Experimental Gerontology, Vol. 17, pp. 213–217, 1982
Printed in the USA.

0531-5565/82/030213-05$03.00/0

QUERCETIN, FLAVONOIDS AND THE LIFE-SPAN OF MICE

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(*Received* 15 *September* 1981)

Abstract—A dietary supplement of 0.1% quercetin significantly reduced the life span of mice. The effect was predominantly on the 'shorter living' males. A blackcurrant juice extract, containing a mixture of flavonoids in addition to quercetin, prolonged significantly the life span of the 'older dying' females. The significance of these results *vis-a-vis* aging mechanisms and the dietary intake of quercetin is discussed.

INTRODUCTION

QUERCETIN (3,5,7,3′,4′-pentahydroxyflavone) and its glycosides, such as rutin (quercetin-3-rutinoside), are of widespread occurrence in plants (Herrmann, 1976; Kühnau, 1976). Little, however, is known of their metabolic significance in man despite their not inconsiderable intake in some diets.

There is evidence that cholesterol metabolism in experimental animals is influenced by dietary quercetin (Basarker and Hatwalne, 1975; Jones and Hughes, unpublished data) and it is well established that in guinea pigs the concentration of tissue ascorbic acid may be modified by dietary flavonoids (Hughes and Wilson, 1977).

Of possibly greater significance are recent indications that quercetin, in *in vitro* tests, possesses considerable direct mutagenicity (Bjeldanes and Chang, 1977; Kimura *et al.*, 1979; Sugimura, 1979)—a finding which could carry important implications in terms of human nutrition. The experiment described in this report was designed to examine the influence of quercetin and other dietary flavonoids on the life-span of mice.

Three groups (A,B,C) of 5-week-old mice (strain LACA, Medical Research Council) were used. Each group contained 50 males and 50 females. Group A received a standard semi-synthetic diet MG1, originally designed as a scorbutogenic diet and shown to be virtually flavonoid-free (Williams and Hughes, 1972). Group B received MG1 to which 'single strength' blackcurrant juice concentrate had been added at the pre-baking stage (220 ml juice per 1000 g diet). The blackcurrant juice concentrate was used as a source of mixed flavonoids; it provided, per 1000 g diet, an estimated 380 mg of total flavonoid material of which c. 40 mg were present as quercetin and its glycosides and the bulk of the remainder as anthocyanins. Group C received MG1 to which 0.1% quercetin had been added; this provided an estimated daily intake of c. 10 mg quercetin per animal.

Citric acid (a high dietary intake of which had been previously shown [Wright and Hughes, 1976] to influence the life span of mice) and ascorbic acid were added to diets A

TABLE 1. INFLUENCE OF BLACKCURRANT CONCENTRATE (GROUP B) AND QUERCETIN (GROUP C) ON CHANGE IN BODY WEIGHT OF MICE. (MEAN WEIGHTS WITH THEIR STANDARD ERRORS.)

Group	Sex	Time (Weeks)			
		6	12	24	50
A	male	22.3 ± 0.3	30.9 ± 0.8	34.6 ± 0.9	34.5 ± 0.7
(control)	female	20.2 ± 0.4	26.2 ± 0.7	29.4 ± 0.9	29.3 ± 0.5
B	male	21.9 ± 0.1	30.2 ± 0.2	33.2 ± 0.2	34.3 ± 0.5
(blackcurrant)	female	21.1 ± 0.2	26.8 ± 0.4	29.9 ± 0.4	30.1 ± 0.4
C	male	23.1 ± 0.2	31.4 ± 0.4	35.1 ± 0.6	36.2 ± 0.7
(quercetin)	female	20.6 ± 0.1	26.2 ± 0.2	29.0 ± 0.3	29.3 ± 0.3

and B in quantities equivalent to those introduced into C by the blackcurrant juice concentrate.

RESULTS

The results are summarized in Tables 1 and 2 and in Fig. 1 and 2. Food intake measurements revealed no differences between the groups, nor were there any significant differences between the times taken to attain a stable mature body weight (Table 1).

The main finding to emerge from the study was a significant overall reduction in the life-span of the quercetin-supplemented group (Kruskall-Wallis rank test [Hull and Nie, 1979]; Fig. 1, Table 2). Analysis of the results revealed that the 'quercetin effect' was attributable to the males rather than the females and that it influenced the 'shorter life-span' animals rather than the 'longer life-span' ones. The life span of the 15 'last dying' animals was unaltered by the quercetin.

The blackcurrant juice concentrate, on the other hand, had no significant influence on the mean overall life span but prolonged significantly the life span of the 'last 15' females (Table 2) (Student's *t*-Test).

DISCUSSION

The effect of quercetin in shortening the life span of mice is perhaps counter to what one would expect on theoretical grounds. Quercetin is a potent antioxidant (Kühnau,

TABLE 2. INFLUENCE OF BLACKCURRANT CONCENTRATE (GROUP B) AND QUERCETIN (GROUP C) ON MEAN LIFE-SPAN (WEEKS) OF MALE AND FEMALE MICE. MEAN LIFE-SPANS WITH THEIR STANDARD ERRORS.

Group	A (control)	B (blackcurrant)	C (quercetin)
Mean for group (males & females)	111.3 ± 2.0	113.5 ± 2.5	100.3 ± 2.6*
Females (total)	116.4 ± 2.8	120.7 ± 3.4	109.6 ± 3.5
Females (first 15)	90.5 ± 3.3	87.5 ± 4.4	80.9 ± 4.3
Females (last 15)	136.8 ± 0.6	141.7 ± 0.8*	138.5 ± 1.7
Males (total)	106.3 ± 2.8	106.9 ± 3.4	91.3 ± 3.3*
Males (first 15)	79.7 ± 2.8	75.1 ± 3.8	65.9 ± 2.1*
Males (last 15)	121.7 ± 7.9	130.9 ± 0.9	122.4 ± 3.1

*Difference between group mean and control mean significant. $P < 0.01$.

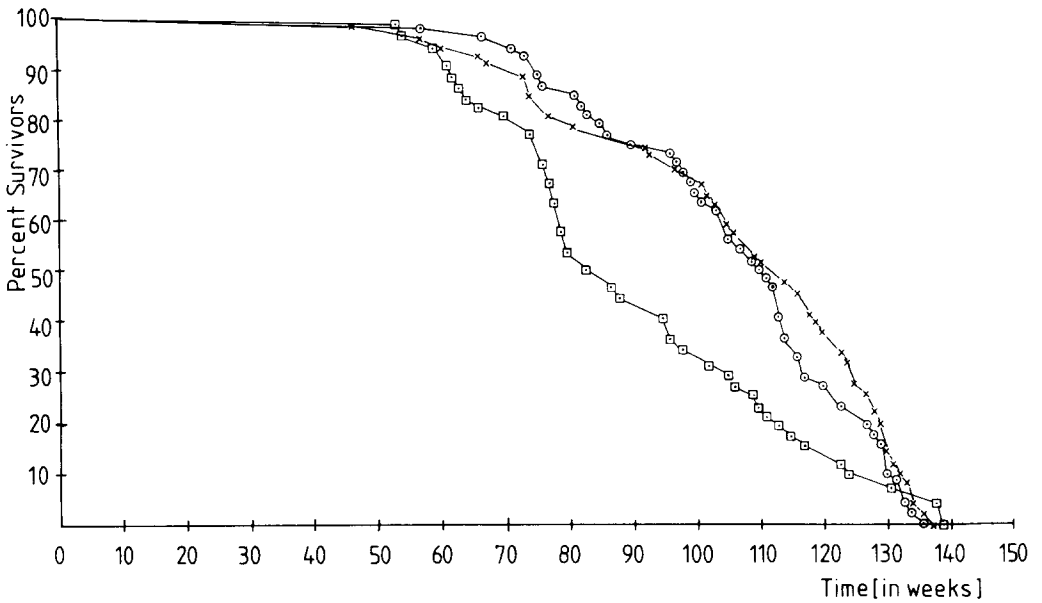

FIG. 1. Survival curves for male mice given dietary supplements of quercetin (⊡—⊡—⊡) or blackcurrant juice (–x–x–) compared with control mice (⊙—⊙—⊙).

1976) and there is evidence that antioxidants, presumably because of a free-radical scavenging action, may increase the life span of experimental animals (e.g. Comfort *et al.*, 1971; Miquel and Economos, 1979). Again, quercetin stabilizes ascorbic acid, retarding its chemical degradation (Hughes and Wilson, 1977). There are indications that breakdown products of ascorbic acid are mutagenic; quercetin, by reducing the formation of such products, would perhaps retard the aging process(es) (Burnet, 1974; Hughes, 1981).

The results of our experiment would appear to suggest that any such general advantages to be expected from flavonoid supplementation are, in the case of quercetin, obscured by less advantageous attributes. Of significance in this respect are reports of the comparatively high mutagenicity of quercetin when tested by *in vitro* techniques (Bjeldanes and Chang, 1977; Kimura *et al.*, 1979; Sugimura, 1979); a quercetin-induced reduction of life-span would therefore be consistent with a theory of aging of the somatic mutation type.

Tissue deprivation of trace elements could also be a contributory factor of significance. Quercetin is able to form chelation compounds with certain metals such as copper (Kühnau, 1976). Prolonged ingestion of quercetin could conceivably result in a state of chronic deficiency of one or more of the essential elements which would, in turn, be reflected as a reduction in life-span. A similar mechanism has been proposed to account for the reduced life-span of mice receiving elevated dietary intakes of citric acid (Wright and Hughes, 1976).

The indication that the blackcurrant extract prolonged the life-span suggests a different mode of action and is more in agreement with the type of result to be expected on a theoretical basis. Quercetin is a relatively minor component of the blackcurrant juice flavonoid complex (Morton, 1968) and it would appear that its deleterious activity is masked by the 'beneficial' influence of the other flavonoids present. The clear difference

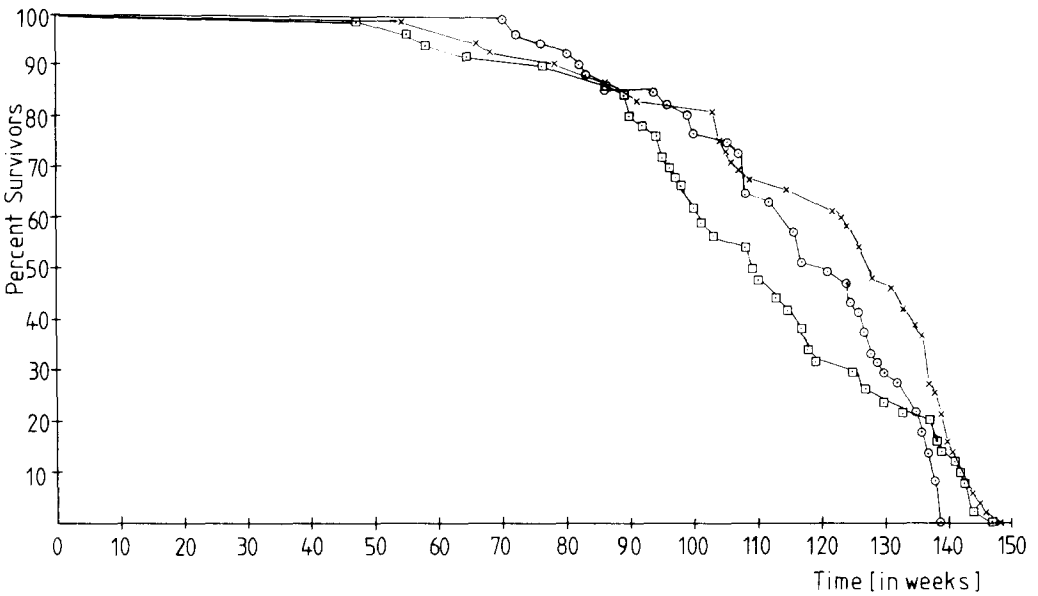

FIG. 2. Survival curves for female mice given dietary supplements of quercetin (⊡—⊡) or blackcurrant juice (–x–x–) compared with control mice (⊙—⊙—⊙).

between the effects of the two dietary supplements underlines the need for caution in generalizing about 'life-prolonging' effects of members of the same group of dietary compounds.

Of greater interest, perhaps, is the result of the analysis of deaths in terms of 'early dying' and 'late dying' mice. The quercetin supplement modified, primarily, the deaths of the 'early dying' animals whereas the 'blackcurrant flavonoid' effect appeared to be located in the 'later dying' animals, thus indicating a *qualitative* difference between the mode of action of the two supplements. In other words, one should perhaps distinguish between a chronic toxicity, likely to influence preferentially animals that, for constitutional reasons are in any case likely to die young, and any 'true' life-span effect which would be located predominantly in those animals genetically predisposed to longevity. Clarke and Maynard-Smith made essentially the same point in seeking to distinguish between ageing *per se* and a reduced 'threshold of vitality' (Clarke and Maynard-Smith, 1961). Analysis of life-span studies in terms of 'early dying' and 'late dying' groups could perhaps serve to remind us that 'prolongation of living' is not necessarily to be qualitatively equated with 'prevention of death.'

The human implications of this study are not without interest. Quercetin is widely distributed in the plant kingdom, typical values being (mg/100g fresh-weight): bilberry 5.0–15.0; blackcurrant 4.0–8.0, cherry 2.0–8.0, chives 30.0, and lettuce 2.0–25.0 (Herrmann, 1976). Usually, however, the quercetin is concentrated in the outer, non-edible layers of fruit and vegetables, the more frequently eaten fleshy parts being virtually quercetin-free. Asparagus tips contain less than 1.0 mg/100 g whereas the leaves contain c. 400 mg/100 g. Onions are of particular interest as the outer dry scales may contain up to 6.5%

quercetin whereas the inner portions of the bulb are comparatively quercetin-free (Herrmann, 1976; Eleri Jones, R.J. Hurley and R.E. Hughes, unpublished data).

The *per capita* daily intake of quercetin in the average diet is therefore unlikely to exceed some 50 mg. On the other hand, salad fiends, those who eat their tomatoes, apples and onions unpeeled, and 'natural food' addicts who indiscriminately include a range of esoteric plant material in their dietaries, could well ingest some 200–500 mg of quercetin daily.

Acknowledgements—Eleri Jones was in receipt of a Beecham Products Research Studentship. Mr Michael Ford (Beecham Products, Royal Forest Factory, Coleford) supplied the blackcurrant juice concentrate.

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