SUPPLEMENTARY TABLE 1

Search strategy:

Online Resource 1: Pubmed Search Strategy

((((((hepatic safety[Title/Abstract]) OR (hepatotoxicity[Title/Abstract])) OR (adverse event[Title/Abstract])) OR (liver function[Title/Abstract])) AND ((((Febuxostat[Title/Abstract]) OR (Allopurinol[Title/Abstract])) OR (xanthin oxidase inhibitor[Title/Abstract])) OR (urate lowering therapy[Title/Abstract])))) AND (((gout[Title/Abstract]) OR (hyperuricemia[Title/Abstract])) OR (uric acid[Title/Abstract])))) AND (((randomized controlled trial[Title/Abstract]) OR (clinical trial[Title/Abstract])) OR (randomised controlled trial[Title/Abstract]))

Online Resource 2: Cochrane Library Search Strategy

Search Name: Febu Alo RCT

Date Run: 06/05/2023 02:17:19

ID Search Hits Comment

#1 (hepatic safety):ti,ab,kw OR (hepatotoxicity):ti,ab,kw OR (adverse event):ti,ab,kw OR (liver function):ti,ab,kw (Word variations have been searched) 181078

#2 (febuxostat):ti,ab,kw OR (allopurinol):ti,ab,kw OR (xanthin oxidase inhibitor):ti,ab,kw OR (urate lowering therapy):ti,ab,kw (Word variations have been searched) 2015

#3 (gout):ti,ab,kw OR (hyperuricemia):ti,ab,kw OR (uric acid):ti,ab,kw (Word variations have been searched) 6534

#4 (randomized controlled trial):ti,ab,kw OR (clinical trial):ti,ab,kw OR (randomised controlled trial):ti,ab,kw (Word variations have been searched) 960413

#5 #1 AND #2 AND #3 AND #4 252

Online Resource 3: Scopus Search Strategy

((TITLE-ABS-KEY (hepatic AND safety) OR TITLE-ABS-KEY (hepatotoxicity) OR TITLE-ABS-KEY (adverse AND event) OR TITLE-ABS-KEY (liver AND function))) AND ((TITLE-ABS-KEY (febuxostat) OR TITLE-ABS-KEY (allopurinol) OR TITLE-ABS-KEY (xanthine AND oxidase AND inhibitor) OR TITLE-ABS-KEY (urate AND lowering AND therapy))) AND ((TITLE-ABS-KEY (gout) OR TITLE-ABS-KEY (hyperuricemia) OR TITLE-ABS-KEY (uric AND acid))) AND ((TITLE-ABS-KEY (randomized AND controlled AND trial) OR TITLE-ABS-KEY (clinical AND trial) OR TITLE-ABS-KEY (randomised AND clinical AND trial)))

SUPPLEMENTARY TABLE 2
PRISMA 2020 FOR ABSTRACT CHECKLIST

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	N/A
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Prospero CRD42023423942

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

SUPPLEMENTARY TABLE 3
PRISMA 2020 CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplement 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
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.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4 and supplementary material
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.	Page 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.	Page 5
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.	Page 5
	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.	Page 5
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.	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
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)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	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.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
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.	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	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.	N/A
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.	Page 8
	23b	Discuss any limitations of the evidence included in the review.	Page 8
	23c	Discuss any limitations of the review processes used.	Page 8
	23d	Discuss implications of the results for practice, policy, and future research.	Page 8
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.	Page 11
Competing interests	26	Declare any competing interests of review authors.	Page 12
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.	Table 1 and Table 2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

SUPPLEMENTARY TABLE 4

PROSPERO
International prospective register of systematic reviews

Hepatic safety of Febuxostat and Allopurinol: A Systematic Review of Randomized Controlled Trial

Christiyanti Dewi, Falerina Puspita, Neily Zakiyah, Irma Melyani Puspitasari

Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation

Christiyanti Dewi, Falerina Puspita, Neily Zakiyah, Irma Melyani Puspitasari. Hepatic safety of Febuxostat and Allopurinol: A Systematic Review of Randomized Controlled Trial. PROSPERO 2023 CRD42023423942 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023423942

Review question

Is the hepatic safety profile of Febuxostat similar to that of Allopurinol?

Searches

Relevant English published studies through 15 MAY 2023 in this following database:
PubMed
Cochrane Library
Scopus

Types of study to be included

All randomized controlled trial

Condition or domain being studied [1 change]

- Study gout or hyperuricemia adult population
- Using Allopurinol vs Febuxostat administration with hepatic safety result
- Randomized controlled trial

Participants/population [1 change]

Adult gout or hyperuricemia patient with age > 18 years old, randomized controlled trial with febuxostat in comparison with allopurinol, it must have assessment on liver function outcome (hepatic safety) i.e. AST, ALT,

ALP, total bilirubin.

Inclusion criteria:
- Adult gout patient > 18 years old
- Studies allopurinol and febuxostat with liver function safety result (hepatic safety)
- Randomized Controlled trial

Exclusion criteria:
- Case report, case series, review and abstracts
- Studies written in a language other than English
- Studies do not compare febuxostat and allopurinol data (different intervention)
- non-RCT (wrong study/ outcome)

Intervention(s), exposure(s)

Febuxostat in adult gout or hyperuricemia patient with age > 18 years old, randomized controlled trial with febuxostat in comparison with allopurinol, it must have assessment on liver function outcome (hepatic safety) i.e. AST, ALT, ALP, total bilirubin

Comparator(s)/control

Allopurinol in adult gout or hyperuricemia patient with age > 18 years old, randomized controlled trial with febuxostat in comparison with allopurinol, it must have assessment on liver function outcome (hepatic safety) i.e. AST, ALT, ALP, total bilirubin

Main outcome(s)

Hepatic Safety of Febuxostat and Allopurinol

Measures of effect

- Hepatotoxicity, Liver function will be reported as number of events related to at least one of the following outcomes:
- elevation of aspartate aminotransferase (AST) > 1.5 × ULN,
- elevation of ALT > 1.5 × ULN,
- elevation of ALT, AST or both > 1.5 × ULN,
- elevation of ALP > 2 × ULN,
- elevation of AST > 1.5 × ULN, and ALP > 2 x ULN
• elevation of ALT > 1.5 × ULN, and ALP > 2 x ULN
• elevation of AST > 1.5 × ULN, and total bilirubin > 2 x ULN
- elevation of ALT > 1.5 × ULN, and total bilirubin > 2 x ULN
- Hy's case (ALT > 3 × ULN and total bilirubin > 1.5 × ULN),
- liver-function abnormalities
- liver-related treatment
- discontinuations, and liver-related hospitalization.

Additional outcome(s)

Not applicable

Data extraction (selection and coding)

Two people will do the selection criteria in both initial and full-text screening,
Eligibility assessment will be performed independently in an unblinded standardized manner by two reviewers. Disagreement between reviewers will be resolved by consensus. All duplicated studies and nonrelevant articles will be excluded. Data extraction and quality assessment will be performed for all included studies
Excel spreadsheet will be used to manage the records.

Risk of bias (quality) assessment

Jadad score will be used to appraise the quality of included studies.

Strategy for data synthesis

Information that will be extracted from the study in order to answer the research question are:
- Study design
- Author
- Publication year
- Population
- Intervention
- Sample size
- Characteristic of patients (gender, age, indication)
- Duration
- Jadad score

Data synthesis will be reported with laboratory test for screening hepatotoxicity (AST, ALT, ALP, total bilirubin, etc) that clinically / not clinically significant.

Analysis of subgroups or subsets

Not available

Contact details for further information

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Organisational affiliation of the review

Padjadjaran University
https://www.unpad.ac.id/

Review team members and their organisational affiliations

Mrs Christiyanti Dewi. Universitas Padjadjaran
Mrs Falerina Puspita. Universitas Padjadjaran
Dr Neily Zakiyah. Universitas Padjadjaran
Professor Irma Melyani Puspitasari. Universitas Padjadjaran

Type and method of review

Systematic review

Anticipated or actual start date

15 May 2023

Anticipated completion date

15 June 2023

Funding sources/sponsors

This study is supported by Universitas Padjadjaran

Conflicts of interest

No conflicts of interest that are relevant to the content of this study.
None known

Language

English

Country

Indonesia

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Allopurinol; Febuxostat; Gout; Gout Suppressants; Humans

Date of registration in PROSPERO

15 May 2023

Date of first submission

04 May 2023

Stage of review at time of this submission [2 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	Yes

Revision note

No major updates. The changes are related to the progress of the systematic review.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

15 May 2023
30 May 2023
03 July 2023
13 July 2023