Abstract: The present paper reviews vasodilator compounds isolated from plants that were reported in the past 22 years (1990 to 2012) and the different mechanisms of action involved in their vasodilator effects. The search for reports was conducted in a comprehensive manner, intending to encompass those metabolites with a vasodilator effect whose mechanism of action involved both vascular endothelium and arterial smooth muscle. The results obtained from our bibliographic search showed that over half of the isolated compounds have a mechanism of action involving the endothelium. Most of these bioactive metabolites cause vasodilation either by activating the nitric oxide/cGMP pathway or by blocking voltage-dependent calcium channels. Moreover, it was found that many compounds induced vasodilation by more than one mechanism. This review confirms that secondary metabolites, which include a significant group of compounds with extensive chemical diversity, are a valuable source of new pharmaceuticals useful for the treatment and prevention of cardiovascular diseases.
Keywords: vasodilator compounds; vascular endothelium; arterial smooth muscle; NO/cGMP pathway; PGI₂/cAMP pathway; potassium channel activators; calcium channel blockers; phosphodiesterases inhibitors; PKC inhibitors

1. Introduction

According to the World Health Organization, cardiovascular diseases are the leading cause of death worldwide. Among these, arterial hypertension has a high prevalence and is associated with other conditions, such as myocardial infarction and stroke [1]. Although there are more than 200 drugs that lower blood pressure, less than a third of the hypertension cases are successfully treated due to their low efficacy, detrimental side effects and lack of cardiovascular risk reduction [2]. In addition, the etiology of hypertension has been associated with vascular endothelial dysfunction, which is characterized by an uncoupling between the release of endothelial factors such as nitric oxide (NO), prostacyclin (PGI₂) and endothelium-derived hyperpolarization (EDH), as well as effects on endothelium-dependent contractile mechanisms, and the associated change in vascular smooth muscle tone [3].

Some studies have suggested that changes in the bioavailability of endothelium-derived NO may be responsible for endothelial dysfunction and the related altered blood pressure and myocardial infarction [4–10]. Such altered NO levels can be due to dysfunction of soluble guanylate cyclase protein (sGC), with changes in the levels of this protein likely related to the pathophysiology of pulmonary hypertension and hypoxia [11,12]. With regard to vascular smooth muscle relaxation, various cardiovascular diseases, such as coronary vasospasm [13,14], cardiac ischemia [15] and hypertension [16] have also been associated with altered expression and activation of various potassium channels. Based on the above evidence, we are currently seeking new therapeutic strategies for preventing and treating these conditions that also have relaxing effects on vascular smooth muscle.

In this context, plants are a major source of new biologically active compounds, and the ethnomedical knowledge of traditional medicine from around the world is a useful starting point for determining their efficacy. In addition, due to the multifactorial nature of cardiovascular disease such as hypertension, knowledge of the mechanisms of action of each of the compounds proposed for use in the treatment for this disease is a crucial element for planning and developing different therapeutic strategies. Therefore, the present work reviews the previously reported vasodilator compounds isolated from plants and the different mechanisms of action involved in their vasodilator effects.

2. Search Strategy

The literature review focused on the past 22 years (1990 to 2012), taking into account studies on the vasodilating activity of plant-based treatments and the compounds derived from them. We reviewed more than 450 abstracts on this topic. The search was focused on those metabolites with a vasodilator effect whose mechanism of action involved the vascular endothelium and the arterial smooth muscle vasorelaxation pathways; we did not consider the antioxidant activity or reactive oxygen species scavenging.
3. Types of Compounds with Vasodilator Effects

We identified 207 vasodilator metabolites together with their possible mechanism(s) of action. First, these compounds were classified according to their chemical nature. It is clear that most compounds with vasodilator activity are alkaloids, flavonoids, or terpenoids (Figure 1). The classification of these compounds offers an overview of the types of compounds that present significant vasodilator activity and of the structural diversity exhibited by these bioactive compounds.

Figure 1. Classification of vasodilator compounds obtained from plants according to their chemical nature.

Some of these compounds have been studied on multiple occasions, and various mechanisms of action have been proposed to explain their vasodilatory activities. These compounds include the flavonoids naringenin [17–19], dioclein [20–23], quercetin [24–28] and (−)-epigallocatechin-3-gallate [29–31]; the polyphenols piceatannol [32,33] and resveratrol [34–36]; the sesquiterpene polygodial [37–39]; the monoterpene rotundifolone [40–42] and the alkaloid rutaecarpine [43–46].

In other cases, mixtures of various compounds obtained from plants or the products generated from them were studied; examples include polyphenols in red wine [47,48], saponins from ginseng [49], proanthocyanidins from persimmon leaf tea [50] and green tea [48,51], as well as the xanthones obtained from Halenia elliptica [52]. In 34 plants, two or more vasodilator compounds were identified, which in some cases had different mechanisms of action. Examples of this are the chalcones isolated from Angelica keiskei [53], the alkaloids obtained from Peganum harmala [54], the glycosides identified in Melaleuca quinquenervia [55] and the macrocyclic bis(bibenzyls) from liverworts [56]. In these examples, the fundamental difference between the mechanisms of action proposed for the isolated compounds is based on their dependence or independence on the endothelium, the involvement of the NO/cGMP pathway and the blockage of voltage-dependent Ca2+ channels.
4. Proposed Mechanisms of Action

Different mechanisms of action were proposed to explain the vasodilator effect of the 207 compounds derived from plants (Figure 2).

**Figure 2.** Classification of compounds obtained from plants according to the main mechanism(s) of action involved in their vasodilator effect.

Analysis of the mechanisms of action of these compounds revealed that, on the one hand, the vasodilator effect of a significant number of compounds (40%) involves two or more mechanisms (Table 1). On the other hand, as shown in Figure 2, over half of the tested compounds have a mechanism of action that requires the participation of the endothelium, at least in part. Therefore, endothelium-derived factors play a key role in the mechanisms of action of these vasodilators. The mechanisms of action most frequently assessed in the vasodilator effects of the plant compounds were activation of the NO/cGMP pathway, blockade of Ca\textsuperscript{2+} channels, and activation of K\textsuperscript{+} channels.

5. Participation of the Endothelium in the Mechanism of Action

The vascular endothelium synthesizes and releases a broad spectrum of vasoactive substances and plays a fundamental role in the regulation and maintenance of cardiovascular homeostasis [57]. Among the main endothelial-derived factors that relax arterial smooth muscle are NO [58,59], PGI\textsubscript{2} [59,60] and the EDH mechanism, which is associated with calcium-activated potassium channel activation [59,61]. Approximately one third of the compounds analyzed utilized both endothelium-dependent and endothelium-independent mechanisms (Table 1). Moreover, among the compounds that produce their vasodilator effect by an endothelium-dependent mechanism, a high percentage (98.4%) involved the NO/cGMP pathway, whereas the PGI\textsubscript{2}/cAMP pathway was involved in the mechanism used by a low percentage (23%) of the vasodilating compounds (Table 1). Among the 130 compounds whose mechanism of action was endothelium-dependent, assays for evaluating the participation of endothelial muscarinic receptors were performed in only 18. Four of these compounds involved the participation of this kind of receptors: diosgenin [62], reticuline [63], rotundifolone [40] and ursolic acid [64].
Table 1. Mechanisms of action proposed for vasodilator compounds obtained from plants.

| Compound                              | Type of artery/vein | EC$_{50}$     | Endothelium | NO/ cGMP | PGI$_2$/ cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ ext/ Ca$^{2+}$ int | Ref. |
|---------------------------------------|---------------------|---------------|-------------|----------|---------------|-----|-----|----------|-------------------------------|------|
| 1 Allicin                              | rat pulmonary       | 0.8 µg/mL     | d           | +        | -             |     |     | +IK$_{Ca}$ |                              | [65] |
| 2 Allyl isothiocyanate                 | rat cerebral        | 164 µM        | d           | x        | x             |     |     | +SK$_{Ca}$ +K$_{IR}$ | +TRPA1/                                      | [66] |
| 3 Alpha-terpineol                      | rat mesenteric      | NR            |             | +        | -             |     |     | +BK$_{Ca}$ |                              | [67] |
| 4 Alpha-zearalanol                     | rat aorta           | NR            | d/i         | +        | -             |     |     | +K$_{ATP}$ | -VOCC/                        | [68] |
| 5 Alpinetin                            | rat mesenteric      | 27.5 µM       | d/i         | +        | x             | -   |     | -VOCC/- IP$_{jR}$, -RyRs | -VOCC/- IP$_{jR}$, -RyRs | [69] |
| 6 Alstonisine                          | rat aorta           | NR            | d/i         | +        | +             |     |     | -VOCC/- ROCC/ |                              | [70] |
| 7 Amentoflavone                        | rat aorta           | NR            | d/i         | +        | -             |     |     | -VOCC/ |                              | [71] |
| 8 Angelic ester of 2-β-hydroxy-8α-H-7(11)-eremophilene-12,8-olide | rat mesenteric       | 4.74 ± 0.1 µM| d           | +        | x             | -   |     | +TRPV4/ | -VOCC/- IP$_{jR}$ | [72] |
| 9 Angelic ester of 2-β-hydroxy-8β-H-7(11)-eremophilene-12,8-olide | rat mesenteric, rat aorta | 4.92 ± 0.09 µM | x | x | -VOCC/ | [72] |
| 10 Apigenin                            | rat aorta           | 3.7 ± 0.5 µM  | d/i         | +        | -             |     |     | +IK$_{Ca}$ +SK$_{Ca}$ | -VOCC/- ROCC/ | [73] |
| 11 Apocynin                            | rat aorta           | 780 ± 80 µM  | d/i         | +        | -             |     |     | +K$_{ATP}$ | -VOCC/- IP$_{jR}$ | [76] |
| Compound                                      | Type of artery/vein | EC₅₀          | Endothelium NO/ cGMP | PGI₂/ cAMP | PDE | PKC | K⁺ Ch | Ca²⁺ext / Ca²⁺int | Ref. |
|-----------------------------------------------|---------------------|---------------|-----------------------|------------|-----|-----|-------|-------------------|------|
| Astragaloside IV                              | rat aorta           | NR            | d/i                   | +          |     |     |       |                   | [77] |
| Backebergine                                  | rat aorta           | NR            | d/i                   | +          |     |     |       |                   | [78] |
| Baicalin                                      | rat mesenteric      | NR            | i                     | +          | +   |     |       | +BK₉Ca           | [79] |
| 4-Benzoyl-2-C-β-glucopyranosyl-3,5-dihydroxy-6-methylphenyl β-D-glucopyranoside | rat aorta           | NR            | d                     | +          |     |     |       |                   | [55] |
| Berberine                                     | rat mesenteric      | 1.48 ± 0.16 µM | d/i                   | +          | x   | x   | +    | +BK₉Ca, +KIR      | [80] |
| Betulinic acid                                | rat aorta           | 1.67 µM       | d                     | +          |     |     |       |                   | [81] |
| Bilobalide                                    | rat aorta           | NR            | i                     |           |     |     | +BK₉Ca, +K₉ATP   | -VOCC/- | [82] |
| Biochanin A                                   | rat aorta           | NR            | i                     |           |     |     |       |                   | [83] |
| Brazilin                                      | rat aorta           | 183 ± 30 µM   | i                     | x         |     |     | +BK₉Ca, +K₉ATP   | -VOCC/- | [84] |
|                                               | rat mesenteric      |               | i                     | x         |     |     | +BK₉Ca, +K₉ATP   | -VOCC/- | [85] |
|                                               | rat aorta           | 4.63 ± 0.15 µM| i                     |           |     |     | +BK₉Ca, +K₉ATP   | -VOCC/- | [85] |
|                                               | rat aorta           | 7.4 ± 1.6 µM  | d                     | +          | x   |     |       |                   | [87] |
| Butylidenephthalide                           | rat aorta           | 4.20 ± 0.07 µM| d/i                   | +          | x   |     |       |                   | [88] |
| Compound                        | Type of artery/vein | EC$_{50}$ | NO/cGMP | PGI$_2$/cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ext/Ca$^{2+}$int | Ref. |
|--------------------------------|---------------------|-----------|----------|--------------|-----|-----|----------|--------------------------|------|
| 24 Cadamine                    | rat aorta           | NR        | d/i      | +            |     |     | x        | -VOCC/-ROCC              | [89] |
| 25 Caffeic acid                | rat aorta           | 400 µM$^1$| d/i      | +            |     |     | x        |                         | [90] |
| 26 Caffeic acid phenethyl ester| porcine coronary    | 4.99 ± 0.17$^3$| d/i      | +            |     |     | x        | -VOCC/                   | [91] |
|                                | rat aorta           | 5.15 ± 0.0$^4$| d       | +            | x   |     |          |                         | [92] |
| 27 Calycosin                   | rat aorta           | 4.46 ± 0.13$^3$| i       | x            | x   |     |          | -VOCC/x                  | [93] |
| 28 Capsaicin                   | rat mesenteric      | NR        | d/i      | +            |     |     | x        |                         | [94] |
| 29 Cardamonin                  | rat mesenteric      | 9.3 µM$^1$| d/i      | +            | x   |     | -BKCa   | -VOCC/-IP$_3$, -RyRs     | [69] |
|                                | rat tail            | 4.63 ± 0.01$^3$| d/i      | +            | x   |     | +SKCa   | -VOCC/                   | [95] |
| 30 Carvacrol                   | rat aorta           | 145.4 ± 6.07 µM$^1$| i       |              |     | +BKCa |          | -VOCC/-IP$_3$            | [96] |
|                                | rat cerebral        | 78.8 ± 11.9 µM$^2$| d        | x            | x   |     | +SKCa   | +BKCa                    | [98] |
| 31 Cassiarin A                 | rat mesenteric      | 6.4 ± 0.8 µM$^1$| d/i      | +            | x   |     | +BKCa   |                         | [70] |
| 32 Cathafoline                 | rat aorta           | NR        | d/i      | +            |     |     | x        | -ROCC/                   | [99] |
| 33 Centaureidin                | rat orta            | 16.7 ± 1.9 µM$^3$| i       |              |     |     |          |                         | [100,101] |
| 34 Chrysin                     | rat orta            | 16 ± 4 µM$^1$| d        | +            |     |     | x        |                         | [102] |
| 35 Chrysin glucoside           | rat aorta           | 52 µM$^5$ | d/i      | +            |     |     | x        | -VOCC/                   | [103] |
| 36 Cinnamaldehyde              | rat aorta           | NR        | d/i      | +            | x   |     |          | -VOCC/                   | [104] |
| 37 Ethyl cinnamate             | rat aorta           | 380 ± 40 µM$^1$| d/i      | +            | +   |     |          |                         | [105] |
| 38 1,8-Cineole                 | rat aorta           | 663.2 ± 63.8 µg/mL$^1$| d      | +            | x   |     |          |                         | [106] |
| 39 (+)-cis-4'-O-Acetyl-3'-O-angeloylkhellactone | rat aorta | NR | d/i | + | x | x | -VOCC/ | [102] |
| 40 Citral                      | rat aorta           | NR        | d/i      | +            | x   |     |          | -ROCC/-                  | [102] |
| Compound                  | Type of artery/vein | EC$_{50}$ | Endothelium | NO/ cGMP | PGI$_2$/ cAMP | PDE | PKC | K$^+$ Ch | Ca$_{2+}^{ext}$/ Ca$_{2+}^{int}$ | Ref. |
|---------------------------|---------------------|-----------|-------------|----------|--------------|-----|-----|---------|-------------------------------|------|
| Citronellol               | rat mesenteric      | 0.71 ± 0.11 $^{3.1}$ | i           | x        |              |     |     |         | -VOCC/ IP$_v$R, -RyRs         | [107]|
| Coptisine                 | rat aorta           | 4.49 ± 0.48 $^{3.5}$ | d/i         | +        | +            |     |     | +K$_V$ | -VOCC$_{ex}$,-ROCC/-          | [108]|
| Cornuside                 | rat aorta           | NR        | d           | +        | x            | x   |     |         | -VOCC$_{ex}$/ROCC/L           | [109]|
| Cryptotanshinone          | rat coronary        | 2.65 ± 0.15 µg/mL $^{6}$ | i           | x        | x            | x   |     |         | -VOCC$_{ex}$/ROCC/L           | [110]|
| Curcumin                  | rat mesenteric      | 4.8 ± 1.9 µM $^{5}$ | i           |         |              |     |     |         | -VOCC$_{ex}$/ROCC/L           | [111]|
|                           | rat aorta           | 7.6 ± 1.6 µM $^{1}$ | i           |         |              |     |     |         | -VOCC$_{ex}$/ROCC/L           | [112]|
| Curcumin                  | porcine coronary    | 6.28 ± 0.28 µM $^{4}$ | d           | +        | x            |     |     |         | -VOCC/L                       | [113]|
| Cyclosquamosin B          | rat aorta           | NR        | i           |         |              |     |     |         | -VOCC/                         | [114]|
| Daidzein                  | rat basilar         | 20 ± 7 µM $^{3}$ | i           | x        | x            | +   |     | +BK$_{Ca}$, +K$_{ATP}$        | -VOCC/                         | [115]|
|                           |                     | 7.4 ± 1.9 µM $^{6}$ | i           | x        | x            |     |     |         | -VOCC/                         | [116]|
| Daidzin                   | rat basilar         | 140 ± 21 µM $^{3}$ | i           | x        | x            | +   |     | +K$_{ATP}$                     | -VOCC/                         | [117]|
| Danshensu                 | rat coronary        | 71.5 ± 11 µg/mL $^{6}$ | i           |         |              |     |     |         | +                            | -VOCC/                         | [118]|
| Dehydroevodiamine         | rat mesenteric      | NR        | d/i         | +        | x            |     |     |         | -VOCC/                         | [119]|
| Demethylpipеритол         | rat aorta           | NR        | d           | +        |              |     |     |         | -VOCC$_{ex}$/ROCC/            | [120]|
| Denudatin B               | rat aorta           | 21.2 µg/mL $^{2}$ | i           | ↑cGMP    | x            |     |     |         | -VOCC$_{ex}$/ROCC/L           | [121]|
| 14-Deoxyandrographolide   | rat aorta           | NR        | d/i         | +        | x            |     |     |         | -VOCC$_{ex}$/ROCC/L           | [122]|
| Dictamnine                | rat aorta           | 15 µM $^{2}$ | i           |         |              |     |     |         | -VOCC$_{ex}$/ROCC/L           | [123]|
| Dihydrotanshinone         | rat coronary        | 10.39 ± 1.69 µM $^{6}$ | i           | x        | x            | x   |     |         | -VOCC$_{ex}$/ROCC/L           | [124]|
| 3,7-Dihydroxy-2,4-         | rat aorta           | NR        | d/i         | +        |              |     |     |         |                               | [125]|
| -dimethoxyphenanthrene    |                     |           |             |         |              |     |     |         |                               | [125]|

**Table 1. Cont.**
| Compound | Type of artery/vein | EC$_{50}$ | Endothelium | NO/PGI$_2$ | PDE | PKC | K$^+$ Ch | Ca$^{2+}_{ext}$/Ca$^{2+}_{int}$ | Ref. |
|----------|-------------------|---------|-------------|----------|-----|-----|---------|----------------|-----|
| Dioclein | rat aorta         | 1.3 ± 3.1 µM$^1$ | d | x |  |  |  |  | [20] |
|          | rat aorta         | 350 ± 80 µM$^5$ | i |  | + | - | +K$_{Ca}$, +K$_V$ |  | [21] |
|          | rat mesenteric    | 0.3 ± 0.06 µM$^1$ | d/i |  |  | - | - |  | [22] |
|          | human saphenous   | 7.3 ± 3.1 µM$^1$ | i | x |  | - | +K$_{Ca}$ |  | [23] |
| Diosgenin| rat mesenteric    | 330 ± 120 µM$^1$ | d | + |  | x  |  | +BK$_{Ca}$ | [62] |
| Echinacoside| rat aorta | NR | d | + | x |  |  |  | [125] |
| Ellagic acid| rat aorta | 5.60 ± 0.03 §,1 | d/i |  | + | x |  | -VOCC$_I$/ | [126] |
| Emolin   | rat aorta         | NR      | i |  | ↑cGMP |  |  |  | [127] |
| Ent-18-hydroxy-trachyloban-3-one| rat aorta | 5.7 ± 0.01 §,2 |  | x |  |  | -VOCC$_I$/ | [128] |
| Ent-8(14), 15-pimaradien-3β-ol| rat aorta | 4.8 ± 0.1 §,1 | d/i |  | + | x |  | -VOCC/x | [129] |
| Epicatechin| rat aorta | 4.72 ± 0.07 §,1 | d |  |  |  |  |  | [130] |
| 7-Epiclusianone| rat aorta | NR | d | + | x |  |  |  | [131] |
| (-)-Epigallocatechin-3-gallate| rat aorta | 191.8 ± 13 µM$^5$ | i |  |  | - | x |  | [29] |
|           | bovine ophtalmic  | 6.21 ± 0.06 §,6 | d |  |  |  | +BK$_{Ca}$ |  | [31] |
|           | rat aorta         | 4.76 ± 0.07 §,1 | d |  |  |  |  | -BOCC/x | [130] |
| Equol (daidzein metabolite) | rat aorta | NR | d |  |  |  |  |  | [132] |
| Eriodictyol| rat aorta         | 61.1 ± 2 µM$^5$ | i |  |  | x |  | -VOCC/ | [133] |
| Erythrodiol| rat aorta        | 3.38 ± 1.27 µM$^1$ | d |  | + | x |  |  | [134] |
| Eudesmin | rat aorta         | 10.69 ± 0.77 µg/mL$^1$ | d |  |  | + |  |  | [135] |
| Eugenol  | rat aorta         | 1200 µM$^1$ | d/i |  |  | + |  |  | -VOCC,-ROCC/x | [136] |
|          | rat mesenteric    | 1200 µM$^1$ | d/i |  | x | x |  |  | -VOCC,-ROCC/ | [137] |
Table 1. Cont.

| Compound | Type of artery/vein | EC$_{50}$ | Endothelium | NO/ cGMP | PGI$_2$/ cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ ex / Ca$^{2+}$ int | Ref. |
|----------|---------------------|-----------|-------------|----------|---------------|-----|-----|----------|---------------------------|------|
| 73 | Euxanthone | rat aorta | 32.5 ± 2.5 µM$^1$ | i | x | x | - | x | -VOCC, -ROCC/-IP$_3$R | [139] |
| 74 | Evocarpine | rat aorta | 9.8 µM$^2$ | | | | | | -VOCC/ | [140] |
| 75 | Evodiamine | rat mesenteric | NR | d/i | | | | | -ROCC/x | [141] |
| 76 | Ferulic acid | rat aorta | NR | i | x | | | | | [142] |
| 77 | Floranol | rat mesenteric rat aorta | 19.9 ± 2.4 µM$^1$ | d/i | + | x | + | x | -VOCC/ | [143] |
| 78 | Formononetin | rat aorta | NR | d/i | + | | | + | -VOCC/ | [144] |
| 79 | Forsythide | rat aorta | NR | i | | | | x | -ROCC/ | [145] |
| 80 | Fraxinellone | rat aorta | 25 µM$^2$ | | | | | | -VOCC/ | [146] |
| 81 | Galangin | rat aorta | NR | d/i | + | | x | | -VOCC/ | [147] |
| 82 | Geissoschizine methyl ether | rat aorta | 0.744 µM$^5$ | d/i | + | | | | -VOCC/ | [148] |
| 83 | Genistein | rabbit coronary human umbilical | NR | i | x | x | | | -VOCC$_{L}$/ -VOCC/- | [149] |
| 84 | Gigantol | rat aorta | NR | d/i | + | | | | +BK$_{Ca}$ +K$_{ATP}$ | -VOCC$_{L}$/ | [150] |
| 85 | Ginsenoside Rg3 | rat aorta | NR | d | + | | | | + | -VOCC/ | [151] |
| 86 | Gomisin A | rat aorta | NR | d/i | + | | | | | -VOCC/ | [152] |
| 87 | Gymnopusin | rat aorta | 63 µM$^5$ | i | x | | | +BK$_{Ca}$ +K$_{ATP}$ | -VOCC$_{L}$/ | [153] |
| 88 | Harmaline | rat aorta | 32.8 ± 1.17 µM$^2$ | d/i | + | | + | - | -VOCC/ | [154] |
| 89 | Harman | rat aorta | 9 µM$^1$ | d/i | + | x | | | x | -VOCC$_{L}$/ -ROCC/ | [155] |
| 90 | Harmine | rat aorta | 3.7 ± 1.2 µM$^5$ | i | x | x | | - | -VOCC/ | [156] |
| 91 | Hematoxylin | rat aorta | NR | d | + | | | | | [157] |
| Compound | Type of artery/vein | EC$_{50}$ | NO/Endothelium | PGI$_2$/cAMP | PDE | PKC | K$_{Ca}$ | Ca$^{2+}$ext/ | Ref. |
|----------|-------------------|----------|----------------|-------------|-----|-----|---------|-------------|-----|
| 92 | Hesperetin | rat aorta | 62.8 ± 5.0 µM | i | x | x | - | VOCC/- | [157] |
| 93 | Hirsutine | rat aorta | 10.6 µM | i | x | x | - | VOCC/ | [148] |
| 94 | 4-Hydroxybenzoic acid | rat aorta | 1780 µM | d | + | x | - | VOCC/ | [90] |
| 95 | 4-Hydroxyderricin | rat aorta | NR | d/i | + | - | VOCC/ | [53] |
| 96 | 1-Hydroxy-2,3,5-trimethoxyxanthone | rat coronary | 1.67 ± 0.27 µM | d | + | x | - | VOCC/ | [130] |
| 97 | Hypogallic acid | rat aorta | 620 µM | d/i | + | +K$_{ATP}$ | - | VOCC/ | [90] |
| 98 | Icariin | rat aorta | NR | d | + | x | - | VOCC/ | [158] |
| 99 | Imperatorin | rat mesenteric | 12.2 ± 2.4 µM | d | + | BK$_{Ca}$ | -VOCC/- | [160] |
| 100 | Isoliquiritinigenin | rat aorta | 7.4 ± 1.6 µM | i | ↑cGMP | x | - | VOCC/ | [162] |
| 101 | Isoplagiochin B | rat aorta | NR | i | + | - | VOCC/ | [56] |
| 102 | Isoplagiochin D | rat aorta | NR | i | x | - | VOCC/ | [56] |
| 103 | Isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate | rat mesenteric | 7.41 ± 0.08 µM | i | +BK$_{Ca}$ | -VOCC/- | [123] |
| 104 | Isorhamnetin | rat mesenteric | 5.89 ± 0.11 µM | i | x | x | -VOCC/- | [163] |
| 105 | Isorhynchophylline | rat aorta | 20–30 µM | i | x | - | VOCC/- | [164] |
| 106 | Iso-S-petasin | rat aorta | NR | i | x | - | VOCC/ | [165] |
| 107 | Isotirumalin | rat aorta | 4.84 ± 0.24 µM | d | + | - | VOCC/ | [166] |
| 108 | Jatrophone | rat aorta | 11.0 µM | d/i | x | + | - | VOCC/ | [167] |
Table 1. Cont.

| Compound                        | Type of artery/vein | EC50 | Endothelium | NO/ cGMP | PGI2/ cAMP | PDE | PKC | K+ Ch | Ca2+ext/Ca2+int | Ref.   |
|---------------------------------|---------------------|------|-------------|----------|------------|-----|-----|-------|-----------------|--------|
| Kaempferol                      | rat aorta           | 580 µM | d/i         | +        |            |     |     |       |                 | [90]   |
| Kaempferol                      | rat mesenteric      | 4.81 ± 0.13 | i         | +        |            |     |     |       |                 | [163]  |
| Kaempferol                      | porcine coronary    | 5.66 ± 0.06 | i         | +        |            |     |     |       |                 | [163]  |
| Kaempferol                      | rat aorta           | d/i   | +           |          |            |     |     |       |                 | [170]  |
| Kaurenoic acid                  | rat aorta           | NR    | d/i         | +        | x          |     |     |       | +BKCa2+, K_V    | [171]  |
| Keayanidine B                   | rat aorta           | 23.3 ± 1.3 µM | i         | +        |            |     |     |       |                 | [172]  |
| Keayanine                       | rat aorta           | 27.5 ± 2.4 µM | i         | +        |            |     |     |       |                 | [172]  |
| Kolaviron                       | rat mesenteric      | NR    | i           |          | +BKCa2+, K_V |     |     |       | -VOCC L/-IP,R   | [173]  |
| Labdane-302                     | rat mesenteric      | 5.4 ± 1.4 µM | d/i   | +        | +          |     |     |       |                 | [173]  |
| Labd-8 (17)-en-15-oic acid      | rat aorta           | 313.6 µg/mL | i         | x        |            |     |     |       |                 | [174]  |
| Lectin (of Pisum arvense)       | rat aorta           | 58.38 ± 1.87 µg/mL | d    | +        | x          |     |     |       |                 | [176]  |
| Leonurine                       | rat aorta           | 86.4 ± 10.4 µM | i    | x        |            |     |     |       | -VOCC L/-       | [177]  |
| Leucocyanidol                   | rat aorta           | 2.75 ± 0.15 | d/i  | +        |            |     |     |       |                 | [178]  |
| Ligustilide                     | rat mesenteric      | 3.98 ± 0.2 | i    | x        | x          |     |     |       | -VOCC,-ROCC/-RyR | [179]  |
| Ligustilide                     | rat aorta           | 4.39 ± 0.11 | i    | x        | x          |     |     |       | -K_tr, +K_V     | [179]  |
| (-)-limacine                    | rat aorta           | NR    | d           | +        |            |     |     |       |                 | [78]   |
| Luteolin                        | rat aorta           | NR    | i           | x        | +K_tr, +K_V |     |     |       | -VOCC L/-       | [17,181] |
| Machilin D                      | rat aorta           | 17.8 µM | d    | +        |            |     |     |       |                 | [180]  |
| Marrubeneol                     | rat aorta           | 11.8 ± 0.3 µM | d    | +        |            |     |     |       |                 | [182]  |
| Marrubiin                       | rat aorta           | NR    | d/i         | +        |            |     |     |       |                 | [184]  |
| Compound                  | Type of artery/vein | EC₅₀ | Endothelium | NO/cGMP | PGI₂/cAMP | PDE | PKC | K⁺ Ch | Ca²⁺ext/Ca²⁺int | Ref. |
|--------------------------|---------------------|------|-------------|---------|-----------|-----|-----|-------|-----------------|------|
| 125 10-Methoxyaffinisine | rat aorta           | NR   | d/i         | +       | x         |     |     |       | -VOCC/           | [70] |
| 126 Methyl brevifolincarboxylate | rat aorta        | NR   | i           |         |           |     |     |       | -ROCC/x          | [185]|
| 127 Methyleugenol        | rat mesenteric      | NR   | d/i         | +       |           |     |     |       |                 | [67] |
| 128 Methylpaeoniflorin   | rat aorta           | 10.1 µM | d   | +       |           |     |     |       |                 | [186]|
| 129 Milonine             | rat mesenteric      | 1.1 µM | d/i | +       | x         |     |     |       | -VOCC,-ROCC/,-IP,R,-RyR | [187] |
| 130 Mollic acid glucoside| rat aorta           | NR   | d           | +       |           |     |     |       |                 | [188]|
| 131 Morolic acid         | rat aorta           | 94.19 µM | d  | +       | x         |     |     |       |                 | [189]|
| 132 Moronic acid         | rat aorta           | 16.11 µM | d  | +       | x         |     |     |       |                 | [189]|
| 133 (+)-Nantenine        | rat aorta           | NR   | i           |         | x         |     |     |       | -VOCC/x          | [190]|
| 134 (+/-)-Naringenin     | rat aorta           | 71.2 ± 5.3 µM | i  | -       | +BKCa⁺,+SKCa⁺,K⁺ATP |     |     |       |                 | [17] |
|                         | rat aorta           | 4.68 µM | i  | -       | +BKCa⁺   |     |     |       |                 | [18] |
|                         | rat aorta           |       | i  | -       |           |     |     |       |                 | [19] |
| 135 Naucline             | rat aorta           | 20 µM | i           |         | x         |     |     |       | -VOCC,-ROCC/     | [89] |
| 136 1-Nitro-2-phenylethane| rat aorta           | 231.5 µM | i  | +       | x         |     |     |       | +K⁺ATP,+K⁺V      | [191]|
| 137 Norathyril           | rat aorta           | NR   | i           | x       | x         |     |     |       |                 | [192]|
| 138 Oleanolic acid       | rat aorta           | 5.58 ± 1.28 µM | d  | +       | x         |     |     |       |                 | [134]|
| 139 12-O-Methylcurine    | rat aorta           | 63.2 ± 8.8 µM | i  | -       |           |     |     |       |                 | [193]|
| 140 Orientin             | New Zealand rabbit aorta | 2.28 µM | d/i | +       | x         |     |     |       | -VOCC,-ROCC/-    | [194]|

**Table 1. Cont.**
| Compound                          | Type of artery/vein | EC$_{50}$ | Endothelium | NO/ cGMP | PGI$_2$/ cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}_{\text{ext}}$/ Ca$^{2+}_{\text{int}}$ | Ref. |
|-----------------------------------|---------------------|-----------|-------------|----------|---------------|-----|-----|----------|-------------------------------------------|------|
| 141 Osthole                       | rat aorta           | NR        | i           | ↑cGMP    |               |     |     |          | -VOCC,-ROCC/-                               | [195]|
| 142 Paeoniflorin                  | rat aorta           | 19.4 µM$^1$ | d           | +        |               |     |     |          |                                           | [186]|
| 143 Paeonidanin                   | rat aorta           | 7.9 µM$^1$ | d           | +        |               |     |     |          |                                           | [186]|
| 144 Pecrassipine A                | rat aorta           | NR        | d/i         | +        |               |     |     | x        | -VOCC,-ROCC/                                 | [78] |
| 145 1,2,3,4,6-Penta-O-galloyl-β-D-glucose | rat aorta         | 3.6 µM$^1$ | d           | +        | +             |     |     | x        |                                           | [196]|
| 146 Perrottetin                    | rat aorta           | NR        | i           |          |               |     |     | x        | -VOCC,-ROCC/                                 | [56] |
| 147 Phlomeoic acid                | rat aorta           | NR        | d/i         | +        |               |     |     |          |                                           | [184]|
| 148 Phloretin                      | rabbit coronary     | NR        | i           |          |               |     |     |          |                                           | [149]|
| 149 Piceatannol                   | rat aorta, rat aorta| 2.4 ± 0.4 µM$^1$ | d           | +        | x             |     |     | +BK$_{Ca}$|                                           | [32] |
| 150 Pimaradienoic acid            | rat aorta           | NR        | i           | +        | +             |     |     | x        | -VOCC/x                                    | [197]|
| 151 Pinocembrin                   | rat aorta           | 4.37 ± 0.02 $^5,5$ | d/i         | +        | x             |     |     | +K$_{ATP}$, +K$_V$| -VOCC/-IP$_3$R                  | [198]|
| 152 Piperitol (sesamin metabolite) | rat aorta           | NR        | d           | +        |               |     |     |          |                                           | [119]|
| 153 Plagiochini A                 | rat aorta           | NR        | d           | +        |               |     |     |          |                                           | [56] |
| 154 Polygodial                     | rabbit pulmonary, rat portal | NR | d           | +        | x             |     |     | x        |                                           | [37] |
| 155 Pomolic acid                  | rat aorta           | 2.45 µM$^5$ | d           | +        | x             |     |     | +K$_{ATP}$|                                           | [199]|
| 156 (+) Praeruptorin A            | rat aorta           | 35.4 ± 3.6 µM$^1$ | d           | +        |               |     |     | x        | -VOCC,-ROCC/-                               | [200]|

$^1$ Estimated EC$_{50}$ value.
Table 1. Cont.

| Compound                  | Type of artery/vein | EC$_{50}$      | Endothelium | NO/PGI$_2$ | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ extr/Ca$^{2+}$ int | Ref.     |
|---------------------------|---------------------|----------------|-------------|------------|-----|-----|---------|-----------------------------|----------|
| 157 (−) Praeruptorin A    | rat aorta           | 45.8 ± 2.5 µM  | i           | x          | x   | -   |          | -VOCC, ROCC/-IP$_3$R        | [200]    |
| 158 Proanthocyanidins*    | rat aorta           | NR             | d           | +          |     |     |         |                              | [50]     |
| 159 Procyanidins*         | human internal mammary | NR             | d           | +          |     |     |         | +K$_{ATP}$, +SK$_{Ca}$       | [201]    |
|                           | rat aorta           | NR             | d           | +          |     |     |         | +K$_V$, +K$_{IR}$            | [202]    |
|                           | porcine coronary    | NR             | +           | +          |     |     |         |                              | [203]    |
| 160 Protosappanin D       | rat aorta           | NR             | d/i         | +          |     |     |         |                              | [85]     |
|                           | rat mesenteric      | NR             | d/i         | +          |     |     |         |                              |          |
| 161 Puerarin              | rat basilar         | 304 ± 49 µM    | d/i         | +          | x   |     |         | +                           | x/       | [115]          |
|                           | rat aorta           | NR             | i           |           |     |     |         | -              |                              | [24]     |
|                           | rat coronary        | 3 mM           | d/i         | x          |     |     |         | +K$_V$                     | [25]     |
|                           | pig coronary        | NR             | i           | +          |     |     |         | +BK$_{Ca}$                 | [27]     |
| 162 Quercetin             | rat aorta           | 4.68 ± 0.08 µM | i           |           | x   |     |         |                              | [163]    |
|                           | rat mesenteric      | 5.35 ± 0.15 µM | i           |           |     |     |         | +K$_V$                     | [163]    |
|                           | rat aorta           | 4.36 ± 0.05 µM | d           | +          |     |     |         | +                          | [204]    |
|                           | rat portal          | 59.5 ± 11.1 µM | i           | x          | x   |     |         |                              | [205]    |
| 163 Quercetin 3,7-dimethyl ether | rat aorta        | 4.70 ± 0.18 µM | d           | +          |     |     |         |                              | [206]    |
| 164 Quercetin-3-O-galactoside | rat basilar      | 20.4 ± 4.49 µM | d/i         | +          | +   |     |         | +                          | [207]    |
| 165 Resveratrol           | rat aorta           | 4.52 ± 0.11 µM | i           |           | +   |     |         | +K$_V$                     | [35]     |
|                           | rat aorta           | d/i            |             |           |     |     |         | +                          | [208]    |
|                           | rat mesenteric      | 4.99 ± 0.11 µM | d/i         | +          |     |     |         | +K$_V$ -VOCC/-              | [209]    |
| Compound                  | Type of artery/vein | EC$_{50}$   | Endothelium | NO/cGMP | PGI$_2$/cAMP | PDE | PKC | K$^+$ Ch | Ca$_{extr}$/Ca$_{int}$ | Ref.   |
|--------------------------|---------------------|-------------|-------------|---------|--------------|-----|-----|----------|------------------------|--------|
| 166 Reticuline           | rat aorta           | 40 ± 10 µM | d/i         | +       | x            |     |     |          | -VOCC$_1$/-IP$_R$       | [63]   |
|                          | rat aorta           | NR          |             |         |              |     |     |          | -VOCC$_1/$             | [210]  |
| 167 Rhynchophylline      | rat aorta           | 20–30 µM   | i           | x       |              |     |     |          | -VOCC$_1$/-IP$_R,-$RyR | [164]  |
| 168 Riccardin A          | rat aorta           | NR          | d           | +       |              |     |     |          | [56]                   |
| 169 Riccardin C          | rat aorta           | NR          | d           | +       |              |     |     |          | [56]                   |
| 170 Riccardin F          | rat aorta           | NR          | d           | +       |              |     |     |          | [56]                   |
| 171 Roseoside            | rat aorta           | NR          | d           | +       |              |     |     |          | [55]                   |
| 172 Rotundifolone        | rat aorta           | 184 ± 6 µg/mL | d/i  | +       | +            |     |     |          | -VOCC$_1$/-IP$_R$       | [40]   |
|                          | rat aorta           | NR          | i           |         |              |     |     |          | -VOCC$_1$/-IP$_R$       | [41]   |
|                          | rat mesenteric      | 4.0 ± 0.02 µg/mL | d/i | +       | +            |     |     |          | +BK$_{Cax}$            | [42]   |
| 173 Rutaecarpine         | rat aorta           | NR          | d           | +       |              |     |     |          | -/-                    | [43]   |
|                          | rat aorta           | NR          | d           | +       |              |     |     |          | -VOCC$_1$/-IP$_R$       | [44]   |
|                          | rat aorta           | NR          | d           | +       |              |     |     |          | -VOCC$_1$/-IP$_R$       | [45]   |
| 174 Rutin                | rat mesenteric      | NR          | d           | +       | +            |     |     | +K$_{ATP}$ | [211]                 |
|                          | rat aorta           |             |             |         |              |     |     |          |                       |        |
| 175 Salvianolic acid B   | rat coronary        | 147.9 ± 17.4 µg/mL | i   |         | +            |     |     |          | -VOCC/                 | [212]  |
| 176 Sanguinarine         | rat aorta           | 3.18 ± 0.37 µM | i   |         |              |     |     |          | -VOCC$_1$/-ROCC/       | [213]  |
|                          |                     |             |             |         |              |     |     |          | -IP$_R$                |        |
| 177 Saponins from Ginseng* | NR                 |             |             |         |              |     |     |          | -ROCC/                 | [49]   |
| 178 Sappanchalcone       | rat aorta           | NR          | d           | +       | +            |     |     |          | [85]                   |
|                          | rat mesenteric      |             |             |         |              |     |     |          |                       | [182]  |
| No.  | Compound          | Type of artery/vein | EC$_{50}$    | Endothelium | NO/ cGMP | PGI$_2$/ cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ext/Ca$^{2+}$int | Ref.  |
|------|-------------------|---------------------|-------------|-------------|----------|---------------|-----|-----|----------|--------------------------|-------|
| 180  | Saucerneol D      | rat aorta           | 12.7 µM     | d           | +        |               |     |     |          |                          |       |
| 181  | Scirpusin B       | rat aorta           | NR          | d           | +        |               |     |     |          |                          |       |
| 182  | Scutellarin       | rat aorta           | 7.7 ± 0.6 µM | i           | x        | x             | x   | x   |          | -VOCC/x                   | [215] |
| 183  | Senkyunolide A    | rat aorta           | 4.32 ± 0.10  | i           | x        | x             | x   |     |          |                          | [180] |
| 184  | S-petasin         | rat mesenteric      | 6.01 ± 0.08  | i           | x        | x             |     |     |          | -VOCC$_{c}$/              | [72]  |
|      |                   | rat aorta           | 4.76 ± 0.16  | i           | x        | x             |     |     |          | -VOCC$_{c}$/              | [72]  |
|      |                   | rat aorta           | 6.6 ± 1.4 µM | i           | x        | x             |     |     |          | -VOCC$_{c}$/              | [72]  |
| 185  | Tetramethylpyrazine| rat aorta         | NR          |             |          |               |     |     |          |                          |       |
|      |                   | rabbit basilar      | NR          |             |          |               |     |     |          |                          |       |
|      |                   | rat aorta           | NR          |             |          |               |     |     |          |                          |       |
|      |                   | rat pulmonary       | 522 µM      | d/i         | +        |               |     |     |          |                          | [217] |
| 186  | Tetrandrine       | NR                  |             |             |          |               |     |     |          |                          |       |
| 187  | Thaligrisine      | rat aorta           | 23.0 ± 0.39 µM | i         | x        |               |     |     |          | -VOCC/                    | [221] |
| 188  | Thymol            | rat aorta           | 106.4 ± 11.3 µM | i      | x        |               |     |     |          | -VOCC/-IP$_3$R           | [96]  |
| 189  | Tiliannin         | rat aorta           | 240 µM      | d/i        | +        | x             | +K$_{V}$ |     |          |                          | [222] |
| 190  | Trans-dehydrocrotonin| rat aorta          | NR          | d          | +        |               |     |     |          |                          | [223] |
| 191  | Trans-resveratrol | rat aorta           | 3.12 ± 0.26 µM | d      | +        |               |     |     |          |                          | [224,225] |
| 192  | Ursolic acid      | rat aorta           | 44.1 ± 6.1 µM | d      | +        | x             |     |     |          |                          | [64]  |
| 193  | Villocarine A     | rat aorta           | NR          | d/i        | +        |               |     |     |          | -VOCC,-ROCC/              | [226] |
| 194  | Vincamedine       | rat aorta           | NR          | d/i        | +        |               |     |     | x        | -VOCC,-ROCC/              | [227] |
| 195  | Visnadine         | rat aorta rat portal| NR      | d/i        | +        |               |     |     |          |                          | [228] |
| Compound                    | Type of artery/vein | EC$_{50}$ | Endothelium | NO/cGMP | PGI$_2$/cAMP | PDE | PKC | K$^+$ Ch | Ca$^{2+}$ ext/Ca$^{2+}$ int | Ref.   |
|-----------------------------|---------------------|-----------|-------------|---------|--------------|-----|-----|----------|--------------------------|--------|
| 196 Visnagin                | rat aorta           | 22 ± 4 µM | i           |         |              |     |     |          | -VOCC$_{L,R}$,-ROCC,-IP$_{R,-RyR}$ | [229]  |
| 197 Vitisin C               | rabbit aorta        | NR        | d +         |         |              |     |     |          | -VOCC/                   | [230]  |
| 198 Vulgarenol              | guinea pig heart    | NR        | d           | +       |              |     |     |          | -VOCC/                   | [231]  |
| 199 Wine polyphenolic      | rat aorta           | 3.27 ± 0.02 $^{1,5}$ | d | + | x | + | | [47,178] |
| compounds *                |                     |           |             |         |              |     |     |          | -VOCC,-ROCC/             |        |
| 200 Xanthoangelol          | rat aorta           | NR        | d           | +       |              |     |     |          | -VOCC/                   | [53]   |
| 201 Xanthoangelol B        | rat aorta           | NR        | i           | x       |              |     |     |          | -VOCC/                   | [53]   |
| 202 Xanthoangelol E        | rat aorta           | NR        | d           | +       |              |     |     |          | -VOCC/                   | [53]   |
| 203 Xanthoangelol F        | rat aorta           | NR        | d           | +       |              |     |     |          | -VOCC/                   | [53]   |
| 204 Xanthone                | rat aorta           | 60.26 ± 8.43 µM | i | ↑cAMP | | | | | -VOCC,-ROCC/x | [232] |
| 205 Xanthorrhizol           | rat aorta           | NR        | i           | x | x | | | | -VOCC,-ROCC/ | [233] |
| 206 Zearalanone             | rabbit coronary     | NR        | i           |         |              |     |     |          | -VOCC/                   | [149]  |
| (Z)-3-methylthioacrylic    | rat mesenteric      | 5.24 ± 0.13 $^{1,3}$ | i | x | x | | | | -VOCC$_{L}$ | [72] |
| ester of 2beta-hydroxy-8betah-7(11)-eremophilene-12,8-olide | rat aorta | 4.26 ± 0.17 $^{1,3}$ | | | | | | | |

**Abbreviations:** d, endothelium-dependent; i, endothelium-independent; +, activation; -, inactivation; x, without involvement; EC$_{50}$, median effective concentration; NO/cGMP, NO/cGMP pathway; PGI$_2$/cAMP, PGI$_2$/cAMP pathway; PDE, phosphodiesterase; PKC, protein kinase C; Ca$^{2+}$ ext, extracellular Ca$^{2+}$ influx; Ca$^{2+}$ int, Ca$^{2+}$ release from intracellular stores; ↑GMP, increased levels of GMP; ↑cAMP, increased levels of cAMP; BK$_{Ca}$, high-conductance Ca$^{2+}$-activated K$^+$ channels; IK$_{Ca}$, intermediate-conductance Ca$^{2+}$-activated K$^+$ channels; SK$_{Ca}$, low-conductance Ca$^{2+}$-activated K$^+$ channels; K$_{ATP}$, ATP-dependent K$^+$ channels; K$_{IR}$, inwardly rectifying K$^+$ channels; K$_{v}$, voltage-dependent K$^+$ channels; VOCC, voltage-operated Ca$^{2+}$ channels; VOCC$_{L}$, L-type voltage-operated Ca$^{2+}$ channels; ROCC, receptor-operated Ca$^{2+}$ channels; IP$_{3}R$, inositol triphosphate receptor; RyR, caffeine/ryanodine receptor. EC$_{50}$ determined in tissues precontracted with ¹ phenylephrine, ² KCl, ³ U46619, ⁴ prostaglandin F2α, ⁵ norepinephrine, ⁶ 5-hydroxytryptamine, ⁷ 4-aminopyridine. § pD2 (−log EC$_{50}$); § IC30 (−log IC$_{30}$). NR, not reported; No symbol, not investigated; * Mixtures of compounds obtained from a single plant species.
6. Compounds Acting on the NO/cGMP Pathway

Although three distinct isoforms of NO synthase (NOS) have been identified (endothelial, eNOS; inducible, iNOS; and neuronal, nNOS), it has generally been accepted that regulation of vascular tone is primarily dependent upon the release of NO from eNOS [234]. However, some studies have suggested that nNOS [235] and iNOS [236] may also be involved in this process. Therefore, NO synthesis can be modulated by regulating the activity or gene expression of the three NOS isoforms [237]. NO, produced by these enzymes, dilates all types of blood vessels by stimulating sGC and increasing cGMP in smooth muscle cells [238].

6.1. Compounds that Regulate eNOS Expression

Although eNOS was initially characterized as a constitutive enzyme of the vascular endothelium, there is evidence to suggest that the expression of this enzyme can be regulated by physiological stimuli or by the actions of certain compounds [239,240]. Some of the compounds obtained from plants that regulate the gene expression of eNOS are betulinic acid, a pentacyclic triterpene isolated from *Zizyphi spinosi*, a plant used in traditional Chinese medicine for the treatment of cardiovascular diseases [241]; several flavonoids, such as cynaroside and luteolin, which are constituents of the plants *Cynara scolymus* L. (artichoke) and *Prunella vulgaris* [242,243]; alkaloids, such as keayanidine B and keayanine, isolated from *Microdesmis keayana*, an African tropical plant whose roots are used in traditional medicine for treating erectile dysfunction [172]; and other metabolites, such as piceatannol [244].

In general, assays for determining the contributions of these compounds to the regulation of eNOS gene expression have been performed on endothelial cells from the human umbilical cord vein (the EA. hy926 cell line) [244]. For example, in the study of icariin, a flavonoid isolated from *Epimedii herba*, this cell line was cultured in the presence of different concentrations of it. Subsequently, reverse transcriptase PCR and western blot techniques were used to determine the change in the levels of mRNA and protein of eNOS, respectively. The results indicated that after incubation for 12 h in the presence of icariin, both the mRNA expression and the protein levels of eNOS increased significantly as a function of time and concentration. Additionally, icariin induced a significant relaxation on rat aorta and canine coronary artery [158,159].

6.2. Compounds that Regulate eNOS Activity

In general, assessment of the participation of the NO/cGMP pathway is accomplished through the use of inhibitors of eNOS and sGC. In the case of eNOS, the most commonly inhibitor used is Nω-nitro-L-arginine methyl ester (L-NAME) or some other derivatives, such as Nω-monomethyl-L-arginine (L-NMMA) [82,162]. In the case of sGC, 1H-[1,2,4]oxadiazole[4,3-a]quinoxaline-1-one (ODQ) or methylene blue [125] are the most commonly used inhibitors.

The tissues commonly used to test the effects of compounds on the NO/cGMP pathway are isolated rat thoracic aorta rings or arteries from the mesenteric artery bed [126,187]. However, other tissues have been used, such as rat basilar artery [115], rabbit thoracic aorta [230], porcine coronary artery [113], canine coronary artery [159], and bovine ophthalmic artery [31]. An example of a study where both models, the isolated aorta and the mesenteric artery bed, were employed comprises evaluation of the
vasodilator effect of alpha-terpineol and methyl eugenol, which were obtained from the essential oil of *Croton nepetaefolius*. It was found that the NO/cGMP pathway was involved in the vasodilatory activity of these compounds, as the pathway was inhibited in the presence of L-NAME and methylene blue [67].

An example of a compound whose mechanism of action involves activation of eNOS is brazilin, a homoisoflavonoid obtained from *Caesalpinia sappan L*. This metabolite induced an increase in cGMP levels and vasodilation of the aorta in a concentration-dependent manner. The effect of brazilin has also been studied in cultured endothelial cells from the umbilical cord vein. In these cell cultures, brazilin induced a concentration-dependent increase in eNOS activity by causing an elevation of intracellular Ca$^{2+}$ in endothelial cells, thus stimulating calmodulin, which in turn activated eNOS [84]. A similar mechanism of action was proposed for gomisin A, a lignane obtained from *Schisandra chinensis*; however, in this case, human coronary endothelial cells were used to determine the activation of eNOS [245].

Mechanisms that activate eNOS through the phosphatidylinositol-3-kinase/protein kinase B (PIK3/Akt) pathway have also been proposed. The vasodilator effect of epigallocatechin-3-gallate, the most abundant catechin in tea (*Camellia sinensis*), was dramatically reduced by the PIK3 inhibitor wortmannin and the Akt inhibitor SH6, suggesting that this compound activates the NO/cGMP pathway by inducing the phosphorylation of eNOS [31]. Moreover, this mechanism has also been suggested to account for the vasodilatory activity of proanthocyanidins from the persimmon leaf, quercetin and resveratrol. The effect of these metabolites was studied in diverse cultured endothelial cells and results have pointed out that these compounds induced vasorelaxation through the endothelium-dependent NO/cGMP pathway via sequential phosphorylation of Akt [28,36,50].

### 6.3. Compounds that Regulate the Activity and Expression of sGC

The results of some studies have suggested that the vasodilator effects of certain compounds produced from plants are mediated by the activation of sGC and, therefore, by an increase in cGMP levels. The levels of sGC have been quantified on rings of isolated rat aortas using immunological techniques [45,162]. In this context, it has been proposed that isoliquiritigenin, a chalcone isolated from *Dalbergia odorifera*, relaxes the aorta by an endothelium-independent mechanism. Furthermore, incubation of the aorta with this chalcone caused an increase in cGMP levels and a slight increase in cAMP [162]. It has also been proposed that the metabolites emodin and osthole produce their vasodilator effects through a mechanism of action involving increased levels of sGC [127,195].

About 40% of the compounds showed more than one mechanism of action (Table 1). For example, alpinetin and cardamonin exert their relaxing effects through both endothelium-dependent and endothelium-independent mechanisms, the former by activation of the NO/cGMP pathway and the latter through the non-selective inhibition of Ca$^{2+}$ channels in smooth muscle cells and the inhibition of the contractile mechanism dependent on protein kinase C (PKC) [69]. Similar mechanisms have been proposed for citral and formononetin; both compounds induced relaxation in rat aortic rings through an endothelium-dependent manner via the nitric oxide pathway, and also involving endothelium-independent vasodilatation by the blockade of Ca$^{2+}$ channels [102,145].
It has also been suggested that the involvement of different mechanisms could depend on the concentration of the metabolite. Low concentrations of caffeic acid phenylethyl ester (CAPE), one of the main components of propolis, induce a relaxing effect on vascular smooth muscle through the activation of the NO/cGMP pathway. In contrast, high concentrations of this compound induce vasodilation in an endothelium-independent manner, likely due to the inhibition of Ca\(^{2+}\) entry into the cytoplasm of muscle cells or due to the inhibition of the release of this cation from intracellular stores [91].

Moreover, the mechanism of action depends on the type of vascular bed and species variations. In this sense it has been demonstrated that vascular relaxation attributable to NO is most prominent in large vessels such as the aorta, while in resistance vessels that regulate blood pressure more directly, NO’s effects are less evident [246]. As an example of the influence of species variations on the action of compounds that affect NO expression, it was shown that resveratrol induced down-regulation of eNOS gene expression in human endothelial cells [247], in contrast, this compound increased eNOS protein expression in bovine endothelial cells [248]. On the other hand, imperatorin, a coumarin obtained from *Angelica dahurica* var. formosana, induced an endothelium-independent relaxation in rat mesenteric arterial rings by blocking the voltage-dependent calcium channel and the receptor-mediated Ca\(^{2+}\) influx and Ca\(^{2+}\) release [160]. However, in mouse thoracic aorta this coumarin elicited vasodilatation via an endothelium-dependent mechanism involving the nitric oxide pathway [161].

Some studies have conducted *in vivo* assays in addition to tests on isolated tissues. Chrysin glucoside, isolated from the leaves and flowers of *Calycotome villosa*, has been observed to have an endothelium-dependent vasodilator effect on isolated rat aortas and a hypotensive effect when administered intravenously to rats [249]. The results of the *in vivo* assays suggest that the hypotensive effect is probably due to increased vascular relaxation [22,63,76,107,119,136,165].

7. Compounds that Activate the PGI\(_2\)/cAMP Pathway

Few studies have proposed the activation of the PGI\(_2\)/cAMP pathway as a mechanism for the vasodilator effects of plant-derived compounds. PGI\(_2\) is an endogenous vasoactive eicosanoid produced by cyclooxygenase (COX) from arachidonic acid in endothelial cells; its production is stimulated by endogenous agonists such as serotonin, histamine, bradykinin and acetylcholine. In addition to inhibiting platelet aggregation, PGI\(_2\) also causes relaxation of vascular smooth muscle through stimulation of a G-protein-coupled receptor that, in turn, activates adenylyl cyclase (AC) and thus raises cAMP levels, inducing vasodilation as a result [250]. The participation of this pathway is determined by using indomethacin as an inhibitor of the COX enzyme [82,154]. Some compounds whose mechanism of action involves the activation of this pathway at the level of the endothelium are ethyl cinnamate, isolated from the rhizomes of *Kaempferia galanga* [104]; eudesmin, a lignan obtained from *Piper truncatum* [135]; labdane-302, a diterpene obtained from *Xylopia langsdorffiana* [174]; rutin [211]; and procyanidins, derived from grape seeds [201].

The vasodilator activity of procyanidins was evaluated in human internal mammary aortic rings. It was determined that both the NO/cGMP and the PGI\(_2\)/cAMP pathways were involved in this process through experiments using inhibitors of eNOS (L-NMMA) and sGC (ODQ) for the first pathway and COX (indomethacin) for the second one. The vasodilator effect of procyanidins was eliminated by the removal of the endothelium. Additionally, inhibition of COX produced a 50% decrease in the
vasodilatory activity of these compounds, suggesting the involvement of the PGI₂/cAMP pathway in their mechanism of action. Subsequent experiments confirmed this finding by observing an increase in PGI₂ release, which was dependent on the concentration of procyanidins [201].

Other studies have suggested that some natural compounds produce a vasodilator effect by directly activating AC or increasing cAMP levels in smooth muscle cells. The experimental protocols of these studies aimed to evaluate the effects of both an AC inhibitor (SQ22536) and an inhibitor of cAMP-dependent protein kinase (PKA) (KT5720) on the vasodilation produced by the test compound [79]. Additionally, analogs and antagonists of cyclic nucleotides have been used in the evaluation of these pathways [251]. For example, puerarin, an isoflavone isolated from *Radix puerariae* that was evaluated using porcine coronary artery rings, was able to shift the dose-response curve of sodium nitroprusside (SNP) to the left. This effect was independent of the endothelium. The SNP-induced relaxation was enhanced by the cAMP analog, 8-Br-cAMP, at a rate similar to that of puerarin, suggesting the involvement of the PGI₂/cAMP pathway in the increased vasodilatory activity. Moreover, the cAMP antagonist Rp-8-Br-cAMP decreased the vasoactive effect of this isoflavone. In this case, analogs of cGMP (agonists or antagonists) had no effect on the activity of puerarin. Based on these results, it was suggested that the mechanism of action whereby this isoflavone increases vasodilation in the porcine coronary artery is the activation of the PGI₂/cAMP pathway [251].

8. Compounds that Inhibit Phosphodiesterases (PDEs)

Cyclic nucleotide phosphodiesterases (PDEs) are enzymes that regulate the cellular levels of cAMP and cGMP by controlling their rates of degradation [252]. The major PDEs in arterial smooth muscle are PDE1, PDE3, PDE4 and PDE5; specifically, PDE5 has been found to be a major cGMP-hydrorlizing PDE expressed in smooth muscle cells. The inhibition of PDEs produces vasorelaxant effects by increasing cyclic nucleotide levels [252–254].

Several compounds, mostly flavonoids, have been described as PDE inhibitors and vasodilators [18,23,29,157]. The involvement of PDEs in the vasorelaxant effect of these compounds was evaluated by measuring the change on PDE activity. PDEs have been isolated from the cytosolic fraction of bovine aortic smooth muscle [18,23] or rat aorta [87] and their activities were measured by radioenzimatic assays [255].

Specific PDEs were inhibited by different compounds. For example, the vasorelaxant effect of dioclein inhibited PDE1, and to a lesser extent PDE4 and PDE5 [23]; meanwhile, epigallocatechin-3-gallate showed activity over PDE1 and PDE2 [29], while butein, a chalcone obtained from *Dalbergia odorifera*, inhibited PDE4 only [87].

9. Compounds that Activate K⁺ Channels

The K⁺ channels in vascular smooth muscle play an important role in vasodilation because the outflow of K⁺ through these channels hyperpolarizes the membrane and thereby inhibits the entry of Ca²⁺. This process eventually results in the relaxation of blood vessels [256]. Four different types of potassium channels have been characterized in arterial smooth muscle: voltage-dependent channels (Kᵥ), Ca²⁺-activated channels (large-conductance, BKCa; intermediate-conductance, IKCa; and small-conductance, SKCa), ATP-dependent channels (KₐTP) and inwardly rectifying channels (KᵢR) [257–260].
It is worth mentioning that there is evidence for cell to cell, segment to segment, and vascular bed to bed diversity of K⁺ channels that could explain the varying responses of arterial segments or different arteries to stimuli such as hypoxia, vasoactive drugs, or arterial wall injury [261–263].

The involvement of different types of K⁺ channels has been evaluated by the use of channel-specific blockers. The following are the most commonly used blockers of K⁺ channels: chloride tetraethylammonium (TEA) and BaCl₂ as nonselective inhibitors [22,86]; glibenclamide, an inhibitor of K<sub>ATP</sub> channels; aminopyridine (4-AP), which blocks Kv channels; and iberiotoxin [35] and charybdotoxin, which block BK<sub>Ca</sub> channels [42,98]. In addition, TEA [82], BaCl₂ [22], and apamin [31] have been used to block BK<sub>Ca</sub>, K<sub>IR</sub>, and SK<sub>Ca</sub> channels, respectively.

BK<sub>Ca</sub>, highly expressed in vascular smooth muscle cells [258], can be activated by both, the NO/cGMP pathway [264] and EDHF [265]. These channels play a key role in blood pressure regulation and therefore, they have been suggested as novel potential drug targets for the treatment of cardiovascular diseases [266]. Recently, a considerable number of natural compounds, especially of the flavonoid type, have been shown to have a vasodilator effect caused, at least in part, by activation of BK<sub>Ca</sub> channels [19,22,198,267,268]. Other compounds with different chemical structures that activate this kind of potassium channels are: diosgenin (steroid sapogenin) [62]; piceatannol (stilbene) [32], isolated from the root of Rheum undulatum; and rotundifolone (monoterpene) [42], the major constituent of the essential oil of Mentha × villosa Hudson.

The study of compounds that activate K⁺ channels also includes the use of electrophysiological techniques, both to demonstrate these compounds’ role as stimulants and to characterize the type of channels involved in their vasodilator mechanisms. The most common strategy is the patch-clamp technique used on isolated muscle cells [116] or in Xenopus oocytes that express K⁺ channels from other organisms [269]. For example, the elucidation of the mechanism of action of rotundifolone was carried out in rat superior mesenteric arteries. For investigating the involvement of K⁺ channels in the vasorelaxant mechanism, several specific channel blockers were used such as TEA, charybdotoxin, 4-AP and glibenclamide. In addition, electrophysiological testing using the patch-clamp technique in mesenteric smooth muscle cells was used to identify the channels activated by rotundifolone. The results indicated that the vasodilator effect of this compound involves the participation of BK<sub>Ca</sub> channels [42]. However, it has been shown that the use of the patch-clamp technique induces apparent phenotypic changes, particularly when it is used on isolated and cultured cells, compared to data derived from intact tissue. Consequently, data gathered in this manner should be interpreted with caution [270].

10. Compounds that Decrease Intracellular Ca<sup>2+</sup> Concentration

The mechanism of vascular smooth muscle contraction involves the participation of different signal transduction pathways, all of which converge to increase cytoplasmic Ca<sup>2+</sup> concentrations. The concentration of this cation increases both by extracellular Ca<sup>2+</sup> entering through voltage-operated Ca<sup>2+</sup> channels (VOCCs) and receptor-operated Ca<sup>2+</sup> channels (ROCCs), and by the release of Ca<sup>2+</sup> from intracellular stores [123]. Therefore, the mechanisms of action associated with vasodilating agents that decrease intracellular Ca<sup>2+</sup> concentration involve blocking VOCCs and ROCCs or inhibiting the release of this cation from intracellular stores. The experimental strategy to determine the involvement
of Ca\(^{2+}\) channels in the vasodilating effect of test compounds involves incubating aortic rings in a Ca\(^{2+}\)-free medium containing a high concentration of K\(^{+}\) and to which CaCl\(_2\) is gradually added to induce contraction, both in the absence and presence of the vasodilating compound [79,123].

Different techniques are used to determine the involvement of VOCCs, ROCCs or the release of intracellular calcium. The inhibitory action of vasodilator compounds on VOCCs can be seen as a rightward shift in the dose-response curve for CaCl\(_2\), as noted in the case of ligustilide, a compound extracted from *Ligusticum chuanxiong*, a plant used in traditional Chinese medicine [179], and naucine, an alkaloid derived from *Nauclea officinalis* [89]. For evaluating the involvement of ROCCs, dose-response curves are performed in the presence of an adrenergic agonist, such as noradrenaline (NA) [123] or phenylephrine (PE) [56] to induce contractions, both in the absence and the presence of the vasodilator compound [89,123]. In addition, the contribution of Ca\(^{2+}\) released from intracellular stores is determined by incubating the tissue in a Krebs solution free of Ca\(^{2+}\) and to which NA is subsequently added to induce phasic contractions with calcium from the sarcoplasmic reticulum. Subsequently, once the contraction is stabilized, CaCl\(_2\) is added to induce a tonic contraction. When incubating segments of the aorta with the test compound under these conditions, a decrease of phasic contractions signals that the effect is produced by the outflow of intracellular Ca\(^{2+}\), whereas a decrease in tonic contraction signals that the effect is mediated by Ca\(^{2+}\) entry through ROCCs [185].

The release of Ca\(^{2+}\) from intracellular stores is regulated by the inositol-1,4,5-triphosphate (IP\(_3\)) system and by the ryanodine receptors (RyRs). RyRs system are a Ca\(^{2+}\) release system where Ca\(^{2+}\) release is induced by the presence of Ca\(^{2+}\) when the receptors are activated by caffeine [179]. For example, isopropyl-3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate has been shown to inhibit both KCl-induced and norepinephrine-induced contractions in the absence and presence of Ca\(^{2+}\) in the rat mesenteric artery. These results suggest that in addition to its activity on VOCCs, this compound also acts on ROCCs and on intracellular calcium stores [123]. In this type of study, blockers of L-type Ca\(^{2+}\) channels, such as nifedipine [271] or diltiazem [154], are used as a positive control. However, calycosin, the main component of *Astragali radix*, was shown to inhibit CaCl\(_2\)-induced vasoconstriction in the presence of KCl and PE but did not affect PE-induced contractions in a calcium-free medium. These results indicated the involvement of VOCCs and ROCCs in the vasodilator effect produced by calycosin, excluding the outflow of intracellular Ca\(^{2+}\) [93]. In contrast, low concentrations of euxanthone, a metabolite isolated from *Polygala caudate*, inhibited the phasic contraction, suggesting that the exit of Ca\(^{2+}\) from the endoplasmic reticulum is involved in the relaxing activity [139]. Moreover, both cardamonin and alpinetin can inhibit the transient contractions produced by PE and caffeine in a Ca\(^{2+}\)-free medium and also the contractions induced by K\(^{+}\). The authors suggest that these compounds act through the nonspecific inhibition of Ca\(^{2+}\) entry and the release of intracellular Ca\(^{2+}\) [69].

Other methodologies have been used to elucidate the mechanisms of action of vasoactive compounds. For example, the involvement of VOCCs in the vasodilator mechanism of marrubeneol, a diterpene extracted from *Marrubium vulgare*, was confirmed by recording the inflow current through calcium channels using patch-clamp and fluorescence techniques [183].
11. Compounds that Activate Endothelial Transient Receptor Potential (TRP) Cation Channels

Transient receptor potential (TRP) cation channels are currently considered as the leading candidate proteins mediating diverse non-voltage-gated calcium entry pathways in vascular endothelium and smooth muscle [272,273]. The TRP superfamily contains three major subfamilies based on sequence homology: TRPV (vanilloid), TRPC (canonical), and TRPM (melastatin). Moreover, three additional subfamilies (the “distant TRPs”), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin) have been proposed [274]. In particular, the endothelial TRP channels are exposed to different agonists that enter the blood stream as dietary molecules. Some of these molecules, found in commonly consumed food and plants used in traditional medical practices of several cultures are able to activate these kinds of channels [97,272,273]. Carvacrol, one of the major components of oregano (*Origanum vulgare*) essential oil, induces an endothelium-dependent vasodilation by activating TRPV3 [97]. Recently, it has been reported that allyl isothiocyanate, which is found in the seeds of mustard (*Brassica nigra* and *B. juncea*) causes endothelium-dependent vasodilation of rat cerebral arteries by a mechanism involving TRPA1 activation [66].

12. Compounds that Inhibit Protein Kinase C

The mechanism of vascular smooth muscle contraction evokes the phosphorylation of myosin light chain by increasing intracellular Ca$^{2+}$ concentration. Additionally, the decrease of the myosin light chain phosphatase (MLCP) increases the sensitivity to Ca$^{2+}$ [275]. Several pathways have been suggested for the Ca$^{2+}$ sensing mechanism. One of them is the PKC/CPI-17 pathway [276]. PKC phosphorilates CPI-17, enhancing its inhibitory activity over MLCP [276] and producing a sustained contraction. PKC has been found in high concentrations in vascular smooth muscle and can be activated by diacylglycerol [277].

Only a few compounds have been found to evoke their vasorelaxant activity through this mechanism; in all cases, PKC inhibition was not the only mechanism. The participation of PKC in the vasorelaxant mechanism has been evaluated using activators of PKC in smooth muscle cells, such as phorbol esters. 12-O-tetradecanoyl phorbol 13-acetate, phorbol 12-myristate-13-acetate (PMA) and phorbol 12,13-dibutyrate (PDB) were used to evaluate the vasorelaxant mechanisms for dioclein [21], quercetin [24] and euxanthone [139], respectively. This last activator was used also in the characterization of the mechanism of action for thymol and carvacrol: PDB induced a sustained contraction that was attenuated when thymol or carvacrol were added (300 and 1,000 µM) [96].

13. Conclusions

The present review focused on the mechanisms of action responsible for the vasodilator activity of plant-derived compounds. From the information obtained, we identified the main mechanisms of action of most of the vasodilator compounds; these mechanisms are the activation of the NO/cGMP and PGI2/cAMP pathways, the activation of K$^+$ channels and the blockade of voltage-dependent Ca$^{2+}$ channels.

It should be noted that more than one mechanism of action has been proposed to be involved in the vasodilator effect of almost half of all of the analyzed compounds. This finding suggests that compounds derived from plants may have great therapeutic potential as they involve multiple
mechanisms of action in their vascular relaxing activity. In this context, it is critical to emphasize the importance of understanding the different mechanisms of action in order to establish new therapeutic strategies for addressing various cardiovascular diseases.

Finally, given the structural diversity of the active compounds derived from natural products and the diversity of mechanisms of action responsible for their vasodilator activity, it is important to continue the search for new active substances that help in the treatment of cardiovascular diseases.

Acknowledgments

Francisco J. Luna-Vázquez acknowledges Consejo Nacional de Ciencia y Tecnología (CONACYT) for his Ph. D. scholarship.

Conflict of Interest

The authors declare no conflict of interest.

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