

Curcuminoid drug interactions

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Summary

The secondary plant metabolite curcumin and the related curcuminoids may be valuable in the prevention and treatment of many different degenerative diseases. As curcuminoids are often taken as supplements by some population groups, it may be asked whether this can lead to changes in the pharmacokinetics or pharmacodynamics of other drugs taken at the same time. It is particularly important to clarify this issue, as native curcumin only exhibits low bioavailability, but many novel formulations are being developed that enhance its absorption in the small intestine and thus lead to higher concentrations of the active drug. Cell culture and animal studies have shown that native curcumin can affect xenobiotic metabolizing enzymes. There are also effects on the pharmacokinetics of active substances in animal studies and in men. On the other hand, it has not been shown that curcumin has any adverse effects on the pharmacological activity of other drugs. However, it must be emphasized that these studies are preliminary rather than conclusive and must be supported by larger scale investigations. It has also not been investigated whether the formulations with better bioavailability can influence the pharmacokinetics of other drugs.

Keywords: curcumin, curcuminoids, turmeric, drug interactions, safety, drug

Older and chronically ill people often attempt to improve their health by taking food supplements. Thus they often take drugs together with plant extracts that might influence the effects of these drugs. In the present article, we describe the evidence for drug interactions involving the secondary plant metabolite curcumin and the related curcuminoids.

Introduction

Curcuminoids are lipophilic secondary plant metabolites isolated from the roots of the plant *Curcuma longa* (turmeric) (■ ■ ■ see SCHIBORR et al., page M636 [1]) and consist of ca. 77 % curcumin, 17 % demethoxycurcumin and 6 % bis-demethoxycurcumin [2]. Because of their many health supporting activities, they have long been used in traditional Chinese medicine for the treatment of respiratory disease, anorexia, diabetic wounds or for digestive disorders [3]. Curcumin supplements are freely commercially available, mostly as capsules or tablets; many people take them to improve their health.

The oral bioavailability of curcumin is low, i.e. it is poorly absorbed, and rapidly metabolized and eliminated. For this reason, curcumin formulations with better bioavailability are being sold increasingly often; these give much higher plasma concentrations of curcumin than native curcumin [1].

People who take curcumin supplements are often older or chronically ill and have to take medicines every day. This article therefore examines

Citation:

Kocher A, Schiborr C, Frank J (2015) Curcuminoid drug interactions. *Ernährungs Umschau* 62(11): 188–195

This article is available online:
DOI: 10.4455/eu.2015.037

Explanation of terms used:

An **active substance** or **drug** is the substance in a medicine which mediates or causes the active effect. The **medicine** may also contain one or several additional substances (“excipients”) for different **formulations** (e.g. tablet or syrups). The preparation of different drug formulations is known as **pharmacy** and can have a major influence on drug activity.

whether there is published scientific evidence for interactions between curcuminoids – primarily curcumin – and medicines (or their active substances) which may modify their activity. The focus is on the pharmacokinetics of various drugs. The effects of curcumin on drug pharmacodynamics are mentioned in passing.

Key terms

Food-drug interaction

We will use the term “food-drug interaction” for changes in the pharmacokinetics or pharmacodynamics of a drug caused by the uptake of a food component [4].

The term “pharmacokinetics” (= what the *organism* does to the *active substance*) means the sum of all processes to which the active substance is subject in the body and includes its absorption, distribution, metabolism and excretion. The kinetic profile of a substance

is often described by the following parameters:

- physiological half-time of elimination ($t_{1/2}$),
- time to reach the maximum plasma concentration (t_{max}),
- maximal plasma concentration (C_{max}) and
- area under the concentration time curve (“area under the curve”, AUC) (♦ Figure 1).

The physiological half-time of elimination ($t_{1/2}$) is the time needed for the (plasma) concentration of the active substance to sink to 50 % of the initial value. The rate of absorption of a substance can be estimated from the time (t_{max}) to reach the maximum plasma concentration (C_{max}). The area under the concentration time curve (“area under the curve”, AUC) reflects the subject’s exposure to the drug or nutrient.

The “bioavailability” describes the proportion of a drug or nutrient that is available to systemic circulation in the body. Intravenous administration is defined as giving 100 % bio-

availability. Because of incomplete absorption and metabolism, an orally or enterally administered drug has a bioavailability of < 100 %.

The so-called “therapeutic index” is an important parameter in assessing the safety of a drug. This is the interval between the minimal active and minimal toxic concentration of the drug [5].

Pharmacodynamics (= what the *active substance* does to the *organism*) signifies the biological activity of an active substance [6].

Food-drug interactions can lead to changes in pharmacokinetics and/or pharmacodynamics and modify the activity and safety profile of the medicine (side effects = adverse drug reactions) in this way. Thus, a reduction in the bioavailability of a drug can lead to treatment failure. On the other hand, enhanced bioavailability can lead to enhanced ac-

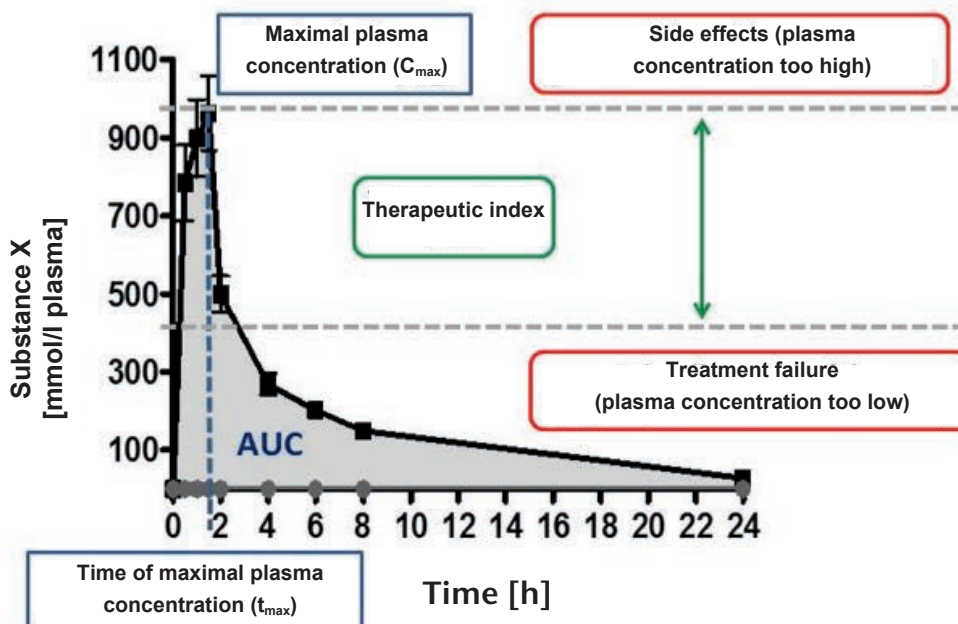


Fig. 1: Typical plasma concentration time curve for a drug

The pharmacokinetics of a substance can be determined by measuring the maximal concentration (C_{max}), the time to reach the maximal concentration (t_{max}), and the “area under the curve” (AUC), which reflects individual exposure to a substance. The therapeutic index describes the concentration range in which the drug is therapeutically active and lies between the minimal effective and the minimal toxic concentrations of the active substance.

tivity and also possibly to enhanced drug toxicity (♦ Figure 1) [4]. These interactions can be split into various categories:

- (1) Inactivation of the drug *ex vivo*, i.e. outside the body,
- (2) Interactions which modify presystemic transport (absorption),
- (3) Interactions which modify systemic metabolism and drug elimination, and
- (4) Interactions which directly influence drug activity (pharmacodynamics), e.g. by binding to target structures such as receptors.

Effect of curcuminoids on enzymes that metabolize foreign compounds

The following cell culture and animal studies examined the influence of curcumin on enzymes that metabolize foreign compounds. These studies provide preliminary evidence that curcumin might influence drug metabolism.

Modulation of phase I metabolism by curcumin

Microsomes are membrane fragments of the endoplasmic reticulum that contain active CYP450

enzymes. Incubation of human liver cell microsomes with a curcuminoid extract led to 50 % inhibition of different CYP450s at the following concentrations: CYP2C19, 7.4 $\mu\text{mol/L}$; CYP2B6, 9.4 $\mu\text{mol/L}$; CYP2C9, 13.5 $\mu\text{mol/L}$; CYP3A, 25.3 $\mu\text{mol/L}$. CYP2D6, CYP1A2 and CYP2E1 were only very weakly inhibited [10]. On the other hand, another *in vitro* study with microsomes found that CYP3A4 and 2D6 were not inhibited by up to 58.3 $\mu\text{mol/L}$ curcumin, while 58.3 $\mu\text{mol/L}$ curcumin inhibited CYP2C9 and 2C8 by 10.5 % and 22.5 %, respectively [11]. The effects of curcumin can also be tissue-specific. After feeding rats for 4 days with curcumin (60 mg/kg body weight [BW]), there was a 42 % reduction in the intestinal content of CYP3A protein, but a 91 % increase in the liver content of this protein [12].

Influence of curcumin on phase II metabolisms

Curcumin can also affect phase II enzymes. Thus 12.1 $\mu\text{mol/L}$ and 5.2 $\mu\text{mol/L}$ of a curcuminoid extract lead to 50 % inhibition of UGT and SULT activity, respectively, in colon adenocarcinoma cells (LS180 cells), an intestinal cell model to examine

absorption and transport processes and metabolism [10]. The opposite effect was observed in a rat model. In this study, the animals were fed for 2 weeks with 1 % curcumin per kg feed and then the microsomes were isolated from the intestine and liver. The UGT activity increased 5.4-, 6.7- and 7.2-fold in the proximal, middle and distal sections of the small intestine, respectively. In comparison to the control, there was a 3.1-fold increase in the large intestine and a 1.5-fold increase in the liver [13].

Effect of curcumin on membrane transporters

As the present article cannot pursue all interactions between curcumin and membrane transport proteins, the discussion will be restricted to **multidrug resistance protein 1** (MDR1; also known as P-glycoprotein [P-Gp]). MDR1 is a transport protein in the plasma membrane and is mainly expressed in the liver, kidneys, gastrointestinal tract and the blood-brain barrier. In the liver, it is expressed on the canalicular apical side of the membrane (towards the lumen), in the intestine on the apical membrane of the mucosal cells and in the kidney on the brush border membrane of the proximal tubulus cells.

Metabolism of foreign compounds

Enzymes metabolizing foreign compounds play a central role in the metabolism, elimination and/or detoxification of foreign compounds (xenobiotics) and thus protect the body from potentially damaging substances. The metabolism of foreign compounds is subdivided into different phases [7].

In **phase I** (functionalization), enzymes introduce reactive functional groups (e.g. OH, NH₂, SH, COOH) into the initial substance, in order to prepare it for phase II reactions (conjugation). The most important class of phase I enzymes are cytochrome P450 mixed function monooxygenases (CYP), which transfer an oxygen atom; these are mainly expressed in the gastrointestinal tract, the lungs and the liver. Isoenzyme CYP3A4 is of particular importance, as it is responsible for the metabolism of 50–60 % of currently marketed drugs [8].

Phase II enzymes catalyze conjugation reactions with water soluble groups (glucuronic acid, sulfate, methyl groups, amino groups, glutathione). This enhances the water solubility of the starting substance and facilitates its elimination in bile or urine. The most important phase II enzymes are as follows: UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT), N-acetyltransferases (NAT), glutathione-S-transferases (GST), methyltransferases (TPMT) and catechol-O-methyltransferases (COMT). UGT1 and UGT2 are responsible for the glucuronidation of 35 % of drugs that are metabolized by phase II enzymes [7, 9].

The transport of foreign compounds or their phase I and II metabolites out of the cell is designated as **phase III**. Transport proteins, such as multidrug resistance-related proteins (MRP) and organic anion transporter 2 (OATP2) are expressed in the cell membranes of many tissues, particularly in the liver, intestine, kidney and brain. There they form a protective barrier, to prevent the penetration of foreign substances (including drugs) and play a decisive role in the absorption, distribution and excretion of drugs [7].

MDR1 acts there as efflux pump and transports endogenous metabolites, exogenous substrates and toxins in an energy-dependent manner against the concentration gradient out of the cell and into the bile, intestinal space (feces) or urine, so that the drug is eliminated from the organism [14]. If membrane transporters are inhibited or induced, this can lead to changes in the systemic or local concentrations of active substances [15].

In an *in vitro* study, intestinal cells (LS180) were incubated for 48 h with 1 or 10 $\mu\text{mol/L}$ curcumin. It was found that curcumin increased the activity of the available MDR1, but not expression of MDR1 mRNA i.e. formation of new MDR1 [16]. However, this enhanced the efflux of drugs from the cell. In another study, rats were administered 60 mg curcumin per kg BW by gavage for 4 days. Expression of MDR1 protein in the small intestine was reduced by 49 % and in the liver increased by 144 % relative to the control group [12].

These studies show that curcumin can influence phase I and phase II studies, as well as the transporter MDR1 in both *in vitro* experiments and in animal studies. Curcumin can therefore potentially change drug metabolism. As, however, there are differences within the study results, as well as tissue-specific differences, no general conclusion can be drawn as to whether curcumin can induce or inhibit drug metabolism. These studies only provide initial evidence that curcumin can potentially influence drug metabolism, or about the underlying molecular mechanisms. Reliable conclusions about the interactions between curcumin and drugs can only be made on the basis of well-planned animal or human studies that specifically examine the effect of curcumin on drug pharmacokinetics.

Influence of curcumin on drug pharmacokinetics

Pharmacokinetic studies can provide evidence whether the AUC, t_{max} or

C_{max} of a drug (or its metabolites) – and thus the quantity of drug in the body – are changed if curcumin is taken at the same time. ♦ Table 1 gives an overview of the drugs considered. ♦ Tables 2 and 3 summarize the results of the individual studies. Before the individual studies are considered, it should be emphasized that only a few studies have been performed that had the primary role of investigating the effect of curcumin on drug pharmacokinetics.

Animal studies

Rats were given 60 mg curcumin per kg BW for 4 days and on day 5 curcumin plus 30 mg/kg **celiprolol** (an antihypertensive and substrate for MDR1). In comparison to controls, the AUC was increased 1.6-fold and C_{max} 1.9-fold. This allows the conclusion that **curcumin inhibits MDR1**. In the same model, a significant increase in AUC was found for **midazolam** (a sedative and CYP3A4 substrate), but not for MDR1, without any effect on C_{max} . This indicates that curcumin can inhibit CYP3A4. If curcumin was only given on day 5 together with one of the drugs, there was no change in the pharmacokinetics in comparison to the control [12]. Thus curcumin could increase the residence time in blood of the drugs celiprolol and midazolam, and thus enhance their activity or the risk of side effects. However, this only applies if curcumin is taken for several days.

Increases in AUC and C_{max} were also found in another study with the antihypertensive **losartan**. Rats were given 100 mg curcumin per kg BW for 7 days; on day 7, they were also given 10 mg/kg losartan. The AUC and C_{max} of the losartan metabolite EXP3174 were also clearly increased [17]. It was also shown in a rat study that a single dose of 50 or 100 mg/kg curcumin significantly reduced the

Drug	Area of use/Indication	Literature
Celiprolol	Antihypertensive	[12]
Clopidogrel	Anticoagulant	[19]
Diclofenac	Analgesic, Anti-inflammatory	[23]
Everolimus	Immune suppressant	[18]
Glibenclamid	Oral Antidiabetic	[22]
Midazolam	Sedative	[12]
NSAID (<i>non-steroidal anti-inflammatory drugs</i>)	Antirheumatic	[24]
Losartan	Antihypertensive	[17]
Talinolol	Antihypertensive	[21]
Warfarin	Anticoagulant	[19]

Tab. 1: Drugs considered in this review, see too ♦ Tables 2 and 3

AUC and C_{max} of **everolimus** (an immune suppressive and substrate of MDR1 and CYP3A4), and this could lead to a decrease in drug activity. In subsequent cell culture studies, it was shown that curcumin inhibits MDR1 and CYP3A4. However, curcumin metabolites (curcumin glucuronide and sulfate), which are present in blood at higher concentrations than curcumin, activate CYP3A4. Thus in this study, curcumin metabolites had a greater effect on everolimus metabolism than did curcumin [18].

In another study, rats were given 25, 50 or 100 mg/kg curcumin for 7 days. After receiving curcumin on day 7, the rats were given one of the two anticoagulants **warfarin** (0.2 mg/kg BW) or **clopidogrel** (30 mg/kg BW). For both these drugs, the AUC and C_{max} were significantly enhanced in the rats given 100 mg/kg curcumin. However, there was no change in drug activity. The higher drug concentrations might nevertheless enhance side effects [19].

Animal studies can provide initial evidence for drug interactions, but do not accurately reflect foreign substance metabolism in man, as

the activities and expression of the different enzymes and transporters may differ between animals and man [20].

Human studies

The antihypertensive drug talinolol (50 mg) was administered together with 300 mg curcumin per day to 12 healthy volunteers. On day 7, there were significant reductions in AUC and C_{max} for talinolol in comparison to the control without curcumin [21]. This reduction in the concentration of talinolol could theoretically lead to reduced drug activity. However, there have been no studies that have detected changes in pharmacodynamics when talinolol and curcumin are administered together.

In another study, with type 2 diabetics ($n = 8$), it was shown that the oral bioavailability of the common oral antidiabetic glibenclamide was slightly increased after simultaneous intake of curcumin. It was also shown that 11-day intake of curcumin and **glibenclamide** led to significantly lower values for blood glucose concentrations (fasting and postprandial), LDL cholesterol, VLDL cholesterol and triacylglycerides (fasting), as well as an increase in HDL cholesterol, in comparison to glibenclamide treatment alone. This study did show that curcumin has favorable effects on the treatment of type 2 diabetes mellitus. However, there were only 8 participants, so the results must be regarded critically until they have been confirmed in a larger study [22].

Other studies

One limitation of these studies is that only native curcumin was examined, not the formulations with better bioavailability. There is a greater risk of drug interactions with these formulations, as they give greater plasma concentrations

of curcumin than native curcumin does. In order to assess the safety of these preparations, we also covered studies of synergism between these formulations and other drugs. Such studies only provide preliminary evidence and would have to be supported by well-planned pharmacokinetic investigations.

In one study, 45 patients with rheumatoid arthritis (chronic inflammation of the joints) were administered for 8 weeks either 50 mg **diclofenac**, an analgesic and anti-inflammatory, or 500 mg curcumin, as the formulation BCM-95TM, or both. BCM-95TM contains not only curcumin, but also curcuma oils to enhance its bioavailability. At the beginning and end of the study, the current state of the disease and its progression were documented with the Disease Activity Score (DAS) and pain sensitivity and joint swelling were documented in accordance with the criteria of the American College of Rheumatology (ACR). DAS and ACR significantly improved in all three groups. No synergy was observed between curcumin and diclofenac, although curcumin did not decrease the activity of curcumin [23].

In another study, patients with osteoarthritis were given the best possible standard therapy for 8 months with **non-steroidal anti-inflammatory drugs**, with or without additional curcumin (200 mg/day), in the form of Meriva, a formulation with enhanced bioavailability (see [1]). It was found that additional curcumin improved clinical parameters such as pain, stiffness and quality of life and reduced the levels of the inflammation markers interleukins 1 and 6. In the group treated with curcumin, there were reductions in the intake of NSAID (-63 %) and of other analgesics (-43 %), so that there may be synergy between curcumin and NSAID in this population [24].

Another study was performed on patients with depression. These were given either 1 g curcumin (BCM-

95TM, $n = 16$), 20 mg of the antidepressive fluoxetine ($n = 17$) or a combination of curcumin and **fluoxetine** ($n = 18$) for a period of 6 weeks. In all three groups, there was a non-significant improvement in depression and to the same extent. There was thus no evidence that curcumin either enhanced or impaired the activity of fluoxetine [25]. Thus, the current evidence indicates that curcumin in formulations with increased bioavailability does not impair the activity of the other drugs. However, the available studies do not allow any statement to be made about the safety of the curcumin formulations with increased bioavailability in combination with other drugs.

Conclusion and outlook

In vitro and *in vivo* studies show that curcumin can influence transporters and enzymes that metabolize foreign compounds, and can also modify drug pharmacokinetics. However, there are some limitations to the studies described here. Thus, the *in vitro* and animal studies do not allow any reliable conclusion about the use of curcumin formulations in man, as there are often non-specific effects *in vitro* and curcumin concentrations may be used that can never be reached *in vivo*. Animal models are of limited relevance, as metabolism of foreign compounds is not identical in animals and in man. Moreover, the studies also differ with respect to the purity or curcuminoid composition of the test substances or formulation, which makes direct comparison more difficult. Plant extracts are normally mixtures of many different substances and this makes it difficult or impossible to assign the observed effects to a specific substance. In addition, few studies in man have been performed that specifically investigate the effect of curcumin on drug pharmaco-

Species	Curcumin dose (mg/kg body weight [BW])	Drug	Intervention	AUC [ng/mL x h]**		C _{max} [ng/mL]		t _{max} [h]		Conclusion	Literature
				Drug alone	Drug + Curcumin	Drug alone	Drug + Curcumin	Drug alone	Drug + Curcumin		
Sprague Dawley rats	60	Celiprolol (30 mg/kg BW)	5 days curcumin; on day 5, the drug was administered 30 min after ingestion of curcumin.	2 140.0 ± 187.9 (0–8 h)	3 440.3 ± 210.5* (0–8 h)	492.7 ± 33.2	960.1 ± 93.4*	2.0 ± 0.0	2.0 ± 0.0	Curcumin significantly increased the AUC and C _{max} of celiprolol.	[11]
	60	Midazolam (20 mg/kg BW)		255.1 ± 27.4 (0–4 h)	657.0 ± 135.6* (0–4 h)	123.2 ± 14.8	259.2 ± 38.7	0.5 ± 0.1	0.5 ± 0.1	Curcumin significantly increased the AUC of midazolam.	
	60	Celiprolol (30 mg/kg BW)	Curcumin was administered simultaneously with the drug.	2 140.0 ± 187.9 (0–8 h)	2 347.63 ± 287.8 (0–8 h)	492.7 ± 33.2	458.2 ± 78.0	2.0 ± 0.0	1.8 ± 0.1	Simultaneous administration of curcumin without pretreatment with curcumin did not affect the pharmacokinetics of celiprolol.	
	60	Midazolam (20 mg/kg BW)		255.1 ± 27.4 (0–4 h)	470.0 ± 88.4 (0–4 h)	123.2 ± 14.8	239.7 ± 46.8	0.5 ± 0.1	0.5 ± 0.1	The pharmacokinetics of midazolam were not influenced by simultaneous administration with curcumin without pretreatment with curcumin.	
Wistar rats	100	Losartan (10 mg/kg BW)	7 days curcumin, on day 7, the drug was administered 30 min after curcumin dosage.	2 080 ± 837 (0–12 h)	3 460 ± 1 350 (0–12 h)	457 ± 63.1	1 660 ± 892*	0.4 ± 0.1	0.4 ± 0.1	Curcumin significantly increased the C _{max} of losartan.	[17]
		Metabolite EXP3174 (measured, but not administered)		766 ± 416 (0–12 h)	1 460 ± 818* (0–12 h)	108 ± 61.1	341 ± 187*	3.3 ± 2.3	1.9 ± 0.6	Curcumin significantly increased the AUC and C _{max} of the metabolite EXP3174.	
Sprague Dawley rats	50	Everolimus (0.5 mg/kg BW)	Curcumin was administered at the same time as the drug.	98 262 ± 15 408 (0–9 h)	28 908 ± 19 668* (0–9 h)	6.0 ± 1.8	1.4 ± 0.9*	-	-	Both high and lower doses of curcumin significantly increased the AUC and C _{max} of everolimus.	[18]
	100	Everolimus (0.5 mg/kg BW)		98 262 ± 15 408 (0–9 h)	27 960 ± 19 812* (0–9 h)	6.0 ± 1.8	1.4 ± 1.2*	-	-		
Wistar rats	25	Warfarin (0.2 mg/kg BW)	7 days curcumin, on day 7, the drug was administered 30 min after curcumin dosage.	16 680 ± 6 900 (0–∞)	21 930 ± 11 070 (0–∞)	1 140 ± 330	1 490 ± 380	3.2 ± 4.3	1.3 ± 0.3	The highest dose of curcumin increased the AUC and C _{max} of warfarin and clopidogrel. However, there was no change in the pharmacodynamics.	[22]
	50	Warfarin (0.2 mg/kg BW)		16 680 ± 6 900 (0–∞)	16 340 ± 5 330 (0–∞)	1 140 ± 330	1 150 ± 290	3.2 ± 4.3	1.7 ± 1.3		
	100	Warfarin (0.2 mg/kg BW)		16 680 ± 6 900 (0–∞)	26 640 ± 5 840* (0–∞)	1 140 ± 330	1 710 ± 530*	3.2 ± 4.3	2.7 ± 2.6		
	25	Clopidogrel (30 mg/kg BW)		142 100 ± 64 540 (0–∞)	144 520 ± 16 410 (0–∞)	17 940 ± 6 840	15 410 ± 3 100	1.4 ± 0.6	1.0 ± 0.0		
	50	Clopidogrel (30 mg/kg BW)		142 100 ± 64 540 (0–∞)	129 380 ± 40 170 (0–∞)	17 940 ± 6 840	18 460 ± 6 360	1.4 ± 0.6	1.0 ± 0.6		
	100	Clopidogrel (30 mg/kg BW)		142 100 ± 64 540 (0–∞)	228 940 ± 71 790* (0–∞)	17 940 ± 6 840	32 610 ± 9 180*	1.4 ± 0.6	1.13 ± 0.5		

Tab. 2: Influence of curcumin on the pharmacokinetics of drugs in animal models

* p < 0.05, significantly different from control (drug without curcumin)

** Hours given after AUC signify the period for which the AUC was calculated.

AUC: area under the curve; C_{max}: maximum plasma concentration; t_{max}: time to reach the maximum plasma concentration

Study participants	Curcumin dose [mg]	Drug	Intervention	AUC [ng/mL x h]		C _{max} [ng/mL]		t _{max} [h]		Conclusion	Literature
				Drug alone	Drug + Curcumin	Drug alone	Drug + Curcumin	Drug alone	Drug + Curcumin		
12 healthy men	300	Talinolol (50 mg)	7 days curcumin, on day 7, curcumin was administered simultaneously to the drug.	1 763.7 ± 377.5 (0–60 h)	1 192.1 ± 309.7*	147.8 ± 63.8	106.4 ± 39.9*	2.0 ± 0.7	1.9 ± 0.7	Curcumin reduced the AUC and C _{max} of talinolol.	[19]
8 Type-2-diabetics	475	Glibenclamid (5 mg)	Curcumin and drug were taken for 11 days.	1 728 000 ± 68 750 (0–12 h)	1 792 000 ± 50 930 (0–12 h)	321 100 ± 11 680	327 800 ± 6 850	2.6 ± 0.3	2.4 ± 0.3	Curcumin tended to increase the AUC and C _{max} of glibenclamide and led to significantly lower blood lipid concentrations and blood glucose concentrations than with glibenclamide alone.	[21]

Tab. 3: Influence of curcumin on the pharmacokinetics of drugs in human studies
 AUC: area under the curve; C_{max}: maximal plasma concentration; t_{max}: time to reach the maximal plasma concentration

netics, and the number of participants is generally too low. Thus, even though none of the cited studies detected adverse interactions after curcumin intake, caution is appropriate when curcumin is administered together with drugs. This must be discussed with the responsible physician until reliable data are available. This would require large human studies to investigate how the pharmacokinetics and pharmacodynamics of drugs are influenced by curcumin and its formulations with enhanced bioavailability. It should also be pointed out that older people often take more than one drug. This multimедication can lead to complex interactions between curcumin and these drugs, or between different drugs. Therefore future studies should also investigate how curcumin influences the pharmacokinetics and pharmacodynamics of drugs which are taken simultaneously. Additional attention should also be paid in cell culture, animal and human studies to the biological activity of curcumin metabolites (phase II metabolites), as these are present in circulation at much higher concentrations than the parent compound.

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Conflict of Interest
 The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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DOI: 10.4455/eu.2015.037