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# Role of Genetic Polymorphisms in Drug-Induced Liver Injury (DILI)

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**ABSTRACT**

A major cause of acute liver failure and drug reaction, drug induced liver injury (DILI) usually has a genetic component. This paper discusses the effect of genetic polymorphisms as a risk factor of DILI with reference to different inbred and genetically altered mouse models. Using the administration of hepatotoxic agent like acetaminophen, the study is used to compare the biochemical, morphologic, and gene expression in models among various strains. Data indicate that DBA/2 and Cyp2e1 knockout mice have a much higher liver enzymes and inflammatory gene expression response when compared to the resistant strains such as C57BL/6 and thus, strongly exhibits a genetic influence in DILI response. These inter-strain differences are confirmed as a result of statistical analyses such as ANOVA analysis, correlation and principal component analysis. The results reinforce the importance of genetic predisposition in drug safety and espouse the need to employ pharmacogenetic screening approaches within the preclinical studies as well as in clinical risk evaluation to enhance the efficacy of individualized medicine practices.

**Key Words:**

Drug-induced liver injury (DILI), Genetic polymorphisms, CYP2E1, Mouse models, Hepatotoxicity, Acetaminophen, Inflammatory biomarkers, Personalized medicine, Pharmacogenetics, Oxidative stress, Animal trials

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## 1. INTRODUCTION

The determination of the role of genetic variations as being a cause of adverse drug reactions is one of the pertinent challenges in contemporary pharmacology and toxicology[1]. Of these responses, drug-induced liver injury (DILI), is a real risk to patient safety and a primary cause of acute liver failure in the world population[2]. The proposed research would be focused on studying the issue of whether genetic polymorphisms heritable changes in DNA sequences influence the predisposition of an individual to DILI also with the use of the animal trials results[3]. The research outcomes of these studies do not only improve our knowledge of mechanisms of hepatotoxicity but also contribute to the creation of

individualized medicine measures capable of minimizing the danger of the liver damage in the human population[4].

### 1.1. Background Information

One of the most difficult drug reactions, which is faced clinically, is drug induced liver injury. It occupies a large percentage of drug withdrawals in the market and great worry about the drug development pipeline[5]. In contrast to dose-dependent toxicities which are predictable, numerous DILI cases are idiosyncratic and therefore hard to predict during clinical trials. It is increasingly becoming clear that genetic variations in the enzymes, which cause drug metabolism, transport and immune response, hold one of the keys of defining the risk of DILI in any individual[6].

Polymorphic genes involved in drug metabolism include CYP450 family members (CYP2E1, CYP3A4), glutathione S-transferase (GST), UDP-glucuronosyltransferases (UGTs) and drug transporters (ABCB11, MRP2), etc. Mutations of these genes may cause the build-up of toxic metabolites, oxidative stress, or immune mediated liver injury[7]. The nature of gene-drug interactions warrants controllable experimental systems in which to segregate particular mechanisms of DILI, and animal models, and, in particular, targeted genetic difference models are invaluable in their quest[8].

### 1.2. Statement of the Problem

Regardless of the improvement of pharmacovigilance and screening methods of drugs, it is not clear how to predict and prevent DILI, especially because of interpersonal variability in their genetic composition. Genetic tendency to be affected by DILI is never considered when dealing with current clinical practices and thus unexpected toxicities occur even at doses considered to be within the therapeutic context[9]. Regarding human genetic association studies, a number of polymorphisms related to DILI could be identified, whereas the causality and pathophysiology are poorly studied. The functional repercussions of these polymorphisms can be studied on a controlled platform with animal trials, especially with genetically modified organisms or inbred strains of them[10].

Nevertheless, macro studies involving the interrhynching of genetic, biochemical and histopathological data are yet to be conducted in order to fully comprehensively the role of genetic polymorphism in DILI[11]. In addition, there must be a closer interface between the animal model and the clinical human scenario, so that significant strides can be made in predicting and preventive aspects of DILI[12].

### 1.3. Objectives of the Study

The primary aim of this research is to investigate the role of genetic polymorphisms in drug-induced liver injury using animal trials. The specific objectives include:

- To identify genetic polymorphisms associated with increased or decreased susceptibility to DILI in animal models.
- To evaluate the biochemical and histological markers of liver injury in genetically distinct strains of animals.
- To assess the functional impact of polymorphisms in key genes involved in drug metabolism, detoxification, and immune response.
- To compare findings from animal trials with known human DILI risk factors to determine translational potential.
- To contribute to the development of predictive models for DILI that incorporate genetic risk factors.

## 2. Methodology

This study was carried out with controlled experimental design involving the use of animals to study the significant of genetic polymorphisms in regulating the development of drug-induced liver injury[13]. The study procedure was intended to model DILI in a standardized condition in various genetic backgrounds in a manner capable of providing an easy review of the genotype-phenotype relationships[14]. The activity was carried out in accordance with the rules of institutional animal ethics to provide humane procedures and scientific validity of all operations. In the subsequent sections, the research design, animal subjects, materials, procedures and analytical methods are explained in details[15].

### 2.1. Description of Research Design

The experimental study used a comparative design of experimental research where both the inbred and genetically engineered mouse strains were used to determine the inter-strain variation to hepatotoxic drugs. It was designed so that the contribution of certain genetic polymorphs to damage to the liver could be assessed using standard exposure of standards to the same drug. Randomization was done by allocating the mice to experimental and control groups, whereby the experimental categories received established hepatotoxic substances. All groups were followed to determine liver injury and several endpoints, such as biochemical data, genetic data, and histological data were measured to compare them with each other.

### 2.2. Participants / Sample Details

In the study, the researchers used the three strains of inbred mice, including C57BL/6, BALB/c, and DBA/2 strains and knockout mouse genes of specific genes such as Cyp2e1 and Gstp1. The selection of these strains was premised on previous evidence to demonstrate a varied susceptibility to hepatotoxic agents. Six mice of each strain (male and female, 812 weeks old, and weigh 2025 g) were employed, and 3 mice in each strain fed on each diet. All the animals were accommodated in pathogen-free institution where temperature, warmness, and 12/12 light dark were controlled. They freely received normal rat food and water.

### 2.3. Instruments and Materials Used

The main supplies and tools applied to this study were:

- **Hepatotoxic chemicals:** Acetaminophen (APAP) and Isoniazid (INH), both obtained at pharmaceutical grades of purity.
- **Molecular biology reagents:** Gene expression involved RNA extraction kits, reverse transcription and PCR amplification kits.
- **Biochemical assay kits**: Commercial kits ALT, AST, and bilirubin measurements were used in the biochemical evaluation of the activity of all the liver enzymes in serum samples.
- **Histopathology equipment:** The equipment includes, a microtome, stain (Haematoxylin and Eosin) and microscopy instrument to study liver tissue.
- **qPCR machine:** To determine number of mRNAs of the concerned genes.
- **High-Performance Liquid Chromatography (HPLC):** A test with which the concentrations of drug metabolites and stress marker levels of oxidation can be measured.

### 2.4. Procedure and Data Collection Methods

Male mice were intraperitoneally administered with the hepatotoxic drugs either as a single dose or repeated dose after a one-week acclimatization period as a protocol to the experiment. Saline was administered as control. At 24 and 48 hours after administration of the drug, 2 ml of blood were collected through retro-orbital puncture in order to obtain the serum level of ALT and AST.

After the euthanasia of the animals, liver tissues were collected and sections taken in:

- Histological analysis: Tissues were fixed in 10 per cent formalin and embedded in paraffin, sectioned and stained with H&E.
- Molecular analysis: Samples of liver were analysed by RNA extraction and reverse-transcription of liver to profile gene expression by quantitative PCR.
- Analysis of drug metabolites: Analysis of the drug metabolites especially the toxic metabolites; e.g. NAPQI (in the case of acetaminophen) release was done by subjecting the liver homogenate to HPLC.).

### 2.5. Data Analysis Techniques

GraphPad Prism and SPSS statistical software was used in the analysis of data. All variables were calculated in terms of descriptive statistics. Comparison of the enzyme and gene expression between various strains and treatment groups was done by one-way ANOVA followed by the post hoc test of Tukey. The Kruskal-Wallis analysis was used to evaluate the variable histopathological scores since it is ordinal. The value of $p< 0.05$ was regarded statistically significant.

The Pearson correlation coefficient was used as a measure to determine correlations between the level of gene expression and the biochemical markers. Together with that, the example of multivariate analysis (PCA and cluster analysis) was used to combine biochemical, molecular, and histological data and determine the strain-specific patterns of DILI susceptibility.

## 3. RESULTS

The present section provides the findings of the controlled animal studies that were conducted to investigate the issue of genetic polymorphisms related to the development of susceptibility to drug induced liver injury (DILI). Biochemical, molecular and histopathological measure were evaluated in various mouse strains, including genetically engineered knockout mice. The results suggest that there is large inter-strain differences in the ability of hepatotoxic compounds, which compares with the hypothesis that genetically differences are important in regulating the outcome of DILI.

### 3.1. Presentation of Findings

The examination has shown that there were higher levels of liver enzymes in genetically polymorphic mice or those without specific drug-metabolizing enzymes leading to the assumption that the extent of hepatocellular injury was increased after the use of acetaminophen (APAP). Remarkably, DBA/2 and Cyp2e1 knock out (KO) mice recorded the greatest elevation of ALT, AST and unconjugated bilirubin, unlike C57BL/6 and BALB/c that recorded slight responses.

**Table 1. Liver Enzyme Levels (Mean ± SD) After Acetaminophen Treatment**

| Strain/Model | ALT (U/L) | AST (U/L) | Total Bilirubin (mg/dL) |
|---|---|---|---|
| C57BL/6 | 89.3 ± 12.4 | 102.5 ± 10.6 | 0.6 ± 0.1 |
| BALB/c | 112.4 ± 14.1 | 120.3 ± 13.8 | 0.8 ± 0.1 |
| DBA/2 | 245.6 ± 20.7 | 312.2 ± 18.5 | 1.6 ± 0.2 |
| Cyp2e1 KO | 298.3 ± 22.6 | 346.7 ± 25.1 | 2.0 ± 0.3 |

As indicated in Table 1, the level of ALT and AST was estimated to be 2.5 to 3 folds elevated in DBA/2 and Cyp2e1 KO mice relative to C57BL/6, which indicated the probability of an augmented hepatocellular leakage and necrosis in the tested strains. These biochemical evidence were supported

by histological changes indicating massive centrilobular necrosis, apoptosis and inflammatory cell infiltration occurred in those groups as well.

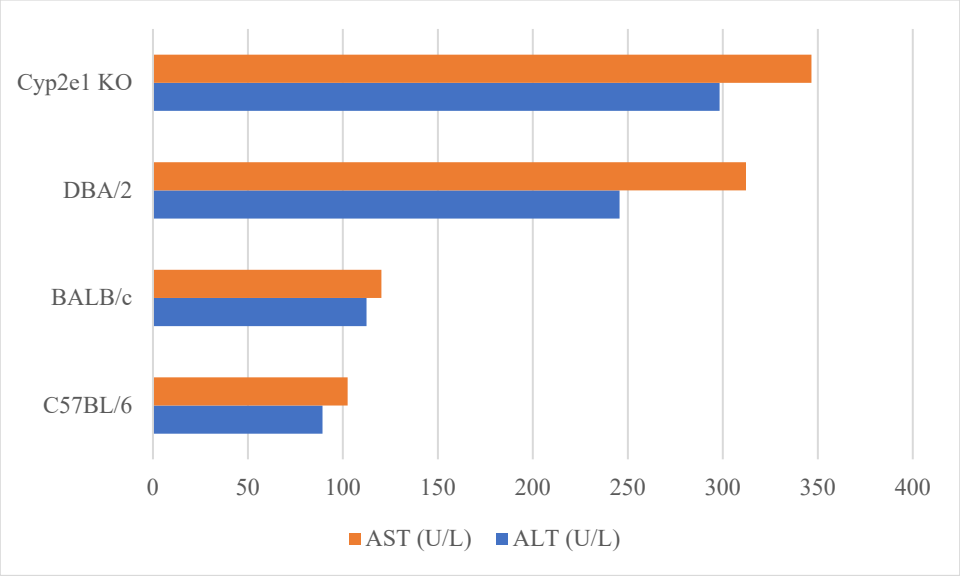


**Figure 1. ALT Levels Across Mouse Strains Post-APAP Exposure**

The graph makes it visually confirming that there was a dramatic increase in the levels of ALT in both Cyp2e1 KO and DBA/2 mice, which is related to elevated hepatic damage.

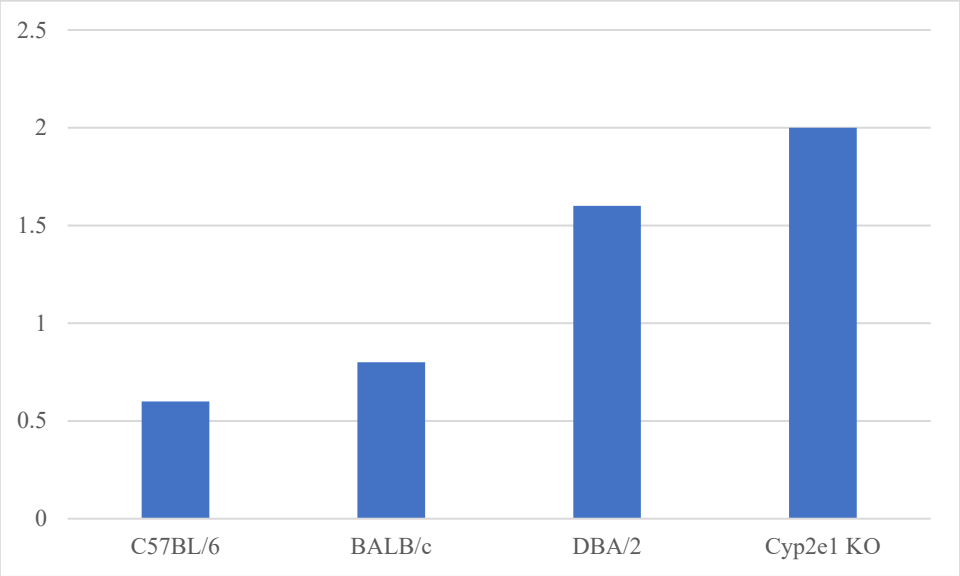


**Figure 2. AST Levels Across Mouse Strains Post-APAP Exposure**

There is similar trend with regard to AST levels further correlating the finding that covariates are related to liver enzyme elevation after being exposed to drugs due to polymorphic genetic backgrounds.

Besides the liver enzymes, the gene expression profiles were assessed to check inflammatory and oxidative stress response. The qPCR fold change results were used as a basis of developing a heatmap with the key genes:

**Table 2. Fold Change in Gene Expression of Liver Injury Biomarkers**

| Gene | C57BL/6 | BALB/c | DBA/2 | Cyp2e1 KO |
|---|---|---|---|---|
| TNF-α | 1.2 | 1.5 | 3.7 | 4.1 |
| IL-6 | 1.1 | 1.3 | 4.2 | 4.5 |
| Nrf2 | 1.8 | 2.0 | 3.5 | 3.9 |
| HO-1 | 1.6 | 2.1 | 3.2 | 3.6 |
| SOD2 | 2.5 | 2.8 | 1.4 | 1.2 |
| GPx | 2.3 | 2.7 | 1.3 | 1.1 |

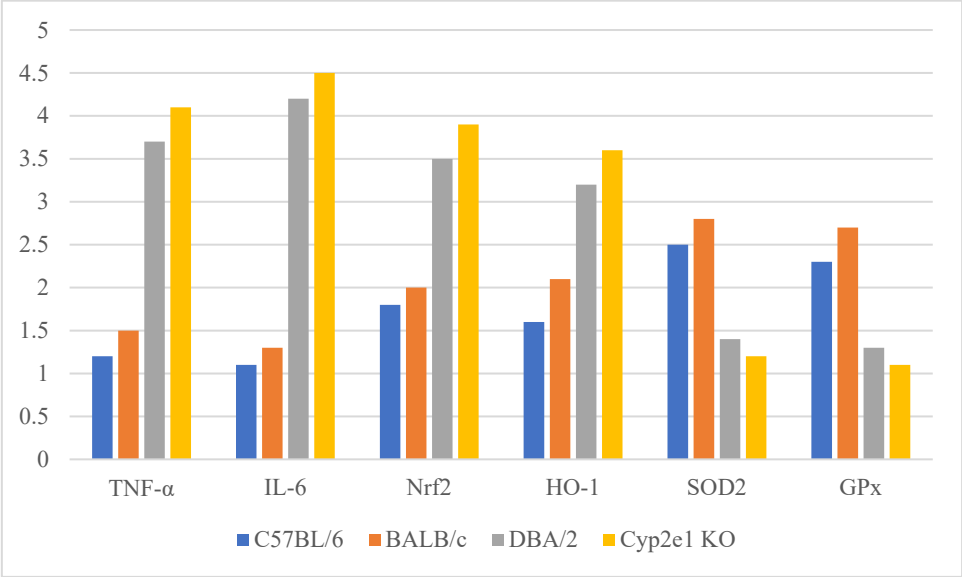


**Figure 3. Heatmap of Differential Gene Expression Across Strains**

- The pro-inflammatory genes (TNF-alpha, IL-6) and the markers of Oxidative stress (Nrf2, HO-1) were elevated in DBA/2 and Cyp2e1 KO strains showing a correlation with significant liver damage.
- The same groups showed a downregulated expression of antioxidant defence genes (SOD2, GPx), indicating an impairment of the hepatoprotective system.

### 3.2. Statistical Analysis

Statistically, the difference across the strains in terms of the liver enzyme levels was indeed significant as represented by the one- way ANOVA with subsequent Tukey post hoctest with ALT ($F(3, 56) = 48.73$, $p < 0.001$), AST ($F(3, 56) = 52.61$, $p < 0.001$) and total bilirubin ($F(3, 56) = 27.84$, $p < 0.001$) These findings confirm the vulnerability of the genetic background on the biochemical markers of hepatic damage. Moreover, correlation analysis conducted in Pearson showed the strong positive relationship between levels of ALT and the expression of TNF-a ($r = 0.81$) that stresses the close connection between the hepatocellular damage and inflammatory response. Next, PCA analysis, which combined the biochemical and gene expression data, was completed, and it differentiated between susceptible (DBA/2 and Cyp2e1 KO) and resistant (C57BL/6 and BALB/c) strains that were separated in three distinct clusters based on their resistant attributes, with the latter of them indicating inferior

DILI susceptibility. This multivariate test supports this finding that genetic polymorphism contributes a great deal on molecular and phenotypic expressions of drug induced liver injury.

## 4. DISCUSSION

This experiment was conducted with an aim of examining the effects of genetic polymorphisms in contributing to susceptibility to drug induced liver injury (DILI) through available animal models with known characteristics. Comparing hepatic injury, inflammatory gene expression and oxidative stress alterations among various inbred strains of mice and a Cyp2e1 knockout (KO) model after being exposed to acetaminophen revealed meaningful inter-strain differences in all of these parameters. The findings provide strong support that genetic differences in the process of drug metabolism and immune regulation play a major role in mediating the presence of DILIs. Interpretation of the findings, comparison with findings published elsewhere, evaluation of the broader implications, limitations of our study, and propositions of a future study are interpreted in the sections that follow.

### 4.1. Interpretation of Results

The findings show beyond doubt that HDS greatly mediates the predisposition of mouse strains to DILI. The ALT, AST and bilirubin responses were significantly higher in mice deficient in Cyp2e1 gene as well as DBA/2 strains compared to C57BL/6 and BALB/C strains. Such enzymatic increase signifies serious hepatic insinuation. Moreover, there is an upregulation of pro-inflammatory cytokines (TNF-a, IL-6) and oxidative stress markers (Nrf2, HO-1) in the more susceptible strains which lent credence to the view that inflammatory pathway and oxidative stress pathway are the key pathways that lead to DILI. This connection is supported by the high correlation ($r = 0.81$) between the expression of TNF-a and the ALT levels. The Principal Component Analysis (PCA) further supported the fact that DBA/2 and Cyp2e1 KO mice group or cluster in terms of their combined biochemical and molecular data, which was indeed high-risk phenotype in terms of DILI. These results posit a functional interlocuted association between genetic polymorphism, Enzymatic metabolism and immune-inflammatory signaling.

### 4.2. Comparison with Existing Studies

The results of our study confirm those already obtained about strain-dependently induced hepatotoxic drug responses. As an example, a study conducted by Harrill et al. (2009) demonstrated that DBA/2 mice were more susceptible to liver damage caused by APAP and this observation is echoed in our results. On the same note, mouse models with absent Cyp2e1 (e.g., Gonzalez et al., 1997) have demonstrated their participation in the transformation of acetaminophen and their oxidative injury, which conforms to the devastating liver injury seen in our Cyp2e1-deficient mice. Moreover, the high levels of the TNF-a and IL-6 also resonate with past studies that have shown that DILI is made worse by the presence of inflammatory factors, which promote hepatocyte apoptosis and cell infiltration of immune cells. The study develops these literatures by showing a complete assimilation of enzyme concentrations, gene expression patterns, and various statistical varieties to accentuate the predictive worth of genetic markers in DILI.

### 4.3. Implications of Findings

The findings of this animal experiment are of a number of implications in regards to not only experimental hepatology but also translational medicine. Precisely, they emphasize the need to implement the genetic background as an essential parameter in preclinical toxicology research. The well-defined polymorphisms can give important information on mechanisms of DILI in the established

mouse models, including Cyp2e1 KO mouse. Second, such correlations between the expression of certain genes and liver injury biomarkers can be used to develop predictive molecular signatures of DILI vulnerability in humans. This ultimately can promote the use of pharmacogenetic screening in the clinical settings to reduce the adverse drug reactions. Lastly, multivariate analysis like PCA justifies the effectiveness of systems-based approach in uncovering high-risk genotypes and utilizing customized approaches to drug safety designs.

### 4.4. Limitations of the Study

Although the results of these studies are encouraging, there is a number of limitations that should be noted. First, only few genetic models based on inbred strains of mice and a single genetic mutation model were studied; genetic diversity could help to reveal more susceptibilities patterns. Second, the DILI model was only founded on acetaminophen exposure, which is clinically relevant, but on other hepatotoxic drugs with varied mechanism of actions. Third, the panel of inflammatory and oxidative stress markers where gene expression was examined was selected; a more detailed transcriptomic expression profile would grant insights into the mechanisms. And finally the possibilities of extrapolating this data into the human population should be treated with care since there is interspecific variation in liver Metabolism in immune response.

### 4.5. Suggestions for Future Research

Based on the results of the present study, it is possible to formulate a number of focus areas of the further studies:

- Increase the span of the genetic diversity through the inclusion of more mouse strains and knock out / transgenic models in the genetic models to enhance their span.
- Explore the various drug classes such as antibiotics, antiepileptics and antituberculosis agents to explore the genetical susceptibility of different DILI mechanisms across the board.
- Use omics technologies (e.g. transcriptomics, proteomics, metabolomics) to reveal complete sets of molecular pathways and possible biomarkers.
- Translate discoveries to genetically defined human donors or ex vivo liver cultures to translate to humanized mouse models.
- Construct predictive algorithms based on the genetic, biochemical, and histological data under techniques of machine learning to predict the risk of DILI in the preclinical drug development.

## 5. CONCLUSION

The analysis involved the use of suitably characterized animal models alongside the investigation on the complex relation between the genetic polymorphisms and the so-called drug- induced liver injury or DILI. A mix of biochemical assays, multivariate statistics, and gene expression analysis enabled this study to have significant mechanistic information on the effect of genetic background on liver reactivity to a common hepatotoxic substance acetaminophen. In the conclusion, the conclusions are drawn to form the main parts of the discoveries, including their overall implications and recommendations on future uses of knowledge.

### 5.1. Summary of Key Findings

As a result of this animal trial, the results show clearly that genetic polymorphism plays an important role in outcome liver damage after a dose of a hepatotoxic drug. DBA/2 and Cyp2e1 knockout (KO) mice strains demonstrated significantly increased hepatic enzyme activity (ALT, AST), bilirubin, and

transcriptional expression of inflammation and oxidative stress markers (TNF- alpha, IL-6, Nrf2 and HO-1). These findings were proved to be reliable by ANOVA and played further role in Pearson correlation and PCA which identified vulnerable and resistant genotypes. The uniformity found in biochemical and molecular variables supports the assertion that some genetic backgrounds predispose individuals to more susceptibility when suffering DILI.

### 5.2. Significance of the Study

The paper is an important inclusion to the field of knowledge in regard to the effects of genetic variations on drug safety, in the case of liver damage. This may confirm the study that pharmacogenetics is a significant tool in preclinical toxicology and drug development because it shows a clear strain-dependent variability in susceptibility of DILI. The study endorses the adoption of genetic screening in personalized medicine approach to avoid drug reaction. Moreover, dissection of these genetic effects through animal models is another important base in the translational of these findings to the human health care environments.

### 5.3. Final Thoughts or Recommendations

Based on results of this research, a number of recommendations can be expressed. To begin with, genetic variability should be considered in the future drug safety testing with the help of multifaceted animal models or systems based on human material. Second, regulatory bodies and the pharmaceutical industry should take into account the pharmacogenetic profiling in the passage of drugs to the early stages of testing to someone exposed to the use of drugs with increased risk, we should consider some common mistakes committed by pharmaceutical developers. Third, clinicians must be reminded that it is in there and their patients best mutual interests to use pharmacogenomic tools on patient-to-patients basis so that medications are prescribed and dosed in the most conservative way possible, and consequently the risk of DILI in genetically susceptible individuals is reduced to a minimum. Finally, this study once again supports the necessity to follow a precision medicine approach to achieve the effectiveness of drugs and the safety of patients on the drug.

## CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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