HUVECs exhibited remarkable cytotoxicity which characterised by a loss of cell viability, an increase in ROS production, an increase in caspase-3 activity, and the apoptosis rate (Xie et al., 2015). In addition, a previous study found that exposing HUVEC cells to H_2O_2 led to high levels of oxidative stress damage in the cells. This was demonstrated by a reduction in cell viability, increased levels of intracellular nitric oxide (NO) and nitric oxide synthase (NOS), as well as enhanced levels of ROS, malondialdehyde (MDA), lactate dehydrogenase (LDH), and decreased levels of superoxide superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity (Li et al., 2009; Zhong et al., 2012). On account of this characteristic, H_2O_2 is widely used to induce oxidative stress in numerous *in vitro* models (Aqilah et al., 2020; Tian et al., 2017). Hence, inhibition of H_2O_2-induced oxidative stress and injury of endothelial cells has been contemplated as a possible therapeutic strategy for cardiovascular diseases (Han et al., 2017; Liu et al., 2019).

Under physiological state, the antioxidant defense system in cells tightly regulates the level of intracellular ROS. ROS is directly detoxified or break down into nontoxic substances by the action of nonenzymatic radical scavengers (e.g., ascorbic acid and glutathione) or antioxidant enzymes (e.g., catalase (CAT), GPx, and SOD). Extra H_2O_2

is eradicated by GPx biochemically where the enzyme neutralizes H_2O_2 using two hydrogen atoms from two molecules of reduced glutathione (GSH) into water and oxidized glutathione (GSSG) (Pastori et al., 2018). Consequently, to maintain acceptable ROS levels in the cytosol while balancing GSH and GSSG the glutathione system acts as an effective redox buffer (Ballatori et al., 2009).

The endothelial barrier integrity comes together as a complex network of intercellular adherens junctions (AJs), tight junctions (TJs) and cytoskeletal structures, whereby when disrupted results in impaired barrier function (Millán et al., 2010; Wallez & Huber, 2008). AJs are located just basal of the TJs, which consists of transmembrane VE-cadherin and cytoplasmic β-catenin. Furthermore, TJs located at the apical end of the endothelial cells, contains both transmembrane proteins including occludin, claudin and junctional adhesion molecules, and cytoplasmic zonula occludens (ZO)-1 proteins. AJs and TJs are important components of the endothelial barrier as they are crucial determinants of the endothelial permeability (Fong et al., 2015). Disruption of endothelial AJs and TJs give rise to paracellular permeability, permeating solutes and fluids to extravasate, which eventually progresses to a number of diseases. Therefore, the ability of restoring the barrier function of endothelial beneficial criterion in evaluating the efficacy of a therapeutic agent in cardiovascular diseases.

Endothelial cell junctions are modulated by many signaling molecules, frequently acting by triggering reconstitution of the actin cytoskeleton. For instance, Rho guanosine triphosphate (GTPases) and its downstream target, rho serine/threonine kinase (ROCK), stimulate actomyosin-based contraction, creating stress fibers and focal adhesion (FA) and with that, cause a rapid rise of endothelial permeability in reaction to thrombin and histamine (Braga, 2002; Carbajal & Schaeffer, 1999; Gavard & Gutkind, 2008; Wojciak-Stothard & Ridley, 2002). Stress fibers generated in response to these stimuli also promote reorganization of junctional complexes (Hurst et al., 1999).

Omentin is an adipokine secreted by visceral adipose tissue that acts as an insulin-sensitizing effect. In human plasma, omentin is detectable at concentrations ranging from 100 to 800 ng/ml (Batista et al., 2007). Lowered omentin levels in plasma were reported in patients with obesity, impaired glucose tolerance, and type 2 diabetes mellitus (Batista et al., 2007; Herder et al., 2017; Pan et al., 2019). Additionally, omentin has been shown to increase vasodilation in isolated blood vessels and inhibit inflammatory responses in cultured endothelial cells (Yamawaki et al., 2011; Yamawaki et al., 2010). Experimented on hindlimb ischemia mouse model, omentin exhibited to enhance blood flow recovery and capillary density in ischemic limbs of mice. At the cellular levels, omentin increased differentiation of EC into vascular-like structures and lowered the apoptotic activity of EC via activation of the PI3K/Akt signaling cascade (Maruyama et al., 2012). Omentin also ameliorates acute ischemic injury in the heart by suppressing cardiomyocyte apoptosis through the AMP-activated protein kinase (AMPK) and the Akt signaling pathways (Kataoka et al., 2014). Although being well studied on the roles of omentin in obesity-related metabolic and cardiovascular complications, it is still unknown if omentin can successfully provide protection to the endothelium from trauma caused by oxidative stress.

Therefore, the roles of omentin in endothelial injury, endothelial permeability, cytoskeletal structure and intercellular junctions were investigated in this study. Furthermore, the mechanism by which omentin ameliorates H_2O_2-induced endothelial injury and endothelial barrier dysfunction was also evaluated.

1.2 Justification of the Study

Endothelial injury is now well established as a pivotal early event in the course of cardiovascular disease-related development risk factors, including hypertension, atherosclerosis, and diabetes. The endothelial barrier plays a critical role for the vascular endothelium to function properly including to maintain vascular homeostasis, but this function can be jeopardized by inflammatory mediators, cytokines and oxidants. When the endothelium is exposed to oxidative stress, a large number of ROS are produced, causing oxidative damage to lipids, proteins, enzymes in endothelial cells, and lead to apoptosis (Boueiz & Hassoun, 2009). The major source of ROS is generated from H_2O_2 who is one of the most powerful oxidants which can easily cross the plasma membrane and damage neighboring cells, including H_2O_2-producing cells (Liu et al., 2013). H_2O_2 at low levels enhance endothelial cell growth and proliferation (Stone & Collins, 2002), whereas high levels contribute to increased endothelial monolayer permeability to fluid, macromolecules, and inflammatory cells, resulting in endothelial injury (Qian et al., 2010). Thus, H_2O_2 has been extensively used to induce oxidative stress in *in vitro* models (Aqilah et al., 2020; Tian et al., 2017). In order to prevent vascular disorders, therapeutic interventions that particularly target the endothelial barrier function may be a promising alternative. Omentin, an adipocytokine mainly found in visceral fat tissue, has been shown to have anti-inflammatory and anti-diabetic properties. Nevertheless, the underlying mechanisms by which omentin repulse oxidative stress-induced endothelial injury and increased permeability remain unclear.

1.3 Overview of Mechanism of Oxidative Stress-induced Endothelial Permeability and Injury

It has been demonstrated that oxidative stress may play a role in endothelial damage. Concurrently, activation of the ROCK signalling pathway appears to play a significant part in the regulation of vascular endothelial permeability. An increasing amount of evidence have shown that treatment with H_2O_2 causes damages to vascular endothelial cells by increased endothelial monolayer permeability, increased production of ROS, depleting GPX activities, and promoting endothelial cell death (Figure 1.1). Moreover, it has been reported that Rho/ROCK2 causes an increase in endothelial permeability, which, as a consequence, causes a deterioration of the barrier function in the endothelium (Majno et al., 1969; Garcia et al., 1986). The hyperpermeability of the vascular endothelium is formed when RhoA is activated by H_2O_2, and an active signal is provided to the effector ROCK2. The activation of the Rho/ROCK pathway promotes actin polymerization and the formation of F-actin stress fibres, both of which are induced by the contraction of the cytoskeleton. This leads to the disruption of AJs and TJs, which ultimately results in endothelial barrier dysfunction and increased vascular permeability**.** The above mechanism is summarized in Figure 1.1.

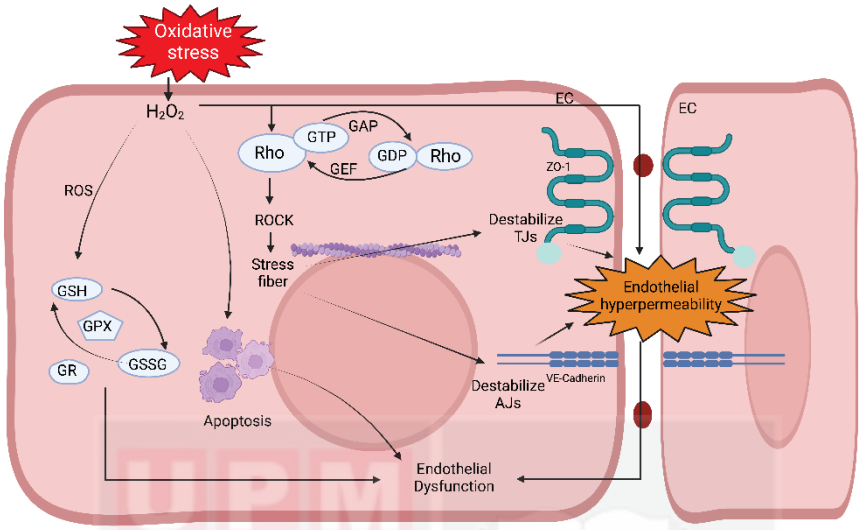

Figure 1.1: Schematic diagram of the putative signaling pathway involved in H_2O_2-induced damage and increased permeability in HUVECs cell. After being exposed to H_2O_2, the production of ROS increased, resulting in a decrease in GPX activity and the induction of endothelial cell death, all of which affect vascular endothelial cells. ROCK is activated when RhoA is triggered by H_2O_2. The activation of the Rho/ROCK pathway causes actin polymerization and the production of F-actin stress fibres, which leads to the destabilisation of AJs and TJs. Finally, it promotes increased paracellular permeability.

1.4 Hypotheses

Omentin will possess endothelial protective effects in H_2O_2-induced endothelial dysfunction by preventing disruption of interendothelial junctions and this effect will be accompanied with the suppression of RhoA/ROCK signaling pathway.

1.5 Objectives

1.5.1 General Objective

The aim of this study was to evaluate the effect of omentin in H_2O_2-induced dysfunction of HUVECs and the underlying mechanism.

1.5.2 Specific Objective

i. To determine the effect of omentin on H_2O_2-induced endothelial injury.
ii. To determine the effect of omentin on H_2O_2-induced endothelial hyperpermeability.
iii. To evaluate the effect of omentin on H_2O_2-induced cytoskeletal rearrangement.
iv. To examine the effect of omentin on H_2O_2-induced disassembly of interendothelial junctions.
v. To examine the mechanism underlying the protective effect of omentin against H_2O_2-induced activation of RhoA/ ROCK signaling pathway.

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