THE EFFECT OF CERTAIN FLAVONOID COMPOUNDS ON THE FORMATION OF EXPERIMENTAL GASTRIC ULCERS IN RATS

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It is reported in the literature that the flavonoids possess anti-ulcer activity when used experimentally [7, 11, 12, 14] and clinically [8, 9, 13, 15]. These authors cited above investigated both the flavonoids as a group and also individual compounds. However, no attempt has yet been made to correlate the activity of these substances with their chemical structure.

We have studied the anti-ulcer action of members of 3 classes of flavonoids: flavonones, chalcones, and flavonols, on two experimental varies of gastric ulcer of different etiology. Of the 6 substances tested, 2 were obtained for the first time [5].

EXPERIMENTAL METHOD

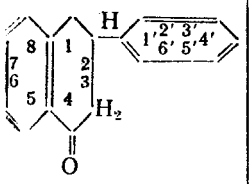
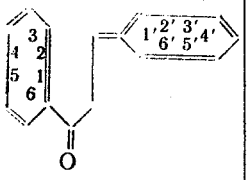
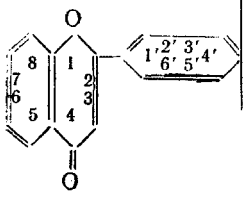
Experiments were conducted on 461 rats of both sexes, weighing from 120 to 200 g. Gastric ulcers were produced in the animals by two methods: parenteral injection of butadione [10] and application of a clamp to the pyloroduodenal region [3]. All the flavonoids—liquiriton, liquiritigenin, liquiritin, likurazid, quercetin, and rutin—were given by mouth in the form of a 1% starch paste. In the butadione model the flavonoids were administered for 12 days simultaneously with the butadione injections, while in the animals with reflex ulcer they were given as a single dose 30-40 min before the operation. Doses of 5, 10, and 50 mg/kg were given. The ulcerative changes were assessed in relation to the previously adopted scheme [1, 6]. The dose diminishing the Pauls index to 50% the control value, i. e., the dose possessing anti-ulcer activity of 1.5, was determined graphically for each flavonoid. This dose was described as ED_{50} and was expressed mg/kg body weight and in mM/kg body weight.

EXPERIMENTAL RESULTS

Under the influence of most flavonoids (liquiriton, liquiritigenin, quercetin, and rutin) in 20-50% of the animals, no ulcers were formed by butadione. All the flavonoids lowered the incidence of hemorrhage, ulcers and erosions in the mucous membrane of the stomach, and the anti-ulcer effect increased with an increase in the dose of the compounds. For instance, liquiriton in a dose of 10 mg/kg lowered the Pauls index from 6.9 (in the control series) to 1.4, so that the anti-ulcer activity of the compound in this dose was 4.9. An increase in the dose of 50 mg/kg almost doubled the effect. Liquiritigenin also possesses fairly high activity: administration of a dose of 10 mg/kg lowered the indices of ulceration by 86%. Liquiritin had the least anti-ulcer action.

It follows from the results given in the table that in the series of flavanones not having a double bond between C_2 and C_3 the composite glycoside preparation liquiriton possessed greatest activity. Liquiritigenin was twice as active as its own glycoside. The opening of the heterocyclic ring, as observed in likurazid, increased the anti-ulcer activity by almost 50%. In the class of the flavonols (double bond between C_2 and C_3) the glycoside rutin was more active than the aglycone quercetin. Of the preparations of the classes of compounds compared, the flavonones possessed highest activity.

Anti-Ulcer Activity of Flavonoids Against Butadione Gastric Ulcer in Rats

Flavonoid compounds			Biological activity				
Class	Substance	Molecular wt.	Dose (in mg/kg)	Anti-ulcer activity	Value of ED_{50}		Comparative activity by molecular concentration
					mg/kg	mM/kg	
Flavanones 	Liquiritigenin (7,4'-dihydroxyflavanone)	256	5	4.0			
			10	7.2	3.7	0.014	1.0
	Liquiritin (liquiritigenin-4'-β-D-glycoside)	418	10	1.0			
			50	2.6	13.5	0.032	0.44
	Liquiriton (complex of 2 monoglycosides and 2 diglycosides of liquiritigenin)	~600	5	1.3			
			10	4.9	4.2	0.007	2.0
			50	8.1			
Chalcones 	Likurazid [trans-iso-liquiritigenin-4-0-β-D-glucopyranosyl-2-0-β-D-apio(D or L)-firanoside]	594	10	1.9	6.2	0.01	1.4
			50	2.6			
Flavonols 	Quercetin (3,5,7,3'-4'-pentahydroxyflavonol)	302	50	4.5	4.7	0.015	0.93
			10	3.0			
	Rutin (quercetin-3-rhamnoglycoside)	610	50	4.2	4.0	0.0067	2.1

In the experiments on the rats with reflex gastric ulcers, all the flavonoids likewise exhibited an anti-ulcer action. In this series, however, the tested compounds were less active than against the butadione ulcer. The greatest activity was displayed by liquiriton and rutin (ED_{50} 0.012 and 0.017 mM/kg respectively). The remaining flavonoids were roughly equal in the strength of their anti-ulcer action. The values of ED_{50} for liquiritigenin, liquiritin, and quercetin was 0.036, 0.040, and 0.056 mM/kg respectively.

It is known [2, 4] that the substances most active against reflex gastric ulcer are those which affect a certain link of the reflex arc: the central cholinolytics, the ganglioplegics, sedatives, and so on. The flavonoids investigated possess marked spasmolytic and anti-inflammatory properties, which evidently account for the basic mechanism of their anti-ulcer action. Because of this peripheral effect, flavonoids may have a weaker action against reflex ulcers than against butadione ulcers, and for this reason they may differ from each other less as regards their activity.

These investigations demonstrated that compounds of the flavonone and flavonol classes have a prophylactic anti-ulcer action against two forms of experimental gastric ulcer in rats.

LITERATURE CITED

1. M. A. Angarskaya, G. V. Obolentseva, and Ya. I. Khadzhai. Vrach. delo, 3, 23, (1961).
2. P. P. Denisenko. In book: Annual Report of the Institute of Experimental Medicine of the AMN SSSR for 1956 [in Russian], Vilnius, 265 (1957).
3. I. S. Zavodskaya. Byull. éksper. biol., 1, 26 (1954).
4. I. S. Zavodskaya. Farmakol. i toksikol., 3, 266 (1962).

5. V. I. Litvinenko, N. P. Maksyutina, et al. Zh. obshchei khimii, 1, 296 (1963).
6. Ya. I. Khadzhai and G. V. Obolentseva. Farmakol. i toksikol., 4, 450 (1962).
7. H. Berger and H. Höller, Sci. pharm. (Wien), 25, 172 (1957).
8. T. Bodi and B. Weiss, Am J. Gastroent.,34, 402 (1960).
9. A. Bonadies, Riv. Gastroent, 10, 161 (1958).
10. S. Bonfils, J. P. Hardouin and M. Bourel, C. R. Soc. Biol., 147, 2016 (1953).
11. K. Formanek, H. Höller, and H. Janisch, Pharm. Acta Helv., 34, 241 (1959).
12. R. A. Paris and M. Guillot, Ann. pharm. franc., 13, 592 (1955).
13. F. E. Revers, Acta med. scand. 154, 749 (1956).
14. E. E. Vogin and G. V. Rossi, J. pharm. Sci., 50, 14 (1961).
15. S. Weiss, J. Weiss, and B. Weiss, Am. J. Gastroent., 29, 629 (1958).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**
