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Research Progress on the Improvement of Endothelial Cell Function by Tianma Gouteng Decoction via Regulation of the lncRNA OIP5-AS1/miRNA Axis

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Abstract

Objective: To review the potential interaction between Tianma Gouteng Decoction and the long non-coding RNA OIP5-AS1/miRNA axis in endothelial protection. **Method:** A review of available literature. **Results:** We found that long non-coding RNA OIP5-AS1 can regulate endothelial function through ceRNA mechanisms, and this regulation is related to inflammation, apoptosis, as well as vascular remodeling. Tianma Gouteng Decoction has anti-inflammatory effect. In fact, it can also protect the vascular system from damage. Also, gastrodin is a core active component. It can modulate long non-coding RNA OIP5-AS1/miRNA axis through pathways like Wnt/β-catenin. But direct molecular evidence remains limited. **Conclusion:** Our results can suggest a possible "multi-target, non-coding RNA" regulatory network. It is worth noting that we should integrate gene expression intervention with herbal treatment in future studies and this can validate the interaction. Also, this approach can support endothelial protection in the cerebrovascular disease.

Keywords

Tianma Gouteng Decoction, Gastrodin, Long Non-Coding RNA OIP5-AS1, Endothelial Cells, Cerebrovascular Diseases

1. Introduction

Cerebrovascular diseases are central nervous system disorders. Their characteristics

is structural and functional abnormalities in cerebral blood vessels. The pathogenesis includes complex interactions among genetic, environmental, metabolic, and hemodynamic factors [1]. When cerebrovascular diseases develop, endothelial dysfunction plays a central role in pathophysiology by disrupting vascular stability, exacerbating inflammation, compromising the blood-brain barrier, and inducing metabolic imbalance [2]. Consequently, the therapeutic strategies were proposed with the aim of protecting endothelial function. Intervention strategies, such as anti-inflammatory, antioxidant, and metabolic-regulatory approaches. They are expected to address the therapeutic limitations of cerebrovascular diseases [3] [4]. Several technologies such as single-cell sequencing, spatial transcriptomics, and cell lineage tracing, have been widely applied across different brain functional regions and vascular segments in recent years. These technologies help characterize the molecular phenotypes and functional heterogeneity of endothelial cells [5]-[7]. Notably, the molecular phenotypes can be regulated by specific pathological environments. Also exogenous exposures influence the functional heterogeneity of endothelial cells [5]. Among these regulatory mechanisms, it is proved that the long non-coding RNA (lncRNA)-microRNAs (miRNAs) axis plays a pivotal role in maintaining cellular homeostasis [8]. Studies have shown that under chronic cadmium exposure, lncRNA OIP5-AS1 is significantly upregulated. It acts as a competing endogenous RNA (ceRNA) and can sponge miR-128-3p, thereby relieving the repression of target gene SLC7A11 by miR-128-3p. Then cell growth is promoted and resistance to ferroptosis can be improved [9]. This mechanism not only reveals the critical role of the lncRNA-miRNA axis in cellular homeostasis but also provides a theoretical basis for understanding how environmental exposures influence endothelial function.

Tianma Gouteng Decoction (TGD) is a classic prescription that can be used to treat Liver Yang Hyperactivity and Internal Liver Wind [10]. In this formula, Gastrodiae Rhizoma (Tianma) and Uncariae Ramulus cum Uncis (Gouteng) are the sovereign herbs that can pacify the liver and extinguishing wind. These are complemented by Concha Haliotidis (Shijueming) to subdue yang hyperactivity, Gardeniae Fructus (Zhizi) and Scutellariae Radix (Huangqin) to clear heat and purge fire, Leonuri Herba (Yimucao) and Cyathulae Radix (Niuxi) to activate blood circulation, promote diuresis, and direct blood downward, while Taxilli Herba (Sangjisheng) and Eucommiae Cortex (Duzhong) to tonify the liver and kidney, and Polygoni Multiflori Caulis (Yejiaoteng) together with Poria cum Radice Pini (Fushen) to calm the mind and stabilize the spirit [10]. In the traditional Chinese medicine (TCM), this formula is expected to alleviate hypertension and associated vascular dysfunction. This mechanism includes pacifying the liver, extinguishing wind, clearing heat, activating blood circulation, and tonifying the liver and kidney [11]. Furthermore, recent studies indicate that this formula has multi-target regulatory effects. Actually, TGD work through multiple mechanisms, including anti-inflammatory effects, antioxidant activity, and it can improve vasomotor function [12]. In recent years, some TCM preparations for vascular protection have been studied, and these include Xiongshao Capsule, Sijunzi Decoction, and Angelica sinensis polysac-

charide. They have been shown to act via the lncRNA OIP5-AS1/miRNA axis, a signaling pathway critical for endothelial cell function [13]-[15]. These reports suggest that TGD may improve endothelial cell function via regulation of ncRNAs, thereby contributing to the treatment of cerebrovascular diseases. However, it is worth noting that the evidence linking TGD directly to lncRNA OIP5-AS1 remains largely indirect, while direct experimental validation is currently lacking.

2. Structural Characteristics and Expression Regulatory Patterns of lncRNA OIP5-AS1

2.1. Biological Significance and Evolutionary Conservation Analysis

lncRNA OIP5-AS1, also called Cyrano, is a new lncRNA with transcript length more than 8 kb. Although its overall sequence conservation across vertebrates is low, it has a highly conserved region with about 300-500 nucleotides. This region is involved in zebrafish embryonic development and cerebellar neuron function [16]. Notably, the majority functions of lncRNA OIP5-AS1 come from intermolecular interactions outside this conserved region, so it can interact with chromatin, RNA, and protein [17]. This structural versatility supports its key roles in different physiological processes. For instance, under chemical stress, lncRNA OIP5-AS1 exhibits a long half-life and shows protective effects by controlling mitosis and cell proliferation [18]. Specifically, during mitosis, it negatively regulates GAK mRNA stability to ensure accurate chromosome alignment and segregation [19]. Furthermore, by interacting with STAT3, lncRNA OIP5-AS1 can maintain Nanog expression in embryonic stem cells, and this helps self-renewal and pluripotency [20]. There are some evidence focusing on endothelial and cerebrovascular mechanisms in vascular and neural systems.

Besides physiological regulation, lncRNA OIP5-AS1 can be found in pathological processes. Recent studies show that it has important roles in various chronic diseases, including endocrine disorders, cardiovascular and digestive system diseases and cancer, where it can regulate cell proliferation, apoptosis, and inflammation [21]-[23]. In summary, structural features of this lncRNA can support its regulatory roles in the physiological and pathological conditions.

2.2. Tissue-Specific Expression Profiles in the Nervous and Endothelial Systems

lncRNA OIP5-AS1 shows high expression in the nervous system and it plays an important role in the development and regeneration of skeletal muscle [24]. Some studies have revealed that it has functions in the muscles [25] [26]. Though these findings about muscle are not directly related to endothelial function, they can show the broad regulatory capacity of lncRNA OIP5-AS1 and provide context for its diverse tissue-specific roles. Also, lncRNA OIP5-AS1 can induce the degradation of miR-7 through complementary binding sites, and this leads to accumulation of Cdr1as, which is negatively regulated by miR-7 in the hippocampus and hypothalamus. So it can modulate neuronal activity [27].

In endothelial system, lncRNA OIP5-AS1 also plays a significant role. When human aortic endothelial cells are stimulated by oxidized low-density lipoprotein (ox-LDL), expression of lncRNA OIP5-AS1 can be upregulated [28]. Similarly, in hemangioma tissues and human hemangioma endothelial cells, lncRNA OIP5-AS1 levels are higher and this can promote endothelial cell proliferation, migration as well as invasion, this effect is mainly mediated via miR-195-5p/NOB1 ceRNA axis [29]. Additionally, in retinal pigment epithelial cells, lncRNA OIP5-AS1 is regulated by inflammatory factor IL-1β, with expression increasing 24 hours after stimulation [30]. Collectively, these findings indicate that lncRNA OIP5-AS1 shows tissue-specific expression in various endothelial cells and is involved in pathological processes such as endothelial proliferation, inflammatory activation, and injury, which suggests it has important functions in related diseases.

2.3. Dynamic Expression Regulation under Pathological Stimulation

lncRNA OIP5-AS1 exhibits a characteristic pattern of dynamic expression regulation under various pathological stimuli. In the atherosclerotic microenvironment, lncRNA OIP5-AS1 expression is significantly upregulated. In vitro studies confirmed that its expression increases significantly in human umbilical vein endothelial cells (HUVECs) following ox-LDL-induced injury, suggesting its involvement in endothelial dysfunction and atherogenesis [31]. lncRNA OIP5-AS1 also displays dynamic activation characteristics in response to inflammatory stimuli. Barros *et al.* reported that lncRNA OIP5-AS1 expression in human retinal endothelial cells increased significantly 24 hours post-stimulation, implying its participation in retinal endothelial inflammatory activation [30]. Furthermore, lncRNA OIP5-AS1 is upregulated in the nasal mucosa of allergic rhinitis patients, in bronchial epithelial cells of asthma models stimulated by house dust mites, and in lipopolysaccharide (LPS)-treated periodontal ligament cells. This further confirms its conserved regulatory role in multi-system inflammatory responses [32]-[34].

Some findings indicate that the dynamic expression of lncRNA OIP5-AS1 under pathological stimulation functionally couples with EMT pathway activation, jointly participating in vascular diseases, inflammatory disorders, and malignancies [35] [36].

3. The Endothelial Cell Regulatory Network of the lncRNA OIP5-AS1/miRNA Axis

3.1. lncRNA OIP5-AS1 Functions as a ceRNA to Modulate Endothelial Cell Function via Mirna Sponging

Accumulating evidence indicates that lncRNA OIP5-AS1 does not function in isolation but acts as a ceRNA. It specifically sponges various miRNAs via sequence complementarity, thereby relieving miRNA-mediated repression of downstream target genes and establishing a multi-layered regulatory network within endothelial cells [29] [37]. Notably, lncRNA OIP5-AS1 is primarily localized in the cytoplasm—

a hallmark of ceRNAs—where it binds to multiple miRNAs through complementary sequences, attenuating miRNA-induced mRNA degradation or translational inhibition. In endothelial cells, lncRNA OIP5-AS1 has been shown to interact with a range of miRNAs associated with endothelial function, including miR-126, miR-143/145, miR-195-5p, miR-204, and miR-320a, thereby modulating cell survival, oxidative stress responses, inflammation, and vascular remodeling [22] [28] [38] [39].

In an ox-LDL-induced endothelial injury model, lncRNA OIP5-AS1 expression is significantly upregulated. Mechanistically, lncRNA OIP5-AS1 functions as a sponge for miR-320a, reducing its bioavailability and thus de-repressing pro-inflammatory or pro-apoptotic target genes such as LOX1. This cascade exacerbates endothelial inflammatory activation and dysfunction [22] [31]. In the context of aortic dissection, lncRNA OIP5-AS1 has been found to aggravate aortic wall injury by sponging miR-143-3p and upregulating TUB [28]. Furthermore, under pathological conditions such as diabetes, the AMPK-p53 pathway regulates the expression of miR-143/145, thereby impacting endothelial function [39]. Collectively, these findings suggest that lncRNA OIP5-AS1 serves as a critical post-transcriptional regulatory hub in endothelial cells, playing a dual role in maintaining vascular homeostasis and contributing to disease pathogenesis.

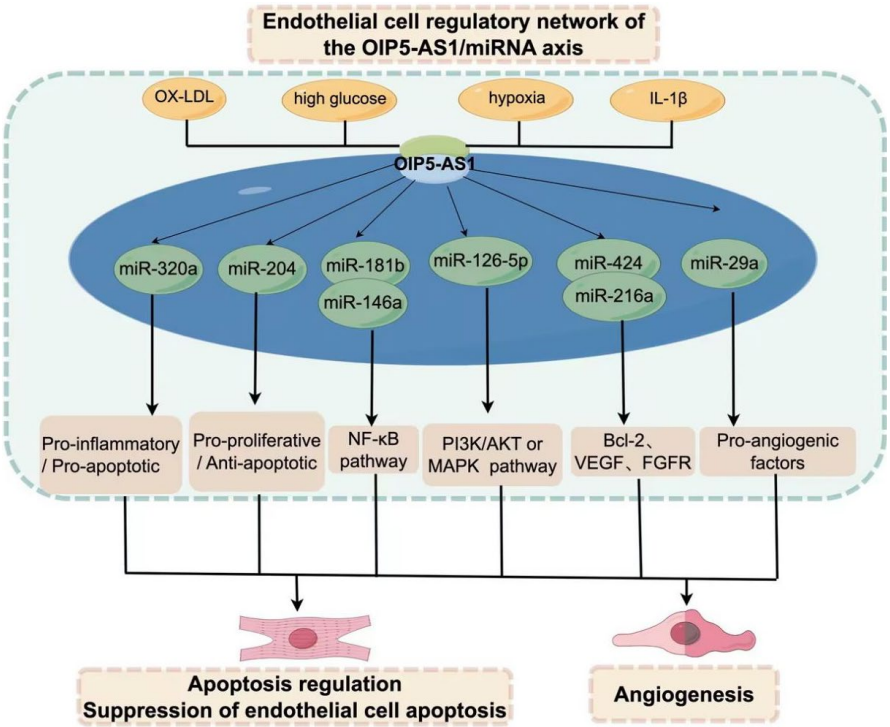
3.2. lncRNA OIP5-AS1/miRNA Axis-Mediated Endothelial Inflammation, Apoptosis, and Angiogenesis

A notable complexity in the lncRNA OIP5-AS1 literature is its seemingly contradictory roles across different pathological contexts. In ox-LDL-induced endothelial injury and aortic dissection models, lncRNA OIP5-AS1 is upregulated and acts as a pro-inflammatory, pro-apoptotic factor that exacerbates vascular damage [29] [30] [39]. Conversely, in diabetic retinopathy, myocardial ischemia-reperfusion injury, and cerebral ischemia-reperfusion models, lncRNA OIP5-AS1 is downregulated and functions as a protective factor, with its reduced expression correlating with disease progression [22] [40]. This apparent paradox can be reconciled by recognizing that the functional outcome of lncRNA OIP5-AS1 modulation is highly dependent on cell type and disease context.

In the early stages of atherosclerosis, the lncRNA OIP5-AS1/miRNA axis plays a critical role by precisely regulating the inflammatory response of endothelial cells. Studies have shown that lncRNA OIP5-AS1 expression is significantly upregulated in ox-LDL-stimulated HUVECs [31]. It may regulate the NF-κB signaling pathway and modulate the expression of adhesion molecules including VCAM-1 and ICAM-1 via targeting specific miRNAs, participating in monocyte adhesion and the endothelial inflammatory cascade [40]. Meanwhile, evidence indicates that miR-126-5p inhibits endothelial cell apoptosis and attenuates atherosclerosis progression through the NF-κB/PI3K/AKT/mTOR signaling pathway [41]. However, whether lncRNA OIP5-AS1 directly regulates this pathway by sponging miR-126-5p requires further validation. Clinical studies indicate that lncRNA OIP5-AS1 is significantly downregulated in the serum of patients with diabetic retinopathy and myocardial ischemia-reperfusion injury. This reduced expression correlates with disease progression, as

lncRNA OIP5-AS1 acts as a protective factor by sponging specific microRNAs such as miR-181a-5p to regulate endothelial cell function and mitigate tissue damage [42].

Furthermore, the lncRNA OIP5-AS1/miRNA regulatory axis is critically involved in endothelial cell apoptosis, tube formation, and neovascularization, thereby playing a pivotal role in the pathogenesis of microvascular diseases, such as ischemic vascular disorders. In the context of cerebral ischemia-reperfusion injury, Zhu found that lncRNA OIP5-AS1 might interact with the TAB2 signaling pathway, mitigating neuronal apoptosis and mitochondrial damage, although the specific miRNA sponging mechanisms in this setting require further elucidation [43]. In another set of experiments, Chen established a cerebral ischemia-reperfusion injury model, and demonstrated that lncRNA OIP5-AS1 can adsorb miR-186-5p through a sponge-like structure, thereby upregulating CTRP3 expression and alleviating neuronal apoptosis and inflammatory and oxidative stress responses [44]. In addition, miR-29a has been shown to possess anti-angiogenic activity in retinal endothelial cells. It can inhibit the proliferation, migration and lumen formation of endothelial cells by regulating PDGF-C and extracellular matrix-related genes [45]. However, whether lncRNA OIP5-AS1 participates in retinal disorders by regulating



OIP5-AS1 is modulated by pathological stimuli including OX-LDL, high glucose, hypoxia, and IL-1β in endothelial cells. As a competing endogenous RNA, OIP5-AS1 sponges multiple miRNAs (miR-320a, miR-204, miR-181b, miR-146a, miR-126-5p, miR-424, miR-216a, miR-29a), thereby regulating downstream pathways (NF-κB, PI3K/AKT/MAPK) and key factors (Bcl-2, VEGF, FGFR). This axis controls endothelial cell apoptosis and angiogenesis under pathological conditions.

Figure 1. Endothelial cell regulatory network of the OIP5-AS1/miRNA axis.

miR-29a still requires further research. In conclusion, the lncRNA OIP5-AS1/miRNA axis is a potential key regulatory network that maintains endothelial homeostasis and regulates pathological vascular remodeling (**Figure 1**).

4. The Active Components and Multi-Target Action Characteristics of the Traditional Chinese Medicine Formula TGD

4.1. The Main Chemical Components and Effects of TGD

TGD is a classic Chinese medicine (TCM) formula. Its core active ingredients are derived from its sovereign herbs, Tianma and Gouteng. Gastrodin is an organic compound extracted from the dried tubers of Gastrodia elata Blume, a species in the Orchidaceae family [46]-[48]. Its chemical formula is $C_{13}H_{18}O_7$ [49]. Gastrodin exerts a wide spectrum of neuropharmacological activities [50]. Studies have shown that gastrodin can exert neuroprotective effects in multiple nerve injury models by inhibiting neuronal apoptosis and attenuating oxidative stress injury, thereby reducing neuronal cell death [49] [50]. In addition, its sedative and hypnotic effects have been validated in both experimental and clinical studies [51]. Based on the above mechanism, TGD and its constituent herbs are widely used clinically for the treatment of neurasthenia, vertigo, vascular headache, and other related disorders [52]. In the field of cardiovascular diseases, gastrodin also exhibits lipid-lowering and anti-inflammatory properties [46] [53]. Evidence indicates that it may participate in the regulation of lipid metabolism by modulating the low-density lipoprotein receptor and proprotein convertase subtilisin/kexin type 9 signaling pathways, yet its precise molecular mechanism remains to be further elucidated [47]. Besides gastrodin, Tianma also contains various active components, such as N-(4-hydroxybenzyl) adenine (T1-11) and parishins A and B. These components act synergistically to improve learning and memory impairments, and the underlying mechanism may be associated with the inhibition of oxidative stress and the regulation of the SH2B1-Akt signaling pathway [54] [55].

Gouteng refers to the hooked stems of Uncaria rhynchophylla, a plant belonging to the Rubiaceae family. Its principal active constituents are rhynchophylline and isorhynchophylline [56]. As isomers, both compounds share the same molecular formula $C_{22}H_{28}N_2O_4$ [57]. Rhynchophylline can inhibit peripheral vasoconstriction and reduce vascular resistance, thereby exerting an antihypertensive effect. Meanwhile, it also possesses antiplatelet aggregation and antithrombotic activities, leading to its wide clinical application in the treatment of hypertension. In the field of neurological disorders, rhynchophylline also exhibits neuroprotective effects. Studies have demonstrated that rhynchophylline can alleviate early brain injury by attenuating inflammatory responses and apoptosis in the hippocampus following subarachnoid hemorrhage [58]. In DAT mouse models, rhynchophylline ameliorates hyperactive behavior and cognitive flexibility deficits by suppressing inflammatory reactions [59]. Furthermore, accumulating evidence has verified that rhynchophylline exerts antioxidant and anti-inflammatory ef-

fects in both in vitro and *in vivo* models of ischemic neuronal injury [60]. Accordingly, rhynchophylline is regarded as a promising therapeutic agent for ischemic stroke, and its underlying mechanisms may be associated with the improvement of synaptic plasticity and sensorimotor function [60].

4.2. Evidence for the Regulation of lncRNA Expression by TCM Formulas

Accumulating evidence indicates that TCM compound prescriptions can significantly modulate the expression profiles of lncRNAs, thereby exerting regulatory effects in the pathological processes of various diseases [61]. Tongmai Zhuyu Decoction has been shown to upregulate the expression of lincRNA-Cox2 in macrophages while inhibiting the release of inflammatory factors including Cxcl10, Ccl3, and Ccl4, thereby alleviating inflammatory responses in carotid atherosclerosis [62]. In the field of neurodegenerative diseases, differentially expressed lncRNAs associated with Danggui Shaoyao San are mainly involved in multiple pathological processes of Alzheimer's disease, including amyloid precursor protein processing, neuronal migration, and synaptic transmission [63]. Furthermore, a study using aging model mice demonstrated via microarray analysis that the aging process induced significant alterations in the expression of 138 lncRNAs, 128 mRNAs, and 7 miRNAs. In contrast, treatment with Dangshen reversed the dysregulated expression of 282 lncRNAs, 283 mRNAs, and 19 miRNAs, suggesting that Codonopsis pilosula possesses the potential to regulate ncRNA networks [64]. In addition, TM-2, an active component derived from Gastrodiae Rhizoma, can improve cognitive function by modulating hippocampal neurogenesis and the SH2B1-Akt signaling pathway, and its mechanism may be related to the epigenetic regulation of ncRNA expression [55]. Recent studies have shown that TCM with multi-target properties has emerged as a potential modulator of various ncRNAs to overcome cancer treatment resistance, although current clinical research is still in the preliminary exploration stage and lacks high-quality, large-scale, prospective randomized controlled trials [65]. However, these studies have provided new molecular evidence for further elucidating the multi-target and multi-level pharmacological mechanisms of traditional Chinese medicine compound prescriptions and single herbs.

4.3. Evidence Categories for the Link between TGD/Gastrodin and the lncRNA OIP5-AS1/miRNA Axis

Gastrodin has been shown to regulate the Wnt/β-catenin signaling pathway across multiple experimental models, covering neuroprotection, anti-inflammation, neurogenesis, and cognitive improvement. In cerebral ischemia models, gastrodin restores the activity of the Wnt/β-catenin pathway, thereby exerting neuroprotection and promoting neurogenesis [65]. Moreover, in chronic stress-induced depression models, gastrodin directly activates the Wnt/β-catenin pathway, promotes the proliferation of neural stem/progenitor cells and neuronal differentiation, enhances adult hippocampal neurogenesis, and consequently improves

stress resilience and reduces depression risk [66]. Concurrently, accumulating evidence indicates that lncRNA OIP5-AS1 is aberrantly upregulated in rheumatoid arthritis, gastric cancer, and pancreatic cancer, and crosstalks with the Wnt/β-catenin pathway via distinct molecular mechanisms [67]-[69]. This suggests that the Wnt/β-catenin pathway serves as a key downstream mediator of lncRNA OIP5-AS1 function, indicating a potential signaling crosstalk and regulatory association with gastrodin. Although there may be a certain correlation between them, unfortunately, there is currently no direct experimental evidence exists demonstrating that gastrodin or TGD specifically regulates lncRNA OIP5-AS1 expression or function.

TGD may exert modulatory effects on lncRNA OIP5-AS1 function through analogous mechanisms, a possibility that has been explicitly corroborated in several other traditional Chinese medicine formulations. For instance, Tongmai Zhuyu Decoction has been demonstrated to modulate the expression profiles of long non-coding RNAs, implying that TGD may similarly influence lncRNA OIP5-AS1 function via comparable pathways [60]. Additionally, Xiongshao Capsule, Sijunzi Decoction, and Angelica sinensis polysaccharide have each been reported to exert their effects through the lncRNA OIP5-AS1/miRNA axis [13]-[15]. Nevertheless, they are best regarded as hypothesis-generating observations that warrant further experimental validation, rather than confirmatory conclusions.

In summary, while the hypothesis that TGD may modulate endothelial function through the lncRNA OIP5-AS1/miRNA axis is scientifically plausible and mechanistically grounded, the current evidence is indirect and preliminary. Future studies employing gene manipulation strategies such as lncRNA OIP5-AS1 knockout or overexpression models combined with gastrodin treatment, and they are warranted to further verify their regulatory relationship and functional significance in vascular disorders.

5. Research Prospects and Future Directions

In conclusion, TGD, as a classic Chinese herbal formula, exhibits multi-target and multi-level pharmacological properties that are highly consistent with the non-coding RNA regulatory network in modern molecular biology [10] [59]. The core active components such as gastrodin have been proven to have clear anti-inflammatory, antioxidant, and endothelial protection effects, while the key functions of the lncRNA OIP5-AS1/miRNA axis in maintaining endothelial homeostasis, regulating inflammatory responses, and vascular remodeling have become increasingly clear [29] [43]. However, current research on the direct interaction between TGD and the lncRNA OIP5-AS1/miRNA axis is still in the initial exploration stage, and the following key scientific questions remain to be addressed urgently.

5.1. The Molecular Evidence for the Direct Interaction of Gastrodin with the lncRNA OIP5-AS1/miRNA Axis Is Lacking

Although some studies have suggested that gastrodin and lncRNA OIP5-AS1 may

form functional crossover through common signaling pathways such as Wnt/β-catenin [70] there is currently no direct experimental evidence indicating that gastrodin can specifically regulate the expression of lncRNA OIP5-AS1 or affect its ceRNA function. Future research should utilize gene expression intervention experiments, such as constructing lncRNA OIP5-AS1 knockout or overexpression models in endothelial cells, and combined with gastrodin treatment. Through techniques such as RNA sequencing, dual luciferase reporter assays, and RNA immunoprecipitation, a systematic analysis of the regulatory effects of gastrodin on the lncRNA OIP5-AS1/miRNA axis and its downstream target genes can be conducted.

5.2. Construction and Application of an Endothelial Cell-Specific lncRNA OIP5-AS1 Function-Deficient Model

lncRNA OIP5-AS1 exhibits tissue-specific expression in endothelial cells [22]. However, current studies mostly rely on in vitro cell lines or non-specific knockdown models, making it difficult to accurately reflect its true function in the *in vivo* endothelial system. In the future, it is necessary to combine conditional gene knockout mouse models to construct endothelial cell-specific lncRNA OIP5-AS1 knockout strains. Combined with the administration of TGD, we will conduct in-depth research on the pathological and physiological significance of this axis in the *in vivo* environment in vascular disease models such as atherosclerosis, ischemic stroke, and diabetic retinopathy.

5.3. Evaluation and Validation of Clinical Translational Potential

The current research on the regulation of ncRNAs by TGD mainly focuses on the cellular and animal levels, and lacks high-quality and prospective clinical studies for verification. In the future, case-control studies based on clinical samples should be conducted to detect the expression levels of OIP5-AS1 and related miRNAs in the serum or vascular tissues of patients with cerebrovascular diseases, and to analyze their correlation with the clinical efficacy of TGD. At the same time, by combining multi-omics technologies, such as lncRNA sequencing and single-cell transcriptomics, key non-coding RNA molecules regulated by TGD should be screened to provide biomarker evidence for the precise application of TCM compound prescriptions.

5.4. A Systematic Research Strategy for Multi-Target TCM in Regulating Non-Coding RNA Networks

TGD, as a multi-component compound, has active ingredients such as gastrodin, rhynchophylline, and isorhynchophylline that may jointly affect the ncRNA network through synergistic or antagonistic effects. In the future, it is necessary to integrate systems pharmacology, network pharmacology, and experimental verification strategies to construct a "molecule of TCM-miRNA-lncRNA-target gene" multi-level regulatory network, and reveal the molecular basis of the "multi-target-non-coding RNA" collaborative regulation of endothelial function by TGD.

In addition, with the development of nano-delivery systems and targeted regulation technologies, combining the active ingredients of TCM with lncRNA-targeted intervention strategies is expected to provide new combined solutions for the endothelial protection treatment of cerebrovascular diseases.

6. Conclusion

This review systematically examines the current evidence regarding the potential of TGD, its core component gastrodin, to protect endothelial cells through the lncRNA OIP5-AS1/miRNA regulatory axis. The main findings are as follow. First, lncRNA OIP5-AS1 is a structurally versatile ceRNA that plays context-dependent roles in endothelial inflammation, apoptosis, and angiogenesis, with its functional outcome, be it protective or detrimental, contingent upon cell type and disease context. Second, TGD and its active components such as gastrodin, rhynchophylline, and isorhynchophylline exhibit well-documented anti-inflammatory, antioxidant, and vascular protective effects, and several other TCM formulas have been shown to regulate lncRNA OIP5-AS1 expression. Third, and most critically, direct molecular evidence linking TGD or gastrodin to specific regulation of lncRNAOIP5-AS1 is currently absent; the proposed connection rests on indirect pathway-level inferences and analogies from other formulas.

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Author Contributions

Diwen Shou was responsible for the overall planning and supervision of the research theme. Xutong Zhu and Shiqi Chen were the primary writer, responsible for drafting the manuscript and contributed to the critical revision and polishing of the article. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Abbreviations

TGD	Tianma Gouteng Decoction
lncRNA	Long Non-Coding RNA
ceRNA	Competing Endogenous RNA
ox-LDL	Oxidized Low-Density Lipoprotein
HUVECs	Human Umbilical Vein Endothelial Cells
EMT	Epithelial-Mesenchymal Transition
TCM	Traditional Chinese Medicine
LPS	Lipopolysaccharide