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# DRUG-INDUCED LIVER INJURY IN THE CONTEXT OF OSTEOARTHRITIS: A LITERATURE REVIEW

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**Abstract**
Drug-induced liver injury (DILI) is a significant complication in patients undergoing long-term pharmacotherapy, especially those diagnosed with osteoarthritis (OA). OA, one of the most prevalent degenerative joint diseases in the elderly population, often requires chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and adjunctive medications. This review examines the mechanisms, risks, and classifications of DILI, with a focus on commonly used pharmacological agents in OA management. The pathophysiological processes of OA, treatment protocols, and implications of hepatotoxicity are analyzed to improve clinical decision-making and minimize liver-related adverse outcomes.

**Keywords**: Osteoarthritis, drug-induced liver injury, NSAIDs, hepatotoxicity, pharmacotherapy, paracetamol, chondroprotectors.

## Introduction

Drug-induced liver injury (DILI) poses a major clinical challenge, particularly in patients with chronic illnesses necessitating extended pharmacological intervention. Osteoarthritis (OA), prevalent among the elderly, is managed primarily with NSAIDs and analgesics—agents with documented hepatotoxic potential. This literature review explores the interrelationship between OA management and the risk of DILI, highlighting the necessity of evaluating hepatic safety in routine pharmacotherapy [14].

## 1. Clinical Aspects and Treatment of Osteoarthritis

### 1.1 Etiology and Pathogenesis

OA is driven by multifactorial causes including aging, obesity, genetic predisposition, joint injuries, and hormonal factors [5, 11, 12]. Its progression involves cartilage degradation, subchondral bone remodeling, and chronic synovial inflammation, mediated by cytokines such as IL-1 and TNF-α [14]. This inflammatory milieu promotes extracellular matrix breakdown and osteophyte formation [7, 9].



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### 1.2. Classification

OA is classified by its etiology (primary or secondary), clinical form (monoarthritis, oligoarthritis, polyarthritis), joint localization (knees, hips, fingers), and radiological stage. Functional assessment and presence of synovitis further refine disease characterization [6].

### 1.3. Diagnosis

Diagnosis relies on clinical symptoms, radiography, MRI, ultrasound, and exclusion of systemic inflammatory diseases through laboratory testing. Radiographic features include joint space narrowing and osteophyte presence [10, 13].

### 1.4. Pharmacotherapy

NSAIDs remain the mainstay of OA treatment, despite associated risks such as gastrointestinal bleeding and liver injury [14]. Paracetamol is a safer alternative but offers limited efficacy [14]. Chondroprotectors (glucosamine, chondroitin) are widely used, though their benefits are debated [14]. New therapies, including biologics and regenerative approaches, are under investigation [14].

## 2. Mechanisms of Drug-Induced Liver Injury

### 2.1. Direct Hepatotoxicity

Certain drugs exert direct toxic effects on hepatocytes by disrupting organelles and inducing oxidative stress. Paracetamol overdose is a classical example, where NAPQI accumulation causes mitochondrial damage and hepatocyte necrosis [3, 4].

### 1.5. Reactive Metabolites

Liver metabolism can generate reactive intermediates more toxic than the parent drug. This is evident in paracetamol, isoniazid, and methotrexate metabolism. These metabolites bind cellular macromolecules or generate free radicals, resulting in cell death [3, 4].

### 1.6. Immune-Mediated Injury

Drugs may modify hepatocyte antigens, triggering immune recognition and cytotoxic T-cell activation. NSAIDs such as diclofenac are implicated in autoimmune hepatitis via IL-17 and TNF-α mediated inflammation [1].

### 1.7. Role of Cytochrome P450 Enzymes

CYP450 enzymes, particularly CYP2E1 and CYP3A4, are pivotal in drug metabolism. Their induction or inhibition can alter hepatotoxic risk. For instance, rifampicin induces CYP3A4, heightening the toxicity of co-administered drugs, whereas ketoconazole inhibits the same, leading to drug accumulation [2].

## 3. Classification of DILI

Type A: Predictable (Dose-Dependent)

Characterized by short latency, reproducibility, and dose-dependence. Histology often reveals necrosis or steatosis [1].



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Type B: Idiosyncratic (Unpredictable)

Unrelated to dose; presents with variable latency and is influenced by genetic predisposition. Includes hypersensitivity reactions or metabolite-mediated injury [1].

Clinical Subtypes

- Hepatocellular: ALT >2× ULN or ALT/ALP ≥5
- Cholestatic: ALP >2× ULN or ALT/ALP ≤2
- Mixed: ALT >2× ULN with ALT/ALP between 2 and 5

Severity grading follows DILIN criteria ranging from mild enzyme elevation to liver failure or death [1].

## 4. Hepatotoxicity of NSAID

### 4.1. Incidence and Risk Factors

While uncommon, NSAID-induced liver enzyme elevation occurs in 1–15% of users. Diclofenac, particularly in high doses, carries a greater risk. Risk is compounded by age, comorbidities (alcoholism, liver disease), polypharmacy, and genetic factors [1].

### 1.8. Types of Injury

NSAIDs can induce asymptomatic enzyme elevations, acute hepatitis, cholestasis, or autoimmune manifestations. Interactions with other drugs can potentiate toxicity [1].

## Analgesics and Liver Function

### 5.1. Paracetamol Toxicity

Though generally safe, paracetamol poses significant hepatic risk in overdose. The formation of NAPQI, a reactive metabolite, causes oxidative stress and mitochondrial dysfunction. Risk increases with alcohol use, malnutrition, or chronic liver disease [3, 4].

### 1.9. Clinical Presentation and Diagnosis

Symptoms include fatigue, jaundice, and elevated transaminases. Diagnosis involves patient history, lab analysis, imaging, and in some cases, liver biopsy. Early administration of N-acetylcysteine is critical in overdose scenarios [4].

## Glucocorticoids and Chondroprotectors

### 6.1. Glucocorticoids

While effective in inflammation control, long-term use of glucocorticoids like prednisone can lead to non-alcoholic fatty liver disease through lipid accumulation and insulin resistance [14].

### 1.10. Chondroprotectors

Generally considered hepatoprotective or neutral, chondroprotectors may mildly elevate liver enzymes in patients with pre-existing liver conditions. Glucosamine shows antioxidant activity and potential in mitigating liver lipid accumulation [14].



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### Risk Factors and Prevention

Risk of DILI is elevated by age, female sex, obesity, diabetes, alcohol use, polypharmacy, and underlying liver disease. Prevention involves baseline and periodic liver function testing, individualized dosing, and caution in drug combinations. Pharmacogenetic screening and clinical vigilance are crucial [1, 2].

### Diagnosis and Management of DILI

Diagnosis is largely exclusion-based, aided by algorithms (e.g., RUCAM). Biomarkers, autoantibodies, or lymphocyte transformation tests may support specific drug-related diagnoses. Management involves immediate cessation of the causative agent and supportive care. Severe cases may require liver transplantation [1]

### Conclusion

Osteoarthritis treatment frequently involves agents with potential hepatotoxicity. Awareness of DILI risk, proper patient assessment, liver function monitoring, and evidence-based drug selection are vital to reducing adverse hepatic outcomes. Future research should focus on safer therapeutics and personalized medicine strategies for OA patients [14].

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