Drug Safety 1998 Apr; 18 (4): 251-272
0114-5916/98/0004-0251/$11.00/0

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Drug Interactions with Grapefruit Juice
Extent, Probable Mechanism and Clinical Relevance

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Contents

Summary

Concomitant intake with grapefruit juice increases the concentrations of many drugs in humans. The effect seems to be mediated mainly by suppression of the cytochrome P450 enzyme CYP3A4 in the small intestine wall. This results in a diminished first pass metabolism with higher bioavailability and increased maximal plasma concentrations of substrates of this enzyme. The effect was most pronounced in drugs with a high first pass degradation and in many cases has the clear potential to reach clinical relevance, as shown by an occasional change in drug effects or tolerability. For felodipine, nitrendipine, nisoldipine and saquinavir, the interaction was most marked with median increases of area under the curve (AUC) and/or the maximum (peak) plasma drug concentration after single-dose administration (C_{max}) values exceeding 70% of respective control periods. Less pronounced, but possibly relevant, concentration increases were found for nifedipine, nimodipine, verapamil, cyclosporin, midazolam, triazolam and terfenadine. This list is not complete because many drugs have not been studied yet.

The components of grapefruit juice which are the most probable causes of the interaction are psoralen derivatives, but the flavonoid naringenin may also contribute. Concomitant grapefruit juice intake does not generally decrease the variability of drug pharmacokinetic parameters. Therefore, it is recommended that

patients refrain from drinking grapefruit juice when they are taking a drug that is extensively metabolised, unless a lack of interaction has already been demonstrated for that drug. It is also recommended that drugs possibly interacting with grapefruit juice should be appropriately labelled.

A place for grapefruit juice as a drug-sparing agent in treatment involving expensive medicine cannot be derived from the information currently available on grapefruit juice interactions.

In an interaction study of felodipine with alcohol (ethanol), where the study participants received grapefruit juice to blind for the administration of alcohol, Bailey and colleagues[1] observed that felodipine concentrations were considerably higher than those reported previously for the dose of felodipine administered. Following from this chance finding, systematic studies of the effect of grapefruit juice coadministration have been carried out for a wide range of drugs. The main finding has been that grapefruit juice increases the bioavailability of many drugs, but also it prolongs the metabolic elimination of a few drugs.[2,3] Mean changes in drug concentrations exceeded 30% in most studies and surpassed 100% in several of them, suggesting that grapefruit juice drug interactions are not negligible.

The objectives of this review are to summarise the current knowledge of grapefruit juice interactions, to evaluate the risks they may cause, and to discuss possible benefits and problems related to intentional inhibition of drug metabolism by the juice from a fruit with the promising name *Citrus paradisi* or by its constituents.

1. Observed Drug Interactions with Grapefruit Juice in Volunteers and in Patients

1.1 Drugs Subject to the Interaction and Extent of Effect

The first studies of the effect of grapefruit juice on drug metabolism were conducted with the dihydropyridine calcium antagonists. Once the presumed main mechanism of action became apparent, i.e. inhibition of CYP3A mediated first pass metabolism (see section 2.1), cyclosporin and terfenadine were recognised as important targets for the effects of grapefruit juice. Besides CYP3A substrates, several other drugs have also been tested.

For the purposes of this review, studies were mainly identified by a MEDLINE search using 'grapefruit' as a keyword. Data from those studies where both drug and grapefruit juice administration were described in detail are summarised in tables I to V.[4-36] In all these studies, a cross-over design including a control period with concomitant administration of water instead of grapefruit juice was applied. With a few exceptions, the order of periods was also randomised. Blinding was obviously not possible. However, statistical evaluation and description of the grapefruit juice effect was not uniform. Where available, mean and range or confidence interval of the effect of grapefruit juice in the individual study was given, calculated as the percentage change in the respective pharmacokinetic parameter. For those studies where only mean values of parameters were published, the change of the mean values by grapefruit juice is listed in the tables. These 2 approaches are not equivalent but are closely related and are expected to provide similar estimates of the average effect.

1.1.1 Felodipine

The most studies have been conducted with the dihydropyridine calcium antagonist felodipine (table I) and doses equivalent to 200 to 500ml single strength grapefruit juice have been administered. In the 9 comparative studies[4-9] where the drug was given together with a single portion of grapefruit juice, the mean increase in AUC ranged from 43 to 234% of the control period, the median AUC growth was 125%. The mean increase in C_{max} values ranged from 70 to 225% (median 147%). Because both AUC and C_{max} were changed to a similar extent, concomitant intake of grapefruit juice with

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felodipine would be equivalent to a 2- to 3-fold increase in the felodipine dose for most patients requiring the drug. The effect of grapefruit juice on the time to reach maximum concentration following drug administration (t_{max}) was equivocal. An increase was also observed consistently for the concentrations of the main metabolite of felodipine, i.e. dehydrofelodipine, although the extent of this increase was smaller than that for the parent compound (see table I). The elimination half-life of felodipine was not changed by grapefruit juice.

A clear relationship between extent of the effect and felodipine dose was not observed. Although the mean effect of double strength juice was higher than that of the single strength juice in 1 study where 2 grapefruit juice doses were compared, statistical significance was not reached.[4] In other studies, low grapefruit juice doses also exerted pronounced effects (table I). In 1 study with several days of grapefruit juice administration before felodipine intake, mean values of AUC and C_{max} were increased by 211 and 335%, respectively.[7] Thus, some grapefruit juice dose/effect relationship, which is possibly cumulative, may be present. However, other factors, such as composition of the juice, are probably of similar importance.

Another important factor, that was addressed in the study of Lundahl and colleagues,[6] appears to be the timing of juice administration relative to drug intake. The effect on AUC and C_{max} was most pronounced when the grapefruit juice was given with the drug or 1 hour before felodipine administration, and steadily declined with an increased time lag. A minor, but significant, effect on felodipine C_{max} was still present when felodipine was given 24 hours after the glass of grapefruit juice (table I).

For those studies where grapefruit juice effects on felodipine pharmacodynamics were also monitored,[4,6,10] a pronounced increase in felodipine plasma concentrations was associated with an increase in the effects of felodipine on lowering blood pressure and/or increasing heart rate and these effects occasionally reached statistical significance at some time points close to the t_{max} values for felodipine. This was shown in a small study in hypertensive men[10] but was also seen in healthy volunteers[4,6] in whom the pharmacodynamic effects of dihydropyridines usually are very limited due to counter-regulation.[37] Grapefruit juice, primarily at high doses, was also related to an increased incidence of adverse effects such as headaches and flushing.[4,6,10] These findings confirm what could be expected from the extent of the pharmacokinetic interaction. Thus, there is strong evidence that the interaction between felodipine and grapefruit juice has clinical relevance and needs to be taken into account for individual treatment.

1.1.2 Calcium Antagonists other than Felodipine

With the exception of nifedipine[10,13,14] and nitrendipine,[17,18] only 1 study was found for each of amlodipine,[11] diltiazem,[12] nimodipine,[15] nisoldipine[16] and verapamil[19] (table II). In these studies, grapefruit juice was found to change the pharmacokinetics of most of these calcium antagonists. In all studies involving oral drug administration, a mean increase of AUC and C_{max} was found, although this increase in some cases was only minor and failed to reach statistical significance (table II).

Taking into account that a single study provides only limited information on the true mean extent of interaction (see section 1.1.1), it appears that amlodipine[11] and diltiazem[12] are not subject to a relevant grapefruit juice interaction. In contrast, for all the other calcium antagonists tested, either AUC or C_{max} (in most cases both) increased by more than 50% (median of studies for the respective drug) when given with grapefruit juice. No difference in grapefruit juice effects on the kinetics of parent drug and metabolite enantiomers was found following chiral drug measurements for nitrendipine[18] and verapamil (U. Fuhr et al., unpublished observations).[19] As has been seen for felodipine, there was no consistent change in t_{max} or elimination half-life of parent drug and an increase in the concentrations of the metabolites was observed, but these increases did not reach those

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Table I. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of a single oral dose of felodipine

Dose (mg)	Amount of GJ (ml)[a]	Time of GJ administration[b]	Study population[c]	Mean change as % of control (range)				Variation with/without GJ[d]		Change of PD with GJ	Ref.
				AUC	C_{max}	t_{max}	metabolite AUC	AUC	C_{max}		
5	200	0	9, mean age 44y	+185[e]	147[e]	62	+82[e]	0.87	0.80	HDEs ↑ with GJ	4
5	400	0	9, mean age 44y	+234[e]	+191[e]	54	+109[e]	0.87	0.81	HDEs and AEs ↑ with GJ	4
5	200	0	9, young	+106[e] (+23 to +230)	+70[e] (+27 to +210)	–19	+30 (–18 to +63)	0.80	1.14	NA	5
10 SR	200	0	9, young	+43[e]	+92[e]	–29	+25[e]	1.00	0.98	NS	6
10 SR	200	–1	9, young	+46[e]	+99[e]	–35	+33[e]	1.00	0.99	NS	6
10 SR	200	–4	9, young	+42[e]	+54[e]	–18	+20[e]	1.00	0.99	Effect on BP ↑	6
10 SR	200	–10	9, young	+25[e]	+54[e]	3	+15	1.00	0.99	NS	6
10 SR	200	–24	9, young	+13	+32[e]	0	+13	1.00	0.98	NS	6
10	232	0	10, young	+116[e]	+225[e]	NA	NA	0.33[e]	0.30	NA	7
10 SR	250	0	12, young	+194[e] (–1 to +550)	+143[e] (+23 to +298)	–20	+44[e]	0.64	0.95	NA	8
20 SR	250	0[f]	12, young	+125[e] (+3 to +369)	+170[e] (+16 to +477)	–7	+54[e]	0.95	0.85	NA	9
20 SR	250	0[g]	12, young	+119[e]	+155[e]	–17	NA	1.28	1.57	NA	9
5	500	0	6, hypertensive	+184[e] (+64 to +369)	+123[e]	+91[e]	+74[e]	0.75	0.67	Effect on BP ↑	10
10	232	8 hourly[h]	10, young	+211[e]	+335[e]	NA	NA	0.53[e]	0.58[e]	NA	7

a For double strength juice, volumes administered were multiplied by 2.

b Hours relative to drug administration.

c All healthy, nonsmoking men unless otherwise stated.

d Variation for each period was calculated as standard deviation (SD), standard error of the mean (SEM) or confidence interval (CI) divided by the mean or point estimate, the value in the column is the ratio of this variation between grapefruit juice and control period.

e Significant ($p < 0.05$) grapefruit juice effects.

f First period.

g Second period.

h Administered from –120 hours to +16 hours.

Abbreviations and symbol: AE = adverse effects; AUC = area under the plasma concentration versus time curve of the unchanged drug; BP = blood pressure; C_{max} = maximal plasma concentration of unchanged drug; GJ = grapefruit juice; HDE = haemodynamic effects; NA = not available; NS = no significant change; PD = pharmacodynamics; SR = slow release; t_{max} = time at which C_{max} occurred; y = years; ↑ = increased.

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Table II. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of single oral doses of calcium antagonists other than felodipine

Drug	Regimen	Amount of GJ (ml)[a]	Time of GJ administration[b]	Study population[c]	Mean change as % of control (range unless otherwise stated)				Variation with/without GJ[d]		Change of PD with GJ	Ref.
					AUC	C_{max}	t_{max}	metabolite AUC	AUC	C_{max}		
Aml	1 × 5mg PO	250	0	12, young	+16[e] (–20 to +55)	+15[e] (–21 to +65)	+9	NA	1.11	1.05	No effect on HD	11
Dil	1 × 120mg PO	200	0, +2, +4, +8 and +12	9, young	+10	+2	+4	–5	0.71	1.35	No effect on HD	12
Nif	1 × 10mg PO	500	0	6, hypertensive	+34[e] (+8 to +69)	+17	–10[e]	+22[e]	1.22	0.67	BP effect unchanged	10
Nif	1 × 10mg PO	400	–2 and 0	8 (5 men), young	+58[e]	+16	+97	+17	1.02	1.05	NA	13
Nif	1 × 2.5mg IV	400	–2 and 0	8 (5 men), young	+14	NA	NA	NA	1.14	NA	NA	13
Nif SR	1 × 20mg PO	200	0, +2, +4, +8 and +12	12, young	+103[e] (+48 to +265)	+94[e] (–23 to +259)	+73[e]	+66[e] (–30 to +236)	0.85	0.91	NA	14
Nim	1 × 30mg PO	250	0	8 (4 smo), young	+51[e] (90% CI +14 to +100)	+24 (90% CI –24 to +101)	+67	↑ in 2 primary metabolites, no change in a secondary metabolite	1.19	1.54	NA	15
Nis SR	1 × 20mg PO	250	0	12, young	+98[e] (–19 to +582)	+306[e] (+7 to +736)	–53[e]	NA	1.52	1.00	Effect on HR↑	16
Nit	1 × 10mg PO	200	0	9, young	+40[e]	+40	+77	0	0.96	NA	NA	17
Nit	1 × 20mg PO	150	–15, –10, –0.25, +5 and +10	9, young	+106[e] (95% CI +64 to +158)	+99[a] (95% CI +50 to +164)	+27	+23	1.42	1.14	HD and AE unchanged	18
Ver SR	120mg PO bid for 7 days	250	–48, –45, –40, –36, –24, –21, –16, –12, 0, +3, +8 and +12	24 (12 men; 6 smo for each gender), young	+42[e] (90% CI +24 to +65)	+61[e] (90% CI +34 to +92)	+0	+28	0.86	0.82	Max. mean PR change +6msec (90% CI 0 to 15.5)	19

a For double strength juice, volumes administered were multiplied by 2.

b Hours relative to drug administration.

c All healthy, nonsmoking men unless otherwise stated.

d Variation for each period was calculated as standard deviation (SD), standard error of the mean (SEM) or confidence interval (CI) divided by the mean or point estimate, the value in the column is the ratio of this variation between grapefruit juice and control period.

e Significant ($p < 0.05$) grapefruit juice effects.

Abbreviations and symbol: AE = adverse effects; Aml = amlodipine; AUC = area under the plasma concentration versus time curve of the unchanged drug; bid = twice daily; BP = blood pressure; C_{max} = maximal plasma concentration of unchanged drug; Dil = diltiazem; GJ = grapefruit juice; HD = haemodynamics; HR = heart rate; IV = intravenous; NA = not available; Nif = nifedipine; Nim = nimodipine; Nis = nisoldipine; Nit = nitrendipine; PD = pharmacodynamics; PO = oral; PR = PR interval; smo = cigarette smoker; SR = slow release; t_{max} = time at which C_{max} occurred; Ver = verapamil; y = years; ↑ = increased.

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levels seen with the respective parent drug (table II).

It is not clear how the significant pharmacokinetic changes in this group of drugs translate into alterations in pharmacodynamics. A mean increase of 34% in nifedipine AUC without a significant change of C_{max} was not related to a more pronounced haemodynamic effect in 6 men with hypertension.[10] Likewise, a doubling of both parameters for nitrendipine when given with grapefruit juice left haemodynamic effects and incidence of adverse events unchanged.[18] In contrast, the increase in heart rate at 4 hours after administration of nisoldipine was more pronounced when the drug was given with grapefruit juice.[16] Long term coadministration of grapefruit juice with steady state verapamil was associated with a transient prolongation of the ECG PR interval to more than 0.24 sec in 4 volunteers, and the mean increase of 6 msec in the maximal difference of the PR interval between grapefruit juice and control periods just failed to reach statistical significance (U Fuhr et al., unpublished observations).[19] Again, these studies, with 1 exception, were conducted in healthy volunteers where haemodynamic effects, at least for dihydropyridine calcium antagonists, are usually less pronounced than in hypertensive patients,[37] and drug effects were not monitored in most cases. The lack of an apparent increase of drug effects by grapefruit juice in these studies does not, therefore, preclude the fact that, in patients with hypertension, a pronounced change in drug concentrations will be accompanied by an according change in drug effect.

1.1.3 Cyclosporin

Particular attention has been paid to the interaction between cyclosporin and grapefruit juice, because cyclosporin is metabolised by the same enzymes as calcium antagonists (see section 2.1) and because of its narrow therapeutic range. For this drug, the majority of studies were conducted in patients who were taking cyclosporin on a regular basis (table III).[20-26]

The mean increase in the AUC for oral cyclosporin measured in the 12-hour dosage interval ranged from 8 to 60% of the control period, the median was 34%. C_{max} mean values were increased by between 10 and 43% (median 22%). The effect on t_{max} was again equivocal.

In the 3 studies where the concentrations of cyclosporin metabolites were measured, a significant AUC increase was observed in 2 of them[25,26] but not in the third[24] (table II). Since metabolite concentrations were obtained from the difference in cyclosporin concentrations, as measured using a method specific for the parent drug and a nonspecific method which also includes cyclosporin metabolites, these indirect results must be regarded with caution. However, it may be important to know what the true effect of grapefruit juice on cyclosporin metabolites is, because these effects might be relevant for toxicity of the drug.[38]

A relationship between grapefruit juice administration schemes and extent of effect on cyclosporin is not obvious (table III).

It is not probable that monitoring the effects of cyclosporin will reveal tolerability changes, e.g. an increase in serum creatinine level, upon short term concentration increases. However, from the 2 studies where effects were noted,[24,25] 1 patient experienced adverse effects such as tremor, nausea, lightheadedness and nonspecific abdominal pain that occurred when taking grapefruit juice.[25]

Taking together all the results for cyclosporin, this interaction with grapefruit juice should not be ignored in clinical practice (see section 4.2).

1.1.4 Terfenadine and Astemizole

The antihistamines, terfenadine and astemizole, are prodrugs that usually undergo extensive first pass metabolism.[39] The parent compounds prolong the QT interval, predisposing for ventricular arrhythmia. From instances of terfenadine overdose, it is known that high plasma concentrations of unchanged terfenadine may precipitate severe or even fatal cardiac arrhythmia.[39] Accordingly, it appears that increased terfenadine concentrations due to interactions with drugs inhibiting CYP3A4 such as ketoconazole or macrolide antibacterials are associated with an increased risk for adverse cardiac effects.[40-42] Serious concern has therefore

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Table III. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of cyclosporin

Regimen	Amount of GJ (ml)[a]	Time of GJ administration[b]	Study population[c]	Mean change as % of control (range)				Variation with/without GJ[d]		Change of PD with GJ	Ref.
				AUC	C_{max}	t_{max}	metabolite AUC	AUC	C_{max}		
Median 113mg PO bid	200	0	6 RTP, mean 42y	+19[e]	+27[e]	NA	NA	0.42	0.94	NA	20
Median 175mg PO bid	232	0	10 RTP, mean 44y	+24[e] (–7 to +93)	+4 (–33 to 160)	+93[e]	NA	0.94	0.92	NA	21
1 × 300mg PO	250	0	14 (8 men) young	+43[e]	+18[e]	+21	NA	1.05	1.21	NA	22
1 × 7.5 mg/kg bw IV	250	0 and +2	10, young	+7	NA	NA	NA	0.73	NA	NA	23
1 × 7.5 mg/kg bw PO	250	0 and +2	10, young	+60[e]	+43[e]	+31[e]	NA	0.81	0.49	NA	23
Median 300mg PO od	150	3 hourly[f]	12 (8 men) RTP	+8	+22[e]	–23	–5	1.01	0.76	No effect on AEs	24
Mean 1.7 mg/kg bw PO bid	150	12 hourly[g]	9 (5 men) AIP, mean 36y	+50[e] (+9 to +125)	+42 (–44 to +181)	NAC	+236[e] (+19 to +1770)	1.01	1.32	AE in 1 patient with GJ	25
Mean 1.8 mg/kg bw PO bid	175	12 hourly[g]	10 (5 men) RTP, mean 48y	+34[e]	+10	NAC	+55[e]	1.98	2.07	NA	26

a For double strength juice, volumes administered were multiplied by 2.

b Hours relative to drug administration.

c All healthy, nonsmoking men unless other wise stated.

d Variation for each period was calculated as standard deviation (SD), standard error of the mean (SEM) or confidence interval (CI) divided by the mean or point estimate, the value in the column is the ratio of this variation between grapefruit juice and control period.

e Significant ($p < 0.05$) grapefruit juice effects.

f Administered from –7.5 hours until +22.5 hours.

g Administered from –144 hours until 0 hours.

Abbreviations: AE = adverse effects; AIP = autoimmune patients; AUC = area under the plasma concentration versus time curve of the unchanged drug; bid = twice daily; bw = bodyweight; C_{max} = maximal plasma concentration of unchanged drug; GJ = grapefruit juice; IV = intravenous; NA = data not available; NAC = no apparent change; od = once daily; PD = pharmacodynamics; PO = oral; RTP = renal transplant patients; t_{max} = time at which C_{max} occurred; y = years.

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been expressed with respect to the interaction between terfenadine and grapefruit juice, which might result in a relevant accumulation of the arrhythmogenic unchanged terfenadine in the plasma of individual patients.[43,44]

A number of recent studies of the effects of grapefruit juice on the pharmacokinetics and pharmacodynamics of terfenadine have been performed (table IV);[27-29] no such investigations have yet been published for astemizole.

In all the terfenadine studies, an increase in terfenadine and terfenadine carboxylate (fexofenadine) plasma concentrations was seen. The median AUC gain for the metabolite was 28% (table IV). It is more difficult to assess to what extent grapefruit juice elevates plasma concentrations of the parent drug, because usually concentrations of terfenadine when taken without an inhibitor are below the limit of detection of 5 μg/L.[27-29] The number of samples with measurable terfenadine concentrations was higher in grapefruit juice periods for all studies, clearly indicating the presence of an interaction.

As observed with felodipine, the timing of juice administration relative to drug intake seems to be important. In 1 study,[29] concomitant intake of drug and juice caused a more pronounced interaction than grapefruit juice administration 2 hours after drug intake.

Heart rate corrected QT intervals (QTc) were monitored in all studies. QTc interval was unchanged following single administration of grapefruit juice and terfenadine,[27] whereas long term intake of terfenadine with grapefruit juice resulted in prolonged QTc intervals.[28,29] This pharmacodynamic consequence of grapefruit juice, however, was less pronounced than that produced by coadministration of erythromycin or imidazole antifungal agents with terfenadine.[45,46] Whether this untoward effect is more severe in patients with chronic heart failure or other conditions where the QT interval is already prolonged remains to be investigated. However, the possibility exists that this interaction has already caused fatal arrhythmia in one individual.[43] Furthermore, epidemiological

Landscape table

Table IV

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Table IV. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of oral terfenadine. Since terfenadine is a prodrug, no pharmacokinetic data for the parent substance are available

Regimen	Amount of GJ (ml)[a]	Time of GJ administration[b]	Study population[c]	Mean C_{max} change (% of control)	Mean metabolite AUC change as % of control (range)	Change of PD with GJ	Ref.
1 × 60mg	250	0	12, young	↑ in all	+43[d]	No change in QTc interval	27
1 × 60mg	500	0	12, young	↑ in all	+33[d]	No change in QTc interval	27
60mg bid for ≈1 week	480	12 hourly[e]	6 (3 men) healthy TPMs	↑ in all	+28[d]	↑ QTc interval	28
60mg bid for 14 days	480	12 hourly[f]	6 volunteers	↑ in all	+55[d] (+26 to +112)	Small ↑ in QTc interval	29
60mg bid for 14 days	480	12 hourly[g]	6 volunteers	↑ in 2	+22[d] (+11 to +88)	No change in QTc interval	29

a For double strength juice, volumes administered were multiplied by 2.

b Hours relative to drug administration.

c All healthy, nonsmoking men unless otherwise stated.

d Significant ($p < 0.05$) grapefruit juice effects.

e Administered from –120 hours until 0 hours.

f Administered from –144 hours until 0 hours.

g Administered from –142 hours until +2 hours.

Abbreviations and symbol: AUC = area under the plasma concentration versus time curve of the unchanged drug; bid = twice daily; C_{max} = maximal plasma concentration of unchanged drug; GJ = grapefruit juice; PD = pharmacodynamics; QTc = QT interval (corrected for heart rate); TPM = terfenadine poor metaboliser; y = years; ↑ = increased.

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studies suggest that other antihistamines may also prolong the QT interval when taken with CYP3A4 inhibitors.[42] Thus, although the true risk is difficult to quantify, terfenadine and possibly other antihistamines should not be taken with grapefruit juice.

1.1.5 Other Drugs

Methylxanthines

Theophylline and caffeine, both metabolised primarily by the hepatic cytochrome P450 enzyme CYP1A2,[47] are 100% bioavailable. Therefore, a decrease in first pass metabolism is not possible. In one caffeine study with repeated grapefruit juice administration, caffeine clearance was decreased by a mean of 23%, resulting in a corresponding AUC increase.[3] This result was in agreement with *in vitro* inhibition experiments,[3] but was not confirmed in 2 other studies with caffeine or theophylline, where grapefruit juice had no effect[30,31] (table V).

Steroid Hormone Derivatives

Data are available for 3 compounds (see table V), which are characterised by a pronounced first pass metabolism.[39] For the estradiol derivatives, the addition of grapefruit juice led to significant increases in the parent drug concentrations[32] or its metabolite.[33] The studies were not designed to monitor drug effects. The pharmacokinetic results of these studies, which are supported by *in vitro* data[48,49] and by *in vivo* effects of grapefruit juice on the oxidation of cortisol, an endogenous substrate for the cytochrome P450 enzyme 11β-hydroxysteroid dehydrogenase,[50] clearly show that grapefruit juice has the potential to modify steroid metabolism. The relevance of this finding is not clear, but it was speculated that grapefruit juice may thus mediate a mineralocorticoid effect at high doses.[50]

Benzodiazepines

Both oral midazolam and triazolam showed a mean AUC increase with grapefruit juice of approximately 50%, accompanied by significantly elevated C_{max} values (table V).[34,35] Elimination half-life was unchanged, but t_{max} was also significantly prolonged. In both studies, the typical CNS effects of benzodiazepines were more pronounced in the grapefruit juice period.[34,35] In contrast, another study found that the effects of single oral doses of midazolam 10mg and triazolam 0.25mg were essentially unchanged by concomitant grapefruit juice administration.[51] However, the study design in this case precludes clear conclusions. Although additional investigations would be desirable, it appears that the interaction between grapefruit juice and midazolam or triazolam deserves more public attention. One may speculate that some of the many road traffic accidents attributed to the use of benzodiazepines[52] could be due to a more pronounced effect of these agents when taken with grapefruit juice.

Miscellaneous Drugs

In a study of the effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of quinidine, t_{max} prolongation was the only effect seen.[36] No change was found for the QT interval.

A study of the effects of grapefruit juice on saquinavir has been conducted (C. Möcklinghoff, et al., unpublished observation), and although this study has not been published it has been made available on the internet. In this study, grapefruit juice caused a clear and dose-dependent increase in saquinavir AUC and C_{max} (see table V). Although a decreased variability of pharmacokinetic parameters of saquinavir was also reported with grapefruit juice, the manufacturer does not recommend grapefruit juice as a means to improve the low bioavailability of the drug.

Coumarin, a specific substrate for the cytochrome P450 isoform CYP2A6, showed a delayed renal excretion of its main metabolite, i.e. 7-hydroxycoumarin, when administered with grapefruit juice.[53,54]

Finally, in a case report, clomipramine and desmethylclomipramine concentrations were higher with concomitant grapefruit juice in 1 patient, resulting in clinical improvement, but not in a second.[55]

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Table V. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of other drugs

Drug	Regimen	Amount of GJ (ml)[a]	Time of GJ administration[b]	Study population[c]	Mean change as % of control (range unless otherwise stated)				Variation with/without GJ[d]		Change of PD with GJ	Ref.
					AUC	C_{max}	t_{max}	metabolite AUC	AUC	C_{max}		
Methylxanthines												
Caf	1 × 165mg PO in coffee	300	–0.5,+6,+12, +18,+24, +30	12 (4 men); 6 smokers	+28[e] (95% CI +11 to +46)	NA	NA	NA	1.29	NA	NA	3
Caf	1 × 3.3 mg/kg bw PO in coffee	200	0	10, young	+4	NA	NA	NA	1.36	NA	No change in HD	30
Caf	1 × 3.3 mg/kg bw PO in coffee	200	–15, –9, –2, 0, +2, +6	6, young	+6	NA	NA	NA	0.61	NA	No change in HD	30
Theo	1 × 200mg PO	100	0, +1	12, young	+2 (90% CI –5 to +11)	–10 (90% CI –19 to 0)	NAC	NA	1.00	1.00	NA	31
		200	+4, +8, +12, +16	12, young								
Steroid hormone derivatives												
Eth	1 × 50µg PO	100	–0.5, 0	13 women, young	+28[e] (–19 to +80)	+37 (–36 to +114)	NAC	NA	1.02	1.60	NA	32
		200	+3, +6, +9, +12	13 women, young								
17β-est	1 × 2mg PO	200	0	8 OEW	+16	+31	–23	+27[e]	0.71	0.51	NA	33
Pred	10mg od steady state	150	3 hourly[f]	12 (8 men) RTP	+50	+39	–29	–13	0.89	0.98	No effect on cortisol level	24
Benzodiazepines												
Mid	1 × 15mg PO	200	–1, –0.25	8, young	+52[e]	+56[e]	+79	+30[e]	0.79	1.34	Effect on CNS↑	34
Mid	1 × 5mg IV	200	–1, –0.25	8, young	+4	NA	NA	+7	0.90	NA	No change	34
Tri	1 × 0.25mg PO	250	0	10 (6 men), young	+48[e]	+25[e]	+67	NA	0.67	0.53	Effect on CNS↑	35
Others												
QS	1 × 400mg PO	232	0	12 vol, young	+8	–7	+106	–25[e]	1.27	1.17	No difference in QT intervals	36
Saq	1 × 600mg PO	150	0, +1	12 vol	+39[e] (90% CI +1 to +91)	+63[e] (90% CI +11 to +138)	NA	NA	Variability ↓	Variability ↓	NA	unpubl., Möcklinghoff et al..
Saq	1 × 600mg PO	300	0, +1	12 vol	+121[e] (90% CI +61 to +203)	+120[e] (90% CI +50 to +221)	NA	NA	Variability ↓	Variability ↓	NA	unpubl., Möcklinghoff et al..

a For double strength juice, volumes administered were multiplied by 2.
b Hours relative to drug administration.
c All healthy, nonsmoking men unless otherwise stated.
d variation for each period was calculated as standard deviation (SD), standard error of the mean (SEM) or confidence interval (CI) divided by the mean or point estimate, the value in the column is the ratio of this variation between grapefruit juice and control period.
e Significant ($p < 0.05$) grapefruit juice effects.
f Administered from –7.5 hours until +22.5 hours.

Abbreviations and symbols: 17β-est = 17β-estradiol; AUC = area under the plasma concentration versus time curve of the unchanged drug; bw = bodyweight; Caf = caffeine; Cmax = maximal plasma concentration of unchanged drug; Eth = ethinylestradiol; GJ = grapefruit juice; HD = haemodynamics; IV = intravenous; Mid = midazolam; NA = data not available; NAC = no apparent change; od = once daily; OEW = ovariectomised women; Pred = prednisone; po = oral; QS = quinidine sulfate; RTP = renal transplant recipients; Saq = saquinavir; Theo = theophylline; t_{max} = time at which C_{max} occurred; vol = volunteers; y = years; Tri = triazolam; ↑ = increased; ↓ = decreased.

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1.2 Change of Pharmacokinetic Variability by Grapefruit Juice

Several authors have reported that grapefruit juice not only increases drug concentrations but also renders first pass metabolism more uniform between individual patients, with the most pronounced increases in AUC and/or C_{max} occurring in those individuals who had the lowest values in the control period (C. Möcklinghoff, et al., unpublished observation).[7,23] Of course, this effect would be highly desirable because there is pronounced interindividual variation in gut wall first pass metabolism[56] and this is a major factor in overall variation of concentrations and response to particular drugs.

If this is a general principle of grapefruit juice interactions, then one would expect that the interindividual variability in pharmacokinetics would decrease when the drug is given with the juice. To address this question, the relative variation in these parameters was estimated (see tables I to V). This relative variation was equal to the coefficient of variation in those studies where standard deviation (SD) or standard error of the mean (SEM) were given. The ratio between grapefruit juice and control periods was used to compare between periods. A value above unity indicates that variation is higher in the grapefruit juice period, whereas values below unity suggest that grapefruit juice indeed lowers variation. Across all drugs, the median of this ratio is very close to unity (tables I to V). This evaluation clearly shows that there is no general difference in pharmacokinetic variability between grapefruit juice and control periods and that grapefruit juice is not the 'leveller of drug metabolism' as proposed recently.[57]

1.3 Grapefruit Juice Interactions during in Long Term Intake

Another important question is whether the extent of grapefruit juice interaction changes with the duration of juice intake, since for other CYP3A4 inhibitors enzyme induction may attenuate the interaction.[7] It appears that this is not the case for grapefruit juice interactions. In one study addressing this question, an increase in the inhibitory effect of grapefruit juice was observed, which may be due to the mechanism of the interaction (see section 2.1).[7] For those other substances where studies of long term and of single dose grapefruit juice administration are available, i.e. cyclosporin (see table III)[24-26] and terfenadine (table IV),[28-29] long term intake was not associated with a smaller degree of interaction, when the lower doses used in repeated administration were taken into consideration. If, however, it is confirmed that psoralens are responsible for grapefruit juice interactions,[58,59] their known potential to induce drug metabolising enzymes[60-62] deserves further attention.

2. Proposed Mechanisms of Interaction

2.1 Gut Wall Cytochrome P450 CYP3A4 as the Main Target of Grapefruit Juice Components *In Vivo*

Most of the drugs subject to grapefruit juice interactions share a common property: dihydropyridine calcium antagonists, verapamil, terfenadine, cyclosporin, ethinylestradiol, 17β-estradiol, prednisone, midazolam, triazolam, quinidine and saquinavir usually are subject to a relevant first pass degradation, known to be mediated by cytochrome P4503A4/5 for most of these drugs and resulting in the formation of phase I metabolites.[39,63-69] From the results of an elegant study by Kolars and colleagues,[70] it appears that the major site of this metabolism is the gut wall. Indeed, increased bioavailability in conjunction with unchanged elimination half-life, as seen for almost all of these drugs, supports the assumption that gut wall metabolism is decreased by grapefruit juice components, whereas drug metabolism in the liver is essentially unchanged. Further support comes from 3 studies where the effects of grapefruit juice on intravenous drug administration were compared with that on oral drug administration. For nifedipine[13] (see table II), cyclosporin[23] (see table III) and midazolam[34] (see table V), it was shown that

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grapefruit juice had no effect on the pharmacokinetics of these agents when they were administered intravenously but clearly altered their pharmacokinetics when they were administered orally.

Recent experimental data by Lown and colleagues[7] directly confirm this hypothesis. In this paper, it was shown that grapefruit juice administration results in a decrease of immunoreactive CYP3A4 by a mean of 62% in the small intestine, without affecting small intestine CYP3A4 mRNA levels, liver CYP3A4 activity, colon levels of CYP3A5, or small bowel levels of P-glycoprotein. The authors concluded that 'a mechanism for the effect of grapefruit juice on oral felodipine kinetics is its selective downregulation of CYP3A4 in the small intestine'.[7] However, unchanged mRNA levels suggest that grapefruit juice components may have a more direct influence on the enzyme, such as mechanism-based inactivation. Assuming that a constant fraction of active intestinal CYP3A4 is removed by grapefruit juice components, one would expect that those drugs that undergo a pronounced first pass metabolism are subject to a higher grapefruit juice effect than drugs with only minor first pass biotransformation.

To test for this hypothesis, average effects of short term grapefruit juice intake on AUC (fig. 1) and C_{max} (fig. 2) values of a drug were compared with its absolute bioavailability published in literature. Using the Spearman's rank correlation test (one-tailed), a significant decrease of the grapefruit juice effect on AUC ($n = 15$ drugs; $r = -0.788$, $p < 0.001$) and on C_{max} ($n = 14$ drugs; $r = -0.773$, $p < 0.001$) was indeed observed with increasing bioavailability. Thus, the expected relationship was confirmed despite the differences in study designs, despite different contributions of intestinal and hepatic metabolism to overall first pass biotransformation of the individual drugs,[68] and despite the complexity of CYP3A4 mediated metabolism.[74]

What makes the interaction confined to the small intestine, in contrast to the effect of other CYP3A4 inhibitors such as ketoconazole?[28] The best explanation available is that the compound(s) causing a decrease of gut wall enzyme activity are also subject to rapid inactivation at this very location. Current data for naringenin, showing extensive phase II metabolism, support this hypothesis[75,76] (see section 3.1.2), whereas no information is yet available for grapefruit juice psoralens. In this context, an important question is why concentrations of drug metabolites are also consistently increased in those cases where the grapefruit juice interaction is present for the parent drug, although this increase does not reach the extent of that seen for the parent compounds (see tables I to V). If the metabolic pattern is unchanged, one would expect delayed metabolite formation but the same AUC values because this parameter reflects the effective metabolite 'dose' which should be unchanged. I suggest one or several of the 3 following mechanisms or a combination thereof.

(i) It may well be that in the absence of grapefruit juice, not only primary but also subsequent metabolites are formed already during the first pass metabolism of a drug by CYP3A4. If this assumption is correct, the increase of primary metabolite concentrations by grapefruit juice components may be due to inhibition of these secondary steps as well as of the primary ones.

(ii) First pass metabolism could also be circumvented for both primary and secondary metabolic steps by a possible additional action of grapefruit juice components as a zonula occludens toxin, which would result in an increase of gut wall permeability with substances bypassing drug metabolising enzymes.[77]

(iii) Grapefruit juice components may have the additional potential to alter renal excretion of metabolites, since it has been shown that naringenin is able to change transport of xenobiotics across membranes.[78]

The observation that drug metabolites are affected implicates that their action also needs to be considered in grapefruit juice interactions. This may be relevant for cyclosporin since a role of its metabolites in the precipitation of cyclosporin neurotoxicity has been suspected.[38]

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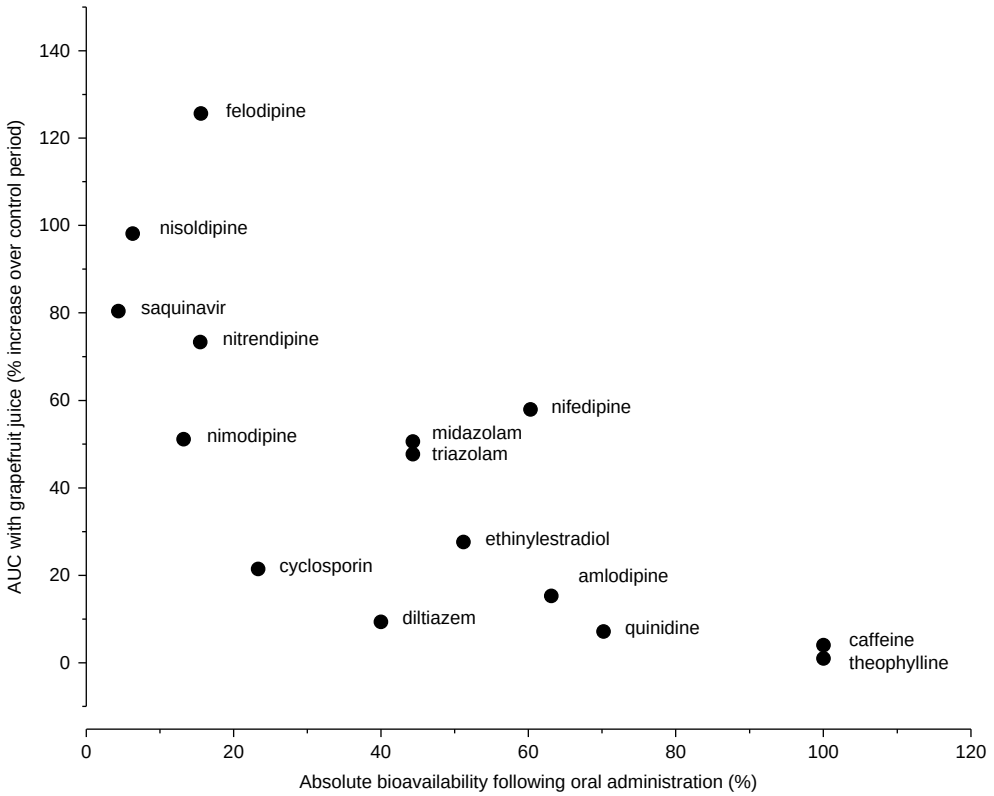

Fig. 1. Relationship between the absolute bioavailability of drugs and the extent of increase in area under the curve (AUC) due to grapefruit juice interactions. Only drugs with reliable information on average bioavailability in the literature[39,71-73] and studies with less than 1 day of grapefruit juice administration prior to drug intake have been included. Grapefruit juice effects shown are median values of the mean effects seen in the studies with the respective drug (see tables I to V).

3. Characteristics of Grapefruit Juice Components Possibly Involved in the Interaction

Several hundred chemical entities have been identified in grapefruit juice.[79] The composition of the juice varies widely depending on the genetic background of the plant, environmental conditions during fruit growth, fruit maturity and fruit processing.[2,79] Most of the components are found not only in grapefruit juice but also in other citrus fruits. However, the amounts of the individual chemical entities are quite different between species. Because drug interactions have been observed with grapefruit juice from many different sources, it appears that the substance(s) which are responsible for drug interactions are consistently present in the juice. Whether the effect is unique to grapefruit juice remains to be proven. In 2 studies, orange juice did not change felodipine[10] or cyclosporin[22] pharmacokinetics. However, due to the widespread occurrence of components similar to those supposed to cause the grapefruit juice interactions, one should not be surprised if more systematic research into the effects of other fruits yielded a large number of drug interactions.

Among the many typical components of grapefruit juice, flavonoid and coumarin derivatives have been suggested to contribute to grapefruit juice drug interactions.

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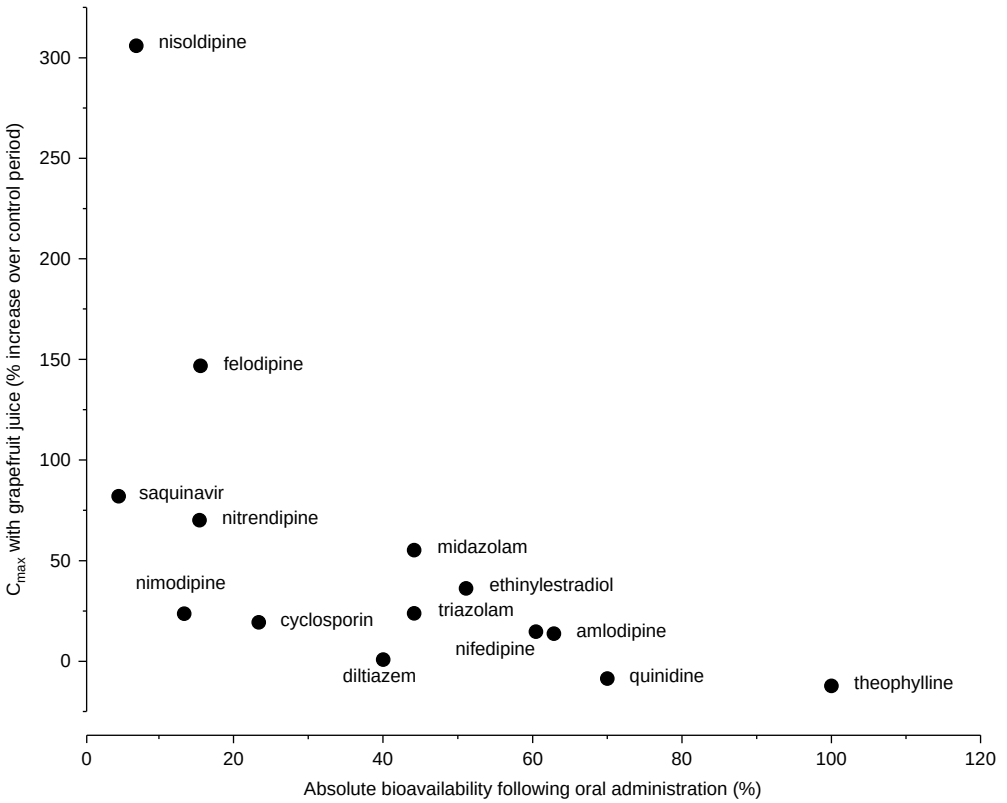

Fig. 2. Relationship between the absolute bioavailability of drugs and the extent of increase in the maximum (peak) plasma drug concentration after single-dose administration (C_{max}) due to grapefruit juice interactions. Only drugs with reliable information on average bioavailability in the literature[39,71-73] and studies with less than 1 day of grapefruit juice administration prior to drug intake have been included. Grapefruit juice effects shown are median values of the mean effects seen in the studies with the respective drug (see tables I to V).

3.1 Flavonoids

3.1.1 Abundance of Flavonoids in Grapefruit Juice

It appears that grapefruit juice is unique with respect to high levels of naringenin (4′,5,7-trihydroxyflavanone) glycosides, mainly naringin (naringenin-7β-neohesperidoside) and narirutin (naringenin-7β-rutinosid) [see figure 3].[75,79]

Naringin concentrations in grapefruit juice are reported to range from 100 mg/L to 800 mg/L, but can reach from 200 to 500 mg/L in most commercial grapefruit juice preparations.[34,75,80] The concentrations of narirutin are reported to be between 100 mg/L and 250 mg/L.[34,75,80] For naringin enantiomers, it is known that the ratio depends on the maturity of the fruit, with more (2*S*)-naringin found in immature fruit.[2,79] High concentrations of naringin are present in the albedo of the fruit; therefore, production procedures that optimise juice yield will result in high levels of this flavonoid.[81]

Further flavonoids found in grapefruit juice at levels up to 70 mg/L include the hesperitin glycosides hesperidin and neohesperidin, the isokuranetin glycosides poncirin and isokuranetin-7β-rutenoside and other glycosides of flavanone, flavone and flavonol derivatives.[34,75,79,80]

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3.1.2 Fate of Grapefruit Juice Flavonoids in the Human Body

Flavonoid glycosides are polar compounds which are poorly absorbed. No unchanged naringin was found in plasma (S. Hensler and U. Fuhr, unpublished observations) and in urine[75,76] following grapefruit juice or naringin ingestion. However, a median of 5 to 7% of the naringin dose was recovered in urine as naringenin glucuronide, whereas renal excretion of unconjugated naringenin reached only 0.05% of the naringin dose given.[75,76] Some individuals may excrete even higher levels of naringenin.[76] Therefore, the removal of the sugar moiety seems to be a prerequisite for the absorption of these compounds. A cleavage of glycosidic bonds has been proposed to occur by hydrolysis in the acidic gastric environment as well as by glucuronidases and glycosidases from gut bacteria.[75] Intestinal bacteria were indeed able to metabolise naringin to naringenin both in cattle and in humans under anaerobic and aerobic conditions.[82,83] In contrast, there was no evidence for naringenin formation by incubation of grapefruit juice or naringin with hydrochloric acid (A. Ben Othman and U. Fuhr, unpublished observations). However, it is tempting to speculate whether naringenin formation may also be mediated by hydrolases excreted from the pancreas.

The observation that naringenin glucuronides were detectable in plasma (S. Hensler and U. Fuhr, unpublished observations) and in high levels in urine[75,76] after grapefruit juice ingestion whereas free naringenin was absent in plasma (S. Hensler and U. Fuhr, unpublished observations) and found only at very low levels in urine[76] suggests that naringenin glucuronidation occurs during first pass of the drug through the intestinal mucosa and/or the liver. Accordingly, naringenin was reported to be a high affinity substrate for a glucuronosyl transferase.[84] The fate of the remaining glycoside is unknown, but it seems probable that the major fraction is excreted unchanged in the faeces (fig. 4).[75,76] The fate of other grapefruit juice flavonoids in the human body may be similar to that described for naringin.[75] A link between those substances and grapefruit juice drug interactions, however, has not been established.

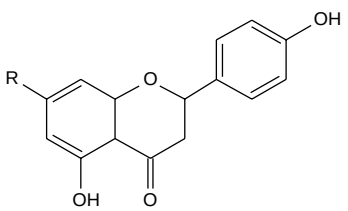

Fig. 3. Chemical structure of naringin and naringenin. For naringenin, R = OH; for naringin, R = β-neohesperidose.

3.1.3 The Possible Role of Grapefruit Juice Flavonoids in Drug Interactions

Naringenin, like many other flavonoids including for example, quercetin, is a potent inhibitor of cytochrome P450 enzymes in humans,[85] namely of CYP3A4.[86] At a substrate concentration of 64 μmol/L, naringenin inhibited midazolam hydroxylation with an IC_{50} value of approximately 120 μmol/L.[87] Naringenin, but not naringin, was also able to inhibit verapamil metabolism[88] and had a clear inhibitory effect on CYP3A4 mediated denitronifedipine degradation in human liver microsomes (A. Ben Othman and U. Fuhr, unpublished observations). Accordingly, recent investigations of the inhibitory action of grapefruit juice on CYP3A4 in human liver microsomes have shown that this action is enhanced by incubation with naringinase (A. Ben Othman and U. Fuhr, unpublished observations).

However, several observations suggest that naringin and its aglycone naringenin are not the major inhibitory constituents of grapefruit juice. In 3 studies, naringin, given as an 'aqueous solution',[5,17] or in an 'encapsulated' preparation,[16] in the same amounts as present in grapefruit juice, had no effect on nitrendipine,[17] felodipine[5] or nisoldipine[16] pharmacokinetics. Furthermore, the extent of inhibition of verapamil first pass metabolism was not correlated to naringenin glucuronide AUC in plasma or to urinary excretion of naringenin or its glucuronides in urine, (S. Hensler and U. Fuhr, unpublished observations) which

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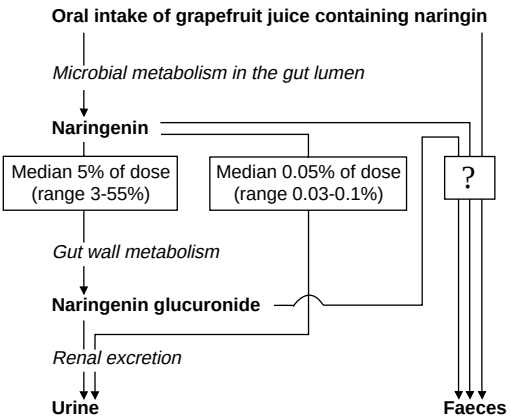

Fig. 4. Presumed fate of naringin in the human body[75,76]

were used as markers for individual naringenin absorption in an interaction study between verapamil and grapefruit juice.[19] Finally, the grapefruit juice interaction was present equally for immediate-release and for prolonged release drug preparations (see tables I to V). If naringenin formation from naringin by faecal bacteria is required for the interaction, one would expect that the effect has a lag time and also that grapefruit juice would change colon rather than small intestine enzyme concentrations. However, the results of a study by Lown and colleagues[7] clearly show that the small intestine is the site of interaction.

Besides inhibition of CYP3A4 mediated first pass metabolism, it has been shown from *in vitro* experiments using human liver microsomes that CYP1A2 and CYP2A6 activities may also be decreased by grapefruit juice flavonoids. Naringenin, but not naringin was a potent competitive inhibitor of CYP1A2 with inhibitor constants (K_i) of less than 50 μmol/L.[3] Coumarin hydroxylation was competitively inhibited by naringenin with a high mean K_i value of 690 μmol/L, indicating a poor inhibitory effect, whereas naringin again had no effect.[89] However, the extent of the resulting interactions *in vivo* is minor or absent for caffeine and theophylline (see table V), both of which are subject to CYP1A2 mediated metabolism,[47] and is not clearly defined for coumarin, which is a CYP2A6 substrate.[53,54]

3.2 Coumarin and Psoralen Derivatives

Many coumarin and psoralen (furocoumarin) derivatives have been found in grapefruit. The location of these substances is primarily in the peel, but concentrations of approximately 10 to 40 mg/L are also found in the juice.[54,58,59,79,90-93] The fate of these moieties from grapefruit juice in the human body is unknown. However, due to their high lipophilicity, one might expect that these compounds are readily absorbed from the gastrointestinal tract and extensively metabolised, as this is the case for coumarin and psoralen drugs such as warfarin, phenprocoumon and methoxsalen.[39]

In contradiction to the naringenin hypothesis, unprocessed grapefruit juice with no free naringenin inhibits human CYP3A4 activity.[94] The main inhibitory activity in native grapefruit juice was mediated from lipophilic compounds extractable by dichlormethane, (A. Ben Othman and U. Fuhr, unpublished observations)[94] or ethyl acetate.[95] In recent publications, such components with potent inhibitory action on rat or human liver CYP3A4 were identified as the psoralen derivative 6′,7′-dihydroxybergamottin (fig. 5)[58] or as psoralen dimers.[59] Other psoralens are known to be potent inhibitors, but also inducers of several cytochrome P450 enzymes in laboratory animals and in humans.[60-62,96-100] The mechanism of enzyme inhibition by psoralens seems to be a reversible binding to the substrate binding site,[101] in some cases followed by formation of active metabolites with irreversible inactivation of the enzyme.[100,102] A study addressing the mechanism of grapefruit psoralen effects on human CYP3A4 activity *in vitro*, which has very recently been published, has fully confirmed this mechanism.[103]

3.3 Which Component is to Blame?

From the recent findings on the inhibitory activity of nonflavonoid compounds, it is highly probable that psoralens, mainly 6′,7′-dihydroxybergamottin, in grapefruit juice are the components

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responsible for the drug interactions. However a, possibly minor, role of naringenin in grapefruit juice interactions cannot be excluded. In contrast, it may well be that naringenin supports the inhibitory action of other juice components as naringin supplementation of grapefruit juice reproducibly increased its effects in a pilot study,[104] or that a more complex synergy among grapefruit juice components is involved.

4. How to Take Grapefruit Juice Interactions into Account in Drug Therapy

4.1 Risks of Grapefruit Juice Interactions

Consumption of fruit and vegetables is generally associated with beneficial health effects. To name the most important ones, cardiovascular diseases and cancer are among the diseases possibly preventable by this kind of food.[105,106] Flavonoids and other grapefruit juice constituents may contribute to this action.[107,108] Therefore, it is difficult to create public awareness that grapefruit juice also confers a health risk.

I have clearly emphasised in this review that grapefruit juice interactions are of potential clinical relevance in the individual patient for a wide range of drugs. Taking the mechanism of the interaction into account, this is not surprising because CYP3A4 is a major drug metabolising enzyme. Other drugs not tested yet, but also subject to CYP3A4 mediated metabolism, include cholesterine synthase inhibitors, macrolide antibacterials, antineoplastic agents such as cyclophosphamide, ifosfamide, taxoids, epipodophyllotoxins and vinca alcaloids, cisapride, indinavir, finasteride, ganisetron and many more. Among others, all these drugs could potentially interact with grapefruit juice.

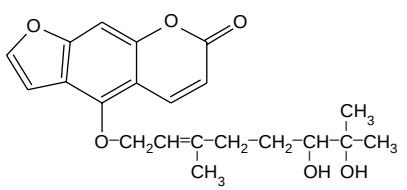

Fig. 5. Chemical structure of 6′, 7′-dihydroxybergamottin.

It appears that the grapefruit juice interactions are exclusively pharmacokinetic in nature. Thus, the risks related to grapefruit juice intake with drugs are those seen with an overdose of the drug in question. Currently, there is no clear evidence that the pattern of metabolites and thus the pattern of adverse effects may change with grapefruit juice at a clinically relevant range. To take this increase in concentrations in to account in drug therapy, I agree with Lown and colleagues[7] that consistency of intake of inhibitory substances could be the key. If a patient likes to take drug doses with grapefruit juice, it would be desirable that she or he does so using the same dose of the very same juice every day. This however is not possible. Even a change in the brand or batch of grapefruit juice may influence the grapefruit juice/drug interaction to an unpredictable extent since grapefruit juice is a natural product with an unknown degree of variability in composition. Standardisation of grapefruit juice with respect to components causing the interaction currently is not feasible because the role of possible candidates is not fully understood.

In addition to the variation in juice composition, one might speculate about the effects that a change in nutritional habits or initiation of antibacterial therapy might have on the extent of the grapefruit juice interaction, if indeed intestinal metabolism is necessary to activate the ingredient(s) of grapefruit juice.

With respect to interindividual differences in drug pharmacokinetics, grapefruit juice did not decrease the variation between patients in AUC or C_{max} (see section 1.2 and tables I to V). Therefore, it appears that drug concentrations obtained by a given dose are more difficult to predict if taken with grapefruit juice. This increases the probability of inappropriate drug treatment. Avoiding the interaction by taking the drug after ingesting grapefruit juice is not possible because of the long duration of the effect.[6] Drug administration before

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drinking grapefruit juice may attenuate the interaction but it was still present during long term drug use, presumably because the next dose was affected.[29]

Thus, as long as it appears that the extent of these interactions is unique for grapefruit juice among vegetables and fruits, it seems to be wise to refrain from grapefruit juice consumption when taking drugs that are subject to a relevant metabolism and for which a lack of interaction by grapefruit juice has not been shown.

When studies have shown that a particular drug interacts with grapefruit juice, most pharmaceutical companies have reacted to the finding by including the information in the package insert of the respective drug and/or by other appropriate measures and prohibiting concomitant intake of the drug with grapefruit juice. This should be extended to all drugs that might interact based on their metabolism unless a lack of interaction has been proven. To improve public awareness, it might be helpful to also place the warning in a more prominent location on the outside of the package. This could be achieved simply by use of a symbol such as a crossed out grapefruit.

4.2 Grapefruit Juice as a Drug-Sparing Agent?

The idea of using grapefruit intentionally as a drug-sparing and cost-reducing agent is a topic of some controversy.[2,22,76,109-111] Grapefruit juice could be used as a drug-sparing agent in a setting such as cyclosporin treatment. In this situation, therapeutic drug monitoring takes place and this would enable the extent of interaction in the individual patient to be taken into account. However, a question of practical importance is whether the grapefruit juice effect might increase the need for dose adjustments. This question is difficult to answer from experimental data because there are no studies with repetitions of both the control and the grapefruit juice period. In one felodipine study, a rechallenge with grapefruit juice has been conducted under identical conditions and pharmacokinetic parameters were similar for both grapefruit juice periods.[9] The periods in this study, however, were only a few days apart.

There is no doubt that grapefruit juice has potential as a drug-sparing agent. This has been demonstrated for example in 2 case reports where antihypertensive[112] or antipsoriasis therapy[113] efficacy was improved by addition of grapefruit juice. Indeed, some patients are known to take cyclosporin with grapefruit juice in order to save money by reducing doses, and a similar successful approach has been described with ketoconazole or diltiazem without apparent serious adverse effects.[22,23] However, the possibility of an increased risk of adverse effects, also associated with subsequent costs, may easily outweigh possible cost savings for cyclosporin that were estimated to reach approximately US$1500 per patient and year.[23]

5. Conclusions

Concomitant intake with grapefruit juice has the potential to increase the concentrations of many drugs in humans and this effect is mediated mainly by suppression of the cytochrome P450 enzyme CYP3A4 in the small intestine wall. The extent of grapefruit juice interactions is more pronounced than that of many well known drug-drug interactions. It is reasonable to assume that increased drug concentrations may be associated with more pronounced drug effects, occasionally even causing toxicity. The grapefruit interaction does not produce a consistent decrease in the variability of drug pharmacokinetic parameters. Therefore, it is recommended that patients refrain from ingesting grapefruit juice when taking a drug that is extensively metabolised unless a lack of interaction has been already been demonstrated for this particular drug. It is also recommended that an appropriate labelled warning should be added to the packaging to such drugs. At present, a place for grapefruit juice as a drug-sparing agent in the treatment with expensive medicine cannot be recognised.

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