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Review article

Assessing clinical evidence of drug interactions between citrus juices and cyclosporine

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Background: Previous studies have demonstrated that grapefruit juice increased the bioavailability of cyclosporine; however, the results from the literature are inconsistent. Other citrus fruits such as pomelo or orange juice had variable effects on the bioavailability of cyclosporine.
Objective: To assess the effect of grapefruit juice and other types of citrus juice on oral bioavailability of cyclosporine in humans using meta-analysis.
Methods: We conducted a meta-analysis of placebo-controlled studies evaluating the effects of citrus juices on bioavailability of cyclosporine. The studies were identified in PubMed, Cochrane CENTRAL, CINAHL, ISI Web of Knowledge, Psych Info International, Pharmaceutical Abstract (IPA), and reference lists of relevant papers. The weighted-mean difference (WMD) was calculated for net changes in the area under the curve (AUC) of cyclosporine. All studies conducted as placebo-controlled crossover studies in humans to compare the effect of citrus juices and control (drinking water) on AUC of cyclosporine and/or Cmin,ss were reviewed. All studies included were evaluated and extracted independently, and discrepancies were resolved through discussion.
Results: Eighteen studies were identified. A subgroup analysis suggested that grapefruit juice significantly increased AUC of cyclosporine (WMD = 1762.5 ng·h/ml, 95%CI = 1178.9–2346.0 ng·h/ml, $p < 0.001$). While a meta-analysis of all other types of citrus juices (tangerine juice, Seville orange juice, sweet orange juice, and citrus soda) except pomelo juice revealed no effect on the AUC of cyclosporine (WMD = –181.0 ng·h/ml, 95%CI = –582.8–220.9 ng·h/ml, $p > 0.5$), a study of pomelo juice indicated a significant increase in the AUC of cyclosporine.
Conclusions: Grapefruit juice intake increases oral bioavailability of cyclosporine in both healthy volunteers and renal transplant patients, whereas all other types of citrus juices may not have an influence on the oral bioavailability of cyclosporine. Current evidence suggests that pomelo juice may be able to increase cyclosporine oral bioavailability.

Keywords: Bioavailability, citrus juice, cyclosporine, drug interaction, meta-analysis

Cyclosporine is a commonly used immunosuppressive agent for solid organ transplantations. Although organ recipients benefit greatly from its efficacy, patients are potentially at risk of adverse reactions of the drug because of its narrow therapeutic index. High concentrations of cyclosporine are associated with a low incidence of organ rejection and high incidence of nephrotoxicity [1, 2]. Thus, the increase of cyclosporine concentrations by drug–drug or herb–drug or food–drug interaction could lead to an increase in its efficacy or toxicity.

Grapefruit juice is well-known as a modifier of the bioavailability of many drugs including cyclosporine (e.g. felodipine, nifedipine, verapamil, simvastatin, lovastatin, cyclosporine, triazolam, buspirone, amiodarone, saquinavir, and sildenafil) [3]. These

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interactions mainly result from an inhibitory effect of grapefruit juice on CYP3A4 in the small intestine. Binding between the intestinal CYP3A4 and active moieties in the juice is considered to be irreversible, leading to a loss of the enzyme activity and decreasing the magnitude of first-pass metabolism. The chemical inhibition is caused by furanocoumarins such as bergamottin and 6′,7′-dihydroxybergamottin [4-9], and to a minor extent by flavonoids such as naringin and naringenin [3, 6, 10]. In addition to the CYP3A4 inhibition, inhibition or downregulation of P-glycoprotein might contribute to the increase of bioavailability of cyclosporine [4, 11-14].

Some in vitro studies showed that other types of citrus juices (e.g., bitter orange, orange, lime, and pomelo) exhibit inhibitory activity against P-glycoprotein [11, 12, 15], and CYP3A4 [16]. Bitter orange (Seville orange) juice caused loss of CYP3A4 activity in human volunteers [17], and increased oral bioavailability of felodipine [18]. Cyclosporine toxicity was observed in swine administered *Citrus* decoctions [19]. However, relatively few pharmacokinetic studies of drug interaction of other types of citrus juices have been conducted in humans [20].

Meta-analysis is a process whereby a collection of research results from individual studies are statistically analyzed in a way that allows one to integrate their findings and increase the power of statistical analyses. It produces a set of parameters that represents average, not individual, finding across studies [21]. Despite many studies indicating that grapefruit juice statistically increased bioavailability of cyclosporine [17, 22-32], results of some studies in humans demonstrated no interaction between grapefruit juice and cyclosporine [33, 34]. Pomelo (*Citrus grandis*), a close relative of grapefruit, was found to increase bioavailability of cyclosporine in humans, whereas bitter orange (Seville orange) and sweet if juices had no effect on bioavailability of the drug [17, 32]. Since, most studies, which reported insignificant effects of citrus juices on bioavailability of cyclosporine had relatively small sample sizes, we aimed to employ a meta-analysis approach to assess the effects of the juices on bioavailability of cyclosporine in humans.

Methods

Data sources and search strategy

The following databases were systematically searched; PubMed, Cochrane CENTRAL, CINAHL, Web of knowledge, and Psych Info International Pharmaceutical Abstract (IPA) from their inception to June 2010. The computerized search on cyclosporine and citrus juice pharmacokinetic interaction used the following key words: *"cyclosporine"*, *"cyclosporine"*, *"citrus"*, *"grapefruit"*, *"pomelo"*, *"orange"*, *"tangerine"*, *"lime"*, *"lemon"*, *"bioavailability"*, and *"pharmacokinetic interaction"*. Additionally, reference lists of relevant papers were searched.

Study selection

Studies were included if they met the following criteria: (1) placebo-controlled drug–food interaction study between cyclosporine and citrus juices (grapefruit, pomelo, orange, etc.),whereas drinking water was used as a control, and; (2) the studies were conducted on human subjects. Review studies and case report studies were excluded. Studies that provided insufficient information for statistical pooling were also excluded.

Data extraction and quality assessment

All studies included were evaluated and extracted independently, and discrepancies were resolved through discussion. Whenever possible, the following information was extracted from the publications: type of study design, source and type of citrus, characteristic and number of participants, concomitant drug used, specificity of measurement, drug formulation, drug dosage, administration procedure of drug and the type of juice, mean ± standard deviation of outcome (or other necessary information required to compute the estimate). Discrepancies between the two investigators were resolved by discussion and consensus.

Data analysis

The outcome measures were minimum concentration at steady state (Cmin,ss), the area under the curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$) and the AUC at steady state from time 0 to time interval ($AUC_{ss,0-\tau}$), which represented bioavailability of the drug for a single dose study and multiple dose study, respectively. Note that at the same dosage, $AUC_{0-\infty}$ value is theoretically equal to $AUC_{ss,0-\tau}$.

Meta-analyses were performed using STATA version 10 (Stata Corporation, College Station, Texas, USA). The results of the meta-analysis were expressed as the difference in mean of the outcomes

of cyclosporine between those subjects who ingested citrus juices and those subjects in the control group. Mean difference of >0 of AUC implies that citrus juices increase oral bioavailability of cyclosporine. The mean difference was calculated for each individual study, and a summary weighted mean difference (WMD) was determined using the random effects model of DerSimonian and Laird. The Q-statistics and I-squared (I^2) were performed for test of heterogeneity. I^2 describes the percentage of variability across studies because of heterogeneity among studies rather than chance. An α error $p \leq 0.1$ and $I^2 \geq 50\%$ were taken as indicators of heterogeneity of outcomes. We also performed subgroup analysis to explore the possible source of heterogeneity e.g. type of juices, type of subject (healthy volunteers vs. renal transplant patients), type of cyclosporine formulation (microemulsion vs. olive oil based formulation). The methodological quality of the studies was assessed by using Jadad score [35]. The publication bias was tested using the Egger regression test for funnel plot asymmetry [36] and Begg–Mazumdar test, which is based on the Kendall τ [37].

Results

Study selection

A flow chart of study selection is shown in **Figure 1**. A total of 49 articles were identified. After exclusion of review articles (17 articles) [3, 38-53], in vitro study (5 articles) [11, 13-15, 54], in vivo animal study (4 articles) [19, 55-57], case reports (2 articles) [58, 59], and 21 potentially relevant articles [17, 20, 22-34, 59-64] were retrieved for further evaluation. One study [64] was not included because there was no placebo control group. Thus, there were 20 human studies remaining for further meta-analysis. Eighteen of the remaining studies [17, 20, 22-26, 28-34, 60-63] reported AUC values as an outcome (**Tables 1 and 2**), and 7 studies reported Cmin,ss of cyclosporine as an outcome (**Table 3**) [24, 25, 27, 33, 34, 59, 62].

Study characteristics

Subjects

One hundred ninety-eight subjects in 20 studies were enrolled. Seven studies [17, 20, 28-32] were conducted in healthy volunteers (90 subjects) with their age ranging between 18 and 64 years. Eleven studies [22-26, 33, 34, 60-63] were conducted in renal transplant patients with stable condition post-surgery (108 subjects) with age range between 7 and 75 years. Average percentage of males in the included studies was 60.9 ± 19.5 [17, 20, 22-24, 26, 28, 29, 32-34, 60, 61, 63]. Most studies in renal transplant patients had excluded patients who had concomitant drugs or herbs with known or suspected interaction with cyclosporine [22, 24, 26, 33, 34, 60-63]. Some studies allowed the concomitant use of calcium channel blockers and/or low-dose oral glucocorticoids [24, 33]. One study did not report the criteria in concomitant use of drug [23].

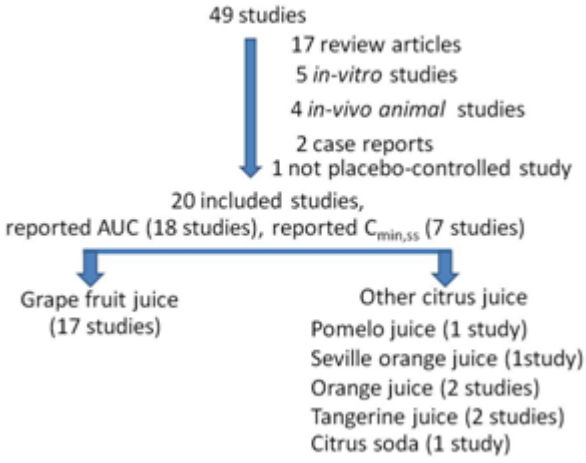

Figure 1. Flow diagram representing study selection for meta-analysis

Study design

All studies were conducted as placebo-controlled crossover studies to compare the effects of citrus juices and control (drinking water) on AUC of cyclosporine and/or Cmin,ss. Doses of cyclosporine in the selected studies are shown in **Tables 1**–**3**. In the studies using healthy volunteers, the drug was administered in a single-dose manner except for one study, in which the drug was administered in a multiple dosing design [32]. In studies using patients with renal transplant, multiple dosing regimens were performed [22-26, 33, 34, 60-63].

Only 6 studies reported using an open-label design [29, 31, 33, 34, 62, 63]. Sequences of drinking were randomized for most studies. Only 4 studies were performed using fixed sequences of drinking [27, 28, 33, 62]. Four studies [27, 28, 33, 62] were conducted without washout period between test and control, whereas other studies were designed with a washout period to separate each intervention by at least a week.

The outcome measures

Area under the drug concentration–time curve (AUC) was measured in all studies. In single dose studies, the values of AUC were calculated using a linear trapezoidal rule. In multiple dosing studies, AUC values were estimated from 0 to 12 hours. Except for 4 studies, in those studies, AUC values were calculated from 0 to 8 hours [22] and from 0 to 24 hours [32, 34, 62]. Minimum concentrations at steady state (Cmin,ss) were measured at the end of dosing interval (12 hours) for most studies. Only 2 studies [34, 62] those reported Cmin,ss collected blood sample at 24 hours after drug administration.

Formulation of cyclosporine

When compared to a conventional olive oil based formulation (non-microemulsified formulation), a microemulsified formulation of cyclosporine (e.g., Neoral) can reduce variability in oral bioavailability. The average oral bioavailability of the microemulsified formulation was 30% higher than that of the conventional formulation [65]. Eight studies used the microemulsified formulation [20, 22, 29-31, 33, 61, 63], 7 studies used the nonmicroemulsified formulation [17, 23, 25, 28, 33, 34, 62], and 6 studies did not report any type of drug formulation [24, 26, 27, 32, 59, 60]. The study by Brunner and co-workers was conducted using both formulations [33].

Table 1. Effect of citrus juice and control (water) on $AUC_{0-\infty}$ of cyclosporine from placebo-controlled crossover pharmacokinetic studies in healthy volunteers

Study	Dosage regimen of cyclosporine	Type of citrus juice	Cumulative ingested volume/ period	Duration of GFJ ingestion/ period	Specificity of assay method	Mean SD of $AUC_{0-\infty}$ of cyclosporine (ng·h/ml)	
						Citrus juice group	Control group
Grenier 2006 (n = 12)	single dose of 200 mg Neoral®	Red pomelo juice	240 ml	1 day	Specific	6835 ± 1435 *	5753 ± 1208
Schwarz 2005 (n = 12)	single dose of 2.5 mg/kg Sandimmun	- Concentrate GFJ - Citrus soda (Sun Drop) - Citrus soda (Fresca)	2364 ml	2 days	Nonspecific	10407 ± 3451* 6007 ± 1702 5944 ± 1730	5635 ± 1367
Lee 2001 (n = 23)	single dose of 5 mg/kg Neoral®	Concentrate GFJ	532 ml	1 day	Specific	AA: 9431 ± 1869* CC: 12636 ± 3581*	AA: 5896 ± 1330 CC: 8772 ± 1667
Edwards 1999 (n = 7)	single dose of 7.5 mg/kg Sandimmun	- Concentrate GFJ - Seville orange juice	946 ml	1 day	Specific	10805 ± 3592* 6981 ± 1191	6974 ± 2732
Ku 1998 (n = 12)	single dose of 5 mg/kg Neoral®	Concentrate GFJ	532 ml	1 day	Specific	12809 ± 3314*	9009 ± 1656

* = statistical difference ($p < 0.05$), AA = African American, CC = Caucasian, GFJ = grapefruit juice

Table 2. Effect of citrus juice and control (water) on $AUC_{0-\tau}$ of cyclosporine from placebo-controlled crossover multiple dose pharmacokinetic studies in stable renal transplant patients

Study	Dosage regimen of cyclosporine	Type of citrus juice	Cumulative ingested volume/ period	Duration of GFJ ingestion/ period	Specificity of assay method	Mean ± SD of $AUC_{0-\tau}$ (ng·h/ml)	Mean SD of $AUC_{0-\tau}$ (ng·h/ml)
						Test group	Control group
Hermann 2002 (n = 10)	150–400 mg/day Neoral®	GFJ	250 ml	1 day	Specific	4266 ± 1604	3460 ± 1326
Bistrup 2001 (n = 8)	5.2 ± 1.9 mg/kg/day Neoral®	GFJ	500 ml	1 day	Nonspecific	4099 ± 2008*	2945 ± 1645
Brunner 2000 (n = 6)	- 150–225 mg/day bid Sandimmun	GFJ	720 ml	1 day	- Nonspecific	6593 ± 539	4523 ± 757
	- 150–225 mg/day bid Neoral				- Nonspecific	5510 ± 780	4087 ± 418
	- 150–225 mg/day bid Sandimmun				- Specific	3301 ± 382	2520 ± 466
	- 150–225mg/day bid Neoral				- Specific	2592 ± 221	1770 ± 328
Brunner 1998 (n = 16)	298 ± 79 mg/day Sandimmun	GFJ	720 ml	1 day	Specific	7972 ± 1476	6728 ± 1844
Herliz 1993 (n = 6)	120.8 ± 24.6 mg/day Sandimmun	GFJ	200 ml	1 day	Unknown	2825 ± 470*	2385 ± 447
Hollander 1995 (n = 12)	- 302.1 ± 105.2 mg/day od Sandimmun	GFJ	1500 ml	1 day	- Nonspecific	10733 ± 3417	6974 ± 2732
	- 302.1 ± 105.2 mg/day od Sandimmun				- Specific	5210 ± 1853	4843 ± 1703
Min 1996 (n = 10)	375 ± 175 mg/day	GFJ	237 ml	1 day	Specific	4218 ± 1497*	3415 ± 1288
Proppe 1995 (n = 10)	2.34–6.25 mg/kg/day bid Sandimmun	GFJ	1750 ml	7 days	Specific	4329 ± 1272*	3241 ± 481
Proppe 1996 (n = 10)	2.3–6.25 mg/kg/day	GFJ	Unknown	7 days	Specific	5312 ± 1249*	3086 ± 518
Sorkhi 2007 (n = 10)	- 3.4 mg/kg/day	-Tangerine juice	250 ml	1 day	Nonspecific	3100 ± 1193	3456 ± 686
	- 3.4 mg/kg/day	- Orange juice				3473 ± 924	
Sorkhi 2008 (n = 10)	4.6 mg/kg/day Neoral®	Tangerine juice	250 ml	1 day	Nonspecific	2797 ± 1261	2912 ± 1713

* = statistical difference, $p < 0.05$

Table 3. Effect of citrus juice and control (water) on Cmin,ss of cyclosporine from placebo-controlled crossover pharmacokinetic studies in stable renal transplant patients.

Study	Dosage regimen of cyclosporine	Type of citrus juice	Cumulative ingested volume/ period	Duration of GFJ ingestion/ period	Specificity of assay method	Mean SD of Cmin,ss of cyclosporine (ng/ml)	
						Citrus juice group	Control group
Brunner 2000 (n = 6)	- 150–225 mg/day bid Sandimmun	GFJ	720 ml	1 day	- Nonspecific	158 20	156 42
	- 150–225 mg/day bid Neoral				- Nonspecific	186 31	131 18
	- 150–225mg/day bid Sandimmun				- Specific	67 6	56 9
	- 150–225 mg/day bid Neoral				- Specific	87 11*	40 13
Brunner 1998 (n = 16)	298 79 mg/day Sandimmun	GFJ	720 ml	1 day	Specific	87.7 6.1	74.2 5.5
Durcharme 1993 (n = 11)	3.7–8.1 mg/kg/day bid	Concentrate GFJ			Specific	145.3 44.7*	116.9 51.6

Table 3. Effect of citrus juice and control (water) on Cmin,ss of cyclosporine from placebo-controlled crossover pharmacokinetic studies in stable renal transplant patients. (Continue)

Study	Dosage regimen of cyclosporine	Type of citrus juice	Cumulative ingested volume/ period	Duration of GFJ ingestion/ period	Specificity of assay method	Mean SD of Cmin,ss of cyclosporine (ng/ml)	
						Citrus juice group	Control group
Hollander 1995 (n = 12)	302.1 105.2 mg/day od Sandimmun	GFJ			Specific	60 22	59 25
Mehrsai 2003 (n = 15)	75–225 mg/day	GFJ			Nonspecific	280.9 78.5	234.4 45.5
Min 1996 (n = 10)	375 175 mg/day	Concentrate GFJ			Specific	244 214*	132 56
Proppe 1995 (n = 10)	2.34–6.25 mg/kg/day bid Sandimmun	GFJ			Specific	241 84*	136 21

Citrus juices

Seventeen studies investigated the effect of grapefruit juice on bioavailability of cyclosporine, whereas only few studies investigated effects of other types of citrus juices (including Seville orange juice, orange juice, tangerine juice, pomelo juice, and citrus soda) on the bioavailability of the drug (**Figure 1**). Commercially finished products of grapefruit juice were used in most studies. Three studies were conducted by using self-prepared juices [17, 20, 60, 61]. Most studies did not report constituents in the juices, except the study by Edwards et al. that reported concentrations of 6′, 7′-dihydroxybergamottin in grapefruit juice and Seville orange juice [17], and the study of Schwarz and colleagues that reported concentrations of bergamottin in citrus soda [31].

Administration of citrus juices

Seventy-two subjects in seven studies were administered a glass of citrus juice (total volume ≤ 250 ml) concomitant with cyclosporine [20, 23, 24, 32, 60, 61, 63], whereas 114 subjects in 11 studies were administered multiple dose of citrus juice (total volume 473–3311 ml) [17, 22, 25, 26, 28-31, 33, 34, 62]. The intervention duration was only 1 to 2 days in most studies, except for the studies by Proppe et al. and another study by Ducharme et al. [25-28]. In both these studies, juices were administered for 7 consecutive days in each study arm. There were many differences in timing of juice ingestion among studies such as juice ingestion prior to drug dosing [17, 22, 31, 34], concomitant ingestion with the dosing [20, 22-30, 32, 33, 60-63], and/or repeated ingestion after drug dosing [17, 25-31, 33, 34, 59, 62].

Specificity of analytical methods

The specificity of an analytical method can affect the levels of measured concentrations. The concentration levels analyzed by the nonspecific assay (i.e., polyclonal immunoassay) were the sum of cyclosporine and of its metabolites, whereas specific assays [e.g., high performance liquid chromatography (HPLC), HPLC with mass spectrometric detection (LC–MS), and monoclonal immunoassay] provide more specificity to cyclosporine and/or its metabolites. Eight studies used the nonspecific assay [22, 26, 31, 33, 34, 59-61] and 14 studies used specific assays [17, 20, 24-30, 32-34, 62, 63]. One study did not provide detailed information regarding its analytical method [23].

Concentration-dependent toxicity of cyclosporine

No toxicity of cyclosporine was reported in the included studies.

Results

In the selected 20 studies, 18 studies with reported AUC values were further included in our meta-analysis. Because some studies could be separated into 2 to 3 substudies. For example, the work of Sorkhi and coworkers [60] was separated into 2 substudies (effect of tangerine vs. effect of orange on bioavailability of cyclosporine). The study of Lee et al. [30] was divided into 2 substudies (effect of grapefruit juice on bioavailability of cyclosporine in African subjects vs. effect of grapefruit juice on bioavailability of cyclosporine in Caucasian subjects). Thus, 25 studies were used for the analysis. Drug concentrations were analyzed by both specific and

nonspecific methods [33, 34], only concentrations of specific methods were used for meta-analysis.

In pooled analysis, citrus juice significantly increased AUC of cyclosporine (WMD = 1762.5 ng·h/ml, 95%CI = 1178.9–2346.1 ngh/ml, $p < 0.005$); however, the data had high heterogeneity ($I^2 = 73.3$, $p < 0.005$). Thus, subgroup analysis was conducted. Subgrouping of studies by juices (grapefruit juice vs. other types of citrus juices including Seville orange juice, sweet orange juice, tangerine juice, pomelo juice, and citrus soda) was specified a priori. The subgroup of the other types of citrus juices showed no significant effect on AUC of cyclosporine (WMD = –22.6 ng·h/ml, 95%CI = –398.4–353.2 ng·h/ml, $p > 0.5$), and demonstrated no heterogeneity ($I^2 = 0.0$, $p < 0.005$). However, as shown in **Figure 2**, among other types of citrus juice studies, only the study using pomelo juice shows a significant increase in AUC of cyclosporine [20]. We excluded the study using pomelo juice [20], and reanalyzed the data. The result was clearly shown no significant effect of other types of citrus juices on bioavailability of the drug. Subgroup of the other types of citrus juices excluding the study using pomelo [20] showed no significant effect on AUC of cyclosporine (WMD = –181.0 ng·h/ml, 95%CI = –582.8–220.9 ng·h/ml, $p > 0.5$), and demonstrated no heterogeneity ($I^2 = 0.0$, $p < 0.005$).

By contrast, the meta-analysis of grapefruit juice subgroup showed that grapefruit juice statistically increases the AUC of cyclosporine when compared with the control (WMD = 1762.5 ng·h/ml, 95%CI = 1178.9–2346.0 ng·h/ml, $p < 0.001$), but substantial heterogeneity was found ($I^2 = 82.3\%$, $p < 0.001$). In studies using grapefruit juice, the heterogeneity was significantly decreased after subgrouping with type of subjects (healthy volunteers vs. renal transplant patients). No heterogeneity ($I^2 = 0.0\%$, $p > 0.1$) was demonstrated in a subgroup of healthy volunteers ingesting grapefruit juice, while low heterogeneity was found in a subgroup of renal transplant patients ingesting grapefruit juice ($I^2 = 35.0\%$, $p > 0.1$). **Figure 3** shows that grapefruit juice significantly increased the AUC of the drug in both healthy volunteer (WMD = 3413.6 ng·h/ml, 95%CI = 2700.1–4127.1 ng·h/ml, $p < 0.001$) and renal transplant patient subgroups (WMD = 970.6 ng·h/ml, 95%CI = 580.9–1360.3 ng·h/ml, $p < 0.001$). The 95%CI of WMD of AUC of the drug in renal transplant patient subgroup did not overlap with the 95% CI of WMD of AUC of the drug in healthy volunteer subgroup. This result indicates a significant difference between the subgroups. However, interpretation of subgroup analysis that were indirectly compared across studies should be done with caution.

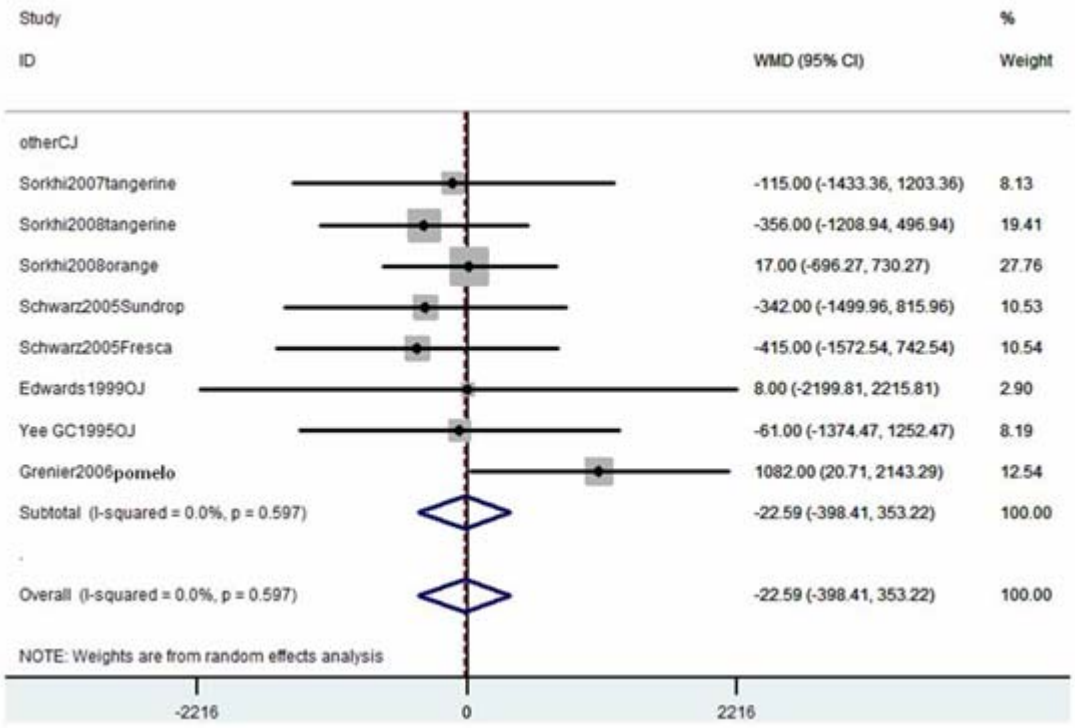

Figure 2. Forest plot results on effect of other types of citrus juices (including Seville orange juice, orange juice(OJ), tangerine juice, pomelo juice, and citrus soda) on AUC of cyclosporine

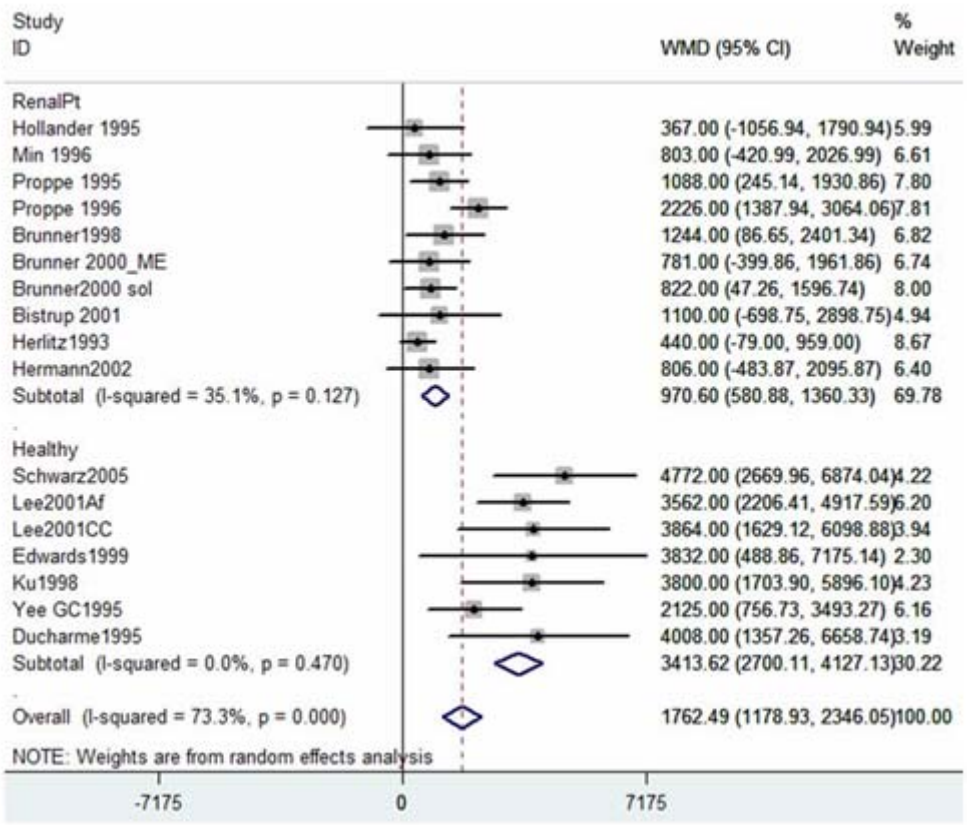

Figure 3. Forest plot results of the effect of grapefruit juice on AUC of cyclosporine in stable renal transplant patients and healthy volunteers

After subgrouping the studies using the stable renal transplant patients ingesting grapefruit juice by type of formulations (microemulsion vs olive oil based formulation), significant increases in AUC were demonstrated in both subgroups, and heterogeneity in both subgroups were not found (I^2 of both subgroups = 0.0%, $p > 0.1$). Indirect comparisons of the increases of AUC between both formulations showed overlap of 95% of WMD of AUC indicating no statistical difference between the two groups (microemulsion: 66.9–1634.7 ng·h/ml vs. olive oil based formulation: 350.3–1056.2 ngh/ml).

The method of juice ingestion (single dose vs. multiple doses) was used for subgrouping analysis in renal patients who ingested grapefruit juice concomitant with cyclosporine. When compared with the control group, the AUC of cyclosporine of patients who ingested a single dose (total administered volume ≤250 ml) of grape fruit juice was significantly increased (WMD = 532.8 ng·h/ml, 95%CI = 84.7–980.9 ng·h/ml, $p < 0.05$, $I^2 = 29.9\%$). Similarly, the AUC of cyclosporine of patients who ingested multiple doses (total administered volume 473–3311 ml) of grapefruit juice was significantly increased (WMD = 1169.95 ng·h/ml, 95%CI = 649.6–1645.3 ng·h/ml, $p < 0.005$, $I^2 = 0.0\%$). Indirect comparisons of the increases of AUC between both groups (single dose of the juice vs. multiple dose of the juice) showed an overlap of 95% of WMD of AUC indicating no statistical difference between the two groups.

Subgrouping by specificity of assay was not performed because of too few studies using a nonspecific assay among the included studies, thus sensitivity analysis was alternatively performed by excluding these nonspecific assay studies. The results were unaffected by removal of the studies using nonspecific analytical methods. Using a random-effect model in the meta-analysis, there was no difference in results with the analysis using a fixed model.

Additionally, we also conducted a meta-analysis to investigate the effect of grapefruit juice on minimum concentration at steady state of cyclosporine in 7 studies [24, 25, 27, 33, 34, 59, 62], the total number of the patients were 86. The result showed that

Cmin,ss of cyclosporine was statistically increased (WMD = 26.6 ng·h/ml, 95%CI = 12.4–40.7 ng·h/ml, $p < 0.001$); however, high heterogeneity ($I^2 = 82.3\%$, $p < 0.001$) was observed. Thus, this result needs to be interpreted with caution. Heterogeneity was explored by rechecking of data that was entered, by excluding individual studies one at a time and by subgrouping the pooling data by many factors such as type of formulation, specificity of assay, and method of grapefruit juice ingestion. However, significant heterogeneity remains. Results remained the same when data were reanalyzed using a fixed effect model instead of a random effects model.

The included studies have relatively low Jadad score (≤2). The studies are no double-blind design. Many studies mentioned randomization, but none of them specified the method of randomization. Only few studies described withdrawal and dropouts. In all subgroups (subgroup of renal transplant patients ingesting grapefruit juice, subgroup of healthy volunteer ingesting grapefruit juice, and subgroup of other types of citrus juice), there was no evidence of publication bias ($p > 0.10$ for the Egger and Begg–Mazumdar tests).

Discussion

To our knowledge, we are the first to report a meta-analysis of the pharmacokinetic interaction between citrus juices and cyclosporine. Our results confirmed that grapefruit juice significantly increases bioavailability of cyclosporine in both healthy volunteers and renal transplant patients. Other types of citrus juices including tangerine juice (*Citrus reticulate* var. Unshio Satsuma), Seville orange juice (*Citrus aurantium*), sweet orange juice (*Citrus sinensis* var Tamson navel), and citrus soda (Sun Drop and Fresca), in contrast, have no effect on the bioavailability of cyclosporine. However, based on a single study of pomelo juice (*Citrus grandis*) evaluating its effect on AUC of cyclosporine, the pomelo juice tended to have a significant interaction with cyclosporine [20].

According to our meta-analysis, there was no evidence of significant pharmacokinetic interaction between other types of the citrus juices and cyclosporine. Nonetheless, it might be possible that other types of citrus juices either have low levels of active entities affecting the bioavailability of cyclosporine [66], or the study had not sufficient power to detect any statistically significant effect of the juices on the AUC of cyclosporine. In addition, the numbers of subjects in those selected studies were relatively small [7-14], whereas the bioavailability of the drug is considered to be highly variable. Orange and tangerine contain neither GF-I-1 nor GF-I-4 [66], whereas, grapefruit juice has significant amount of both compounds. These furocoumarins have high affinity for CYP3A4 [66]. Interestingly, when orally administered to healthy volunteers, bitter orange (Seville orange) juice was shown to significantly increase the AUC values of felodipine and saquinavir by about 80% and 70%, respectively [53], whereas it had no effect on the AUC values of cyclosporine [17]. One possible explanation is that the juice is devoid of P-glycoprotein inhibitory activities, nonetheless, it possesses enteric CYP3A4 inhibitor (i.e. 6′,7′-dihydroxybergamottin) [53].

Among other types of the citrus juices, only pomelo juice has been shown to be able to statistically increase the bioavailability of cyclosporine in humans [20]. However, in the study, pomelo juice was produced from all other parts of the fruit (fruit meat, seeds, and white layer) except the outer green layer. Thus, it is not clear whether normal ingestion of the fruit meat (flesh) would affect the bioavailability of cyclosporine or not. Currently, no pharmacokinetic interaction study between pomelo and cyclosporine in renal transplant recipients has been conducted. Thus, to clarify this issue, a well design clinical study of the interaction is warranted.

Our results clearly demonstrated that grapefruit juice significantly increased the bioavailability of cyclosporine in terms of both AUC and Cmin,ss in both healthy volunteers and stable renal transplant recipients. In healthy volunteer subgroups, the data has no heterogeneity, and the increases of AUC in healthy volunteer subgroup were higher than those of the patients (**Figure 3**). All studies in healthy volunteers showed statistically significant differences of AUC of cyclosporine between control and grapefruit juice group (**Table 1**), whereas, in only 5 in 9 studies, the stable renal transplant patients showed such a difference (**Table 2**). This implys that normal subjects have a higher sensitivity for detecting the difference of bioavailability of high variability drugs (i.e. cyclosporine). In the stable renal transplant patient subgroup, statistical heterogeneity of WMD of AUC was low, and might not be important. The heterogeneity was probably a result of many contributing factors such as formulation [microemulsion (Neoral) vs. olive

oil based solution (Sandimmun)], specificity of measurement, randomization method, grapefruit juice ingestion procedure, and difference in dosage regimens of the drug.

According to meta-analysis within subgroups, there was no evidence indicating that the formulations used (microemulsion and olive oil based solution) can affect the interaction between grapefruit juice and cyclosporine. Brunner et al. reported that pediatric renal transplant patients received either microemulsion formulation or olive oil based formulation concomitant with grapefruit juice. In both groups, AUCs were increased. However, when compared between the two formulations, there was no statistical difference. As a result of the higher intraindividual variability of bioavailability of cyclosporine in the olive oil based formulation [67], the patients administered with grapefruit juice concomitantly might have higher risk of cyclosporine-induced toxicity.

From our findings, it appeared that a single ingestion of a glass of grapefruit juice with cyclosporine was sufficient to significantly increase the oral bioavailability of cyclosporine. This can be supported by the fact that grapefruit juice irreversibly inhibits CYP3A, and biosynthesis of a new enzyme is necessary [40]. Furthermore, difference in sources of grapefruit juice might lead to high variation of the active ingredients. Only few studies reported the amount of the active moieties [17, 31]. However, Proppe et al. [26] reported that patients chronically ingested grapefruit juice for 7 consecutive days showed a high increase of AUC. The increase of AUC value was the highest when indirectly compared with the results in other included studies conducting in the stable renal transplant patients ingesting grapefruit juice for 1–2 consecutive days (**Figure 3**). Notably, the other study by Proppe et al. [25] conducted with the same procedure was inconsistent with their previously mentioned study [26].

In the patients coadministered with grapefruit juice, the levels and AUC were increased. However, there was no report of the cyclosporine toxicity in those patients with or without grapefruit coadministration. In addition, cyclosporine concentrations in the patients ingesting grapefruit juice were within its therapeutic range. This probably implies that grapefruit juice ingestion may not lead to severe cyclosporine toxicity in most stable renal transplant patients using regular maintenance cyclosporine doses. However, grapefruit juice is clearly a factor contributing to the increase of cyclosporine systemic exposure, and high variation in its oral bioavailability (about 20% to 60%) [67] and may still lead to increases in serum creatinine in those with higher baseline drug levels of cyclosporine. Therefore, it is still necessary for patients to be aware of this interaction and its possible toxicity. They should report to their physicians when grapefruit juice is concomitantly administered to avoid unnecessary dose adjustments in cyclosporine and subsequent under-treatment once grapefruit juice is no longer ingested. In addition, a pharmacokinetic model describing the interaction between cyclosporine and active substances in grapefruit juice should be developed with an incorporation of an enzyme inhibition principle. The conceptual model can be a physiologically-based pharmacokinetic model with segmental intestine compartments [68, 69].

Our meta-analysis study has some limitations. First, the values of outcome measure used in this study were average values, because it was not possible to obtain the values from individual subjects. Second, the reliability of the majority of the included studies is low because of small sample size in most studies, and no double-blind design in any studies. However, the low Jadad score do not necessarily mean that the included studies are poor quality as it seems to be not possible to perform a double blind design, because of the completely different taste of citrus juice and water. Third, the difference of dosing regimen within and between studies might affect WMD of AUC and Cminss. Fourth, only stable renal transplant patients were included in this study.

In summary, there is strong evidence indicating that grapefruit juice intake increases the bioavailability of cyclosporine in humans. Based on current evidence, intake of other types of citrus juices (tangerine juice, Seville orange juice, sweet orange juice, and citrus soda) had no effect on the bioavailability of cyclosporine. However, coadministration of pomelo with cyclosporine should be conducted with caution, and further study needs to be carried out to clarify the effect of normal ingestion of fruit meat of pomelo on the bioavailability of cyclosporine.

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