Original Article

Endothelium-dependent Vasorelaxation by *Adansonia digitata L.* : Possible Involvement of NO and EDH in Porcine Coronary Arteries

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Abstract

Introduction: *Adansoniadigitata* leaves are used in the traditional treatment of arterial hypertension in Senegal. The objective of this study was to determine the vasorelaxant effect of the hydro-ethanol leaf extract of Adansoniadigitata (ADF) on porcine coronary arteries and to elucidate the mechanisms involved

Material and Methods: Porcine coronary arteries were suspended in organ chambers for the recording of changes in isometric forces. Rings with intact endothelium were incubated with or without various inhibitors. L-nitro-arginin (L-NA), an inhibitor of endothelial NO synthase; Mn (III) tetrakis (1-methyl-4-pyridyl) porphyrin (MnTMPyP); Polyethylene glycol catalase (PEG-CAT); N-acetyl-L-cysteine (NAC), inhibitors of intracellular production of reactive oxygen species; Catalase (CAT), an inhibitor of extracellular reactive oxygen species; Wortmannin, an inhibitor of the redox-sensitive pathway PI3 kinase/Akt; PP2 (4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine), an inhibitor of Src kinase; apamin (APA), an inhibitor of small conductance calcium-dependent potassium channels (SKCa); and Tram-34, an inhibitor of intermediate conductance calcium-dependent potassium channels (IKCa); and indomethacin (INDO), an inhibitor of cyclooxygenase, were applied before contraction with U46619 and the generation of a concentration-relaxation curve to ADF. In some experiments, the endothelium was removed before contraction with U46619 and the generation of a concentration-relaxation curve to ADF. The phosphorylation levels of Akt and eNOS were assessed by Western blot analysis.

Results: ADF produced 100% relaxation at 10 µg/ml in endothelium intact arteries pre-contracted with U46619. ADF induces a redox-sensitive endothelium-dependent relaxation in porcine coronary arteries. This effects is mediated by NO and endothelium-derived hyperpolarizing (EDH) whereas prostacyclins do not appear to play a role in the vascular effects. However, ADF induced sustaining phosphorylation of Akt and eNOS in endothelial cells.

Conclusion: *Adansoniadigitata* induces vasodilation, which may explain its antihypertensive effect and its use in traditional African medicine.

Keywords: *Adansoniadigitata*, vasorelaxant, porcine coronary.

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Introduction

Hypertension represents a significant global public health issue due to its prevalence and the associated risks of cardiovascular diseases. Over a quarter (26.6%) of the adult population is hypertensive, and this proportion is projected to increase to 29.2% by 2025, which would amount to approximately 1.6 million hypertensive individuals [1]. Among the 17 million patients who die each year from cardiovascular diseases, it is estimated that 7 to 8 million are hypertensive [2]. Developing countries are particularly affected; by 2025, it is anticipated that almost three-quarters of the global hypertensive population will reside in these regions. Senegal is no exception to this trend [3,4], which may exacerbate health disparities. This is why the WHO encourages the use of traditional medicine [5]. In this context, our study focuses on *Adansoniadigitata* L., a plant in the Senegalese pharmacopoeia. Although many ethnobotanical studies have attributed various therapeutic properties, including antihypertensive effects, to this plant [6], these claims have not been thoroughly validated by experimental scientific research. The objective of our study is to determine the *in-vitro*vasorelaxant effects of the hydro-ethanolic crude extract of *Adansoniadigitata* leaves in porcine coronary arteries and to characterize the mechanisms involved in these effects.This model is chosen in our study, due to the great anatomo-histological similarity between the pig's heart and that of humans.

Materials and Methods

Vegetal Material

Adansoniadigitata L. leaves were collected in August 2015 in the botanical garden of the Faculty of Medicine, Pharmacy, and Odontology at Cheikh Anta Diop University of Dakar (Senegal). They were identified in the botanic laboratory of IFAN at Cheikh Anta Diop University of Dakar. Voucher specimens were deposited in the university herbarium under No. IFAN55364. The conditions for drying, processing dried leaves into powder, extraction, and preservation of the raw extract were described by Sene et al.([7]). This step allowed for the obtainment of a solid content to be used in vascular reactivity tests and Western blot analysis.

Phytochemical Screening

Phytochemical tests were performed on the crude hydroethanolic extract of *Adansoniadigitata* leaves to determine the presence of secondary metabolites using standard protocols. [8].

Determination of Total Phenolic Contents

The total phenolic contents were determined in triplicate and expressed as mg gallic acid equivalents (GAE) using the Folin–Ciocalteu method [9].

Chemical Material

Nω-nitro-L-arginine (L-NA), indometacin (INDO), apamin (APA), Tram-34, catalase, polyethylene glycol catalase (PEG-catalase) and N-acetyl-L-cysteine (NAC) were obtained from Sigma Chemical Co. (Saint Louis, MB, U.S.A). Wortmannin and the SOD mimetic Mn(III) tetrakis (1-methyl-4-pyridyl) porphyrin (MnTMPyP) were purchased from Alexis Chemicals. U46619 (9, 11-dideoxy-9α-methanoepoxy prostaglandin $F_{2\alpha}$) and PP2 (4-amino-5-(4-chlorophenyl)-7-(t-butyl) pyrazolo [3,4-d]pyrimidine) from Calbiochem. Bradykinin was purchased from Cayman Chemical (Ann Arbor, MI, U.S.A.)

Vascular Reactivity Studies

The left circumflex coronary artery was removed and carefully cleaned of fat and connective tissue in a physiological Krebs bicarbonate solution at 4 ° C. The artery was cut into rings of 3 to 4 mm length. For some experiments the endothelium was removed mechanically by rubbing the intimal surface of the rings by means of a notched clamp. The rings were subsequently suspended between two metal hooks in tanks isolated organ 10 ml thermostated at 37 ° C and oxygenated with carbogen (95% O_2 and 5% CO_2), and containing Krebs solution (composition in mM: NaCl 119, KCl 4.7, KH_2PO_4 1.18, $MgSO_4$ 1.18, $CaCl_2$ 1.25, $NaHCO_3$ 25, and D-glucose 11, pH 7.4).

Each ring was connected to an isometric tension sensor which measures the variations. Following an equilibration period of 45 min to 1 hour under a resting tension of 5 g. After an equilibration period of 60 minutes, the rings were contracted with a Krebs solution containing 80 mMKCl to verify the integrity of the artery. After washing and a further 30 min equilibration period, rings of porcine coronary arteries were contracted with the thromboxane mimetic U46619 (1-60 nM) to about 80% of the maximal contraction before addition of bradykinin (0.3 µM) to check the presence of a functional endothelium. After washing and a 30 min equilibration period, rings were again contracted with U46619 before a concentration-relaxation curve to ADF. In some experiments, rings were exposed to inhibitor(s) 30 to 45 min. The global component was defined as the relaxation obtained in the absence of inhibitors. The NO- plus EDHF-mediated relaxation was determined in the presence indomethacin (10 µM) to rule out the formation of vasoactive prostanoids. The NO-mediated component of relaxation was recorded in the presence of indomethacin (10 µM) and Tram-34 plus apamin (100 nM each) to rule out the formation of vasoactive prostanoids and EDH, respectively. Relaxations were expressed as a percentage of the contraction induced U46619.

Culture of Porcine Coronary Artery Endothelial Cells

Segments of porcine coronary arteries were flushed with PBS without calcium to remove the remaining blood. Thereafter, endothelial cells were isolated by collagenase treatment (type I, Worthington, 1 mg/ml for 15 min at 37 ° C), and cultured in culture dishes containing MCDB 131 medium (Invitrogen) supplemented with 15% fetal calf serum, penicillin (100 U/ml), streptomycin (100 U/ml), fungizone (250 µg/ml) and L –glutamine (2 mM) (all from Cambrex) and grown for 48–72 h. All experiments were performed with confluent cultures of cells used at first passage. Cells were exposed to a serum-free culture medium in the presence of 0.1% bovine serum albumin (QBiogene) for 6 h prior to treatment.

Western Blot Analysis

The level of phosphorylation of Akt and endothelial eNOS was determined in cultured endothelial cells using Western blot analysis. After treatment, the endothelial cells were washed twice with PBS and then lysed in an extraction buffer of the following composition in mM :Tris/HCl 20 (pH 7.5; QBiogene), NaCl 150, Na_3 VO_4 1, sodium pyrophosphate 10, NaF 20, okadaic acid 0.01 (Sigma), a tablet of protease inhibitor (Roche) and 1% Triton X-100 (QBiogen). Total proteins (20 µg) were separated on 8% SDS-polyacrylamide (Sigma) gels at 70 V for 2.5 h. Separated proteins were transferred electrophoretically on to polyvinylidine difluoride membranes (Amersham) at 100 V for 120 min. Membranes were blocked with a blocking buffer containing 5% bovine serum albumin for p-Akt and p-eNOS, Tris-buffered saline solution (Biorad) and 0.1% Tween 20 (Sigma) for 1h. For detection of phosphorylated proteins, membranes were incubated with the respective primary antibody (p-Akt Ser473 and p-eNOS Ser1177, Cell Signaling Technology; dilution 1: 1,000) overnight at 4 °C. After washing, membranes were incubated with the secondary antibody (peroxidase-labeled anti-rabbit IgG, dilution 1: 10,000; Cell Signaling Technology) at room temperature for 60 min. Prestained markers (Invitrogen) were used for molecular mass determinations. Immunoreactive bands were detected by enhanced chemiluminescence (Amersham). Ponceau staining was performed to verify the quality of the transfer and equal amounts of proteins in each lane. Densitometric analyses were performed with the software ImageJ.

Statistical Analysis

The results are expressed as means ± SEM of 6-8 experiments. Statistical significance was determined through a one-way analysis of variance (ANOVA) followed by Bonferroni's test or with Student's t test for paired data as required. Statistical analysis was performed using Graph*Pad. Prism version 6.01* ® for Windows (GraphPad Software, San Diego, Calif., USA). Values of $p < 0.05$ were considered statistically significant.

Results

Phytochemical analysis of crude hydro-ethanolic extract of A. digitata leaves

Reagent-based phytochemical screening of the crude hydro-ethanolic extract of Adansoniadigitata leaves revealed the presence of flavonoids, tannins, sterols, and triterpenes (**Table 1**).

Table 1. Class of phytochemical constituents of *crude hydro-ethanolic extract of A. digitata extract (ADF)*

Compounds screened for	ADF
Tannin	+
Flavonoid	+++
Sterol and Triterpen	+++

The test was positive (**+**) when compound screened for was detected, negative (-) when it was not found.

The content of total phenolic compounds was 543.0 ± 2.1 mg of gallic acid equivalents (GAE) per gram of extract.**(Table 2).**

Table 2. Concentration of total phenols in *Adansoniadigitata* **extracts by** Folin–Ciocalteuassay.

	Total polyphenolic contents (mg GAE/g)
ADF	**543,0 ±2.1**

Results are expressed as mg of gallic acid equivalent (GAE) per gram of extract under the form of mean±SEM

(n = 3).

ADF Induces Endothelium-Dependent Relaxations in Coronary Artery Rings

The addition of cumulative concentrations of ADF to isolated porcine coronary artery rings contracted with U46619 induced concentration-dependent relaxations in endothelium-intact but not in endothelium-denuded preparations (**Fig. 1A**). The endothelium-dependent relaxation started at concentrations greater than 1 µg/ml and reached a nearly maximal value at 10 µg/ml (Emax = 102.31%). Relaxations to ADF were significantly reduced by L-NA (300 µM), an inhibitor of eNOS (approximately 52.46% inhibition of Emax) (Fig. 1B), and were maximally affected (around 72%) by the combination of Tram-34 (1 µM) plus apamin (100 nM), two inhibitors of EDH-mediated responses (**Fig. 1D**). The relaxations were almost abolished (90% inhibition of Emax) by the combination of L-NA with indomethacin and Tram-34 plus apamin(Fig. 2B). Indomethacin (10 µM) induced a slight rightward shift of the concentration-response curve for ADF without affecting the maximal relaxation (**Fig. 1C**). These findings indicate that ADF causes endothelium-dependent relaxations, primarily dependent on an EDH component and also an L-NA-sensitive component (NO), while prostacyclins do not appear to play a role in the vascular effects of ADF.

Role of ROS, Src Kinase and the PI3-Kinase/Akt Pathway ADF-Induced Relaxations

Porcine coronary arteries by a mechanism involving endothelial production of ROS and activation of PI3-kinase/Akt and Src kinase pathway [10, 11], leading to eNOS phosphorylation. The consequent activation of eNOS through this pathway has been found to occur even in a Ca^{2+}-free medium [12]. Therefore, experiments were performed using MnTMPyP (10^{-4} µM), a membrane-permeant SOD mimetic, catalase (500 U/ml), PEG-catalase (500 U/ml), a membrane-permeant catalase mimetic, and N-acetyl-L-cysteine (NAC, 10 mM) to determine whether a ROS signaling pathway is involved in ADF-induced relaxations. The relaxations induced by ADF (0.1-10 µg/ml) were markedly reduced by the membrane-permeant SOD mimetic MnTMPyP, the cell-permeable PEG-catalase, native catalase, and N-acetyl-L-cysteine (NAC) (approximately 95%, 69%, 98%, 97%, and 90% inhibition of Emax, respectively) (**Fig. 2A, 2B**). Experiments were also performed to determine the role ofSrc kinase/PI3-kinase/Akt pathway in relaxations induced by ADF. Inhibition of PI3-kinase by wortmannin (30 nM) and Src kinase by PP2 (10 µM) almost completely inhibited the relaxations to ADF (99% and 70% inhibition of Emax, respectively) (**Fig. 2C, 2D**).

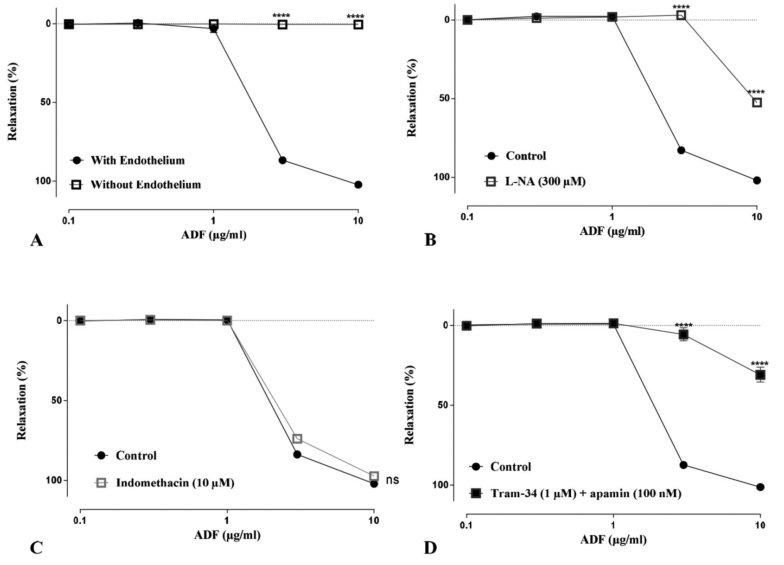

Figure 1: Characterization of ADF-induced relaxations in isolated porcine coronary artery rings. Intact and endothelium-denuded rings were contracted with U46619 before the addition of cumulative concentrations of ADF. AEndothelium-dependent relaxations induced by ADF. B Effect of L-NA (300 µM). C Effect of indomethacin (10 µM) on ADF-induced relaxations in coronary artery rings with endothelium. D Relaxant effect of ADF in the presence of apamin (APA, 100 nM) plus Tram-34 (1 µM) in intact arteries. Results are shown as means ± SEM of 6 different experiments. **** p < 0.0001 for inhibitory effect versus control. ns :non significant difference versus control.

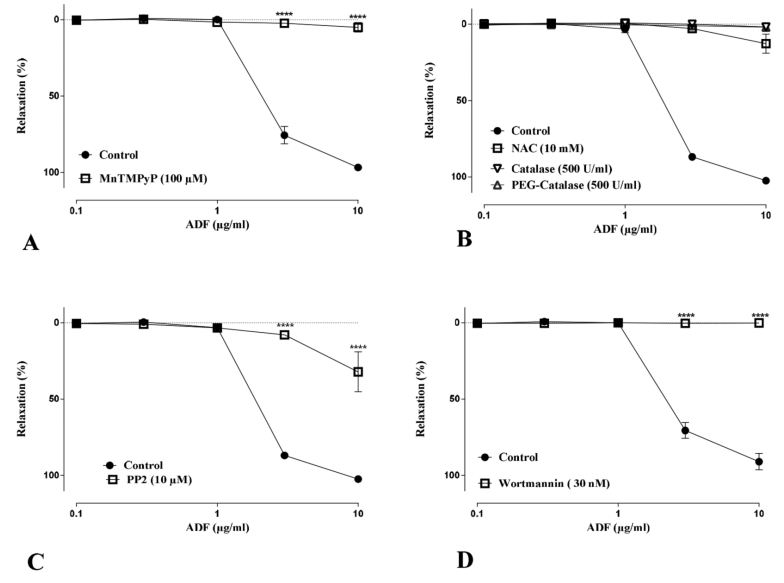

Figure 2: Role of the redox-sensitive Src kinase and the PI3-kinase/Akt pathway in ADF-induced endothelium dependent relaxations. Coronary artery rings with endothelium were incubated with MnTMPyP (100 µM), a cell permeable SOD mimetic (A), native catalase (CAT, 500 U/ml) or PEG-catalase (PEG-CAT, 500 U/ml), a membrane-permeant analog of catalase and N-acetyl- L-cysteine (NAC, 10 mM) (B) ; the Src kinase inhibitor PP2 (10 µM) (C) and the PI3-kinase inhibitor wortmannin (30 nM) (D) for 30 min before contraction to U46619 and subsequent relaxation to TAE. Results are shown as means ± SEM of 6 different experiments. **** p < 0.0001 for inhibitory effect versus control.

ADF Causes the Redox-Sensitive Activation of Src with Subsequent PI3-Kinase/Akt-Dependent Phosphorylation of eNOS

To better charsignaling the signaling pathways involved in eNOS activation in response to ADF, levels of phosphorylated Akt and eNOS were assessed in endothelial cells by Western blot analysis. ADF (1-100 µg/ml, 10 min) inducedconcentration-dependent phosphorylation of Akt at Ser473 and eNOS at Ser1177 in endothelial cells **(Fig. 3).**

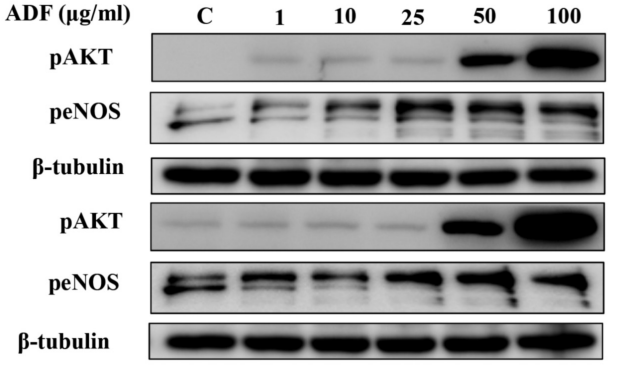

Figure 3: ADF causes a concentration-dependent phosphorylation of Akt at Ser473and eNOS at Ser1177 in cultured porcine coronary artery endothelial cells. Results are shown as means ± SEM of 3 different experiments.

Discussion

This study shows that *Adansoniadigitata extract* is a powerful inducer of endothelium-dependent relaxation involving EDH (mainly) and NO *via* a redox-sensitive mechanism.

Most cardiovascular diseases, including high blood pressure, are associated with endothelial dysfunction, characterized by reduced endothelium-dependent vasorelaxation. The subsequent increase in vascular tone and hence increased arterial blood pressure could be the result of none or decreased endothelial release of factors such as NO, PGI_2, and EDH. Therefore, increased and/or restoration of endothelial relaxant factors production by natural products is an interesting approach to normalize vascular tone, and thus blood pressure [13].

Endothelial dysfunction is often associated with pathological oxidative stress, which is at least partly due to increased expression of NADPH oxidase, an enzyme that generates superoxide anions in the arterial wall. Superoxide anions react with NO, reducing its bioavailability and, consequently, its vascular protective effects [14].

In this study, we evaluated the potential of *Adansoniadigitata* leaf extract to induce endothelium-dependent relaxation in rings derived from porcine coronary arteries. Our findings indicate that ADF induces endothelium-dependent relaxation with a strong involvement of EDH. These results are contradictory to those previously obtained in our research laboratory. Indeed, results obtained with those plant extracts reported vasorelaxant effects on rat aorta mediated exclusively by NO via a redox-sensitive mechanism[14, 15, 16, 17]. Moreover, the contribution of EDH to vasorelaxation in large arterial trunks is described as weak by numerous authors [18, 19]**.** Indeed, EDH is especially present in microvessels such as the mesenteric bed and carotid artery.

The data also indicate that ADF induces endothelium-dependent relaxation, with the lesser involvement of NO compared to EDH. Moreover, relaxations are reduced by a membrane-permeant analog of superoxide dismutase and catalase (MnTMPyP and PEG-catalase). The relaxation induced by ADF is also reduced by native catalase and NAC, an inducer of reduced glutathione, indicating that relaxation induction involves a redox-sensitive event. Therefore, the vascular relaxation induced by ADF proceeds through the redox-sensitive Src-PI3-Kinase/Akt pathway, as shown by incubation with wortmannin and PP2, which is the main pathway of endothelial NO synthase activation by plant polyphenols [11].

In endothelial cells, the generation of superoxide anion can activate the Src-PI3-kinase/Akt pathway, leading to the phosphorylation of eNOS at Ser1177 in response to polyphenols [21]. This pathway can also be activated in response to several physiological stimuli, including estrogens, shear stress, vascular endothelial growth factor, H_2O_2, and high-density lipoprotein [22]. ADF- induced activation of the redox-sensitive PI3-kinase/Akt pathway, as indicated by

the concentration-dependent phosphorylation of Akt at Ser473 and eNOS at Ser1177 in endothelial cell cultures.

Many questions remain unanswered regarding the pro-oxidant mechanism of polyphenols involved in the activation of the Src/PI3-kinase/Akt pathway, leading to the activation of endothelial NO synthase in endothelial cells (ECs). Previous studies conducted in the laboratory on the vasorelaxant properties of red wine extract and tea catechins, as well as pharmacological inhibitors of the mitochondrial respiratory chain, xanthine oxidase, and cytochrome P450, showed no effect on endothelium-dependent relaxation, suggesting that these sources of reactive oxygen species (ROS) are not involved [23, 11, 24]. Collectively, these findings suggest that the persistent formation of ROS induced by active polyphenols in ECs involves a novel and significant mechanism, as it leads to sustained NO production, which is a key factor in cardiovascular protection. Several hypotheses can be proposed regarding the source of ROS in ECs in response to polyphenols. One hypothesis is that the active phenolic structure itself generates ROS. Indeed, studies have shown that certain polyphenols can produce O2-. and H_2O_2 through auto-oxidation, leading to the formation of semiquinones and quinones, catalyzed by metal ions such as Cu2+ and Fe^{2+}[23, 25, 26].

Phytochemical analysis of ADF provided insights into the nature of the compounds involved in its vasorelaxant activity. Indeed, the quantification of total polyphenols using the Folin-Ciocalteu method showed that ADF is very rich in polyphenols, particularly flavonoids, tannins, sterols, and triterpenes. These results are in accordance with other studies which reported that Adansoniadigitata leaves contain numerous phenolic compounds (especially flavanols and tannins) and some potent oxalic acid complexes with calcium [27, 28]. Several other studies also indicated that phenolic compounds constitute a new class of stimuli for NO endothelial synthesis. Indeed, polyphenols are able to induce eNOS activation by two different mechanisms. The first one is independent of intracellular calcium concentration [Ca^{2+}]i and involves the phosphoinositide-3 kinase (PI3-kinase)/Akt pathway, resulting in the phosphorylation of eNOS at the serine 1177 residue. The second mechanism involves an increase of [Ca^{2+}]i leading to NO synthesis [29, 30]. Studies carried out in our laboratory have shown that polyphenols are also able to induce EDH formation in porcine coronary arteries [30]. Moreover, these relaxations are associated with a hyperpolarization of vascular smooth muscle cells, which is sensitive to the combination of charybdotoxin (CTX) and apamin (APA), indicating a link to EDH [31]. Other studies have highlighted the importance of PI3-kinase/Akt pathway as well as ROS formation, crucial steps in the formation of EDH (and NO) by polyphenols [11, 10]. Endothelial potassium channels could be a potential target of this signaling pathway, but evidence in the literature is still lacking. An in-vitro study conducted on endothelial cell line demonstrated an increase in the opening probability of IKCa channels by direct action of resveratrol [32].

Moreover, ADF could also induce an increase in the opening probability of IKCa and SKCa channels through direct action on these channels. These results are in agreement with previously published studies showing that polyphenol-rich sources (for example, grape juice, red wine, and Crataegus extract) induce endothelium-dependent relaxation mediated by the NO-redox-sensitive pathway and EDH [33]. It was also shown that relaxation induced by polyphenol-rich sources is mediated by activation of the redox-sensitive Src-PI3-kinase/Akt pathway, leading to the activation of endothelial NO synthase by phosphorylation [34].

Conclusion

This study has demonstrated the capacity of the hydroethanolic crude extract of *Adansoniadigitata* leaves to induce redox-sensitive, endothelium-dependent vasorelaxation in porcine coronary arteries. This vasorelaxation induced by the extract is mediated primarily by endothelium-derived hyperpolarizing (EDH) and, to a lesser extent, by nitric oxide (NO). Moreover, these results indicate

that *Adansoniadigitata* has beneficial effects on functional endothelium by reducing vascular tone.

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Conflict of Interest: Nil

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