RESEARCH PAPER

Analysis of Drug Interactions Linked To CYP3A4 or CYP2D6 Substrates to Identify Preventable Interactions

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ABSTRACT

Background: Drug–drug interactions (DDIs) mediated by cytochrome P450 (CYP) enzymes remain a major source of preventable medication-related harm. CYP3A4 and CYP2D6 are among the most clinically important isoenzymes involved in the metabolism of commonly prescribed medications and are frequently implicated in clinically significant interactions. However, contemporary evidence regarding the preventability of these interactions has not been comprehensively synthesized.

Objective: To map and evaluate published evidence on clinically significant CYP3A4- and CYP2D6-mediated drug interactions and identify interactions that may be preventable through evidence-based medication management strategies.

Methods: A scoping review was conducted following the PRISMA-ScR framework. PubMed/MEDLINE was searched for English-language studies published between January 2020 and January 2025. Eligible studies reported clinically relevant CYP3A4- or CYP2D6-mediated drug interactions. Data on interaction mechanisms, severity, therapeutic classes, clinical outcomes, and preventability were extracted and synthesized descriptively.

Results: Of 234 records identified, 75 studies met the eligibility criteria and were included in the review. These studies yielded 60 unique clinically significant CYP-mediated drug interactions. CYP3A4 accounted for most interactions (63.3%), while CYP2D6 represented 36.7%. Enzyme inhibition was the predominant mechanism (58.3%), and severe interactions constituted the largest severity category (51.7%). Antineoplastic agents, antimycobacterial drugs, cardiovascular medications, psychotropic agents, antivirals, and immunosuppressants were most frequently involved. Overall, 42 interactions (70.0%) were classified as potentially preventable.

Conclusion: A substantial proportion of clinically significant CYP3A4- and CYP2D6-mediated drug interactions are potentially preventable. Optimized medication management, pharmacist-led interventions, therapeutic drug monitoring, and integration of pharmacogenomic information may improve medication safety and support precision pharmacotherapy.

Keywords: *Cytochrome P450 Enzyme System; CYP2D6; CYP3A4; Drug-Related Side Effects and Adverse Reactions; Drug Interactions; Medication Safety; Pharmacogenomics.*
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1. INTRODUCTION

Drug–drug interactions (DDIs) remain a significant challenge in contemporary healthcare and are an important contributor to avoidable medication-related harm. Such interactions may result in adverse drug reactions, reduced therapeutic effectiveness, prolonged hospitalization, and increased healthcare resource utilization. The rising prevalence of polypharmacy, multimorbidity, and complex treatment regimens has further increased the likelihood of clinically significant DDIs, making their identification and prevention a critical component of patient safety and optimized pharmacotherapy[1-4].

Cytochrome P450 (CYP450) enzymes play a central role in the biotransformation of many therapeutic agents, with CYP3A4 and CYP2D6 being among the most clinically relevant isoenzymes. CYP3A4 is involved in the metabolism of approximately 50% of currently prescribed medications, whereas CYP2D6 contributes substantially to

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the disposition of several cardiovascular, neuropsychiatric, analgesic, and anticancer drugs. Alterations in enzyme activity resulting from inhibition, induction, or genetic variability can significantly influence systemic drug exposure, thereby increasing the risk of toxicity or therapeutic failure[5-9].

Advances in pharmacogenomics, therapeutic drug monitoring, and electronic clinical decision support have improved the recognition and management of CYP-mediated interactions. Despite these developments, clinically significant interactions continue to occur across diverse therapeutic settings, particularly among patients receiving oncology treatments, antimicrobial agents, anticoagulants, immunosuppressants, and psychotropic medications. Many of these events may be avoidable through timely medication review, individualized prescribing, and evidence-based risk mitigation strategies[10-14].

Although CYP-mediated DDIs have been widely investigated, existing evidence is largely dispersed across individual drugs, therapeutic classes, and disease-specific populations. Consequently, a comprehensive evaluation of preventable CYP3A4- and CYP2D6-mediated interactions remains limited. Furthermore, recent evidence has not been systematically synthesized to identify recurring patterns, severity profiles, and opportunities for prevention. Therefore, this scoping review aimed to systematically map contemporary evidence on CYP3A4- and CYP2D6-mediated drug interactions and identify clinically significant interactions that may be prevented through targeted clinical interventions[15-18].

2. MATERIALS AND METHODS

2.1 Study Design

A scoping review was conducted to systematically identify and map published evidence regarding clinically significant drug interactions involving CYP3A4 and CYP2D6 substrates. The study followed the methodological framework proposed by Arksey and O'Malley and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)[19-22]. This study aimed to characterize CYP3A4- and CYP2D6-mediated interactions, evaluate their clinical significance, and identify interactions that were potentially preventable through evidence-based clinical interventions.

2.2 Information Sources and Search Strategy

A comprehensive literature search[23,24] was performed in PubMed/MEDLINE for studies published between January 2020 and January 2025. Search terms included combinations of Medical Subject Headings (MeSH) and free-text keywords related to: (a) CYP3A4, (b) CYP2D6, (c) Drug–drug interactions, (d) CYP inhibitors, (e) CYP inducers, (f) Drug substrates, (g) Pharmacokinetics, (h) Adverse drug reactions, and (i) Medication safety.

Representative search syntax included: ("CYP3A4" OR "Cytochrome P450 3A4") AND ("Drug Interaction"); ("CYP2D6" OR "Cytochrome P450 2D6") AND ("Drug Interaction"); and ("Cytochrome P450") AND ("Preventable Drug Interactions").

Reference lists of relevant studies were also screened to identify additional eligible publications.

2.3 Eligibility Criteria

Studies were included if they: (a) Were published between 2020 and 2025; (b) Were available in English; (c) Reported clinically relevant CYP3A4- or CYP2D6-mediated interactions; (d) Included clinical studies, observational studies, pharmacokinetic studies, case reports, systematic reviews, or meta-analyses; and (e) Reported interaction mechanisms and/or clinical outcomes.

Studies were excluded if they: (a) Were non-English publications, (b) Were animal or in vitro studies without clinical relevance, (c) Did not specifically involve CYP3A4 or CYP2D6, (d) Were editorials, commentaries, or conference abstracts lacking sufficient methodological information, and (e) Contained duplicate data.

2.4 Study Selection

- The search yielded 234 records. After removal of duplicates and title/abstract screening, potentially eligible articles underwent full-text assessment. Studies meeting all predefined inclusion criteria were included in the final review.
- The selection process resulted in the inclusion of 75 studies and was documented using a PRISMA-ScR flow diagram.

2.5 Data Extraction

A standardized data extraction form was used to collect information on: (a) Author and publication year, (b) Study design, (c) CYP enzyme involved, (d) Interacting medications, (e) Mechanism of interaction, (f) Therapeutic class, (g) Clinical outcomes, (h) Severity of interaction, and (i) Preventability measures.

Data extraction focused on identifying patterns of clinically significant interactions and opportunities for prevention[20-22].

2.6 Classification of Interactions

Interactions were classified according to:

I. Mechanism: (a) Enzyme inhibition, (b) Enzyme induction, and (c) Mixed mechanisms.

II. Severity: (a) Mild, (b) Moderate, and Severe

Severity classification was based on reported clinical consequences, including toxicity, hospitalization, therapeutic failure, or life-threatening outcomes.

2.7 Preventability Assessment

Interactions were considered preventable if one or more of the following applied: (a) Availability of safer therapeutic alternatives, (b) Existing guideline recommendations to avoid the combination, (c) Dose adjustment recommendations, (d) Therapeutic drug monitoring

availability, (e) Clinical decision support alerts, and (f) Pharmacist-led intervention opportunities.

2.8 Data Synthesis

Due to heterogeneity among included studies, quantitative meta-analysis was not performed. Data were synthesized descriptively using frequencies, percentages, and thematic evidence mapping. The analysis focused on interaction mechanisms, severity, therapeutic classes involved, and preventability characteristics.

3. RESULTS

3.1 Study Selection and Characteristics

The literature search identified 234 records through PubMed database searching. After removal of 36 duplicate records, 198 articles underwent title and abstract screening. A total of 102 full-text articles were assessed for eligibility, of which 27 were excluded because they did not meet the predefined inclusion criteria. Ultimately, 75 studies were included in the final scoping review. The study selection process is presented in Figure 1. These studies yielded 60 unique CYP3A4- and CYP2D6-mediated drug interactions, including 42 interactions classified as potentially preventable (70.0%).

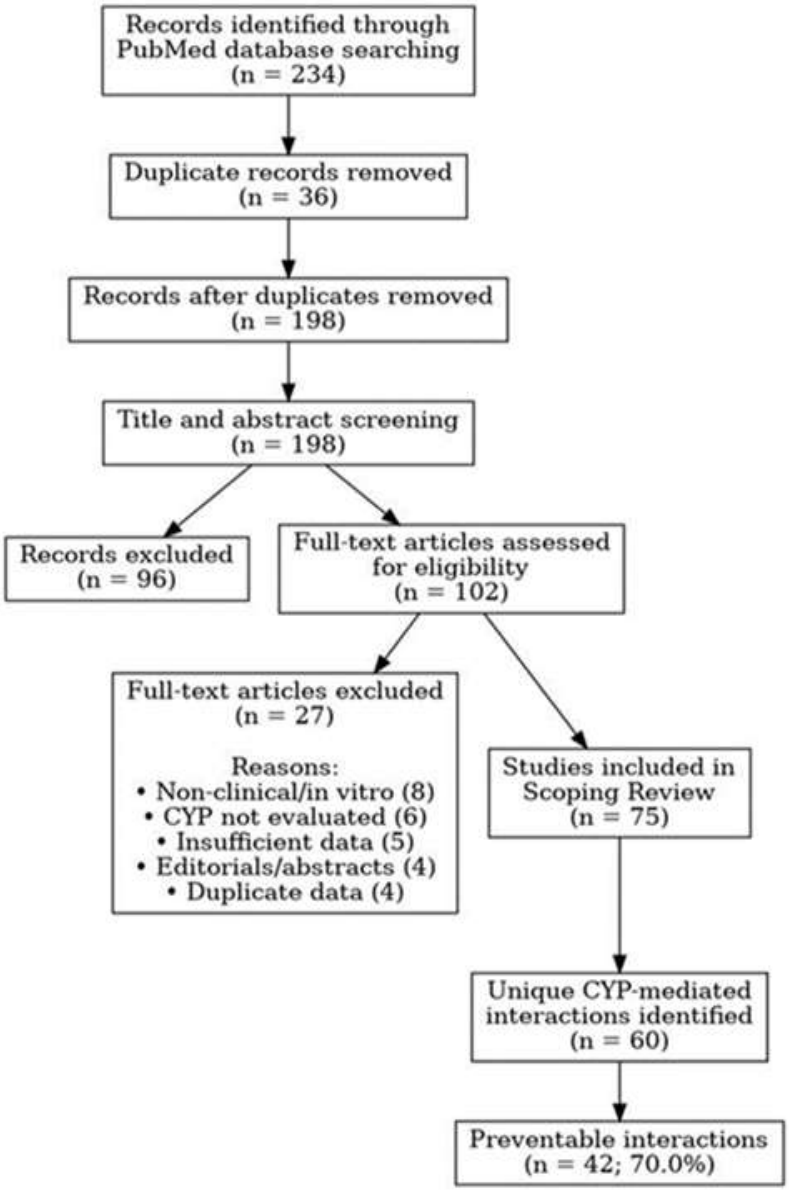

Figure 1. PRISMA-ScR Flow Diagram

The 75 eligible studies encompassed a range of study designs, including pharmacokinetic investigations, observational studies, clinical trials, systematic reviews, retrospective analyses, and case reports assessing CYP3A4- and CYP2D6-mediated drug interactions (Table 1).

Table 1. Characteristics of Included Studies	
Study Design	**Number (%)**
Pharmacokinetic studies	28 (37.3)
Observational studies	17 (22.7)
Clinical trials	11 (14.7)
Case reports/case series	9 (12.0)
Systematic reviews	7 (9.3)
Retrospective analyses	3 (4.0)
Total	75 (100)

3.2 Distribution of Identified Interactions

A total of 60 unique clinically significant CYP-mediated drug interactions were identified, with CYP3A4 accounting for the majority of interactions relative to CYP2D6 (Table 2).

Table 2. Distribution by CYP Isoenzyme	
Enzyme	Interactions (%)
CYP3A4	38 (63.3)
CYP2D6	22 (36.7)
Total	60 (100)

3.3 Severity and Mechanisms

Enzyme inhibition emerged as the predominant mechanism underlying the identified drug interactions (Table 3), while severe interactions constituted the largest severity category (Table 4).

Table 3. Interaction Mechanisms	
Mechanism	**Number (%)**
Inhibition	35 (58.3)
Induction	18 (30.0)
Mixed mechanisms	7 (11.7)

Table 4. Severity Classification	
Severity	**Number (%)**
Mild	8 (13.3)
Moderate	21 (35.0)
Severe	31 (51.7)

3.4 Therapeutic Classes Involved

Antineoplastic agents and antimycobacterial drugs emerged as the predominant therapeutic classes involved in clinically significant CYP-mediated drug interactions (Table 5).

Table 5. Therapeutic Classes	
Class	**Number (%)**
Antineoplastic agents	14 (23.3)
Antimycobacterial agents	9 (15.0)
Cardiovascular drugs	8 (13.3)
Psychotropic agents	7 (11.7)
Antiviral agents	6 (10.0)
Immunosuppressants	5 (8.3)
Others	11 (18.4)

3.5 Preventability Analysis

Preventability analysis demonstrated that 42 (70.0%) of the identified drug interactions were potentially avoidable through proactive medication management approaches, including alternative drug selection, dose adjustment, therapeutic drug monitoring, pharmacist intervention, and clinical decision support systems (Table 6).

Table 6. Preventability Assessment	
Category	**Number (%)**
Preventable	42 (70.0)
Non-preventable	18 (30.0)

4. DISCUSSION

4.1 Interpretation of Findings

In this study, we identified 60 clinically significant CYP3A4- and CYP2D6-mediated drug interactions from 75 studies, with CYP3A4 accounting for the majority of interactions. The predominance of CYP3A4-mediated interactions is consistent with its extensive role in the metabolism of commonly prescribed medications across multiple therapeutic areas[5,6,8,9,25]. Enzyme inhibition emerged as the most frequent mechanism, often leading to increased drug exposure and toxicity, whereas enzyme induction primarily contributed to therapeutic failure[6,8,9,25,26].

A notable finding was that severe interactions constituted the largest severity category, emphasizing the clinical importance of CYP-mediated interactions. Antineoplastic agents, antimycobacterial drugs, cardiovascular medications, and psychotropic agents were disproportionately represented, reflecting the complexity of pharmacotherapy in these therapeutic areas[27-31].

A key finding of this review was that 42 of the 60 identified interactions (70.0%) were classified as potentially preventable. This finding suggests that a substantial proportion of medication-related harm associated with CYP-mediated interactions may be avoided through proactive risk identification and evidence-based clinical management[32-35].

4.2 Clinical Implications

These findings have important implications for clinicians, pharmacists, and other healthcare professionals involved in medication management[36-38]. Prescribers should routinely assess interaction potential when initiating or modifying therapy, particularly among patients receiving multiple medications or drugs with narrow therapeutic indices.

Several preventive strategies emerged consistently across studies, including selection of alternative therapies, dose adjustment, therapeutic drug monitoring, individualized therapeutic optimization [39-42], and enhanced clinical surveillance. These interventions are especially relevant in oncology, transplantation, infectious disease, and cardiovascular medicine, where drug exposure is closely linked to therapeutic outcomes.

The current study reinforces the importance of pharmacist-led medication review. Pharmacists play a critical role in identifying potential interactions, recommending safer therapeutic alternatives, optimizing dosages, and providing patient counseling[43-46]. Previous studies have demonstrated reductions in adverse drug events and hospitalization rates following implementation of pharmacist-led medication management programs.

Clinical decision support systems may further reduce preventable interactions by providing real-time prescribing alerts. However, alert fatigue remains a challenge[47-49], highlighting the need for more sophisticated systems capable of prioritizing clinically meaningful interactions.

4.3 Pharmacogenomics and Future Practice

The growing integration of pharmacogenomics into clinical practice has important implications for the management of CYP-mediated interactions. CYP2D6 is highly polymorphic, and genetic variability significantly influences drug metabolism and treatment response[10-12,50].

An important concept emerging from contemporary literature is phenoconversion, whereby concomitant administration of potent inhibitors alters an individual's functional metabolic phenotype[14,17,51,52]. Consequently, a genetically normal metabolizer may behave phenotypically as a poor metabolizer, increasing susceptibility to adverse drug reactions.

The interaction between tamoxifen and strong CYP2D6 inhibitors exemplifies the clinical relevance of drug–drug–gene interactions. Similar concerns apply to opioid analgesics, antidepressants, and cardiovascular medications that depend on CYP2D6-mediated metabolism[12,17,53].

Integration of pharmacogenomic testing into routine prescribing workflows may improve medication safety by enabling individualized therapeutic decision-making[13,16,54]. Future clinical decision support systems should incorporate both pharmacogenomic data and drug interaction screening to provide patient-specific recommendations.

Artificial intelligence and machine learning technologies may further enhance interaction prediction[55-58] by integrating pharmacokinetic, pharmacogenomic, and clinical data into comprehensive risk assessment models.

4.4 Strengths, Limitations, and Future Directions

A major strength of this review is its focus on the two most clinically important CYP enzymes involved in drug metabolism. The use of a PRISMA-ScR framework enhanced methodological transparency and reproducibility[22,23]. Furthermore, the emphasis on preventability provides clinically actionable information that may directly inform medication safety initiatives.

Several limitations should be acknowledged. The review was restricted to PubMed-indexed English-language literature and may not have captured all relevant studies. Heterogeneity among included studies precluded quantitative meta-analysis. Additionally, assessment of preventability involved some degree of subjective interpretation based on available evidence.

Future investigations should prioritize prospective evaluation of pharmacist-led intervention programs, implementation of pharmacogenomic-guided prescribing strategies, development of epigenetic-based therapeutic approaches[57,59], and advanced clinical decision support tools[13,54-57] capable of predicting clinically significant interactions in real-world practice, and application of artificial intelligence for prediction of clinically significant

drug interactions. Particular attention should be directed toward oncology, transplantation, and geriatric populations, where interaction burdens are greatest.

Overall, the findings demonstrate that CYP3A4- and CYP2D6-mediated interactions continue to represent a major source of preventable medication-related harm. Integration of pharmacogenomics, clinical pharmacy services, therapeutic drug monitoring, and precision prescribing strategies may substantially improve medication safety and therapeutic outcomes.

5. CONCLUSION

This scoping review synthesized contemporary evidence on CYP3A4- and CYP2D6-mediated drug interactions and identified substantial opportunities for preventing medication-related harm. Among 75 included studies, 60 unique clinically significant interactions were identified, of which 42 (70.0%) were considered potentially preventable. CYP3A4-mediated interactions predominated, enzyme inhibition was the most common mechanism, and severe interactions represented the largest severity category. Antineoplastic agents, antimycobacterial drugs, cardiovascular medications, psychotropic agents, antivirals, and immunosuppressants were the therapeutic classes most frequently implicated.

The findings underscore the clinical value of proactive medication management strategies, including pharmacist-led medication review, therapeutic drug monitoring, clinical decision support systems, and evidence-based prescribing. Furthermore, the growing relevance of pharmacogenomics, particularly for CYP2D6-mediated drug–drug–gene interactions, highlights the need for more individualized approaches to medication management. Integrating pharmacokinetic, pharmacogenomic, and clinical data into routine practice may improve medication safety, reduce preventable adverse outcomes, and support the advancement of precision pharmacotherapy.

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CONFLICTS OF INTERESTS (IF ANY)

There are no conflicts of interest.

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AUTHORS CONTRIBUTION

Conceptualization and Methodology: Abdelhamid Eldoma Adam Haroun, Veerendra Uppara, Mohanraj Rathinavelu; Literature Search and Data Curation: Abdelhamid Eldoma Adam Haroun; Data Analysis: Abdelhamid Eldoma Adam Haroun and Veerendra Uppara; Writing - Original Draft Preparation: Abdelhamid Eldoma Adam Haroun; Writing - Review and Editing: Abdelhamid Eldoma Adam Haroun, Veerendra Uppara, Mohanraj Rathinavelu; Visualization: Abdelhamid Eldoma Adam Haroun; Supervision: Veerendra Uppara; Project Administration: Veerendra Uppara; and Final Approval of Manuscript: Abdelhamid Eldoma Adam Haroun, Veerendra Uppara, Mohanraj Rathinavelu.

ABBREVIATIONS

ADR: Adverse Drug Reaction; CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: Cytochrome P450; CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6; CYP3A4: Cytochrome P450 Family 3 Subfamily A Member 4; DDI: Drug–Drug Interaction; DDGI: Drug–Drug–Gene Interaction; DPWG: Dutch Pharmacogenetics Working Group; JBI: Joanna Briggs Institute: MeSH: Medical Subject: Headings; PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews; TDM: Therapeutic Drug Monitoring.

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