Review Article

Plant-Derived Products for Treatment of Vascular Intima Hyperplasia Selectively Inhibit Vascular Smooth Muscle Cell Functions

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Natural products are used widely for preventing intimal hyperplasia (IH), a common cardiovascular disease. Four different cells initiate and progress IH, namely, vascular smooth muscle, adventitial and endothelial cells, and circulation or bone marrow-derived cells. Vascular smooth muscle cells (VSMCs) play a critical role in initiation and development of intimal thickening and formation of neointimal hyperplasia. In this review, we describe the different originating cells involved in vascular IH and emphasize the effect of different natural products on inhibiting abnormal cellular functions, such as VSMC proliferation and migration. We further present a classification for the different natural products like phenols, flavonoids, terpenes, and alkaloids that suppress VSMC growth. Abnormal VSMC physiology involves disturbance in MAPKs, PI3K/AKT, JAK-STAT, FAK, and NF-κB signal pathways. Most of the natural isolate studies have revealed G1/S phase of cell cycle arrest, decreased ROS production, induced cell apoptosis, restrained migration, and downregulated collagen deposition. It is necessary to screen optimal drugs from natural sources that preferentially inhibit VSMC rather than vascular endothelial cell growth to prevent early IH, restenosis following graft implantation, and atherosclerotic diseases.

1. Introduction

Intimal hyperplasia (IH) is a fibroproliferative disorder observed in vascular pathogenesis particularly in vessel anastomotic stenosis, atherosclerosis, blockage of vessel grafts, angioplasty, and in-stent restenosis [1]. IH is characterized by enhanced cell migration, proliferation, and differentiation that cause narrowing of the tunica intima. Several cells are associated with initiation and progression of IH, namely, vascular smooth muscle cells (VSMCs) [2], vascular adventitial cells [3], vascular endothelial cells (VEC) [4], and circulating bone marrow-derived cells [5]. These cells have different origins but may contribute to IH formation. For example, endothelial cells may undergo endothelial-tomesenchymal transition (EndMT) acquiring a fibroproliferative mesenchymal phenotype whereas adventitia-derived stem cells may migrate to the intimal lesion site and differentiate into fibroblasts. VSMCs play a critical role in the initiation and development of intimal thickening and formation of neointimal hyperplasia [6, 7].

Many herbal medicines sourced from plants or foods have been used to prevent cardiovascular disease over the millennia. For example, green tea contains various flavonoids that have antioxidative [8, 9], anti-inflammatory
model. Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a typical polyphenol extracted from red wine, has been proven to inhibit proliferation of VSMCs in vitro [15]. Many natural compounds have been reported to be active and to have potential utility as clinical medicines. Tanshinone is an isolate from Salvia miltiorrhiza that has been used against cardiovascular disease in China [16]. Therefore, many active compounds with cosmopolitan distribution are being used as herbal medicines or foods, giving hope for screening for potential therapeutic agents against IH (Figure 1).

Recent clinical studies have shown that rapamycin A, an VSMC inhibitor, prevents development of IH-induced vascular endothelial dysfunction [17]. This nonspecific cytotoxicity leads to stenosis and eventually to failure of vascular reconstruction after injury. Therefore, the ideal drug to prevent restenosis or IH is one that inhibits VSMC proliferation selectively while having minimal inhibitory effect on VEC proliferation.

2. Diverse Cells Involved in Vascular IH

As stated earlier, four different cell types are involved in the initiation and progression of IH. These are VSMCs, vascular adventitial cells, VECs, and circulating bone marrow-derived cells (Figure 2). VSMCs play a critical role in the initiation of intimal thickening and the formation of neointimal hyperplasia. Physiologically VSMCs exist in two phenotypes, i.e., differentiated cells and proliferating cells, which are responsible for maintaining the homeostasis and function of vascular vessels [2, 6]. Stimulation by certain growth and inflammatory factors, such as platelet-derived growth factor (PDGF) are used for inducing abnormal VMSCs to attenuate IH-induced proliferation of VSMCs. For the in vitro experiments, inflammatory cytokines like TNF-α or some growth factors such as platelet-derived growth factor (PDGF) are used for inducing abnormal proliferation and migration of VSMCs. For the in vivo experiments, IH is usually induced using the vascular endothelial denudation model or carotid artery ligation injury.

Dietary supplements and traditional herbal medicines are complementary medication approaches used in every society and are widely used for preventing IH in Asia and in other developed countries [26]. Many herbal drugs and foods have been verified as suppressing abnormal VSMC growth and inhibiting intima formation. The positive effects of the herbal medicines and plants depend on their active natural compounds including phenols, flavonoids, terpenes, and alkaloids. These natural products are involved in different signaling pathways that regulate abnormal VMSCs to attenuate IH.

3. Antiproliferation, Migration, and Cellular Functions of Abnormal VMSCs as a Target to Decrease Intimal Hyperplasia

VSMCs in the normal vascular tunica media express a range of smooth muscle cell markers including smooth muscle cell myosin heavy chain (MYH11), 22-kDa SMC lineage-restricted protein (SM22α/β), alpha smooth muscle actin (ACTA2), and smoothelin. VSMCs in vitro and in atherosclerosis undergo phenotypic switching with reduced expression of these markers, while increasing capacity for cell proliferation, migration, and secretion of various ECM proteins and cytokines. These phenotypic switches have long been considered of fundamental significance in IH progression.

Most studies investigating inhibition of VSMCs adopt drugs like rapamycin, sirolimus, or tacrolimus to induce VSMC apoptosis and cell cycle arrest at GI/S phase, suppress ROS production, inhibit VSMC migration, and downregulate collagen deposition. These approaches do not recover the mature VSMC immunophenotypes, but they do decrease neointimal formation and prevent stenosis following vascular injury. To investigate the antcellular function of drugs on VSMCs many models have been established in vitro and in vivo. For the in vitro experiments, inflammatory cytokines like TNF-α or some growth factors such as platelet-derived growth factor (PDGF) are used for inducing abnormal proliferation and migration of VSMCs. For the in vivo experiments, IH is usually induced using the vascular endothelial denudation model or carotid artery ligation injury.

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4. Typical Signal Pathways Involved in Growth and Physiology of VMSCs in IH Disease

The six signaling pathways involved in most drug inhibitory VSMC studies (Figure 3) are mitogen-activated protein
Figure 1: Graphic abstract for different natural compounds for inhibiting vascular smooth muscle cells proliferation and migration.

Figure 2: Four different cell origins contribute to blood vessel stenosis.
kinases/extracellular signal-regulated kinase (MAPKs/ERK), phosphatidylinositol 3-kinases/Akt (PI3K/Akt), Janus kinase-signal transducer and activator of transcription (JAK-STAT), focal adhesion kinase (FAK), and nuclear factor kappa-light-chain-enhancer of activated B (NF-κB). MAPKs are involved in cell proliferation, differentiation, mitosis, cell survival, and apoptosis [27]. Three major families of MAPKs are extracellular signal-regulated kinase (ERK) [28], p38 kinase, and c-Jun N terminal kinase (JNK). These contribute to the two important signaling pathways, Ras/ERK-MAPK and JNK/p38-MAPK, which are involved in regulating VSMCs [29]. In antiproliferation studies of VSMCs, PI3K/Akt signaling pathway includes many key factors such as GSK3β, p21, and p27, which all inhibit cyclins and CDKs thereby interfering with cell cycle processes. GSK3β is one of the critical downstream molecules of the Akt signaling pathway involved in cell proliferation, metabolism, growth, and survival. It is reported that cyclin D is regulated by GSK3β [30] and that activation of GSK3β leads to exportation into cytoplasm for proteolysis, thus downregulating cyclin D1 expression [31]. The JAK-STAT signaling pathway transmits information from extracellular chemical signals to the nucleus resulting in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, and apoptosis [32]. The downstream proteins in this pathway include cyclin D, p21, Bcl-2, and c-Myc, which are all directly involved in growth, apoptosis, and cell cycle progression in VSMC studies [33]. FAK is involved in cellular adhesion and migration [34]. FAK is typically located at structures known as focal adhesions, which are multiprotein structures including actin, filamin, and vinculin which link the ECM to the cytoplasmic cytoskeleton [35–37]. In addition, FAK interacts with PI3K and p53 [38, 39] and with the PI3K/Akt and MAPKs signaling pathways that are involved in cell cycle regulation. NF-κB controls many genes involved with inflammation which are crucial to progression of diseases including arthritis, asthma, and atherosclerosis [40, 41]. Inflammation also mediates abnormal movement and growth of VSMCs, while suppressing inflammation could attenuate neointimal hyperplasia significantly [42–45]. Therefore, different signaling pathways are involved in VSMC inhibition, which provides preferential protein targets for future drug screening.

### 5. Different Natural Compounds Being Used for Preventing Neointimal Formation and Focus on VSMCs

#### 5.1. Flavonoids Regulate Cell Cycle and Functions Inhibiting VSMCs Proliferation and Migration. Flavonoids are distributed throughout the plant kingdom and fulfill a diverse range of biological and pharmacological effects such as anti-inflammatory [46], antioxidant [47], antibacterial [48], anti-tumor [49], and antidiarrheal activities [50]. For treatment of cardiovascular disease, flavonoid studies have focused on reducing hypertension, risk of atherosclerosis, oxidative stress, and related signaling pathways in blood vessel cells, as well as modifying vascular inflammatory mechanisms [51, 52]. In this review, we described the chemical structure, category, source, and mechanism of action of some typical flavonoids that suppress VSMC function and inhibit IH (Table 1).

Nobiletin is widely distributed in citrus fruits and has been reported to inhibit VSMC proliferation and migration in vitro [44]. In addition, carotid balloon injured rats given nobiletin 25 mg/kg/day by gavage had significantly decreased neointimal hyperplasia via regulation of the ROS derived NF-κB pathway and decreased serum TNF-α and IL-6 concentrations [44]. Cyanidin-3-O-glucoside, an anthocyanin flavonoid, inhibited TNF-α-induced NoxA1 (a type of NADPH oxidase) and downregulated expression of both TNF-α and NoxA1 at transcriptional and translational levels [53]. (2S)-Naringenin, a typical flavonoid isolated from *Typha angustata*, inhibited PDGF-BB-induced proliferation in VSMCs.
Table 1: The structure, cells, category, source, and mechanism of typical flavonoid compounds on inhibiting VSMCs proliferation and migration.

| Compound name        | Structure | Cells and animals | Category | Sources               | Mechanism                                                                 |
|----------------------|-----------|-------------------|----------|-----------------------|---------------------------------------------------------------------------|
| (2S)-naringenin      | ![Structure](image1) | rASMCs            | Flavonoid | *Typha angustata*     | G0/G1 ↓; cyclins D1 ↓; cyclins E ↓; CDK2/4 ↓; PCNA ↓; phosph of rb protein ↓ |
| Catechins            | ![Structure](image2) | rASMCs and rat balloon injury (Flavanols) | Green tea | Green tea | TIMP-2 ↑; in vivo: TIMP-2 ↑ |
| Icariin              | ![Structure](image3) | hASMCs            | Flavonoid (Prenylated flavonol glycoside) | *Epimedium brevicornum* | pERK1/2 ↓; G1/S ↓; PCNA ↓ |
| Morelloflavone       | ![Structure](image4) | mVSMCs and mouse artery injury (Biflavonoid) | *Garcinia dulcis* | | FAK ↓; Src ↓; ERK ↓; RhoA ↓ |
| Puerarin             | ![Structure](image5) | rASMCs and rat balloon injury (Isoflavone) | *Radix puerariae* | | ROS ↓; Nox ↓; P65 ↓; Rac1 ↓; p47phox ↓; p67phox ↓ |
| Kaempferol           | ![Structure](image6) | hpASMCs           | Flavonoid | Widely (grapefruit, Ginkgo biloba) | miR-21 ↑; ROCK4/5/7 ↓ |
| Nobiletin            | ![Structure](image7) | rASMCs and rat balloon injury (Flavonoid) | Widely (citrus fruits) | | ROS ↓; pERK1/2 ↓; NF-κB p65 ↓; in vivo: TNF-α ↓; IL-6 ↓ |
| Alpinetin            | ![Structure](image8) | rASMCs            | Flavonoid | Widely (Alpinia katsumadai, Amomum subulatum, and etc.) | LDH ↓; NO ↓ |
| Cyanidin-3-O-glucoside | ![Structure](image9) | mASMCs            | Flavonoid | *Hibiscus sabdariffa* | ROS ↓; NoxA1 ↓; pSTAT3 ↓ |
| Hesperetin           | ![Structure](image10) | rpASMCs           | Flavonoid | Widely (lemons and sweet oranges) | Block G1/S; cyclin D1 ↓; cyclin E ↓; CDK2/4 ↓; p38 ↓; p27 ↑; regulate AKT/GSK3β signaling pathway |
| Pinocembrin          | ![Structure](image11) | rAMSCs and rat aortic rings injury (Flavonoid) | *Propolis* | | ERK1/2 ↓; MLC2 ↓; ATIR ↓ |
| Glyceollins          | ![Structure](image12) | hASMCs            | Isoflavone | *Soybean* | | Arrest G1/S phase; CDK2 ↓; cyclin D1 ↓; p27kip1 ↓; p53 ↓; ROS ↓; pPDGFr-β ↓; phospholipase C↓; Akt ↓; ERK1/2 ↓ |
downregulating CDK2, cyclinD1, pPDGFr-PDGF-BB-induced hVSMC proliferation and migration by [59]. Glyceollins, which are isoflavonoids, inhibit way through upregulating p27 expression while suppressing pASMC proliferation via the AKT/GSK3 [57]. Hesperetin, a flavonoid, inhibits PDGFa-BB-induced and inhibits production of NO in TNF-protective effects on VSMCs as it decreases LDH leakage of ERK1/2 [55]. Puerarin, isolated from Radix puerariae, regulates VSMC mitosis and DNA synthesis, terpenes [54]. Hu and colleagues found that icariin reduced the amount of ox-LDL-induced proliferation of VSMCs through suppression of PCNA expression and inactivation of ERK1/2 [55]. Puerarin, isolated from Radix puerariae, exerts inhibitory effects on high glucose-induced VSMC proliferation via interfering with PKCβ2/Rac1-dependent ROS pathways, thus resulting in attenuation of neointimal formation [56]. Alpinin is a well-known flavonoid isolated from a variety of plants such as Alpinia katsumadai, Amomum subulatum, and Scutellaria rivilars. It may have some protective effects on VSMCs as it decreases LDL leakage and inhibits production of NO in TNF-α-induced VSMC [57]. Hesperetin, a flavonoid, inhibits PDGFβ-BB-induced pASMC proliferation via the AKT/GSK3β signaling pathway through upregulating p27 expression while suppressing cyclin D1/E, CDK2/4 and p38 [58]. Pinocembrin reduces the increased ERK1/2 phosphorylation that occurs in response to angiotensin II in both rat aortic rings ex vivo and VSMCs in vitro [59]. Glyceollins, which are isoflavonoids, inhibit PDGFβ-BB-induced hVSMC proliferation and migration by downregulating CDK2, cyclin D1, pPDGF-Re-β, phospholipase Gp1, Akt, and ERK1/2 and inhibits ROS formation, while upregulating p27Kip1 and p53 expression levels [60]. Morelloflavone is a biflavonoid, which has been found to block injury-induced neointimal hyperplasia via inhibition of VSMC migration and downregulation of FAK, Src, ERK and RhoA expression [61]. Some studies have demonstrated that a natural flavonoid, kaempferol, may induce miR-21. This results in downregulation of ROCK4, 5, and 7, which are critical for cytoskeletal organization and cell motility, leading to decreased cell migration [62]. Finally, green tea is beneficial for health due to its antioxidant, anticarcinogenic, anti-inflammatory, and antiradiation effects [63–65]. A large number of flavonoids, especially flavan-3-ols ("catechins"), inhibit IH in a rat balloon injury model through upregulation of TIMP-2 expression to modulate MMP activity [66]. From the above review, flavonoids are an important candidate compound type for screening natural drugs capable of inhibiting VSMC growth.

5.2. Polyphenols as an Antioxidants Restrain VSMC Proliferation and Migration to Attenuate IH. Polyphenols are distributed widely in vegetables and plants, green tea, black tea, and red wine. Recent studies have shown that they possess antioxidant, anti-inflammatory, and cardioprotective effects [67–69]. Some typical polyphenols prevent IH by restraining VSMC function including proliferation, migration, and fibrosis (Table 2). Salvianolic acid B is a typical polyphenol that is usually isolated from Salvia miltiorrhiza. It markedly reduces neointimal thickness by inducing neointimal cell apoptosis through upregulating p53 expression levels [70]. In another study, salvianolic acid B protected hAECs and neointimal formation through inhibition of LDL oxidation by reducing ROS generation [71]. Magnesium lithospermat, a derivative of salvianolic acid B, prevented diabetic atherosclerosis via the Nrf2-ARE-NQO1 transcriptional pathway [72]. Magnolol (a phenol) is a powerful antioxidant that inhibited balloon injury-induced rabbit IH by downregulating MCP-1 expression [73]. In another work, magnolol inhibited VSMC migration via the cytoskeletal remodeling pathway through inhibition of β1-integrin expression, phosphorylation of FAK and MLCK, and activation of RhoA and Cdc42 [74]. Lithospermic acid, a polyphenol, arrested cell cycle progression at the G1 phase via downregulating expression of cyclin D1 and inhibiting ROS generation and ERK1/2 phosphorylation [75]. Moreover, lithospermic acid attenuated LPS-induced VSMC migration by inhibiting MMP-9 expression in a dose-dependent manner (25–100 μmol/L). Hispolon blocked balloon injury-induced neointimal hyperplasia via inhibition of VSMC proliferation. It also inhibited VSMC migration by lowering MMP-2/9 expression and increasing TIMP-1/2 expression through suppression of the FAK signaling pathway [76]. Lim and colleagues were of the view that obovatol blocked the cell cycle in G1 phase by downregulating expression of cyclins and CDKs, while selectively upregulating expression of p21Cip1, a well-known CDK inhibitor, both in vitro and in vivo [77].

Some studies have shown that curcumin (diarylheptanoid phenol) has potent antioxidant properties, which can be used for attenuating neointimal hyperplasia [78]. Curcumin has also been shown to inhibit PDGF-induced VSMC migration, proliferation, and collagen synthesis in a concentration-dependent manner [79], with a concentration range of 0.01 to 10 μmol/L inhibiting VSMC proliferation and migration. Curcumin-coated stents inhibited neointimal formation in the rabbit iliac artery stent model. Moreover, curcumin inhibited LPS-induced MMP-2 activity in rat VSMCs through Ras/MEK1/2 and NF-κB signaling [80].

Curcumin shows the ideal biological effects of inhibiting abnormal VSMC proliferation and migration without compromising VEC proliferation or delaying reendothelialization after blood vessel injury. Curcumin inhibited platelet adhesion to brain microvascular endothelial cells by decreasing expression of P-selectin, E-selectin, and GPIIb/GPIIIa in a concentration-dependent manner (30–240 μmol/L). Curcumin antagonized the detrimental effect of rapamycin on aortic endothelial cells in vitro, through upregulation of eNOS [81]. Hence, curcumin very selectively inhibited abnormal VSMC functions, such as PDGF-induced proliferation or migration, without impairing VECs. As a result, curcumin has been regarded as an ideal drug for attenuating atherosclerosis and restenosis. In summary, polyphenols exhibit beneficial and wide ranging biological effects relevant to prevention of IH. Polyphenols are worthy candidate compounds to be screened as natural drugs for inhibiting VSMCs.

5.3. Terpenes Suppress Abnormal VSMC Function against Neointimal Formation. Terpenes are proven cell cycle inhibitors for various cell types, especially tumor cells [82, 83]. Like similar compounds with active sites for regulating VSMC mitosis and DNA synthesis, terpenes lead cell proliferation and function arrest via cell cycle blockade or apoptosis induction (Table 3). Betulinic acid, a typical terpene, has been reported to inhibit growth and proliferation of VSMCs via arresting G1/S cell cycle in a dose-dependent manner [84]. A monoterpene, (S)-(−)-perillic
| Compound name          | Structure | Cells and animals                                      | Category | Sources                                                                 | Mechanism                                                                 |
|------------------------|-----------|-------------------------------------------------------|----------|------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Salvianolic acid B     |           | NeCs; HAECS and cholesterol-fed rabbits; rTASMCs and rats balloon injury | Polyphenol | Salvia miltiorrhiza                                                     | (1) p53 ↑; NeCs apoptosis, (2) ROS ↓; LDL oxidation ↓; lipid deposition ↓; (3) PCNA ↓; NQO1 ↓; via Nrf2-ARE-NQO1 pathway |
| Caffeic acid phenethyl ester (CAPE) |           | rASMCs                                                | Polyphenol | Honeybee propolis                                                      | Blocking G0/1 to S phase; pp38 ↑; HiF1α ↑; HO-1 ↑                             |
| Hispolon               |           | rTA-A10-VSMCs                                          | Polyphenol | Phellinus linteus                                                      | MMP2 ↓; MMP9 ↓; TIMP-1 ↑; TIMP-2 ↑; pFAK ↓; pERK1/2 ↓; PI3K/AKT ↓              |
| [6]-shogaol            |           | rASMCs                                                | Phenols   | Zingiber officinale                                                   | Inhibit DNA synthesis; activation of (Nrf2)/HO-1 pathway                   |
| Resveratrol            |           | ncTASMCs; mASMCs                                      | Polyphenol | Widely (grapes, blueberries, raspberries, and etc.)                     | c-Src ↓; Rac1 ↓; cdc42 ↓; IRS-1 ↓; MEKK1 ↓; MEKK4 ↓; p-Src; pFAK ↓; pAkt ↓; pERK1/2 ↓ |
| Lithospermic acid      |           | rTASMCs                                               | Polyphenol | Salvia miltiorrhiza                                                    | ROS ↓; pERK1/2 ↓; cyclin D1 ↓; arresting cell cycle progression at the G1 phase; MMP9 ↓ |
| Magnolol               |           | Cholesterol-fed rabbits; rVSMCs; rats balloon injury  | Polyphenol | Magnolia officinalis                                                  | (1) MCP-1 ↓; (2) Reduce collagen type I deposition; β1-integrin ↓; pFAK ↓; pMLC20 ↓; RhoA ↓; Cdc42 ↓ |
| Obovatol               |           | rASMCs; rats balloon injury                           | Biphenol  | Magnolia obovata                                                       | Blocks the cell cycle in G1 phase; CDKs ↓; p21cip1 ↓; pERK1/2 ↓; pAkt ↓; (2) P-selectin ↓; E-selectin ↓; GPlb/GPllla ↓; (3) MMP2 ↓; pRas ↓; MEKK1/2 ↓; NF-xB p65 ↓; (4) Curcumin protects aortic endothelial cells; eNOS ↓; caveolin-1 ↓ |
| Curcumin               |           | rTASMCs; rabbit artery injury; VECs; RAECs            | Phenols   | Curcuma longa                                                          |                                                                           |

acid, has been reported to decrease protein prenylation leading to DNA synthesis and inhibition of VSMCs [85]. A sesquiterpene lactone, parthenolide, arrested VSMC G0/G1 cell cycle via upregulating p21 and p27. It also increased IkBα expression and reduced Cox-2 expression in a time-dependent manner [86]. A special terpene, plumericin, arrested VSMCs in the G1/G0 phase of the cell cycle along with causing abrogated cyclin D1 expression, hindered [87]. pRb protein [87], and blockade of STAT3 signaling via S-glutathionylation. Paclitaxel, a diterpenoid, has been used as an anticancer drug for decades and has been shown to prevent neointimal formation in oral administration studies [88]. Moreover, paclitaxel arrested VSMC G1/S phase by upregulating p21 and p53 in vitro [89]. Epothilone D is a paclitaxel-like microtubule-stabilizing agent that was isolated originally from the myxobacterium Sorangium cellulosum. It inhibits neointimal hyperplasia through blockade of VSMC CDK2 and pRb [90]. β-Elemene protected VECs from injury induced by H2O2 in vitro via downregulating MDAR while upregulating T-AOC, SOD, GSH-Px, and CAT [91]. Meanwhile, β-elemene selectively inhibited VSMC proliferation/migration and inhibited neointimal formation in vivo following vascular injuries [91]. Recent studies have indicated that artemisinin effectively inhibited VSMC proliferation induced by TNF-α through apopotic induction of the caspase pathway and cell cycle arrest [92, 93]. It also significantly inhibited neointimal formation in rat balloon injured carotid arteries. Therefore, terpenes are also notable candidate compounds for screening natural drugs capable of inhibiting VSMCs.
Table 3: The structure, cells, category, source, and mechanism of terpenes on inhibiting VSMCs abnormal proliferation, migration, and functions.

| Compound name | Structure | Cells and animals | Category | Sources | Mechanism |
|---------------|-----------|------------------|----------|---------|-----------|
| Betulinic Acid | ![Structure](image1) | VSMCs | Terpene | Various plant sources widespread throughout the tropics | Inducing G1 Arrest and Apoptosis |
| Parthenolide | ![Structure](image2) | rVSMCs | Sesquiterpene lactone | Tanacetum parthenium | G0/G1 cell cycle arrest; p21 ↑; p27 ↑; IκB ↑; Cox-2 ↓ |
| Plumericin | ![Structure](image3) | rAVSMCs | Iridoid (Terpene) | Himatanthus succuuba | Block STAT3 signaling; arrest VSMCs in the G1/G0-phase; cyclin D1 ↓; pRb ↓ |
| Paclitaxel | ![Structure](image4) | Rat balloon injury; hCASMCs (CC-2583) and VSMCs (CC-2571); rTASMCs and VECs | Diterpenoid | Taxus cuspidata | (1) prevent neointimal formation via oral administration, (2) arrest G1/S phase; p21 ↑; p53 ↑ |
| Epothilone D | ![Structure](image5) | Rat ASMCs; carotid artery injury; hUVECs and VSMCs (A7r5); rat balloon injury | Diterpenoid | Sorangium cellulosum | CDK2 ↓; pRb ↓ |
| β-elemene | ![Structure](image6) | rVSMCs and rat balloon injury; rTASMCs | Terpene | Curcuma wenyujin | Antioxidant; Casp 3/7/9 ↓; Migration ↓ |
| Artemisinin | ![Structure](image7) | rVSMCs and rat balloon injury; rTASMCs | Sesquiterpene lactone | Artemisia annua | (1) arrest G0/G1 phase; cyclin D1/E ↓; CDK2/4 ↓; caspase 3/9 ↑; Bax ↑; Bcl-2 ↓, (2) PCNA ↓; caspase 3↑; Bax ↑; Bax/Bcl-2 ratio ↑ |
| (S)-(−)-Perillic acid | ![Structure](image8) | rASMCs | Monoterpene | Widely | Protein prenylation ↓ |

5.4. Alkaloids Exhibit Antiproliferation Biological Effect on VSMCs. Alkaloids are a group of naturally occurring chemical compounds that mostly contain basic nitrogen atoms. Alkaloids have diverse biological effects including those against tumors, hypertension, and pain. For vascular IH, some studies indicate that alkaloids hinder cell cycle progress, decrease ROS production, and inhibit VSMC migration (Table 4). A classic alkaloid, piperine, selectively inhibits VSMC proliferation with an IC50 of 11.8 μmol/L without influencing VEC growth [94]. Coptisine was isolated from Coptis chinensis and suppresses VSMC proliferation selectively at lower concentrations with a GI50 of 3.3 μmol/L (1.2 μg/mL) [95]. Vinpocetine, a potential derivative of vincamine, inhibits high glucose-induced proliferation of VSMCs by preventing ROS generation and affecting MAPK, PI3K/Akt, and NF-κB signaling, Wang, Wen, Peng, Li, Zhuang, Lu, Liu, Li, Li, and Xu [96]. Vinpocetine arrested G1/S phase of the cell cycle by downregulating cyclin D1 and pERK1/2. Alongside these effects, vinpocetine also inhibited VSMC migration and ROS production [97]. A quinazolinone alkaloid, halofuginone, selectively inhibited cell proliferation, ECM deposition, and type I collagen synthesis in VSMCs versus VECs, which attenuated injury-induced IH [98]. Carbazole or murrayafoline A inhibited PDGF-BB induced abnormal proliferation of VSMCs by downregulating cyclin D1/E, CDK2/4, and PCNA and phosphorylation of Rb [99].
Review of these recent studies on the effects of alkaloids provides hope for identification of useful drugs capable of inhibiting VSMC growth and preventing IH.

5.5. Other Promising Natural Compounds for Preventing Intima Hyperplasia. As shown in Table 5, emodin is a typical anthraquinone compound beneficial for prevention of atherosclerosis due to its effects against inflammation, proliferation, and migration and its ability to induce apoptosis in VSMCs [100]. Moreover, emodin arrested growth and induced apoptosis and autophagy via enhanced ROS production and upregulation of p53 expression [101]. Emodin inhibited VSMC proliferation induced by angiotensin II through downregulation of PCNA and c-myc expression [102]. Moreover, emodin showed anti-inflammatory effects by inhibiting Hcy-induced CRP generation, a key inflammatory molecule in atherogenesis in VSMCs [103]. Emodin has also been shown to inhibit TNF-α-induced hASMC proliferation via caspase signaling and a mitochondrial-dependent apoptotic pathway by downregulating Bcl-2 and upregulating Bax expression [104]. Additionally, emodin reduced TNF-α induced migration of VSMCs by suppressing NF-κB activation and MMP2/9 expression levels [105]. Our recent study demonstrated that emodin efficiently and concentration-dependently (0.05 to 5 μmol/L) inhibited hVSMC proliferation more than hVEC proliferation in vitro, with less influence on reendothelialization of VECs in rat carotid artery balloon injury [106].

Methyl-protodioscin is a steroidal saponin that has been reported to inhibit neointimal formation by restraining VSMC proliferation and migration through downregulation of ADAM15, FAK, ERK, PI3K, Akt, and MMP-2/9 expression levels [107]. Salvia miltiorrhiza has been used to prevent cardiovascular diseases in traditional Chinese medicine over the millennia. Tanshinone-IIA is a principal active component of Salvia miltiorrhiza that suppresses abnormal VSMC proliferation by cell cycle arrest at G0/G1 phase and inhibits phosphorylation of ERK1/2 and c-fos expression [108]. It has been reported that ajoene (1-50 μmol/L) interfered with progression of the G1 phase in the cell cycle and restrained VSMC proliferation via inhibiting protein prenylation [109]. Gastrodin influenced the S phase entry of VSMCs and stabilized p27KIP1 expression. It also inhibited VSMC proliferation and attenuated neointimal hyperplasia by suppressing phosphorylation of ERK1/2, p38 MAPK, Akt, and GSK3β [110]. Genipin has been reported to inhibit TNF-α-induced VSMC proliferation and migration in a dose-dependent manner by upregulating HO-1 expression, preventing ERK/MAPK and Akt phosphorylation, and additionally blocking generation of ROS [111]. Ginsenoside Rgl is one of the main active components of Panax ginseng and is said to arrest G1/S phase in VSMCs by interfering with GRKs, PKC, and N-ras while upregulating p21 expression [112]. Vascular IH is significantly decreased when carotid artery balloon injured rats are intraperitoneally injected with ginsenoside Rgl for 14 days [113]. Moreover, ginsenoside Rgl significantly inhibited TNF-α-induced hASMC proliferation dose-dependently through downregulating cyclin D1, inactivating ERK1/2 and PKB, and upregulating expression of p53, p21^WAF1/CIP1, and p27^KIP1 [114]. A coumarin called ostruthin is a major bioactive constituent of Peucedanum ostruthium and inhibited serum (10%)-induced VSMC proliferation in a dose-dependent manner [115].

Most foods contain various biologically active constituents that act to prevent and cure neointimal hyperplasia by inhibiting abnormal VSMC proliferation and migration. A well-known carotenoid, lycopene, is abundant in tomatoes and its products and has been reported to inhibit neointimal hyperplasia in a rabbit restenosis model. It does this by

| Compound name | Structure | Cells and animals | Category | Sources | Mechanism |
|---------------|-----------|------------------|----------|---------|-----------|
| Piperine      | ![Piperine Structure](image1) | rASMCs          | Alkaloid | *Piper nigrum* | Selectively inhibit VSMCs |
| Coptisine     | ![Coptisine Structure](image2) | rVSMCs          | Alkaloid | *Coptis chinensis* | Arrest G1/S phase |
| Vinpocetine   | ![Vinpocetine Structure](image3) | rVSMCs          | Alkaloid | *Quinazolinone* | (1) ROS ↓; apoptosis ↓; pAkt ↓; pJNK1/2 ↓; IκBα ↓; PCNA ↓; cyclin D ↓; Bcl-2 ↓; (2) Arrest G1/S phase; cyclin D1 ↓; p27^KIP1 ↑; inhibit migration; pERK1/2 ↓; ROS ↓ |
| Halofuginone  | ![Halofuginone Structure](image4) | bASMCs          | Alkaloid | *Dichroa febrifuga* | ECM synthesis and deposition ↓; Col I ↓ |
| Murrayafoline A | ![Murrayafoline A Structure](image5) | rASMCs          | Carbazole alkaloid | *Glycosmis stenocarpa* | Arrest G1/S phase; cyclin D1/E ↓; CDK2/4 ↓; PCNA ↓; pRb ↓ |
Table 5: The structure, cells, category, source, and mechanism of promising compounds on suppressing VSMCs.

| Compound name       | Structure | Cells and animals                  | Category       | Sources                                         | Mechanism                                                                 |
|---------------------|-----------|------------------------------------|----------------|------------------------------------------------|---------------------------------------------------------------------------|
| Bilirubin           |           | rVSMCs and mVSMCs; rat balloon injury | Ferrocenporphyrins | Heme                                           | Inhibit MAPK signaling pathway; CDK2 ↓; Cyclin A/D1/E ↓; pRb ↓; YY1 ↓; p38 ↓ |
| capsicin            |           | rASMCs                             | Capsaicinoids   | Chili peppers                                  | Inhibit DNA synthesis                                                     |
| Emodin              |           | hUVSMCs; rTASMCs; hASMCs; rat balloon injury | Anthraquinoine  | Rheum officinale                               | (1) Arrest cell cycle, induce apoptosis and autophagy; ROS ↑; p53 ↑; (2) PCNA ↓; c-myc ↓; (3) CRP ↓; ROS ↓; pERK1/2 ↓; p38 ↓; PPARy ↑; (4) Induce apoptosis; Bcl-2 ↓; Bax ↑; (5) MMP2/9 ↓; NF-κB activation ↓ |
| Rhein               |           | hASMCs                             | Anthraquinoine  | Rheum palmatum                                 | Col I/III ↓; Wnt4/Dvl-1/β-catenin ↓; miR-126 ↑                           |
| Ajoene              |           | rASMCs                             | Organosulphur compound | Allium sativum                                   | Inhibit protein prenylation and cholesterol biosynthesis                 |
| Gastrodin           |           | rASMCs, mice artery injury          | Glucoside       | Gastrodia elata Bl                             | Block S-phase; stabilised p27Kipl; PCNA ↓; pERK1/2 ↓; pp38 ↓; pAkt ↓; pGSKβ2 ↓ |
| Genipin             |           | rTASMCs                            | Aglycon         | Gardenia jasminoides                           | HO-1 ↓; pERK/MAPK ↓; pAkt ↓; ROS ↓                                      |
| Ginsenoside Rgl     |           | hASMCs; rat balloon injury          | Steroid glycosides | Panax ginseng                                   | (1) PCNA ↓; pERK2 ↓; c-fos ↓; MKP-1 ↓; (2) Arrest G1/S phase; GRKs ↓; PKC ↓; N-ras ↑; p21 ↑; (3) Cyclin D1 ↓; p53 ↑; p2lWAF/CHP1 ↑; p27KIP1 ↑; inactivate PKB and ERK1/2 |
| Ostruthin           |           | rTASMCs                            | Coumarins       | Peucedanum ostruthium                          | Inhibit DNA synthesis                                                     |
| Lycopene            |           | Rabbit artery injury                | Carotenoid      | Widely (tomatoes, red carrots,)                | TG ↓; TC ↓; LDL-C ↓; HDL-C ↑; SOD ↑; T-AOC ↑; MDA ↓; PCNA ↓; pERK1/2 ↓; Nox1 ↓; p23↑abot; HMG-CoA ↓; ABCA1 ↑ |
| Methyl Protodioscin |           | A7r5 VSMCs; rat balloon injury      | Steroidal saponin | Dioscorea colletti                             | Arrest G1/S phase; ADAM15 ↓; MMP2/9 ↓; FAK ↓; ERK ↓; PI3K ↓; Akt ↓     |
| Tanshinone IIA      |           | rASMCs; rat balloon injury          | Phenolic acids  | Salvia miltiorrhiza                            | Block cell cycle in G0/G1 phase; pERK1/2 ↓; c-fos ↓                    |
| Sulforaphane        |           | rASMCs; rat balloon injury          | Organosulfur compounds | Widely (cruciferous vegetables such as broccoli, Brussels sprouts, and cabbages) | p21 ↑; p53 ↓; CDK2 ↓; Cyclin E ↓; PCNA ↓ |
regulation of blood lipid concentrations and suppression of oxidative stress [116]. Sulforaphane, an organosulfur compound, mostly found in cruciferous vegetables significantly inhibited PDGF-BB-induced VSMC proliferation by upregulating p21 and p53 expression, while CDK2, cyclin E, and PCNA expression was suppressed [117].

6. Selective Inhibition of VSMCs versus VECs Shows Significant

Although many natural products inhibit VSMC function, most anti-smooth muscle proliferation drugs such as rapamycin (in-stent coating) also inhibit VEC proliferation and delay reendothelialization. This nonspecific cytotoxicity leads to restenosis and final graft or stent implantation failure. When screening for selective natural drugs that inhibit smooth muscle cell proliferation and migration, it is necessary to combine computer-aided design, bioinformatics, and a high-throughput screening platform. In this review, we selected certain drugs including chemosynthetic (idarubicin) and some natural (β-elemene, coptisine, halofuginone, piperine, and curcumin) compounds that possess specificity for suppressing proliferation of VSMCs over VECs. The chemical structure of the natural compounds has no typical similarity and cannot be analyzed using structural-activity relationships of molecular-protein binding sites. However, an online tool “Swiss Target Prediction” was used to predict potential targets of these compounds [118]. Most of the predicted targets of these drugs were membrane receptors, enzymes, kinases, proteases, or transporter proteins (Table 6). The analyses showed that microtubule-associated protein TAU (MAPT) is the most frequent protein target among them (Figure 4). This stabilizes microtubules and influences transportation of cellular secretory proteins. Moreover, MAPT has been reported to accelerate cancer cell growth [119], while its inactivation through gene knockdown suppressed cell proliferation [120]. Therefore, it is speculated that the diverse affinity of a natural drug to different functional protein targets may be one of the key factors for different selectivity profiles on VSMCs or VECs. Common targets like MAPT could be used as one of the important indicators in screening selective inhibitory drugs in future studies.

7. Conclusion

This review highlighted the originating four cells that may contribute to IH and then focused on VSMCs due to their involvement in intima formation as a consequence of abnormal proliferation, migration, and physiology. It further summarized typical signaling pathways such as MAPKs, PI3K/Akt, JAK-STAT, FAK, and NF-κB and their involvement in the abnormal activities of VSMCs. Based on these the above cell origins and pathways, we organized and classified different natural isolates including phenols, flavonoids, terpenes, and alkaloids that have suppressing effects on VSMCs. In addition, many natural drugs not only induce apoptosis and arrest cell cycle in VSMCs, but also impair VECs leading to vascular restenosis and failure of blood vessel remodeling. Thus, it is crucial to screen desirable drugs from natural sources that preferentially inhibit VSMCs versus VECs to prevent IH in the early stages, restenosis following graft implantation, and even atherosclerotic diseases.

Abbreviations

| Abbreviation | Definition                        |
|-------------|----------------------------------|
| IH          | Intimal hyperplasia               |
| EndMT       | Endothelial-to-mesenchymal transition |
| rASMCs      | Rat aortic smooth muscle cells    |
| rTASMCs     | Rat thoracic aortic smooth muscle cells |
| VSMCs       | Vascular smooth muscle cells      |
| CA          | Carotid artery                    |
| RAECs       | Rat aortic endothelial cells      |

Table 6: The selected potential targets of the compounds.

| Seq | Idarubicin | Halofuginone | Piperine | β-elemene | Curcumin | Coptisine |
|-----|------------|--------------|----------|-----------|----------|-----------|
| 1   | MAPT       | BCHE         | MAOA     | MAPT      | MAPT     | CHRM4     |
| 2   | MBNL1      | ACH          | MAOB     | TDP1      | TLR9     | CHRM1     |
| 3   | MBNL2      | MAPK8        | SIGMAR1  | CXXR3     | TDP1     | CHRM2     |
| 4   | MBNL3      | MAPK9        | MBNL1    | SLC6A2    | Unknown  | CHRM5     |
| 5   | MMP2       | MAPK10       | MBNL2    | SLC6A3    | MBNL1    | CHRM3     |
| 6   | MMP9       | MAPK1II      | MBNL3    | LDLR      | MBNL2    | BCH       |
| 7   | APP        | MAPK14       | MAPT     | VLDLR     | MBNL3    | ADRA2A    |
| 8   | SNCA       | HTRIA        | DRD2     | LRP8      | GLO1     | CYP2D6    |
| 9   | APLP2      | HTRIB        | DRD3     | HSD11B1   | AKT1     | ADRA2B    |
| 10  | SNCG       | MAPT         | HDAC3    | BACE1     | AKT2     | ADRA2C    |
| 11  | SNCB       | HTR2A        | HDAC1    | HSD11B2   | AKT3     | ACH       |
| 12  | TDP1       | DRD2         | HDAC2    | BACE2     | HSD17B3  | HTR2A     |
| 13  | EGFR       | DRD1         | DYROK1A  | HTRIA     | HSD17B2  | HTR2C     |
| 14  | ERBB2      | OPRM1        | HDAC6    | HTRID     | CRYZ     | HTR2B     |
| 15  | ERBB3      | OPRD1        | CTSL1    | HTRIB     | APP      | SIGMAR1   |
Figure 4: The compounds potential target: MAPT which is a common target.

| HAECs: | Human aortic endothelial cells |
| VECs: | Vascular endothelial cells |
| hUVECs: | Human umbilical vein endothelial cells |
| hUYSMCs: | Human umbilical vein smooth muscle cells |
| NeCs: | Neointimal cells |
| rTA-A10-VSMCs: | Rat thoracic aorta A10 vascular smooth muscle cells |
| ncTASMCs: | Newborn calf thoracic aorta smooth muscle cells |
| mASMCs: | Mice aortic smooth muscle cells |
| hPASMCs: | Human pulmonary artery smooth muscle cells |
| rPASMCs: | Rat pulmonary artery smooth muscle cells |
| hCASMCs: | Human coronary artery smooth muscle cells |
| bASMCs: | Bovine aortic smooth muscle cells |
| MYH11: | Smooth muscle cell myosin heavy chain |
| SM22α/tgln: | SMC lineage-restricted protein |
| ACTA2: | Alpha smooth muscle actin |
| ECM: | Extracellular matrix |
| TNF-α: | Tumor necrosis factor-α |
| PDGF: | Platelet-derived growth factor |
| ERK: | Extracellular signal-regulated kinase |
| MMP: | Matrix metalloproteinase |
| MAPK: | Mitogen-activated protein kinase |
| JNK: | c-Jun N terminal kinase |
| PCNA: | Proliferating cell nuclear antigen |
| PI3K: | Phosphatidylinositol-4,5-bisphosphate 3-kinase |
| AKT: | Serine/threonine kinase 1 |
| CDK: | Cyclin-dependent kinase |
| JAK: | Janus kinase |
| STAT: | Signal transducer and activator of transcription protein |
| FAK: | Focal adhesion kinase |
| NF-κB: | Nuclear factor kappa B |
| LDL: | Low-density lipoprotein |
| ROS: | Reactive oxygen species |
| IL-1β: | Interleukin 1-β |
| LPS: | Lipopolysaccharide |
| Nox: | NADPH oxidase |
| TIMP: | Tissue inhibitors of metalloproteinase |
| NOS: | Nitric oxide synthase |
| IC50: | Half maximal inhibitory concentration |
| miR-21: | MicroRNA-21 |
| NO: | Nitric oxide |
| LDH: | Lactate dehydrogenase |
| eNOS: | Nitric oxide synthase |
| pPDGFr-β: | β-type platelet-derived growth factor receptor |
| ROCK: | Rho-associated protein kinase |
| Rb: | Retinoblastoma tumor suppressor protein family |

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Kang Xu, Mohanad Kh Al-ani, and Xin Pan designed the project, performed the experiments, collected the data, and wrote the manuscript. Qingjia Chi analyzed the data and wrote and revised the manuscript. Nianguo Dong and Xue-feng Qiu designed the project, gave financial support, and wrote and revised the manuscript. All authors read and approved the final manuscript.
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