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Review Article

Clinical Significance of the Potential Amlodipine–Metformin Interaction: A Systematic Review

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Amlodipine and metformin are frequently co-administered in patients with hypertension and type 2 diabetes mellitus (T2DM). Although their concomitant use has been identified as a potential drug–drug interaction (pDDI), the clinical significance of this interaction remains uncertain. This systematic review aimed to evaluate the frequency, severity, proposed mechanism, and clinical significance of the potential interaction between amlodipine and metformin. A comprehensive literature search was conducted using PubMed, ScienceDirect and supplementary searches through Google Scholar with the keywords “amlodipine” AND “metformin” AND “drug interaction”. Study selection was conducted according to the PRISMA framework. Methodological quality was assessed using the appropriate Joanna Briggs Institute (JBI) Critical Appraisal Tools according to the design of each study. A total of 702 records were identified, 42 full-text articles were assessed for eligibility, and seven studies met the inclusion criteria and were included in the final narrative synthesis. Concomitant amlodipine and metformin use was consistently identified as a potential DDI, although the reported frequency varied across studies and was based on different reporting units, including patients, prescriptions, and total identified DDI events. The interaction was generally classified as moderate or requiring monitoring, with pharmacodynamic antagonism and a potential reduction in metformin effectiveness being the most frequently reported interaction profile. Current evidence demonstrates a recurring potential interaction signal between amlodipine and metformin but does not establish that concomitant use causes clinically meaningful deterioration in glycemic control. Therefore, routine avoidance of this combination is not supported by the available evidence. Individualized therapeutic monitoring should be considered when both drugs are clinically indicated. Further prospective longitudinal studies evaluating objective glycemic outcomes are needed to determine the actual clinical significance of this potential interaction.

Drug–drug interactions (DDIs) are recognized as an important source of treatment failure and variability in clinical outcomes, particularly among patients receiving long-term combination therapy for chronic

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diseases [1,2]. Individuals with type 2 diabetes mellitus (T2DM) and hypertension commonly require concomitant treatment with metformin and antihypertensive agents such as amlodipine, making this combination one of the most frequently encountered in clinical practice [3–5]. Although several drug-interaction references classify this combination as a moderate interaction, the available clinical evidence has not consistently demonstrated clinically meaningful adverse outcomes. This discrepancy raises the possibility that the interaction may exert subtle effects that are not readily detectable during routine clinical monitoring.

Metformin is widely recommended as the first-line pharmacological therapy for type 2 diabetes mellitus (T2DM) because of its effectiveness in improving glycemic control and reducing diabetes-related complications [6]. Its antihyperglycemic effect is primarily mediated through suppression of hepatic glucose production and activation of adenosine monophosphate-activated protein kinase (AMPK) signaling [7]. Hypertension frequently coexists with T2DM and often requires long-term antihypertensive therapy, with calcium channel blockers such as amlodipine remaining widely used because of their established efficacy and favorable tolerability profile [8,9]. The frequent combined use of amlodipine and metformin highlights the importance of understanding their potential interaction.

Metformin disposition is strongly influenced by membrane transporters, particularly organic cation transporters (OCTs) and multidrug and toxin extrusion (MATE) transporters, which are involved in its distribution and renal elimination [10]. Changes in the activity of these transporters can alter metformin exposure and contribute to transporter-mediated drug–drug interactions [11,12]. There is currently no clear evidence that amlodipine directly affects OCT- or MATE-mediated transport of metformin. In the clinical literature, the potential interaction between amlodipine and metformin has more commonly been described as a pharmacodynamic antagonism, with amlodipine suggested to reduce the glucose-lowering effect of metformin [9,13]. This potential interaction has generally been classified as moderate, indicating that clinical monitoring may be warranted, although its underlying mechanism and actual clinical significance remain uncertain [14].

Despite the widespread clinical use of this drug combination, no previous systematic review has comprehensively synthesized the available evidence regarding the frequency, proposed mechanism, and clinical significance of the potential amlodipine–metformin interaction. This systematic literature review aimed to critically evaluate and synthesize the available evidence regarding the interaction between amlodipine and metformin, with particular emphasis on frequency, severity, proposed mechanism, clinical consequences, and clinical significance.

Results and Discussion

A total of seven studies published between 2021 and 2026 met the eligibility criteria and were included in the final narrative synthesis. The included studies varied in study design, population, clinical setting, and methods used to identify potential drug–drug interactions (pDDIs). Despite this methodological heterogeneity, concomitant use of amlodipine and metformin was consistently identified as a potential DDI across all included studies. However, the reported frequency, severity classification, proposed mechanism, and interpretation of clinical significance varied across studies. The reporting basis for interaction frequency also differed, with some studies reporting interactions at the patient or prescription level, whereas others reported them as a proportion of the total identified DDI events. The characteristics and extracted findings of the studies included are summarized in Table 1.

Methodological appraisal using the appropriate Joanna Briggs Institute (JBI) Critical Appraisal Tools according to the design of each study indicated variation in methodological quality across the seven included studies. Recurring methodological limitations included the use of non-probability sampling in some studies, limited identification or control of potential confounding factors, and limitations inherent in cross-sectional or

retrospective study designs. In addition, most studies identified potential DDIs using drug-interaction databases or screening tools rather than directly evaluating patient-level clinical outcomes.

The seven studies demonstrate that the amlodipine–metformin combination is repeatedly identified as a potential DDI across different populations and clinical settings. However, the reporting basis for the interaction varied among studies. Sapkota et al. reported the interaction in 10 of 200 patients/prescriptions (5.0%), whereas Tuladhar et al. reported it in 35 of 127 patients (27.6%) [4,9]. Other studies reported the amlodipine–metformin interaction relative to the total number of identified DDI events rather than the number of patients or prescriptions. Therefore, these frequencies were interpreted according to the reporting basis used in each study and were not directly compared or pooled as an overall prevalence estimate.

The classification of the interaction showed greater consistency. The combination was generally categorized as moderate or requiring close monitoring, rather than as a major interaction requiring routine avoidance. This distinction has practical importance. A moderate classification indicates the potential need for monitoring or therapeutic consideration but does not establish that clinically important harm will occur in every patient receiving the combination.

Pharmacodynamic antagonism was the most frequently reported mechanism across the included studies. Sapkota et al., Gürel et al., and Giri et al. described amlodipine as potentially decreasing the pharmacological effect of metformin. Saputri et al. similarly reported that pharmacodynamic interactions predominated among the identified DDIs [5].

Limitations of DDI Identification and Clinical Evidence

A major limitation of the available evidence is that the amlodipine–metformin interaction was predominantly identified using drug-interaction databases or screening tools rather than through documented clinical cases or direct assessment of patient outcomes. Consequently, the reported interactions should primarily be interpreted as potential DDIs rather than confirmed clinical interactions. The included studies did not consistently evaluate whether concomitant amlodipine use was associated with clinically meaningful changes in fasting blood glucose, HbA1c, treatment failure, or other glycemic outcomes. Therefore, although the interaction was repeatedly identified across the included studies, its actual clinical impact remains uncertain.

Saputri *et al*. identified metformin–amlodipine as the most frequent interaction pair in their study but framed the findings in terms of the potential for drug interactions and the need for therapeutic monitoring rather than demonstrating deterioration in glycemic outcomes caused by the combination [5]. The available evidence supports awareness and monitoring for potential changes in glycemic response but remains insufficient to conclude that amlodipine causes clinically significant impairment of metformin effectiveness.

Clinical Significance

Although the amlodipine–metformin combination was repeatedly identified as a potential DDI across the included studies, its clinical significance remains uncertain. Most of the included studies identified the interaction using drug-interaction databases or screening tools and classified it as moderate or requiring monitoring, with a potential reduction in metformin effectiveness being the most frequently reported consequence. However, these classifications primarily represent potential interaction signals rather than evidence of clinically demonstrated harm.

The included studies did not consistently evaluate whether concomitant use of amlodipine and metformin was associated with measurable deterioration in glycemic outcomes, such as fasting plasma glucose, postprandial glucose, HbA1c, or the need for treatment intensification. Moreover, a prospective cohort study outside the included studies

reported that the addition of amlodipine to standard diabetes treatment was not associated with deterioration in glycemic control; instead, HbA1c was significantly lower after 24 weeks in patients receiving additional amlodipine therapy [19]. This finding further indicates that identification of a potential DDI does not necessarily translate into clinically significant impairment of glycemic control.

Therefore, the current evidence supports clinical awareness and monitoring rather than routine avoidance of concomitant amlodipine and metformin. In patients receiving both medications, glycemic response may be monitored using objective parameters such as fasting plasma glucose and HbA1c, particularly when unexplained deterioration in glycemic control occurs. Further prospective studies with longitudinal assessment of glycemic parameters and treatment-response outcomes are needed to determine the actual clinical significance of this potential interaction.

This discrepancy may partly reflect differences in the drug-interaction resources used across studies. The included studies did not employ a uniform DDI screening database; several studies used Medscape, whereas others used Lexi-Interact, Stockley's Drug Interactions, MedFacts, Drugs.com, or combinations of these resources.

Such variation may partly reflect differences in the evidence sources, interaction classification criteria, and updating procedures applied by individual DDI resources. For example, Drugs.com currently reports no direct interaction between metformin and amlodipine, while also cautioning that the absence of an identified interaction does not necessarily establish that no interaction exists. Therefore, discrepancies across interaction resources should be considered when interpreting the clinical significance of this potential interaction.

Clinical Implications

From a clinical perspective, the available evidence does not support routine avoidance of concomitant amlodipine and metformin when both drugs are clinically indicated [14]. Instead, the potential interaction should be considered within an individualized therapeutic monitoring approach rather than being assumed to directly cause deterioration in glycemic control. In patients receiving both medications, changes in glycemic response should be interpreted alongside other clinically relevant factors, including renal function, medication adherence, changes in concomitant therapy, and progression of diabetes. Clinical pharmacy practice therefore plays an important role through systematic medication review, assessment of potential drug–drug interactions, and individualized monitoring of therapeutic response to ensure the effectiveness and safety of pharmacotherapy[20].

Monitoring of glycemic response may be particularly relevant when otherwise unexplained deterioration in glucose control occurs after initiation or modification of amlodipine therapy. However, therapeutic changes should be guided by the patient's actual clinical and glycemic response rather than solely by an automated interaction alert. This distinction is particularly important for pharmacists and other healthcare professionals because a database-generated moderate interaction represents a signal for clinical evaluation rather than confirmation of an adverse clinical event [21].

Table 1. The characteristics and extracted findings of the included studies

Study	Design; Sample	DDI Assessment	Amlodipine–Metformin Interaction	Severity	Proposed Mechanism	Potential/Observed Clinical Consequence	Management / Clinical Significance
Gürel *et al.*,2024 [1]	Cross-sectional; 123 patients with hypertension	Medscape Drug Interaction Checker	12 interaction events among 511 identified DDI events	Significan/ monitoring required	Pharmacodynamic antagonism; amlodipine was reported to decrease metformin effect	Potential loss of blood glucose control; actual deterioration attributable specifically to the combination was not demonstrated	Use caution and monitor blood glucose
Tuladhar et al., 2021[4]	Descriptive cross-sectional; 127 patients with diabetes and comorbidities	Medscape Drug Interaction Checker	35 of 127 patients (27.6%)	Monitor closely	Pharmacodynamic interaction predominated at study level; pair-specific molecular mechanism was not directly investigated	Potential DDI identified; no life-threatening, serious, or significant DDI was reported in the study population	Clinical monitoring; evidence reflects potential rather than clinically demonstrated interaction
Saputri *et al.*, 2026[5]	Descriptive retrospective observational; 44 T2DM outpatients with hypertension	MedFacts, Stockley's, Medscape, and Drugs.com	10 of 129 identified DDI events (7.7%)	Moderate	Pharmacodynamic	Potential alteration in therapeutic response; actual glycemic deterioration specifically attributable to the combination was not established	Monitoring and therapeutic adjustment may be considered according to the patient's clinical condition
Sapkota et al, 2022 [9]	Cross-sectional medication therapy management study; 200 patients with T2DM	Medscape Drug Interaction Checker	10 of 200 patients/prescriptions (5.0%)	Monitor closely	Pharmacodynamic antagonism; amlodipine was reported to decrease the effect of metformin	Potential reduction in metformin effect; no clinical outcome directly attributable to this drug pair was demonstrated	Monitor glycemic response; interaction was identified through DDI screening
Giri *et al.*, 2025 [13]	Prospective cross-sectional; 140 geriatric cardiac outpatients	Medscape Drug Interaction Checker	17 of 337 identified DDI events (5.04%)	Monitor closely	Pharmacodynamic antagonism; amlodipine was reported to decrease metformin effect	Potential reduction in metformin effectiveness; no directly demonstrated deterioration in glycemic outcomes attributable to the combination	Close monitoring of therapeutic and glycemic response
Khawagi *et al.*, 2026 [14]	Cross-sectional; 173 community-dwelling adults ≥60 years	Stockley's Drug Interactions	26 interaction events among 285 identified DDI events (9.1%)	Moderate	Specific molecular mechanism was not experimentally investigated	Potential unexplained deterioration in diabetic control; no demonstrated clinical deterioration specifically attributable to the pair	Low clinical relevance—awareness only; no particular precautions normally required unless diabetic control deteriorates
Faizah *et al.*, 2025[18]	Descriptive observational prescription study	DDI screening database	30 of 145 patients/prescriptions with pDDIs (21%)	Moderate	Potential reduction in metformin effect	Potential impairment of glycemic control; actual clinical effects were not evaluated	Close blood glucose monitoring; clinical consequences remain unconfirmed

Note: The reporting basis for the amlodipine–metformin interaction varied across studies. Frequencies are presented according to the original reporting unit used in each study (patients/prescriptions or total identified DDI events) and therefore should not be directly compared across studies

Evidence Gap and Future Research

The principal evidence gap identified by this review is the limited availability of studies specifically designed to determine whether concomitant amlodipine exposure alters the clinical effectiveness of metformin. Most of the included studies were observational or DDI-screening studies and were therefore more suitable for identifying potential interactions than for establishing causality. This limitation is reflected across the included literature, in which interaction classifications and predicted consequences were considerably more common than direct longitudinal measurements of glycemic outcomes.

Future prospective and longitudinal studies should directly compare metformin-treated patients with and without concomitant amlodipine exposure and evaluate serial fasting plasma glucose, postprandial glucose, HbA1c, treatment intensification, metformin dose modification, and clinically relevant adverse outcomes. Pharmacokinetic and mechanistic investigations are also needed to determine whether the repeatedly proposed pharmacodynamic antagonism represents true biological interaction or primarily reflects classifications derived from existing DDI databases.

Overall, the seven included studies demonstrate a recurring potential DDI signal but limited direct evidence of clinical manifestation. The amlodipine–metformin interaction is frequently classified as moderate or requiring monitoring, and pharmacodynamic antagonism is commonly proposed; however, the available evidence does not establish that concomitant use causes clinically meaningful deterioration in glycemic control.

Conclusion

This systematic review identified a recurring potential drug–drug interaction between amlodipine and metformin across seven studies published between 2021 and 2026. The interaction was generally classified as moderate or requiring monitoring, with pharmacodynamic antagonism and a potential reduction in metformin effectiveness being the most frequently reported interaction profile. However, the available evidence was predominantly derived from drug-interaction screening tools and reference databases, with limited direct evidence demonstrating clinically meaningful deterioration in glycemic outcomes. Therefore, current evidence does not establish that concomitant amlodipine and metformin use causes clinically significant impairment of glycemic control, and routine avoidance of this combination is not supported when both drugs are clinically indicated. Instead, therapeutic response should be monitored individually. Further prospective longitudinal studies evaluating objective patient-level glycemic outcomes are needed to determine the actual clinical significance of this potential interaction.

Materials and Methods

This study employed a systematic literature review (SLR) design to identify and synthesize recent evidence regarding the potential drug–drug interaction between amlodipine and metformin. The review focused on the frequency and severity of the reported interaction, proposed interaction mechanisms, potential and observed clinical consequences, recommended clinical management, and reported clinical significance.

The study selection process was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to provide a structured and transparent approach to study identification, screening, eligibility assessment, and inclusion. The review focused on the frequency and severity of the reported interaction, proposed interaction mechanisms, potential and observed clinical consequences, recommended clinical management, and reported clinical significance [15]. The complete study-selection process is presented in the PRISMA flow diagram **Figure 1**.

A comprehensive literature search was performed using PubMed, ScienceDirect and supplementary literature from Google Scholar to identify potentially relevant studies not retrieved from the two primary

databases. The search terms included “Amlodipine”, “Metformin”, and “Drug Interactions”, together with the free-text terms “amlodipine” AND “metformin” AND “drug interaction”. The literature search covered studies published from January 2021 to May 2026. This period was selected to focus the review on the most recent five-year evidence regarding the potential interaction between amlodipine and metformin.

The search strategy was designed to identify relevant studies investigating the interaction between the two drugs from both experimental and observational perspectives. Only articles published in English and Bahasa and available in full text were included to ensure sufficient data extraction and analysis.

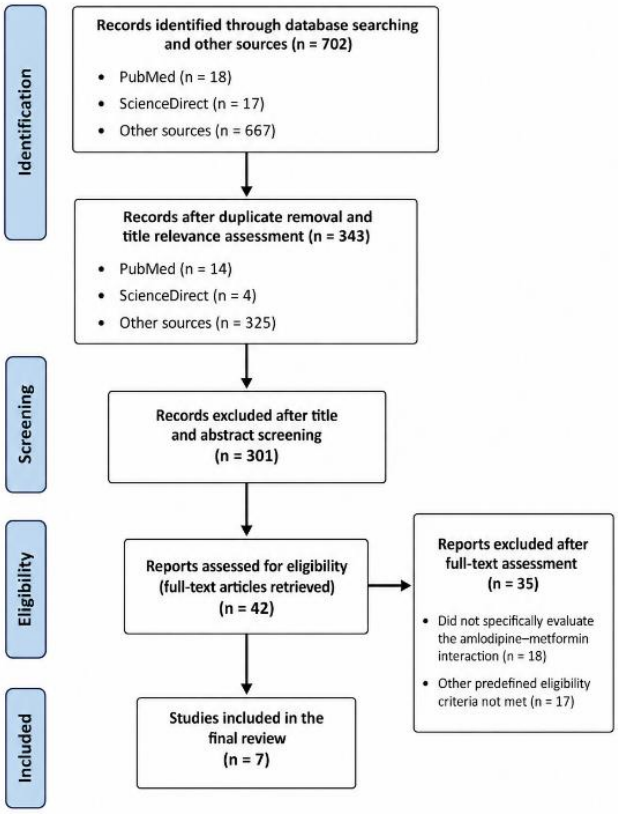

Figure 1. Flowchart for searching and selecting articles used as study material by following the PRISMA method

Studies were included if they met the following criteria: (1) original research articles published between 2021 and 2026; (2) written in English or Bahasa Indonesia; (3) involved patients receiving amlodipine and metformin concomitantly; (4) explicitly identified or evaluated the amlodipine–metformin combination as a potential or actual drug–drug interaction; (5) provided extractable information concerning the interaction, including its occurrence or frequency and at least one additional variable such as severity, proposed mechanism, potential or observed clinical consequences, recommended management, or clinical significance; and (6) were available as full-text articles.

All records identified from the literature search were compiled and screened for duplication and title relevance. Duplicate records were identified by comparing bibliographic information, including article title, authors, publication year, journal, and DOI where available. Following duplicate removal and preliminary title relevance assessment, 343 records remained, comprising 14 records from PubMed, 4 from ScienceDirect, and 325 from other sources.

During the screening stage, the titles and abstracts of the remaining records were carefully evaluated to determine their relevance to the research question. The records were screened based on whether the title and abstract indicated relevance to concomitant amlodipine and metformin use, potential or actual drug–drug interactions, a relevant patient or prescription population, and an eligible original research design. Records clearly unrelated to these criteria were excluded. A total of 301 records were excluded at this stage because their titles or abstracts did not indicate sufficient relevance to the research question. Consequently, 42 full-text articles were retrieved and assessed for eligibility.

Following full-text assessment, 35 articles were excluded. 18 articles did not specifically evaluate the amlodipine–metformin interaction, while 17 did not meet one or more of the remaining eligibility criteria. Finally, seven studies fulfilled all eligibility criteria and were included in the final narrative synthesis. Data from the included studies were extracted using Microsoft Excel. The extracted variables were study design and sample characteristics, DDI assessment method, reported frequency of the amlodipine–metformin interaction and its reporting basis,

interaction severity, proposed mechanism, potential or observed clinical consequences, and recommended management or clinical significance.

The methodological quality of each included study was independently assessed by two authors using the appropriate Joanna Briggs Institute (JBI) Critical Appraisal Tool according to the respective study design[16]. Each appraisal item was rated as “Yes,” “No,” “Unclear,” or “Not Applicable,” as appropriate [17]. Any discrepancies between the two reviewers were resolved through discussion and consensus; when consensus could not be reached, a third author was consulted. The appraisal findings were considered in interpreting the strength and limitations of the available evidence.

Study selection and data extraction were independently reviewed by two authors. Any discrepancies were resolved through discussion and consensus, with consultation of a third author when necessary. The appraisal considered relevant methodological domains, including clarity of inclusion criteria, appropriateness of study population and setting, validity of exposure or DDI assessment, identification and management of potential confounding factors, validity of outcome measurement, and appropriateness of statistical analysis.

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