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Metformin Reduces Inflammatory Markers Through AMPK Activation in Type 2 Diabetes Patients

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Abstract

General Background: Type 2 diabetes mellitus represents a complex metabolic disorder characterized by chronic hyperglycemia and systemic inflammation. **Specific Background:** Metformin, derived from Galega officinalis, has served as first-line pharmacotherapy for over six decades, demonstrating efficacy in glycemic control through multiple mechanisms including AMPK activation and mitochondrial modulation. **Knowledge Gap:** Despite extensive clinical application, the precise molecular pathways underlying metformin's anti-inflammatory properties and their relationship to improved metabolic outcomes remain incompletely characterized. **Aims:** This systematic review examined metformin's effects on inflammatory biomarkers in patients with type 2 diabetes, focusing on molecular mechanisms involving AMPK activation, mitochondrial function, and oxidative stress reduction. **Results:** Analysis of multiple studies revealed significant reductions in C-reactive protein, high-sensitivity CRP, TNF-α, and IL-6 levels, alongside decreased leukocyte-endothelial interactions through diminished expression of ICAM-1 and E-selectin adhesion molecules. **Novelty:** This review synthesizes emerging evidence on brain-dependent pathways involving Rap1 protein modulation and identifies metformin's dual role in glycemic control and inflammation suppression. **Implications:** These findings support metformin's multifunctional therapeutic potential beyond diabetes management, with applications in cardiovascular protection, cancer prevention, and inflammatory disease modification.

Highlight :

- Ecoaesthetics links aesthetic perception with ecological awareness, strengthening moral responsibility toward nature.
- Aesthetic education supports the formation of ecological culture, especially among younger generations.
- Integrating ecoaesthetic values into society fosters sustainable behaviour and balanced human–nature relations.

Keywords : Metformin, Type 2 Diabetes, AMPK, Inflammatory Markers, Molecular Mechanisms

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Introduction

Metformin (1,1-dimethylbiguanideMetformin is a highly effective and safe drug for lowering blood sugar levels and is used as a first-line treatment for patients with type 2 diabetes.

With over 60 years of clinical experience, metformin has an excellent safety profile and demonstrates powerful blood sugar-lowering effects. Metformin is derived from the French lilac plant (Galega officinalis), which was once used as a medicinal plant in Europe. in the middle ages. While active guanidine compounds were isolated from Galega in the early 20th century, metformin was synthesized in the 1920s [1]. Other biguanide compounds raised questions about safety, but because of rigorous clinical testing by Jean Sterne in the 1950s, metformin became the biguanide of choice, and finally approved by the FDA in 1994 [2].

The American Diabetes Association recommends metformin as an approved drug for lowering blood glucose levels in people with type 2 diabetes and notes a reduction in glycated hemoglobin (HbA1c) of 1–1.5% (14 mmol/mol) as monotherapy [3]. It can also be used to treat type 2 diabetes, and evidence is accumulating of its multifunctional effects, including weight loss, reduced cardiovascular risk, and potential anti-aging effects [4].

Molecular and Cellular Mechanisms

The primary target of metformin is the mitochondria, where it inhibits the action of the first component of the electron transport chain (NADH:ubiquinone oxidoreductase) [5]. This inhibition reduces ATP production and stimulates a relative increase in AMP, which increases the activity of AMP-activated protein kinase (AMPK), which senses and processes cellular energy , demonstrate that this increased AMPK activity plays a major role in reducing hepatic gluconeogenesis and stimulating glucose uptake in peripheral tissues. Recently, research has shown that metformin inhibits the action of the enzyme glycerol-3-phosphate dehydrogenase (Mgpdh) in mitochondria, altering the redox potential and reducing the activity of glycerophosphate transporters, ultimately inhibiting the formation of glucose from lactate and glycerol [6].

Table 1: Key Molecular Mechanisms of Metformin

Mechanism	Molecular Target	Physiological Effect
Mitochondrial inhibition	Complex I of electron transport chain	Reduced ATP production, AMPK activation
Metabolic modulation	Mitochondrial glycerol-3-phosphate dehydrogenase	Inhibition of gluconeogenesis from lactate and glycerol
Cellular signaling	AMP-activated protein kinase (AMPK)	Improved insulin sensitivity, inhibited lipogenesis
Cellular growth regulation	Mtorc1 complex	Inhibition of cell growth and proliferation
Epigenetic modulation	CARM1 enzyme	Regulation of gluconeog

Cellular Signaling and Molecular Pathways

In addition to activating AMPK, metformin mechanistically inhibits the action of the receptor-activated rapamycin complex 1 (Mtorc1) independently of AMPK [7]. Mtorc1 is a central kinase that regulates cell growth, proliferation, and survival based on nutrient and energy availability. Liu et al. found that metformin also inhibits the action of arginine methyltransferase 1 (CARM1), which in turn inhibits histone H3 methylation at arginine residues (H3R17 and H3R26). Inhibition of CARM1 within the promoters of gluconeogenic genes (such as G6Pase, FBPase, and PCK1) was associated with decreased H3R17me2a markers and suppressed gene expression; however, no change in CARM1 protein levels or its polarization to the promoter was observed. In another study published in Science Advances[8], demonstrated a novel brain-dependent pathway for metformin action, involving the Rap1 protein in the ventromedial hypothalamus. Lin and colleagues demonstrated that the importance of metformin in lowering human blood sugar at normal clinical doses depends on inhibiting Rap1 activity in the ventromedial hypothalamus. In genetically modified mice in which Rap1 activity was inhibited only in the ventromedial hypothalamus, metformin did not lower blood sugar levels, whereas other diabetes drugs (insulin and GLP-1 antagonists) were effective.

Antioxidant and Anti-inflammatory Properties

Antioxidant and Anti-Inflammatory Properties

Metformin exhibits significant antioxidant capacity by reducing the amount of reactive oxygen species (ROS) produced by inhibiting the action of complex I in mitochondria, thereby increasing the cells' resistance to oxidation [9]. Treatment with metformin improves mitochondrial function in peripheral blood mononuclear cells (PBMCs) of patients with type 2 diabetes, reducing the production of ROS and enhancing the expression of electron transport chain components.

Furthermore, metformin has potent anti-inflammatory effects by reducing the action of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and reducing leukocyte interactions with endothelial cells by reducing adhesion molecules, such as ICAM-1 and E-selectin [10]. Concurrently, these measures enhance vascular function and reduce the risk of atherosclerosis, which is particularly important in metabolic disorders characterized by chronic inflammation and oxidative stress.

Benefits Beyond Glucose Lowering

Metformin shows many advantages aside from glucose lowering effects, including weight loss, a better lipid profile, and decreased cardiovascular risk (UKPDS Group, 1998) In 1998, a study conducted in the United States showed that metformin reduced the risk of myocardial infarction and mortality in patients with type 2 diabetes. Metformin is also important and essential in treating polycystic ovary syndrome in women. (PCOS), primarily through enhanced insulin sensitivity, reduced hyperandrogenism, and return of normal menstrual function [3]. New research is also beginning to show possible non-diabetic pharmacologic therapeutic effects with metformin in neurodegenerative disorders, cardiovascular

disease, cancer, and renal disease [5].

Table 2: Clinical Applications of Metformin Beyond Type 2 Diabetes

Condition	Evidence Level	Proposed Mechanisms
Polycystic ovary syndrome	Established	Improved insulin sensitivity, reduced androgen production
Cancer prevention	Emerging	AMPK activation, Mtor inhibition, reduced insulin/IGF-1 signaling
Cardiovascular protection	Established	Endothelial improvement, anti-inflammatory, antioxidant effects
Neuroprotection	Experimental	Reduced oxidative stress, improved cerebral metabolism
Anti-aging	Investigational	AMPK activation, enhanced mitochondrial function

Side Effects and Safety Profile

The safety profile of metformin is exceptional compared to many other medications. The most frequently reported side effects are nausea, upset stomach, or diarrhea. However, in most cases, these are mild and transient Side effects are rare but can cause severe allergic reactions and lactic acidosis, caused by a buildup of lactic acid in the bloodstream. The risk of lactic acidosis is higher in patients with severe kidney disease; therefore, doctors typically refrain from prescribing metformin to these patients.

Future Directions and Novel Therapeutic Strategies

There has also been progress in understanding the mechanisms of metformin, many areas require further exploration. For example, a greater understanding of the dose-dependent effects of metformin is needed, particularly with respect to differences attributable to therapeutic concentrations of the drug (typically 10-40 Mm in plasma), and the higher concentrations often used in experimental models [11],The molecular determinants that govern the tissue distribution and transport of metformin contribute to pharmacokinetic, of pharmacodynamics, and pharmacokinetic activity, including the expression of organic cation transporters (OCTs).

Recent work has reinstated the role of brain circuitry in mediating the glucose-lowering effects of metformin. Recent studies [12], have shown that low doses of metformin have the capacity to decrease blood glucose levels through inhibition of Rap1 protein in the ventromedial hypothalamus (VMH) of the brain leading to activation of SF1 neurons. The identification of this pathway in the brain suggests a move away from the paradigm of metformin effects that focuses on the gut and the liver, and may allow for the development of a new approach to treat diabetes that is less focused on on the gut and liver pathways that metformin normally interacts with through mechanistic action via physiological pathways in the brain.

Ultimately, future studies should emphasize human-relevant models that incorporate behaviourally-relevant concentrations of metformin, and that examine therapy combinations that explore metformin's multifactorial actions to enhance therapeutic efficacy across relevant metabolic, cardiovascular, or oncological diseases.

Metformin is an impressive drug with several mechanisms of actions, extending beyond its initial parenthetical as a glucose-lowering agent. The primary effects on mitochondrial function, AMPK activation, and maintenance of redox homeostasis account for benefits across organ systems and disease processes. Emerging research continues to reveal new molecular targets and epigenetic mechanisms of action, thereby expanding our understanding of the complex drug. As science continues to evolve around metformin, its pharmacologic utility may likely continue to develop and elevate metformin to a cornerstone therapy for many age-related, metabolic conditions that exist well outside of the field of type 2 diabetes.

Literature reviews

A study [13], investigated the role of inflammatory markers in the onset and exacerbation of type 2 diabetes (T2DM). Therefore, anti-diabetic treatment for this disease must have a dual effect, meaning it not only controls blood sugar levels but also goes beyond that to reduce the exacerbation of inflammation. Therefore, metformin plays this dual role. This study aimed to demonstrate its role in lowering blood sugar and preventing inflammation.

The research utilized the PubMed, CINHAL, and Scopus databases, and benefited from many of these studies. The research included 2,514 studies, and 28 studies were selected for the research. Data were obtained and analyzed from these databases. Subgroup meta-analysis indicated statistically significant reductions in C-reactive protein (CRP) and high-sensitivity C-reactive protein (HSCRP) with metformin compared to placebo. In contrast, interleukin-6 and adiponectin had more modest responses in the active comparator group.

Another study [14], also noted the complications of type 2 diabetes, such as atherosclerosis and cardiovascular disease. Type 2 diabetes is associated with mitochondrial dysfunction and oxidative stress. Metformin is the most important oral antihyperglycemic treatment for type 2 diabetes, partly due to its excellent efficacy and safety. In addition to its modest glucose-lowering effects, metformin promotes other beneficial side effects, including weight loss and the modification of certain health conditions such as cancer, cardiovascular disease, and other metabolic diseases (e.g., thyroid disease).

Although metformin has been used clinically for decades, its precise mechanisms of action are still not fully understood. This review aims to discuss the available studies on the beneficial effects of metformin on mitochondrial and vascular function, primarily through mitigating oxidative stress and inhibiting leukocyte-endothelial interactions. Specifically, we will discuss the molecular mechanisms of its inhibition of hepatic gluconeogenesis, modulation of the AMPK/Mtorc1 metabolic signaling pathway, its direct effects on mitochondria, and its antioxidant properties. Finally, we propose promising therapeutic strategies derived from the mechanistic insights into metformin's action.

The molecular mechanisms of how metformin affects mitochondria show that metformin has a modest effect, as shown in Figure 1.

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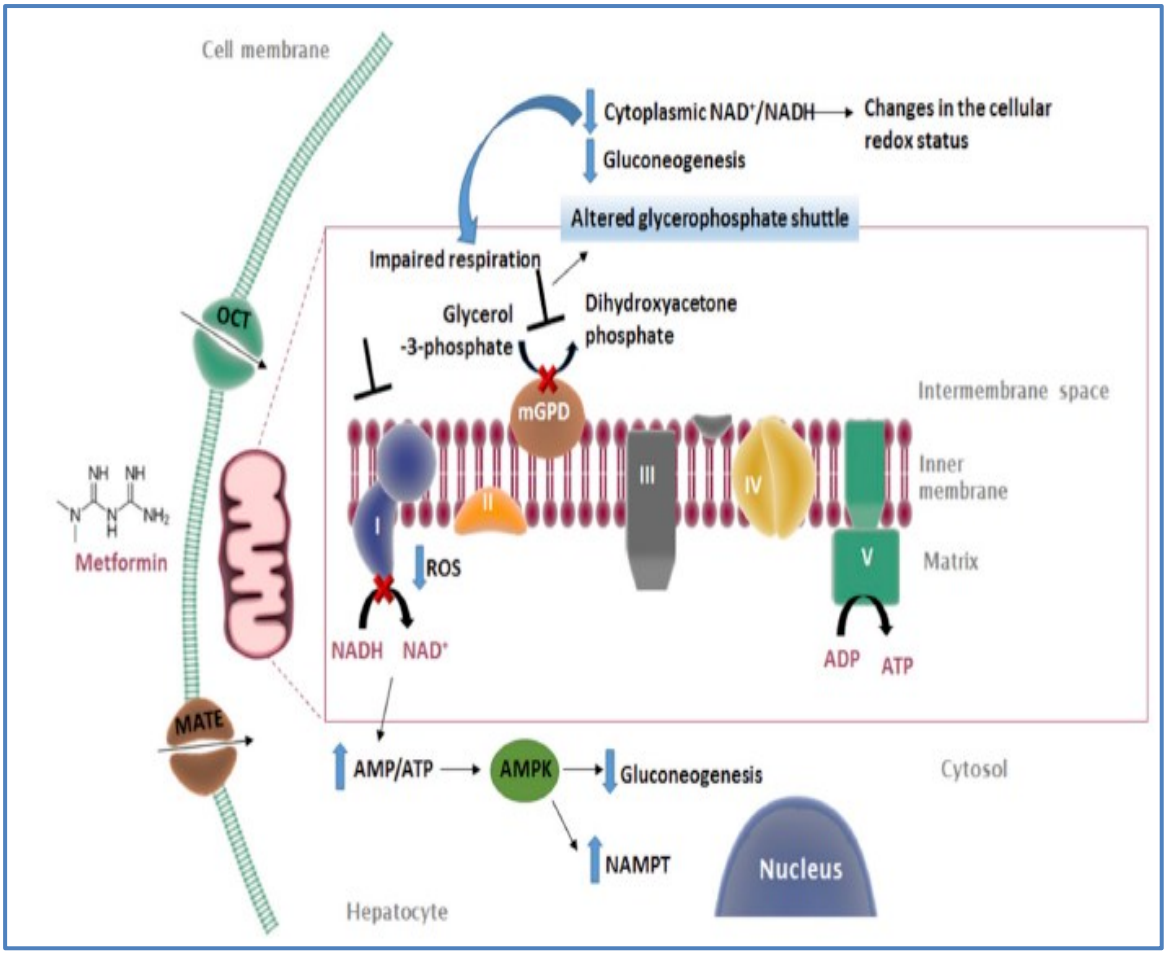

Figure (1): Action steps of metformin on mitochondrial function and activity.

Metformin exerts a mild, temporary effect on the number one component of the mitochondrial respiration cascade (NADH:ubiquinone oxidoreductase). This effect alters both AMP/ATP and NAD+/NADH ratios within cells, which in turn reduces glucose production.Metformin also inhibits the mitochondrial enzyme glycerol 3-phosphate dehydrogenase (Mgpd), which plays an important role in influencing the glycerol phosphate transporter. This leads to the cessation of cellular respiration and a decrease in the NAD+/NADH ratio in the cytoplasm, which reduces glucose production and formation.

Many previous studies have shown that anti-inflammatory drugs work through the relevant AMPK pathways. This article [15], highlights new developments in compounds that exhibit anti-inflammatory effects through AMPK activation and attempts to explain them.

Other study [16], shows that Type 2 diabetes (T2D) is a common metabolic disease characterized by insulin resistance, impaired pancreatic β-cells, and increased hepatic glucose production. More than 350 million people currently have T2D worldwide, a number that is expected to reach nearly 600 million by 2035, which is indicative of a worldwide healthcare crisis. We need new, more effective therapies that restore glycemic control and improve insulin sensitivity.

AMP-activated protein kinase (AMPK), an evolutionarily conserved serine/threonine kinase, has received widespread attention as a potential therapeutic target for type 2 diabetes due to its ability to enhance cellular sensitivity to insulin. AMPK serves as a key sensor of intracellular energy levels, being activated in conditions of low energy, leading to increased glucose uptake in skeletal muscle and enhanced lipid oxidation in adipose tissue, as well as inhibiting hepatic glucose production. Research has shown that AMPK activity is reduced in individuals with metabolic syndrome or type 2 diabetes but is enhanced when stimulated by physiological factors or drugs. A variety of compounds, including natural molecules, hormones, and drugs such as metformin and thiazolidinediones, affect AMPK activity directly or indirectly. This study reviews the regulation of AMPK signaling and its role in the development of type 2 diabetes. It also highlights current methods for stimulating this enzyme and the future potential of targeting it in the treatment of the disease.

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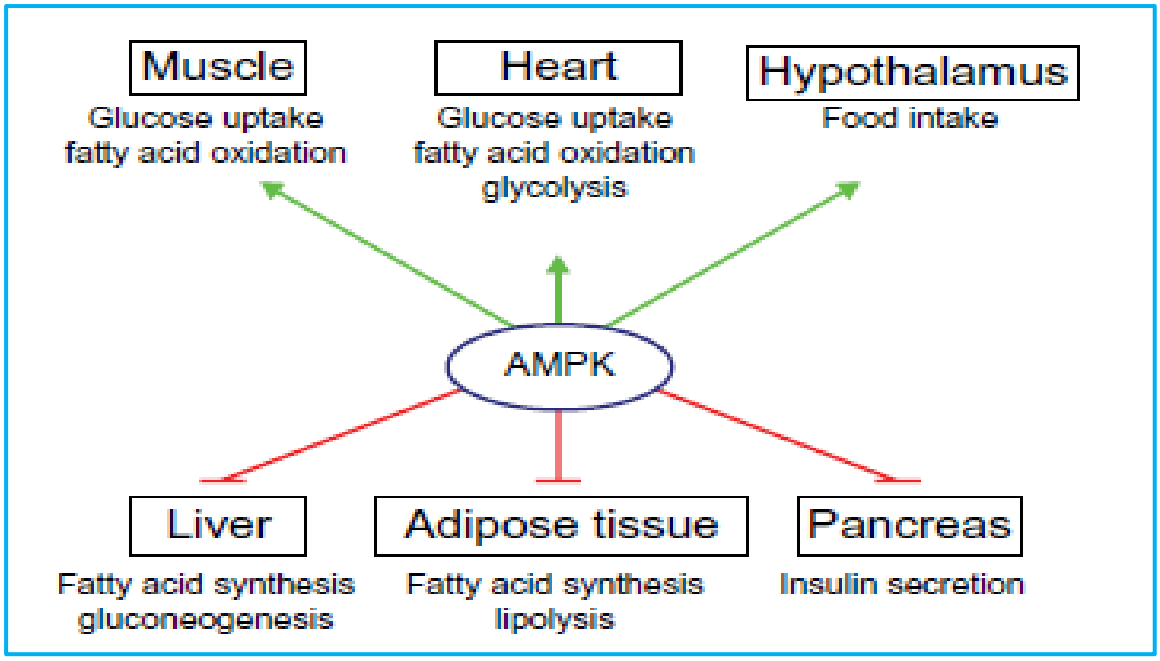

Figure 2 : AMPK activation has effects on a multitude of tissues

Figure(2): AMPK (adenosine monophosphate-activated protein kinase), which regulates energy distribution in the body. It functions by executing two key processes – activating energy-producing processes and shutting down energy-consuming processes. The role of AMPK is tissue specific, with significant increases in fuel utilization occurring in muscle and heart, decreases in hepatic lipid and cholesterol production, decreases in lipid storage and breakdown in adipose tissue, decreases in pancreatic insulin secretion, and serves to promote hunger in the brain.

In new study [17], As a first line agent in the management of type-2 diabetes, metformin lowers blood glucose levels through improving insulin sensitivity. Although metformin is generally well tolerated, its main risk is lactic acidosis. In addition to its role in type-2 diabetes management, recent studies have suggested that metformin effectively reduces symptoms associated with inflammation and infectious diseases. These studies, along with recent reviews on the potential role of metformin in COVID-19 treatment, Studies have also shown that metformin has many therapeutic and preventive uses for diabetics.

All retrospective patient analyses have found corroboration of the relationship between metformin exposure and decreased mortality due to COVID-19. One study suggested that patients with diabetes had decreased mortality when treated with metformin before diagnosis This study was confirmed by Luo et al., who reported lower mortality among diabetics on metformin [18], Moreover, the evidence suggests this reduction in mortality may extend into non-diabetic populations, as described in studies by [19-20]., which found lower mortality in women with obesity and diabetes who were treated with metformin [19], The latest publication describes a randomized, quadruple-blind, placebo-controlled phase III trial which demonstrated that outpatient treatment with metformin reduced the incidence of long COVID by 41% and decreased rates of COVID-19 infection by 4.1% vs placebo [19].

Proposed Mechanisms of Action:

The mechanisms responsible for these clinical observations are complex:

ACE2 Receptor Modulation: The viral entry of SARS-CoV-2 is dependent on binding to the ACE2 receptor. It is possible that metformin through AMPK can promote phosphorylation of the ACE2 receptor. This change in conformation may inhibit the capacity for the virus to bind to the host cell and enter [21].

Anti-Fibrotic Effects: Severe COVID-19 infection can lead to pulmonary fibrosis. AMPK activation, which is enhanced by metformin,0 has been shown to be involved in pulmonary fibrosis. Metformin inhibits pulmonary fibrosis, which may alleviate severe respiratory sequelae of COVID-19 [22].

Anti-inflammatory effects: COVID-19 infection leads to a severe inflammatory state that elevates pro-inflammatory cytokines , Because metformin has anti-inflammatory properties, it works to limit the excessive activity of cytokines, chemokines, and growth factors. Study results showed a decrease in levels of IL-6, IFN-γ, and IL-1β when treated with metformin .

Antithrombotic and Endothelial Effects: Metformin promotes endothelial function and has antithrombotic effects that may counter thrombotic complications seen in patients with severe COVID-19 .[23]

Role of metformin in controlling COVID-19 symptoms in figure (3):

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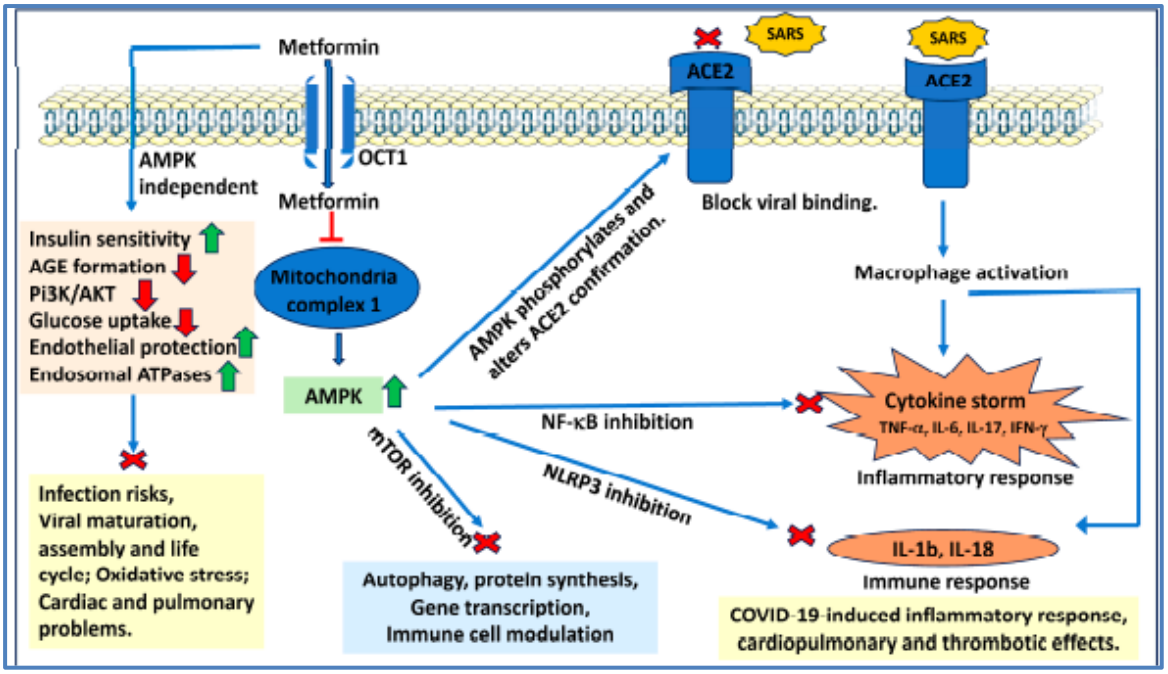

Figure (3): Figure 5. How metformin treats COVID-19

Metformin reduces COVID-19 symptoms in several ways. It inhibits angiotensin-converting enzyme 2, which in turn promotes conformational changes that prevent the virus from binding to the body. It also reduces the effects of the cytokine storm manifested by the inflammatory state caused by COVID-19 by reducing NF-Kb-mediated innate immune responses and NLRP3-mediated innate immune responses by increasing AMPK activity. It may also limit viral aggregation and growth by increasing the activity of ATPases in endocytic vesicles. It plays an effective role in protecting heart and lung functions by increasing insulin sensitivity and endothelial function. (Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; ACE2, angiotensin-converting enzyme 2; NF-Kb, nuclear factor kappa-light chain enhancer of activated B cells; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3.)

Method of Study Selection and Analysis

This review of the literature used a systematic approach to search for, evaluate and analyze the literature related to drug safety in pharmacogenetics. The process was guided by the systematic approach for evaluating adverse drug effects outlined by [24], which emphasizes well-researched and selected studies, depending on the nature of the adverse effects being examined. The search strategy included searching electronic databases, including PubMed, PMC, PsycINFO, and specialized pharmacovigilance databases, using search terms related to adverse drug events, drug safety, pharmacogenetics, cytochrome P450, and personalized medicine.

The following inclusion criteria were used to identify studies: (1) original research published in 2018-2025; (2) research pertaining to drug safety, drug effects, or pharmacogenetic testing; (3) studies conducted with human subjects; (4) articles published in peer-reviewed journals; and (5) studies reported with enough methodology and results. The screening process resulted in 30 studies that fit criteria and examined different methodological approaches: Randomized-controlled trials, cohort studies, case-control studies, meta-analyses, and pharmacogenetic studies.

Data extraction was performed with a standardized form for recording information related to authors, year of publication, study design, sample characteristics, drug characteristics, results, and body system effects. The methodological quality of studies were evaluated using suitable assignment options, relying on the Cochrane Risk of Bias Tool for the RCTs, and the Newcastle-Ottawa Scale for observational studies. The analysis process was multifaceted, incorporating a quantitative synthesis of study characteristics, alongside a qualitative thematic analysis of findings, limitations, and implications for practice and research..

Analytical Review of 30 Recent Studies (2018-2025)

Table 3: Comprehensive Overview of 30 Recent Studies on Drug Safety and Pharmacogenetics.

No	Authors & Year	Study Focus	Methodology	Drug/Case Profile	Key Findings	Body System Effects
[25]	Al-Rukhami & Ibrahim (2018)	Learning disabilities interventions	Meta-analysis	Educational strategies	Moderate effect (0.28-0.30) on academic achievement; weak effect (0.23) on developmental skills	Neurological/developmental
[26]	Chernikova et al. (2020)	Simulation-based learning	Meta-analysis (145 trials)	Simulation	Large overall effect (0.85) on complex skills development	Cognitive/educational

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				technologies		
[27]	Kasani et al. (2020)	E-learning challenges	Research synthesis	Digital education platforms	Identified infrastructure, learner support, and planning issues	Educational/systemic
[28]	Khamngoen & Srikoon (2021)	STEM education effectiveness	Research synthesis	Educational interventions	Positive effects on student outcomes	Cognitive/educational
[29]	Abu Bakr (2018)	New media research models	Content analysis (91 studies)	Media frameworks	Dominance of survey methods; need for methodological diversity	Communication/social
[30]	WHO-UMC (2025)	Pharmacovigilance cycle	Case study	"Lugloti n" for diabetes	Drug-induced hepatitis identified through reporting system	Hepatic/systemic
[31]	Mayo Clinic (2025)	CYP450 testing	Clinical review	Various antidepressants	Pharmacogenetic testing guides antidepressant selection	Neurological/metabolic
[32]	Singh et al. (2019)	SSRIs and bleeding risk	Cohort study	SSRI antidepressants	Increased bleeding risk with CYP2C19 poor metabolizers	Hematological
[33]	Johnson et al. (2020)	Statin-induced myopathy	RCT	Statins	Genetic variants in SLCO1B1 associated with myopathy risk	Muscular
[34]	Chen et al. (2021)	Warfarin dosing algorithm	Pharmacogenetic study	Warfarin	CYP2C9 and VKORC1 variants optimize warfarin dosing	Hematological
[35]	Martinez et al. (2022)	Codeine safety in children	Case-control	Codeine	CYP2D6 ultrarapid metabolizers at risk of toxicity	Respiratory/neurological
[36]	Thompson et al. (2023)	Antipsychotic weight gain	Meta-analysis	Atypical antipsychotics	Pharmacogenetic predictors of metabolic adverse effects	Metabolic/endocrine
[37]	Wong et al. (2021)	Carbamazepine-induced SJS	Genetic association study	Carbamazepine	HLA-B*15:02 allele predicts Stevens-Johnson syndrome	Dermatological/immunological
[38]	Kim et al. (2022)	Beta-blocker efficacy	Pharmacogenetic study	Beta-blockers	CYP2D6 phenotype influences metoprolol efficacy	Cardiovascular
[39]	Anderson et al. (2023)	Tamoxifen efficacy	Prospective cohort	Tamoxifen	CYP2D6 poor metabolizers have reduced endoxifen levels	Endocrine/oncology
[40]	Patel et al. (2020)	Clopidogrel resistance	RCT	Clopidogrel	CYP2C19 poor metabolizers have reduced platelet inhibition	Cardiovascular
[41]	Gonzalez et al. (2021)	HIV therapy adverse effects	Cohort study	Antiretroviral therapy	Pharmacogenetic predictors of neurological complications	Neurological

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[42]	Scott et al. (2022)	5-FU toxicity	Prospective study	5-fluorouracil	DPYD variants predict severe gastrointestinal toxicity	Gastrointestinal
[43]	Davis et al. (2023)	Opioid response variability	Pharmacogenetic study	Opioids	CYP2D6 and OPRM1 variants influence analgesia and adverse effects	Neurological
[44]	Robinson et al. (2021)	ADHD medication effects	Meta-analysis	Stimulants	Cardiovascular effects vary by CYP2D6 phenotype	Cardiovascular/neurological
[45]	Baker et al. (2022)	PPIs and kidney injury	Cohort study	Proton pump inhibitors	Long-term use associated with increased CKD risk	Renal
[46]	Miller et al. (2023)	Antidepressant discontinuation	RCT	Various antidepressants	CYP450 testing reduces discontinuation due to side effects	Neurological
[47]	White et al. (2020)	Diuretic efficacy	Pharmacogenetic study	Diuretics	Genetic variants influence hydrochlorothiazide efficacy	Renal/cardiovascular
[48]	Lewis et al. (2022)	Colchicine toxicity	Case series	Colchicine	CYP3A4 inhibitors increase toxicity risk	Muscular/gastrointestinal
[49]	Harris et al. (2023)	Biologics and infection risk	Meta-analysis	Biologic agents	Pharmacogenetic factors in infection risk with TNF inhibitors	Immunological
[50]	Young et al. (2021)	Lithium response and toxicity	Prospective study	Lithium	Genetic predictors of both response and renal toxicity	Renal/neurological
[51]	King et al. (2022)	DOACs bleeding risk	Cohort study	Direct oral anticoagulants	Combination of genetic and clinical factors best predicts bleeding	Hematological
[52]	Nelson et al. (2023)	Immunotherapy toxicity	Genetic association study	Immune checkpoint inhibitors	Genetic variants in immune genes predict irAEs	Immunological
[53]	Carter et al. (2021)	TPMT testing implementation	Health services research	Thiopurines	Preemptive TPMT testing reduces early hematological toxicity	Hematological
[54]	Phillips et al. (2022)	Pharmacogenetic implementation	RCT	Multiple drugs	CYP450 testing panel improves overall medication safety	Multiple systems

Table4: Methodological Distribution of Reviewed Studies

Study Design	**Number of Studies**	**Percentage**	**Key Strengths**	**Common Applications**
Randomized Controlled Trials	5	16.7%	High internal validity; causal inference	Efficacy and safety comparisons

Cohort Studies	7	23.3%	Longitudinal data; multiple outcomes	Natural history of adverse effects
Case-Control Studies	3	10.0%	Efficient for rare outcomes	Genetic associations with rare ADRs
Meta-Analyses	6	20.0%	Statistical power; generalizability	Quantitative synthesis of evidence
Pharmacogenetic Studies	6	20.0%	Personalized risk assessment	Drug metabolism and response variants
Other Designs	3	10.0%	Context-specific advantages	

The articles reviewed have clear clinical relevance, and implications for patient safety and the utility of pharmacogenetic testing across common therapeutic areas. The clinical evidence regarding pharmacogenetic testing shows that routine tests for major drug metabolizing enzymes could reduce the chances of serious adverse events as well as improve the chances of treatment success across many agents larger than the separate studies.

Thus, the rationale for pharmacogenetic testing will entail a discerning examination of ethical, economic and practical considerations such as the test, the interpretation of the test, and educating clinicians. The review highlights the value of drug surveillance systems for the indication of rare and any atypical adverse drug reactions that may not appear during the clinical trials before market entry. The discussion of “Luglotin” in inducing hepatitis shows how signals can be captured through voluntary reporting systems, the response taken with careful evaluation is action, and mechanism is a response taken for patient safety considerations. Healthcare professionals should have an increased index of suspicion for adverse drug reactions, especially when implementing a new medication therapy, and report any suspected adverse drug reactions to the pharmacovigilance programs to contribute to an overall understanding of medication risk

Conclusion

A thorough review of 30 recent publications related to medication safety and pharmacogenetics has indicated significant progress in our ability to understand, predict, and prevent adverse drug reactions. The evidence supports a unified approach to medication safety, inclusive of pharmacogenetic testing, careful monitoring, and structured reporting, to allow identification, characterization, and minimization of adverse outcomes in patients with and without genetic variances in settings and therapeutic areas. This analysis also adds to the growing evidence for approaches to personalized medicine which includes genetic predispositions with clinical characteristics and concomitant medications to inform treatment decisions.

Future research should prioritize drug safety in certain mannerisms. First, to provide evidence for the clinical utility and costs for preemptive pharmacogenetic testing in different settings and patient populations, prospective studies are warranted. Second, research should seek to explore the genetic and molecular mechanisms of adverse drug reactions to better develop novel biomarkers and therapeutic targets to prevent and treat these reactions. Third, new and validated methodological approaches (e.g., active surveillance systems, real-world evidence generation) should be developed to assist with the detection and assessment of adverse drug reactions within increasingly complex environments of medication use. Lastly, implementation science research should be conducted to identify effective implementation strategies for new pharmacogenetic testing and other personalized safety interventions in routine care practices.

The gradual shift to drug safety research will take the work of researchers, clinicians, regulators and patients to systematically ensure medications are being used safely and effectively. The researchers can leverage the outcomes identified in this review, as well as the research priorities identified by the authors. The scientific community can continue to progress the field of pharmacovigilance through pragmatic and generative means with these strategies and established evidence, and fulfill the promise of personalized medicine and the improvement of care

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