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SYSTEMATIC REVIEW

Interaction of Citrus Juices with Cyclosporine: Systematic Review and Meta-Analysis

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Abstract

Introduction Cyclosporine is an immunosuppressant with narrow therapeutic window, metabolized mainly by cytochrome P450 3A4 (CYP3A4) and minimally by cytochrome P450 3A5 (CYP3A5). Citrus juices such as grapefruit juice (GFJ), orange, lemon, pomelo and lime were known to interact with cyclosporine in several randomized controlled trials. The present review is a systematic compilation and quantitative synthesis on the changes of cyclosporine pharmacokinetics with concomitant citrus juice administration.

Methods Electronic databases were searched for randomized controlled trials evaluating the effect of any citrus juice on the pharmacokinetics of cyclosporine comparing with water or placebo in healthy volunteers using appropriate search strategies. Percent mean difference with standard error was used to assess the magnitude of difference in the following outcome measures: area under curve from time of drug administration to 24 h (AUC_{0-24}), area under curve from time of drug administration to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to achieve C_{max} (T_{max}), elimination half-life ($T_{1/2}$), clearance (CL), volume of distribution and frequency for adverse drug reactions following administration of cyclosporine. RevMan 5.3 software was used to assess heterogeneity (by I^2 statistics), use random-effects model and generate pooled results and Forest plot.

Results A total of 57 studies were obtained with the search strategy, of which seven were found eligible to be included in the present review. The pooled percent mean difference [95 % CI] for GFJ in comparison to controls for AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and T_{max} of cyclosporine was observed to be 53 [43, 64], 53 [45, 62], 24 [12, 36] and 19 [12, 26], respectively. Similarly, pomelo juice was found to significantly increase both $AUC_{0-\infty}$ and C_{max} with the pooled percent mean difference [95 % CI] as 23 [13, 32] and 25 [1, 50], respectively but decrease $T_{1/2}$ {−8 [−15, −1]} of cyclosporine. Orange juice did not alter any of the pharmacokinetic parameter of cyclosporine significantly.

Conclusion Citrus juices especially GFJ and pomelo juice were found to significantly increase the plasma exposure of cyclosporine while orange juice did not exhibit any significant interaction with cyclosporine.

Key points

Citrus fruits especially grapefruit and pomelo juice significantly increase the plasma exposure of cyclosporine

Orange juice does not have any significant interaction with cyclosporine

1 Introduction

Cyclosporine is a well-known immunosuppressant found to be efficacious in auto-immune diseases and preventing transplant rejections especially in patients with renal transplantation with reports of 5 year graft survival of

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nearly 75 % [1, 2]. Cyclosporine is metabolized in the liver mainly by cytochrome P450 enzymes (CYP3A4 and CYP3A5) and the metabolites are predominantly excreted in bile [3]. Due to narrow therapeutic index, a high pharmacokinetic variability in patients due to alterations in liver and renal functions and the interaction with concomitantly administered drugs, therapeutic drug monitoring has been advised for cyclosporine [4]. Cyclosporine also exhibits a narrow therapeutic window with a bioavailability ranging between 20 and 50 %, associated with significant drug and food interactions and toxicities such as greater risks of cardiovascular disease, nephrotoxicity, metabolic syndrome, opportunistic and community-acquired infections and malignancies [5, 6]. Clinically, area under concentration curve ($AUC_{0–4}$ or $AUC_{0–9}$ or $AUC_{0–12}$) or cyclosporine pre-dose plasma concentrations or 2 h post dose concentrations have been recommended for therapeutic drug monitoring [7, 8]. A lower concentration of cyclosporine in the plasma has been associated with a higher rate of graft versus host disease in patients with bone marrow transplantation [9].

Citrus is a common term that is inclusive but not limited to commonly used fruits such as grapefruit, orange, lemon, pomelo and lime. Despite the fact that fruits are vital constituents for healthy diet, low intake of fruits has been identified to be one of the top 10 risk factors contributing to mortality [10]. Citrus fruits have been found to contribute to nearly half of the total fruit intake, of which orange juice tops the list in the United States of America (USA) [11]. GFJ is also widely consumed, contributing to 100 % of the daily value (DV) of vitamin C, 35 % of the DV for vitamin A, 8 % of the DV for fiber, 5 % of the DV for potassium, and less than 5 % of the DV for folate, calcium, magnesium, vitamin B6, thiamin, and niacin [12]. Consumption of GFJ has been associated with a favorable change in body weight, waist circumference, body mass index (BMI), triglycerides, C-reactive protein (CRP), and higher high-density lipoprotein (HDL) cholesterol [13]. GFJ also carries American Heart Association's check-mark considering the ability of the juice to lower low density cholesterol and risk of cardiovascular diseases [14]. Further, extracts from grapefruit and orange have been shown to inhibit the expression of CYP3A4 in the intestines and liver [15]. Additionally, reports also indicate that the above-mentioned extracts also reduce the activity of p-glycoprotein, the principal efflux drug transporter both in the intestines and liver thus interacting with drugs that predominantly depend on these metabolizing enzymes or transporters [16]. Citrus fruit administration has been found to significantly elevate the plasma concentrations of cyclosporine in Swine that can be attributed to its inhibition of CYP3A4 and p-glycoprotein [17]. Several traditional pharmacokinetic studies have been performed evaluating the effect of citrus fruits or juices with cyclosporine. A previous systematic review [18] that assessed the effect of citrus fruits on cyclosporine pharmacokinetics has serious methodological flaws precluding any scientific conclusion. Hence, the present systematic review and quantitative synthesis were carried out to assess the interaction of various citrus fruits with cyclosporine.

2 Methods

2.1 Information Sources and Search Strategy

The protocol for this review was registered with International prospective register of systematic reviews (PROSPERO) with the registration number CRD42016037491 [19]. A thorough literature search was conducted and was completed on 13 April 2016. The primary database used was Medline (via PubMed), Cochrane central register of clinical trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Google Scholar. The keywords used were citrus [tiab] AND cyclosporine [tiab]; grapefruit [tiab] AND cyclosporine [tiab]; pomelo [tiab] AND cyclosporine [tiab]; orange [tiab] AND cyclosporine [tiab]; lime [tiab] AND cyclosporine [tiab] and lemon [tiab] AND cyclosporine [tiab]. This search was further supplemented by hand searching of relevant cross-references that were obtained from the included studies in this review. No limits were applied to the year of study but only studies published in English language were included in the present review.

2.2 Eligibility Criteria

Only those studies with randomized controlled design with the following requirements were included in the present study:

1. Type of participants—healthy human beings as assessed by clinical history, physical and laboratory examination.
2. Type of intervention—administration of any citrus fruit or juices such as grapefruit, pomelo, orange, lime or lemon.
3. Comparison—water or placebo.
4. Outcome—the primary outcome measures considered in the study were area under concentration curve (AUC), maximum concentration achieved in the plasma (C_{max}) and time to achieve maximum concentration (T_{max}) of cyclosporine. The secondary outcome measures were elimination half-life, clearance, volume of distribution, absorption rate constant and adverse effects of cyclosporine.

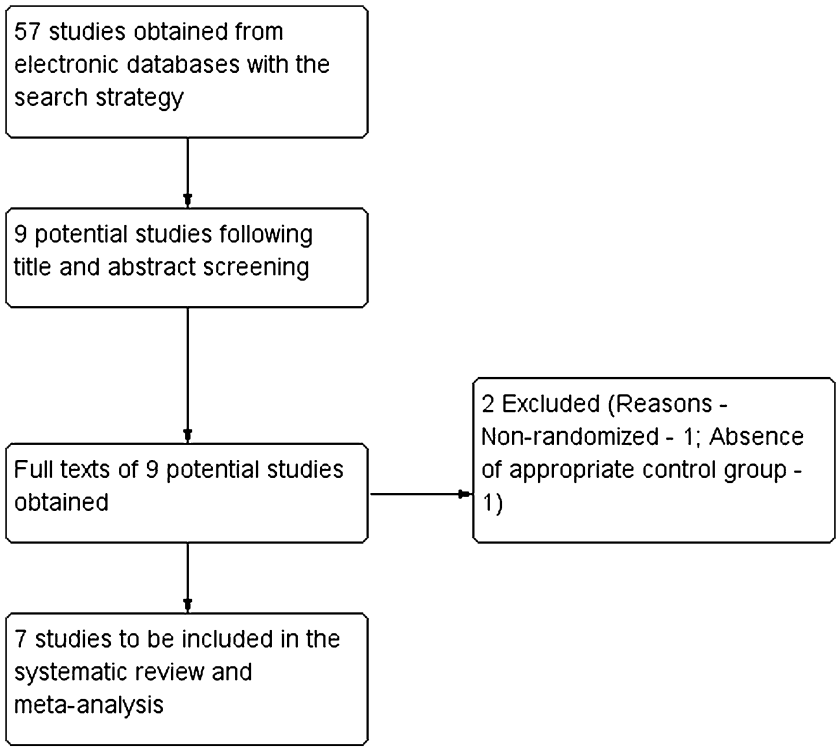

Fig. 1 Study flow diagram. The search strategy led to a hit of 57 studies of which finally a total of 7 studies were found to be eligible to be included in the present review and meta-analysis

2.3 Study Procedure

Two authors independently screened the databases and independently reviewed the identified abstracts for suitability. Full-texts articles were obtained following abstract screening for those found to be eligible to be included in the review. A pre-tested data extraction form was created and the two authors independently extracted the following data from each eligible study: trial site, year, trial methods, participants, interventions, and outcomes. The two authors independently extracted data with disagreement resolved through discussion. The extracted data were analyzed using non-Cochrane mode in RevMan 5.3 software. The methodological quality of eligible trials was independently assessed by both the authors using The Cochrane collaboration's tool for assessing the risk of bias. We followed the guidance to assess whether trials took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. The judgment was categorized into low, high or unclear risk of bias [20]. Generic inverse variance method was used and the percent mean differences with standard error were considered for the final assessment from individual studies. 95 % confidence interval (95 % CI) was used to represent the deviation from the point estimate for both the individual studies and the pooled estimate. The heterogeneity between the studies were assessed using Forest plot visually, I^2 statistics wherein more than 50 % was considered to have moderate to severe heterogeneity and Chi-square test with a statistical P value of less than 0.10 to indicate statistical significance. Random-effect models were used in case of moderate to severe heterogeneity (I^2 values more than 75 %). The present meta-analysis was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

3 Results

3.1 Search Results

A total of 57 studies were obtained with the search strategy of which 9 potential studies were selected by title and abstract screening. However, one was not randomized and one did not have an appropriate control group to be included in the present review; thus, seven studies [22–28] were found to be finally eligible to be included. Figure 1 depicts the study flow diagram. Considering the presence of only seven eligible trials that can be included in the review, publication bias could not be assessed. All the studies were cross-over studies with a minimum wash out period of 7 days, conducted in a total of 94 healthy adults. Key details of the individual studies are mentioned in Table 1 and no clinical heterogeneity was observed between the included studies. Two studies [22, 24] have

Table 1 Characteristics of the included studies

Study Id; country	Population; sample size; study design	Intervention	Comparator	Outcome
Yee et al. 1995 [11]; USA	Non-smoking, non-obese healthy adults aged 18–33 years; Total number of participants—14; cross-over	250 ml GFJ orally with 300 mg cyclosporine at one period; 250 ml orange juice with 300 mg cyclosporine orally at another period	250 ml water with 300 mg cyclosporine	AUC_{0-24}, C_{max}, T_{max} of cyclosporine
Ku et al. 1998 [12]; USA	Healthy individuals as assessed by complete history, physical examination and laboratory tests; Total number of participants—12; cross-over	5 mg/kg cyclosporine orally with GFJ	5 mg/kg cyclosporine orally with water	AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, CL of cyclosporine
Edwards et al. 1999 [13]; USA	Healthy volunteers who were non-smokers, within 20 % of ideal body weight, refrained from alcohol and medications throughout the study; total number of participants—7; cross-over	7.5 mg/kg cyclosporine with 8 oz of GFJ orally during one period; 7.5 mg/kg cyclosporine with 8 oz of orange juice orally during another period	7.5 mg/kg cyclosporine with 8 oz of water orally	AUC_{0-24}, C_{max}, T_{max} of cyclosporine
Schwarz et al. 2005 [14]; USA	Healthy, non-smoking, Caucasians with nil significant medical history, normal physical and routine hematological and serum chemical tests. In case of females, pregnancy excluded; total number of participants—12; cross-over	2.5 mg/kg cyclosporine microemulsion preparation with 591 ml GFJ	2.5 mg/kg cyclosporine microemulsion preparation with 227 ml water	AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, CL of cyclosporine
Lee et al. 2001 [15]; USA	Healthy non-smoking, non-alcoholic, individuals with normal medical history, physical examination and electrocardiogram were recruited in the study. Total number of participants—23 (11 African Americans and 12 Caucasians); Cross-over	5 mg/kg cyclosporine with 6 oz of GFJ	5 mg/kg cyclosporine with 6 oz of water	$AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, CL of cyclosporine
Anlamlert et al. 2015 [16]; Thailand	Thai males aged between 18 and 45 years of age with BMI 18–25 kg/m^2 with overall good health and normal laboratory tests; Total number of participants—14; cross-over	Single dose of 200 mg cyclosporine with 500 g pomelo pulp	Single dose of 200 mg cyclosporine with 200 ml water	$AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$ of cyclosporine
Grenier et al. 2006 [17]; Canada	Healthy adult males aged between 18 and 45 years without any drugs or substances that are strong inhibitors or inducers of CYP family of enzymes; total number of participants—12; cross-over	Single dose of 200 mg cyclosporine with 240 ml cranberry juice during one period; 200 mg cyclosporine with 240 ml of pomelo juice during another period	Single dose of 200 mg cyclosporine with 240 ml water	AUC_{0-36}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$ of cyclosporine

GFJ grapefruit juice, AUC_{0-24}, area under the curve from the time of administration till 24 h, C_{max} maximum concentration achieved in the plasma, T_{max}, time to achieve C_{max}, *BMI* body mass index, *CYP* cytochrome P450

assessed the effect of GFJ and orange juice in comparison to water. Lee et al. [26] have mentioned the results separately for African-American and Caucasians and so suffix 'AA' and 'C' have been used along with the conventional way in the Forest plots to represent the same. A summary of risk of bias as per Cochrane's tool is depicted in Fig. 2.

3.2 Pooled Results

3.2.1 Area Under the Curve (AUC)

AUC_{0-24} of cyclosporine has been evaluated in 4 studies that compared the effect of GFJ and 2 studies that compared the effect of orange juice to water with cyclosporine in a total of 45 and 21 healthy human beings. Figure 3a depicts the Forest plot of the estimate that shows a significant increase in AUC_{0-24} of cyclosporine with GFJ ($P < 0.00001$). No significant change in AUC_{0-24} of cyclosporine was observed with orange juice compared to water (Fig. 3b). $AUC_{0-\infty}$ of cyclosporine has been assessed in 4 studies with a total of 47 participants with GFJ and 2 studies with a total of 26 participants with pomelo juice. Figure 4a, b depicts the Forest plots of $AUC_{0-\infty}$ of cyclosporine with GFJ and pomelo juice, respectively, and a statistically significant increase in $AUC_{0-\infty}$ of cyclosporine was observed with both ($P < 0.00001$).

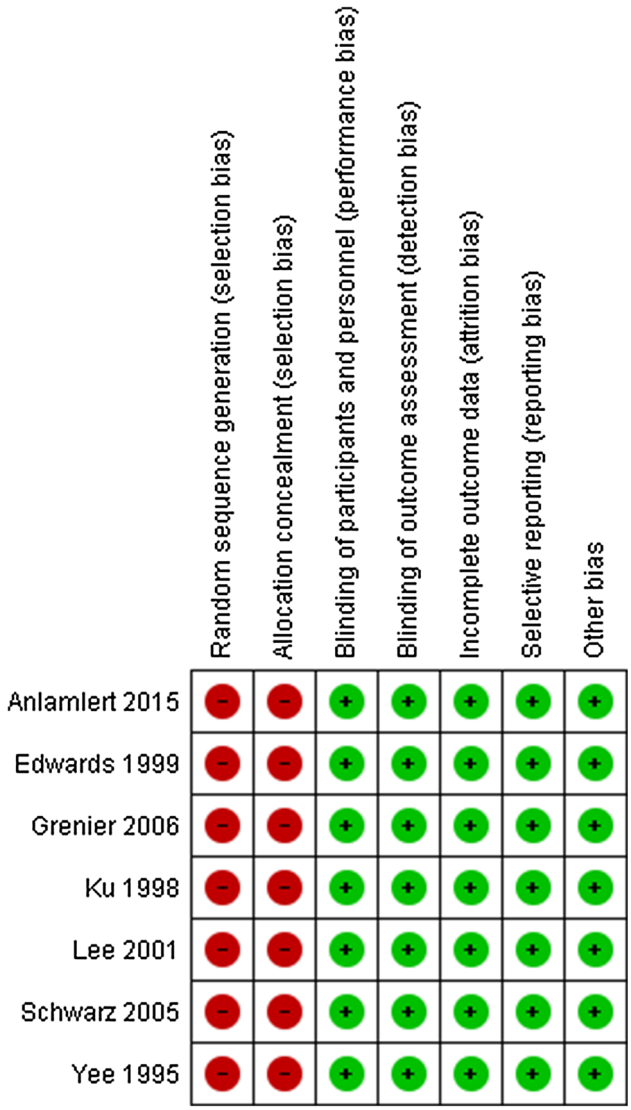

Fig. 2 Summary of risk of bias of the included studies. *Green circle* with *plus symbol* indicates the report of the particular entity in the article and *red circle* with *minus symbol* indicates the absence of the same. All the included studies did not report the method used for generating randomization sequence and for concealing the allocation. No other bias was detected

3.2.2 Maximum Concentration (C_{max})

C_{max} of cyclosporine was assessed in 5 studies with a total of 68 participants for GFJ, 2 studies with a total of 21 participants for orange juice and 2 studies with a total of 26 participants with pomelo juice. GFJ (Fig. 5a) and pomelo juice (Fig. 5b) significantly increase C_{max} of cyclosporine in comparison to controls ($P < 0.00001$ and $P = 0.04$, respectively) but not the orange juice (Fig. 5c).

3.2.3 Time to Achieve C_{max} (T_{max})

A total of 5 studies evaluated T_{max} of cyclosporine with GFJ, 2 with pomelo juice and one with orange juice. A significant increase in T_{max} of cyclosporine was observed with GFJ (Fig. 6a; $P < 0.00001$) but not with pomelo juice (Fig. 6b) and orange juice {Pooled percent difference [95 % CI]–8 [−7, 25]}.

3.2.4 Elimination Half-Life ($T_{1/2}$)

Three studies compared the effect of GFJ on $T_{1/2}$ of cyclosporine with water in a total of 47 participants and 2 studies in a total of 26 participants with pomelo juice. No significant changes were observed with GFJ (Fig. 7a) while pomelo juice significantly decreased $T_{1/2}$ of cyclosporine (Fig. 7b; $P = 0.03$).

3.2.5 Clearance (CL)

A total of 3 studies in a total of 47 participants reported the changes in clearance of cyclosporine following the administration of GFJ and no significant change was observed in the same (Fig. 8).

3.2.6 Volume of Distribution and Adverse Effects

None of the included studies reported any adverse drug reactions with cyclosporine or the changes with volume of distribution with concomitant administration of citrus juice.

4 Discussion

We carried out the present study to systematically gather the evidence pertaining to randomized controlled trials that had assessed the effect of citrus fruit administration on the pharmacokinetics of cyclosporine in healthy human beings. A total of 7 eligible studies were included in the present review with a total of 98 participants. Concomitant administration of GFJ has been shown to increase AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and T_{max} of cyclosporine by 53, 53, 24 and 18.7 %, respectively. The effect of pomelo juice was assessed in 2 studies and was found to significantly increase $AUC_{0-\infty}$ and C_{max} by 23 and 25 %, respectively, while $T_{1/2}$ was observed to decrease by 8 %. Orange juice was not found to have any significant interaction with cyclosporine.

A survey from USA have shown that nearly one-tenth of the US population aged above 2 years consume GFJ [29].

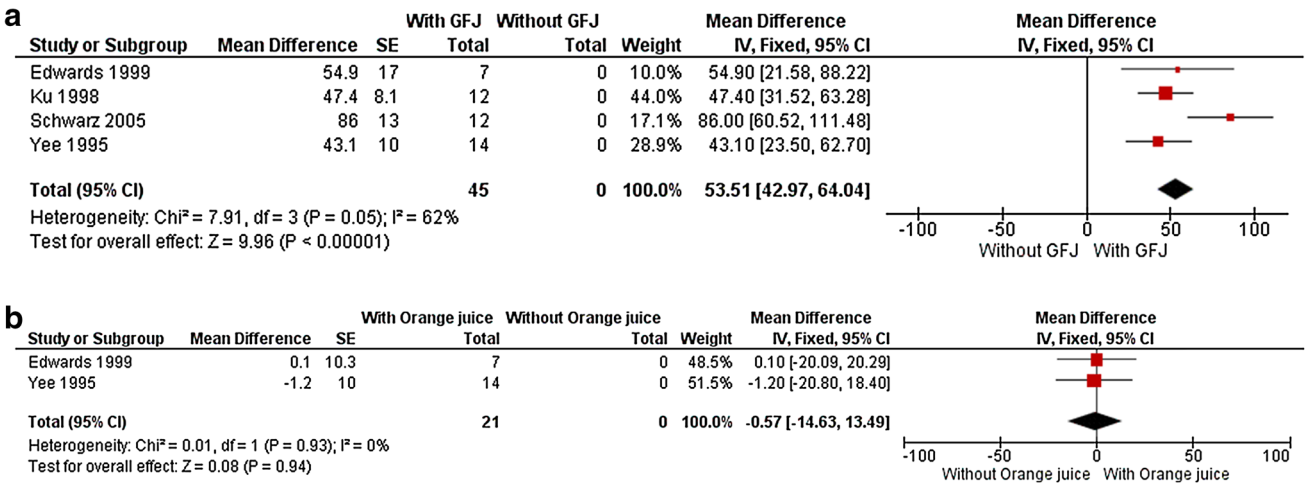

Fig. 3 **a** Forest plot of $AUC_{0\text{-}24}$ of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant increase in $AUC_{0–24}$ of cyclosporine was observed with GFJ in comparison to control. **b** Forest plot of $AUC_{0–24}$ of cyclosporine with orange juice. Both the mean difference and SE were estimated as percent changes with respect to control. No significant changes were observed in $AUC_{0–24}$ of cyclosporine with orange juice in comparison to control

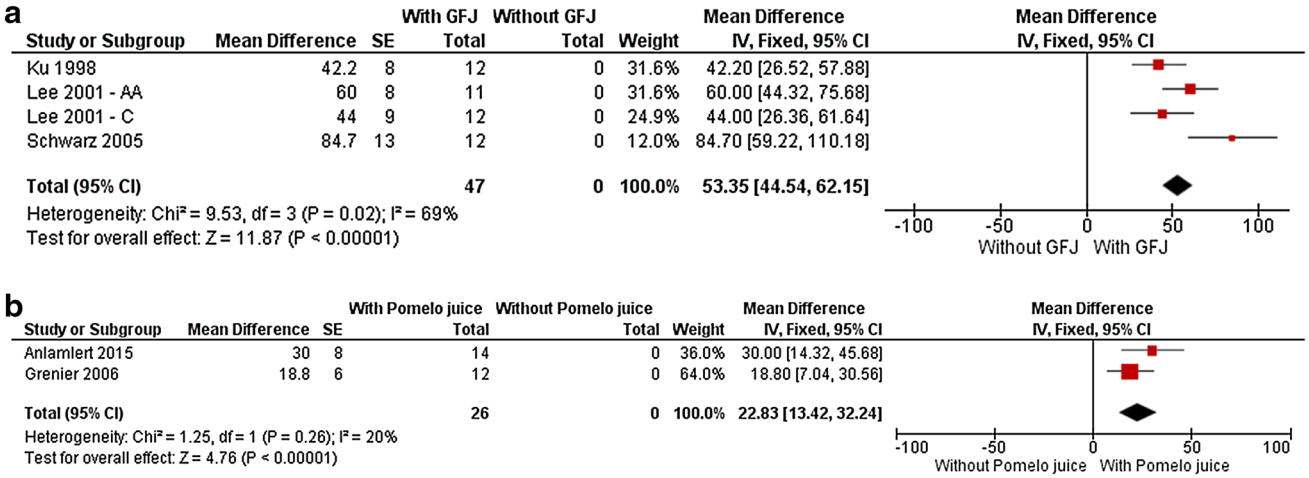

Fig. 4 **a** Forest plot of $AUC_{0–\infty}$ of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant increase in $AUC_{0–\infty}$ of cyclosporine was observed with GFJ in comparison to control. **b** Forest plot of $AUC_{0–\infty}$ of cyclosporine with pomelo juice. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant increase in $AUC_{0–\infty}$ of cyclosporine was observed with pomelo juice in comparison to control

GFJ contains active principles such as naringin, quercetin, kaempferol and 6′7′ dihydroxybergamottin which were found to significantly inhibit the metabolizing enzymes and principal efflux transporter [P-glycoprotein (P-gp)], thereby resulting in drug interactions [30]. Lown et al. [31] established that liver CYP3A4 accounted for 32 % of the variability of peak blood concentration of cyclosporine while P-gp accounted for 30 % variability and both these are inhibited by GFJ. We found a significant increase in the plasma exposure of cyclosporine with GFJ administration in the present review. Sermsappasuk et al. [18] did a similar quantitative synthesis for interaction of citrus juices with cyclosporine but the review was biased in the following ways: results of a non-randomized study was included along with other studies that were randomized, risk of bias of the included studies were not assessed, results were pooled between the juices despite their significant differences in the nature and amount of active principles they contain and the effect estimate used was weighted mean difference instead of percent difference from the baseline values. A similar increase in the extent of absorption of cyclosporine has also been noted with the administration of pomelo juice but not with orange juice. Besides the above-mentioned active principles, two other

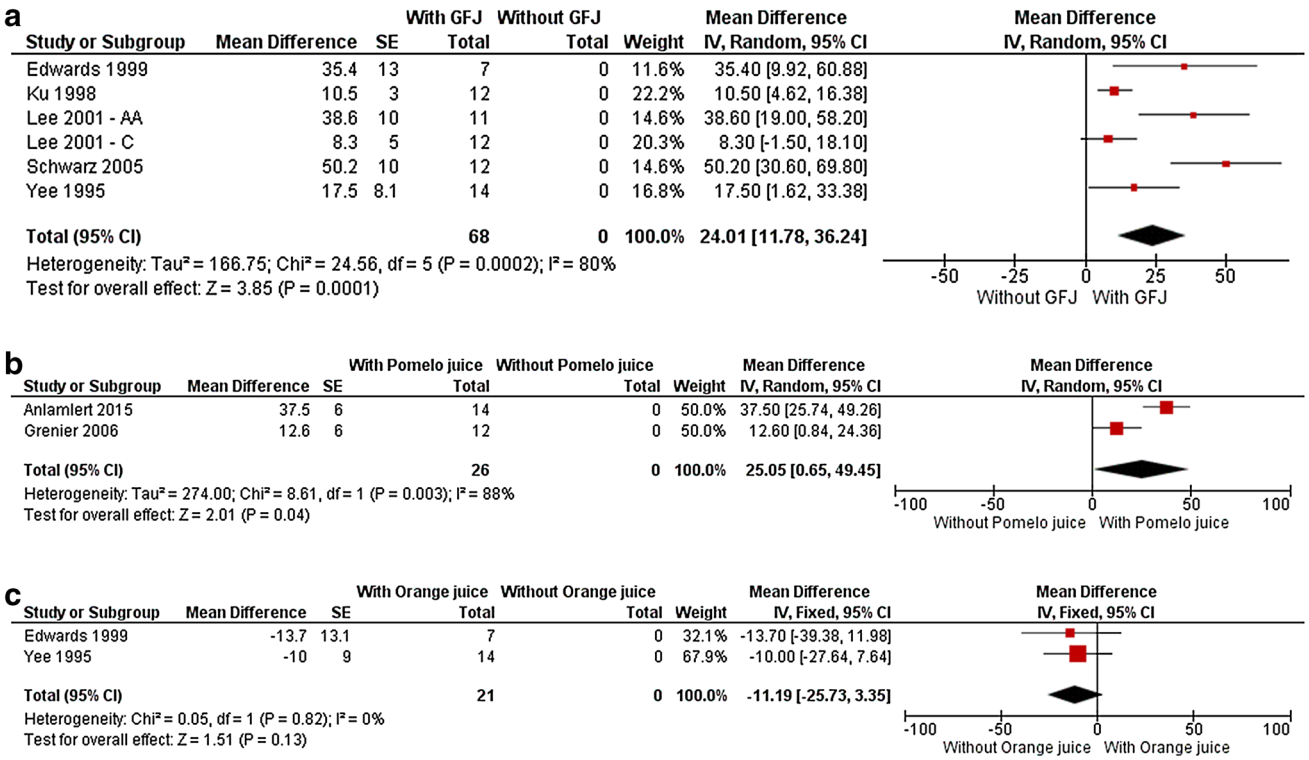

Fig. 5 **a** Forest plot of C_{max} of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant increase in Cmax of cyclosporine was observed with GFJ in comparison to control. **b** Forest plot of C_{max} of cyclosporine with pomelo juice. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant increase in C_{max} of cyclosporine was observed with pomelo juice in comparison to control. **c** Forest plot of C_{max} of cyclosporine with Orange juice. Both the mean difference and SE were estimated as percent changes with respect to control. No significant change in C_{max} of cyclosporine was observed with orange juice in comparison to control

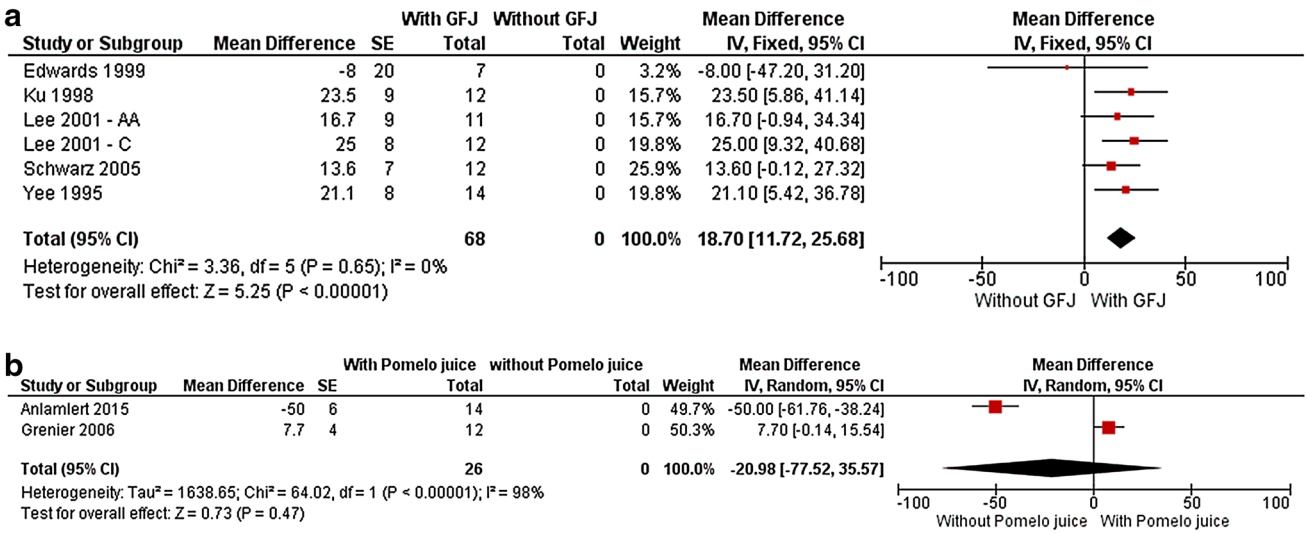

Fig. 6 **a** Forest plot of T_{max} of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. T_{max} of cyclosporine was observed to significantly prolong with GFJ in comparison to control. **b** Forest plot of T_{max} of cyclosporine with Pomelo juice. Both the mean difference and SE were estimated as percent changes with respect to control. No significant change in T_{max} of cyclosporine was observed with pomelo juice in comparison to control

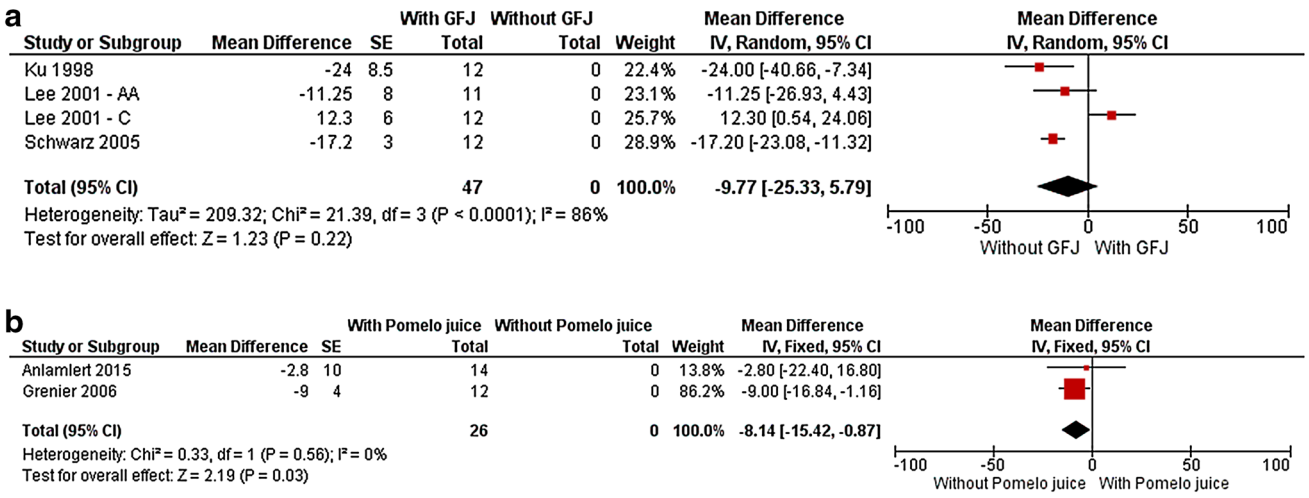

Fig. 7 **a** Forest plot of $T_{1/2}$ of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. No significant change was observed in $T_{1/2}$ of cyclosporine with GFJ in comparison to control. **b** Forest plot of $T_{1/2}$ of cyclosporine with Pomelo juice. Both the mean difference and SE were estimated as percent changes with respect to control. A statistically significant decrease in $T_{1/2}$ of cyclosporine was observed with pomelo juice in comparison to control

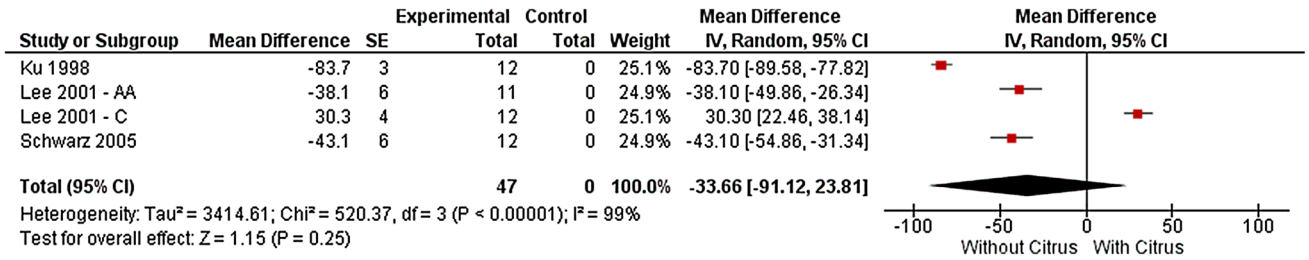

Fig. 8 Forest plot of CL of cyclosporine with GFJ. Both the mean difference and SE were estimated as percent changes with respect to control. No significant changes were observed with the clearance of cyclosporine with citrus juice as compared to water

bergamottin derivatives, GFJ inhibitor-1 and 4, have been reported to be present in GFJ that inhibit CYP 3A4 100 times more [32]. Both these compounds are not present in orange juice that may explain the absence of a significant interaction with cyclosporine [33]. Further, scanty evidence exists regarding the timeline of administration of juices and cyclosporine during which interaction could occur or could be averted. Also, reports indicate that GFJ reduces the levels of CYP 3A4 by as much as 47 % within four hours of ingestion and even after 24 h, 30 % of its effect is still present in the intestinal cells and hepatocytes [33]. Hence, a single glass of regular strength of GFJ ingestion is enough in most of the cases to adequately interact with the concomitantly ingested drugs [34]. Considering the narrow therapeutic window of cyclosporine, administration of GFJ might significantly result in increased risk of toxicity [35].

The present review is limited in not searching for the potential studies from EMBASE and not including the studies that were conducted in patients due to the possible interaction factors with the disease process and concomitant drugs. To conclude, we found a significant increase in the plasma exposure of cyclosporine following GFJ and pomelo juice thus patients receiving cyclosporine should avoid consuming the above-mentioned juices to reduce the risk of toxicity due to cyclosporine. No significant changes were observed in the pharmacokinetics of cyclosporine with concomitant administration of orange juice.

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Compliance with Ethical Standards

Conflict of Interest KS and GS have no conflict of interest.

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