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Safety Aspects of the Use of Quercetin as a Dietary Supplement

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The flavonoid quercetin is frequently found in low amounts as a secondary plant metabolite in fruits and vegetables. Isolated quercetin is also marketed as a dietary supplement, mostly as the free quercetin aglycone, and frequently in daily doses of up to 1000 mg d^{-1} exceeding usual dietary intake levels. The present review is dedicated to safety aspects of isolated quercetin used as single compound in dietary supplements. Among the numerous published human intervention studies, adverse effects following supplemental quercetin intake have been rarely reported and any such effects were mild in nature. Published adequate scientific data for safety assessment in regard to the long-term use (>12 weeks) of high supplemental quercetin doses (≥1000 mg) are currently not available. Based on animal studies involving oral quercetin application some possible critical safety aspects could be identified such as the potential of quercetin to enhance nephrotoxic effects in the predamaged kidney or to promote tumor development especially in estrogen-dependent cancer. Furthermore, animal and human studies with single time or short-term supplemental quercetin application revealed interactions between quercetin and certain drugs leading to altered drug bioavailability. Based on these results, some potential risk groups are discussed in the present review.

1. Introduction

The flavonol quercetin (synonyme: 3,3′,4′5,7-pentahydroxyflavone, structure see **Figure 1**) is one of the most abundant naturally occurring polyphenol in our foods. Its occurrence as a secondary plant metabolite is widespread in the plant kingdom, where it is mostly present in the form of quercetin glycosides (quercetin molecule conjugated with sugar residues).[1,2] In this form, quercetin is a common constituent of the human diet via vegetables and fruits (e.g., onions and apples). By contrast, dietary supplements with quercetin as ingredient contain mostly the free form of quercetin, the aglycone.

Numerous biological effects of quercetin have been published in a great number of scientific studies based on in vitro experiments, as well as animal and human studies. Among others, the substance is presumed to have antioxidant, anti-inflammatory, immunoprotective, and even anticarcinogenic effects. Therefore, the benefits of a quercetin application has been discussed, e.g., with respect to cardiovascular diseases, diabetes, inflammation, asthma, viral infections, or regarding cancer prevention.[2–5] Quercetin has also been of interest due to its assumed potential as ergogenic substance. Studies in athletes have focused on effects on postexercise inflammation, oxidative stress, immune function, endurance performance, or reduction of illness rates after strenuous exercise. However to date, most of the proposed benefits for athletes could not be affirmed. Yet, orally applied quercetin displayed some effects in the reduction of illness rates in exercise stressed athletes and in improving endurance performance especially in untrained subjects.[6] Currently, rather combinations of quercetin with other bioactive substances is used with hope that these interventions might achieve more promising effects with special interest to athletes.[6]

Currently, quercetin as aglycone is marketed as an ingredient of dietary supplements with different claims or purported benefits which are not within the focus of the present review and reviewed elsewhere.[2,3,5,7–12] However, the European Commission did not authorize certain health claims, e.g., for protection of DNA, proteins, and lipids from oxidative damage for the general population.[13] In Canada, quercetin may be used in "Natural Health Products" with two different statements of effects "an antioxidant" *or* "used in Herbal Medicine as a capillary/blood vessel protectant".[7]

The focus of this review was laid on the identification of possible critical health aspects regarding the safe use of quercetin as single compound in dietary supplements. In this regard, the focus was laid on adult persons. Pregnant and breastfeeding women as well as children and adolescents were not taken into account here. Primarily the databases PubMed/Medline and Embase were used for retrieval of relevant publications, with the last

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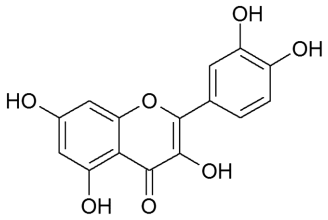

Figure 1. Structure of quercetin.

update being in autumn 2016. In addition, the reference lists, particularly of currently published reviews and relevant scientific articles as well as websites of different scientific bodies and national authorities were checked.

2. Dietary Occurrence and Exposure

Naturally occurring quercetin is present (primarily as glycosides) in many fruits (e.g., apples, cranberries, cherries, grapes) and vegetables (e.g., onion, peppers, asparagus), and other food items such as wine and black or green tea.[3] The composition pattern of the diverse quercetin glycosides varies between different food items. Onions, the most important quercetin source in the human diet, contain primarily quercetin-4'-glucoside and quercetin-3,4'-diglucoside,[14] while apples contain, among others, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, quercetin-3-*O*-rhamnoside, and quercetin-3-*O*-rutinoside.[15,16]

Estimated daily quercetin intakes have been observed in the range of 3–40 mg (expressed as aglycone equivalents) in Western diets.[17–21] On the other hand, it has been estimated that quercetin intake of "high-end consumers" of fruits and vegetables is ≈250 mg d^{-1}.[22]

In dietary supplements, recommended daily doses of quercetin aglycone are usually in the range of up to 1000 mg (most commonly 500 mg). Thus, the intended quercetin intake via dietary supplements is often considerably higher than background dietary intake levels of quercetin. Furthermore, it is to be taken into account that quercetin is primarily present as aglycone in dietary supplements whereas food items contain mainly quercetin glycosides. In addition, some supplements which combine quercetin with bromelain and partly other substances contain also higher daily quercetin doses in the range of about 1.2–2.4 g d^{-1}. However, this review is dedicated to safety aspects of isolated quercetin used as single ingredient.

3. Kinetics and Metabolism

Following oral ingestion, certain quercetin glycosides are hydrolyzed by β-glucosidases in the gut.[23,24] Subsequently, the released quercetin aglycone has been assumed to passively permeate the intestinal epithelial barrier. Quercetin glycosides may also be absorbed directly via the intestinal sodium/glucose cotransporter-1.[25,26]

Quercetin is extensively metabolized in the enterocytes and further in the liver, forming a plethora of metabolites.[27–29] Thus, quercetin can be glucuronidated, sulfated, or/and methylated.[30,31] In addition, it is suggested that quercetin is also oxidized in vivo, forming quercetin–quinone and quercetin–quinone methides[32,33] which is further discussed in section 4.3.2.1 Genotoxicity and carcinogenicity. Non-absorbed quercetin can be degraded by the colonic microbiota to different phenolic acids (e.g., 3,4-dihydroxyphenylacetic acid) and carbon dioxide.[30,34] An overview of the complex (but not exhaustive) metabolism of quercetin is shown in the Supporting Information Figure S1.

Human kinetic studies recovered primarily quercetin conjugates in blood plasma after oral intake of quercetin, while only very low levels of quercetin aglycone were found. Hence, many studies measured "total quercetin" levels which mostly encompass glucuronidated and/or sulfated quercetin conjugates without the corresponding conjugates of the methylated quercetin forms. After an intake of 500 mg quercetin (following a supplementation of three times 500 mg quercetin per day for 6 d), a maximal plasma concentration of only ≈15 μg L^{-1} quercetin as aglycone (≈50 nM, t_{max} of 3 h) was observed while the maximal concentration of the measured nonmethylated quercetin conjugates (glucuronides and sulfates) was clearly higher, comprising around 450 μg L^{-1} (t_{max} of 4 h).[35] In another study, methylated quercetin conjugates were measured after an intake of 1095 mg quercetin. Total maximal concentrations (including free and sulfated/glucuronidated metabolites) of the nonmethylated quercetin as well as of tamarixetin (4'-methylquercetin) and isorhamnetin (3-methylquercetin) reached plasma levels of ≈1.2 μM (t_{max} of around 5 h), 0.4 μM (t_{max} of around 7 h), and 0.2 μM (t_{max} of around 10 h), respectively, after ingestion with a low-fat breakfast.[36] The pattern of quercetin conjugates (sulfates or glucuronides) may modulate the biological action of quercetin in vivo.[37–39] The pharmacokinetics of quercetin can show a high interindividual variability, depending on, for example, genetic variations, individual antioxidative status, food matrices, and the co-administration of other dietary components such as fiber or fat.[24,36,40] With respect to quercetin glycosides as the major quercetin source in foods, the sugar moieties of the quercetin glycosides could cause also a modulation of the quercetin bioavailability.[41–43]

Regarding the tissue distribution of quercetin, data are available for rats and pigs, whereby pigs seem to be the more appropriate model for human metabolism than rats. In rats treated with 50 or 500 mg quercetin per kg bodyweight (bw) and day for 11 weeks, the highest quercetin levels were found in lung, testis, and kidney (with lower levels than in plasma) and the lowest in brain, spleen, and white fat tissue. In pigs treated with 500 mg quercetin per kg bw and day for 3 d, an accumulation of quercetin was observed primarily in liver and kidney (testis not analyzed), even exceeding plasma levels, while low levels were observed in brain, heart, and spleen.[44] Higher levels of quercetin, isorhamnetin, and tamarixetin aglycones and their conjugates were found in certain tissues like colon, kidney, and jejunum compared to plasma levels in pigs treated with 50 mg quercetin per kg bw and day for 4 weeks. Some tissues such as colon, mesentery, diaphragm, liver, lung, jejunum, and brain contained quercetin either exclusively or at higher proportions as aglycone (~90%), while in other investigated tissues such as the kidney or lymph nodes the unconjugated quercetin was present in smaller proportions (30–60%).[45] However, there are uncertainties regarding

the real proportion of the quercetin aglycone in tissues because there are indications that postmortem deconjugation of flavone conjugates during the extraction procedure may occur to varying degrees in different organs.[44]

4. Safety Aspects

4.1. Information Based on Evaluations by Scientific Bodies and National Authorities

In 1999, the International Agency for Research on Cancer (IARC) examined the potential carcinogenic risk of quercetin to humans and, based on data available at that time, came to the overall conclusion that "quercetin is not classifiable as to its carcinogenicity to humans".[46]

In 2010, in a response letter to a GRAS notification for the use of high-purity quercetin as food ingredient in different food products, the American Food and Drug Administration (FDA) had no questions regarding the conclusion that high-purity quercetin is GRAS ("Generally Recognized As Safe") under the intended conditions of use.[47] Here, an additional mean intake of around 200 mg high-purity quercetin per day was estimated for all age groups and of around 460 mg d^{-1} for high consumers (90^{th} percentile). According to conservative estimates, it was assumed that the target consumer with an additional daily intake of 1000 mg high-purity quercetin, who is also a "high-end consumer of fruits and vegetable" with an estimated maximal background intake of approximately 250 mg d^{-1}, may consume in total ≈1250 mg quercetin per day.[22,47]

According to a regulation in Italy, the maximum daily amount of quercetin aglycone in dietary supplements is limited to 200 mg and of mixed, nonspecified flavonoids to 1000 mg.[48]

In Canada, the daily dose of quercetin as an ingredient in "Natural Health Products" is limited to 1200 mg. Products providing 40–1200 mg quercetin per day have to be divided into two or three doses and taken together with food/meals. Moreover, an additional statement is required on the package label that a healthcare practitioner should be consulted for a use exceeding 12 weeks. Pregnant and breastfeeding women should also consult a healthcare practitioner prior use. Known adverse reactions are not mentioned.[7]

4.2. Information from Human Studies

The majority of human intervention studies with high repeated oral quercetin doses (exceeding considerably the dietary quercetin intake) comprise studies with administration of quercetin aglycone as a single compound or in combination with high amounts of vitamin C with or without lower amounts of niacin/nicotinamide. In this review, emphasis was laid on these both supplementation groups. However, it was recognized, that the used doses of vitamin C and niacin/nicotinamide may be also biologically active and may have an impact on the bioavailability of quercetin.[49] In addition, other intervention studies, involving the administration of quercetin aglycone in combination with one or more other probably biologically active substances (e.g., bromelain, curcumin, (green) tea-extracts, or cinnamon bark extract), were identified. These studies were considered of minor relevance regarding the safety assessment of quercetin aglycone, due to open questions on the applicability of these study results to the administration of quercetin as a single ingredient.

Regarding the application of quercetin in combination with vitamin C, there are open questions as to whether vitamin C might mask or alleviate possible pro-oxidative effects of quercetin. Primarily in vitro but also some in vivo studies have shown that, although quercetin displayed antioxidative effects in several kinds of cells and tissues, quercetin itself was converted to the reactive oxidation products, *o*-semiquinone and *o*-quinone, which may react with thiols and cause loss of protein function and cytotoxic effects.[32,33,50–54] The occurrence of possible anti- or pro-oxidative effects of quercetin may be dependent on the quercetin dose, time of exposure, and the cellular redox state. The intake of antioxidative compounds such as vitamin C may theoretically mask the suggested pro-oxidative effects of quercetin. In human intervention studies, pro-oxidative effects of quercetin were not found with quercetin doses at 500–1000 mg d^{-1} applied for 3–12 weeks (n_Q = 6–333),[55–59] but it is still an open question whether quercetin may exhibit pro-oxidative effects in the human body, especially after a long-term use of high quercetin doses.[30,60,61]

In general, oral intake of quercetin in humans seems to be well tolerated and only a very low incidence of adverse effects has been observed to date (for details see Supporting Information Table S1). Several intervention studies with administration of quercetin as single ingredient or in combination with vitamin C are available which primarily investigated the efficacy of quercetin in healthy adults or in patients suffering from different ailments. Most of these studies either did not include any information regarding the occurrence or absence of adverse events or simply stated that adverse effects were not reported without giving further details. Only a few studies provided detailed information on the occurrence of adverse events or on relevant safety lab parameters (a situation which frequently can be found with substances used as ingredients of dietary supplements). In this context, it is noted that the fact that no adverse events were mentioned for many of the published human intervention studies cannot be taken as proof that no adverse events occurred. Basically, for risk assessment purposes only studies can be considered which provide detailed information on the occurrence/absence of adverse effects or which provide at least the information that no adverse events were reported. The intervention studies with administration of quercetin as a single compound or in combination with vitamin C and a clearly stated duration of quercetin administration usually used quercetin doses of up to 1000 mg d^{-1} for a maximum duration of 12 weeks (for details see Supporting Information Table S1).

After intake of a relatively low quercetin dose of 150 mg quercetin per day for 6 weeks (n_Q = 93), certain parameters of liver and kidney function, hematology and serum electrolytes were measured in overweight or obese individuals. All evaluated parameters remained within normal ranges.[62]

At least the information that no adverse events were reported by the enrolled individuals is given after the repeated intake of 500 mg quercetin per day for 4–8 weeks (n_Q = 20–22),[63,64] 730 mg for 4 weeks (n_Q = 41)[65] or 1000 mg for 5 d, for at least 2 weeks (no further information on duration of quercetin dosage)

or for 12 weeks (n_Q = 11–42).[66–68] After intake of 1000 mg quercetin per day for 1 month conducted in patients with chronic pelvic pain syndrome (n_Q = 15), one patient developed headaches after the first few quercetin doses which resolved and one individual experienced mild tingling of the extremities after each quercetin dose.[69]

In addition, there are some small short-term studies (5–14 d, n_Q = 3–20), primarily pharmacokinetic or drug interaction studies, with higher daily quercetin doses of 1500 mg and in one study of 2000 mg (for details see also Supporting Information Table S1).[35,70–77] However, due to the short-term application, the combined administration with drugs in some cases and/or missing or unprecise information on the occurrence/absence of adverse events, these studies provide no adequate basis for the safety assessment of daily doses of 1500–2000 mg quercetin as single ingredient.

A dose-escalating phase 1 study is available with patients suffering from chronic hepatitis C which were treated with quercetin doses of 250–5000 mg d^{-1} (in total 11 doses, 2–3 patients per dose level) for 28 d. All patients tolerated the quercetin supplement without significant adverse events. Some patients experienced mild stomach discomfort when quercetin was taken without food, which was relieved if quercetin was taken after a meal. No information was given at which doses these mild complaints occurred. Blood count, complete metabolic panel, cholesterol panel, or coagulation parameters remained unchanged on week 2 and 4 (data were not shown). In this group of patients, a discernable pattern of liver enzyme changes was not observed.[78] The applicability of these results to the general population is limited due to the short duration and the small number of the enrolled individuals. In addition, there are open questions whether the underlying liver disease might cause alterations of the quercetin metabolism.

Regarding the combinational treatment involving quercetin with vitamin C and niacin, there is, in addition to several other studies (for an overview see Supporting Information Table S1), one study with a relatively high number of participants which investigated either 500 mg quercetin with 500 mg vitamin C and 20 mg nicotinamide per day or 1000 mg quercetin with 1000 mg vitamin C and 40 mg nicotinamide per day or placebo for 12 weeks (partly unclear information to vitamin C and nicotinamide dosages, for details see Supporting Information Table S1). Each group included about 330 individuals of which 37% had a past or current history of one or more chronic diseases. No negative changes were observed in safety parameters (hematocrit, hemoglobin, glucose, and kidney function parameters) after quercetin treatment.[79] Patients documented their disease status, medication use, and gastrointestinal (constipation, heartburn, bloating, diarrhea, nausea, and vomiting), skin (rash, dryness, flushing), allergy, and mental symptoms (energy, headache, stress, focus/concentration) in a monthly log. It was stated that no group differences over time were observed for gastrointestinal, skin, allergy, and mental symptoms. Details on these safety-relevant outcomes were not provided. Nine dropouts were reported due to adverse symptoms. In the follow-up, no consistent pattern of symptoms was revealed that could be ascribed to quercetin supplementation.[79,80] There was no specific information regarding the experienced symptoms, whether affected persons had underlying diseases and in which study group the dropouts occurred complicating the interpretation of this study.

In a review dealing with the use of quercetin in prostatic diseases (typical quercetin dose: 1000–1500 mg d^{-1}), it was mentioned that side effects with quercetin therapy were rare. Some patients experienced nausea if the substance was taken on an empty stomach. There were rare reports of transient joint pain when quercetin was taken at high doses (no doses specified). In addition, in these patients orange pigment may show up in some semen preparations, which can be ascribed to the coloring property of quercetin. However, no further scientific data was given in regard to this information and it is not clear whether it applies to the application of quercetin alone or in combination with other substances.[81]

In addition, further studies are available with quercetin (500–1000 mg d^{-1} for usually 4–12 weeks, n_Q = 11–64) given in combination with other substances, e.g., bromelain, papain, mixed bioflavonoids, omega-3 fatty acids, epigallocatechin gallate or (green) tea-extracts, cinnamon bark extract, or other substances.[69,82–88] These studies include one study with administration of 650 mg quercetin per day in combination with nine other possible bioactive substances for 6 or 12 month and one study with 1000 mg quercetin per day in combination with bromelain and papain and possibly different drugs for 6 months or longer (the last one provides no information on the occurrence/absence of adverse events).[86,87] Although in these studies no serious adverse effects were reported, there are open questions regarding the applicability of these study results to quercetin applied as a single compound.

Regarding the use of quercetin as a single compound, scientific information for safety evaluation of quercetin from human intervention studies is limited due to lack of relevant safety data, especially considering the long-term treatment (>12 weeks) with high-dose supplemental quercetin applications (≥1000 mg d^{-1}). This constitutes a major data gap that impedes risk assessment especially in the case when long-term use of high supplemental quercetin doses is intended. Along these lines, the importance to include a detailed documentation regarding the incidence of adverse effects and measurements of clinical safety parameters in any future intervention studies is underlined.

4.3. Specific Endpoints of Concern

4.3.1. *Organ Toxicity*

Chronic toxicity studies in rats revealed several adverse effects such as reduced body weights, elevated relative organ weights, e.g., of kidney and liver in both sexes (possibly attributable to the reduced body weight), increase in the incidence of non-neoplastic hyperplastic polyps of the cecum in males and females and parathyroid hyperplasia in males (which was regarded as renal secondary hyperparathyroidism) and the presences of calcium oxalate crystals in urine at high dietary quercetin doses of 4–5% in feed (corresponding to ≈1900 and 2100 mg kg^{-1} bw per day).[89–91] In addition especially at the high quercetin doses, yellow-brown pigmentation was found in the glandular stomach and the intestine primarily in the small intestine which could be

caused by the yellow colored quercetin compound itself or by one of its metabolites.[89,91]

The question was raised whether quercetin might adversely affect thyroid function, based on in vitro studies showing an inhibition of thyroid peroxidase, the thyroid type 1 deiodinase and of the expression of thyroid-restricted genes by quercetin[92–95] as well as based on a rat study showing a decrease in radioiodine uptake into the thyroid after intraperitoneally applied quercetin (50 mg kg^{-1} bw per day for 14 d).[95] However, in studies involving oral application of quercetin, adverse effects on thyroid hormone levels were not observed in animal models for obesity and hypothyroidism at quercetin doses between 10 and 25 mg kg^{-1} bw per day for 2–6 months[96,97] or in chronic toxicity studies in rats investigating histopathological effects on the thyroid gland at quercetin doses of up to 2000 mg kg^{-1} bw per day.[89–91]

Only limited human studies were identified measuring any parameters regarding the kidney function (described in the next section: nephrotoxicity) or liver function. Parameters for liver function (e.g., alanine transaminase, aspartate transaminase, and γ-glutamyl-transpeptidase) remained within normal ranges in overweight or obese individuals after intake of a relatively low quercetin dose of 150 mg quercetin per day for 6 weeks.[62] In addition, quercetin did not exacerbate liver enzymes (aspartate transaminase and alanine transaminase) in a dose-escalating study with patients suffering from chronic hepatitis C which were treated with daily quercetin doses of 250–5000 mg (in total 11 doses, two to three patients per dose) for 28 days.[78]

4.3.1.1. Nephrotoxicity. In the US National Toxicology Program (NTP) a chronic study was conducted in rats which were treated with 0.1, 1, or 4% quercetin in feed for 2 years (corresponding to approximately 40, 400, or 1900 mg kg^{-1} bw per day, respectively). A dose-related increase of chronic nephropathy and a slight increased incidence in focal hyperplasia of the renal tubule epithelium were observed only in male animals fed quercetin. A higher incidence of kidney adenomas was observed at 1 and 4% quercetin doses in male rats (step sections, i.e., producing addition samples of the formalin-fixed kidney: 0%, 1/50; 0.1%, 2/50; 1%, 7/50; 4%, 6/50).[89,91] There was no apparent effect of quercetin on the kidney in female rats. The renal histopathology was re-evaluated by Hard et al.,[98] confirming the exacerbation of the chronic progressive nephropathy, the induction of renal hyperplasia and the increase of renal tumors in the mid- and high-dose groups of male rats. The nephropathy was already enhanced by the high quercetin dose in interim investigations of 6 and 15 months. The authors suggested that renal tumor development may be associated with or may be a consequence of the chronic progressive nephropathy occurring only in male rats, with probably no or only little relevance for extrapolation to humans.[98] This point of view was also accepted by other researchers.[22,30] However, taking another cautious interpretation into consideration, quercetin may have the ability to exacerbate adverse effects in predamaged kidneys.

This assumption was supported by two other studies investigating the effects of quercetin on chemically induced nephrotoxicity in male rats. In one study streptozotocin (50 mg kg^{-1} d^{-1}, intraperitoneal) was used for induction of diabetes mellitus in test animals. Orally applied quercetin at a concentration of 70 mg kg^{-1} diet for 28 weeks (corresponding to approximately 3 mg kg^{-1} bw d^{-1}) caused an increase in the incidence of renal cell tumors with severe to high renal lesions and an enhancement of the malignancy (streptozotocin: 2/6, combination with quercetin: 6/6 animals; no quercetin control group). Authors suggested several possible modes of action of quercetin, such as pro-oxidative effects, insulin-secretagogue bioactivity, or inhibition of the *O*-methyltransferase (causing a shift to carcinogenic estrogen metabolites).[99]

Heeba and Mahmoud[100] analyzed the impact of orally applied quercetin on a doxorubicin-induced rat model for nephrotoxicity. Quercetin doses of 10, 50, and 100 mg kg^{-1} bw per day for 14 d and intraperitoneal injection of doxorubicin of 15 mg kg^{-1} bw on application day 7 were applied. A dose-dependent effect of quercetin was found with protective effects in preserving renal function at the low dose of 10 mg kg^{-1} bw and rather pro-oxidative and pro-inflammatory effects at the highest quercetin dose of 100 mg kg^{-1} bw, resulting in an enhanced renal dysfunction induced by doxorubicin.[100] Alternatively, the results of the two last cited studies may be also explainable by an increased bioavailability of the nephrotoxic drugs. For doxorubicin as example, quercetin caused an increase in the drug bioavailability, when the drug was applied orally (but not intravenously), via an inhibition of P-glycoprotein and CYP3A4 in the small intestine and/or liver.[101] However, the cited work by Heeba and Mahmoud[100] applied doxorubicin intraperitoneally so that it is unclear if quercetin alters drug kinetics also after this kind of application.

Based on the chronic NTP study and the two animal studies involving chemically induced nephrotoxicity in rats, the question is raised whether quercetin may exacerbate already underlying deleterious processes in the kidney not only in animals but also in humans with a pre-damaged kidney. Human intervention studies investigating possible adverse effects of quercetin on kidney function are limited. One study with overweight or obese subjects with metabolic syndrome traits was identified, in which a relatively low quercetin dose of 150 mg quercetin per day was applied for 6 weeks. In this study, the serum creatinine level remained within normal ranges after quercetin administration.[62] In addition, one large study investigated either 500 mg quercetin in combination with 500 mg vitamin C and 20 mg nicotinamide per day for 12 weeks or twice of these doses in approximately 330 individuals per group (partly unclear information to vitamin C and nicotinamide dosages, for details see Supporting Information Table S1). Parameters of kidney function (serum creatinine and glomerular filtration rate) were not adversely affected after quercetin administration.[79] In another study with cancer patients, intravenous bolus application of quercetin was investigated. Renal toxicity and emesis were observed at doses equal to 630 mg/m^2 or above (about 1090 mg per person).[102] However, in this study very high plasma quercetin levels of 200 to 400 μM were observed immediately after intravenous injection of 945 mg quercetin/m^2, which cannot be achieved with an oral quercetin intake. Due to these very high circulating quercetin levels, the seriously underlying disease status and the concomitant drug intake, this study is not appropriate for risk evaluation of orally applied quercetin intake for the general population. However, based on the findings in animals, there might be an adverse effect of quercetin on kidney function primarily in the pre-damaged

kidney, which could not be invalidated considering the available limited human data.

4.3.2. Cancer

4.3.2.1. Genotoxicity and Carcinogenesis. Quercetin was tested positively for mutagenicity in diverse bacterial and eukaryotic cell systems in vitro, including a number of standard tester strains of *Salmonella typhimurium, Escherichia coli* (both independent of metabolic activation), yeast and somatic cells. In vitro, quercetin caused, among others, mutations, chromosomal aberrations, DNA single strand breaks and the induction of micronuclei which is reviewed elsewhere.[30,46,103,104] The oxidation of quercetin to the reactive metabolites *o*-quinone and quinone methide can result in the formation of DNA adducts which has been suggested as a possible genotoxic mechanism.[32,33]

By contrast, the in vitro genotoxic effects of orally applied quercetin could not be confirmed in in vivo studies with mice or rats. Quercetin caused no induction of DNA strand breaks, DNA damage, micronuclei formation or chromosomal aberrations in bone marrow cells.[30,105–109] Quercetin also did not induce unscheduled DNA synthesis in hepatocytes[106] or genotoxic related pathways in liver and the small intestine as demonstrated by transcriptome analyses.[110] It was suggested that the DNA adducts formed with quercetin oxidation products are chemically instable which may explain the lack of genotoxicity in vivo.[32,33]

Regarding the impact of quercetin on carcinogenicity, Sak et al.[111] reviewed in vitro studies investigating the impact of quercetin on the growth of human cancer cells. Quercetin was able to inhibit the growth of human cancer cells derived from a varity of tissues/organs such as pancreas, ovaries, cervix and colon suggesting a preventive role of quercetin in the cancer development and treatment. In vivo, a number of chronic studies either show no or even anti-carcinogenic effects of orally applied quercetin.[22,30,46,104] Many different mechanisms have been suggested for the possible anti-carcinogenic effects of quercetin e.g. an induction of cell death or cell cycle arrest, inhibition of topoisomerases and tyrosine kinases, down-regulation of oncogenes and an up-regulation of tumor suppressor genes leading to the elimination of cancer cells.[112–116] However, there is some evidence that quercetin may have a tumor enhancing effect under specific conditions/in combination with certain substances which is reviewed in the following sections tumor promotion and estrogen-mediated carcinogenesis in more detail.

4.3.2.2. Promotion of Already Existing Cancer Cells. Tumor-promotion models in animals use usually high doses of substances with cancer-initiating properties which do not well reflect the human situation.[112] However, such studies are considered as appropriate to identify possible tumor-promoting compounds. Over 20 published studies investigated the effect of quercetin on tumor promotion in certain organs/tissues. Most studies revealed no or even chemo-preventive effects of quercetin (details see[30]). However, a few studies using different carcinogens (N-ethyl-N'-nitro-N-nitrosoguanidin, azoxymethane, nitrosomethylurea or 17β-estradiol) reported also an enhanced tumor development in duodenum,[117] colon,[118] pancreas,[119,120] kidney[121] or mammary glands[122] of rodents after quercetin treatment with 0.2 to 3.4 % in feed (corresponding to approximately 150 to 3400 mg per kg bw and day). Two of these studies started the quercetin treatment in pregnant rats continuing in their offspring and investigated the tumorigenesis in the offspring.[119,120] Furthermore, two other studies investigated the effects of quercetin on the tumor-development mediated by exogenously applied estradiol,[121,122] the results of which are described in more detail in a separate chapter (section 4.3.2.3).

Taken together, the findings regarding the effects of quercetin on tumor promotion are contradictory which might be explained by different study designs using different animal species, quercetin doses and duration, different applied carcinogens and kinds of treatments (e.g. quercetin application prior or after carcinogen application). Because most of these in vivo studies did not investigate the underlying mechanisms, further studies should clarify the mode of action causing the possible tumor promoting or tumor protective effects of quercetin. For quercetin doses used in dietary supplements, no information from human studies is available as to how quercetin might impact tumorigenesis in humans.

Regarding possible mechanisms causing (anti-)carcinogenic effects, it is known that quercetin affects transport proteins and the activity of xenobiotic metabolizing enzymes which can result in altered bioavailability of carcinogens and other xenobiotics.[123,124] In mice, quercetin at doses of 0.5, 1 or 2 g per kg bw and day for 90 days inhibited DNA damage and pulmonary precancerous pathological changes induced by benzo[a]pyrene. Inhibition of CYP1A1 activity was suggested as one mechanism preventing the activation of this procarcinogen.[125] Human data also indicate that quercetin modulates xenobiotic metabolizing enzymes. A decrease in CYP1A2 activity and an increase in activities of CYP2A6, CYP3A activity (CYP3A5 genotype) and some other enzymes were observed after an intake of 500 mg quercetin per day for 13 days.[126,127] However, direct carcinogens, which may not need any activation, may be degraded slower by the co-treatment with quercetin.

Furthermore, quercetin may also modulate cellular transport mechanisms. As example, quercetin (25 μM) induced in vitro the expression of the breast cancer resistance protein (BCRP) in the human colon carcinoma cell line Caco-2. This elevated protein expression may cause an enhancement of the apical outward transport of the food carcinogen benzo[a]pyrene-3-sulfate, a sulfoconjugate of benzo[a]pyrene, and may therefore contribute to the detoxification of this procarcinogen.[128] In contrast, Schutte et al.[129] found an increased bioavailability of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), probably due to inhibition of BCRP, multidrug resistance protein-2 and P-glycoprotein in Caco-2 cells diminishing PhIP efflux. The subsequently conducted in vivo study revealed an increased "area under the curve" (AUC) value of PhIP (applied dose of approximately 0.3 mg per kg bw) to around 130 % after co-treatment with quercetin (approximately 9 mg per kg bw) in rats.[130]

Therefore, depending on the xenobiotic, the quercetin dose, the duration of exposure and/or the timing of exposure, quercetin may increase or decrease the bioavailability of xenobiotics due to its impact on the expression and activity of xenobiotic metabolising enzymes or on transport proteins. However, there are sometimes conflicting results regarding

specific enzyme activations or inhibitions which may be due to differences in the species, gender, race, sample size, genetic variations, molecular heterogeneity of cancer and genotyping methodologies.[60,123,131–134]

4.3.2.3. Effects on Estrogen-Mediated Carcinogenesis. A few animal studies revealed tumor promoting effects of quercetin, whereby we put emphasis on the effects of quercetin on the estrogen-mediated carcinogenesis. In vitro studies revealed biphasic effects of quercetin on the growth of certain cancer cell lines such as human colon carcinoma cells (HCT116 and HT29) or human breast cancer cells (MCF-7 and T47D). At low concentrations (depending on the cell type between 0.1 and 60 μM) quercetin caused cell proliferation, but growth inhibition at higher concentrations.[135–139]

Because quercetin caused cell growth primarily in estrogen receptor (ER) positive and not in ER-negative breast cancer cells in vitro, an involvement of ER-dependent pathways was suggested.[139] This suggestion is further supported by the fact that quercetin can transactivate both types of estrogen receptors, ER-α and ER-β.[135] Especially in cell lines with a predominance for ER-α, which plays a particular role in cell proliferation, quercetin at low concentrations of already 0.1 μM induced cell proliferation. By contrast, in cell lines expressing also ER-β, which has a particular role in the inhibition of cell growth, quercetin did not cause such a cell growth stimulation. The growth-inhibitory effects of quercetin at higher concentrations may be mediated via other mechanisms such as apoptosis induction.[138] Based on these results obtained primarily in breast cancer cell lines, the question is raised whether quercetin might have possible promoting effects in estrogen mediated carcinogenesis in vivo.

Two studies in rodents indicated that quercetin could enhance carcinogenesis mediated by exogenously applied estradiol treatment (subcutaneous implantation of estradiol implants). In male hamsters, quercetin doses of 0.3 or 3 % in the diet (corresponding to around 150 and 1500 mg per kg bw and day, respectively) for around 6 months caused an increase in the number of larger tumors in the kidney (> 5 mm) and an increase in abdominal metastases compared to the estradiol group.[121] The other study with female rats reported especially enhanced cell proliferation and shortening of the tumor latency of mammary glands by quercetin at a dose of 0.25 % in the diet (corresponding to around 150 mg per kg bw) in animals co-treated with estradiol for 8 months compared to the estradiol control group.[122] Both working groups suggested a direct inhibition of the catechol-O-methyltransferase activity by quercetin as a possible mechanism resulting in an elevated formation of the carcinogenic estradiol metabolite 4-hydroxyestradiol and an accompanied reduction of the anti-carcinogenic metabolite 2-methoxyestradiol.[121,122]

The described animal studies used certain artificial conditions by inducing tumor development with application of high exogenous estradiol doses which does not necessarily reflect the human condition. However, there is an open question whether quercetin may also promote estrogen dependent tumor diseases in humans which should be persued in further human intervention studies e.g. via the measurements of estrogen metabolites or other suitable biomarkers.

4.3.3. Effects on the Endocrine System

4.3.3.1. Effects on the Reproductive System in Males. Some but not all identified in vivo studies indicated effects of quercetin on the reproductive system in male rodents. It should be considered that several studies analyzed primarily the effectiveness of quercetin against chemically induced toxicity toward the reproductive system and not the safety of quercetin itself. Other studies used young immature animals being within a hormonally sensitive stage of life. Only few studies investigated more than one quercetin dose complicating the determination of a dose-response relationship.

Some animal studies did not find adverse effects of quercetin on spermatogenesis and/or testosterone levels in male rats. Farombi et al.[140] did not reveal any adverse effects on spermatogenesis in the quercetin group with male rats receiving 20 mg quercetin per kg bw per day for 16 days. This study used probably young animals (unknown age, an average body weight of 131 g was reported) and applied only a relatively low quercetin dose.[140] Other studies with adults male rats, investigating primarily beneficial effects of quercetin against chemically induced reproductive toxicity, did not find any deleterious effects on sperm parameters, reproductive organ weights, and histopathology or on testicular and plasma testosterone levels after administration of 50 mg quercetin per kg bw per day for 7 or 10 weeks[141–143] or 150 mg quercetin per kg bw per day for 10 weeks.[144]

Other studies with a shorter duration than the already described studies indicated a change in circulating levels of reproductive hormones in male rats. Ma et al.[145] observed increased serum testosterone levels in male rats (10 weeks old) receiving quercetin doses of 50, 100, or 150 mg per kg bw per day for 10 days, whereas dihydrotestosterone levels tended to increase at the lowest dose and to decrease at the highest quercetin dose. Quercetin caused a dilatation of the prostate lumen filled with secretory material. Another study in adult male rats, which received 90 mg per kg bw per day for 16 d, also reported elevated testosterone concentrations in serum without an alteration of the relative testis weight and sperm parameters (e.g., sperm motility and daily sperm production).[146] Because the cited longer lasting studies with comparable quercetin doses did not find any effects on testosterone levels in adult male rats, the question is raised whether the increase of testosterone level after the relatively short treatment duration of 10–16 d might be considered to be a temporary effect of quercetin.

In immature male rats (1 month old), ElMazoudy et al.[147] reported an increase in testosterone levels associated with a stimulation of spermatogenesis at 10 and 20 mg per kg bw per day for 28 d. By contrast, a higher quercetin dose of 40 mg per kg bw per day caused a decrease in testosterone level accompanied by impaired spermatogenesis, measured, e.g., as a decrease in spermatozoa count and sperm motility, and increase in total abnormal sperm numbers. Quercetin did not cause a change of organ weights of testis and epididymis.[147] However, a decrease in testosterone levels and the consequent occurrence of adverse clinical effects on spermatogenesis were not observed in the studies with mature rats.

Taken together, studies involving adult rats and differing with respect to the study duration yielded different results in relation to changes in testosterone levels. Some studies involving a

treatment duration of 7 to 10 weeks did not find an impact of quercetin on testosterone concentration, whereas two shorter studies over 10–16 d using comparable quercetin concentrations revealed increased testosterone levels. Therefore, there is an open question whether the effect of quercetin to increase testosterone levels may be considered to be a temporary effect. Elevated testosterone levels in the above mentioned animal studies were not associated with an adverse effect on spermatogenesis. Whether other tissues, e. g., prostate, may be affected by elevated testosterone levels induced by quercetin cannot be evaluated based on the available information provided by the cited animal studies.

Other findings (decrease of plasma testosterone level and subsequently reduced spermatogenesis) were obtained in immature male animals which may be potentially related to the particular stage of life. Therefore, immature animals may be more sensitive as compared to adult animals toward exogenous influences affecting the hormone system.

In humans, one intervention study with young healthy men (mean age of around 30 years) did not reveal an impact of quercetin on testosterone levels in plasma after intake of 1000 mg quercetin per day for 8 weeks.[57] To date, no other human studies examining an influence of quercetin on hormone levels or on parameters related to male reproduction (spermatogenesis) have been identified. The absence of studies extending beyond 8 weeks makes it difficult to conclude on any long-term effects of quercetin on the reproductive system in men.

4.3.3.2. Effect on the Reproductive System in Pregnant Females. In female rats, repeated oral quercetin doses of 10,[148] 50, and 100 mg per kg bw,[149] and even up to 2000 mg per kg bw,[150] during pregnancy did not cause any signs of maternal or fetal toxicity (with exception to some minor changes in fetal bw and pregnancy weight gain).

In another study female mice received 5 mg quercetin per kg bw per day via drinking water for 9 months during two breeding periods and were mated with quercetin-exposed male mice. There was no impact on maternal bw, male fertility, birth weight, and the growth of the offspring. Quercetin caused an increase in birth spacing and therefore a reduction in the number of litters. The litter size was increased in young animals and decreased in older females.[151]

Although critical adverse effects were not observed in animal studies, human data are not available.

4.3.3.3. Estrogenic Effects in Nonpregnant Females. Inconclusive data are available regarding possible estrogenic effects of quercetin in nonpregnant female rodents. For instance, quercetin (10 or 30 mg kg^{-1} bw per day for 3 d) caused an increase in relative uterine weight to a similar extent as 17β-estradiol exposure (4 mg per kg bw per day) in immature female rats (21–22 days old). A higher quercetin dose of 90 mg kg^{-1} bw per day did not show such effects and caused rather a decrease in the endometrial thickness.[152] In female young mice (3 weeks old), oral exposure to 5, 25, or 45 mg quercetin per kg bw per day for 50 d caused estrogen-like effects on ovarian development measured as changes in ovary weight, follicle proportion, and plasma hormone levels. However, only the abstract of this publication was available in English language, complicating the interpretation of study results (article in Chinese).[153] By contrast, in a study with female ovariectomized rats, quercetin did not show any estrogenic effects on uterine weight or histopathology, uterine expression of estrogen regulated genes or serum LH level after exposure to relatively low quercetin doses of 0.02 or 0.1 % in feed for 3 months (corresponding to around 10 or 60 mg kg^{-1} bw per day, respectively).[154]

In conclusion, although there are some indications of possible estrogenic effects of quercetin in female rodents (primarily in immature animals), the outcome of the rodent studies is inconsistent. No further data from human studies investigating any modulation of the estrogenic system by quercetin in women are available.

4.4. Potential Drug Interactions

In animal and human studies with single time or short-term quercetin application, it has been shown that quercetin could modulate the bioavailability of different drugs. An elevated drug bioavailability by quercetin may cause an increase in the effectiveness of the drug but may also increase the potential for adverse drug effects in which case an adjustment of the applied drug dosage may be required. Otherwise, a diminished drug bioavailability by quercetin would cause a reduced effectiveness of the drug.

Some animal studies with rats, rabbits, or pigs investigated the drug interaction of quercetin as single or repeated doses for several days of 0.6–100 mg quercetin per kg bw per day (in one study up to 300 mg kg^{-1} bw per day). Increased drug bioavailabilities (increase in AUC and/or in maximum plasma concentration) at least with one of the applied dose regiments were observed with oral intake of irinotecan, etoposide, tamoxifen, paclitaxel, doxorubicin (all anticancer drugs), digoxin (drug against heart insufficiency), verapamil, and diltiazem (calcium channel blockers used in the treatment of hypertension, angina pectoris, and some types of heart arrhythmia), valsartan (antihypertensive drug), ranolazine (drug to treat angina pectoris), and paracetamol.[101,155–164] With orally applied pioglitazone (drug to treat type 2 diabetes), an increase in bioavailability ($AUC_{0-\infty}$) was seen in nondiabetic rats with co-administration of quercetin, whereas in diabetic rats the increase in AUC did not reach statistical significance.[165,166] Decreased bioavailabilities were seen with oral intakes of simvastatin (cholesterol-lowering drug) and cyclosporine (immunosuppressive drug).[167–169] In the case of paracetamol, quercetin (5–20 mg kg^{-1} bw) increased the bioavailability of paracetamol in rats[155] and on the other hand in a second rat study with a quercetin dose at 100 mg kg^{-1} bw it reduced the hepatotoxicity of high orally applied paracetamol doses.[170]

In regard to clinical aspects, in rats orally applied quercetin at doses of 25–100 mg kg^{-1} bw reduced dose-dependent catalepsy induced by intraperitoneally administered perphenazine or reserpine/α-methyl-p-tyrosine.[171] In another study, quercetin at oral doses of 25–300 mg kg^{-1} bw decreased haloperidole-induced catalepsy (intraperitoneal administration) in a U-shaped manner with the greatest reduction at 100 mg quercetin per kg bw.[172] The underlying mechanisms (e.g., alterations in

drug bioavailability or other drug interactions) remain to be elucidated.

In humans, mixed results regarding drug interactions were observed with single or repeated intakes of 300–1500 mg quercetin per day (**Table 1**). No significant changes of drug bioavailability were observed for nifedipine (antihypertensive drug),[173] rosiglitazone (antidiabetic drug),[174] saquinavir (anti-HIV drug),[175] digoxin,[74] warfarin (anticoagulant),[75] or cefprozil (antibiotic drug).[176] Reduced bioavailabilities (or only a trend without statistical significance) were reported for midazolam (sedative)[73,127] and talinolol (antihypertensive drug).[72,177] An increased bioavailability was observed for cyclosporine,[178] pravastatin (cholesterol-lowering drug),[179] and fexofenadine (antihistamine drug).[70]

In some cases, different results regarding the drug bioavailability were obtained in human and animal studies. As an example, in an animal study with pigs, co-administration of 50 mg quercetin per kg bw with digoxin increased the serum levels of digoxin and caused the death of two of three animals,[162] whereas in humans, an increased drug bioavailability was not observed after intake of 1500 mg quercetin per day for 5 d.[74] A reduced bioavailability of cyclosporine was observed in animals (rats and pigs) treated with 50 mg quercetin per kg bw,[168] while an increased drug bioavailability was revealed in humans with an intake of 5 or 10 mg quercetin per kg bw.[178] These discrepancies may be caused by species differences, the used doses of quercetin, and the drug tested and the duration of treatment. In addition, the temporal spacing between quercetin and the drug administration may also affect the drug bioavailability. For example, a higher increase in the bioavailability of verapamil in rabbits and cyclosporine in humans was observed when quercetin was given 30 min prior to the drug administration in comparison to a concomitant administration.[158,178]

Several molecular mechanisms that may lead to increased drug bioavailabilities by quercetin have been discussed such as the inhibition of P-glycoprotein-mediated cellular xenobiotic export and/or inhibition of xenobiotic-metabolizing enzymes (particularly CYP3A4), primarily in intestinal cells.[70,101,161–165,178] However, other data are not in agreement with this hypothesis, revealing no change or a decrease in the bioavailability of drugs where primarily CYP3A4 and/or P-glycoprotein may be involved in the drug pharmacokinetics.[74,167–169,173,175] Decreases in plasma levels of drugs during treatment with quercetin might also be explained by induced gene expressions of xenobiotic metabolizing enzymes or xenobiotic-transporting systems. Such processes would be expected to become more likely with increasing duration of quercetin exposure. Quercetin may also have a different impact on certain genotypes, e.g., encoding for P-glycoprotein (possibly via multi-drug resistance gene induction) which could be also associated with an altered drug level.[177] In addition, an inhibition of the organic anion-transporting polypeptide 1B1 by quercetin has also been suggested.[179] Other mechanisms may be also possible depending on individual drugs. Some of the above mentioned drugs which showed no interaction with quercetin are primarily metabolized by other cytochrome P-450-enzymes (e.g., rosiglitazone metabolized by CYP2C or S-warfarin metabolized by CYP2C9) or are no substrates of P-glycoprotein.

5. Conclusions

The focus of the present review was laid on the evaluation of the safety of isolated quercetin (i.e., when used as single compound) as dietary supplement in adult individuals. Pregnant and breastfeeding women as well as children and adolescents were not included into the target population. These particular vulnerable subgroups were excluded due to several reasons. It was noted that primarily adult persons are the main target population for such a supplementation and the pertaining (advertised) benefits. However, certain hormonal effects of quercetin were observed in animal studies with growing rodents (e.g., alteration in testosterone levels) which may reveal possible safety concerns regarding the administration of isolated quercetin to children and adolescents, which deserve further clarification. But in general, there is a lack of relevant safety data from human intervention studies for children and adolescents to draw firm conclusions in regard to this population group.

Similarly, there is a lack of adequate safety data from human intervention studies regarding a supplemental intake of quercetin to pregnant and breastfeeding women. The reviewed effects of quercetin on the reproductive system in pregnant animals did not indicate to any serious adverse effects of quercetin, but the data are not sufficient to affirm the safety of quercetin for pregnant women. In general, pregnant women should consult a physician prior the use of dietary supplements especially with isolated ingredients at high doses.

For the present review, animal and human intervention studies were considered as particularly relevant regarding the evaluation of the safety profile of supplemental quercetin. Findings from in vitro studies were only included for mechanistic aspects, keeping in mind that in vitro studies mostly use high nonphysiological quercetin concentrations and cannot take into account the complex pattern of quercetin kinetics (involving processes of metabolism, transport, and distribution) which occur in vivo.

In animals treated orally with quercetin, several potential critical safety aspects could be identified. Based on one chronic toxicity animal study and two studies investigating the effects of quercetin on chemically induced nephrotoxicity in rats, some evidence has been provided that especially high quercetin doses may cause an enhancement of nephrotoxic effects primarily in the predamaged kidney. The limited data available so far from human intervention studies has not indicated adverse effects on kidney function, but they are not sufficient (especially for individuals with a kidney dysfunction) to invalidate the findings obtained in animal studies.

Although there are animal tumor studies (in which tumors were induced by diverse well-known carcinogens) revealing no or even protective effect of quercetin on tumor development, a few tumor promotion studies also suggested that quercetin may have the potential to promote the growth of already existing cancer cells, particular in estrogen sensitive cancer cell types. One mechanism for the possible anticarcinogenic effect as well as for the possible tumor-promoting potential of quercetin could be the impact of quercetin on the bioavailability of carcinogens used in the animal models. In addition, other mechanisms such as the induction of oxidative stress leading to adverse effects in tumorigenesis are also conceivable. Therefore, there is an open question

Table 1. Effects of Quercetin on the bioavailability of orally administered drugs in humans.

Drug	Therapeutic use	Drug dose and duration	Quercetin dose and duration	Drug bioavailability	Reference
Nifedipine	Antihypertensive drug	10 mg as single dose	400 mg in three doses over 1 d ($n = 8$, preparation was not defined)	No effect (based on AUC)	[173]
Rosiglitazone	Antidiabetic drug	4 mg as single dose on day 21	500 mg per day for 21 d ($n = 10$, as capsules)	No effect	[174]
Saquinavir	Anti-HIV drug	3.6 g in 3 doses per day for 11 d	1500 mg in three doses per day for 8 d ($n = 10$, as capsules, beginning 3 d after saquinavir application)	No effect (based on geometric mean rations of AUC, $C_{(max)}$, $C_{(min)}$)	[175]
Digoxin	Drug against heart insufficiency	0.5 mg as single dose on day 6	1500 mg per day for 18 d ($n = 14$, mixed in beverages)	No effect	[74]
Warfarin	Anticoagulant	10 mg as single dose on day 5	1500 mg per day for 14 d ($n = 15$, mixed in beverages)	No effect	[75]
Cefprozil	Antibiotic drug	500 mg as single dose on day 14 (1 h after quercetin administration)	500 mg plus 1400 mg vitamin C per day for 14 d ($n = 24$, as capsules)	No effect	[176]
Cyclosporine	Immunosuppressive drug	300 mg as single dose	5 mg kg^{-1} bw as single dose ($n = 8$, as capsules) co-administered with the drug (a) 5 mg kg^{-1} bw as single dose ($n = 8$, as capsules) applied 30 minutes prior drug administration (b) 10 mg kg^{-1} bw in two doses per day for 3 d ($n = 8$, as capsules) followed by a single dose of cyclosporine (c)	Increased bioavailability (application b and c)	[178]
Pravastatin	Cholesterol-lowering drug	40 mg as single dose on day 14 (1 h after quercetin application)	500 mg per day for 14 d ($n = 16$, as capsules)	Increased bioavailability	[179]
Fexofenadine	Antihistamine	60 mg as single dose on day 7	1500 mg in three doses per day for 7 d ($n = 12$, as capsules)	Increased bioavailability	[70]
Midazolam	Sedative	7,5 mg as single dose on day 7	40 mg per day for 6 d and 1500 mg on day 7 ($n = 10$, as capsules) (a) or 1500 mg in three doses per day for 7 days ($n = 10$, as capsules) (b)	No statistically significant effects with both applications Authors conclusion regarding application b: there was a trend to reduced midazolam exposure	[73]
		7,5 mg as single dose on day 14 (applied 1 d after last quercetin administration)	500 mg per day for 13 d ($n = 18$, preparation was not defined)	Decreased bioavailability with different results for different CYP3A5 genotypes	[127]
Talinolol	Antihypertensive drug	100 mg as single dose on day 7	40 mg per day for 6 d and 1500 mg on day 7 ($n = 10$, as capsules) (a) 1500 mg in three doses per day for 7 d ($n = 10$, as capsules) (b)	No statistically significant effects (a, b) Authors conclusion: quercetin provoked a trendency to reduced talinolol bioavailability	[72]
		100 mg as single dose on day 14 (applied 1 d after last quercetin administration)	500 mg per day for 13 d ($n = 18$, preparation was not defined)	Decreased bioavailability with different results for different MDR1 genotypes	[177]

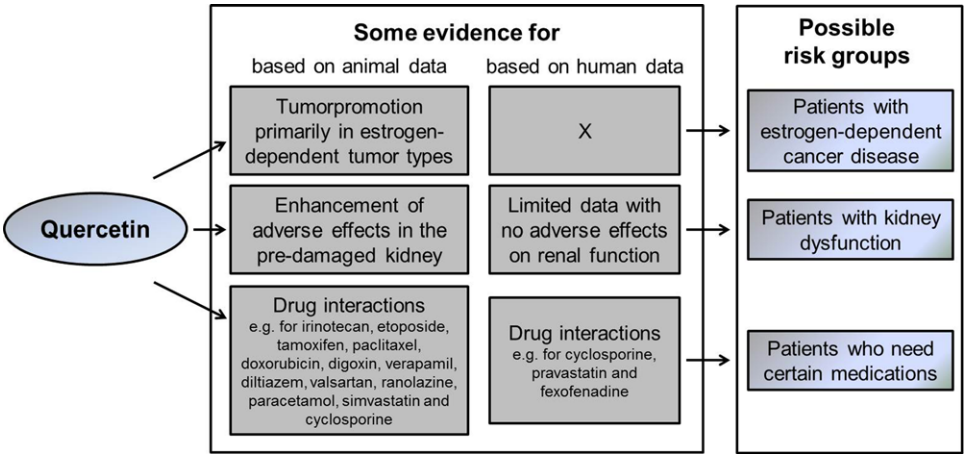

Figure 2. Identification of possible risk groups for the use of high quercetin doses in dietary supplement.

whether supplemental isolated quercetin at doses clearly exceeding dietary quercetin intake may have tumor-promoting effects also in humans under certain conditions, i.e., for example, in individuals with estrogen-dependent tumor diseases.

In addition, some short-term animals studies (10–16 d) with mature male rats revealed that quercetin may also have an impact on circulating hormone levels causing an increase of plasma testosterone concentration, whereas such effects were not observed in longer lasting studies (7–10 weeks) with comparable quercetin doses (50–150 mg per kg bw per day), suggesting rather temporary effects. In humans, one identified intervention study did not indicate an alteration of the testosterone level after an supplemental intake of 1000 mg quercetin per day for 8 weeks in young men. However, this issue deserves further clarification.

Regarding the effects of quercetin after single time or short-term quercetin administration on the bioavailability of drugs and the possible underlying mechanisms, mixed results were obtained, depending on the used species, the applied drug, the quercetin dose and drug dose, treatment duration, and the temporal spacing between quercetin and drug administration. For humans, the observed interactions of supplemental quercetin with some individual drugs (e.g., increased bioavailability of cyclosporine, pravastatin, and fexofenadine) warrant cautions with respect to a concomitant quercetin supplementation. However, the clinical relevance caused by an altered drug bioavailability remains to be elucidated. An elevated drug bioavailability by quercetin may result in an increase in the effectiveness of the drug but may also increase the potential for adverse drug effects in which case an adjustment of the applied drug dosage may be required. Otherwise, a diminished drug bioavailability by quercetin would cause a reduced effectiveness of the drug. Further research on potential interactions between quercetin and drugs is required, with a special focus on drugs with an unknown interaction profile with quercetin or showing an interaction with quercetin in animal studies (e.g., tamoxifen, verapamil, or cyclosporine) or on drugs which have already shown an altered drug bioavailability by quercetin in humans requiring confirmation in further studies (e.g., midazolam and talinolol).

Regarding the occurrence of adverse effects in human intervention studies investigating high supplemental doses of isolated quercetin of mostly up to 1000 mg d^{-1} (exceeding considerably dietary quercetin intake) as a single compound or in combination with vitamin C for a maximum duration of 12 weeks in adult individuals, the reported incidence of adverse effects was very low and any such effect was mild in nature. However, it is noted that only few human studies provided detailed information on the occurrence or absence of adverse events or information on measurements of relevant safety parameters (a situation also frequently seen with other substances used as ingredients of dietary supplements). Consequently, the fact that no adverse events were mentioned in certain human intervention studies cannot be taken as proof that no adverse events were observed.

The available intervention studies with application of supplemental quercetin as single compound or in combination with vitamin C observed one case of headache and one of mild tingling after intake of up to 1000 mg quercetin per day for 1 month. Mild stomach complaints at unspecified quercetin doses (250–5000 mg d^{-1} for 28 d) were reported in a small study with patients suffering from hepatitis C, which were resolved upon quercetin administration with a meal. However, these studies mostly encompassed short treatment duration (≤12 weeks), in some cases applied quercetin in combination with other substances (in addition to the cotreatment with vitamin C with or without niacin), investigated individuals with partly serious underlying diseases or give no detailed information on the occurrence/absence of adverse events. Furthermore, information on other safety-relevant parameters from intervention studies with supplemental quercetin as single compound or in combination with vitamin C is scarce. These limitations should be kept in mind, so that the results of these studies should be interpreted with some caution with respect to the safety of supplemental isolated quercetin as a single compound (exceeding considerably dietary intake levels) for the general population, in particular in the context of long-term application (>12 weeks) of high supplemental quercetin doses (≥1000 mg d^{-1}). Any future intervention studies conducted with supplemental isolated quercetin should also include the investigation of possible adverse effects and ideally the measurement of certain clinical safety parameters such as for kidney function with a clear detailed description in pertainig scientific publications.

With regard to the results obtained in animals and to the consideration of uncertainties due to limited human data and the difficulties to extrapolate findings in animals to humans, certain potential risk groups have been identified (see **Figure 2**). Patients with a kidney dysfunction may be a potential risk group for the long-term quercetin supplementation at high doses considering the possible nephrotoxic effects of quercetin particularly on the predamaged kidney in rodents. Due to the potential tumor-promoting effects of quercetin primarily in estrogen-dependent cancer revealed in animal studies, the supplementation of isolated quercetin at high doses were considered as critical for patients with a currently diagnosed estrogen-dependent cancer disease or a history for such a disease keeping also in mind that occasionally such disease has not yet been diagnosed. Individuals who take medications, especially regarding the drugs with known quercetin interaction or where no interaction data are available, are recommended to consult a physician prior the use of isolated quercetin as a dietary supplement.

Abbreviations

AUC, area under the curve; BCRP, breast cancer resistance protein; bw, body weight; ER, estrogen receptor; FDA, US Food and Drug Administration; GRAS, generally recognized as safe; n_Q, number of the participants of the quercetin supplementation group; NTP, US National Toxicology Program; PhIP, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflicts of Interest

The authors have declared no conflict of interest.

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adverse effects, drug interaction, nephrotoxicity, quercetin, tumor promotion

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