https://doi.org/10.31925/farmacia.2026.1.2 **REVIEW**

MOLECULAR PERSPECTIVES ON THE IMPACT OF INFLAMMATORY PROCESSES ON DRUG METABOLISM

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Abstract

In the complex, well-coordinated process of inflammation, a variety of cell types and molecules cooperate in a cascading network. Numerous physiological and pathological processes are rooted in inflammation. The mechanism of inflammation comprises a number of dynamic, coordinated reactions, including cellular and vascular events and specific humoral secretions. The liver is adversely affected by proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumour necrosis factor (TNF-α). IL-6 has been shown to selectively regulate several cytochrome P450 (CYP) enzymes, including CYP3A4. Some CYPs actively contribute to inflammation by converting fatty acids into mediators that are either pro- or anti-inflammatory. Genetic variability within inflammatory transcription factors is of great interest due to its critical role in inflammatory signalling.

Rezumat

În procesul complex și bine coordonat al inflamației, o varietate de tipuri celulare și molecule cooperează într-o rețea în cascadă. Numeroase procese fiziologice și patologice își au originea în inflamație. Mecanismul inflamației este alcătuit dintr-o serie de reacții dinamice și coordonate, care includ fenomene celulare și vasculare, însoțite de secreții umorale specifice. Ficatul este afectat în mod negativ de citokinele proinflamatorii, cum ar fi interleukina-1β (IL-1β), IL-6 și factorul de necroză tumorală-α (TNF-α). S-a demonstrat că IL-6 reglează selectiv mai multe izoforme ale citocromului P450 (CYP), inclusiv CYP3A4. Unele enzime CYP contribuie activ la inflamație prin conversia acizilor grași în mediatori cu efecte fie proinflamatorii, fie antiinflamatorii. Variabilitatea genetică în cadrul factorilor de transcripție implicați în inflamație prezintă un interes major datorită rolului lor esențial în semnalizarea inflamatorie.

Keywords: inflammation, pharmacokinetics, CYP enzymes, drug metabolism, pharmacogenetics

Introduction

The inflammatory process is a fundamental physiological response characterized by complex molecular signatures and cellular events involving both the innate and adaptive immune systems. A series of cellular and vascular events are involved in these processes, which are triggered by inflammatory mediators such as cytokines, chemokines, and other molecules. An autoimmune reaction, tissue damage, or infections by bacteria, viruses, or fungi can all trigger inflammation, the body's defensive response. Increasing blood flow, vascular permeability, and leukocyte recruitment are hallmarks of inflammation, driven by immunological, biochemical, and physiological alterations that release pro-inflammatory chemical mediators at the site of injury (1).

Furthermore, inflammation alters key transporters and enzymes involved in drug metabolism, thereby increasing variation in drug exposure within and between people. More understanding of how inflammation affects drug metabolism and the resulting clinical outcomes may help develop more individualized treatment plans (2).

The root cause of many physiological and pathological processes is inflammation. Although the pathological characteristics of many types of inflammation are well established, little is known about their physiological functions. At the other end of the spectrum, classic triggers of inflammation, infection, and tissue damage attract leukocytes and plasma proteins to the affected site (3).

Signal transduction, homeostasis regulation, and the number and affinity of target receptors at the site of action all affect a drug's pharmacological effect (4).

The inflammatory response, in any case, occurs in two phases: acute and chronic. Each stage is mediated by a distinct mechanism. For instance, acute inflammation caused by an infection typically subsides within a few days after the immune system clears it (5).

People experience episodes of acute infections or injuries throughout their lives, which are interrupted by sporadic flare-ups of inflammation. However, several studies have proposed that inflammation can alter the activity of drug-metabolizing enzymes and transporters (DMET) (6).

Immune responses to invasive pathogens or acute traumatic injuries depend on acute inflammation. Cell turnover and repair in various tissues are made possible by this process (7). Severe inflammation can trigger systemic inflammatory response syndrome, although acute inflammation is inherently beneficial. Hyperinflammation is the hallmark of this syndrome, which in its most extreme forms can result in organ damage, shock, and death (8).

Typically, chronic inflammation results in tissue degeneration through persistent, low-grade inflammation (9). Numerous diseases, including cancer, autoimmune diseases, and cardiometabolic diseases, can result from this type of inflammation, which is characterized by the simultaneous destruction and healing of the tissue from the inflammatory process, as well as the lack of any resolution of inflammation (10). Pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) can weaken anabolic signalling cascades, which include insulin and erythropoietin signalling, and cause sarcopenia. Many tissues in the elderly are chronically inflamed, and this could represent a problem in drug metabolism (11). Additionally, long-term tissue damage and repair cycles are hallmarks of chronic inflammation, which can seriously harm tissues and raise the risk of autoimmune inflammatory diseases (12).

The present study aims to investigate the intricate interplay between inflammatory processes and CYP450 enzyme activity, with particular focus on its involvement in personalized medicine. The primary objectives include examining the molecular mechanisms by which the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α suppress CYP450 enzyme transcription *via* multiple signalling pathways, including nuclear factor-kB (NF-κB) regulation and epigenetic modifications. Additionally, this research analyzes the relationship between inflammatory biomarkers and altered drug metabolism, emphasizing phenoconversion phenomena and their implications for therapeutic drug monitoring strategies.

Markers of the inflammatory process

A series of coordinated, dynamic reactions, including cellular and vascular events with particular humoral secretions, make up the mechanism of inflammation. These processes entail altering the physical distribution of fluids, plasma, and white blood cells (monocytes, basophils, eosinophils, and neutrophils) at the site of inflammation (13). The circulatory system, inflammatory cells, and injured tissue all actively contribute to and modulate the inflammatory response through various chemical mediators (14).

Cytokines

The function of many cells is significantly influenced by cytokines. Nonetheless, their importance in immune system regulation makes them especially significant (15).

Proinflammatory cytokines like IL-1β, IL-6, and TNF-α have a negative impact on the liver (16). In particular, IL-6 has been shown to modulate several CYPs, including CYP3A4 (17). Common inflammatory markers that may be elevated in the elderly include cytokines such as IL-6, TNF-α, and C-reactive protein (CRP). Keeping an eye on these could reveal important details about the elderly patient's overall health and risk of developing different ailments.

Certain chronic inflammatory conditions, including persistent infections, cancer, congestive heart failure, chronic obstructive pulmonary disease, and HIV infections, are associated with clinical syndromes that resemble accelerated ageing and frailty, characterized by sarcopenia, involuntary weight loss, reduced energy, and increased fatigability (18). The chronic state of inflammation generated by recurrent cycles of tissue injury and immune activation is often referred to as inflammaging. This inflammatory state accelerates biological aging, promotes age-related diseases, and contributes to progressive decline in organ function and physiological processes (19). On this basis, many researchers consider inflammaging both a hallmark of accelerated ageing and a major conceptual pillar in the biology of ageing (20).

Prolonged exposure to pro-inflammatory, immunogenic stimuli is one of the most obvious signs of immune dysregulation associated with aging (21). Older adults tend to have higher baseline inflammatory tone. They suffer from inflammation, which is characterized by elevated levels of blood inflammatory markers and raises the risk of frailty, chronic morbidity, disability, and early death. IL-1, IL-1 receptor antagonist protein (IL-1RN), IL-6, IL-8, IL-13, IL-18, CRP, interferons (IFN-α and IFN-β), transforming growth factor-β (TGF-β), TNF and its soluble receptors (TNF receptor superfamily members 1A and 1B), and serum amyloid A are among the pro-inflammatory markers that are found in high concentrations in the bloodstream (18). Most older people have high levels of age-associated pro-

inflammatory markers, even in the absence of risk factors or clinically active disease (22). Genetic predisposition, central obesity, altered gut permeability, cellular senescence, activation of the NOD (nucleotide-binding and oligomerization domain)-like receptor protein 3 (NLRP3) inflammasome, oxidative stress brought on by malfunctioning mitochondria, immune cell dysregulation, and persistent infections are some possible causes of inflammation (18).

Inflammatory cytokines, particularly IL-6 and TNF-α, can be elevated in older people and are associated with DNA damage that may contribute to cancer and muscle atrophy in some cases (23). Another feature of senescent cells is that they cause tissue inflammation and repair. This pattern of secretion includes proinflammatory cytokines such as IL-6, IL-8, IL-1α, and IL-1β, as well as chemokines. As a person ages, replicative senescence accumulates, causing tissue function to gradually deteriorate (24). Oxidative stress leads to oxidative damage to biomolecules, particularly DNA, which triggers the body to produce endogenous damage-associated molecular patterns (DAMPs) and release cytokines (25). Through telomere shortening and DNA double-strand breaks, oxidative stress has been demonstrated to be a critical component of cellular senescence (26). Cytokines cause systemic chronic inflammatory responses by activating downstream signalling pathways of pattern recognition receptors (27).

A number of "negative acute phase reactions" involving most drug-metabolism enzymes and transporters are linked to clinical inflammatory markers such as CRP, supporting the well-known detrimental effects of inflammation on drug metabolism (28).

Eicosanoids

One of the most crucial building blocks for the production of physiologically active inflammatory mediators is arachidonic acid (AA) (eicosatetraenoic acid), a 20-carbon PUFA, the primary constituent of membrane phospholipids in all cells (29). Phospholipase A2 can release it. Since it is the direct precursor of bioactive lipid metabolites of eicosanoids like prostaglandins (PGs), leukotrienes (LTs), and epoxyeicosatrienoic acid derived from three different enzymatic metabolic pathways - the cyclooxygenase (COX), lipoxygenase (LOX), and CYP450 pathways - accumulating evidence suggests that AA plays crucial biochemical roles (30).

Hepatic inflammation is complicated by AA, which functions as a precursor to several eicosanoids that can both cause and stop inflammation, including PGs, LTs, and thromboxanes. While some AA metabolites are involved in fibrosis and liver damage, others are involved in tissue repair and defence mechanisms. There are at least two forms of COX, type 1 and type 2, which are involved in the metabolism of AA and the synthesis of prostanoids, including strong proinflammatory PGs (31). PGE2 plays an important role in both acute and chronic inflammatory responses (32). Numerous cell types, such as fibroblasts, infiltrating inflammatory cells, and epithelial cells, produce PGE2. Physiological and pathological responses, including vascular homeostasis, inflammatory processes, nociception, and renal function, are mediated by it (33). This results in increased blood flow, redness, and plasma exudation in the area of acute inflammation, which ultimately causes oedema (34).

Molecular characterization of the inflammatory process

A complex natural defence response to biological, chemical, or physical stimuli, inflammation is closely linked to innate immunity and its inflammatory mediators, which are regulated by both innate and adaptive immune cells, as well as by molecular mechanisms (35).

A complex and well-coordinated process, inflammation involves a variety of cell types and molecules that work together as a cascade network. Some of these molecules initiate, intensify, or maintain the process, while others attenuate or resolve it (36).

The process of inflammation is strictly regulated. Usually lasting only a few days, the acute phase gives the immune system just enough time to contain and eradicate the threat without causing undue tissue damage (37). The leukocyte recruitment-conditioning chemotactic gradients are gradually diluted, and their survival program is turned off, enabling an effective depletion of the professional inflammatory cells in the inflammatory tissue. Pro-resolving mediators are also upregulated, whereas pro-inflammatory molecule production is inhibited. These coordinated efforts facilitate tissue repair and wound healing. Failure to maintain this control will delay the resolution process, hindering the return to homeostasis by causing persistent inflammation (38).

Inflammation and cytokine-mediated enzyme suppression

Like hormones, cytokines are small, soluble proteins that allow cells to communicate with their surroundings. TNF-α, ILs, colony-stimulating factors (CSFs), lymphokines, monokines, and IFNs are the most common of these. In contrast to reactive oxygen species (ROS), which are reactive molecules essential for cellular signalling but can also cause oxidative stress, they can function as signalling molecules that are essential for immune responses and inflammation (39).

Because cytokines have redundant activity, different cytokines can stimulate similar functions. Since one cytokine stimulates the production of other cytokines by its target cells, they are frequently produced in a cascade. Additionally, cytokines can have antagonistic or synergistic effects (40).

Antibody disorders, infectious diseases, and cancer are among the illnesses that have been linked to cytokine dysregulation. TNF-α and IL-6 are two pro-inflammatory cytokines that are produced or signalled abnormally in autoimmune diseases like rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus, which lead to tissue damage and chronic inflammation (41).

Activated macrophages are the main source of proinflammatory cytokines, which contribute to the upregulation of inflammatory responses. Numerous studies have demonstrated that pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Figure 1), participate in various processes beyond the pathological pain process (40). In response to inflammation, the immune system secretes systemic pro-inflammatory cytokines.

Proinflammatory cytokines may be transported through the bloodstream to initiate inflammatory responses in distant tissues, and they are also produced locally around pathological areas under inflammatory conditions. The expression of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 can be decreased in cultured human hepatocytes by direct administration of TNF-α, IL-1β, IL-6, IFN-γ, and TGF-β (42). The cytokines' involvement in inflammation is described in Figure 2.

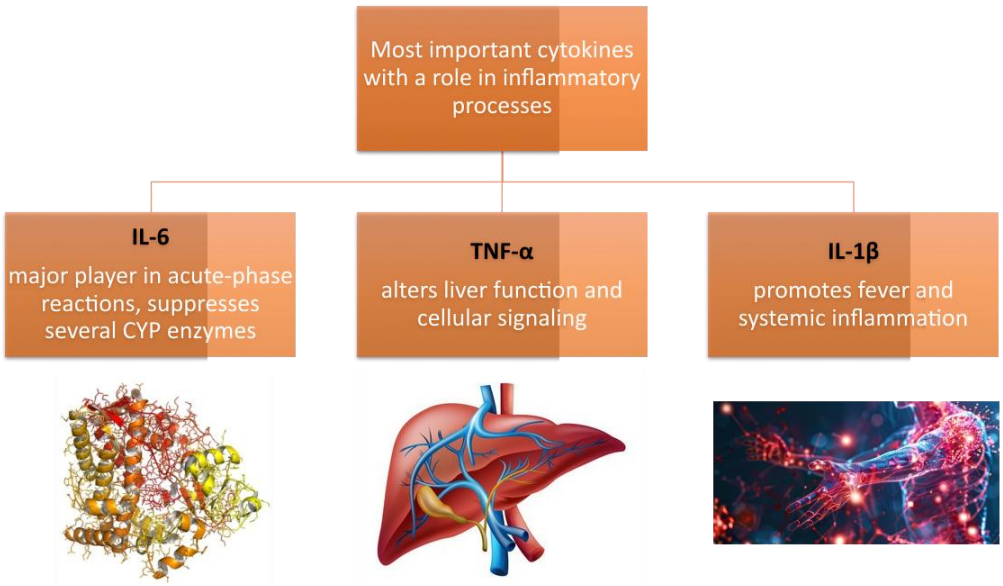

Figure 1.
The roles of cytokines in inflammation

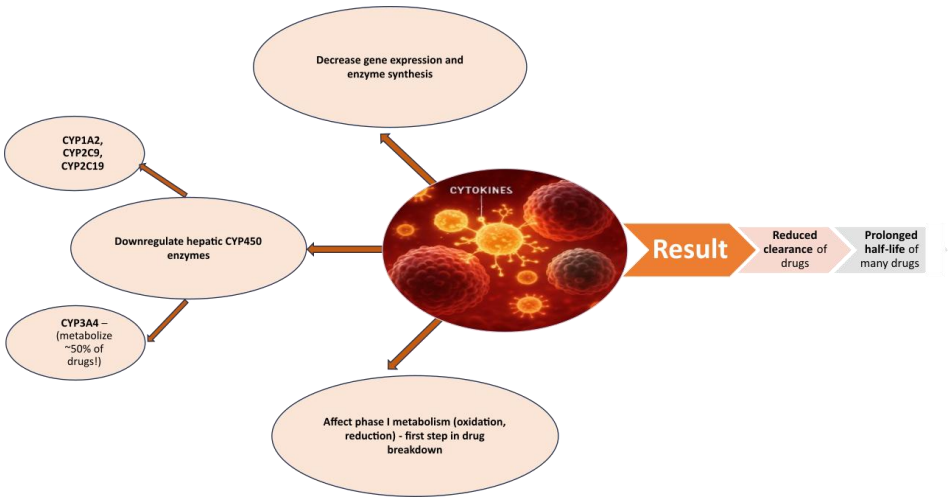

Figure 2.
The main effects of cytokines in the inflammatory process

The inhibition of CYP1A2 and CYP3A4 activities in human hepatocytes caused by IL-6 can be eliminated by blocking IL-6 signalling with a particular antibody (43).

Inflammatory process in hepatocytes

To maintain liver homeostasis, hepatocytes, the main parenchymal cells in the liver, are responsible for detoxification, immune cell activation, and the metabolism of proteins, fats, and carbohydrates (44). They are protected by Kupffer cells (KCs), endothelial cells, stellate cells, and the perisinusoidal space (or space of Disse). Chronic liver disease, which is largely driven by factors that contribute to its onset and progression, is linked to pathogen-associated molecular patterns (PAMPs), especially lipopolysaccharides (LPSs), which are found in the outer membranes of Gram-negative bacteria (45).

Local macrophages, or KCs, make up about 15% of liver cells and are essential for stopping the spread of pathogens from the gut to other parts of the body (46).

Liver disease is exacerbated by chronic alcohol consumption because the production of LPS in the intestine is transferred to the liver, where it combines with hepatocyte death to cause systemic inflammation (47).

The combination of alcohol and LPS activates liver macrophages, including KCs. Alcohol and LPSs can stimulate KCs, which can raise proinflammatory cytokines like TNF-α, IL-1β, and IL-6. When LPS and alcohol interact, hepatocytes, neutrophils, and macrophages can all produce reactive oxygen species more quickly (48).

Influence of the inflammatory process on drug-metabolizing CYP450

CYP450 enzymes are crucial for drug detoxification, cell metabolism, and homeostasis. In humans, almost 80% of oxidative metabolism and approximately 50% of the overall elimination of common clinical drugs can be attributed to one or more of the various CYPs from the CYP families 1-3. Importantly, the analysis estimates the contribution of CYP families 1–3 to overall oxidative metabolic flux, rather than the proportion of drugs undergoing CYP-mediated metabolism or the number of CYP isoforms involved (49). CYP450s have the ability to alter drug toxicity, safety, bioavailability, and drug response (45, 50). Comprehensive analyses indicate that around three-quarters of P450 reactions in drug metabolism are catalysed by a core group of CYP1–3 enzymes (1A2, 2C9, 2C19, 2D6, 3A4) (51).

By transforming fatty acids into pro- or anti-inflammatory mediators, certain CYPs actively contribute to inflammation. The metabolism of other ω-6 polyunsaturated fatty acids (PUFAs), such as ω-3 fatty acids like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), is gaining attention, although most attention has focused on the products of AA (52).

CYPs can contribute to the initiation, maintenance, and resolution of inflammation. The three directions of AA metabolism are the LOX pathway, which produces LTs, and the COX pathway, which produces PGs. CYPs are frequently referred to as the third pathway of this metabolism (52). The effectiveness and safety of medications are determined by CYP450, the primary drug-metabolizing enzyme (DME) (53).

Inflammation generally suppresses CYP metabolic activities, though the effect varies by specific CYP isoform and inflammatory context (54). According to information in the literature, cytokines and their intracellular signalling on drug transporters and metabolizing enzymes, either directly or through interaction with the nuclear receptor pathway, are what cause this effect on drug pharmacokinetics (55). Crucially, the alterations across the entire CYP family cannot be explained by a single common pathway involving both distinct transcription factors and mediators (56). Pre- and post-transcriptional mechanisms specific to cytokines and CYP can modulate CYP during inflammation (57).

Transcriptional downregulation of transcription factors, disruption of the dimerization or translocation of (nuclear) transcription factors, modification of liver-enriched transcription factors signalling, and direct regulation by nuclear factor-κB (NF-κB) are pre-transcriptional mechanisms that are currently being described in the literature (56).

The hepatic and extrahepatic metabolism of medications is known to be impacted by inflammation, and inflammation is frequently linked to a number of chronic illnesses (58).

Hepatocyte inflammation has a major effect on drug metabolism by regulating hepatic drug transporters and DMEs (CYP450s). The release of pro-inflammatory cytokines during inflammation may reduce drug clearance by CYP450s. Furthermore, inflammation can impair hepatic processes essential to drug metabolism, potentially leading to higher drug levels and increased toxicity. The inflammatory cytokines IL-1β, IL-6, TNF-α, and IFNs α/γ are released when a tissue tries to adapt to cellular stress. It is believed that these cytokines influence (suppress) the expression of CYP enzymes (59, 60).

A number of commonly used medications were taken off the market due to severe adverse drug reactions (ADRs) caused by drug-drug interactions (DDIs) that also affect CYPs (61).

Therefore, CYP450s are the focus of interrelated problems in the pharmacology of inflammation: they are targets for developing novel anti-inflammatory medications, but they also influence variation in

drug toxicity and efficacy in inflammatory diseases (62).

The pharmacokinetics of prescribed drugs are altered during inflammation, as cytokines modulate the expression of hepatic drug-metabolizing CYP450s. It is thought that inflammation significantly affects drug transporters and metabolism. The downregulation of inflammation in the expression and activity of DMETs is attributed to several proposed mechanisms. The well-supported mechanisms include NO-dependent proteasome degradation, a post-transcriptional mechanism that can reduce levels of drug-metabolizing enzymes, thereby affecting their activity (63), and epigenetic changes in genes due to DNA methylation and histone modification (64). Additional contributing factors include inhibition of DME transcription (2), changes in the differentiation state of hepatocytes that can affect enzyme expression (65), or changes in hepatic blood flow and functional liver mass (66).

Inflammation is a major regulator of DMEs

To control liver damage, repair, and inflammation, hepatocytes can generate a variety of cytokines (44). Inflammatory processes in the liver are actively influenced by the cytokines. Particularly after organelle damage, such as endoplasmic reticulum (ER) stress and mitochondrial dysfunction, hepatocytes play a crucial role in liver inflammation by actively releasing pro-inflammatory cytokines that drive the inflammatory cascade. There are many ligand-activated transcription factors and mediators involved in the complex regulatory mechanisms governing hepatic CYP levels and their interactions with CYP gene regulators. The primary regulatory mechanism that alters CYP450 activity in response to inflammation is believed to be cytokine-mediated modification of gene transcription. Significantly, no single common pathway has been identified across all CYP enzymes, and the underlying mechanisms are cytokine-specific. During inflammation, there are several ways that key CYP enzymes can be repressed (Figure 3) (56).

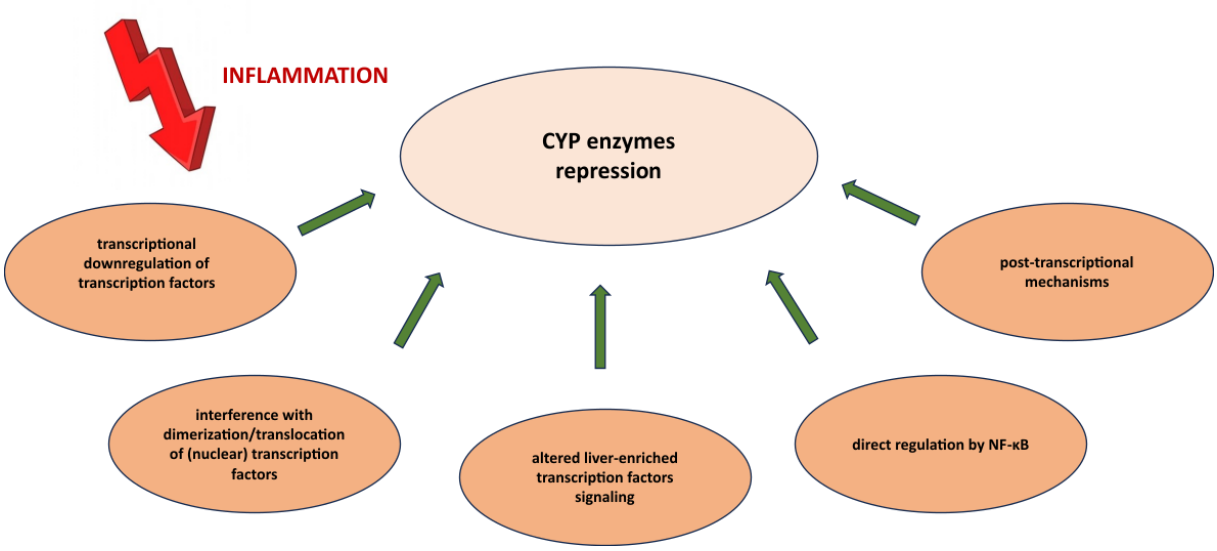

Figure 3.
Suppression of CYP enzymes during the inflammatory process

The variety of disease states that alter CYP expression is being investigated using an increasing number of model systems, which also show that the pattern of change differs depending on the disease (62). The degree of inflammation, the suppression of hepatic CYP expression, and the removal of CYP substrates were all correlated in studies using rodent models of arthritis. It was also shown that antibodies against TNF-α and IL-6 desensitized CYP expression (67).

Inflammation amplification, immune cell activation, and hepatocyte damage are all greatly influenced by inflammasome activation. An innate immune response is triggered when immune cells activate the inflammasome protein complex. Inflammasomes are innate immune system cytosolic multiprotein complexes that initiate inflammatory reactions and cause cell death (68). An intricate system made up of upstream sensors, adapters, and downstream effectors assembles the inflammasome and initiates the inflammatory signalling cascade (69).

Drug metabolism and transporters are thought to be significantly regulated by inflammation (2).

The CYP450 and NLRP3 inflammasome pathways have a complex, possibly interrelated relationship, particularly when inflammation and disease are involved. Hepatocyte inflammation and liver diseases are significantly influenced by NLRP3-mediated inflammation, which also regulates several

metabolic enzymes (70). Pro-inflammatory cytokines IL-1β and IL-18 are released when it is activated by a variety of stimuli, including DAMPs and PAMPs. Hepatocyte damage and senescence are caused by ROS, which are produced by activating NLRP3 inflammasomes. ROS also affects how liver sinusoidal endothelial cells (LSECs) react to immune stimuli (71).

The key to anti-inflammatory processes is limiting inflammation by blocking NLRP3 (72). Since the pathophysiology of liver diseases primarily involves inflammasome activation, inhibiting this process is a desirable therapeutic target. The inflammasome signalling pathway can be pharmacologically inhibited by endogenous IL-1β inhibitors, caspase inhibitors, or antibodies (72).

Hepatocyte inflammation and metabolic disorders can be managed by the endogenous metabolite bile acid, which inhibits the NLRP3 inflammasome (73). Different receptors found in various tissues and cell types are believed to be activated by bile acids. An investigation by Guo *et al*. revealed that the most powerful effect on NLRP3 inflammasome activation was caused by the bile acid, lithocholic acid (73). Understanding the anti-inflammatory characteristics of Takeda G protein-coupled receptor 5 (TGR5) has been enabled by its discovery as a bile acid-activated membrane receptor (74). Bile acids may prevent NLRP3 inflammasome activation through TGR5 signalling, according to a theory based on the strongest effect of lithocholic acid on this activation (73).

High levels of proinflammatory markers, such as IL-1, IL-1 receptor antagonist protein (IL-1RN), IL-6, IL-8, IL-13, IL-18, CRP, IFN-α and IFN-β, TGF-β, TNF-α and its soluble receptors (TNF receptor superfamily members 1A and 1B), and serum amyloid A, are identified in the pro-inflammatory state.

Hepatic DME activity and metabolism, including lipid metabolism, are reduced by various immune reactions. Identifying the clinical causes of abnormal drug metabolism and developing biomarkers can be aided by analyzing hepatic DMEs in disease states and by understanding their mechanisms of action. By identifying drug-related metabolic enzyme activities, these biomarkers can help prevent adverse drug reactions and adjust medication timing and dosing (45).

The impact of therapeutic proteins and inflammation on a patient's drug disposition is hard to predict. The type of disease, how long it lasts, and which CYP is involved most likely affect the responses. Furthermore, CYP expression varies significantly amongst people according to many factors, including age, sex, and genetics (75).

Drug pharmacokinetics in critically ill patients are affected by the degree of inflammation. This could reduce the effectiveness of treatment. Dosing strategies may be optimized if the precise effects of inflammation, as indicated by biomarkers, on drug absorption, distribution, metabolism, and excretion are understood. The behaviour of drugs is controlled by processes known as absorption, distribution, metabolism, and excretion (ADME) (76). Figure 4 illustrates the influence of inflammation on the pharmacokinetic mechanism.

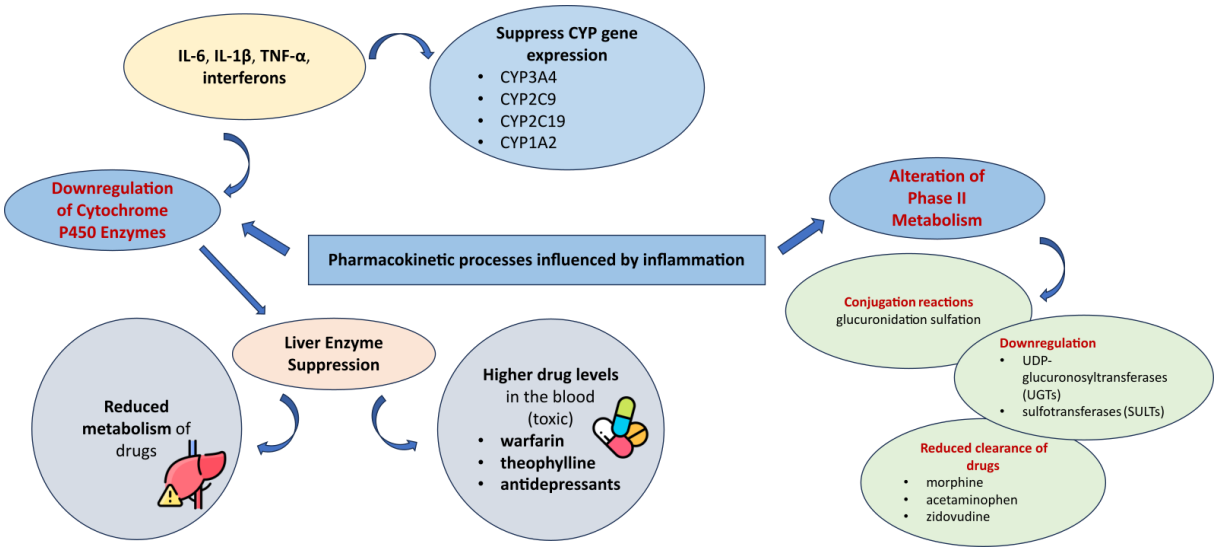

Figure 4.
The influence of inflammation on drug pharmacokinetics

With the development of appropriate biomarkers, a personalized approach would make decisions about therapy selection and medication dosage adjustments easier. Because cytokine action is pleiotropic, measuring plasma levels of inflammatory cytokines, such as IL-6, may be helpful in certain situations.

Progress has been made in developing endogenous indicators of CYP metabolism, and a more direct assessment of CYP activity is preferred. Since the most important drug-metabolizing CYPs are expressed in blood leukocytes, and their expression levels correlate with hepatic CYP expression, isolating and analysing blood cells may offer an alternative method for monitoring CYP activity (77).

Research on CYP3A4 mRNA in blood and liver revealed a strong association between blood and liver tissue levels of CYP3A4 mRNA, indicating that blood CYP mRNA might occasionally represent hepatic expression (78). According to a study assessing the messenger RNA (mRNA) concentration of CYP enzymes in peripheral blood leukocytes, predicting systemic enzyme activity from mRNA expression profiles of CYP2D6 and CYP2C19 is not supported. Therefore, *in vivo* functional enzyme activity may not be accurately reflected by blood cell CYP mRNA levels alone (79).

CYP phenotyping involves quantifying plasma clearance or metabolite/parent drug ratios for CYP-specific probe drugs, providing a direct measure of *in vivo* CYP enzyme activity (80). To estimate *in vivo* CYP enzyme activity, CYP450 (CYP) phenotyping involves measuring a person's plasma clearance of CYP-specific probe drugs. It is increasingly used to investigate changes in CYP enzyme activity across various (patho)physiological settings (80). An essential part of phenotyping assays is evaluating the activity of the human CYP enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, which metabolize more than 85% of medications used in patients. CYP enzyme activity is derived from (patho) physiological conditions on enzyme activity in this approach. However, this assumption is called into question because, in addition to CYP enzyme activity, other non-metabolic determinants, such as the fraction of drug that is not bound to plasma protein, the blood-to-plasma ratio, and hepatic blood flow, may also have an impact on the plasma clearance of probe drugs (81). The fact that probe drugs are never completely removed by a single isoenzyme, and that small elimination pathways affect the concentration of the parent compound, are limitations that apply to clinical plasma clearance values. Establishing the sensitivity and specificity of medications in phenotyping cocktails is enabled by the physiologically based pharmacokinetic approach, which allows study of the main elimination routes in isolation, something that would not be feasible *in vivo* (80).

Pharmacogenetic changes produced by inflammatory processes

Expression of genes involved in drug metabolism and action may be disrupted by the inflammatory process. Also, some genetic variations can exacerbate the inflammatory response, which can further alter how drugs behave pharmacologically.

The pharmacokinetics and pharmacodynamics of medications can be altered by genetic polymorphism. These changes give rise to variations among individuals in how they react to drug treatment (82, 83).

Through the downregulation of CYP enzymes, inflammation and disease states have been shown to significantly impact drug metabolism. As a result, they may contribute to phenoconversion, the discrepancy between genotype-predicted and actual phenotypic drug response (84). Individual patients' experiences with inflammation-induced phenoconversion vary considerably, influenced by multiple interconnected factors. The extent of CYP suppression is strongly correlated with the severity of inflammation, as higher inflammatory burdens typically result in more pronounced metabolic alterations (2). Equally important are the specific cytokine profile and the type of inflammation present, which significantly determine the magnitude of effects on drug metabolism. This relationship has been convincingly demonstrated through studies with IL-targeting biologics, which show cytokine-specific reversal of inflammatory suppression on CYP proteins (84).

Furthermore, inflammation has been shown to downregulate CYP activities in an isoform-specific manner, meaning that the degree of inflammation-induced phenoconversion largely depends on the particular metabolic pathway utilized by individual drugs (85). This pathway-dependent variability means that patients may experience different degrees of metabolic alterations depending on which specific enzymes metabolize their medications. Additionally, underlying genetic variability adds another crucial layer of complexity to drug metabolism, creating further patient-to-patient differences in how inflammation affects therapeutic outcomes (86). The intricate relationship between these factors is further emphasized by the frequently observed inverse connection between drug metabolism and signature indicators of inflammation (56), highlighting the fundamental impact that inflammatory states can have on pharmacokinetic processes and ultimately on clinical outcomes.

The effects of genetic variation on inflammatory processes

The genetic diversity of inflammatory mediators creates significant variability in patient responses to drug metabolism. Polymorphisms in cytokine genes can substantially influence immune responses that impact drug metabolism, as these genetic variations predispose individuals to altered susceptibility to immune-related diseases (87). This genetic influence extends beyond cytokines to encompass inflammatory receptors, where pathogen-associated molecules activate

toll-like receptors (TLRs), potentially reducing CYP3A4 expression and altering drug metabolism pathways.

TLRs are transmembrane receptors expressed on various cell types, including immune and epithelial cells, where they detect pathogens and initiate inflammatory and immune responses. Importantly, endogenous molecules can also activate TLRs, such as DNA molecules released during ischemia-reperfusion injury in organ transplant recipients (88). Genetic variations in TLRs are hypothesized to change the impact of inflammation and its consequences for drug metabolism (56). Research demonstrates that genetic variations in specific receptors, such as IL-6R or IL-1R, can directly contribute to CYP enzyme downregulation and may play particularly significant roles in regulating inflammation and its metabolic effects (89).

The genetic variability of inflammatory transcription factors, particularly NF-κB, is a critical area of interest given their central role in inflammatory signalling (90). Genetic variations in NF-κB or its adaptor protein genes are expected to have a substantially greater impact on the effects of inflammation on drug metabolism than genetic variability in individual receptors or mediators (56). This occurs because these transcription factors regulate the inflammatory signalling cascade that ultimately modulates CYP expression and drug-metabolizing capacity.

While genetic variations in CYP enzymes are well established as contributors to interindividual pharmacokinetic variability (86), the precise mechanisms by which CYP polymorphisms may modify the effects of inflammation on drug metabolism remain unclear. Although CYP2C19 exhibits high polymorphism, the full spectrum of CYP isoforms affected by inflammation is still being elucidated. An individual's CYP metabolizer genotype significantly influences the alterations in CYP450-mediated drug metabolism induced by inflammation. *In vitro* studies have shown that CYP isoforms differ in susceptibility to downregulation by inflammatory mediators, with CYP3A4 appearing most vulnerable, consistent with clinical observations in CYP3A4 drug substrates (56).

The concept of personalized medication therapy has become increasingly prominent in contemporary clinical pharmacy, necessitating tailored treatment protocols to optimize therapeutic outcomes for individual patients (91). The complex interplay between inflammation and genetics represents a fundamental determinant of modern treatment efficacy and safety. Future advances will likely integrate inflammatory biomarkers with comprehensive genetic profiling to enable truly personalized medicine, substantially minimizing adverse effects while maximizing therapeutic benefits.

CYP450 as a target for anti-inflammatory drugs

Geniposide and genipin

Geniposide (GP), an iridoid glycoside derived from gardenia fruit, which belongs to the Rubiaceae family, demonstrates potent anti-inflammatory effects against both acute and chronic inflammation (45). In experimental studies using mice with 3,5-diethoxycarbonyl-1,4-dihydrocollidine-induced sclerosing cholangitis, GP inhibited CYP2E1 expression, attenuated hepatic glutathione (GSH) depletion and malondialdehyde (MDA) accumulation, reduced inflammatory responses, and enhanced bile acid secretion (92). The compound markedly decreased activation and expression of the pain-signaling receptors TLR4 and NF-κB, while reducing inflammatory cell infiltration. These findings indicate that GP effectively protects hepatocytes from acetaminophen hepatotoxicity by downregulating CYP2E1 expression and the NF-κB signalling pathway (93). Limited studies examining metabolic alterations in GP-treated liver fibrosis models suggest the compound may provide antioxidant benefits in hepatic fibrosis (94).

Genipin is the aglycone form of GP and results from intestinal hydrolysis by β-D-glucosidase (52). Pharmacological research has identified genipin, rather than its parent compound GP, as the primary active constituent of gardenia responsible for therapeutic effects (95). While genipin retains anti-inflammatory properties (96), additional *in vivo* and *in vitro* research reveals that it can enhance cytotoxic effects (97) and functions as a potential substrate for P-glycoprotein (P-gp) and an inhibitor of uncoupling protein 2 (98). P-gp, encoded by the human multi-drug resistance gene and belonging to the ATP-binding cassette transporter superfamily, plays a crucial role in xenobiotic elimination across concentration gradients (99). Given genipin's effects on CYP450-dependent monooxygenases, GSH, and GSH S-transferase, researchers emphasize the need for careful consideration of drug safety. Particular caution is warranted regarding potential induction or inhibition of CYP isoenzymes, and strong P-gp induction, when combining drugs, to prevent both toxicity enhancement and therapeutic effect reduction (52).

According to an *in vitro* study, genipin significantly reduces the activity of CYP3A4 and CYP2C19 and increases CYP2D6 in HepG2 cells. It also affects P-gp expression, suggesting that xenobiotic metabolism may be modulated *in vitro* (52). Experimental studies have shown that genipin has antioxidant and cell-protective effects by reducing oxidative mitochondrial damage during hepatic ischemia/ reperfusion (100).

When interpreting *in vitro* CYP data, it is crucial to consider the lack of well-characterized human

pharmacokinetic studies on genipin in the literature and the absence of clinical drug interaction trials involving genipin. No published human DDI study has quantified CYP inhibition/induction *in vivo*, but rat pharmacokinetics and *in vitro* CYP modulation data show mechanistic potential. Comprehensive reviews on genipin's bioactivity also emphasize poor bioavailability and metabolic transformation, indicating caution when interpreting *in vitro* activity (101).

Curcumin

It is a naturally occurring bioactive compound in turmeric (*Curcuma longa*) that exhibits broad inhibitory effects on the CYP450 family, specifically suppressing CYP1A2, CYP2C, and CYP3A4 (102). The compound also prevents aryl hydrocarbon receptor (AhR) activation, thereby reducing CYP1A expression and contributing to its hepatoprotective benefits through CYP450 modulation (45). As a transcription factor involved in detoxification and inflammation, AhR reduction by curcumin helps decrease liver inflammation and associated damage. Curcumin demonstrates additional anti-inflammatory effects by inhibiting hepatic pro-inflammatory cytokine synthesis and inflammatory cell activation (103).

However, poor pharmacokinetics severely limit its therapeutic application. To realize curcumin's full potential, biodistribution improvements through modifications such as nanoformulations, including cell membrane-derived systems and nanoemulsions with exceptional biocompatibility, are essential (104). Human data are limited, and curcumin bioavailability is low without specific formulations, despite strong *in vitro* signals. Curcumin was found to cause significant PK changes in one clinical trial, highlighting the rarity of clear clinical CYP DDIs for most phytochemicals under study (105).

Silybin

A flavonoid lignan extracted from silymarin seed coats within the *Compositae* family influences liver function through interactions with CYP450 enzymes, and has potential effects on drug metabolism. Research indicates silybin can inhibit specific CYP enzymes, particularly CYP3A4 and 2C9, while potentially altering other hepatic glucuronosyl-transferases (106). Despite its CYP450 inhibitory properties, silybin's primary characteristic remains its hepatoprotective effects, which can influence both hepatic responses to inflammation and the metabolism of specific drugs and toxins. As a commonly used hepatoprotective agent in liver disease treatment, silybin is a CYP3A inhibitor that can prevent declines in CYP3A expression (107). The compound disrupts NF-κB-regulated transduction cascades by interfering with this widely expressed, inducible DNA-binding protein that serves as a transcription factor for genes related to growth, differentiation, inflammation, and cell survival (108).

Some studies show that silybin inhibits CYPs *in vitro*, but it is highlighted that the concentrations required to achieve this are higher than those found in human plasma, creating a discrepancy between mechanistic evidence and practical applications (109). Although improved formulations can raise systemic concentrations, it is unclear if these will reach levels that significantly inhibit CYPs *in vivo*; this will probably depend on the formulation, dosage, and timing (110).

Gevokizumab

Represents a unique therapeutic approach as an IL-1 signalling regulator rather than a conventional blocker (45). The compound significantly regulates CYP450 and transporter activities (111) by binding to a specific epitope near the IL-1 receptor interface without completely overtaking the interface. This mechanism reduces IL-1 binding to the IL-1 receptor type I signaling receptor and decreases recruitment of IL-1 helper proteins, primarily by reducing association rates of these interactions. In human hepatocytes, gevokizumab attenuates, though does not completely abolish, IL-1-mediated functional repression of CYP3A4 and drug transporters. This attenuation of IL-1-mediated downregulation of hepatic detoxifying proteins must be carefully considered against potential therapeutic protein drug-drug interactions in future development and clinical applications (111).

The inflammatory cytokine IL-6 inhibits hepatocytic CYP450 and transporter expression by activating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway. Therapeutic proteins, including monoclonal antibodies targeting IL-6 or its receptors, may partially restore CYP expression or activity in some settings, demonstrating how drug-drug interactions associated with inflammatory diseases can be managed (112). Therapeutic proteins (TPs) with pro-inflammatory activity include agents that either mimic endogenous pro-inflammatory cytokines (*e.g.*, peginterferon) or modulate pro-inflammatory cytokine pathways (*e.g.*, blinatumomab) (113). The administration of TPs with pro-inflammatory activities may cause a temporary or permanent increase in the body's cytokine levels; consequently, a cytokine-drug interaction may result in DDIs with co-administered medications (114).

Certain phytochemicals, such as flavonoids, resveratrol, and curcumin, have been demonstrated to inhibit or modify CYP enzymes *in vitro* at micromolar concentrations. Mechanistic insights and particular inhibitory constants have been documented in cell and microsomal systems. Unfortunately, due to their extensive first-pass metabolism and poor oral bioavailability, many of

these compounds have low systemic exposure in humans, meaning that blood levels frequently fall below the concentrations required for the significant CYP inhibition seen *in vitro* (105).

Due to formulation variability, bioavailability limitations, and varying metabolic fates, the translation of many phytochemicals from *in vitro* to *in vivo* is still unclear, underscoring the importance of carefully planned clinical studies (115).

Understanding and monitoring the role and mechanisms of inflammation in CYP450 activity, supported by both theoretical and experimental data, enables appropriate clinical use of CYP450-substrate medications.

Conclusions

Inflammation remains a critical regulator of drug metabolism through its profound impact on CYP450 enzymes. There are two distinct phases of the inflammation: the acute phase, serving as a protective mechanism, and the chronic phase, contributing to pathological tissue degeneration and metabolic dysfunction.

Pro-inflammatory cytokines, particularly TNF-α, IL-1β, and IL-6, are primary mediators that suppress hepatic CYP450 expression through transcriptional and post-transcriptional mechanisms. CYP3A4 contributes to the metabolism of a substantial fraction of marketed drugs (often quoted ~ 30–50% depending on the dataset), and is notably downregulated by inflammation (116). CYP3A4 activity is reduced in association with inflammatory biomarkers in patients, suggesting that inflammation suppresses CYP3A4-mediated metabolism (117).

The concept of phenoconversion highlights how inflammation-induced changes create discrepancies between genotype-predicted and actual drug responses, varying significantly based on inflammation severity and genetic polymorphisms.

Clinical implications are substantial, particularly for elderly populations experiencing chronic low-grade inflammation. The research emphasizes the critical need for inflammation-guided dosing strategies and personalized medicine approaches that integrate inflammatory biomarkers with genetic profiling. Therapeutic opportunities exist through natural compounds such as geniposide, curcumin, and silybin, as well as targeted biologics such as gevokizumab. Future treatment protocols must effectively manage inflammatory conditions while preserving drug metabolism capacity, ensuring both therapeutic efficacy and patient safety in precision medicine.

The field is advancing toward personalized medicine approaches that integrate inflammatory biomarkers with comprehensive genetic profiling. Future research will focus on elucidating CYP isoform-specific responses to different inflammatory conditions, enabling precision medicine strategies that optimize therapeutic efficacy while minimizing adverse effects in inflammatory diseases.

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