Table 1. Effect of Aspirin and Rutaecarpine on Mortality and Platelet Count of Acute Pulmonary Thrombosis Caused by Intravenous Injection of ADP in Experimental Mice

	Number of deaths	Total number	Mortality (%)	Platelet count (10^3/mm^3)
Control	0	5	0	223 ± 28 (6)
ADP(0.7mg/g)	17	21	81	147 ± 19* (12)
+ Aspirin (μg/g)				
20	6	20	30	168 ± 21 (10)
50	6	20	30	189 ± 23 (10)
+ Rutaecarpine (μg/g)				
25	15	20	75	173 ± 19 (8)
50	7	20	35	195 ± 20 (8)

Platelet count is presented as the mean ± S.E.M. (n). *: $P < 0.05$ as compared with the control group (normal saline). See Ref. 23.

s, respectively. Rutaecarpine (200 μg/g) and aspirin (250 μg/g) significantly prolonged the occlusion times induced by fluorescein sodium (10 μg/kg) in venous, with occlusion times of 201 ± 20 and 193 ± 19 s, respectively. On a molar basis, rutaecarpine was about 2-fold more potent than aspirin at inhibiting fluorescein sodium-induced platelet plug formation in microvessels of mice. However, heparin (0.75 and 1.5 U/g) and a lower concentration of aspirin (150 μg/g) or rutaecarpine (100 μg/g) showed no significant effects on occlusion times.[22]

We further demonstrated the effect of rutaecarpine in preventing death due to acute pulmonary embolism in mice. Acute pulmonary thromboembolism was induced as previously described.[21] Various doses of rutaecarpine (25 and 50 μg/g), heparin (1.5 U/g), or aspirin (20 μg/g) were administered by injection into a tail vein. Four minutes later, ADP (0.7 mg/g) was injected into the contralateral vein.[23] The mortality of mice in each group after injection was determined within 10 min. As shown in Table 1, both rutaecarpine and aspirin significantly lowered the mortality of mice challenged with ADP (0.7 mg/g). Rutaecarpine (50 μg/g) and aspirin (20 μg/g) reduced the mortality from 81% to 35% and 30%, respectively (Table 1). By contrast, heparin (1.5 U/g) showed no significant effect in reducing mortality (81% and 80%) in ADP-treated mice.[22] Therefore, rutaecarpine is an effective antithrombotic agent in preventing thromboembolism in these 2 *in vivo* models.

Effect on Blood Vessels

Rutaecarpine caused concentration-dependent (0.1-100 μM) relaxation of isolated rat mesenteric arterial segments which were precontracted with phenylephrine.[9] The phenylephrine-induced contraction was 90% relaxed in endothelium-intact mesenteric arterial segments by 0.1 mM rutaecarpine. Removal of the endothelium markedly attenuated the rutaecarpine-induced relaxation.[9] Treatment with the nitric oxide synthase inhibitor,[24] *L*-N^G-nitroarginine (0.1 mM), or a guanylyl cyclase inhibitor,[25] methylene blue (10 μM), significantly diminished but did not completely abolish the vasorelaxing effect of rutaecarpine. Maximal relaxations in response to rutaecarpine were significantly reduced from 87.8 ± 3.7% to 30.6 ± 2.5% in *L*-N^G-nitroarginine-treated rings, and from 90.2 ± 4.2% to 37.9 ± 2.5% in methylene blue-treated arterial rings.[9] These findings strongly suggest that nitric oxide is responsible, albeit not completely, for the relaxing effect of rutaecarpine. On the other hand, the vasodilator effect of rutaecarpine was not significantly attenuated by pretreatment with the muscarinic receptor antagonist, atropine (0.1 μM), the histamine H1 receptor antagonist,[26] triprolidine (0.1 mM), or the selective α_2-adrenoceptor agonist,[27] yohimbine (0.3 μM). It appears that the vasorelaxing effect of rutaecarpine is endothelium dependent and involves nitric oxide and guanylyl cyclase.

In addition, the vascular endothelium secretes a number of vasoactive substances, among which nitric oxide (NO), prostaglandin I_2 (PGI_2), and endothelium-derived hyperpolarizing factor (EDHF) are[3] likely candidates as mediators that could lead to relaxation of vascular smooth muscles. Systemic examination with appropriate antagonists revealed that the cyclooxygenase inhibitor, indomethacin (30 μM), or the nonselective K^+ channel blocker, tetramethylammonium (TEA; 10 mM), had no significant effects, suggesting