Institute of Legal Medicine[1], Department of Pharmacology[2]; Institute of Pharmaceutical Chemistry[3], Johann Wolfgang Goethe University/ZAFES, Frankfurt am Main, Germany

Isoquercitrin provides better bioavailability than quercetin: comparison of quercetin metabolites in body tissue and brain sections after six days administration of isoquercitrin and quercetin

A. Paulke[1], G. P. Eckert[2], M. Schubert-Zsilavecz[3], M. Wurglics[3]

Received February 26, 2012, accepted April 14, 2012

Dr. Mario Wurglics, Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe University/ZAFES; Max-von-Laue Str. 9, 60438 Frankfurt am Main, Germany
wurglics@pharmchem.uni-frankfurt.de

Pharmazie 67: 991–996 (2012) *doi: 10.1691/ph.2012.2050*

In the present study, over a period of 8 days 12 mg/kg/d quercetin aglycone and 18 mg/kg/d isoquercitrin were orally given to rats, respectively. Four hours after administration, plasma samples were taken as well as tissue samples of liver, lung, heart, kidney and the brain sections hippocampus, cerebellum, striatum, cortex and the remaining brain. A HPLC-FD method with in-line post-column complexation was employed to quantify the quercetin metabolites (QM) in plasma and tissues. Compared to the quercetin gavage the isoquercitrin gavage consistently produced higher levels of QM in tissues (double to five-fold) as well as in plasma (double to three-fold). In body tissues, the highest amounts of QM were observed in the lung. In brain tissue, the highest levels of QM were found in the cerebellum, while the striatum contained the lowest levels of QM. In conclusion, this study clearly demonstrates that orally given isoquercitrin leads to higher levels in plasma and in all investigated tissue than quercetin aglycone.

1. Introduction

Flavonols with the quercetin structure are widely distributed throughout the plant kingdom and many herbal pharmaceutical products contain quercetin flavonols (QF) as active ingredients. However, the pharmacological profile of QF is not completely understood, and there are many studies dealing with different pharmacological effects of QF. Most of these studies focused on the antioxidant activities and researched the radical oxygen species (ROS) scavenging activities (Hanasaki et al. 1994; van Acker et al. 1995; Heijnen et al. 2001; Boots et al. 2008a) or anti-inflammatory effects (Read 1995; Manjeet K, Ghosh 1999; Bureau et al. 2008a; Boots et al. 2008b; Boots et al. 2009). Furthermore, QF showed *in vivo* hepatoprotective and antifibrotic effects against liver injury in the dimethylnitrosamine (DMN)-induced hepatic fibrosis model (Lee et al. 2003), antimicrobial activity (Cushnie and Lamb 2005), antihypertensive effects (Duarte et al. 2001; Perez-Vizcaino et al. 2009; Edwards et al. 2007), immunomodulatory effects (Orsolić et al. 2004), and inhibited platelet aggregation, secretion and platelet procoagulant activity *in vitro* (Bucki et al. 2003). – In addition, it is also reported that QF show antidepressant activities (Anjaneyulu et al. 2003; Butterweck et al. 2000, 2004; Nöldner, Schötz 2002; Paulke et al. 2008), as well as anti-dementive properties (Rangel-Ordóñez et al. 2010; Ramassamy 2006; Tchantchou et al. 2009). Although the mechanisms of action remain unknown, several herbal extracts used in rational phytotherapy are nevertheless standardisized on the QF content (e.g., St. John's wort extract or *Ginkgo biloba* extract). Overviews of the potentials and pharmacological effects of QF is given by Bischoff (2008), Boots et al. (2008a) and Murakami et al. (2008).

QF pharmacokinetics is complex: QF are subject to a distinctive multiple step metabolism starting in the intestine during absorption. This first step pre-metabolism is caused by intestinal bacteria and depends on the nature, amount and position of glycosidic sugar moieties present in the digestates. However, much about these gastrointestinal processes remains unknown, and even the precise mechanism of absorption of QF is still under discussion (Nait Chabane et al. 2009; Cermak et al. 2003; Walle et al. 2000; Ader et al. 2001; Cermak et al. 2003; Day et al. 1998). After absorption the quercetin aglycone is glucuronidated by the intestinal brush border cells (BBC) and transported into the plasma. Further hepatic metabolism follows, leading to generation of glucuronidated, methylated and sulphurated forms of quercetin (Spencer et al. 1999; Day et al. 2001; O'Leary et al. 2003). Therefore, it is likely that *in vivo*, no native QF or free quercetin are available in plasma after oral administration, and QF are bioavailable only as metabolites (Day et al. 2001; O'Leary et al. 2003; Graefe et al. 2001; Erlund et al. 1999; Morand et al. 2000; Paganga, Rice-Evans 1997).
Figure 1 gives a short example about the metabolic pathway of QF and the structure of the metabolites.
Several pharmacokinetic studies of the bioavailability of different QF in plasma have been conducted (Ader et al. 2000; Cermak et al. 2003; Erlund et al. 2000; Graefe et al. 2001; Hollman et al. 1996; Manach et al. 1997; Olthof et al. 2000), and taken together these studies suggest that the bioavailability of glucosylated QF is superior compared to non-glucosylated forms or the quercetin aglycone. To elucidate these findings more deeply and to examine the role of QF in mental disorders, our group investigated plasma levels and bioavailabilities of isoquercitrin, pure quercetin and QF standardized herbal extracts (St. John's

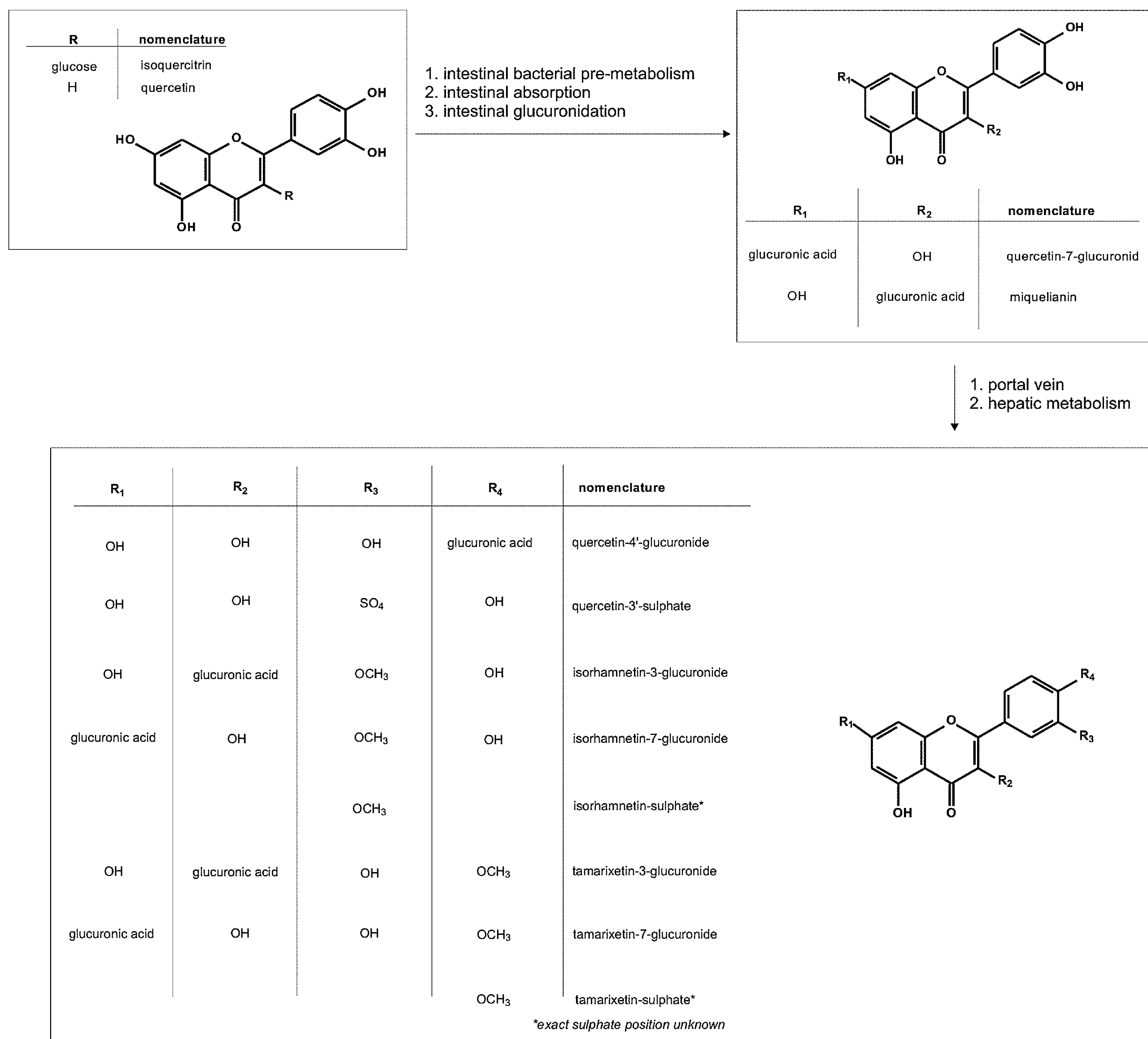

Fig. 1: Metabolic pathway of QF

wort and *Ginkgo biloba*) in brain tissue, in former studies. Again, the glucosylated quercetin showed the best bioavailability (Paulke et al. 2008, 2006; Paulke 2007; Rangel-Ordóñez et al. 2010). Beyond these pharmacokinetic investigations in plasma and brain tissue, two studies deal with the distribution pattern of orally given quercetin in body tissue (Bieger et al. 2008; de Boer et al. 2005). Nevertheless, until now no systematic comparison of the bioavailability of glucosylated and pure quercetin in different body tissues has been published. To fill this gap and to complete our investigations, in the present study we compared the levels of orally administered isoquercitrin and quercetin aglycone in plasma, body tissues and different brain sections.

2. Investigations and results

Over a period of 8 days, 12 mg/kg/d quercetin and 18 mg/kg/d isoquercitrin were orally administered to 9 rats, respectively. Four hours after the last gavage the animals were killed and samples were collected. To facilitate anlysis, the plasma and tissue samples were hydrolyzed using hydrochloric acid prior to the HPLC separation. This procedure reduced the number of metabolites to the three aglycone types: quercetin, isorhamnetin and tamarixetin (Hollman et al. 1996). Subsequently, we separated quercetin from isorhamnetin and tamarixetin (these two analytes coelute) (Paulke et al. 2006, 2008).

In Table 1 body tissue, brain and plasma levels of QM 4 h after the last oral administration of quercetin and isoquercitrin are summarised. The most pronounced differences between quercetin and isoquercitrin uptake were observed in the liver, whereas in heart tissue the concentration ratios were more equal to plasma. In Fig. 2, body tissue levels of QM are given. Both quercetin and isoquercitrin gavage led to measurable evels of quercetin and isorhamnetin/tamarixetin in all analysed tissue. However, isorhamnetin/tamarixetin type metabolites seemed to be more dominant than the quercetin type metabolites. The highest amounts of QM were found in lung tissue.

Table 2 gives the ratio of the concentrations in tissue compared to plasma. In Fig. 3 we present the amounts of QM in brain ordered by different brain sections. After quercetin gavage, quantifiable amounts of quercetin were only found in the cerebellum, whereas no quercetin was detected in the hippocampus, striatum, cortex and the rest of the brain. After administration of isoquercitrin, quercetin was found to be concentrated predominantly in the cerebellum. No quercetin was detected in the hippocampus and the striatum. Isorhamnetin/tamarixetin

Table 1: Body tissue, brain and plasma levels (± standard deviation) of QM 4 h after the last oral administration of quercetin and isorhamnetin

Tissue (n = 9)	Quercetin		Isoquercitrin	
	Quercetin (ng/g)	Isorhamnetin/tamarixetin (ng/g)	Quercetin (ng/g)	Isorhamnetin/tamarixetin (ng/g)
Liver	186.2 ± 42.0	322.8 ± 90.5	930.2 ± 325.0	1 248.5 ± 486.0
Lung	428.8 ± 154.3	1 015.7 ± 224.0	1 303.5 ± 481.3	2 164.0 ± 704.8
Heart	165.0 ± 42.9	526.0 ± 212.9	374.8 ± 67.4	925.3 ± 209.5
Kidney	214.0 ± 63.9	377.2 ± 155.4	848.8 ± 277.2	1 200.0 ± 338.0
Brain (n = 9)				
Hippocampus	0	34.3 ± 25.8	0	78.5 ± 44.7
Cerebellum	26.3 ± 6.4	104.7 ± 18.4	96.1 ± 44.7	194.7 ± 65.1
Striatum	0	14.6 ± 8.3	0	33.2 ± 14.5
Cortex	0	78.8 ± 20.0	34.9 ± 11.9	106.9 ± 22.4
Rest brain	0	54.1 ± 20.5	34.8 ± 11.8	97.4 ± 16.9
Plasma* (n = 9)	1 682.1 ± 456.6	2 173.0 ± 575.8	3 385.5 ± 1290.8	6 131.6 ± 2448.5

* amounts in ng/mL

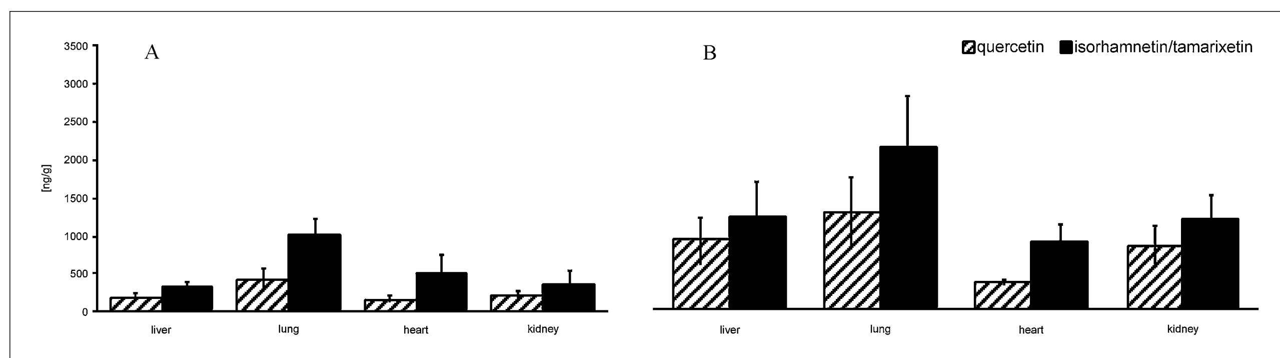

Fig. 2: QM levels (± standard deviation) in tissues after consumption of 12 mg/kg/d quercetin (A) or 18 mg/kg/d isoquercitrin (B)

were quantified after gavage with both quercetin and isoquercitrin. Again, isoquercitrin gavage led to higher levels of the metabolites, especially in the cerebellum. In Table 3, the ratio of the concentrations in brain tissue compared to plasma is presented.
In the control group (flavonoid-free feed, n = 4), no QM could be detected in either the plasma or in body or brain tissue.

3. Discussion

In recent years, many pharmacokinetic data of different QF or QF-enriched herbal extracts have been published. Researchers have heretofore focused mainly on plasma pharmacokinetics (Ader et al. 2000; Cermak et al. 2003; Erlund et al. 2000; Graefe et al. 2001; Hollman et al. 1996; Manach et al. 1997; Olthof et al. 2000; Morand et al. 2000), and have consistently found that orally administered quercetin monoglucosides lead to higher QM levels than orally administered quercetin aglycone. We confirmed these findings, as we found two- to three-fold concentrations of quercetin metabolites in the plasma after isoquercitrin intake. Therefore, we agree with the conclusions of Cermak et al. (2003), i.e., that quercetin monoglucosides (e.g., isoquercitrin), are transported actively into the intestinal brush border cells, whereas the quercetin aglycone is able to cross the brush border cell membrane only via passive diffusion.
Compared to the administration of quercetin aglycone, isoquercitrin gavage led to higher QM levels in body tissues as well. This effect was surprisingly more pronounced than in plasma: two- to five-fold concentrations were observed after isoquercitrin intake. However, the reason for the discrepancy between the tissue absorption of QM from isoquercitrin and QM from quercetin aglycone is unclear. Additional studies will be necessary to elucidate this question. Nevertheless, the tissue distribution of QM in both the quercetin and the isoquercitrin intake groups showed a comparable pattern. Highest tissue levels were found in lung after the isoquercitrin and the quercetin gavage, whereas lowest concentrations of QM were found in heart tissue. These findings concur with those of de Boer et al. (2005), who reported a similar distribution pattern of QM after quercetin intake. The apparent affinity of QM for lung tissue is noteworthy, as beneficial health effects of QM have been reported in patients suffering from sarcoidosis (Boots et al. 2009). Additional research will be required to clarify these findings, as the tissue distribution pattern of QM seems to depend strongly on the animal species (de Boer et al. 2005; Bieger et al. 2008). Furthermore, the exact distribution pattern of each single QM cannot be stated, as the employed analytical method only differed between methylated and non-methylated QM. Hence, further

Table 2: Percentaged concentrations of QM in body tissue compared to plasma after quercetin or isoquercitrin gavage

	Quercetin		Isoquercitrin	
	Quercetin	Isorhamnetin/tamarixetin	Quercetin	Isorhamnetin/tamarixetin
Liver	11%	15%	27%	20%
Lung	26%	47%	39%	35%
Heart	10%	24%	11%	15%
Kidney	13%	17%	25%	20%
Plasma	100%	100%	100%	100%

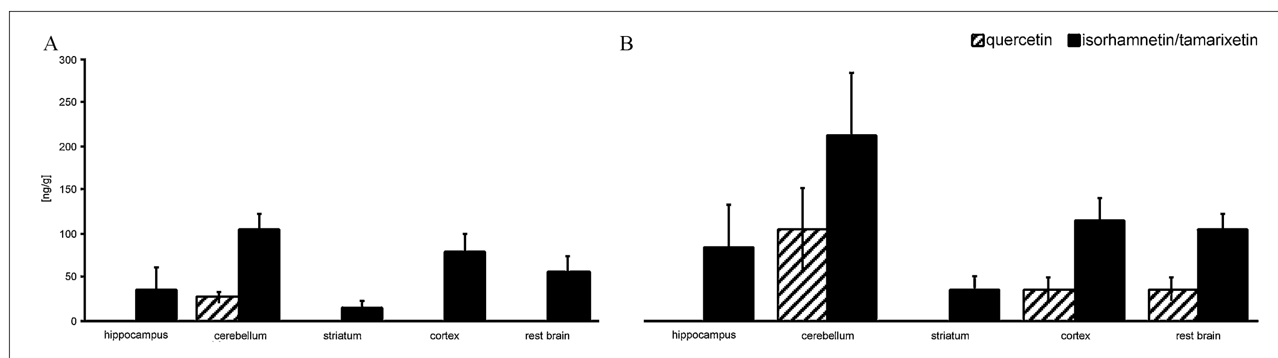

Fig. 3: QM levels (± standard deviation) in brain after consumption of 12 mg/kg/d quercetin (A) or 18 mg/kg/d isoquercitrin (B)

research employing e.g. mass-spectrometry technique will be necessary to elucidate the significance of each single QM more deeply.

In brain tissue, QM levels were much lower than in body tissue. Again, isoquercitrin gavage produced higher concentration levels, and two- to three-fold levels were found. After both quercetin and isoquercitrin gavage, predominant levels of QM were found in the cerebellum. However, the role of QM in the cerebellum remains unclear. Further, distinct levels of QM were found in cortex and the rest of the brain after isoquercitrin gavage. This may partly explain the antidepressant properties of QM, as the frontal cortex plays a dominant role in pathophysiology of depression (Koenigs and Grafman 2009a, b; Koenigs et al. 2008).

In conclusion, our results strongly suggest that the bioavailability of QM can be enhanced using isoquercitrin as QM source. Consequently, the pharmacological activity of quercetin-containing phytopharmaceuticals is expected to be highly affected by the presence or absence of the glycoside moeity. Thus, to enhance the pharmacological effectiveness, QF extracts should contain, or be enriched with, isoquercitrin. Furthermore, to avoid variability in pharmacological activity, QF-based herbal extracts should be standardised to the content of isoquercitrin.

4. Experimental

4.1. Chemicals

Quercetin (HPLC grade) and isorhamnetin (HPLC grade), methanol (gradient grade), and acetonitril (gradient grade) were delivered by Roth, Karlsruhe. Isoquercitrin (HPLC grade) and *tert.*-butylhydroquinone (HPLC) were purchased from Fluka, Steinheim. Chloracetic acid 99%, sodium chloroacetate 98%, tris buffer 99.9% and ethanol (gradient grade) were purchased from Sigma-Aldrich, Taufkirchen. Aluminium nitrate nonahydrate (p.a.) was delivered by Acros, Geel, Belgium. Acetic acid 100% (p.a.) and hydrochloric acid 30% (suprapure) were purchased from Merck, Darmstadt. Water was purified by a Milli-Q system (Millipore, Bredford, MA).

Table 3: Concentrations of QM in brain tissue compared to plasma after quercetin or isoquercitrin gavage

	Quercetin		Isoquercitrin	
	Quercetin	Isorhamnetin/tamarixetin	Quercetin	Isorhamnetin/tamarixetin
Hippocampus	—	2%	—	1%
Cerebellum	2%	5%	3%	3%
Striatum	—	1%	—	1%
Cortex	—	4%	1%	2%
Rest brain	—	2%	1%	2%
Plasma	100%	100%	100%	100%

4.2. Animal Study

Male Wistar rats (Crl:Wi) (n = 9; 350–450 g) (Charles River, Sulzbach, Germany), housed under standard conditions (25 °C; 12 h light cycle) were treated with a daily dose of quercetin (12 mg/kg b.wt., freshly prepared in 0.2% (w/v) agarose gel, Merck Darmstadt, Germany) or isoquercitrin (18 mg/kg b.wt., freshly prepared in 0.2% (w/v) agarose gel, Merck Darmstadt, Germany) by oral gavage (pharyngal tube) for 8 days, respectively. Free access to water and flavonoid-free feed (C1000 Altromin, Lage, Germany) was provided and rats were weighed for dose adjustment. 4 control rats received the same volume of pure vehicle (0.2% (w/v) agarose gel) based on body weight. At the end of the study, rats received the last treatment 4 h prior to tissue extraction. After decapitation the brain, liver, kidneys, lung and heart were removed, carefully washed with ice cold tris-buffer (5 mM, pH 7.4), weighed and homogenized using a Potter-S, Braun (1 mL buffer/100 mg tissue). Before the homogenization of the brain, the brain stem was discarded and hippocampus, cerebellum, cortex and striatum were dissected and immediately snap-frozen in liquid nitrogen. All samples were stored for approximately 12 h at −20 °C before analysis. The blood samples were collected from the trunk immediately after decapitation and transferred to tubes containing 16 I.E. heparin/mL blood to avoid coagulation. They were centrifuged at 2000× g for 10 min to obtain the plasma fractions, which were then stored at −20 °C until analysis. All experiments were carried out according to the European Communities Council Directive (86/609/EEC) by individuals with appropriate training and experience.

4.3. Sample preparation

Tissue, brain and blood samples were defrosted slowly. 200 μL heart, lung and kidney homogenate, respectively, were mixed with 1000 μL methanol, 400 μL *tert.*-butyl hydroquinone (TBHQ) solution (5 mg/mL in methanol) and 400 μL HCl (conc.). The reaction mixture was vortexed for 20 s. For the liver 150 μL of the homogenate were mixed with 1050 μL methanol, 400 μL TBHQ solution (5 mg/mL in methanol) and 400 μL HCl (conc.). The reaction mixture was vortexed for 20 s. The tissue homogenates were centrifuged at 107 x g for 10 s and the centrifugate was used for further preparation. The brain homogenates were prepared as follows: 600 μL of the homogenates each were mixed with 600 μL methanol, 400 μL TBHQ solution (5 mg/mL in methanol) and 400 μL HCl (conc.). The reaction mixture was vortexed for 20 s. 30 μL plasma were mixed with 1200 μL of methanol. This mixture was vortexed for 20 s, and 400 μL of TBHQ solution (5 mg/mL in methanol) and 400 μL HCl (conc.) were added. The mixture was vortexed again for 20 s. The vials were sealed tightly with caps, inserted into a preheated aluminium block (Liebisch, Bielefeld) at 90 °C for 2 h, allowed to cool and centrifuged at 3700 g for 10 min. The supernatant was then transferred to the HPLC system for the separation.

4.4. Quantitation and standards

A stock solution of quercetin and isorhamnetin was used as external standard and quality control. Standard curves were obtained at two levels: 1–30 and 0.4–1 ng/mL for quercetin and 1–30 and 0.05–1 ng/mL for isorhamnetin. Standard solutions were prepared directly before the preparation of tissue, brain and blood. Standard solutions contain 100 μg/mL of TBHQ and 20% HCl (conc.). Aqueous methanol (50% v/v) was used as a solvent for quercetin, and aqueous ethanol (50% v/v) for isorhamnetin. To monitor the reliability of the method, pure methanol as well as quercetin in aqueous methanol (50% v/v) in the concentrations 0.65, 1 and 15 ng/mL and isorhamnetin in aqueous ethanol (50% v/v) in the concentrations 0.65, 1.5, 15 and 25 ng/mL were used as quality control samples. Quality controls with quercetin

and isorhamnetin contained 100 µg/mL TBHQ and 20% HCl. The quality control vials were mixed randomly with the vials containing the tissue, brain and plasma samples.

4.5. Chromatographic instrumentation and conditions

The analytical method employed is well established and, with variations, commonly used in QF analytics (Hertog et al. 1992; Hollman et al. 1996, 1997; Rangel-Ordóñez et al. 2010; Paulke et al. 2008, 2006). For chromatographic instrumentation and conditions see Paulke et al. (2006).

References

Acker SA van, Tromp MN, Haenen GR, Vijgh WJ van der, Bast A (1995) Flavonoids as scavengers of nitric oxide radical. Biochem Biophys Res Commun 214: 755–759.

Ader P, Block M, Pietzsch S, Wolffram S (2001) Interaction of quercetin glucosides with the intestinal sodium/glucose co-transporter (SGLT-1). Cancer Lett 162: 175–180.

Ader P, Wessmann A, Wolffram S (2000) Bioavailability and metabolism of the flavonol quercetin in the pig. Free Radic Biol Med 28: 1056–1067.

Anjaneyulu M, Chopra K, Kaur I (2003) Antidepressant activity of quercetin, a bioflavonoid, in streptozotocin-induced diabetic mice. J Med Food 6: 391–395.

Bieger J, Cermak R, Blank R, Boer VCJ de, Hollman PCH, Kamphues J, Wolffram S (2008) Tissue distribution of quercetin in pigs after long-term dietary supplementation. J Nutr 138: 1417–1420.

Bischoff SC (2008) Quercetin: potentials in the prevention and therapy of disease. Curr Opin Clin Nutr Metab Care 11: 733–740.

Boer VCJ de, Dihal AA, Woude H van der, Arts ICW, Wolffram S, Alink GM, Rietjens IM, Keijer J, Hollman PC (2005) Tissue distribution of quercetin in rats and pigs. J Nutr 135: 1718–1725.

Boots AW, Drent M, Swennen ELR, Moonen HJJ, Bast A, Haenen GRMM (2009) Antioxidant status associated with inflammation in sarcoidosis: a potential role for antioxidants. Respir Med 103: 364–372.

Boots AW, Haenen GRMM, Bast A (2008a) Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 585: 325–337.

Boots AW, Wilms LC, Swennen ELR, Kleinjans JCS, Bast A, Haenen GRMM (2008b) *In vitro* and *ex vivo* anti-inflammatory activity of quercetin in healthy volunteers. Nutrition 24: 703–710.

Bucki R, Pastore JJ, Giraud F, Sulpice JC, Janmey PA (2003) Flavonoid inhibition of platelet procoagulant activity and phosphoinositide synthesis. J Thromb Haemost 1: 1820–1828.

Bureau G, Longpré F, Martinoli MG (2008) Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. J Neurosci Res 86: 403–410.

Butterweck V, Hegger M, Winterhoff H (2004) Flavonoids of St. John's Wort reduce HPA axis function in the rat. Planta Med 70: 1008–1011.

Butterweck V, Jurgenliemk G, Nahrstedt A, Winterhoff H (2000) Flavonoids from Hypericum perforatum show antidepressant activity in the forced swimming test. Planta Med 66: 3–6.

Cermak R, Landgraf S, Wolffram S (2003) The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. J Nutr 133: 2802–2807.

Cushnie TPT, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 26: 343–356.

Day AJ, DuPont MS, Ridley S, Rhodes M, Rhodes MJ, Morgan MR, Williamson G (1998) Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver beta-glucosidase activity. FEBS Lett 436: 71–75.

Day AJ, Mellon F, Barron D, Sarrazin G, Morgan MRA, Williamson G (2001) Human Metabolism of Dietary Flavonoids: Idendification of Plasma Metabolites of Quercetin. Free Radic Res 35: 941–952.

Duarte J, Pérez-Palencia R, Vargas F, Ocete MA, Pérez-Vizcaino F, Zarzuelo A, Tamargo J (2001) Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. Br J Pharmacol 133: 117–124.

Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T (2007) Quercetin reduces blood pressure in hypertensive subjects. J Nutr 137: 2405–2411.

Erlund I, Alfthan G, Siren H, Ariniemi K, Aro A (1999) Validated method for the quantitation of quercetin from human plasma using high-performance liquid chromatography with electrochemical detection. J Chromatogr B Analyt Technol Biomed Life Sci 727: 179–189.

Erlund I, Kosonen T, Alfthan G, Maenpaa J, Perttunen K, Kenraali J, Parantainen J, Aro A (2000) Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol 56: 545–553.

Graefe EU, Wittig J, Mueller S, Riethling AK, Uehleke B, Drewelow B, Pforte H, Jacobasch G, Derendorf H, Veit M (2001) Pharmacokinetics and bioavailability of quercetin glycosides in humans. J Clin Pharmacol 41: 492–499.

Hanasaki Y, Ogawa S, Fukui S (1994) The correlation between active oxygens scavenging and antioxidative effects of flavonoids. Free Radic Biol Med 16: 845–850.

Heijnen CG, Haenen GR, Acker FA van, Vijgh WJ van der, Bast A (2001) Flavonoids as peroxynitrite scavengers: the role of the hydroxyl groups. Toxicol *In Vitro* 15: 3–6.

Hertog MGL, Hollman PCH, Venema DP (1992) Optimization of a quantitative HPLC determination of potentially anticarcinogenic flavonoids in vegetables and fruits. J Agric Food Chem 40: 1591–1598.

Hollman PC, Gaag M van der, Mengelers MJ, Trijp JM van, Vries JH de, Katan MB (1996) Absorption and disposition kinetics of the dietary antioxidant quercetin in man. Free Radic Biol Med 21: 703–707.

Hollman PC, van Trijp JM, Buysman MN, van der Gaag MS, Mengelers MJ, Vries JH de, Katan MB (1997) Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett 418: 152–156.

Koenigs M, Grafman J (2009a) Prefrontal asymmetry in depression? The long-term effect of unilateral brain lesions. Neurosci Lett 459: 88–90.

Koenigs M, Grafman J (2009b) The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res 201: 239–243.

Koenigs M, Huey ED, Calamia M, Raymont V, Tranel D, Grafman J (2008) Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. J Neurosci 28: 12341–12348.

Lee E, Lee H, Shin J, Yoon S, Moon J (2003) The flavonoid quercetin inhibits dimethylnitrosamine-induced liver damage in rats. J Pharm Pharmacol 55: 1169–1174.

Manach C, Morand C, Demigne C, Texier O, Regerat F, Remesy C (1997) Bioavailability of rutin and quercetin in rats. FEBS Lett 409: 12–16.

Manjeet KR, Ghosh B (1999) Quercetin inhibits LPS-induced nitric oxide and tumor necrosis factor-alpha production in murine macrophages. Int J Immunopharmacol 21: 435–443.

Morand C, Manach C, Crespy V, Remesy C (2000) Quercetin 3-O-beta-glucoside is better absorbed than other quercetin forms and is not present in rat plasma. Free Radic Res 33: 667–676.

Murakami A, Ashida H, Terao J (2008) Multitargeted cancer prevention by quercetin. Cancer Lett 269: 315–325.

Nait Chabane M, Al Ahmad A, Peluso J, Muller CD, Ubeaud G (2009) Quercetin and naringenin transport across human intestinal Caco-2 cells. J Pharm Pharmacol 61: 1473–1483.

Nöldner M, Schötz K (2002) Rutin is essential for the antidepressant activity of Hypericum perforatum extracts in the forced swimming test. Planta Med 68: 577–580.

O'Leary KA, Day AJ, Needs PW, Mellon FA, O'Brien NM, Williamson G (2003) Metabolism of quercetin-7- and quercetin-3-glucuronides by an *in vitro* hepatic model: the role of human beta-glucuronidase, sulfotransferase, catechol-O-methyltransferase and multi-resistant protein 2 (MRP2) in flavonoid metabolism. Biochem Pharmacol 65: 479–491.

Olthof MR, Hollman PC, Vree TB, Katan MB (2000) Bioavailabilities of quercetin-3-glucoside and quercetin-4'-glucoside do not differ in humans. J Nutr 130: 1200–1203.

Orsolić N, Knezević AH, Sver L, Terzić S, Basić I (2004) Immunomodulatory and antimetastatic action of propolis and related polyphenolic compounds. J Ethnopharmacol 94: 307–315.

Paganga G, Rice-Evans CA (1997) The identification of flavonoids as glycosides in human plasma. FEBS Lett 401: 78–82.

Paulke A (2007) Untersuchungen zur ZNS-Bioverfügbarkeit wirksamkeitsbestimmender Inhaltsstoffe von Johanniskraut Diss. Frankfurt, Institut für Pharmazeutische Chemie.

Paulke A, Nöldner M, Schubert-Zsilavecz M, Wurglics M (2008) St. John's wort flavonoids and their metabolites show antidepressant activity and accumulate in brain after multiple oral doses. Pharmazie 63: 296–302.

Paulke A, Schubert-Zsilavecz M, Wurglics M (2006) Determination of St. John's wort flavonoid-metabolites in rat brain through high performance

liquid chromatography coupled with fluorescence detection. J Chromatogr B Analyt Technol Biomed Life Sci 832: 109–113.
Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A (2009) Antihypertensive effects of the flavonoid quercetin. Pharmacol Rep 61: 67–75.
Ramassamy C (2006) Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. Eur J Pharmacol 545: 51–64.
Rangel-Ordóñez L, Nöldner M, Schubert-Zsilavecz M, Wurglics M (2010) Plasma levels and distribution of flavonoids in rat brain after single and repeated doses of standardized Ginkgo biloba extract EGb 761(R). Planta Med 76: 1683–1690.
Read MA (1995) Flavonoids: naturally occurring anti-inflammatory agents. Am J Pathol 147: 235–237.
Spencer JP, Chowrimootoo G, Choudhury R, Debnam ES, Srai SK, Rice-Evans C (1999) The small intestine can both absorb and glucuronidate luminal flavonoids. FEBS Lett 458: 224–230.
Tchantchou F, Lacor PN, Cao Z, Lao L, Hou Y, Cui C, Klein WL, Luo Y (2009) Stimulation of neurogenesis and synaptogenesis by bilobalide and quercetin via common final pathway in hippocampal neurons. J Alzheimers Dis 18: 787–798.
Walle T, Otake Y, Walle UK, Wilson FA (2000) Quercetin glucosides are completely hydrolyzed in ileostomy patients before absorption. J Nutr 130: 2658–2661.