European Journal of Pharmaceutics and Biopharmaceutics 108 (2016) 41–53

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

Quercetin topical application, from conventional dosage forms to nanodosage forms

T. Hatahet [a], M. Morille [a], A. Hommoss [b], J.M. Devoisselle [a], R.H. Müller [b], S. Bégu [a,*]

[a] Institut Charles Gerhardt Montpellier, UMR 5253 CNRS-ENSCM-UM, Equipe Matériaux Avancés Pour La Catalyse Et La Santé, 8 Rue de L'Ecole Normale, 34296 Montpellier Cedex 5, France
[b] Institute of Pharmacy, Department of Pharmaceutics, Biopharmaceutics and NutriCosmetics, Free University of Berlin, Kelchstr. 31, Berlin 12169, Germany

ARTICLE INFO

Article history:
Received 3 May 2016
Revised 19 August 2016
Accepted in revised form 22 August 2016
Available online 24 August 2016

Keywords:
Quercetin
Antioxidant activity
Antiinflammatory activity
Wound healing
Skin antiaging
In vitro skin penetration
In vivo skin penetration
Franz cells

ABSTRACT

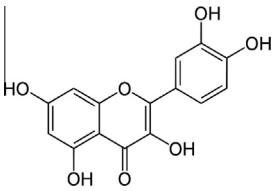
Skin is a multifunctional organ with activities in protection, metabolism and regulation. Skin is in a continuous exposure to oxidizing agents and inflammogens from the sun and from the contact with the environment. These agents may overload the skin auto-defense capacity. To strengthen skin defense mechanisms against oxidation and inflammation, supplementation of exogenous antioxidants is a promising strategy. Quercetin is a flavonoid with very pronounced effective antioxidant and antiinflammatory activities, and thus a candidate of first choice for such skin supplementation. Quercetin showed interesting actions in cellular and animal based models, ranging from protecting cells from UV irradiation to support skin regeneration in wound healing. However, due to its poor solubility, quercetin has limited skin penetration ability, and various formulation approaches were taken to increase its dermal penetration. In this article, the quercetin antioxidant and antiinflammatory activities in wound healing and supporting skin against aging are discussed in detail. In addition, quercetin topical formulations from conventional emulsions to novel nanoformulations in terms of skin penetration enhancement are also presented. This article gives a comprehensive review of quercetin for topical application from biological effects to pharmaceutical formulation design for the last 25 years of research.

Contents

* Corresponding author.
E-mail address: sylvie.begu@enscm.fr (S. Bégu).

http://dx.doi.org/10.1016/j.ejpb.2016.08.011
0939-6411/

Table 1
Quercetin main physicochemical parameters.

Quercetin physicochemical properties	Values
Chemical structure	
Molecular formula	$C_{15}H_{10}O_7$
Molecular weight	302.2 g/mol
Chemical name (IUPAC)	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
Solubility in MilliQ water	0.48 ± 0.1 μg/ml [16]
Solubility in PBS pH 3	0.44 ± 0.1 μg/ml [18]
Solubility in DMSO	30 mg/ml [17]
Solubility in ethanol	2 mg/ml [17]
Partition coefficient (log P)	1.82 ± 0.3 [19]
Polymorphism	Three polymorphic forms [25]

Quercetin partition coefficient is determined experimentally.

1. Introduction

Skin is the largest organ of the human body, which secures the internal homeostasis and regulates the temperature of the body. Besides that, skin has barrier function, and it prevents germs from passing into internal organs, and protects human body from exogenous pollutants and oxidizing agents such as radiation and corrosive materials. As a result, skin is continuously exposed to oxidants and inflammogens, even if skin possesses several antioxidative systems to withstand external oxidation sources. However, in case that oxidative stress is superior to the defense mechanism of skin, skin damage can occur [1,2].

Supporting skin defense mechanisms by exogenous antioxidants is a promising strategy. Antioxidants such as Coenzyme Q10 [3,4], vitamin C [5], β-carotene [6,7] and polyphenols [8,9] were tested to evaluate their benefits on skin. Among them, flavonoids, which are strong polyphenolic antioxidants, are potential good candidates. They are plant pigments found in several fruits and vegetables such as apples [10], onions [11] and peas [12]. With the presence of several hydroxyl groups on their structures, quercetin is the strongest antioxidant among flavonoids and the most common in nature [13]. At the same time, quercetin has the broadest antiinflammatory activity compared to apigenin, morin, (-)-epicatechin and biochanin A [14]. In spite of these promising activities, quercetin suffers from poor water solubility and inability to penetrate skin (Table 1) [15]. Quercetin shows water solubility less than 0.5 μg/ml and higher solubility in polar organic solvents (2 mg/ml in ethanol) [16–18]. Quercetin also has a partition coefficient of 1.82 ± 0.32 due to the presence of nonpolar groups in its structure [19]. But despite this log P, quercetin polar hydroxyl groups hinder its skin penetration capacity [13]. Focusing on topical delivery from formulation approach, the use of nanoformulations with therapeutic agents such as linoleic acid within ethosomes and transfersomes [20], paclitaxel-loaded within ethosomes [21] and asiaticoside in ultradeformable vesicles [22] showed to enhance their topical delivery. This is linked to nanoformulation characteristics such as their lipid nature and their small particle size along with their elasticity that facilitate their deep penetration. The presence of ethanol conferred higher skin penetration for encapsulated molecules compared to liposomes, and the rigid nature of liposomal bilayer is fluidized by the ethanol presence that facilities ethosomes penetration. Consequently, quercetin is also formulated within several nanoformulations in order to enhance topical drug delivery [23,24].

In this paper, recent studies on quercetin skin activities from *in vitro* models to *in vivo* animal studies will be presented. Then, formulation strategies followed to overcome quercetin limited water solubility and to increase its stability in formulation will be discussed. The effect of formulating quercetin in conventional dosage forms to enhance its skin penetration capacity will be explored. Finally, recent nanoformulations of quercetin and their potential as novel strategy for quercetin skin delivery will be discussed.

2. Quercetin physiological activities on skin

2.1. Quercetin antioxidant activity

Skin is the largest organ in the human body exposed to oxidizing agents from environment such as solar radiation (visible/UV) and chemicals (xenobiotic). These environmental pollutants can induce oxidative stress to skin tissue either directly or indirectly by the generation of reactive oxygen species (ROS). Skin tissue contains several defense mechanisms for the prevention or inception of oxidative stress and for the initiation of cellular repair afterward. Skin has many mechanisms to prevent the formation of free radicals. For example (i) metallothionein, present in cutaneous tissue, chelates metal ions, has a great importance in controlling free radical generating reactions; (ii) there was an increase in melanin production upon exposure to UV radiation. For the oxidative damage control, skin also has endogenous mechanisms based on two categories: nonenzymatic and enzymatic. Among nonenzymatic mechanisms, small molecular size antioxidants such as glutathione (GSH), α-tocopherol, carotenoids and oxycarotenoids found in skin cells, are molecules able of both neutralizing free radicals and relocalizing radical damaging functions from sensitive targets (as an example from lipid membrane to cytosol). Enzymatic activities depend on molecules such as superoxide dismutase, catalase and glutathione peroxidase. These enzymes serve as a backup for the regeneration of consumed antioxidants, like in the replenishment of GSH by glutathione disulfide (GSSG) reductase, as well as for the elimination of reactive compounds, such as the transfer system for glutathione S-conjugates [26].

Quercetin antioxidant activity will be explored in three parts. The first part will take into consideration all the chemical assays used to determine quercetin activity *in vitro*. Then, a second part will deal with quercetin activities tested at the cellular level, and the molecular mechanism underlining quercetin potentials. Finally, animal-based studies regarding quercetin protection to cutaneous tissue after its exposure to oxidative stress stimulators such as UV irradiation will be reviewed.

2.1.1. In vitro antioxidant activity (chemical tests)

In vitro tests for antioxidant activity provide information about the antioxidant activity of quercetin without the need for complex cellular based assays. They can ensure quercetin activity from batch to batch and can be set as routine analysis. Three aspects can be investigated *in vitro*. (i) Hydrogen donating activity can be measured with 2,2-diphenyl-1-picrylhydrazyl (DPPH assay) [27]. (ii) Superoxide anion formation inhibition and scavenging activity can both be quantified by means of xanthine oxidase and cytochrome C assays [28]. (iii) Metal chelating activity can be determined using metal specific methods [29]. Finally antioxidants can inhibit the peroxidation of unsaturated lipids, and thus antilipoperoxidative activity can be analyzed using the colorimetric detection of thiobarbituric acid reactive species (TBARS) by a reaction mediated by Fe^{2+}/Citrate [30]. In 2006 Casagrande et al. [31] evaluated iron-chelating activity of 4 μg/ml quercetin solution. Quercetin chelated 65% of total iron within 15 min contact