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Quercetin for dogs

Quercetin occurs in various vegetables and fruits. From a chemical standpoint, quercetin is a polyphenol that can act as antioxidant. Thus, it is believed that quercetin neutralizes the free radicals formed in body cells, thereby preventing damage to cellular structures and DNA. As a result, quercetin would act as longevity promoter and cancer inhibitor. Moreover, quercetin is thought to negate overactive inflammation in the body. Unsurprisingly, quercetin made its way into few canine nutritional products.

Dog foods with plant ingredients contain some quercetin, but the amount is (slightly) sent upwards by tomato pomace, apple and/or onion in the ingredient list. Quercetin in supplements for dogs may be provided by a purified onion extract. The intestine of dogs probably takes up only a small fraction of ingested quercetin. Once quercetin has entered the canine body, it likely is converted into more soluble compounds for excretion with urine and bile fluid.

Some canine supplements, treats and complete foods make quercetin-based, allergy-relief claims. Those products position quercetin as a natural antihistamine that averts itching as symptom of allergy. The selling story is largely based on one study showing that quercetin lowered histamine release by isolated dog immune cells. However, an effect in singular cells not necessarily takes place in the whole body (Note 1). Anyhow, in dogs there is no scientific proof that dietary quercetin reduces the clinical responses to inhaled and ingested allergens (Note 2).

As a polyphenol, quercetin can act as antioxidant in the test tube, but so far it is unknown whether ingested quercetin does so in the dog's body (Note 3). Likewise, the claims of quercetin promoting longevity and inhibiting cancer are not substantiated. It is clear that an experiment, lasting from weaning to death, is difficult to perform in dogs. One experiment in mice showed that dietary quercetin reduced life span (1), while another study found no effect (2).

Structure

Quercetin is a pentahydroxy flavonol with $C_{15}H_{10}O_7$ as chemical formula. It is composed of a heterocycle (five carbons, one oxygen atom) fused and bound with benzene rings that are both dihydroxylated. The carbon backbone structure can be abbreviated as $C_6-C_3-C_6$. The heterocycle has a keto and hydroxyl group that are adjacent (Note 4).

Food ingredients

In plants, quercetin mainly occurs as glycosides, with mono/di/tri/tetra-saccharides bound for the most part to C3 in the middle ring. Glucose, galactose and rhamnose are common sugar residues. Major quercetin glycosides are rutin or rutoside (quercetin-3-O-rutinoside or quercetin-rhamnosyl-D-glucose, $C_{27}H_{30}O_{16}$) and isoquercetin or isoquercitrin (quercetin-3-O-glucoside, $C_{21}H_{20}O_{12}$). Quercetin in foods is usually analysed and quantified as aglycone.

Corn (3, 4) and faba beans (5) may contain 16 and 23 mg quercetin/kg dry matter (dm, Note 5). Quercetin was undetectable in meats from broiler chickens fed regular diets (6, 7, Note 6). Some petfood ingredients that are less often used, and also in smaller quantities, are relatively high in quercetin. Tomato pomace (8), the edible part of unpeeled apples (5), onions (5) and grape pomace (9), may hold 168, 277, 2892 and 104 mg quercetin/kg dm (Note 7).

Apple pomace was found to contain 151 mg quercetin/kg dm (10), but polyphenol enriched fractions of industrial apple pomace only held up to 47 mg quercetin/kg dm (11). In contrast, the skin of Idared and Northern Spy apples had an approximate quercetin concentration of 990 mg/kg dm (10, Note 8). Food-grade, high-purity quercetin preparations, as offered via the internet (12), are extracts derived from onions or flower buds of the Japanese pagoda tree.

Dietary quercetin

Petfood with 25% corn, 30% faba beans and 30% poultry meal may include 11 mg quercetin/kg dm. A dry, complete dog food declares 100 mg quercetin/kg (Note 9). Three dog-treat products, in the form of soft chews or small bars, provide an equivalent of 167-333 mg quercetin/kg dietary dm as based on the stated compositions and feeding guides (Note 10). Similarly, using one of four dog supplements corresponds with 167-1333 mg quercetin/kg dietary dm (Note 11). All seven supplementary food products claim to provide allergy relief.

Absorption and metabolism

Caco-2 cells, a model of intestinal epithelial cells, absorbed quercetin aglycone more effectively than quercetin 3-glucoside (13). Thus, enzymatic cleavage of glycosidic linkages in the intestinal lumen may limit mucosal uptake of quercetin from ingested quercetin glycosides. In dogs, bioavailability of oral quercetin aglycone was only 3.6%, while that of isoquercitrin was higher and that of rutin similar (14).

Bioavailability, or the fraction reaching the systemic circulation, was assessed by oral and intravenous administration of the flavonols and taking into account plasma metabolites with intact flavonol structure (14). Low bioavailability of an ingested flavonol does not necessarily relate to low intestinal absorption, but could be caused by elimination via bile during first-pass metabolism or by metabolites unaccounted for.

In the bioavailability study (14), quercetin (10 mg/kg body weight) was mixed into a flavonol-free test meal and supplied to fasting dogs. Plasma concentrations of quercetin and its methylated metabolite (3-O-methyl-quercetin) plateaued between 1 and 4 hours post-dosing at about 300 and 20 nmol/l. The concentration of quercetin's dehydroxylated metabolite (kaempferol) was much lower (Note 12).

Beagles were given a single oral dose of 100 mg tartary-buckwheat extract in 50% (v/v) ethanol per kg body weight (15). The extract contained 61% rutin, 5% quercetin, 0.2% kaempferol and 4.8% kaempferol-3-O-rutinoside. The mixture was also administered intravenously (5 mg/kg body weight) in order to determine the bioavailabilities of quercetin and kaempferol, which were found to be 4.6 and 1.6%. In plasma, urine and feces, methylated, sulfated and glucuronidated compounds with the quercetin-base structure were identified. This indicates that dogs convert absorbed quercetin and other flavonols for excretion with urine and/or bile.

Allergy relief

In isolated, antigen-sensitized mast cells from dogs, the addition of quercetin to the incubation medium inhibited histamine release (16). In case of atopic or food allergy, histamine is involved in the inflammatory response and mediates itching. The in-vitro study lies at the heart of dog treats and supplements that claim an anti-histamine and allergy-relief effect for their quercetin constituent (Notes 10, 11). So far, there is no additional proof from clinical studies in dogs.

A dry, veterinary prescription diet asserts to be effective in the treatment of canine atopic dermatitis (Note 13). The food contains an undisclosed amount of quercetin that is added as constituent of a complex with undisclosed composition. The therapeutic food reduced the severity of atopic dermatitis in dogs, but the trial was open and uncontrolled (17). Clearly, the change from habitual to prescription diet involved multiple dietary variables.

Safety

Dog data on acute and chronic quercetin toxicity are unavailable. A dog study that set up a quercetin intake level equivalent to 33.3 mg/kg dietary dm for 6 weeks did not report adverse health effects (18). In rats, life-long consumption of food with 1100 mg quercetin/kg dietary dm may be considered safe (19).

Note 1

Under in-vitro conditions, quercetin inhibited the production of lipopolysaccharide-induced tumor necrosis factor-alpha (LPS-induced TNF α) in blood of healthy volunteers (20). That observation points to an anti-inflammatory effect of quercetin. However, ex-vivo LPS-induced TNF α production was not altered by a 4-week dietary quercetin intervention. The lack of effect of dietary quercetin possibly related to the absence of inflammation in the healthy subjects. In sarcoidosis patients, quercetin supplementation was found to reduce two pro-inflammatory blood markers, namely the ratios of TNF α /interleukin (IL)-10 and IL-8/IL-10 (21).

Note 2

Various types of studies suggest that dietary quercetin as sole treatment may be beneficial in human respiratory allergic diseases (22). However, the indications await confirmation by a randomized, double-blind, placebo-controlled study in human patients.

Note 3

Dogs fed one of two diets daily received 200 mg of a herb extract or did not (18). The percentage energy distributions (protein:fat:non-structural carbohydrates) of the diets were 24:24:52 and 19:43:38. The 200-mg supplement, which was based on six herbs, provided 5 mg quercetin. The adult dogs weighed about 10 kg so that the supplement was equivalent to 33.3 mg quercetin/kg dietary dm ($5 \times 1000 / (10 \times 15) = 33.3$). After six weeks, the supplement had reduced group-mean plasma concentrations of malondialdehyde by 20 and 33% in dogs on the low- and high-fat diet. This observation points to an antioxidative effect of the supplement, but it cannot be simply ascribed to quercetin.

Compounds other than quercetin are also recommended as health-supporting antioxidants for dogs. Those compounds are coenzyme Q10 (23), resveratrol (24), alpha-lipoic acid (25) and epigallocatechin gallate (26, Note 4). The five compounds share antioxidant capacity in vitro. However, they also have in common that their consumption did not, or least not convincingly, raised antioxidant capacity of dog blood. Except for alpha-lipoic acid, the (reduced forms of the) other compounds comprise one or more hydroxylated phenyl rings. The proton and one electron of a hydroxyl group can connect with the unpaired electron of a free radical, thereby neutralizing and inactivating the radical.

Note 4

The base structure of catechins is similar to that of flavonols, but their heterocycle has a hydrogen atom in place of a keto group at the C4 position. Green-tea extract is used quite frequently as additive in petfood (26). Its appealing component is EGCG (epigallocatechin gallate), which makes up about 10% of dried green-tea leaves and 60% of authentic, green-tea extract.

Note 5

In one study, the analysed quercetin content of corn grains was 15.8 mg/kg (3). Another study reported a mean value of 1274 mg/100 g for five different cultivars (4). Presumably, “mg” should read “μ” so that the amount was 12.7 mg/kg. Mean moisture content was 10.8%. The approximate quercetin concentration in corn is 16 mg/kg dry matter (dm). Faba beans (*Vicia faba* L.) had 20 mg quercetin/kg of fresh edible part (5) or 23 mg/kg dm.

Note 6

Quercetin was not detectable in liver, thigh or breast of broiler chickens fed regular finisher diets based on corn, soybean meal and wheat (6). Quercetin was detectable when it was added to the diet in the form of an unspecified pure/purified quercetin preparation, dried apple-skin powder or apple-skin extract. The apple products were prepared from Northern Spy apples (Note 8). In another study, one-day old broiler chickens were fed a diet based on corn, soybean meal and sunflower meal, without or with industrially produced quercetin (7). Quercetin was not detectable in breast meat from birds fed the unsupplemented diet for six weeks, but it was after quercetin feeding.

Note 7

It was assumed that the fresh edible parts of apples and onions contain 13 and 12% dry matter.

Note 8

Free quercetin and four glycosides were analysed in apple pomace (cultivar Gravenstein) and apple skin (cultivars Northern Spy and Idared). It was assumed that 65 and 50% of the reported weights for mono- and di-glycosides represents free quercetin.

Note 9

A complete dry food, recommended for working adult dogs with a high level of activity, declares “quercetin (100 mg/kg)” in its ingredient list (a). The food presents quercetin as a powerful antioxidant with anti-inflammatory properties. It is mentioned that the added quercetin is derived

from citrus fruits, including oranges. Fresh orange juice may contain 3.4 mg quercetin/L (27), or about 17 mg/kg dm. Thus, the food likely contains a purified quercetin preparation.

a. Arden Grange Performance – with fresh chicken & rice.

<https://www.ardengrange.com/products/arden-grange-performance-with-fresh-chicken-rice-ape68.html>

Note 10

The quercetin contents and feeding guidelines of three treat products can be converted into dietary intake equivalents. The suggested daily use of a soft-chew product (b) is 4 chews (= 50 mg quercetin) daily for a 20-kg, adult dog. At a food intake of 300 g dm/day, quercetin intake equals 167 mg/kg dietary dm. Another soft-chew product (c) advises two chews/day (= 100 mg quercetin) for a 20-kg dog, which corresponds with 333 mg quercetin/kg dietary dm. For a bar-shaped treat (d) the suggested feeding is 6 bars/day for a 20-kg dog (= 75 mg quercetin) or 250 mg quercetin/kg dietary dm.

b. FitaPet Allergy Relief for Itchy Dogs, soft chews. <http://www.fitapet.com/product/fitapet-allergy-relief-for-itchy-dogs-with-turmeric-omega-3-quercetin-and-bromelain-60-soft-chews/>

c. Pet Parents Immunue& Allergy, soft chews. <https://petparentsbrand.com/products/dog-allergies-supplement>

d. PETIPET turmeric bars, advanced inflammation and allergy complex. <https://petipetfood.com/products/turmeric-bars>

Note 11

A quercetin supplement in the form of chewable tablets (e) advises a daily dose of two tablets (= 50 mg quercetin) for a 20-kg dog. Two other tablet products recommend a dose of four tablets (= 400 mg quercetin)/day (f, g). The doses correspond with 167 or 1333 mg quercetin/kg dietary dm. A powdered supplement (h) suggests to supply 2.5 scoop (=250 mg quercetin)/day to 20-kg dog, which amounts to 833 mg quercetin/kg dietary dm.

e. VET'S+BEST Seasonal Allergy Support, chewable tablets. <https://www.amazon.com/Vets-Best-Healthy-Supplements-Chewable/dp/B0002I9O98>

f. HappyPet Allergy Relief, chewable tablets. <https://www.amazon.com/HAPPY-PET-VITAMINS-LLC-Itch/dp/B07R23V5QW>

g. Now® Pets, Pet Allergy, PET ALLERGY For DOGS/CATS, chewable tablets <https://www.nowfoods.com/pet-health/pet-allergy-chewable-tablets>

h. Bio SKIN&COAT, Healthy Skin & Coat and Allergy Support Formula, powder <https://biologicvet.ca/products/bioskincoat/>

Note 12

Dogs were orally administered a persimmon-leaf extract in the form of either commercially available tablets or a self-nanoemulsifying drug delivery system (28). One tablet contains 5 mg total

flavonoids, including quercetin and kaempferol. The delivery system increased the area under the concentration-time blood plasma curve for quercetin and kaempferol by 48 and 61%.

Note 13

A dry, veterinary prescription diet (Hill's® Prescription Diet® Derm Defense™ Canine) contains quercetin “to help normalize a hyperactive immune response to environmental irritants”(i). The amount of quercetin is not disclosed. It is mentioned that the food contains Histaguard™ Complex, which is “formulated to reduce signs of environmental allergies by disrupting the internal allergy response and creating a barrier against future episodes”. Hista-Guard® is available as capsules containing 50 mg quercetin and 50 mg rutin (j). The “Nutritional Evidence Summary” of the prescription diet (k) does not provide evidence of diet efficacy.

i. <https://www.hillsvet.com/products/dog-food/pd-derm-defense-canine-dry>

j. <https://www.nutricionholistica.es/ficha/id/1029/histaguardnutrigold>

k. <https://www.vetclub.com.au/uploads/attachmentfile/15/data/9184e9322b8f154748e7484487fd5c23.pdf>

Note 14

Two brands of dog supplements (Note 11, f, g) also have cats as target animals. The suggested daily intake of one tablet (= 100 mg quercetin) or half a tablet (= 50 mg quercetin) equals 1667 (l) or 833 (g) mg quercetin/kg dietary dm for a 4-kg cat consuming 60 g dm/day.

l. <https://www.amazon.com/HAPPY-PET-VITAMINS-LLC-Allergy/dp/B07R742FST>

Note 15

In rats, the area under the concentration-time blood plasma curve for orally administered clopidogrel was increased by co-administration of quercetin, but it was not in dogs (29).

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