

# Hepatic Safety of Febuxostat and Allopurinol for Gout Patients: A Systematic Review of Randomized Controlled Trial

Christiyanti Dewi<sup>1</sup>, Falerina Puspita<sup>1</sup>, Irma Melyani Puspitasari<sup>1,2</sup>, Neily Zakayah<sup>1,2</sup>

<sup>1</sup>Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia; <sup>2</sup>Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia

Correspondence: Neily Zakayah, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, 45363, Indonesia, Tel +62 22 84288888, Ext. 3510, Email neily.zakayah@unpad.ac.id

**Purpose:** This study aims to systematically review the hepatic safety of febuxostat and allopurinol in adult gout patients.

**Methods:** We searched for information using the following databases: PubMed, Cochrane Library, and Scopus. The inclusion criteria were to review all randomized controlled trials (RCT) that compared allopurinol and febuxostat for adult gout patients that had an assessment of liver function outcomes. Non-English studies on case reports, case series, reviews, and abstracts only were excluded. We extracted information from the studies to answer the research question, ie, study design, publication year, population, sample size, patient characterization, duration, Jadad score, and liver function outcomes.

**Results:** We screened 512 publications from the databases and identified 11 studies that met the inclusion criteria. Ten out of 11 included studies were double-blind RCTs. In the majority of the included studies, no statistically significant differences were observed in terms of hepatic safety data between febuxostat and allopurinol. However, in studies where allopurinol titration was used, it posed a challenge to maintain blinding. Notably, consistent adverse events related to liver function findings were observed across all reviewed RCTs. These abnormal liver function test results sometimes led to study withdrawal based on the investigators' assessment. Nevertheless, the investigators classified most liver function test elevations as mild to moderate in severity.

**Conclusion:** Our analysis concluded that adult gout patients enrolled in the included RCTs exhibited similar hepatic safety profiles for both febuxostat and allopurinol treatment. Liver function abnormalities were identified in all RCTs included in this systematic review. Consequently, it is important for the product labeling information of both allopurinol and febuxostat to present and describe the current safety data to guide healthcare practitioners when prescribing these medications to patients. Pharmacovigilance and post-marketing pharmacoepidemiology data are essential in establishing the comprehensive safety profile.

**Keywords:** febuxostat, allopurinol, gout, hepatic safety

## Introduction

Both febuxostat and allopurinol have been extensively studied in clinical trials and have shown efficacy and safety as urate-lowering therapies for gout patients.<sup>1-4</sup> Gout is a metabolic disease characterized by elevated serum uric acid levels and the deposit of monosodium urate crystal, resulting of inflammation and pain.<sup>5-8</sup> It primarily affects males over 40 years of age, with a higher risk observed in individuals with cardiovascular disease, diabetes, obesity, renal disease, hyperlipidemia, and post-menopausal women.<sup>5,7,9-11</sup> Optimal control of serum uric acid levels can reduce the clinical and financial burden linked to gout.<sup>12,13</sup>

Allopurinol is a xanthine oxidase inhibitor that is typically initiated at a starting dose of 100 mg/day and can be gradually increased to 900 mg/ day for patients with good renal function.<sup>14,15</sup> The effective daily dose of allopurinol is generally 300 mg.<sup>2,5,16,17</sup> Allopurinol is metabolized by xanthine oxidase to an active metabolite called oxypurinol, which inhibits xanthine oxidase. Due to the renal excretion of oxypurinol, patients with impaired renal function may

experience prolonged excretion and elevated level of uric acids, which have been associated with the development of allopurinol hypersensitivity syndrome.<sup>15,18–20</sup>

On the other hand, febuxostat is a non-purine selective inhibitor of Xanthine Oxidase (NP-SIXO) and belongs to the class of 2-arylthiazole derivatives. Febuxostat selectively inhibits the Xanthine Oxidase enzyme to reduce serum uric acid levels. Unlike allopurinol, febuxostat does not significantly affect other enzymes involved in purine or pyrimidine metabolism at therapeutic doses. It is primarily metabolized in the liver through glucuronide formation and oxidation.<sup>21,22</sup>

Based on both efficacy and safety data for both drugs in several countries, including the United States, United Kingdom, Spain, and Korea, have designated allopurinol and febuxostat as first-line medications for gout patients.<sup>6,23–27</sup>

While there have been numerous clinical trials demonstrating the superior efficacy of febuxostat compared to allopurinol,<sup>1–4</sup> there is currently a lack of systematic analysis data regarding the hepatic safety of febuxostat compared to allopurinol in gout patients. This study aims to assess the hepatic safety of febuxostat and allopurinol in adult gout patients through a systematic review.

## Materials and Methods

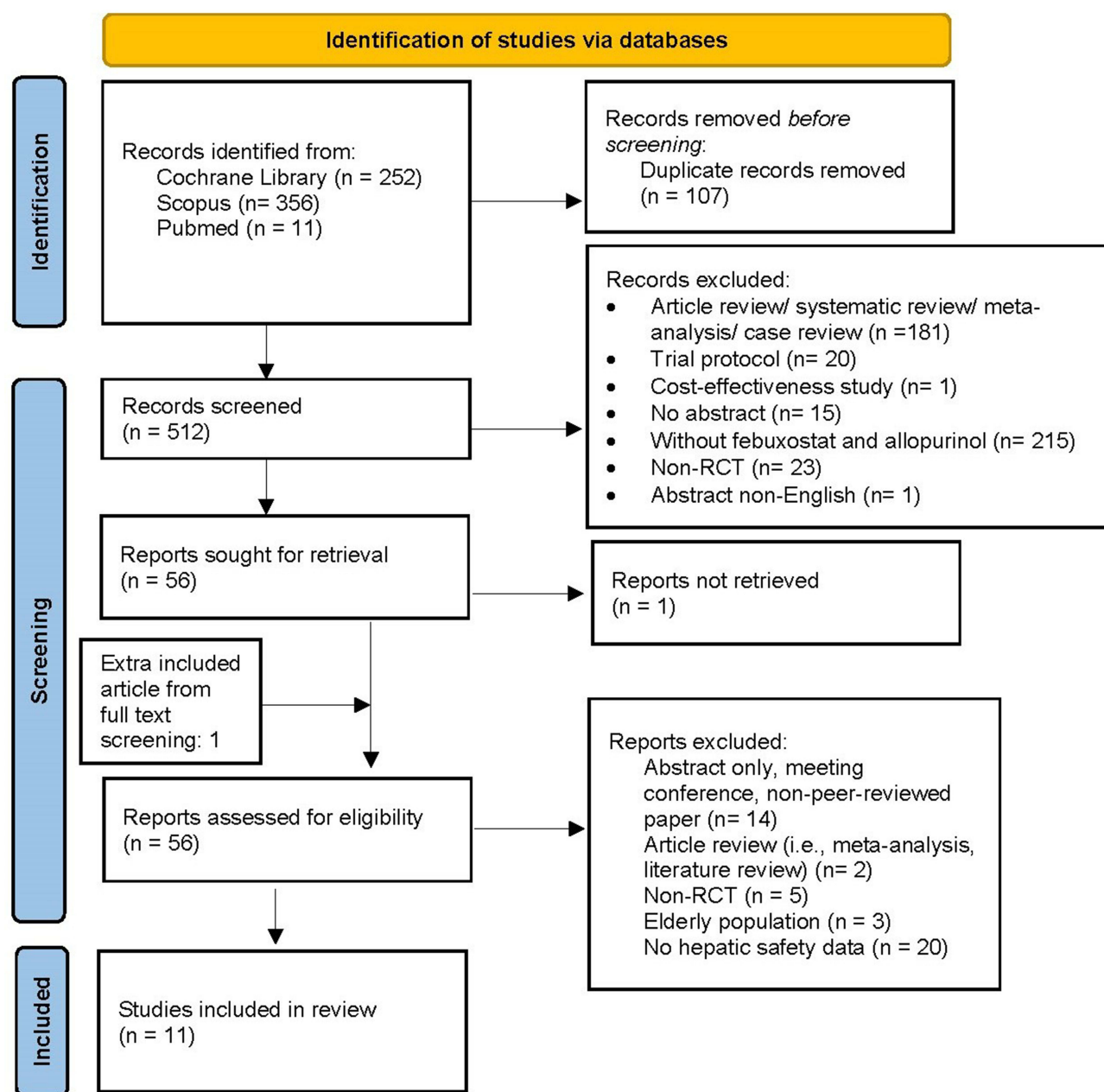
### Systematic Search Strategy

For this systematic review, multiple databases, including PubMed, The Cochrane Library, and Scopus, were utilized to gather relevant data until May 15th, 2023. The search was conducted to discover articles that provide information on the hepatic safety data of febuxostat and allopurinol in adult gout patients. The electronic search terminologies used in this study include “febuxostat”, “allopurinol”, “randomized controlled trial”, “gout”, “hyperuricemia”, and “adverse event”. The search was limited to the English language. The detail of the search terms in the databases is provided in [Supplementary Table 1](#). References from identified articles were also reviewed to determine relevant publications. Furthermore, The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used for this systematic review. The objectives and methods of this review were registered in the International Prospective Register of Systematic Reviews (PROSPERO) 2023, number CRD42023423942. The details are provided in [Supplementary Tables 2–4](#).

### Eligibility and Study Selection

The eligibility criteria comprised published randomized controlled trials (RCTs) involving adult patients ( $\geq 18$  years -  $< 65$  years) with gout. Specifically, the studies that compared allopurinol and febuxostat reported liver function safety results as a means of identifying hepatic safety outcomes. We excluded case reports, case series, article reviews, conference proceedings, non-peer-reviewed papers, protocols, abstracts-only publications, and studies with non-RCT design. The collected studies included assessments on liver function outcomes outweigh upper limits normal (ULN) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or total bilirubin. The assessment of the effects in this study will focus on hepatotoxicity and liver function outcomes. These outcomes will be evaluated based on the number of events reported as a percentage, pertaining to specific criteria to at least one of the following outcomes ie, elevation of  $AST \geq 1.5 \times ULN$ , elevation of  $ALT \geq 1.5 \times ULN$ , elevation of  $ALT$ ,  $AST$  or both  $\geq 1.5 \times ULN$ , elevation of  $ALP \geq 2 \times ULN$ , Hy's case ( $ALT \geq 3 \times ULN$  and total bilirubin  $\geq 1.5 \times ULN$ ), liver-related treatment, discontinuations, and liver-related hospitalization.

To ensure the accuracy of the selection process, two reviewers independently screened the articles during both initial title-and-abstract and full-text screening. Any duplicates and irrelevant articles were excluded. The eligibility of the remaining studies was assessed independently by the two reviewers, and any disagreements were resolved through consensus. The full-text data extraction and quality assessment were performed for all included studies. The full-text articles were thoroughly reviewed, and relevant information regarding study characteristics and safety outcomes was extracted. [Figure 1](#) depicts the PRISMA flow diagram illustrating the study selection process.



**Figure 1** PRISMA 2020 flow diagram of the study selection process.

**Note:** Adapted from Page M J, McKenzie J E, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372. Creative Commons.

## Data Collection and Quality Assessment

The records were manually managed using an Excel spreadsheet to organize the information obtained from the included studies. Information from the included studies was extracted ie, study design, author, publication year, population (indication), intervention (type, dose, duration, and frequency), sample size, characteristic of patients (gender, age), study duration, type of safety outcomes (ie, liver function test abnormality, liver-related treatment discontinuation, hospitalization due to hepatic cause or acute liver failure, or death).

Jadad score was used to appraise the quality of included studies to evaluate the validity of the eligible RCTs. The Jadad score assesses the methodological quality of the included studies and comprises three components: randomization,

blinding, and extent of loss to follow-up.<sup>28</sup> Two reviewers independently assessed the methodological quality of the studies using the Jadad score, and any disagreements were resolved through consensus.

## Results

### Systematic Search

In this systematic review, a total of 619 electronic citations were initially identified from PubMed, the Cochrane Library, and Scopus. After removing 107 duplicate records, 512 records were screened based on their title and abstract up to May 6th, 2023. We further excluded 181 records that were article reviews, systematic reviews, meta-analyses, and case reviews, as well as 20 trial protocols, 1 cost-effectiveness study, 15 records without abstracts, 215 studies that did not involve febuxostat and allopurinol, 23 non-RCTs, and 1 non-English abstract.

Following the title and abstract screening, we sought the full text of 56 studies; however, one study could not be retrieved. During the full-text screening, we identified one additional article through snowballing, resulting in a total of 56 studies for final eligibility review. In total, 11 studies met the inclusion and exclusion criteria and were included in this systematic review. The remaining studies were excluded for various reasons, including 14 records with abstracts only or conference proceedings, non-peer-reviewed papers, 2 article reviews (meta-analysis, literature review), 5 non/poor RCTs, 3 studies focusing solely on the elderly population ( $\geq 65$  years), and 20 trials lacking hepatic safety data.

### The Main Characteristics of Included Studies

Table 1 presents the final inclusion of 11 studies.<sup>1,2,16–18,29–34</sup> These studies were conducted in different countries, including 3 RCTs from United States,<sup>2,16,34</sup> 2 from the United States/ Canada,<sup>1,16</sup> 4 from China,<sup>29,30,32,33</sup> 1 from Japan,<sup>18</sup> and 1 from multi countries (11 European countries and Brazil).<sup>31</sup> The most recent study was conducted in 2022<sup>33</sup> while the oldest dates back to 2005.<sup>1</sup>

The baseline demographic of the included studies mainly comprised male patients  $\geq 18$  years old, reflecting the higher prevalence of gout in males over 40 years old. The total number of patients included in the RCTs comparing febuxostat and allopurinol was 7810 patients.<sup>1,2,16–18,29–34</sup> The studies evaluated various daily doses of febuxostat, ranging from low doses of 10/20 mg,<sup>18,33</sup> 40 mg,<sup>2,29,30,32</sup> 80 mg,<sup>1,2,16,17,29,30,32,34</sup> 120 mg<sup>1,16,17,31</sup> and 240 mg<sup>17</sup> per day, compared to different doses of allopurinol (50/100/200/300/600 mg per day).<sup>1,2,16,17,30,34</sup> The duration of the studies varied, ranging from 7–9 days<sup>31</sup> to up to 3 years.<sup>16</sup> The gout study population was mainly referred to the American College of Rheumatology, American Rheumatism Association, or American Rheumatology Association categorization.<sup>1,2,16,17,30</sup>

### Study Design

The majority of studies included in this systematic review were conducted with double-blind randomized study design (9 of 11).<sup>1,2,17,18,29–32,34</sup> Two studies were performed as open-label or not explicitly described as double-blind.<sup>16,33</sup> However, it should be noted that in studies involving the titration of allopurinol, blinding may be compromised.<sup>1,2,16,17,32</sup>

### Hepatic Safety Data

Table 2 presents the hepatic safety data from all the studies included in this analysis.<sup>1,2,16–18,29–33</sup> The hepatic safety data described in the studies were defined as abnormal findings on liver function tests, investigator-defined liver function abnormalities leading to discontinuation/ withdrawal, ALT increased, AST increased, both ALT and AST increased, AST/ALT and total bilirubin increased, AST/ALT and alkaline phosphatase elevation, hepatobiliary disorders, liver-related treatment-emergent Adverse Event (TEAE) or Treatment-emergent signs and symptoms (TESS), cholestasis, hepatotoxicity, and increased levels of gamma-glutamyltransferase. In addition, there were no reported data in the full-paper studies regarding Hy's cases, liver-related hospitalization, and death.

### Main Findings

We observed consistent adverse events in liver function for both febuxostat and allopurinol. These abnormalities, as identified through liver function tests, sometimes resulted in study withdrawal, according to investigators' assessment.

**Table 1** Characteristics of Included Studies

Author	Publication Year	Country	Study Design	Study Population (Indication)	Intervention (Dose per Day)	Number of Subjects	Characteristics of Patients: Gender, Mean Age, Etc	Study Duration	Jadad Score
Schumacher et al <sup>17</sup>	2008	United States	Randomized, Double-blind, Parallel-Group Trial	Gout (defined by American College of Rheumatology), hyperuricemia (SUA level $\geq$ 8 mg/dl), normal or impaired renal function	Febuxostat 80 mg, Febuxostat 120 mg, Febuxostat 240 mg, Allopurinol 100/300 mg, Placebo	1072	Placebo: male 92%, mean age $52 \pm 12$ years Febuxostat 80 mg: male 94%, mean age $51 \pm 12$ years, Febuxostat 120 mg: male 95%, mean age $51 \pm 12$ years Febuxostat 240 mg: male 94%, mean age $54 \pm 13$ years, Allopurinol 100/300 mg: male 93%, male $52 \pm 12$ years,	28 weeks	3
Becker et al <sup>16</sup>	2009	United States, Canada	Open label extension study	Gout (according to ARA, SUA $\geq$ 8.0 mg/dl)	Febuxostat 80 mg, Febuxostat 120 mg, Allopurinol 100/300 mg	1280	Majority male, Caucasian, in the age range of 45 to 65 years. Most subject were obese BMI $\geq 30$ kg/m <sup>2</sup>	Up to 3 years	1
Becker et al <sup>2</sup>	2010	United States	Double-blind Randomized Controlled Trial	Gout (fulfilling ARA), SUA $>$ 8.0 mg/dl)	Febuxostat 40 mg, Febuxostat 80 mg, Allopurinol 200/300 mg	2268	Febuxostat 40 mg: male 95.4%, mean age $52.5 \pm 11.68$ years, Febuxostat 80 mg: male 93.9%, mean age $53.0 \pm 11.79$ years, Allopurinol 200/ 300 mg: male 93.8%, mean age $52.9 \pm 11.73$ years	6 months	5
Goldfarb et al <sup>34</sup>	2013	United States	Phase II, double-blind randomized controlled trial	Higher Elevated uUA excretion ( $>$ 700 mg/ 2g h)	Febuxostat 80 mg, Allopurinol 200/300 mg, Placebo	99	Febuxostat 80 mg: male 81.8%, mean age $49.1 \pm 9.6$ years Allopurinol 300 mg: male 93.9%, mean age $46.5 \pm 9.9$ years Placebo: male 81.8%, mean age $46.5 \pm 11.5$ years	6 months	3
Kamatani et al <sup>18</sup>	2011	Japan	Allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study	SUA $>$ 8.0 mg/dl	Febuxostat 10/20 mg, Allopurinol 100 mg	244	Febuxostat 10/20 mg: male 97.5%, mean age $51.6 \pm 13.1$ years Allopurinol 100 mg: male 91.67%, mean age $52.6 \pm 14.0$ years	8 weeks	3
Huang et al <sup>29</sup>	2014	China	Allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study	SUA $>$ 8.0 mg/dl	Febuxostat 40 mg, febuxostat 80 mg, Allopurinol 300 mg	516	Febuxostat 40 mg: male 97.09%, mean age $46.42 \pm 10.90$ years Febuxostat 80 mg: male 98.25%, mean age $47.40 \pm 11.18$ years Allopurinol 300 mg: male 97.67%, mean age $46.17 \pm 11.56$ years	8 weeks	5

(Continued)

Table 1 (Continued).

Author	Publication Year	Country	Study Design	Study Population (Indication)	Intervention (Dose per Day)	Number of Subjects	Characteristics of Patients: Gender, Mean Age, Etc	Study Duration	Jadad Score
Xu et al <sup>30</sup>	2015	China	Randomized, allopurinol-controlled, double-blinded, triple-dummy, parallel study	Gout (defined by ARA criteria), hyperuricemia (defined SUA 480 µmol/L), normal renal function	Febuxostat 40 mg, febuxostat 80 mg, Allopurinol 100 mg	504	Febuxostat 80 mg: male 92.4%, mean age 48.2 ± 12.0 years, Febuxostat 40 mg: male 98.8%, mean age 45.5 ± 11.9 years, Allopurinol 300 mg: male 93.7%, mean age 46.6 ± 10.7 years	24 weeks	5
Spina et al <sup>31</sup>	2015	11 European countries and Brazil	Double-blind, randomized, parallel-group, comparative pivotal study	Hematologic malignancies patient, SUA < 10 mg/dl	Allopurinol 200/ 300/ 600 mg, Febuxostat 120 mg	346	Febuxostat: male 62.4%, mean age 58.5 ± 14.26 years, Allopurinol: male 61.3%, mean age 58.3 ± 13.27 years	7–9 days	2
Zhang et al <sup>32</sup>	2019	China	Randomized, Double-blinded, non-inferiority study	SUA > 7.0 mg/dl with a history of gout, SUA ≥ 8 mg/dl with complications or SUA ≥ 9.0 mg/dl without complication	Febuxostat 40 mg, Febuxostat 80 mg, Allopurinol 300 mg	599	Febuxostat 40 mg: male 99.4%, mean age 46.5 ± 11.0 years Febuxostat 80 mg: male 97.9%, mean age 47.2 ± 12.9 years, Allopurinol 300 mg: male 98.9%, mean age 48.3 ± 13.1 years	24 weeks	5
Yang et al <sup>33</sup>	2022	China	Double-center, randomized, controlled study	Confirmed diagnosis of CKD stage 2–3, complicated with SUA ≥ 7 mg/dl for male and SUA ≥ 6 mg/dl for female.	Febuxostat 20 mg, Allopurinol 50/100/ 200 mg	120	Febuxostat: male 71.7%, mean age 61.7 ± 6.9 years, Allopurinol: male 75.00%, mean age 62.2 + 9.2 years	6 months	2
Becker et al <sup>1</sup>	2005	United States and Canada	Randomized, double-blind controlled trial	Gout and with SUA concentration of at least 8.0 mg/dl, met the preliminary criteria of the American College of Rheumatology for acute arthritis of gout.	Febuxostat 80 mg, Febuxostat 120 mg, Allopurinol 300 mg	762	Febuxostat 80 mg: male 95%, mean age 51.8 ± 11.7 years, Febuxostat 120 mg: male 97%, mean age 52.0 ± 12.1 years, Allopurinol 300 mg: male 96%, age 51.6 ± 12.6 years	52 weeks	4

**Abbreviations:** SUA, serum urate; uUA, urinary uric acid; ARA, American Rheumatism Association; CKD, Chronic Kidney Disease; BMI, Body Mass Index; mg, milligram; mg/dl, milligram per deciliter; mg/kg, milligram per kilogram; %, percentage; µmol/L, micromole per liter.

**Table 2** Reported Liver Function Result and Other Hepatic Safety Evidence

Study	Definition of Hepatic Safety Data	Results of Hepatic Safety Data							Clinical Significance	Remarks
		FEB 10/20 mg	FEB 40 mg	FEB 80 mg	FEB 120 mg	FEB 240 mg	ALO	Placebo		
Schumacher et al 2008 <sup>17</sup>	Abnormal findings on liver function tests, designated as AEs by individual investigators	–	–	6%	4%	4%	6%	2%	No statistically significant difference	These events were classified by the investigator as mild to moderate in severity, and only 1 was not transient. This subject (receiving FEB 80 mg) had concurrent hepatitis C and entered the study with elevated hepatic enzymes that persisted and led to premature discontinuation.
	Abnormal findings on liver function tests leading to withdrawal	–	–	2%	1%	0%	1%	0%	No statistically significant difference	
	ALT ≥ 1.5 times the ULN	–	–	25%*	22%	19%	20%	15%	*Statistically significant versus placebo	
	AST > 1.5 times the ULN	–	–	19%*	15%	10%	13%	11%	*Statistically significant versus placebo	
	ALT ≥ 1.5 times the ULN and AST ≥ 1.5 times the ULN	–	–	15%	11%	9%	9%	8%	No statistically significant difference	
	ALT ≥ 1.5 times the ULN and total bilirubin ≥ 2 mg/dl	–	–	<1%	0%	<1%	<1%	<1%	No statistically significant difference	
	AST ≥ 1.5 times the ULN and total bilirubin ≥ 2 mg/dl	–	–	<1%	0%	<1%	<1%	<1%	No statistically significant difference	
	ALT ≥ 1.5 times the ULN and alkaline phosphatase ≥ 2 times the ULN	–	–	<1%	0%	0%	0%	0%	No statistically significant difference	
	AST ≥ 1.5 times the ULN and alkaline phosphatase ≥ 2 times the ULN	–	–	<1%	0%	0%	0%	0%	No statistically significant difference	
Becker et al 2009 <sup>2</sup>	Serious hepatobiliary disorders	–	–	<1%	<1%	–	2%	–	No statistically significant difference	The majority of laboratory elevations were transient and were < 3 times the ULN. Two subjects receiving febuxostat 80 mg had > 10 times the ULN of normal ALT/AST, with concurrent bilirubin > 2 times the ULN: 1 subject with a bile duct stone and none other with fatal bile duct cancer.
	Liver function analyses abnormalities as reasons for withdrawal	–	–	1.1%	0.8%	–	1.1%	–	No statistically significant difference	

(Continued)



Table 2 (Continued).

Study	Definition of Hepatic Safety Data	Results of Hepatic Safety Data							Clinical Significance	Remarks
		FEB 10/20 mg	FEB 40 mg	FEB 80 mg	FEB 120 mg	FEB 240 mg	ALO	Placebo		
Becker et al 2010 <sup>2</sup>	Investigator-defined liver function abnormalities leading to discontinuation	–	2%	1%	–	–	1%	–	No statistically significant difference	–
	Liver function analyses	–	8.3%	6.9%	–	–	6.6%	–	No statistically significant difference	Most frequently (> 5%) reported AEs
Goldfarb et al 2013 <sup>34</sup>	Treatment-emergent AEs	–	–	–	–	–	–	–	No statistically significant difference	No elevated hepatic enzyme tests were reported of Febuxostat 80 mg and Allopurinol 300 mg
Kamatani et al 2011 <sup>18</sup>	AST increased	2.5%	–	–	–	–	5.8%	–	No statistically significant difference	No significant differences of AEs with age (< 65 years old, ≥ 65 years old) and complication of hepatic diseases
Huang et al 2014 <sup>29</sup>	Liver function test abnormalities	–	2.91%	1.16%	–	–	3.49%	–	No statistically significant difference	One of the most frequent or important treatment-related AEs. Most aminotransferase elevations were mild (except is one subject exceeding the upper limit or normal by three-fold) and reversible by discontinuing treatment. A mild serum bilirubin increase was found in one subject in allopurinol group.
Xu et al 2015 <sup>30</sup>	Liver function test abnormalities	–	10.1%	13.1%	–	–	10.7%	–	No statistically significant difference	Most frequent treat-related adverse events. Most adverse events related to abnormal findings on liver function tests happened at 2nd month and 4th - 6th month and resolved within 3 months
Spina et al 2015 <sup>31</sup>	Hepatobiliary disorders (overall)	–	–	–	0%	–	0.6%	–	No statistically significant difference	TESS
	Cholestasis	–	–	–	0%	–	0.6% <sup>a</sup>	–	No statistically significant difference	TESS
	Hepatotoxicity	–	–	–	0%	–	0.6% <sup>a</sup>	–	No statistically significant difference	TESS



Zhang et al 2019 <sup>32</sup>	ALT increased	–	6.2%	6.5%	–	–	7.1%	–	No statistically significant difference	The only TEAEs occurring in > 5% of subjects in all treatment group were increased alanine aminotransferase.
	Gamma-glutamyl-transferase increased	–	3.1%	2.0%	–	–	1.5%	–	No statistically significant difference	
	AST increased	–	2.1%	2.5%	–	–	3.0%	–	No statistically significant difference	
	Hepatobiliary disorder	–	4.1%	7.0%	–	–	3.0%	–	No statistically significant difference	
	Hepatic function abnormal	–	1.0%	3.5%	–	–	1.0%	–	No statistically significant difference	
Yang et al 2022 <sup>33</sup>	Dysregulated hepatic function	1.7%	–	–	–	–	5.0%	–	No statistically significant difference	No difference of drug-related AE of dysregulated hepatic function (P= 0.619) between Febuxostat 20 mg group and Allopurinol group.
Becker et al 2005 <sup>1</sup>	Liver function test abnormalities	–	–	4%	5%	–	4%	–	No statistically significant difference, treatment-related adverse events	Most adverse events were mild to moderate in severity and reversible after discontinuation of febuxostat.
	The most frequent adverse event leading to withdrawal was abnormal liver-function test results	–	–	1.95%	2.79%*	–	0.40%	–	*Statistically significant (P=0.04) for the comparison between 120 mg febuxostat and allopurinol groups.	

**Notes:** \*Statistically significant. <sup>a</sup>Severe in intensity.

**Abbreviations:** FEB, febuxostat; ALO, allopurinol; ALT, alanine transaminase; AST, aspartate transaminase; AE, adverse event; ULN, Upper Limit Normal; TESS, Treatment-emergent signs and symptoms; TEAE, Treatment-emergent adverse event; mg, milligram; %, percentage.

However, the majority of elevations in liver function parameters were classified as mild to moderate in severity. Many of the included studies did not show statistically significant differences in hepatic safety data between febuxostat and allopurinol.<sup>2,16,18,27,29,31–34</sup> However, the study by Schumacher et al in 2008 reported a significant increase in ALT ( $\geq 1.5$  times the ULN) and AST ( $\geq 1.5$  times the ULN) with febuxostat 80 mg compared to placebo. These events were classified as mild to moderate in severity, except for one case that was not transient. This particular subject, who received febuxostat 80 mg, had pre-existing hepatitis C and entered the study with elevated hepatic enzymes that persisted and led to premature discontinuation.<sup>17</sup>

Another study by Becker et al, 2005 showed significant differences in abnormal liver function test results, which were the most frequent adverse event leading to subject withdrawal. The comparison between 120 mg febuxostat (2.79%) and the allopurinol group (0.4%) demonstrated statistical significance ( $P=0.04$ ). However, most adverse events were assessed as mild to moderate in severity and reversible after discontinuation of febuxostat.<sup>1</sup>

In another study by Spina et al in 2015 which assessed febuxostat versus allopurinol in patients with hematologic malignancies at intermediate to high risk of tumor lysis syndrome (TLS), the hepatobiliary disorders were experienced in the allopurinol group (0.6% for both overall hepatobiliary disorders, cholestasis, and hepatotoxicity preferred terms) and none were reported in the febuxostat 120 mg group.<sup>31</sup>

## Discussion

To date, there is currently a lack of systematic analysis data regarding hepatic safety of febuxostat compared to allopurinol of gout patients. In this systematic review, we aimed to evaluate the hepatic safety profile of febuxostat compared to allopurinol in published RCTs. We identified a total of 11 eligible studies conducted between 2005 to 2022.<sup>1,2,16–18,29–34</sup> The findings of this review indicate that most of the hepatic safety parameters assessed in adult patients did not show statistically significant differences between allopurinol and febuxostat (9 out of 11 studies).<sup>2,16,18,27,29,31–34</sup> These results suggest that the hepatic safety data of febuxostat is comparable to that of allopurinol. This finding aligns with a meta-analysis conducted by Guo et al, in 2020, which assessed the risk of liver damage associated with both allopurinol and febuxostat. The meta-analysis included geriatric patients and found no statistically significant differences in the risk of liver damage between allopurinol (RR: 1.42; 95% CI: 0.89, 2.40) and febuxostat (RR: 1.47; 95% CI: 0.96, 2.40).<sup>35</sup> Aside of that, indirectly comparison of allopurinol and febuxostat in a network meta-analysis (NMA) of six trials (1269 patients) did not result in a higher risk of impaired liver function of urate-lowering therapies.<sup>36</sup>

Regular monitoring of liver function tests is recommended in the management of chronic gout with urate-lowering therapy to identify self-limited liver test abnormalities and resolve them by discontinuing the medication.<sup>6,24,36</sup> The hepatotoxicity mechanism of febuxostat is believed to be associated with its metabolism in the liver, primarily through glucuronidation and to a lesser extent via Cytochrome (CYP) 450 system.<sup>37</sup> Based on the historical cohort data in Japan, liver disease was a common clinical comorbidities and demographic characteristic of hyperuricemia (31.4%) or gout (15.5%) patients.<sup>38</sup> There is a limited review that discusses the hepatic safety of those two drugs as a comparison.

Allopurinol-induced hepatotoxicity is believed to be related to immunoallergic reactions, such as severe allopurinol hypersensitivity skin reaction, which are closely associated with the HLA B\*58:01 allele. These reactions are commonly seen in cases of allopurinol liver injury accompanied by drug reaction with eosinophilia and systematic symptoms (DRESS syndrome) or Stevens Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN).<sup>19,20,39–43</sup> An included study showed hepatobiliary disorders were experienced in allopurinol groups only for cholestasis (0.6%) and hepatotoxicity (0.6%) and assessed as severe in intensity. These liver abnormalities did not appear in the febuxostat groups.<sup>31</sup> Concerning this finding, we believed that all treatment-related adverse events found in the respective clinical trials should be reflected in the product labeling information, although for old-mature products like allopurinol.

The product labeling information of both allopurinol and febuxostat should provide accurate and up-to-date safety data to guide healthcare practitioners in prescribing these medications to patients. According to the U.S National Library of Medicine, transient and minor liver test abnormalities are associated with allopurinol therapy in 2–6% of patients,<sup>42</sup> which is categorized as common in the latest product labeling information or summary product characterization (SmPC) of allopurinol.<sup>44</sup> Similarly, the SmPC for febuxostat mentions the common occurrence of liver function abnormalities,<sup>45</sup>

which is consistent with the average of hepatotoxic adverse reactions (3.5%) reported in the US National Library of Medicine data.<sup>37</sup>

Nowadays, the shared decision-making (SDM) between patients and healthcare practitioners increases patients' knowledge, and awareness and allows active interactions role in decision-making across diseases, especially gout. United States rheumatologists reported that they engaged in SDM for three of the five medication decisions with gout patients and need more support for patients in making choices for gout treatment.<sup>46</sup> In fact, it was literate that the comprehensive patient information leaflet of both allopurinol and febuxostat would be valuable to support gout SDM decision.

The strength of our study was that we focused on intervention studies with minimal variability or bias, comparing allopurinol and febuxostat head-to-head and describing liver function outcomes. We also described the treatment duration in the eligible studies; however, the long-term safety studies of more than 3 years of monitoring were still lacking. In studies where allopurinol titration was used, it posed a challenge to maintain blinding. Meanwhile, febuxostat undergoes hepatic metabolism, and its dose adjustment and effect are less affected by the patient's renal function to maintain blinding. The number of included studies was too few to describe the gout adult heterogeneous population treated with allopurinol and febuxostat. In the included studies, we also found that the hepatic safety result was not completely described and compared in the different ethnic groups, age, gender, and other patient demographic data.

Due to the limited number of patients involved in clinical trials of febuxostat and allopurinol, continuous monitoring of pharmacovigilance databases is crucial. An accurate description of the hepatic safety profile of allopurinol and febuxostat will assist healthcare practitioners in determining appropriate liver monitoring for patients receiving these medications for the management of gout.

Although this systematic review focused on the adult gout population in the setting of trials, we consistently observed liver function-related adverse events in all the reviewed RCTs. It is recommended further to examine available pharmacovigilance databases for hepatic safety data, encompassing a more diverse patient population and real-world data. The roles of pharmacovigilance and post-marketing pharmacoepidemiology data are crucial in establishing the comprehensive safety profiles of both febuxostat and allopurinol. Conducting future pharmacoepidemiology studies to explore the hepatic safety data of allopurinol and febuxostat is of utmost importance, given their frequent use by patients to treat this chronic disease. Such studies would be highly beneficial for ensuring patient safety and understanding any potential risks associated with these medications.

## Conclusion

Based on our analysis, the hepatic safety data of adult gout patients enrolled in the included RCTs indicate that febuxostat and allopurinol have comparable safety profiles. Liver function abnormalities were observed in all studies. Regular monitoring of liver function tests is recommended in the management of chronic gout with urate-lowering therapy to identify self-limited liver test abnormalities. In addition, it is important to incorporate this information for the product labeling information and patient information leaflet of both allopurinol and febuxostat to provide accurate and current safety data as a reference for healthcare practitioners in prescribing these medications to patients indicating the roles of pharmacovigilance and post-marketing surveillance data in establishing the ultimate safety profile for both febuxostat and allopurinol.

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## Disclosure

The authors report no conflicts of interest in this work.

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