Structure-Activity Relationships of Flavonoids on cGMP-Mediated Relaxation of Coronary Artery by PDE5 inhibition

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BACKGROUND

- Flavonoids, which are found naturally in various food and plants, have been shown to have a wide range of advantageous biological activities. One of them is antihypertensive.[1]
- Various studies show that the potency of such activity is dependent on chemical structure, particularly the presence or absence of specific functional groups at certain location within the structure.[2]
- Flavonoids are found to be capable of inhibiting cGMP-phosphodiesterase (PDE5), hence increased cGMP level.[3] Duarte *et al.* reported that absence of the 3'-OH in B ring of flavonoids was essential for the potentiation of the sodium nitroprusside(SNP)-induced vasorelaxation.[4]
- Despite this, little is known about the structure–activity relationships (SAR) between flavonoids and their inhibitory effects on PDE isozyme.

AIMS

- To evaluate the vasodilatory effect of four different flavonoids (galangin, chyrsin, quercetin and luteolin) on the cGMP-mediated pathway.
- To investigate the possible relationships between –OH substitution variations in the flavonoid phenolic rings and their importance for PDE5 inhibition. The -OH substitutions studied were 3-OH group in C ring, 3’-OH and 4’-OH in B ring.
- Group data comparison with results collected by peers who studied other types of structurally related flavonoids, using same experimental approach, to find out the effects of other functional groups (e.g.: 5-OH & 7-OH in A ring) on the reported ability of flavonoids to inhibit PDE activity.

METHOD

1. Excess fat and tissue were removed from the surrounding of porcine coronary artery. Four aortic rings of the same length (~5mm) were obtained.
2. The aortic rings were suspended between two wire hooks and connected to isometric transducer via a cotton thread.
3. The rings were then placed into four separate tissue baths, each containing 20ml KREBS solution.
4. Two successive KCl responses were carried out for each aortic rings before pre-incubation with 10 μM of the investigative flavonoids.
5. U46619 was added accordingly to induce submaximal contraction (60-70% of max. KCl response). Once achieved, the SNP was added in cumulative manner.
6. Concentration-response curves were plotted respectively for both the control and active compounds for use in statistical analysis.

CONCLUSION

- Flavones are more potent than flavonols.
- Lack of 3-OH in C ring increased flavonoids activity in the presence of SNP, hence could be essential for inhibiting PDE5 activity.
- Removal of both 3’-OH and 4’-OH from B ring of flavonoids enhanced the SNP potency, thus suggesting a possible role in PDE5 inhibition.
- Nevertheless, presence of 4’-OH alone potentiated the SNP activity.

RESULTS

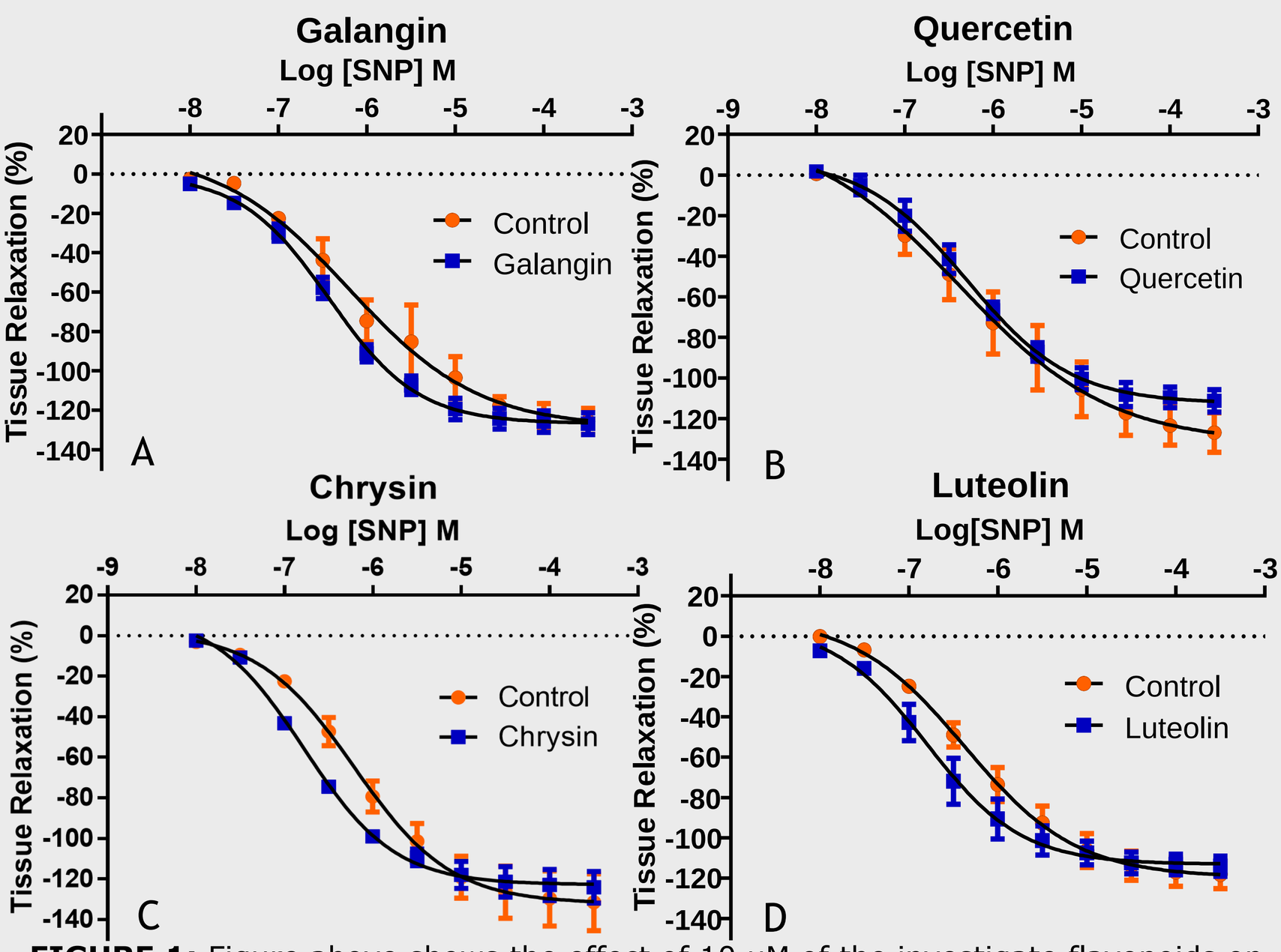

FIGURE 1: Figure above shows the effect of 10 μM of the investigate flavonoids on the relaxation response of SNP. X axis represents the concentration of SNP expressed in logarithm value and Y axis shows the percentage of tissue relaxation achieved.

	pEC_{50} value	Fold Shift	R_{max} value	
Control	-6.084 ± 0.29	1.67	-125.6 ± 6.68	
+ 10μM Galangin	-6.434 ± 0.11		-126.8 ± 5.69	(n = 5)
Control	-6.200 ± 0.13	3.71	-131.5 ± 14.00	
+ 10μM Chrysin	-6.773 ± 0.02**		-124.2 ± 7.82	(n = 5)
Control	-6.256 ± 0.38	-1.21	-126.9 ± 9.76	
+ 10μM Quercetin	-6.419 ± 0.22		-111.2 ± 5.49	(n = 4)
Control	-6.325 ± 0.11	2.66	-118.1 ± 7.14	
+ 10μM Luteolin	-6.700 ± 0.17*		-114.1 ± 5.09	(n = 5)

TABLE 1: Table 1 summarises the effect of the investigative flavonoids on the concentration-relaxation parameters obtained from paired t-test for SNP-evoked relaxations. The responses are means ± SEM of potencies (pEC_{50}), fold-shift of the curves and means ± SEM of the maximal responses (R_{max}) to SNP, where *p < 0.05, **p < 0.01. Only effects exerted by the flavones (Figure 1: C, chrysin ; D, luteolin) were found be statistically significant.

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