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Genetic Insights Into Psoriasis Therapy: A Review of Polymorphisms in the Genes of Both TNF-α and the TNF Signaling Pathway on the Response to Anti-TNF-α

Abeer Kadhim Jamaah[1*], Fadya Y. AL-Hamadani[1], Ali Fadhil Al-Saadi[2]

1. *Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq*
2. *Dermatology and Venereology Center, Medical City, Baghdad, Iraq*

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***Corresponding author:**
Abeer Kadhim Jamaah,
Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Email:
abeer.jomaa@copharm.uobaghdad.edu.iq

ABSTRACT

Tumor necrosis factor-alpha (TNF-α) inhibitors are widely used as first-line treatments for moderate to severe plaque psoriasis, yet clinical responses vary considerably among patients despite their overall safety and efficacy. Genetic factors that influence the effectiveness of biologic therapies may contribute to this variability. This review, conducted between May and June 2024 using the Google Scholar and PubMed databases, examined studies exploring associations between genetic polymorphisms in TNF-α and various genes within the TNF signaling pathway and patient responses to anti-TNF-α therapy. A total of 20 relevant studies were identified, assessing polymorphisms in TNF-α (−238/rs361525, −1031/rs1799964, −308/rs1800629, −857/rs1799724), TNF receptor genes such as TNFRSF1B (rs1061622), and additional related genes including TNFAIP3 (rs610604), IL1B (rs1143623 and rs1143627), FCGR2A (H131R/rs1801274), and FCGR3A (V158F/rs396991). Overall, these genetic variations demonstrate potential significance in modulating therapeutic responses to anti-TNF-α agents in psoriasis. However, inconsistencies across existing studies highlight the need for larger, multi-center investigations to confirm their clinical relevance and support the integration of genetic markers into personalized treatment strategies.

Keywords: Psoriasis, Tumor Necrosis Factor Inhibitors, Pharmacogenetics, Polymorphism, Genetic

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1. Introduction

About 3% of Americans and an estimated 125 million individuals worldwide suffer from psoriasis, a chronic, immune-mediated skin condition (1-3) Over 80% of psoriasis cases are plaque psoriasis, making it the most prevalent type. Erythematous, scaly patches or plaques are its defining features, It most often appears on the outer sides of the knees and elbows, but can also affect the nails, the palms of the hands, the soles of the feet, and skin folds. Adults are more affected than children, and men and women are equally affected (1, 3, 4). The field of plaque psoriasis has advanced most rapidly in pathophysiology, genetics, comorbidities, and biological therapies.

Psoriasis is characterized by a dysregulated immune system, specifically a T cell-mediated immune disorder with an up regulation of T helper type 1/17 (Th1/Th17) cytokines (5), including Tumor Necrosis Factor-alpha (TNF-α), various interleukins, and IFN-γ. The complex interplay of numerous cytokines and growth factors has led to advancements in treatment, particularly biologic therapies that target these cytokines (6). The anti-TNF medications adalimumab, etanercept, and the IL-12/23 inhibitor ustekinumab are the top choices for treating moderate to severe plaque psoriasis. The IL-17 inhibitors secukinumab and ixekizumab are used as second-line therapies, whilst brodalumab targets the IL-17RA receptor. Inhibitors of IL-23 or its receptor IL-23R include

guselkumab, tildrakizumab, and the newly approved risankizumab (5, 7, 8). The first biologics to be launched for the treatment of psoriasis were anti-TNFs; infliximab has demonstrated the highest efficacy, followed by certolizumab, adalimumab, and etanercept (9). Etanercept functions as a soluble TNF receptor, binding to and inactivating the cytokines TNF-α and TNF-β. In contrast, monoclonal antibodies like infliximab and adalimumab specifically target and deplete only TNF-α (10-12).

Not all patients respond to biologics, despite their remarkable effectiveness. However, both short-term and long-term treatment outcomes vary from patient to patient (13, 14). Patient's genetic makeup, specifically the presence of genetic variations that may affect the efficacy of therapy, influences the variability in response to treatment. Optimizing and offering individualized treatment options requires identifying genetic biomarkers that predict a patient's response to treatment. This benefits health systems in addition to enhancing the general efficacy of treatments. In this context, pharmacogenetics, which studies how specific genes can affect drug responses, becomes highly significant (15). Response has been linked to specific cytokines (16-18) and several genetic variants (19-26). Investigations into the influence of genetic polymorphisms, particularly single-nucleotide polymorphisms (SNPs) in TNF and interleukin (IL) genes, on responsiveness to biologic therapies have been undertaken in recent studies, including a number conducted in Iraq (27-31). This comprehensive review systematically evaluates the role of TNF-α and TNF signaling pathway gene polymorphisms in determining psoriatic patients' variable responses to anti-TNF-α therapy. By critically assessing these genetic markers, this review aims to identify potential predictors of clinical response, which can ultimately guide more informed and cost-effective treatment choices to maximize therapeutic efficacy.

2. Materials and Methods

2.1 Data collection and examination

This review was conducted between May and June 2024, utilizing the Google Scholar and PubMed databases. Search terms included: "psoriasis", "psoriatic", together with "treatment", "biological therapy", "Anti-TNF alfa", "polymorphisms", "TNF alfa gene"," TNFRSF1B, TNFRSF1A, TNFAIP3, FCGR2A, FCGR3A. IL1B" and "response". The search included studies published from 2010 to 2024. The inclusion criteria were: Full-text articles published between 2010 and 2024 that were written in the English language; studies addressing the genetic polymorphism effect on TNF-α inhibitor response in psoriasis with only TNF-α, TNF-α receptor, TNFAIP3, FCGR, and IL1B genes.

The exclusion criteria were: Articles written in a language other than English, abstract-only articles, systematic and narrative reviews, articles with genes other than TNF-α, TNF-α receptor, TNFAIP3, FCGR, and IL1B, case studies, editorials, and opinion pieces lacking empirical data; and publications with insufficient data or ambiguous methods.

Study selection: The studies were screened by the author. Relevance was evaluated for titles and abstracts, and full-text articles that might be eligible were acquired for in-depth evaluation.

Data extraction: Data are taken from the studies, including sample size, study design, gene, SNP or variant, Allele or genotype, outcome measures, and duration of treatment.

3. Result

A thorough search of PubMed and Google Scholar identified 20 studies that examined the relationship between genetic polymorphism and response to anti-TNF-α therapy in patients with moderate-to-severe psoriasis. The studies assessed polymorphisms in TNF-α, TNF receptors, TNFAIP3, Fcγ receptors, and IL1B, highlighting both consistent and contradictory results, as shown in Figure 1, Table 1, and Table 2.

3.1 Polymorphism in the TNF-α gene

TNF-α gene variations have become the subject of numerous investigations due to their role in mediating inflammatory responses that anti-TNF medications target. Research into the relationship between TNF-α polymorphisms and the response to anti-TNF-α therapy in patients with psoriasis has yielded conflicting results. Studies by Song et al (32) Vasilopoulos et al (33) observed an association between specific single-nucleotide polymorphisms (SNPs) and therapeutic outcomes. Song and colleagues discovered that the TNF-α-857 C allele correlated with an improved response to TNF antagonists, particularly among patients with psoriasis (32). This finding was confirmed by Vasilopoulos, who also noted that the carriage of the -857C allele was positively associated with a response to etanercept in a study of Greek patients. However, Vasilopoulos discovered no such correlation with infliximab or adalimumab (33).

On the other hand, some research has produced inconsistent or disparate results. De Simone et al (34) reported that the presence of the -238 G>A and -308 G>A polymorphisms in Italian psoriasis patients was associated with a poor response to etanercept, but no correlation was found for the -857 C>T polymorphism. Likewise, a study by Gallo et al (35) on Spanish patients indicated that the -238 GG and -857 CT/TT genotypes were associated with greater improvements in disease severity scores and a higher rate of positive outcomes.

Not all studies, though, find a significant correlation Daprà et al (36) and Ovejero-Benito et al (37) both found no significant correlation between key TNF-α polymorphisms (-238, -308, -857, and -1031) and the response to anti-TNF-α therapy in their respective studies of Italian and Spanish patients.

3.2 Polymorphism in TNF signaling pathway genes

Polymorphism in the tumor necrosis factor receptor

TNF-α signaling is mediated by two receptors, TNFRI (p55) and TNFRII (p75), which are products of the TNFRSF1A and TNFRSF1B genes. These receptors initiate largely divergent cellular responses. The TNFRI pathway is primarily responsible for pro-inflammatory and pro-apoptotic signals, whereas signaling through TNFRII tends to promote immune regulation and processes related to tissue regeneration (38).

The findings from various studies on these polymorphisms are conflicting. For instance, the TNFRSF1B rs1061622 G-allele (p.M196R polymorphism) was associated with a poor response to biological therapy in a study conducted by Leire Gonzalez-Lara on 90 patients with psoriasis from Spain. This was particularly true for patients who were also positive for the Cw6 allele (39). In a contradictory finding, Vasilopoulos et al (33) found in a study of 63 Greek patients with psoriasis that the T-allele of the same TNFRSF1B rs1061622 polymorphism was associated with a positive response to anti-TNF treatment. This correlation became more obvious when the analysis was limited to patients receiving etanercept (33).

Further research has added to this complexity. In a study encompassing several autoimmune diseases, Chen et al (40) investigated polymorphisms in both TNFRSF1A and TNFRSF1B. This study found no association between the TNFRSF1A rs767455 genotype and non-response to anti-TNF medication (40). Finally, M.C. Ovejero-Benito presented findings that utilized multiple outcome measurements in addition to the traditional PASI score, including the Numeric Rating Scale for Pain (NRS-Pain50) and the Percentage improvement of the European Quality of Life Visual Analog Scale (%EQ-VAS). His study revealed that after three months of treatment, there was a significant association only between the improvement in NRS-Pain50 and the TNFRSF1B rs1061624 polymorphism (37).

Polymorphism in tumor necrosis factor-alpha-induced protein

An important protein that functions as a negative regulator pathway the NF-kB signaling, a path necessary for the immune response to be activated, is encoded by the tumor necrosis factor-alpha-induced protein 3 (TNFAIP3) gene. It also has a role in apoptosis mediated by TNF (41). However, studies on the association between TNFAIP3 polymorphisms and treatment response have yielded contradictory results.

Several studies suggest an association between specific TNFAIP3 variants and a better response to etanercept. In research of 250 Greek psoriasis patients, Sofia Masouri et al (42) revealed that the TNFAIP3 rs610604 polymorphism A allele, not its C allele, was associated with a better response. This finding was only significant for etanercept (42). These results were reinforced by an Iraqi study by Hassan Hadi et al (43), which found that non-responders to etanercept had a higher prevalence of the mutant homozygous CC genotype (43). Similarly, Tejasvi et al (44)'s multi-cohort study, which examined the impact of the TNFAIP3 rs610604 and rs2230926 SNPs on the response to anti-TNF alfa in 632 patients from Michigan and Toronto, also identified a significant association only with etanercept; those with the rs610604-G allele responded better than those with the A allele. Additionally, the same study also found that a specific haplotype, rs2230926 T-rs610604 G, was associated with a better response, even though there was no linkage between treatment response and the rs2230926 SNP (44).

In contrast, other studies have reported different or no associations. Ovejero-Benito et al (37) found that the rs610604 AC/CC genotype was significantly associated with improvement in the %EQVAS but not with the A allele alone. Additionally, this study noted an association between %EQVAS and the rs6920220 AA SNP in TNFAIP3 (37). However, other research has found no correlation at all. Van den Reek's study of 234 Dutch psoriasis patients did not find an association between the response to etanercept or adalimumab and the GG genotype of rs610604 (45). Similarly, Michiko Ito et al (46) found no significant correlation between the TNFAIP3 rs610604 SNP and anti-TNF-α treatment response in 49 Japanese patients, even when responders were defined as those with a 50% or greater decrease in their PASI score (46).

Polymorphism in the Fc fragment of IgG receptors

The search for genetic biomarkers to predict a patient's response to anti-TNF-α therapy in psoriasis has also led researchers to investigate polymorphisms within the genes for the Fc fragment of IgG receptors (FCGRs). The constant portion of immunoglobulin G (IgG) is bound by the Fc fragment of IgG receptors IIA (FCGR2A) and IIIA (FCGR3A), which are surface receptors involved in antibody-dependent cellular toxicity in phagocytic or cytotoxic cells. The receptor's affinity for the immune complex in biological treatments that contain FC, such as anti-TNF-α, can be impacted by genetic changes in these genes (41). The substitution of asparagine (R) with histidine (H) at position 131 (rs1801274) in FCGR2A and phenylalanine (F) with valine (V) at position 175 (rs396992) in FCGR3A results in higher-affinity receptors. There are conflicting results from various studies regarding the clinical significance of these polymorphisms. In a survey conducted on Spanish patients by R. Prieto-Pérez et al (47) found that carriers of the low-affinity C allele of FCGR2A rs1801274 were significantly more likely to be non-responders to anti-TNF therapy after six months (47). In direct opposition, Julià et al (48), also in Spain, observed that patients with low-affinity FCGR2A RR131 and FCGR3A FF158 genotypes actually responded better to anti-TNF medication than those with high-affinity genotypes, indicating that low-affinity alleles may be generating lower levels of FcγR-mediated drug clearance (48). The inconsistencies continue with research on specific drugs. Mendrinou et al (49) found no association between the

FCGR2A-H131R polymorphism and anti-TNF-α response; No significant association was observed between the FCGR2A-H131R genetic variant and the efficacy of etanercept treatment (49). Batalla et al (50) supported the finding of no association with FCGR2A-H131R but found that patients with the low-affinity FCGR3A FF genotype responded better than those with the V allele; this effect was evident only when using etanercept (50). Lastly Antonatos et al (51) multi-disease analysis in Asian and Caucasian individuals revealed no correlation between the FCGR2A-R131H SNP and psoriasis response at all (51).

Polymorphism in the IL1B gene

Psoriasis pathophysiology involves interleukin 1 beta (IL-1β), a cytokine encoded on chromosome 2 (2q14.1) that is critical for initiating the acute-phase response (52). The cytokine IL1B has multifaceted roles in immunity. It directs T-cell fate by promoting Th17 differentiation and collaborating with IL-12 to induce IFN-γ in Th1 cells. Furthermore, IL1B exerts broad inflammatory effects by activating T and B lymphocytes, stimulating cytokine and antibody production, and initiating innate responses like prostaglandin synthesis and neutrophil influx/activation (53). Furthermore, IL-1β increases Protein Kinase C activity, which is necessary for the subsequent stimulation of TNF-α mRNA (54). To put it briefly, IL1B is a powerful pro-inflammatory cytokine, and any genetic changes may have a significant impact on how well anti-TNF medications or cytokine inhibitors work.

The results of two studies evaluating the relationship between IL1B polymorphisms and patient with psoriasis reactions to anti-TNF treatment were inconclusive. A Danish study of 376 patients found that individuals with the rs1143623-GG or rs1143627 TT genotypes responded poorly to anti-TNF medication after three months. Additionally, the study noted that haplotypes associated with higher transcription of IL-1β had a lower propensity to respond to treatment (19). In contrast, the rs1143623 polymorphism was linked to a better clinical outcome, with patients achieving a considerably lower Psoriasis Area and Severity Index score, according to a Spanish study of patients treated with four different biologics (16 of whom received anti-TNF medication). Additionally, the authors proposed that this association was specific to TNF-α inhibitors (55).

Table 1. Association of TNF-α gene polymorphisms with Anti-TNF-α response in psoriasis.

Outcome measure	Length of treatment (months)	Number of patients	Responsive Allele/gene	SNP	Gene	years	References
PASI 75	6 months	80	C	rs1799724 (-857)	TNF-α	2012	Vasilopoulos et al (33)
PASI 75	3months	97	GG* GG*	rs1800629 (-308) rs361525 (-238)	TNF-α	2015	De Simone et al (34)
PASI 75	6 months	109	GG CT/TT TT	rs361525 (-238) rs1799724 (-857) rs1799964 (-1031)	TNF-α	2013	Gallo et al (35)

Note: only studies with significant results included in the table, * mean the SNP has a worse effect on the response, PASI 75:75% change in psoriasis area and severity index score.

Table 2. Polymorphism in TNF signaling pathway genes associated with anti-TNF-α response.

Outcome measure	Length of treatment (months)	Number of patients	Responsive Allele/gene	SNP	Gene	years	References
PASI 75	-	90	G*	rs1061622	TNFRSF1B	2015	Julià et al (23)
PASI 75	6 months	80	T	rs1061622	TNFRSF1B	2012	Vasilopoulos et al (33)
NRS-Pain50 % EQ-VAS	6 months 3 months 3 and 6 months	20	- AC/CC AA	rs1061624 rs610604 rs6920220	TNFRSF1B TNFAIP3 TNFAIP3	2019	Ovejero-Benito et al (37)
PASI 75	6 months	250	A	rs610604	TNFAIP3	2016	Masouri et al (42)
PASI 75	6 months	100	C*	rs610604	TNFAIP3	2020	Hadi et al (43)
self-assessed on a visual analog scale from 0 to 5.	12 months	632	G TG	rs610604 rs2230926 / rs610604 haplotype	TNFAIP3	2012	Tejasvi et al (44)
PASI 75	6 months	144	CT/CC	rs2916205	FCGR2A	2018	Prieto-Pérez et al (47)
PSA	6-8 Week	70	HH VV	rs1801274 (H131R) rs396991 (V158F)	FCGR2A FCGR3A	2013	Julià et al (48)
PASI 75	6 months	100	G	rs396991	FCGR3A	2016	Mendrinou et al (49)
PASI 75	6 months	115	F	rs396991	FCGR3A	2015	Batalla et al (50)
PASI 75	3 months	376	GG* AA*	rs1143623 rs1143627	IL1B	2018	Loft et al (19)
PASI<1 and PASI90	3 and 12 months	16	-	rs1143623	IL1B	2024	Loras et al (55)

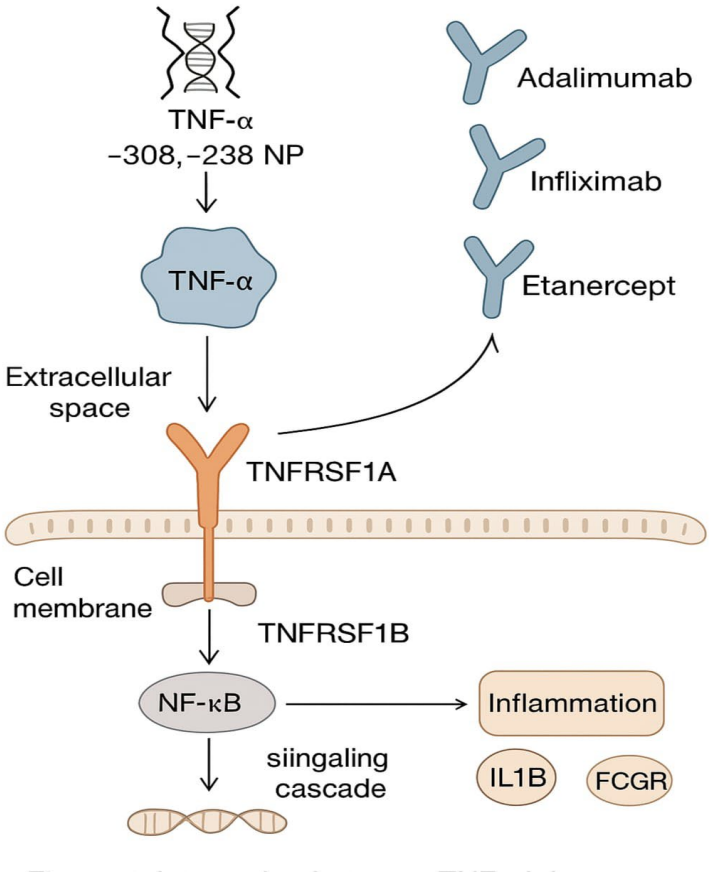

Figure 1. Interaction between TNF-α, TNF receptors, signaling genes, and anti-TNF drug in psoriasis (**Prepared by Authors, 2025**).

4. Discussions

It has been established that psoriasis is genetically influenced (56-58). When inexplicable and unsatisfactory responses and side effects have been documented, an increasing number of psoriasis susceptibility genes have been identified and examined as predictive markers of response to treatment since the development of genetic analysis approaches (59-61). Furthermore, over the past 11 years, several reviews have emphasized the results of pharmacogenomics in psoriasis (59, 60, 62-64). This review examines the relationship between psoriasis patients' responses to TNF-alpha inhibitors and genetic variations in the TNF-alpha gene, as well as a few other genes in the TNF signaling pathway. The findings underscore the importance of genetic variations in predicting treatment outcomes, which can inform personalized medicine approaches for psoriasis. Notably, the TNF-α-857 C allele has been associated with a better response to TNF antagonists in patients with psoriasis. The TNF-α-238 G>A and -308G>A polymorphisms have yielded inconsistent results, potentially due to variations in the timing of endpoint assessment. While some studies have reported a poor response at three months (34) a single study demonstrating a positive response utilized a six-month endpoint (35).

The TNF alpha receptors genes encode receptors that mediate TNF-α signaling. Research on TNFRSF1B gene variations and anti-TNF response in psoriasis is inconclusive. One study linked a specific allele to poor response (39), while another linked a different allele to positive response, especially with etanercept (33). Another study tied a TNFRSF1B variation to pain improvement, but not a PASI score. Population variations could cause this discrepancy in results.

The TNFAIP3 gene encodes a protein that regulates the NF-kB signaling pathway. Polymorphisms in TNFAIP3, such as rs610604, have been shown to have varying associations with treatment response. Some studies showed that the A allele of rs610604 is associated with a better response, while others showed that it's associated with a poor response This discrepancy in results could be caused by variations in outcome measurement. Some studies use PASI scores while others use %EQVAS or visual scale, and this may cause improper distribution of patients based on their response.

The FCGR gene encodes receptors involved in antibody-dependent cellular toxicity. Studies investigating the link between Fcγ receptor (FCGR) gene variations and the response to anti-TNF therapy in psoriasis have yielded inconsistent results. While some initial findings suggested a connection, particularly with the FCGR2A gene, subsequent research has largely failed to replicate these associations. The FCGR3A gene presents a more complex picture, with some studies indicating a link to treatment response, specifically for the

drug etanercep, but not for other anti-TNF agents. This discrepancy might be due to variations in study design, patient populations (e.g., disease severity, ethnicity), or the specific anti-TNF drug used.

Protein Kinase C activity is raised by IL-1β, and this is necessary for the following stimulation of TNF-α mRNA (54). IL1B is a very potent pro-inflammatory cytokine.

Two studies examining IL1B gene variations and anti-TNF response in psoriasis yielded conflicting results. A larger Danish study found that certain IL1B genotypes were linked to a worse response, while a smaller Spanish study found the same variation to be linked to improved outcomes with TNF inhibitors. Sample size variation may be the cause.

A genetically determined high level of IL-1β is linked to nonresponse to anti-TNF treatment. In the single-polymorphism context, the variant alleles of IL1B (rs1143623 and rs1143627) are associated with reduced IL-1β transcription (65, 66). However, in the haplotype context, which is the dominant haplotype in Caucasians, the variant alleles of these two SNPs led to increased transcription of IL-1β (67).

The genetic polymorphisms reviewed herein influence patient response to anti-TNF therapy, and the identification of predictive genetic markers for TNF-alpha inhibitor response has the potentialto improve personalized treatment strategies for psoriasis significantly. By tailoring therapies based on genetic profiles, Clinicians can maximize healthcare resources, minimize side effects, and increase therapeutic efficacy. While the review provides valuable insights, it also highlights the variability in study results, which may be due to differences in study design, sample size, and patient populations. Larger, multi-center studies should be the main focus of future research to confirm these results and investigate other genetic markers. Moreover, integrating pharmacogenetic data with clinical factors such as smoking and body weight (68-70), can influence response and potentially dilute the result s; this could further refine personalized treatment approaches. In addition, the difficulty may be resolved by combining novel genetic techniques, such as genome-wide association studies, with extensive clinical research to identify susceptibility genes in complex disorders.

5. Conclusion

This review demonstrates that genetic polymorphisms in genes such as TNF-α, TNFRSF1B, TNFAIP3, FCGR, and IL1B can significantly influence a patient's response to anti-TNF-α therapy for psoriasis. The identification of these markers holds great promise for personalizing treatment, which can lead to improved therapeutic outcomes and reduced side effects. The reviewed studies, however, often present conflicting results. To overcome these inconsistencies, future research should prioritize large, multi-center studies and incorporate pharmacogenetic data with other clinical factors, such as smoking and body weight, to enable a more accurate approach to medicine.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

Ethics committee approval is not required for the review paper.

6.3 Authors' Contributions

The first author was mainly responsible for study design, data collection, analysis, and drafting the manuscript. The second author assisted with data collection, analysis, and manuscript editing. The third author provided supervision, guidance, and final review. All authors approved the final manuscript.

6.4 Conflict of Interest

The authors declare no conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

7. Publisher's Note

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