

MOLECULAR-BIOLOGICAL PROBLEMS OF DRUG DESIGN AND MECHANISM OF DRUG ACTION

BIOAVAILABILITY AND SAFETY OF DIHYDROQUERCETIN (REVIEW)

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Dihydroquercetin (DHQ) is a bioflavonoid with high antioxidant, capillary-protective, and anti-inflammatory activity. DHQ has previously been used for treating Middle East respiratory syndrome coronavirus (MERS-CoV) infection and is currently considered a potential regulator of oxidative stress as part of COVID-19 multipurpose therapy. DHQ has a high safety profile but low bioavailability that limits its use. Innovative techniques (liposomization, crystal engineering, etc.) can be used to increase its bioavailability.

Keywords: dihydroquercetin, bioavailability, toxicity, safety, SARS-CoV-2.

Dihydroquercetin (DHQ, international nonproprietary name Taxifolin) is a natural antioxidant or bioflavonoid. It occurs in plants of various families but is isolated in large amounts (up to 4.5%) only from Siberian larch (*Larix sibirica*) or Dahurian larch (*L. gmelinii*). Therefore, they are the principal raw-material base for industrial production of DHQ by aqueous EtOH extraction and further chromatographic purification. The production technology for DHQ as a valuable biologically active compound was first developed at A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, in the 1990s [1]. According to several scientific investigations, DHQ exhibits antioxidant, capillary-protective, anti-inflammatory, gastro- and hepatoprotective, radioprotective, hypolipidemic, and diuretic activity [2 – 6].

Toxicity evaluation *in silico*

The risk of adverse pharmacological and side effects is a drawback of using therapeutic agents for unapproved indications. The toxic potential (in the range from 0 to 1) was pre-

dicted using the VirtualToxLab platform for selected compounds [7] by calculating models for the interaction of ligands with 16 various targets, including nuclear receptors such as intracellular proteins, metabolic enzymes, and specific cardiac K-channels (the whole list of receptor proteins has been published [8]). The toxic potential of DHQ calculated in this manner was 0.289, which was one of the lowest values in the proposed compound set [7]. The toxic potential for three of the selected promising synthetic compounds was >0.35; for four compounds, >0.4. Values >0.6 were indicative of high toxicity.

A study of toxicity parameters using the ORISIS DataWarrior program showed that DHQ did not exhibit any toxicity while quercetin possessed mutagenic and oncogenic properties [9]. Eriodictyol and luteolin were also nontoxic promising flavonoids, i.e., protease blockers. The former was present as an impurity in DHQ substance obtained from larch with a content of tenths of a percent [10].

Possible doses, pharmacokinetics, and safety

According to methodical recommendations of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rosпотребнадзор) for consumption levels of food and biologically active substances [11], an adequate level of DHQ consumption is 25 mg/day with an upper allowed consumption level of 100 mg/day (the recom-

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mended values were approved in 2004). Methodical recommendations of the Research Institute of Influenza, Ministry of Healthcare of the Russian Federation [12], for the Middle East respiratory syndrome coronavirus (MERS-CoV) of 2012 recommended the use of antioxidant therapy to provide cytoprotection and enhance the antiviral effect. Prescription of DHQ at doses of 60–100 mg/day was proposed for these purposes. Prescription of DHQ at 40–60 mg four times daily and at 20 mg four times daily (a 3–4-week course) was recommended for treating and preventing influenza in adults using detoxification and antioxidant therapy [13].

The use of DHQ in complex therapy of the new coronavirus infection COVID-19 is currently under discussion [14]. The usually used daily doses could be inappropriate because of extensive damage to tissues and severe inflammation (including a cytokine storm). The DHQ doses recommended at this time very often cannot provide even preventive consumption as antioxidants reaching 10,000 μmol on the ORAC scale. The DHQ plasma concentration that could be required to saturate tissues for COVID-19 cannot be continuously maintained without increasing these daily doses because it has a short elimination half-life. The pharmacokinetics of DHQ differ for different substances and their modifications [14, 15] and depend considerably on the administration mode [16] and excipients [17]. The properties of the dosage form, which determine the bioavailability, absorption time, elimination half-life, etc., which can significantly differ, must be considered in prescribing doses because DHQ is marketed in various forms and in combinations with other compounds.

Intravenous (i.v.) administration of DHQ to rats at doses of 3–30 mg/kg caused a biphasic drop of the concentration [18], which may have been due to saturation during DHQ binding to blood-plasma proteins and metabolism. The slow β -phase was not observed if a dose of 1 mg/kg was used. This could be explained by saturation not being observed at the corresponding DHQ plasma concentration or the HPLC being insufficiently sensitive in this instance. DHQ was initially distributed in blood and the extracellular milieu although it rather strongly penetrated peripheral tissues. The total clearance was comparable to the mean rate of rat liver blood flow (2.2 L/h/kg) [19]. DHQ mass transfer through biological membranes was rather efficient. The migration rate of the front through lipid layers was ~ 30 nm/s [20]. Saturation of tissues was not observed after i.v. administration to rats at doses of 3–30 mg/kg because the initial slope of the dependence of the logarithm of the concentration on time did not decrease with increasing dose. Also, the initial distribution volume remained constant. DHQ at high doses (50 mg/kg) could be retained in kidneys, liver, heart, spleen, brain, skeletal muscle, and lungs up to 24 h after administration [21]. The daily excretion of unaltered DHQ with urine after i.v. administration to rats at doses of 1–10 mg/kg was 2–6% [18]; at a dose of 50 mg/kg, 8% [21].

In general, DHQ is a rather short-lived compound. It is rapidly biotransformed. Experiments in rats showed that the elimination half-life $t_{1/2}$ after i.v. administration at doses of 3–15 mg/kg could vary from 16 min [18] to 2.24 ± 0.42 h [14]. A nanodispersion of DHQ (15 mg/kg) after peroral administration gave $t_{1/2} = 4.83 \pm 2.54$ h; after administration in a mixture, 6.03 ± 1.42 h [14]. However, the used substances had very low bioavailabilities. Experiments in rabbits with i.v. administration at a dose of 8 mg/kg gave $t_{1/2} = 0.56 \pm 0.06$ h [17]. Peroral administration of the same dose of a lipid solution gave $t_{1/2} = 2.22 \pm 0.30$ h; at a dose of 80 mg/kg, 1.69 ± 0.07 h. A pharmacokinetic study in rats using liposomes as carriers and a dose of 50 mg/kg gave $t_{1/2} = 1$ h [15]. Afterward, comparable data were obtained for humans [22]. Analogous results were reported in a monograph with a reference to an inaccessible report on preclinical pharmacokinetic studies of 2007 [23], where $t_{1/2}$ was <1.25 h after administration to rats at doses of 12.5–50 mg/kg. Several other DHQ modifications used at a dose of 50 mg/kg gave $t_{1/2}$ values in the range 2–3 h [24].

Elimination after i.v. injection was significantly faster than after peroral administration. The plasma concentration using a dose of 50 mg/kg reached a maximum after 0.1 h, after which it gradually decreased. A unified approach for interspecies translation of doses does not now exist. Coefficients considering the difference in body surface area are commonly used as one method of accounting for interspecies differences. Thus, the equivalent dose for man was calculated by multiplying the dose for rats by a coefficient of 0.16 [25]. It is important to note that the total blood volume and extracellular milieu in which DHQ was initially distributed in rats was $\sim 15\%$ of the mass [18] while in man this volume was 1.5–2 times greater.

The safety of DHQ is rather well studied [10, 19, 21, 23, 26]. Toxic effects from overdoses in man have not been reported in the literature, presumably because they have not been observed. According to the Russian national standard [27], DHQ belongs to hazard class 4 (marginally hazardous substances) with respect to effects on humans. DHQ belongs to hazard class 6 (low risk) with respect to the risk of causing harm to health [28]. The safety of DHQ does not currently raise any doubts. This was confirmed in 2017 in a scientific conclusion of the European Food Safety Authority (EFSA) [21] that relied primarily on experimental data.

The median lethal dose (LD_{50}) could not be obtained after intragastric administration of DHQ to mice and rats. No animals died even at the daily limiting peroral doses of 10–15 g/kg for seven days. No toxic effects were observed during a study of chronic toxicity over six months in rats and dogs (including pregnant animals) using doses of 150–1500 mg/kg. DHQ did not exhibit immunotoxicity, embryotoxicity, and mutagenicity. Also, DHQ was shown to be non-phototoxic and photostable (in contrast to quercetin), i.e., it was stable to sunlight (including UV radiation) [29]. However, this issue required additional research because

DHQ is a polymorphic compound and can exist in both crystalline and amorphous forms [30].

The bioavailability problem

The efficacy of drugs and physiologically functional food ingredients depends directly on the ability of the body to absorb them. Therefore, research directed at increasing the bioavailability of compounds is being conducted in the global pharmaceutical sector. The basic drawback of peptides and peptide mimetics that are widely used to battle viral proteases is their limited peroral bioavailability due to their poor metabolic stability, high molecular masses, and topological polar surface area, because of which they have difficulty penetrating the cell membrane. As a result, comparatively small molecules with balanced and favorable pharmacokinetic properties have the greatest potential for use as viral protease inhibitors [7].

DHQ can penetrate the cell membrane. However, isolation of it from natural raw material in a bioavailable form and preservation of its biological activity are rather challenging problems. As a rule, the bioavailability of marketed DHQ substances is very low, which considerably limits its use in clinical practice [14, 31–33]. It was found that the absolute bioavailability of 99% pure DHQ in a mixture after peroral administration was 0.49%; after administration of a nanodispersion of DHQ, 0.75% [14]. Previously published data gave an even lower absolute bioavailability of 0.17% for 98% pure DHQ in solution [34]. Bioavailability of DHQ of 23.79% was reported in a monograph [23].

Sublingual administration of DHQ, which reduced the risk of altering the enantiomeric composition of the compound by aggressive stomach media and metabolic liver reactions, was tested to increase the efficacy. Sublingual administration is one of the most effective and safe modes because the appearance of significant quantities of the oxidized forms of vitamins C and E, quercetin, and other phenolic derivatives were reported to exhibit prooxidant effects *in vivo* [28, 35], i.e., they promoted oxidative stress. Also, poorly soluble DHQ can accumulate in the liver [36]. In this respect, the most important factor affecting the bioavailability of DHQ is its water solubility, which is determined mainly by the crystal form and structure.

Various methods for increasing the bioavailability of DHQ have been described in the literature. A significant part of the corresponding research over the last decade was directed toward nanotechnology development.

Experiments using porcine biomaterial showed that up to 87% of DHQ could penetrate the mucous membrane after intervaginal administration of an oil-in-water emulsion while penetration of human skin in the same emulsion reached up to 48% [16]. The bioavailability of a perorally administered DHQ lipid solution increased to 36% [17]. Ultrasound micronization, which allowed the antioxidant activity to be increased by decreasing the particle size to 60–100 nm and evened out their sizes, was used to increase the bioavail-

ability of liquids containing DHQ [37–39]. However, the antioxidant activity was observed to decrease if high-power ultrasound was used.

The bioavailability of DHQ could be increased by 1.59 times and its uptake prolonged as compared to the pure poorly soluble substance by using solutions with liposomes that encapsulated it [15]. Encapsulation of DHQ in β -cyclodextrin (glucose oligomer) allowed its peroral bioavailability to be increased because the resulting nanocomplex had improved solubility and DHQ in aqueous solution could be released from the β -cyclodextrin inner cavity over several hours. This also provided prolonged accumulation of DHQ in the blood pool [36].

DHQ was modified in China by precipitating it from EtOH solution in gaseous supercritical antisolvent (SAS) CO_2 . This approach enabled the production of long needlelike and rod-shaped DHQ microcrystals, which were four times more soluble than the starting substance [40]. Later, amorphous nanoparticles that were 1.7 times more soluble, dissolved three times faster, and had seven times the peroral bioavailability than the raw material were obtained using liquid antisolvent deionized water and γ -cyclodextrin cryoprotectant for lyophilization [41]. Another DHQ modification that was prepared using an ionic liquid as the solvent and dichloromethane as the antisolvent showed improved solubility by 1.26 times in artificial stomach juice as compared to the raw material [24]. The solubility of DHQ in complexes with γ -cyclodextrin could be increased by 18.5–19.8 times, the dissolution rate by 2.8 times, and the bioavailability by 3.7 times as compared to the native substance by using an emulsion solvent in combination with lyophilization [42]. Increased antioxidant activity was reported for modifications [40–42].

Studies of DHQ solid nanodispersions with particle sizes in the range 119–201 nm found that DHQ was practically completely released from them in aqueous solution with a release rate 5–23 times faster than for particles of the pure substance, from which DHQ was ~20% released. The release time could be significantly lengthened (up to 3 h and more) with ~90% of DHQ released by using self-microemulsifying delivery systems with particle sizes of 10–20 nm [43, 44].

Special attention should be paid to research conducted recently at I. M. Sechenov First Moscow State Medical University [30, 32, 33, 45–50]. Their results showed that crystal engineering aimed at activation of self-assembly of microtubes from cylindrical crystalline nanoparticles was the most promising approach to increasing the solubility of DHQ. Such single crystals are a pseudopolymorphic modification of the commercially available crystalline substance. The solubility of the starting crystalline substance varies in the range 0.0001–0.001 g/mL. The solubility of the microtubes can be 100–1000 and more times greater [33]. Crystal engineering allowed the physicochemical properties of flavonoids to be significantly optimized and modified [49]. Molecular modeling showed that separate DHQ nanopar-

ticles and microtubes had cavities [32, 48] and may be used in the future for drug delivery in analogy with carbon nanotubes. The presence of cavities in the tubes was experimentally confirmed by filling them with sublimed iodine vapor [32, 46]. Furthermore, the electron density did not correlate with the microtube thickness. Elevated density was observed on their edges in several instances, which confirmed the hypothesis that the microtubes were hollow [51].

An analysis of the crystal geometry enabled the quality of pharmaceutical substances to be monitored, in particular, the solubility of the DHQ to be quickly assessed [33]. Considering the above peculiarities of the microtube morphology and porous structure, the solubility of such DHQ modifications can be assessed not only using fractal analysis but also data on the specific surface area of the sublimed powder. The volume of the same mass of dry DHQ produced by different technologies can significantly differ. In particular, the specific surface area of DHQ was reported to increase from 0.0994 to 2.47 m²/g after SAS micronization [40].

DHQ exists in microtubes as the crystal hydrate 2C₁₅H₁₂O₇·5H₂O [52]. Lyophilization is one of the possible finishing stages during engineering of such crystals. It entails freezing of a concentrate and drying it *in vacuo*. This enables a dry powder with microtubes to be produced from ice, circumventing the liquid phase. Lyophilization is needed because chemically bonded water is lost starting at 89°C upon heating [48]. The lyophilization is carried out at low temperatures and can preserve the crystal hydrate.

Commercial availability

Active forms of DHQ are complicated to produce because of the limited availability of manufacturing and technical equipment that could allow a high-quality product to be manufactured not in laboratories but on industrial scales. In this instance, costly and specific technologies (processing of large volumes of wood and extraction, preparation of nanosuspensions and nanoemulsions, production of nanosuspensions and nanoemulsions, crystal engineering, lyophilization, etc.) must be enlisted.

DHQ is registered in Russia as a pharmaceutical substance and is included in the State Drug Registry under the name Dihydroquercetin. Most of manufactured DHQ is marketed as a food additive and then as raw material for manufacturing drugs and biological food additives. The extract of *L. dahurica* containing DHQ is regarded as a safe food ingredient in the EU [21]. Greater than 340 biological food additives, food additives, and specialized food products, including beverages containing DHQ, are registered in the Eurasian Economic Union. Many of them are manufactured under contract and, as a rule, such products do not have high bioavailability and bioactivity. Aggressive organic solvents are still used in several instances. Concentrates are dried at high temperatures, as a result of which crystals are sintered. Safe and effective products should be manufactured using green chemistry principles [53] that stipulate the use of the

minimal number of excipients (sorbents, solvents, co-formers, and separation agents). It is assumed that biologically active compounds such as DHQ will need to be used constantly during lifetimes under current conditions. Therefore, excipients should not be used if possible in technological manufacturing processes or long-term consequences from the possible accumulation *in vivo* of traces of them (by analogy with persistent organic pollutants) should be avoided.

CONCLUSION

DHQ is currently considered a potential regulator of oxidative stress in complex therapy of COVID-19. DHQ is characterized by a high safety profile and low bioavailability that limits its use. Innovative technologies (liposomes, crystal engineering, etc.) can be used to improve the bioavailability of DHQ.

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