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# Antihypertensive efficacy of allopurinol; a mini-review on current concepts

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## ABSTRACT

Allopurinol, primarily used to treat gout, has shown potential as an antihypertensive agent due to its effects on oxidative stress and endothelial function. This agent is not typically used as a first-line treatment for hypertension; however, some studies have suggested that it may have potential antihypertensive effects. More research is needed to establish its efficacy and mechanisms in treating hypertension.

*Keywords:* Allopurinol, Hypertension, Hyperuricemia, Oxidative stress, Blood pressure

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*Implication for health policy/practice/research/medical education:*
High levels of uric acid have been associated with hypertension, and by lowering uric acid levels, allopurinol may help improve endothelial function and reduce oxidative stress, which can contribute to hypertension.

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## Introduction

Allopurinol is a xanthine oxidase inhibitor that is primarily used for the management of hyperuricemia and gout (1). However, recent studies have suggested that allopurinol may also have antihypertensive effects, potentially through its anti-inflammatory and antioxidant properties (2). One proposed mechanism for the antihypertensive effects of allopurinol is its ability to inhibit xanthine oxidase, an enzyme involved in the production of uric acid. By reducing uric acid levels, allopurinol may help improve endothelial function and reduce oxidative stress, which can contribute to hypertension (3,4). Several small studies have shown promising results in terms of allopurinol's antihypertensive effects. Previously, Agarwal et al showed that allopurinol administration in patients with hypertension and hyperuricemia led to a meaningful reduction in blood pressure compared to placebo (5). Another study by Freilich et al noted that allopurinol treatment in patients with heart failure and hyperuricemia resulted in a significant improvement in systolic and diastolic blood pressure, as well as a reduction in the risk of hospitalization for heart failure (6). In the study on patients with early-stage chronic kidney disease, Goicoechea et al demonstrated that allopurinol therapy led to a statistically significant improvement in the estimated glomerular filtration rate (eGFR) over the 12-week study period (7). This mini-review discusses the current concepts on the antihypertensive efficacy of allopurinol, its proposed mechanisms of action, and the potential implications for clinical practice.

## Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including; allopurinol, hypertension, hyperuricemia, oxidative stress, blood pressure.

## Mechanisms of antihypertensive action of allopurinol

The antihypertensive effects of allopurinol are thought to be mediated through its inhibition of xanthine oxidase, an enzyme involved in the production of reactive oxygen

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species and the metabolism of purines (8). By reducing the production of reactive oxygen species, allopurinol may help to mitigate oxidative stress and inflammation, which are known to contribute to the development and progression of hypertension (9). Additionally, allopurinol may also exert antihypertensive effects through its modulation of the renin-angiotensin-aldosterone system (RAAS) (10). In previous studies, allopurinol treatment has been shown to reduce the expression of angiotensinogen, angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AT1R), potentially leading to a decrease in the production of angiotensin II, a potent vasoconstrictor and pro-inflammatory molecule (11-13). Allopurinol has been also shown to have anti-inflammatory effects by reducing the production of inflammatory cytokines and markers of inflammation. Chronic inflammation is associated with hypertension, and by reducing inflammation, allopurinol may help lower blood pressure (14,15). Moreover, allopurinol has been suggested to improve endothelial function, which is important for regulating blood vessel tone and blood flow. Dysfunction of the endothelium is a common feature of hypertension, and by improving endothelial function, allopurinol may help lower blood pressure (16). Additionally, allopurinol has antioxidant properties and can help reduce oxidative stress in the body. Oxidative stress is a key contributor to hypertension, and by reducing oxidative stress, allopurinol may help lower blood pressure (17). Some studies have also suggested that allopurinol may affect other pathways involved in blood pressure regulation, such as the nitric oxide pathway (18). Allopurinol has been shown to decrease systemic vascular resistance, which can also contribute to blood pressure control (19). Allopurinol has been detected to improve kidney function in patients with kidney disease, which can also contribute to blood pressure control (20). The potential antihypertensive effects of allopurinol may have significant implications for the management of hypertension, particularly in patients with hyperuricemia or other risk factors for cardiovascular disease (21). For example, the meta-analysis conducted by Agarwal et al on 15 randomized controlled trials found that after treatment with allopurinol over a mean follow-up period of 6.2 months, the systolic blood pressure decreased by 3.3 mmHg and the diastolic blood pressure decreased by 1.3 mmHg compared to the control group (5). A clinical trial by Feig et al on hyperuricemic adolescents with newly diagnosed hypertension found that allopurinol treatment directed to the normal blood pressure in 20 out of 30 individuals, containing 19 out of 22 (86%) whose uric acid levels were dropped to less than 5.0 mg/dL(4).

## Interaction of allopurinol with other medications for hypertension

Allopurinol can interact with medications for hypertension, potentially affecting their efficacy and safety. Combining allopurinol with thiazide diuretics like hydrochlorothiazide can increase the risk of side effects such as skin rash, diarrhea, nausea, and gout attacks (22,23). Taking specific antibiotics like amoxicillin, ampicillin, or amoxicillin/clavulanic acid with allopurinol may increase the risk of a skin rash, requiring prompt medical attention if any signs of a serious skin reaction occur (24). Allopurinol can enhance the effects of warfarin, a blood thinner, increasing the risk of bleeding. Close monitoring and potential dosage adjustments may be necessary when using these medications together. While alcohol doesn't directly interact with allopurinol, it can exacerbate gout symptoms (25). Alcohol may raise uric acid levels, worsening gout, and making it harder for the kidneys to clear uric acid from the body. Individuals with kidney disease may have difficulty clearing allopurinol from their bodies, leading to potential side effects (26). Allopurinol may also pose risks of kidney problems, particularly harmful for those with kidney disease (7).

## Conclusion

Allopurinol, a xanthine oxidase inhibitor, has been shown to have potential antihypertensive effects in various clinical trials and observational studies. These effects may be mediated through its anti-inflammatory and antioxidant properties, as well as its modulation of the RAAS. The potential implications for clinical practice include the use of allopurinol as an adjunctive therapy for the management of hypertension, predominantly in individuals with hyperuricemia or other risk factors for cardiovascular disease. However, further research is required to establish the safety and effectiveness of allopurinol in this context.

## Authors' contribution

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**Writing–review and editing:** All authors.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

Ethical issues (including plagiarism, data fabrication,

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## Declaration of generative AI and AI-assisted technologies in the writing process

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