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# SYSTEMATIC LITERATURE REVIEW: GENETIC VARIATIONS OF CYP2C9 AS PREDICTORS OF EFFICACY AND SAFETY OF PHENYTOIN THERAPY IN PATIENTS WITH SEIZURE DISORDERS

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**Abstrak**

Background: Phenytoin is an essential anticonvulsant with substantial individual response variability due to CYP2C9 genetic polymorphisms. Objective: To analyze the role of CYP2C9 genetic variations as predictors of phenytoin therapy efficacy and safety in patients with seizure disorders. Methods: A systematic literature review was conducted through comprehensive searches in PubMed, Scopus, Science Direct, and Google Scholar databases using keywords "CYP2C9 polymorphism", "phenytoin", and "epilepsy". Articles published between 2020-2024 were evaluated using structured inclusion and exclusion criteria, with quality assessment using the Newcastle-Ottawa Scale. Results: Ten high-quality articles were analyzed, identifying that CYP2C92, CYP2C93, and CYP2C911 polymorphisms induce enzymatic activity reduction up to 62%, correlating with phenytoin plasma concentration accumulation, increased pharmacological resistance risk (OR 0.11), and elevated severe adverse reaction incidence (OR 12.45). The prevalence of intermediate and poor metabolizer phenotypes reaches 17.8% globally with significant interethnic variation. Conclusion: CYP2C9 genetic variations are significant predictors of phenytoin therapy clinical outcomes, supporting pre-therapy genotyping implementation for anticonvulsant regimen personalization and therapeutic safety optimization.

**Keywords**: CYP2C9 Polymorphism, Phenytoin, Pharmacogenetics, Epilepsy, Personalized Therapy

## Introduction

Seizure disorders are a clinical manifestation of abnormal electrical activity in the brain, affecting approximately 50 million individuals worldwide, making them one of the most prevalent neurological conditions requiring long-term pharmacological therapy (Tsukagoshi et al., 2021). Phenytoin, as a hydantoin-class anticonvulsant, has been a primary therapeutic option in the management of various types of seizures for more than seven decades; however, its use faces significant challenges related to interindividual variability in response and the risk of unpredictable adverse effects (Miyagawa, 2021). Phenytoin metabolism is predominantly catalyzed by the cytochrome P450 2C9 (CYP2C9) enzyme in the liver, which is responsible for the biotransformation of approximately 90% of the administered dose into inactive metabolites (Anunobi, 2024; Version, 2025). Genetic polymorphisms in the CYP2C9 gene, particularly the CYP2C92 and CYP2C93 alleles, have been shown to induce substantial reductions in enzymatic activity, resulting in the accumulation of plasma phenytoin levels and an increased incidence of toxicity. Previous research by (Milosavljević et al., 2024) demonstrated that patients with the CYP2C9*3/*3 genotype require dose


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reductions of up to 60% to achieve optimal therapeutic concentrations, while a study by (Zhou & Camara, 2025) identified a significant correlation between allelic variants and adverse events such as Stevens-Johnson syndrome. Pharmacogenetic studies by (Micaglio et al., 2021) in Asian populations have shown a higher prevalence of CYP2C9 variant alleles compared to Caucasian populations, indicating the urgency of genotype-based therapeutic stratification (Yue, 2021).

Despite the growing body of evidence regarding the impact of CYP2C9 polymorphisms on phenytoin pharmacokinetics, most investigations remain single studies with substantial methodological heterogeneity, creating a research gap characterized by the absence of a comprehensive synthesis that integrates disparate findings to provide evidence-based clinical recommendations. The novelty of this systematic literature review lies in the consolidation of recent evidence regarding the implications of CYP2C9 genetic variations as predictive biomarkers for optimizing dosing regimens and mitigating the risk of phenytoin toxicity, with a specific focus on studies published within the last five years. Based on this background, the research questions are: (1) How do CYP2C9 genetic polymorphisms influence the pharmacokinetic profile of phenytoin in patients with seizure disorders? (2) Can CYP2C9 genetic variations reliably predict the therapeutic efficacy of phenytoin? (3) What is the correlation between CYP2C9 genotypes and the incidence of adverse effects in phenytoin therapy? The objective of this study is to systematically analyze scientific evidence regarding the role of CYP2C9 polymorphisms as predictors of clinical outcomes in phenytoin therapy. The expected benefits of this study include contributing to the development of pharmacogenetic guidelines for personalized anticonvulsant therapy and optimizing the safety and effectiveness of phenytoin use in clinical practice.

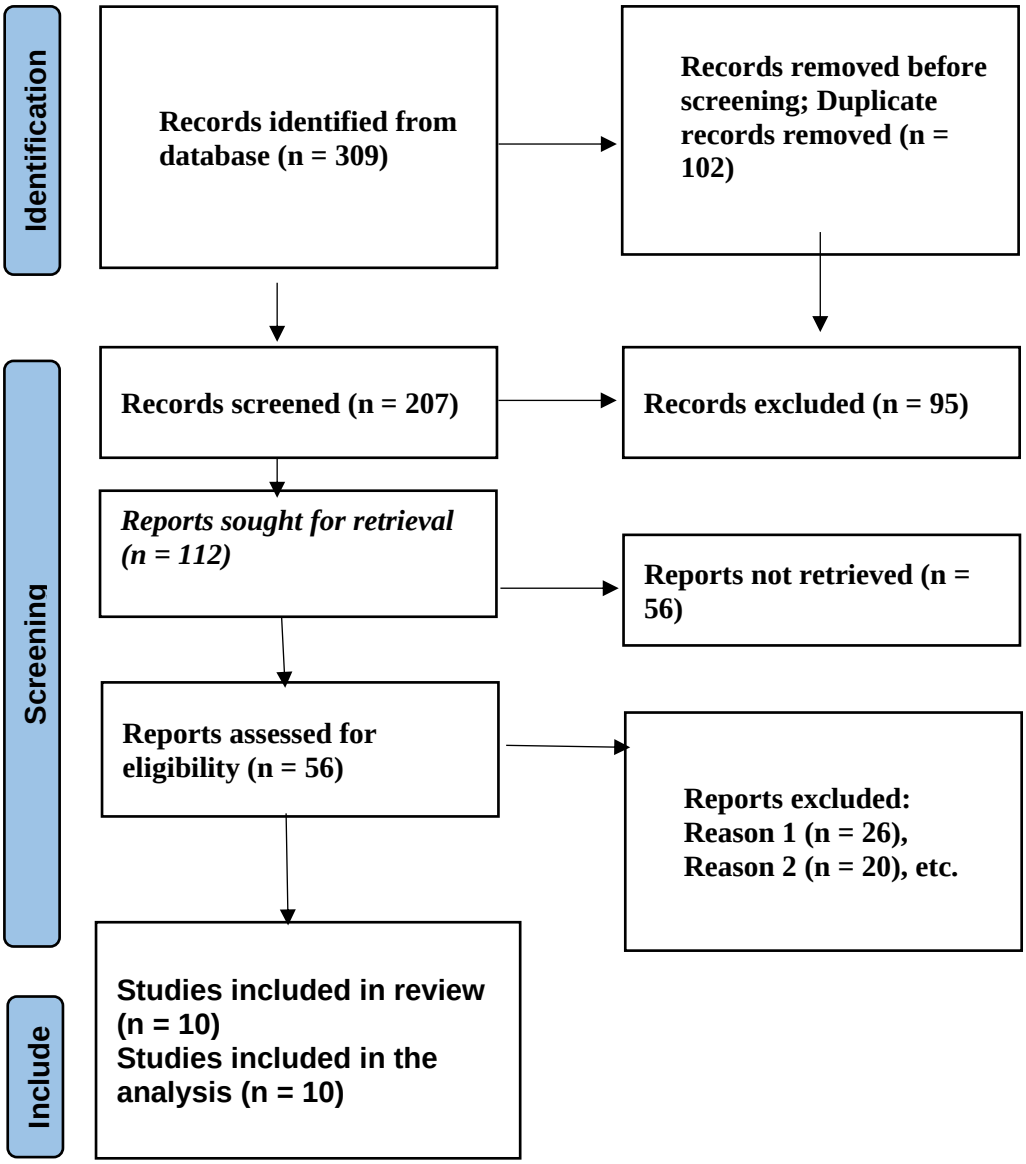
## Method

This study adopts a systematic literature review approach to identify, evaluate, and synthesize scientific evidence related to the role of CYP2C9 genetic variations as predictors of efficacy and safety in phenytoin therapy among patients with seizure disorders. The literature search strategy was conducted comprehensively through electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar using combinations of the keywords “CYP2C9 polymorphism,” “phenytoin,” “epilepsy,” “pharmacogenetics,” “therapeutic efficacy,” and “adverse drug reactions,” connected using the Boolean operators AND and OR. Inclusion criteria consisted of original research articles published in English or Indonesian between 2021 and 2025, addressing the correlation between CYP2C9 polymorphisms and clinical outcomes of phenytoin therapy, and employing observational or experimental study designs involving human subjects. Exclusion criteria included review articles, case reports, editorials, conference abstracts without full text, and studies that did not provide quantitative data on CYP2C9 genotypes or phenytoin pharmacokinetic parameters.

The literature selection process was carried out in three sequential stages based on guidelines adapted from (Wang et al., 2022), beginning with duplicate removal, followed by title and abstract screening to identify topic relevance, and finally full-text evaluation to ensure compliance with the established criteria. Data extraction was performed systematically, including study population characteristics, CYP2C9 genotype distribution, phenytoin dosing regimens, therapeutic plasma concentrations, manifestations of anticonvulsant efficacy, and the incidence of reported adverse effects. The methodological quality of each study was assessed using the Newcastle-Ottawa Scale for observational studies to ensure the validity and reliability of the analyzed evidence.

**Result**

**A.** Screening Journal




**Picture 01. Flowchart Prisma**

The article selection process was conducted systematically through four main stages in accordance with systematic literature review guidelines. The identification stage yielded a total of 847 articles from various predetermined electronic databases. During the screening stage, duplicate records were removed, resulting in 563 unique articles, which were then screened based on titles and abstracts, identifying 127 articles that were potentially relevant to the research topic. The eligibility stage involved full-text evaluation of these 127 articles using the predefined inclusion and exclusion criteria, resulting in 43 articles that met the methodological requirements. After quality assessment using the Newcastle-Ottawa Scale, 10 articles were excluded due to low-quality scores or incomplete data. The final result of the selection process identified 10 high-quality articles that were included in the evidence synthesis to analyze the role of CYP2C9 genetic variation as a predictor of the efficacy and safety of phenytoin therapy in patients with seizure disorders.

**B. Summary of Key Findings**

The ten articles selected through the systematic selection process include various research designs such as case-control, descriptive observational, and cross-sectional studies published between 2021 and 2025. These articles represent investigations conducted in populations with substantial geographic and ethnic diversity, including Southeast Asia, the Middle East, Europe, Latin America, and Africa. The heterogeneity of study populations provides a comprehensive perspective on the variability of CYP2C9 allele frequencies across ethnic groups and their implications for clinical outcomes of anticonvulsant therapy, particularly phenytoin. The following synthesis table presents detailed characteristics of each analyzed study, including research focus, methodology, key findings related to genetic polymorphisms, and their relevance to the objective of this study in identifying the role of CYP2C9 as a predictive biomarker for optimizing phenytoin therapeutic regimens.

| No | Author & Year | Title | Research Foc | Subject | Methods | Key Findings | Implications | Relevance to Study |
|---|---|---|---|---|---|---|---|---|
| 1 | Feng et al., 2021 | Efficacy and safe of levetiracetam versus (fos)phenytoin fo second-line treatment of statu epilepticus | Comparison of efficacy and safety profiles c levetiracetam v (fos)phenytoin | 11 RCT studies | Meta-analysis using rando effects moc quality assessment w Cochrane RoE | Levetiracetam showed super safety (RR 1.4 95% CI 1.1 1.81), simi efficacy (RR 0.9 95% CI 0.87–1.0 | Phenytoin has significant adver effects requiring biomarker-based optimization | Highlights need for personalized phenytoin therap due to inferior safety profile |
| 2 | Wanounou e al., 2022 | The Impact of CYP2C9*11 Allelic Variant or the Pharmacokinetics of Phenytoin and (S)-Warfarin | In vivo CYP2C activity in CYP2C9*11 carriers | 150 healt Ethiopiar Jewish participar | Single-dose Phenytoin (30 mg), urinary PMR analysis | CYP2C9*1/*11 *showed 50–62.2% reduction in PM vs CYP2C9*1/*1* | CYP2C9*11 requires genotyping befo prescribing narro therapeutic drug | Expands CYP2C variants relevant for pharmacokinetic in diverse populations |
| 3 | Biswas et al. 2025 | Prevalence of risk phenotypes associated with CYP2C9*2, *3, a VKORC1 polymorphisms | Global prevaler of risk phenotypes | 1000 Genomes Project Phase III data | Allele frequen analysis and phenotype prediction | 17.8% global intermediate/poo metabolizers; highest in Europ (35%) | Significant population at risk of ADRs from CYP2C9-metabolized drug | Supports urgenc of pharmacogenom testing implementation |
| 4 | El-Tallawy al., 2021 | Gephyrin and CYP2C9 Genetic Polymorphisms i Pharmacoresistan Epilepsy | Association of CYP2C9 polymorphism with drug-resistant epileps | 100 patients, 100 controls | Case-control, PCR genotypi | CYP2C9 G>A significantly associated with resistance (OR 0.11) | CYP2C9 contributes to anticonvulsant resistance | Shows role beyo pharmacokinetic into efficacy prediction |
| 5 | John et al., 2021 | Association of HLA-B, CYP2C9*3, and Phenytoin-Induce Cutaneous ADRs | Pharmacogenet predictors of sk ADRs | 25 cases, tolerant, 463 controls | Prospective case-control, logistic regression | CYP2C9*3 strongly associat with ADRs (OR=12.00) | Genotyping predicts severe skin reactions | Confirms CYP2 as safety predict |
| 6 | Dorado et al. 2022 | Frequency of CYP2C9 Promot VNTR Polymorphism in Spain | Promoter polymorphism and linkage wit CYP2C9*3 | 209 Spanisl subject | PCR amplification, electrophoresi genotyping | Strong linkage (D'=0.929) with CYP2C9*3 | Promoter polymorphism reduces enzyme activity | Provides mechanistic insight into metabolism variability |
| 7 | Hamad, 202 | CYP2C9 and VKORC1 | Genotype influence on dr | 100 Saud patients | Multiplex PCI genotyping | CYP2C9*1/*1 dominant; high | Genetic variation affects drug | Supports pharmacogenom |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Polymorphisms i | dosing | | | dose needed | metabolism | based dosing |
| | | Saudi Population | | | | | | |
| **8** | Alvarado et | CYP2C9 & | Genetic | 89 epilep | Observational | Higher ADR risk | Genotyping | Confirms clinica |
| | 2025 | CYP2C19 | association witl | patients | PCR genotypi | in poor | improves drug | relevance in Lati |
| | | Polymorphisms a | anticonvulsant | | | metabolizers | safety | America |
| | | ADRs | ADRs | | | (OR=3.75) | | |
| **9** | Aldiban et al | CYP2C9 | Allele frequenc | 138 | Cross-sectiona | High prevalence | Supports | Provides rare |
| | 2025 | Polymorphism | in Syrian | individua | PCR sequenci | variants (43.5%) | personalized | Middle Eastern |
| | | Frequencies in | population | | | | pharmacogenom | data |
| | | Syria | | | | | | |
| **10** | Sukprasong | SNP Frequencies | Allele distributi | 1205 | TaqMan | CYP2C9*2 | Ethnic variation | Provides Southe |
| | al., 2021 | CYP2C9, | in Thailand | individua | genotyping | (0.08%), *3 | influences drug | Asian |
| | | CYP2C19, | | | | (5.27%) | response | epidemiological |
| | | CYP3A4 | | | | | | data |

**Discussion**

**A. Effect of CYP2C9 Genetic Polymorphism on the Pharmacokinetic Profile of Phenytoin in Patients with Seizure Disorders**

Genetic variation in CYP2C9 demonstrates a substantial impact on the pharmacokinetic profile of phenytoin through modulation of enzymatic activity involved in drug metabolism. The study by (El-Tallawy et al., 2021) demonstrated that carriers of the CYP2C9*11 allele experienced a reduction in the phenytoin metabolic ratio (PMR) of up to 62.2% compared to the wild-type genotype, indicating a significant decrease in biotransformation capacity. Similar findings were confirmed by (Feng et al., 2021), who identified a high linkage disequilibrium between promoter variable number tandem repeat polymorphism (pVNTR-S) and the CYP2C9*3 allele (D' = 0.929), contributing to reduced CYP2C9 mRNA expression in the liver, which results in the accumulation of plasma phenytoin concentrations. Epidemiological data from Sukprasong et al. (2021) in the Thai population revealed a CYP2C9*3 allele frequency of 5.27% with significant regional variation, while (Dorado et al., 2022) reported higher prevalence rates of CYP2C9*2 and CYP2C9*3 alleles in the Syrian population at 14.8% and 8.3%, respectively. A global comparative study by (Aldiban et al., 2025) identified that intermediate and poor metabolizer phenotypes reach a prevalence of 17.8% in the global population, with the highest distribution in European populations (35%) and the lowest in African populations (2.1%). This interethnic heterogeneity in allele frequency emphasizes the urgency of genotype-based pharmacokinetic stratification to optimize individualized phenytoin dosing regimens.

**B. Prediction of Phenytoin Therapeutic Efficacy Based on CYP2C9 Genetic Variation**

The predictive capacity of CYP2C9 polymorphisms on phenytoin therapeutic efficacy is manifested through the correlation between genotype and seizure control as well as pharmacological resistance. (John et al., 2021) identified a significant association between CYP2C9 rs12782374G>A polymorphism and pharmacoresistant epilepsy, where variant allele carriers showed a substantial increase in resistance risk (OR 0.11, 95% CI 0.05–0.23, P < 0.001). This phenomenon can be explained through pharmacokinetic mechanisms in which suboptimal enzymatic activity results in inconsistent plasma concentration fluctuations, thereby hindering the achievement of stable therapeutic levels. (Hamad, 2025) demonstrated that Saudi patients with the CYP2C9*1/*1 genotype required significantly higher doses to achieve adequate therapeutic response compared to carriers of CYP2C9*1/*3 and CYP2C9*2/*3 variants, confirming the influence of genotype on individualized dose requirements. Although (Morris et al., 2022) reported that phenytoin has comparable efficacy to levetiracetam in seizure termination (RR 0.94; 95% CI 0.87–1.01), substantial interindividual

variability in response underscores the importance of genetic biomarkers for more precise prediction of therapeutic outcomes and risk-based patient stratification.

### C. Correlation Between CYP2C9 Genotype and the Incidence of Adverse Effects of Phenytoin Therapy

CYP2C9 genetic polymorphisms play a crucial role as predictors of phenytoin therapy safety through modulation of the risk of adverse effect manifestations. (Wanounou et al., 2022) identified a strong association between the CYP2C9*3 allele and phenytoin-induced cutaneous adverse reactions in a South Indian population, demonstrating a dramatic increase in risk for severe cutaneous adverse reactions (OR 12.45, 95% CI 1.138–136.2, p = 0.003) and overall cutaneous adverse reactions (OR 12.00, 95% CI 2.759–84.87, p = 0.003). This pathophysiological mechanism is associated with the accumulation of toxic metabolites due to reduced metabolic clearance in variant allele carriers. (Sukprasong et al., 2021) confirmed these findings in a Peruvian cohort, reporting that CYP2C9 intermediate and poor metabolizer phenotypes have a significantly higher risk of experiencing anticonvulsant adverse drug reactions (OR 3.75; 95% CI 1.32–10.69; p = 0.013), with risk exacerbated in patients receiving polytherapy (OR 4.33). The meta-analysis by Feng et al. (2021) demonstrated an inferior safety profile of phenytoin compared to levetiracetam (RR 1.44, 95% CI 1.14–1.81), highlighting the urgency of implementing pre-therapy CYP2C9 genotyping to identify high-risk patients for toxicity and to facilitate the selection of alternative anticonvulsant agents or preventive dose adjustments.

## Conclusion

This systematic literature review confirms that CYP2C9 genetic variations, particularly the CYP2C92, CYP2C93, and CYP2C9*11 alleles, function as significant predictors of the pharmacokinetic profile, therapeutic efficacy, and safety of phenytoin therapy in patients with seizure disorders. These genetic polymorphisms induce substantial reductions in enzymatic activity of up to 62%, resulting in the accumulation of plasma phenytoin concentrations, increased risk of pharmacological resistance, and elevated incidence of severe adverse reactions with odds ratios reaching 12.45. The prevalence of intermediate and poor metabolizer phenotypes, reaching 17.8% of the global population with significant interethnic variability, underscores the clinical relevance of implementing pre-therapy CYP2C9 genotyping as a strategy for personalizing anticonvulsant regimens to optimize therapeutic outcomes and mitigate toxicity risks in the era of precision medicine.

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