

Clinical Pharmacokinetics of Fexofenadine: A Systematic Review

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Supplementary Table S1. PRISMA Checklist 2020

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of	4

Section and Topic	Item #	Checklist item	Location where item is reported
measures		results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	6,7,8,9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and it's precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9,12,13,14,18, 19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	4,6

Section and Topic	Item #	Checklist item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6 (Supplementary Tables S3,S4,S5,S6)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21, 22, 23
	23b	Discuss any limitations of the evidence included in the review.	23
	23c	Discuss any limitations of the review processes used.	23
	23d	Discuss implications of the results for practice, policy, and future research.	23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

Supplementary Table S2. Screening of articles based on title, abstract, involvement of animals, and accessibility

Sr #	Title of article	Exclusion basis
1	Allocco, F. T., V. Votypka, M. deTineo, R. M. Naclerio and F. M. Baroody (2002). "Effects of fexofenadine on the early response to nasal allergen challenge." <u>Annals of allergy, asthma & immunology</u> 89 (6): 578-584.	Abstract
2	Asahina, A., T. Etoh, A. Igarashi, S. Imafuku, H. Saeki, Y. Shibasaki, Y. Tomochika, S. Toyoizumi, M. Nagaoka and M. Ohtsuki (2016). "Oral tofacitinib efficacy, safety and tolerability in Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis: a randomized, double-blind, phase 3 study." <u>Journal of dermatology</u> . 43 (8) (pp 869-880), 2016. Date of publication: 01 aug 2016.	Title
3	Barrett-O'Keefe, Z., R. E. Kaplon and J. R. Halliwill (2013). "Sustained postexercise vasodilatation and histamine receptor activation following small muscle-mass exercise in humans." <u>Experimental physiology</u> 98 (1): 268-277.	Title
4	Bensch, G. W., H. S. Nelson and L. C. Borish (2002). "Evaluation of cytokines in nasal secretions after nasal antigen challenge: lack of influence of antihistamines." <u>Annals of allergy, asthma & immunology</u> 88 (5): 457-462.	Title
5	Blum, R. A., W. Kraft, J. A. Stewart, S. Meeves, G. Georges and S. J. Kovacs (2005). "Short-term safety, tolerability, and pharmacokinetics of desloratadine and fexofenadine in healthy adults identified as desloratadine slow metabolizers (DSMs)." <u>Journal of allergy and clinical immunology</u> 115 (2 Suppl): S127.	Full text
6	Bosilkovska, M., C. F. Samer, J. Deglon, A. Thomas, J. A. Desmeules and Y. Daali (2016). "Validation of the Geneva cocktail for cytochrome P450 phenotyping using innovative dried blood sampling method." <u>Drug metabolism reviews</u> 48 : 21.	Title
7	Botson, J., P. M. Peloso, K. Obermeyer, B. Lamoreaux, M. E. Weinblatt and J. Peterson (2020). "Pegloticase response improvement by co-treatment with methotrexate: results from the mirror open-label clinical trial in patients with uncontrolled gout." <u>Annals of the rheumatic diseases</u> 79 (SUPPL 1): 446.	Title
8	Bulan, K., M. Aydogan, R. Siraneci and C. Y. Aydogmus (2013). "The effect of montelukast on wheal reactions in skin prick tests: a double-blind-placebo-controlled randomized trial." <u>International journal of pediatric otorhinolaryngology</u> 77 (10): 1655-1658.	Title
9	Chi, C. T. (2012). "A randomised, placebo-controlled, two-period crossover pharmacokinetic study on modulation of human P-gp by multiple doses of Astragalus root extract granules using fexofenadine as a phenotyping probe." https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-TTRCC-12002288 .	Title
10	Ellis, A. K., M. Murrieta-Aguttes, S. Furey and C. Carlsten (2020). "Efficacy of fexofenadine HCL 180 mg vs placebo in seasonal allergic rhinitis aggravated in presence of air pollutants: phase 3, sequential and parallel-group, double-blind, randomized study." <u>Allergy</u> 75 (SUPPL 109): 508.	Abstract

11	Ellis, A. K., M. Murrieta-Aguttes, S. Furey and C. Carlsten (2020). "Phase 3, single-center, sequential and parallel-group, double-blind, randomized study evaluating the efficacy and safety of Fexofenadine Hydrochloride 180 mg (Allegra®/Telfast®) versus placebo in subjects suffering from Allergic Rhinitis with symptoms aggravated in presence of pollutants: analysis of individual symptom scores." <u>World Allergy Organization journal</u> 13 (8).	Abstract
12	Ely, M. R., S. A. Romero, D. C. Sieck, J. E. Mangum, M. J. Luttrell and J. R. Halliwill (2017). "A single dose of histamine-receptor antagonists before downhill running alters markers of muscle damage and delayed-onset muscle soreness." <u>Journal of applied physiology</u> (Bethesda, Md. : 1985) 122 (3): 631-641.	Title
13	EU/EEA, E. O. (2017). "Safety, Efficacy and Pharmacokinetic Study of Allegra in Pediatric Patients With Atopic Dermatitis (AD)." https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-000251-74-Outside-EU/EEA .	Not Accessible
14	EU/EEA, E. O. (2017). "Safety, Efficacy and Pharmacokinetic Study of Allegra in Pediatric Patients With Perennial Allergic Rhinitis (PAR)." https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-000239-15-Outside-EU/EEA .	Not Accessible
15	Euctr, B. E. (2008). "CYP3A4/5 and PGP activity in renal transplantation. A study assessing in vivo hepatic and intestinal CYP3A4/5 and PGP activity in kidney transplant recipients and its relationship with genetic and non-genetic variables and the pharmacokinetics and metabolism of Tacrolimus." https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2008-004158-33-BE .	Title
16	Glaeser, H., D. G. Bailey, G. K. Dresser, J. C. Gregor, U. I. Schwarz, J. S. McGrath, E. Jolicoeur, W. Lee, B. F. Leake, R. G. Tirona and et al. (2007). "Intestinal drug transporter expression and the impact of grapefruit juice in humans." <u>Clinical pharmacology and therapeutics</u> 81 (3): 362-370.	Title
17	Grant, J. A., L. Danielson, J. P. Rihoux and C. DeVos (1999). "A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24 h in." <u>Allergy</u> 54 (7): 700-707.	Abstract
18	Grant, J. A., J. M. Riethuisen, B. Moulaert and C. DeVos (2002). "A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects." <u>Annals of allergy, asthma & immunology</u> 88 (2): 190-197.	Abstract
19	Gupta, S., C. Banfield, J. Lim, M. Marino, R. P. Clement, M. B. Affrime and V. Batra (2001). "Unlike Fexofenadine, the pharmacokinetics of desloratadine are minimally altered by coadministration with azithromycin." <u>Journal of allergy and clinical immunology</u> 107 (2): S159.	Title
20	Hiraoka, K., M. Tashiro, T. Grobosch, M. Maurer, K. Oda, J. Toyohara, K. Ishii, K. Ishiwata and K. Yanai (2015). "Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine." <u>Expert opinion on drug safety</u> 14 (2): 199-206.	Title
21	Ieiri, I., Y. Doi, K. Maeda, T. Sasaki, M. Kimura, T. Hirota, T. Chiyoda, M. Miyagawa, S. Irie, K. Iwasaki and et al. (2012). "Microdosing clinical study: pharmacokinetic, pharmacogenomic (SLCO2B1), and interaction (grapefruit juice) profiles of celiprolol following the oral microdose and therapeutic dose." <u>Journal of clinical pharmacology</u> 52 (7): 1078-1089.	Title

22	Irct20180620040164N (2021). "bioequivalence study of Fexofenadine 180 mg tablets in 24 healthy male under fasting conditions." https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20180620040164N7 .	Abstract
23	Irct20180620040164N (2023). "Comparative in vivo evaluation of 2 Fexofenadin 30 mg/5 ml Suspension formulations." https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20180620040164N42 .	Abstract
24	Irct20200513047423N (2022). "Bioequivalence study of Fexofenadine 180 mg Tablets." https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20200513047423N6 .	Abstract
25	JapicCti (2019). "A Study to Assess the Effect of S-600918 on the Pharmacokinetics of Fexofenadine, Rosuvastatin, and Atorvastatin in Healthy Adult Subjects." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-JapicCTI-194757 .	Not Accessible
26	Kaliner, M. A., M. V. White, A. Economides, T. Crisalida, M. Hale, Y. Liao, C. D. Christian, G. C. Georges, T. H. Woodworth and S. G. Meeves (2003). "Relative potency of fexofenadine HCl 180 mg, loratadine 10 mg, and placebo using a skin test model of wheal-and-flare suppression." <i>Annals of allergy, asthma & immunology</i> 90 (6): 629-634.	Abstract
27	Kaur, G., R. Dhingra and M. Singh (2017). "Assessment of clinical effectiveness of various drugs in the patients of allergic rhinitis visiting tertiary care hospital of Punjab, India." <i>Clinical rhinology</i> 10 (3): 132-136.	Title
28	Kharasch, E. D., A. Walker, C. Hoffer and P. Sheffels (2005). "Evaluation of first-pass cytochrome P4503A (CYP3A) and P-glycoprotein activities using alfentanil and fexofenadine in combination." <i>Journal of clinical pharmacology</i> 45 (1): 79-88.	Full text
29	Lennox, R. D. and M. J. Leahy (2004). "Validation of the Dermatology Life Quality Index as an outcome measure for urticaria-related quality of life." <i>Annals of allergy, asthma & immunology</i> 93 (2): 142-146.	Title
30	Magen, E., C. Yosefy, R. J. Viskoper and J. Mishal (2006). "Treatment of allergic rhinitis can improve blood pressure control." <i>Journal of human hypertension</i> 20 (11): 888-893.	Title
31	Mahatme, M. S., G. N. Dakhale, K. Tadke, S. K. Hiware, S. D. Dudhgaonkar and S. Wankhede (2016). "Comparison of efficacy, safety, and cost-effectiveness of montelukast-levocetirizine and montelukast-fexofenadine in patients of allergic rhinitis: a randomized, double-blind clinical trial." <i>Indian journal of pharmacology</i> 48 (6): 649-653.	Not Accessible
32	Mann, R. D. (2002). "Executive summary fexofenadine." <i>Journal of drug evaluation: respiratory medicine</i> 1 (1): 9-11.	Title

33	Mody, D., W. Yu, J. Lin and P. Ibrahim (2022). "Clinical Evaluation of Cudetaxestat for Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Potential Drug-Drug Interactions." <u>American journal of respiratory and critical care medicine</u> 205 (1).	Title
34	Nct (2002). "Effects of Ginseng and Ginkgo on Drug Disposition in Man." https://clinicaltrials.gov/show/NCT00029692 .	Title
35	Nct (2008). "Fexofenadine (Allegra®) in Healthy Adults Who Have Been Identified as Slow Metabolizers for Desloratadine." https://clinicaltrials.gov/show/NCT00636870 .	Abstract
36	Nct (2012). "Safety Study of Levocetirizine and Fexofenadine." https://clinicaltrials.gov/show/NCT01586091 .	Not Accessible
37	Nct (2013). "Dose Proportionality of Fexofenadine in Healthy Human Egyptian Volunteers." https://clinicaltrials.gov/show/NCT01767272 .	Not Accessible
38	Nct (2014). "Clinical Trials on Evaluate the Red Ginseng and Fermented-Red Ginseng Affect to Drug Metabolizing Enzyme and Transporter in Healthy Volunteers." https://clinicaltrials.gov/show/NCT02056743 .	Not Accessible
39	Nct (2015). "Evaluation of the Potential Pharmacokinetic Interactions Between Probe Drugs in the Geneva Phenotyping Cocktail." https://clinicaltrials.gov/show/NCT02391688 .	Not Accessible
40	Nct (2017). "The Effect Dialysis on the Pharmacokinetics of Fexofenadine." https://clinicaltrials.gov/show/NCT03078777 .	Abstract
41	Nct (2017). "Study to Evaluate the Pharmacokinetics and Pharmacodynamics of JMI-001." https://clinicaltrials.gov/show/NCT03183297 .	Title
42	Nct (2017). "Oral Pharmacokinetics of Sulfasalazine, Paracetamol, Fexofenadine and Valsartan Using Different Administration Mediums." https://clinicaltrials.gov/show/NCT03012763 .	Not Accessible
43	Nct (2020). "Excipient Effect on Drug Absorption in Humans." https://clinicaltrials.gov/show/NCT04534153 .	Title
44	North, M. L., T. J. Walker, L. M. Steacy, B. G. Hobsbawn, R. J. Allan, F. Hackman, X. Sun, A. G. Day and A. K. Ellis (2014). "Add-on histamine receptor-3 antagonist for allergic rhinitis: a double blind randomized crossover trial using the environmental exposure unit." <u>Allergy, asthma and clinical immunology</u> 10 (1).	Abstract

45	Okubo, K., M. Gotoh, M. Asako, Y. Nomura, M. Togawa, A. Saito, T. Honda and Y. Ohashi (2017). "Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study." <u>Allergology international</u> 66 (1): 97-105.	Title
46	Okubo, K., M. Togawa, T. Honda and K. Hashiguchi (2016). "Efficacy of bilastine in Japanese cedar pollinosis: results of a randomized, double-blind, 4-way crossover, placebocontrolled, phase II study using an artificial exposure chamber (OHIO Chamber)." <u>Allergy</u> 71 : 384.	Title
47	Otsuka, H., K. Otsuka, S. Matsune and K. Okubo (2019). "Nasal symptoms reduction and decreased neutrophilia in japanese cedar pollinosis with prophylactic treatment with a combination of montelukast, fexofenadine, and fluticasone nasal spray." <u>American journal of rhinology & allergy</u> 33 (4): 369-377.	Abstract
48	Pawlowicz, R., K. Wytrychowski and B. Panaszek (2018). "Eradication of helicobacter pylori, as add-on therapy, has a significant, but temporary influence on recovery in chronic idiopathic urticaria: a placebo-controlled, double blind trial in the polish population." <u>Postepy dermatologii i alergologii</u> 35 (2): 151-155.	Abstract
49	Pellinger, T. K., B. R. Dumke and J. R. Halliwill (2013). "Effect of H1- and H2-histamine receptor blockade on postexercise insulin sensitivity." <u>Physiological reports</u> 1 (2).	Abstract
50	Sanchez, J., J. Zakzuk and R. Cardona (2016). "Clinical impact in quality of life of EAACI/GA2LEN/EDF/WAO guidelines for chronic spontaneous urticaria: evaluation step by step." <u>Allergy</u> 71 : 39.	Title
51	Sanofi, A. (2008). "A randomized, double-blind, repeat-dose, crossover study to evaluate the pharmacokinetics, safety, and tolerability of desloratadine (clarinex) compared to fexofenadine (allegra) in healthy adults who have been identified as slow metabolizers for desloratadine." <u>Clinicaltrials.gov [accessed 31 jul 2008]</u> : ClinicalTrials.gov ID: NCT00636870.	Not Accessible
52	Setiawati, A., M. S. S. Wiria, F. D. Suyatna, J. T. Sion and M. Hamadian (2005). "Interaction of erythromycin and clarithromycin with orange juice." <u>Medical journal of indonesia</u> 14 (2): 78-86.	Title
53	Sieck, D. C., J. E. Mangum, M. R. Ely, M. E. Francisco, E. A. Larson, B. W. Kaiser, C. T. Minson and J. R. Halliwill (2020). "Effect of Histamine-receptor Antagonism on VO2Peak Improvements to Exercise Training." <u>FASEB journal</u> 34 (SUPPL 1).	Abstract
54	Simons, F. E., N. A. Silver, X. Gu and K. J. Simons (2001). "Skin concentrations of H1-receptor antagonists." <u>Journal of allergy and clinical immunology</u> 107 (3): 526-530.	Abstract
55	Snidvongs, K., C. Rotjanasiriphong, C. Phannaso, S. Chusakul and S. Aeumjaturapat (2015). "Fexofenadine and levocetirizine have equivalent effectiveness for persistent allergic rhinitis." <u>Asian biomedicine</u> 9 (3): 387-395.	Short Communication

56	Takahashi, H., Y. Zhang and E. Morita (2008). "Evaluation of the antihistamine effects of olopatadine, cetirizine and fexofenadine during a 24 h period: a double-blind, randomized, crossover, placebo-controlled comparison in skin responses induced by histamine iontophoresis." <u>Archives of dermatological research</u> 300 (6): 291-295.	Abstract
57	Tanizaki, H., A. Ikoma, M. Fukuoka, Y. Miyachi and K. Kabashima (2012). "Effects of bepotastine and fexofenadine on histamine-induced flare, wheal and itch." <u>International archives of allergy and immunology</u> 158 (2): 191-195.	Short Communication
58	Tashiro, M., H. Mochizuki, K. Iwabuchi, Y. Sakurada, M. Itoh, T. Watanabe and K. Yanai (2002). "Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain." <u>Life sciences</u> 72 (4-5): 409-414.	Abstract
59	Tctr (2018). "A Single Dose, Randomized, Open-label, Two-way Crossover Bioequivalence Study of Generic Fexofenadine Hydrochloride 180 mg Film-coated Tablets and Reference Product (Telfast® 180mg) in Healthy Thai Volunteers under Fasting Conditions." https://trialsearch.who.int/Trial2.aspx?TrialID=TCTR20180517002 .	Not Accessible
60	Tctr (2023). "A Bioequivalence study of a randomized, open-label, single dose, full replicate crossover design with four-period, two-treatment, and two-sequence of Fexofenadine 180 mg tablets relative to Telfast 180 mg tablets in healthy Thai volunteers under fasting condition." https://trialsearch.who.int/Trial2.aspx?TrialID=TCTR20230915004 .	Not Accessible
61	Umin (2010). "Clinical research to evaluate the contribution of drug transporters and drug metabolizing enzymes for PI boosting by ritonavir." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000004370 .	Title
62	Umin (2010). "Exploratory trials evaluating the pharmacokinetics of Quinidine and Verapamil after oral administration in healthy male subjects." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000004094 .	Title
63	Umin (2013). "Effect of timing of apple juice intake on the pharmacokinetics of fexofenadine: an open-label, randomized study in healthy volunteers." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000011034 .	Not Accessible
64	Umin (2014). "The effect of apple juice on the pharmacokinetics of fexofenadine -evaluation of dose-effect relationship." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000014773 .	Not Accessible
65	Umin (2018). "Influence of green tea on pharmacokinetics of fexofenadine in healthy volunteers." https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000032828 .	Not Accessible
66	Wetter, T. J., Z. Xiang, D. A. Sonetti, H. C. Haverkamp, A. J. Rice, A. A. Abbasi, K. C. Meyer and J. A. Dempsey (2002). "Role of lung inflammatory mediators as a cause of exercise-induced arterial hypoxemia in young athletes." <u>Journal of applied physiology (Bethesda, Md. : 1985)</u> 93 (1): 116-126.	Title

67	Yakusheva, E. N., I. V. Chemykh, A. V. Shchulkin, M. V. Gatsanoga and A. A. Nikiforov (2019). "Influence of afobazole on the abcb1 protein functional activity in volunteers with low anxiety level." <u>Eksperimental'naya i klinicheskaya farmakologiya</u> 82 (3): 17-21.	Title
68	Yan, H., M. A. Behun, M. D. Cook, S. M. Ranadive, A. D. Lane-Cordova, R. M. Kappus, J. A. Woods, K. R. Wilund, T. Baynard, J. R. Halliwill and et al. (2016). "Differential post-exercise blood pressure responses between blacks and caucasians." <u>Plos ONE</u> . 11 (4) (no pagination), 2016. Article number: e0153445. Date of publication: april 2016.	Title
69	zmfs, R. B. R. (2013). "Evaluation of Green Propolis as a oral Anti-inflammatory Drug." https://trialsearch.who.int/Trial2.aspx?TrialID=RBR-9zmfs9 .	Title
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Supplementary Table S3. JADAD Scoring

JADAD Questions						
Reference	Was the study described as randomized	Was the method used to generate the sequence of randomization described and appropriate	Was the study described as double blind	Was the method of double blinding described and appropriate	Was there a description of withdrawals and dropouts	Total score
Simons et al., 1996 [38]	1	1	0	0	0	2
Russell et al., 1998 [1]	1	1	1	1	0	4
Robbins et al., 1998 [2]	1	1	0	0	1	3
Gupta et al., 2001 [3]	1	1	0	0	0	2
Hamman et al., 2001 [4]	0	0	0	0	0	0
Drescher et al., 2002 [5]	0	0	0	0	0	0
Wang et al., 2002 [6]	0	0	0	0	0	0
Banfield et al., 2002 [7]	1	1	0	0	1	3
Dresser et al., 2002 [8]	1	1	0	0	0	2
Hofmann et al., 2002 [9]	0	0	0	0	0	0
Tannergren et al., 2003 [10]	0	0	0	0	0	0
Dresser et al., 2003 [11]	0	0	0	0	0	0
So-Young Yi et al., 2004 [12]	0	0	0	0	0	0
Shon et al., 2005 [13]	1	1	1	1	0	4
Boyle et al., 2005 [14]	1	1	1	1	0	4
Xie et al., 2005 [15]	0	0	0	0	0	0
Yasui-Furukori et al., 2005 [16]	0	0	0	0	0	0
Dresser et al., 2005 [17]	1	1	0	0	0	2

Rolf et al., 2006 [18]	1	1	0	0	0	2
Lemma et al., 2006 [19]	0	0	0	0	0	0
M. Shimizu et al., 2006 [20]	1	1	0	0	1	3
Uno et al., 2006 [21]	1	1	0	0	0	2
Shimizu et al., 2006 [22]	1	1	0	0	0	2
Mendoza et al., 2007 [23]	1	1	0	0	0	2
Miura et al., 2007 [24]	0	0	0	0	0	0
Bailey et al., 2007 [25]	1	0	0	0	0	1
Teng et al., 2007 [26]	1	0	0	0	0	1
Robertson et al., 2008 [27]	0	0	0	0	1	1
Bharathi et al., 2008 [28]	0	0	0	0	0	0
Kharasch et al., 2008 [29]	0	0	0	0	0	0
Tateishi et al., 2008 [30]	1	1	1	1	0	4
Segall et al., 2008 [31]	0	0	0	0	1	1
Liu et al., 2009 [32]	1	1	0	0	1	3
Kharasch et al., 2009 [33]	0	0	0	0	0	0
Kim et al., 2009 [34]	1	1	0	0	0	2
Kharasch et al., 2009 [35]	0	0	0	0	0	0
Valizadeh et al., 2009 [36]	1	1	0	0	0	2
Sakugawa et al., 2009 [37]	1	1	0	0	0	2
Nolin et al., 2009 [38]	0	0	0	0	0	0
Yamada et al., 2009 [39]	1	1	0	0	0	0
Kim et al., 2010 [40]	1	1	0	0	0	2
Akamine et al., 2010 [41]	0	0	0	0	0	0
Guo et al., 2010 [42]	1	1	0	0	0	2

Yamazaki et al., 2010 [43]	1	1	0	0	0	2
Penzak et al., 2010 [44]	0	0	0	0	1	1
Lappin et al., 2010 [45]	0	0	0	0	0	0
Imanaga et al., 2010 [46]	1	1	0	0	0	2
Malati et al., 2012 [47]	0	0	0	0	1	1
Saruwatari et al., 2012 [48]	1	1	0	0	1	3
Akamine et al., 2012 [49]	1	1	0	0	0	2
Kharasch et al., 2012 [50]	0	0	0	0	0	0
Croft et al., 2012 [51]	0	0	0	0	0	0
Kharasch et al., 2013 [52]	0	0	0	0	0	0
Won et al., 2013 [53]	1	1	0	0	0	2
Zhou et al., 2013 [54]	1	1	0	0	0	2
Kusuhara et al., 2013 [55]	1	1	0	0	0	2
Ieiri et al., 2013 [56]	0	0	0	0	0	0
Muppavarapu et al., 2014 [57]	1	1	0	0	0	2
Bedada et al., 2014 [58]	0	0	0	0	0	0
Kim et al., 2014 [59]	0	0	0	0	0	0
Akamine et al., 2014 [60]	1	1	0	0	0	2
Chen et al., 2014 [61]	0	0	0	0	0	0
Qiu et al., 2014 [62]	0	0	0	0	0	0
Joy et al., 2014 [63]	0	0	0	0	0	0
Tomaru et al., 2015 [64]	0	0	0	0	0	0
Akamine et al., 2015 [65]	1	1	1	1	0	4
Akamine et al., 2015 [66]	1	1	0	0	0	2

Yehia et al., 2015 [67]	1	1	0	0	0	2
Thomson et al., 2015 [68]	0	0	0	0	0	0
Kullak-Ublick et al., 2016 [69]	0	0	0	0	0	0
Helmy et al., 2016 [70]	0	0	0	0	0	0
Luo et al., 2016 [71]	1	1	0	0	0	2
Bedada et al., 2017 [72]	0	0	0	0	0	0
Bedada et al., 2017 [73]	1	1	0	0	0	2
Cusinato et al., 2019 [74]	0	0	0	0	0	0
Calvo et al., 2019 [75]	0	0	0	0	1	1
Cusinato et al., 2019 [76]	0	0	0	0	0	0
Bosilkovska et al., 2019 [77]	1	1	0	0	0	2
Pinto et al., 2020 [79]	0	0	0	0	0	0
Egeland et al., 2020 [80]	0	0	0	0	0	0
Zhao et al., 2021 [81]	1	1	0	0	0	2
Everardo et al., 2021 [82]	1	1	0	0	1	3
Misaka et al., 2022 [83]	1	1	0	0	0	2
Rauch et al., 2023 [84]	1	1	0	0	1	3
Chretien et al., 2023 [85]	1	1	0	0	1	3

Supplementary Table S4. Critical Appraisal Skill Program (CASP)

CASP Questions											
Reference	Was there a clear statement of the aims of the research?	Is a qualitative methodology appropriate?	Was the research design appropriate to address the aims of the research?	Are the study's theoretical underpinnings clear, consistent and conceptually coherent?	Was the recruitment strategy appropriate to the aims of the search?	Was the data collected in a way that addressed the research issue?	Has the relationship between the researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	CASP Score
Russell et al., 1998 [1]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Robbins et al., 1998 [2]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Gupta et al., 2001 [3]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Hamman et al., 2001 [4]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Drescher et al., 2002 [5]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Wang et al., 2002 [6]	N	Y	Y	Y	Y	Y	CT	Y	Y	Y	8
Banfield et al., 2002 [7]	Y	Y	Y	Y	Y	Y	CT	CT	Y	Y	8
Dresser et al., 2002 [8]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Hofmann et al., 2002 [9]	Y	Y	Y	Y	CT	Y	CT	Y	Y	CT	7
Tannergren et al., 2003 [10]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Dresser et al., 2003 [11]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
So-Young Yi et al., 2004 [12]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Shon et al., 2005 [13]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Boyle et al., 2005 [14]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9

Xie et al., 2005 [15]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Yasui-Furukori et al., 2005 [16]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Dresser et al., 2005 [17]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Rolf et al., 2006 [18]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Lemma et al., 2006 [19]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
M. Shimizu et al., 2006 [20]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Uno et al., 2006 [21]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Shimizu et al., 2006 [22]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Mendoza et al., 2007 [23]	Y	Y	Y	Y	Y	CT	CT	Y	Y	Y	8
Miura et al., 2007 [24]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Bailey et al., 2007 [25]	N	CT	Y	Y	Y	Y	CT	Y	Y	Y	8
Teng et al., 2007 [26]	Y	Y	Y	Y	Y	Y	CT	CT	Y	Y	8
Robertson et al., 2008 [27]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Bharathi et al., 2008 [28]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Kharasch et al., 2008 [29]	Y	Y	CT	Y	CT	Y	CT	Y	Y	Y	7
Tateishi et al., 2008 [30]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Segall et al., 2008 [31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Liu et al., 2009 [32]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kharasch et al., 2009 [33]	Y	Y	Y	CT	Y	Y	CT	Y	Y	Y	8
Kim et al., 2009 [34]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kharasch et al., 2009 [35]	Y	Y	Y	CT	Y	Y	CT	Y	Y	Y	8
Valizadeh et al., 2009 [36]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Sakugawa et al., 2009 [37]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Nolin et al., 2009 [38]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Yamada et al., 2009 [39]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9

Kim et al., 2010 [40]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Akamine et al., 2010 [41]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Guo et al., 2010 [42]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Yamazaki et al., 2010 [43]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Penzak et al., 2010 [44]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Lappin et al., 2010 [45]	N	Y	CT	Y	Y	Y	CT	Y	Y	Y	7
Imanaga et al., 2010 [46]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Malati et al., 2012 [47]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Saruwatari et al., 2012 [48]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Akamine et al., 2012 [49]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kharasch et al., 2012 [50]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Croft et al., 2012 [51]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kharasch et al., 2013 [52]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Won et al., 2013 [53]	Y	Y	Y	CT	Y	Y	CT	Y	Y	Y	8
Zhou et al., 2013 [54]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kusuhara et al., 2013 [55]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Ieiri et al., 2013 [56]	Y	Y	Y	CT	Y	Y	CT	Y	Y	Y	8
Muppavarapu et al., 2014 [57]	Y	Y	Y	CT	Y	Y	CT	Y	Y	Y	8
Bedada et al., 2014 [58]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Kim et al., 2014 [59]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Akamine et al., 2014 [60]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Chen et al., 2014 [61]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Qiu et al., 2014 [62]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Joy et al., 2014 [63]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8

Tomaru et al., 2015 [64]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Akamine et al., 2015 [65]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Akamine et al., 2015 [66]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Yehia et al., 2015 [67]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Thomson et al., 2015 [68]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Kullak-Ublick et al., 2016 [69]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Helmy et al., 2016 [70]	Y	CT	CT	Y	Y	Y	CT	Y	Y	Y	7
Luo et al., 2016 [71]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Bedada et al., 2017 [72]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Bedada et al., 2017 [73]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Cusinato et al., 2019 [74]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Calvo et al., 2019 [75]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Cusinato et al., 2019 [76]	Y	Y	CT	Y	Y	Y	CT	Y	Y	Y	8
Bosilkovska et al., 2019 [77]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Simons et al., 1996 [38]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Pinto et al., 2020 [79]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Egeland et al., 2020 [80]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Zhao et al., 2021 [81]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Everardo et al., 2021 [82]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Misaka et al., 2022 [83]	Y	Y	Y	Y	Y	Y	CT	Y	CT	Y	8
Rauch et al., 2023	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9
Chretien et al., 2023 [85]	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	9

Y= Yes; N=No; CT= Can't tell

Supplementary Table S5. Critical Appraisal Clinical Pharmacokinetic (CACPK) Tool

Critical Appraisal Clinical Pharmacokinetic Tool																						
Reference	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Q 15	Q 16	Q 17	Q 18	Q 19	Q 20	Q 21	Total Score
Russell et al., 1998 [1]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	16
Robbins et al., 1998 [2]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	Y	Y	IDK	Y	15
Gupta et al., 2001 [3]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	16
Hamman et al., 2001 [4]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Drescher et al., 2002 [5]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Wang et al., 2002 [6]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	IDK	N	N	N	Y	Y	Y	Y	IDK	Y	15
Banfield et al., 2002 [7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	IDK	N	N	Y	N	IDK	Y	IDK	Y	14
Dresser et al., 2002 [8]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Hofmann et al., 2002 [9]	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	IDK	N	N	N	Y	N	Y	Y	IDK	Y	12
Tannergren et al., 2003 [10]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	IDK	Y	N	N	Y	Y	Y	Y	IDK	Y	16
Dresser et al., 2003 [11]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	Y	N	N	Y	Y	IDK	Y	IDK	Y	16

So-Young Yi et al., 2004 [12]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	Y	Y	IDK	Y	15
Shon et al., 2005 [13]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	IDK	Y	IDK	Y	14
Boyle et al., 2005 [14]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	Y	Y	IDK	Y	16
Xie et al., 2005 [15]	Y	Y	IDK	Y	Y	Y	Y	N	Y	Y	N	IDK	N	IDK	IDK	Y	Y	Y	Y	IDK	Y	13
Yasui-Furukori et al., 2005 [16]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	Y	Y	IDK	Y	14
Dresser et al., 2005 [17]	Y	Y	Y	Y	Y	N	Y	IDK	Y	Y	Y	IDK	N	IDK	IDK	Y	N	Y	Y	IDK	Y	13
Rolf et al., 2006 [18]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	Y	Y	IDK	Y	15
Lemma et al., 2006 [19]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	IDK	IDK	Y	N	IDK	Y	IDK	Y	14
M. Shimizu et al., 2006 [20]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Uno et al., 2006 [21]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Shimizu et al., 2006 [22]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	N	N	IDK	Y	Y	Y	Y	IDK	Y	14
Mendoza et al., 2007 [23]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Miura et al., 2007 [24]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	N	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	13
Bailey et al., 2007 [25]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	N	N	IDK	Y	Y	IDK	Y	IDK	Y	12
Teng et al., 2007 [26]	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	IDK	Y	IDK	Y	12

Robertson et al., 2008 [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	16
Bharathi et al., 2008 [28]	Y	Y	IDK	Y	Y	N	N	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	12
Kharasch et al., 2008 [29]	Y	Y	IDK	Y	Y	Y	Y	N	IDK	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	14
Tateishi et al., 2008 [30]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Segall et al., 2008 [31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	IDK	IDK	N	IDK	Y	N	IDK	Y	IDK	Y	14
Liu et al., 2009 [32]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15
Kharasch et al., 2009 [33]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	IDK	IDK	Y	N	IDK	Y	Y	IDK	Y	IDK	Y	14
Kim et al., 2009 [34]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Kharasch et al., 2009 [35]	Y	Y	Y	Y	IDK	Y	N	N	Y	Y	IDK	IDK	IDK	N	IDK	Y	Y	Y	Y	IDK	Y	12
Valizadeh et al., 2009 [36]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	16
Sakugawa et al., 2009 [37]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Nolin et al., 2009 [38]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Yamada et al., 2009 [39]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Kim et al., 2010 [40]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14

Akamine et al., 2010 [41]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13
Guo et al., 2010 [42]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	IDK	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	12
Yamazaki et al., 2010 [43]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	N	N	IDK	Y	N	IDK	Y	IDK	Y	13
Penzak et al., 2010 [44]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15
Lappin et al., 2010 [45]	N	N	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	IDK	Y	IDK	Y	10
Imanaga et al., 2010 [46]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15
Malati et al., 2012 [47]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15
Saruwatari et al., 2012 [48]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	16
Akamine et al., 2012 [49]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	IDK	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	14
Kharasch et al., 2012 [50]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Croft et al., 2012 [51]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Kharasch et al., 2013 [52]	Y	IDK	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13
Won et al., 2013 [53]	Y	Y	Y	Y	Y	N	Y	N	IDK	IDK	IDK	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	11
Zhou et al., 2013 [54]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15

Kusuhara et al., 2013 [55]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Ieiri et al., 2013 [56]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Muppavarapu et al., 2014 [57]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Bedada et al., 2014 [58]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Kim et al., 2014 [59]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Akamine et al., 2014 [60]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Chen et al., 2014 [61]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	IDK	IDK	Y	N	IDK	Y	N	IDK	Y	IDK	Y	11
Qiu et al., 2014 [62]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Joy et al., 2014 [63]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13
Tomaru et al., 2015 [64]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Akamine et al., 2015 [65]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Akamine et al., 2015 [66]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Yehia et al., 2015 [67]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Thomson et al., 2015 [68]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	16
Kullak-Ublick et al., 2016 [69]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	IDK	Y	IDK	Y	13

Helmy et al., 2016 [70]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	IDK	Y	IDK	Y	12
Luo et al., 2016 [71]	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Bedada et al., 2017 [72]	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Bedada et al., 2017 [73]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	15
Cusinato et al., 2019 [74]	Y	Y	Y	Y	Y	Y	Y	N	IDK	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Calvo et al., 2019 [75]	Y	IDK	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13
Cusinato et al., 2019 [76]	Y	Y	IDK	Y	Y	N	Y	N	Y	Y	IDK	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	12
Bosilkovska et al., 2019 [77]	Y	Y	Y	Y	Y	N	Y	N	IDK	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13
Simons et al., 1996 [38]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Pinto et al., 2020 [79]	Y	IDK	IDK	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	12
Egeland et al., 2020 [80]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	Y	Y	Y	IDK	Y	15
Zhao et al., 2021 [81]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Everardo et al., 2021 [82]	Y	Y	Y	Y	Y	Y	Y	N	IDK	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	14
Misaka et al., 2022 [83]	Y	Y	Y	Y	Y	N	Y	N	IDK	Y	Y	IDK	Y	N	IDK	Y	N	Y	Y	IDK	Y	13

Rauch et al., 2023 [84]	Y	IDK	Y	Y	Y	N	Y	N	IDK	Y	Y	IDK	IDK	N	IDK	Y	N	Y	Y	IDK	Y	11
Chretien et al., 2023 [85]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	IDK	IDK	N	IDK	Y	N	Y	Y	IDK	Y	13

Y= Yes; N= No; IDK= I don't know

Background

Q1: Was a clear description of the objectives of the study provided?

Q2: Was a valid and comprehensive rationale provided to support the purpose of the study?

Design

Q3: Was the chosen study design appropriately selected and justified?

Q4: Was the dosing (dose, route of administration, dosing interval) of the drug in the study justified for the intended study?

Q5: Were the endpoints of the study appropriate to answer the objectives of the study?

Q6: Were the exclusion criteria of participants included AND appropriate for the intended outcomes of the study?

Q7: Where applicable, were the relevant baseline characteristics of the participants adequately described?

Q8: Were plausible interacting covariates described a priori or in post hoc evaluation?

Q9: Was the description of the used sample analysis methods or citations of prior validation studies provided in the publication or affiliated appendix?

Sampling

Q10: Was the method of data sampling appropriate for the study?

Q11: Was a clear description of the sampling site and the sampling interval (the exact times at which samples are obtained) provided and justified?

Q12: Was the number of half-lives elapsed within the sampling period appropriate for the analyzed drug?

Q13: Were sample storage conditions appropriate and described in a manner that could be accurately replicated?

Q14: If applicable, was there a clear description of the pharmacokinetic model, its development, validation and justification for use?

Q15: Was the described population pharmacokinetic approach validation method appropriate for the analysis?

Q16: Were the essential pharmacokinetic parameters required to make the results applicable in clinical settings addressed?

Q17: Were the pharmacokinetic equations used to calculate patient pharmacokinetic parameters disclosed or cited within the article?

Applied Statistics

Q18: Were the chosen statistical tests and software to perform the statistical analysis appropriate to achieve the study objectives?

Results

Q19: Were all patients enrolled in the study accounted for?

Q20: In the event of missing data or outliers, was the process for analysis justified and appropriate?

Q21: Were appropriate summary statistics to describe centrality and variance used to document the pharmacokinetic results?

Supplementary Table S6: Cochrane Collaboration Tool

Cochrane Collaboration Questions								
Reference	Random sequence (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and researchers (Performed bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias	Total score
Simons et al., 1996 [38]	LR	LR	HR	HR	UR	LR	LR	4
Russell et al., 1998 [1]	LR	LR	LR	LR	LR	LR	UR	5
Robbins et al., 1998 [2]	LR	LR	HR	UR	LR	LR	LR	5
Gupta et al., 2001 [3]	LR	HR	HR	LR	LR	LR	LR	5
Hamman et al., 2001 [4]	HR	HR	HR	UR	LR	LR	LR	3
Drescher et al., 2002 [5]	HR	LR	HR	UR	UR	LR	LR	3
Wang et al., 2002 [6]	HR	HR	HR	HR	LR	LR	LR	3
Banfield et al., 2002 [7]	LR	LR	HR	UR	LR	LR	LR	5
Dresser et al., 2002 [8]	LR	LR	UR	UR	LR	LR	LR	5
Hofmann et al., 2002 [9]	HR	HR	UR	LR	LR	LR	LR	4
Tannergren et al., 2003 [10]	UR	UR	LR	LR	UR	LR	LR	4
Dresser et al., 2003 [11]	HR	LR	HR	HR	LR	LR	LR	4
So-Young Yi et al., 2004 [12]	HR	LR	UR	UR	LR	LR	LR	4
Shon et al., 2005 [13]	LR	LR	LR	LR	UR	LR	LR	6
Boyle et al., 2005 [14]	LR	LR	LR	LR	UR	LR	LR	6
Xie et al., 2005 [15]	UR	LR	UR	UR	LR	LR	LR	4
Yasui-Furukori et al., 2005 [16]	LR	LR	UR	UR	LR	LR	LR	5
Dresser et al., 2005 [17]	LR	LR	HR	HR	LR	LR	LR	5
Rolf et al., 2006 [18]	LR	LR	UR	LR	UR	LR	LR	5

Lemma et al., 2006 [19]	HR	HR	HR	LR	LR	LR	LR	4
M. Shimizu et al., 2006 [20]	LR	LR	HR	UR	LR	LR	LR	5
Uno et al., 2006 [21]	LR	LR	HR	UR	UR	LR	LR	4
Shimizu et al., 2006 [22]	LR	LR	HR	HR	LR	LR	LR	5
Mendoza et al., 2007 [23]	LR	LR	HR	UR	LR	LR	LR	5
Miura et al., 2007 [24]	HR	HR	HR	UR	LR	LR	LR	3
Bailey et al., 2007 [25]	LR	LR	HR	UR	LR	LR	LR	5
Teng et al., 2007 [26]	LR	LR	HR	HR	UR	LR	LR	4
Robertson et al., 2008 [27]	HR	UR	HR	HR	HR	LR	LR	2
Bharathi et al., 2008 [28]	HR	HR	HR	UR	UR	LR	LR	2
Kharasch et al., 2008 [29]	HR	HR	HR	UR	LR	LR	LR	3
Tateishi et al., 2008 [30]	LR	LR	LR	UR	HR	LR	LR	5
Segall et al., 2008 [31]	HR	HR	HR	HR	LR	LR	LR	3
Liu et al., 2009 [32]	LR	HR	UR	HR	LR	LR	LR	4
Kharasch et al., 2009 [33]	HR	HR	UR	UR	LR	LR	LR	3
Kim et al., 2009 [34]	LR	LR	HR	HR	UR	LR	LR	4
Kharasch et al., 2009 [35]	HR	HR	UR	UR	LR	LR	LR	3
Valizadeh et al., 2009 [36]	LR	LR	HR	UR	UR	LR	LR	4
Sakugawa et al., 2009 [37]	LR	LR	HR	HR	UR	LR	LR	4
Nolin et al., 2009 [38]	HR	HR	HR	HR	UR	LR	LR	2
Yamada et al., 2009 [39]	LR	LR	HR	UR	UR	LR	LR	4
Kim et al., 2010 [40]	LR	LR	HR	UR	UR	LR	LR	4
Akamine et al., 2010 [41]	HR	HR	UR	UR	UR	LR	LR	2
Guo et al., 2010 [42]	LR	UR	UR	UR	UR	LR	LR	3
Yamazaki et al., 2010 [43]	LR	LR	HR	HR	LR	LR	LR	5

Penzak et al., 2010 [44]	UR	UR	HR	HR	LR	LR	LR	3
Lappin et al., 2010 [45]	UR	UR	UR	UR	UR	LR	LR	2
Imanaga et al., 2010 [46]	LR	LR	HR	HR	LR	LR	LR	5
Malati et al., 2012 [47]	LR	LR	HR	HR	LR	LR	LR	5
Saruwatari et al., 2012 [48]	LR	LR	HR	HR	LR	LR	LR	5
Akamine et al., 2012 [49]	LR	LR	HR	HR	UR	LR	LR	4
Kharasch et al., 2012 [50]	UR	UR	UR	UR	UR	LR	LR	2
Croft et al., 2012 [51]	UR	UR	UR	UR	UR	LR	LR	2
Kharasch et al., 2013 [52]	UR	UR	UR	UR	UR	LR	LR	2
Won et al., 2013 [53]	LR	LR	UR	UR	UR	LR	LR	4
Zhou et al., 2013 [54]	LR	LR	UR	UR	UR	LR	LR	4
Kusuhara et al., 2013 [55]	LR	LR	UR	UR	UR	LR	LR	4
Ieiri et al., 2013 [56]	UR	UR	HR	HR	UR	LR	LR	2
Muppavarapu et al., 2014 [57]	LR	LR	UR	LR	UR	LR	LR	5
Bedada et al., 2014 [58]	UR	UR	UR	UR	UR	LR	LR	2
Kim et al., 2014 [59]	UR	UR	UR	UR	UR	LR	LR	2
Akamine et al., 2014 [60]	LR	LR	UR	UR	UR	LR	LR	4
Chen et al., 2014 [61]	UR	UR	UR	UR	UR	LR	LR	2
Qiu et al., 2014 [62]	UR	UR	HR	HR	UR	LR	LR	2
Joy et al., 2014 [63]	UR	UR	UR	UR	UR	LR	LR	2
Tomaru et al., 2015 [64]	UR	UR	HR	HR	UR	LR	LR	2
Akamine et al., 2015 [65]	LR	LR	LR	UR	UR	LR	LR	5
Akamine et al., 2015 [66]	LR	LR	HR	HR	UR	LR	LR	4
Yehia et al., 2015 [67]	LR	LR	HR	HR	UR	LR	LR	4

Thomson et al., 2015 [68]	UR	UR	UR	UR	LR	LR	LR	3
Kullak-Ublick et al., 2016 [69]	UR	UR	UR	UR	UR	LR	LR	2
Helmy et al., 2016 [70]	UR	UR	UR	UR	UR	LR	LR	2
Luo et al., 2016 [71]	LR	LR	HR	UR	LR	LR	LR	5
Bedada et al., 2017 [72]	HR	UR	HR	HR	LR	LR	LR	3
Bedada et al., 2017 [73]	HR	UR	HR	HR	LR	LR	LR	3
Cusinato et al., 2019 [74]	HR	UR	HR	HR	LR	LR	LR	3
Calvo et al., 2019 [75]	HR	HR	HR	HR	UR	LR	LR	2
Cusinato et al., 2019 [76]	UR	UR	UR	UR	UR	LR	LR	2
Bosilkovska et al., 2019 [77]	LR	LR	HR	HR	UR	LR	LR	4
Pinto et al., 2020 [79]	UR	UR	UR	UR	UR	LR	LR	2
Egeland et al., 2020 [80]	HR	HR	HR	HR	UR	LR	LR	2
Zhao et al., 2021 [81]	LR	LR	HR	HR	UR	LR	LR	4
Everardo et al., 2021 [82]	LR	LR	HR	HR	LR	LR	LR	5
Misaka et al., 2022 [83]	LR	LR	HR	HR	UR	LR	LR	4
Rauch et al., 2023 [84]	LR	LR	HR	HR	UR	LR	LR	4
Chretien et al., 2023 [85]	LR	LR	HR	HR	LR	LR	LR	5

LR= Low risk; HR= High risk; UR= Unclear risk

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