Pharmacogenetics of isoniazid-induced hepatotoxicity

By Dyah Aryani Perwitasari
Pharmacogenetics of isoniazid-induced hepatotoxicity

Dyah Aryani Perwitasari, Jarir Atthobari & Bob Wilffert

To cite this article: Dyah Aryani Perwitasari, Jarir Atthobari & Bob Wilffert (2015) Pharmacogenetics of isoniazid-induced hepatotoxicity, Drug Metabolism Reviews, 47:2, 222-228, DOI: 10.3109/03602532.2014.984070

To link to this article: http://dx.doi.org/10.3109/03602532.2014.984070

Published online: 19 Nov 2014.

Submit your article to this journal

Article Views: 157

View related articles

View Crossmark data
Pharmacogenetics of isoniazid-induced hepatotoxicity

Dyah Aryani Pervitasari1, Jarir Atthobari2, and Bob Wilffert3,4

1Faculty of Pharmacy, University of Ahmad Dahlan, Yogyakarta, Indonesia, 2Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia, 3Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands, and 4Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Abstract

Tuberculosis is still a major problem in some developed and developing countries. The poor compliance to the treatment of tuberculosis patients due to adverse events was supposed to be an important factor contributing to the high prevalence. This review aims to clarify the role and the pharmacological mechanisms of the genes involved in the isoniazid-induced hepatotoxicity. We selected English articles of studies in human from PubMed up to 27 April 2014 with the keywords: pharmacogenetics, isoniazid and hepatotoxicity, N-acetyltransferase (NAT2), CYP2E1, and glutathione S-transferase (GST). Polymorphisms of NAT2, CYP2E1 and GST1 could increase patients' susceptibility to isoniazid-induced hepatotoxicity. The rapid acetylators of NAT2 and rapid metabolizers of CYP2E1 showed increased concentrations of hepatotoxic metabolites. However, the rapid metabolizers of GST1 could decrease the concentration of hepatotoxic metabolites. Some studies of human leukocyte antigen (HLA) U42, S-domain, and S-transferase (GST) nitric oxide synthase (NOS), Broad complex, Trypsin-like, Erc-a-brac (BTA) and capn collar type of basic region leucine zipper factor family (CNC) homolog (RACH) and Maf basic leucine zipper protein (MOMA) polymorphisms showed their roles in isoniazid-induced hepatotoxicity by modifying the expression of cytokinetic enzymes. A better insight into the role of polymorphisms of HLA, UGT, NOS, RACH and MAF in addition to NAT2, CYP2E1 and GST1 in the hepatotoxicity of isoniazid may support physicians in monitoring patients hepatotoxicity symptoms and laboratory data and optimizing pharmacotherapy. Future studies about the role of such polymorphisms in different ethnicities are suggested.

Keywords

Genetic, hepatotoxicity, oral antituberculosis, polymorphism, tuberculosis

History

Received 3 September 2014
Accepted 31 October 2014
Published online 19 November 2014

Introduction

Tuberculosis is still a major problem in many countries over the world, especially in developing countries (Cai et al., 2012). The “WHO” reported that there were 9 million TB sufferers annually (Anonymous, 2014). Currently, the problem of tuberculosis has become complex with the prevalence of multi-drug-resistant tuberculosis, which reaches 600 000 cases in central Asian countries. One of the causes of the high prevalence of multi-drug-resistant tuberculosis is presumed to be the poor compliance of patients, which reflected the treatment failure (Singla et al., 2014; Soei & Migliori, 2014). The poor patients’ compliance to the first-line treatment for tuberculosis, which are rifampicin, isoniazid, pyrazinamide and ethambutol, could partly be caused by the occurrence of liver injury as adverse event (Babulik et al., 2012; Huang, 2007; Li et al., 2013; Wada, 2001).

Among the oral antituberculosis drugs, isoniazid caused in 15–20% of the patients an increase in alanine and aspartate transaminase, and in about 1% of the patients’ hepatotoxicity was observed (Lee, 1995; Metushi et al., 2011). The hepatotoxicity prevalence due to the isoniazid might be predicted by age, acetylator status, alcohol use and rifampicin use in an additional fashion (Steele et al., 1991). Rifampicin was proposed to stimulate 47 activities of amidase and CYP2E1, thus increasing the isoniazid-induced hepatotoxicity (Huang, 2014; Hussain et al., 2003). Currently, by affecting the isoniazid metabolism, genetic factors are also supposed to play a role in the isoniazid-induced hepatotoxicity (Metushi et al., 2011). Some patient characteristics like age, alcohol use and nutrition status were also general risk factors of antituberculosis-induced hepatotoxicity (Babulik et al., 2012; Roy et al., 2008).

Many reviews show the premeditated isoniazid metabolism pathway (Huang, 2014; Metushi et al., 2011; Roy et al., 2008); however, there is no review about the pharmacological mechanisms of the genes involved in the hepatotoxicity of isoniazid, which could be related to the isoniazid metabolism. The genes mostly examined to understand the association between genetic polymorphism and isoniazid-induced hepatotoxicity are N-acetyltransferase 2 (NAT2), CYP2E1 and glutathione S-transferase 1 (GST1) (Cai et al., 2012; Huang, 2007, 2014; Li et al., 2013; Metushi et al., 2011; Roy et al., 2008; Singla et al., 2014; Steele et al., 1991; Teixeira et al., 2007). Isoniazid is a derivative of hydrazine, which is...
hepatotoxic. There are two metabolites of isoniazid, hydrazine and acetylhydrazine, which are primarily involved in the mechanism of isoniazid-induced hepatotoxicity (Figure 1). The proposed metabolic pathways are the hydrolysis of isoniazid into hydrazine and isonicotinic acid and the acetylation of isoniazid into acetylisoniazid by NAT2. The next role of NAT2 is acetylation of hydrazine into acetylhydrazine (monoacetylhydrazine). Hydrazine and acetylhydrazine are known as toxic agents, thus they should be acetylated into non-toxic agents. Acetylhydrazine is metabolized into reactive acetylated intermediates, which can bind to tissue macromolecules and can cause isoniazid-induced hepatotoxicity (Timbrell et al., 1980). To date, the role of GST in detoxifying the toxic metabolites (Metushi et al., 2011; Roy et al., 2008). To date, the role of human leukocyte antigen (HLA) and superoxide dismutase (SOD) in the isoniazid metabolism is still being explored (Boeser et al., 2014; Du et al., 2013). Some genetic variants could interfere with the activity of the enzymes.

Metushi et al. (2014) found anti-isoniazid antibodies and antibodies against CYP2E1, CYP3A4, and CYP2C9 in patients with isoniazid-induced liver injury. Isoniazid was found to form adducts with CYP2E1, CYP3A4, and CYP2C9. This suggests that the immune system is involved in the isoniazid-induced liver injury. Furthermore, it is suggested that mild cases of isoniazid-induced liver injury resolve with immune tolerance and only when this immune tolerance fails more severe liver injury results.

This review is intended to shed more light on the role and the mechanism of the genes, which seem to be involved in the isoniazid-induced hepatotoxicity. The novelty of our study is that we reviewed pharmacogenomic and genetic variations in antituberculosis-induced hepatotoxicity or liver injury (Huang, 2014; Roy et al., 2008). However, to obtain the articles on the pharmacological mechanism of some genes related to the isoniazid-induced hepatotoxicity, we searched in PubMed with the keywords isoniazid AND pharmacogenetic AND NAT2, isoniazid AND pharmacogenetic AND CYP2E1, isoniazid AND GST, isoniazid AND HLA, isoniazid AND HLA AND pharmacogenetic, isoniazid AND pharmacogenetic AND NAT2 AND CYP2E1 AND GST, isoniazid AND NAT2 AND CYP2E1 AND GST, as well as isoniazid AND polymorphism AND NAT2 AND CYP2E1 AND GST. Figure 2 shows the search strategy for retrieving articles related to the above-mentioned keywords. We limited the search strategy up to May 2014.

Results and discussion

Regarding the search strategy for pharmacogenetics of isoniazid-induced hepatotoxicity, we found eight articles, but we limited the articles to the human species, thus we only retrieved five articles. According to the search strategy of the pharmacological mechanism of some genes related to the isoniazid-induced hepatotoxicity, we found 30 articles related to NAT2 and 25 articles related to human species, 6 articles related to CYP2E1 with 5 articles among them were related to the human species. There were 20 articles related to GST with 7 articles among them related to the human species, 29 articles related to HLA and 3 articles related to the polymorphisms of HLA with 27 and 2 articles among them related to the human species, respectively. Furthermore, it was only 1 review article related to the three genes, 5 articles with 1 review article and 4 articles related to the isoniazid and polymorphisms of the three genes in the human species.

Pharmacological mechanisms of isoniazid-induced hepatotoxicity

In the proposed isoniazid metabolism pathway, NAT2 has a role in the acetylation of isoniazid to acetylisoniazid, which will be hydrolyzed to acetylhydrazine. CYP2E1 oxidizes...
Acetyldihydrazine into toxic agents. These toxic agents are detoxified by GST by conjugation (Huang, 2007). Isoniazid has a role in the imbalance between pro-oxidant and antioxidant activity. It can both stimulate the pro-oxidant level or decrease the level of antioxidant (Boeckstrij & Lee, 2014). The ROS was proposed to be associated with Isoniazid-induced hepatotoxicity by producing the oxidative stress (Bhadauria et al., 2007; Chowdhury et al., 2006). Mechanisms that were proposed were the damage of enzyme by superoxide resulting from molecular oxygen reduction, the inflammatory response of the immune system and the increase of mitochondrial dysfunction (Bhadauria et al., 2010; Boeckstrij & Lee, 2014). With respect to ROS, hydrazine can produce oxygen radicals or superoxide, which can disrupt proteins and cause degradation of polypeptide chains (Timperio et al., 2005). Superoxide was found to be increased along with the isoniazid treatment.

With respect to the mitochondrial activity, isoniazid can translocate cytochrome c from the mitochondrion to the cytosol. This translocation can alter the mitochondrial permeability and start the hepatotoxic pathway in isoniazid treatment (Bhadauria et al., 2010). ROS was also produced in HepG2 cells in which NAT2 and CYP2E1 were expressed. The low expression of HepG2 cells explained the slow alteration of isoniazid into metabolites. This condition led to a high concentration of isoniazid, which means that the risk of occurrence of isoniazid-induced hepatotoxicity is increased (Bhadauria et al., 2010; Brandon et al., 2003). Some of the mitochondrial defects which was discussed could be due to a limited number of carbon-centered reactive intermediates that contribute to the aberrant redox chemistry additional to ROS.

Isoniazid was hydrolyzed into hydrazine and isonicotinic acid. Hydrazine and its derivatives were oxidized by the enzyme systems of cytochrome P-450 (NADPH-dependent hydrazine oxidase) and NADPH-independent hydrazine oxidase (Coomes & Prough, 1983). Cytochrome P-450 and monooxidase oxidize the nitrogen of hydrazine and its derivatives. In addition, cytochrome P-450 also removes nitrogen of monoalkylhydrazines (Erikson & Prough, 1986). In this way, monoalkylhydrazines are converted into hydrocarbon forms with involvement of oxygen and a NADPH-regenerating systems. Monoalkylhydrazines rapidly form monoalkylisazene intermediates leading to the formation of alkane and nitrogen using free radicals (Prough et al., 1969).

With respect to the role of alkane production cytochrome P450 metabolism, it should be mentioned that for iproniazid is shown that reactive metabolites involved in the hepatotoxicity are propylene and propyl (Moloney et al., 1983). These metabolites could be react as GST's substrates, which would increase the toxicity of iproniazid by decreasing the GSH levels and also by the inhibiting GST's function (Spearman et al., 1984).

Furthermore, hydrazine and some derivatives also decreased the function of cytochrome P-540, which was demonstrated by the loss of enzyme activity in the hepatocyte during the preincubation with hydrazine derivatives (Wiebkin et al., 1982).

Related to the oxidative stress, isoniazid not only can produce ROS but also can interfere with glucose-6-phosphate dehydrogenase (G6PD). G6PD can protect the erythrocyte cells from ROS activity. The mechanism of protection is proposed by the regeneration of glutathione from glutathione disulfide. Glutathione can protect the cells from oxidative stress (Bhadauria et al., 2007, 2010). However, hydrazine can decrease the glutathione formation directly and can also reduce the expression of G6PD. This mechanism can alter the antioxidant activity of glutathione (Bhadauria et al., 2007).

Besides the mechanism of PD as antioxidant, SOD, also has antioxidant activity by catalyzing the conversion of superoxide radical anions to hydrogen peroxide (H2O2) (Davies et al., 2013). H2O2 is a strong oxidizing agent that can cause oxidative damage and generate ROS. Isoniazid can diminish the catalase activity of SOD, resulting in the accumulation of H2O2 (Bhadauria et al., 2007).

Besides the role of ROS, the distraction of endogenous metabolism by isoniazid metabolites was proposed to be involved in the isoniazid hepatotoxicity. Hydrazine as a reactive metabolite of isoniazid could react to some endogenous factors. One of this mechanisms was known as the
that the slow acetylator had a higher risk of isoniazid-induced hepatotoxicity than rapid acetylators (Huang et al., 2007; Lee et al., 2010; Singla et al., 2014). The NAT2*2 and is known as the highest activity variant (Cai et al., 2012; 3202a et al., 2013). The other variants of NAT2, such as NAT2*5, NAT2*6 and NAT2*7, are known as decreased activity alleles. The availability of variant alleles, such as two variants of decreased activity alleles, one variant of decreased activity allele and two wild-type could be phenotyped into slow acetylators, intermediate acetylators and rapid acetylators, respectively (Huang, 2007; Roy et al., 2008; Xiang et al., 2014). A study in China showed that most of the patients recruited in the study were intermediate acetylators (37%), followed by slow acetylators (25%) and rapid acetylators (15%) (Xiang et al., 2014). This study is also in accordance with other reviews and studies, which showed that Chinese and Japanese as a part of the Asian ethnicity have a high frequency of intermediate acetylators. However, populations from India showed in most of the patients the slow acetylator genotype (Roy et al., 2008). The high frequency of slow acetylators and intermediate acetylators in the Asian population showed that these populations are more susceptible for isoniazid-induced hepatotoxicity (An et al., 2012; Huang, 2014). There are 36 variants of the NAT2 gene identified in humans, which is the most common SNPs of alpha-tocopherol binding protein (Teixeira et al., 2009; Zang et al., 2007). The polymorphism of the NAT2 gene, the occurrence of isoniazid-induced toxicity will be more.

CYP2E1 oxidizes the acetylhydrazine into toxic agents. Isoniazid and hydrazide could inhibit CYP2E1 activity, and isoniazid could also inhibit the variant of CYP2E1 with a lower activity than the wild type (Roy et al., 2008). The polymorphisms of CYP2E1 were detected by PstI, Rsal and Dral restriction enzymes (Huang et al., 2003). The variant alleles Rsal* and PstI* are translated into c1 and c2. Furthermore, the wild-type of c1, the variants of c2 and the Dral are known as CYP2E1*a1A, CYP2E1*a5 and CYP2E1*a6. These variants showed increased activity (Roy et al., 2008). According to the previous studies, the presence of homozygous *1A/*1A was high in India and less frequent in China. However, variants could increase the individual susceptibility to the isoniazid-induced hepatotoxicity (An et al., 2012; Roy et al., 2008).

GST is encoded by GSTM1, GSTT1 and GSTP1 (Strange et al., 2001). The presence of null homozygous of GSTM1 and GSTT1 may cause decreased enzyme activity thereby decreasing the detoxification of hepatotoxic metabolites. The frequencies of null homozygous of GSTM1 and GSTT1 among the Asian populations were heterogeneous. The frequencies of null homozygous GSTM1 in Chinese, Malaysian and Indians were 35-63%, 62-100% and 20-75%, respectively. However, the frequencies of null homozygous in GSTT1 were 58%, 38% and 3-39% in those particular races (Huang, 2007, 2014; Roy et al., 2008).

The high concentration of ROS due to hydrazine’s activity should be reduced by manganese SOD (MnSOD). It was found that patients heterozygous and homozygous for the variant allele in the 47 position of the MnSOD gene experienced higher risk of an acute hepatitis induced hepatotoxicity (Huang, 2014; Huang et al., 2007).
Table 1. Genetic variations in the metabolism of hepatotoxic metabolites of isoniazid.

<table>
<thead>
<tr>
<th>References</th>
<th>Patients (number and characteristics)</th>
<th>Gene</th>
<th>Gene variations</th>
<th>Phenotype</th>
<th>Possible mechanism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>MAT2</em></td>
<td>*2, *5, *6, <em>7</em></td>
<td>Rapid acetylator</td>
<td>Rapid acetylators can induce the production of hepatotoxic agents, which increased ROS concentration</td>
<td>Increase of the concentration of hepatotoxic agents by acetylation</td>
</tr>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>CYP2E1</em></td>
<td>*1A, *5, <em>6</em></td>
<td>Rapid metabolizers</td>
<td>Rapid metabolizers can induce the production of hepatotoxic agents which increased ROS concentration</td>
<td>Increase of the concentration of hepatotoxic agents by metabolism</td>
</tr>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>GST</em></td>
<td>GSTM1 and GSTT1 null homozygous</td>
<td>Rapid eliminators</td>
<td>Rapid eliminators can quickly eliminate the toxic metabolites</td>
<td>Decrease of the concentration of hepatotoxic agents by elimination</td>
</tr>
<tr>
<td>Chang et al., 2012</td>
<td>98 tuberculosis patients</td>
<td><em>UGT</em></td>
<td>UGT1A</td>
<td>Insertion of TA in UGT1A</td>
<td>The insertion could inhibit bilirubin glucuronidation</td>
<td>Increase of bilirubin glucuronidation</td>
</tr>
<tr>
<td>Sharma et al., 2002</td>
<td>346 tuberculosis patients who were compared to 275 healthy subjects</td>
<td><em>HLA</em></td>
<td>HLA-DQ</td>
<td>Susceptibility in drug-induced hepatotoxicity</td>
<td>Affect the peptide-binding preference and presentation of T cells (Balaramurugan et al., 2004)</td>
<td>Increase of the susceptibility of drug-induced hepatotoxicity</td>
</tr>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>NOS</em></td>
<td>NOS2A</td>
<td>Upregulation of NOS2A</td>
<td>Gain function of iNOS activity</td>
<td>Increase of the production of reactive nitrogen species</td>
</tr>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>BACH</em></td>
<td>CC genotype at n11080344</td>
<td>Expression of genes related to the antioxidant-responsive elements</td>
<td>Heterodimer complex of BACH and small Maf protein down regulates the antioxidant enzyme expression</td>
<td>Increase of the reactive oxygen species</td>
</tr>
<tr>
<td>Nanashima et al., 2012</td>
<td>100 unrelated new diagnosed Japanese tuberculosis patients</td>
<td><em>MAFK</em></td>
<td>Homozygous mutant genotype at rs4720833</td>
<td>Expression of genes related to the antioxidant-responsive elements</td>
<td>Heterodimer complex of small Maf protein and BACH/Nrf 2  will downregulate the antioxidant enzyme expression</td>
<td>Increase/decrease of the reactive oxygen species</td>
</tr>
</tbody>
</table>
Other possible genetic variations mechanisms involve HLA, UDP glucuronosyltransferase (UGT), nitric oxide synthase (NOS), BNB and CNC homolog (BACH) and Maf basic leucine zipper protein (MAFK). The last three enzymes are supposed to be involved in the antioxidative activity, and HLA is involved in the immunological reaction (Huang, 2014; Nanashima et al., 2012).

The principal product of heme catalysis, bilirubin, is eliminated by a conjugation reaction with glucuronic acid. The glucuronidation reaction is mediated by UGT. Currently, there are 15 isoforms of UGT in human, and 8 of these are encoded by UGT1A. An increase of bilirubin was supposed to be related with the insertion of TA in the UGT1A, which encodes UGT1A1. This insertion inhibits the bilirubin glucuronidation (Zucker et al., 2001). In the Taiwan population, it was shown that the variants of UGT1A were associated with antituberculosis-induced hepatotoxicity (Chang et al., 2012).

The high concentration of ROS should be eliminated by enzymes like GST, NQO1 (NADPH dehydrogenase quinone) and heme oxygenase. The activation of these enzymes must be supported by the mechanisms of antioxidation and repression of antioxidative pathways. These mechanisms will support the transcriptional regulation of antioxidative enzymes (Nanashima et al., 2012). During high concentrations of ROS, MAFAK can associate with antioxidant-responsive elements (ARE), which allows the antioxidant enzymes expression. On the contrary, the association of BACH with ARE prevents the association between MAFAK and ARE and results in the repression of antioxidative enzymes (Nanashima et al., 2012; Ovake et al., 1996). NO is one of the reactive nitrogen species, which is produced by NOS. If NOS is available in the cells, the inducible isoform of NOS (iNOS) will be upregulated. iNOS is encoded by NOS2A, therefore by this mechanism the increased activity of the NO2A variant could result in the overproduction of NO (Jacobske et al., 2003; Nanashima et al., 2012).

In the Japanese population, it was shown that the CC genotype of rs11080344 in NOS2A, and the CC genotype at rs11080344 in BACH1, and the heterozygous and homozygous mutant genotype at rs4720833 in MAFAK were associated with the occurrence of antituberculosis drugs-induced hepatotoxicity (Nanashima et al., 2012).

HLA is possibly involved in the resistance or susceptibility to tuberculosis. It is responsible for the presentation to T cells which initiate the protective immune response. It was shown that the high frequency of HLA class I could influence the TB treatment outcome. Its mechanism could be related with recognizing the common epitope in the peptide-binding and regulating NK cells activity (Balanamuran et al., 2004).

One study showed that the presence of DQB1*0201 and the absence of HLA-DQA1*0102 are risk factors for drug-induced hepatotoxicity (Sharma et al., 2002).

Conclusion

Many studies showed that polymorphisms of NAT2, CYP2E1 and GST1 could influence the concentration of hepatotoxic isoniazid metabolites in the blood. Some of the gene polymorphisms of HLA, UGT, NOS, BACH and MAFAK are supposed to contribute to isoniazid-induced hepatotoxicity by modifying the antioxidant enzyme expression. However, the studies which explored this mechanism are still limited. A better insight into the role of polymorphisms in the hepatotoxicity of isoniazid may support physicians in monitoring patients hepatotoxicity symptoms and laboratory data and optimizing pharmacotherapy. Future studies about the role of such polymorphisms in different ethnicities are suggested.

Declaration of interest

All authors have no conflict of interest.

References


oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. J Hepatol 47:128-134.


Pharmacogenetics of isoniazid-induced hepatotoxicity

ORIGINALITY REPORT

12%

SIMILARITY INDEX

PRIMARY SOURCES

1. [www.medicine.wisc.edu](http://www.medicine.wisc.edu) (Internet) - 57 words — 1%

2. [eprints.whiterose.ac.uk](http://eprints.whiterose.ac.uk) (Internet) - 25 words — 1%

3. [jnm.snmjournals.org](http://jnm.snmjournals.org) (Internet) - 21 words — 1%


6. [onlinelibrary.wiley.com](http://onlinelibrary.wiley.com) (Internet) - 14 words — < 1%

7. Chen, Ru, Jing Wang, Yuan Zhang, Shaowen Tang, and Siyan Zhan. "Key factors of susceptibility to anti-tuberculosis drug-induced hepatotoxicity", Archives of Toxicology, 2015. Crossref
<table>
<thead>
<tr>
<th></th>
<th>Citation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Pessayre, Dominique, Bernard Fromenty, Alain Berson, Marie-Anne Robin, Philippe Lettéron, Richard Moreau, and Abdellah Mansouri. &quot;Central role of mitochondria in drug-induced liver injury&quot;, Drug Metabolism Reviews, 2012. Crossref</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>9</td>
<td>Shen, C.. &quot;Isoniazid-induced hepatotoxicity in rat hepatocytes of gel entrapment culture&quot;, Toxicology Letters, 20061101 Crossref</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>10</td>
<td>en.wikipedia.org Internet</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>13</td>
<td><a href="http://www.dovepress.com">www.dovepress.com</a> Internet</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>14</td>
<td>Verma, Mukesh, and Hirendra Banerjee. &quot;Metabolomic Approaches in Cancer Epidemiology&quot;, Diseases, 2015. Crossref</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>15</td>
<td>eprints.kingston.ac.uk Internet</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>16</td>
<td>Mihaylova, Violeta, Velina Guergueltcheva, Sylvia Cherninkova, Luchezar Penev, Galina Georgieva, Katya Stoyanova, Albenaa Todorova, and Ivaylo Tournev. &quot;Possible Toxicity of Tuberculostatic Agents in a Patient With a</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>ID</td>
<td>URL</td>
<td>Title</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>18</td>
<td><a href="http://www.ijper.org">www.ijper.org</a></td>
<td>Gao, Xin, Hengyan Qu, Chun-Zhi Ai, Yun-Feng Cao. &quot;Regulation profile of phosphatidylcholines (PCs) and lysophosphatidylcholines (LPCs) components towards UDP-glucuronosyltransferases (UGTs) isoforms&quot;, Xenobiotica, 2015.</td>
</tr>
<tr>
<td>19</td>
<td>science.utep.edu</td>
<td>Ganguly, Nirmal Kumar, and Gautam Kumar Saha. &quot;Pharmacogenomics and Personalized Medicine for Infectious Diseases&quot;, Omics for Personalized Medicine, 2013.</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Zhai, Q.. &quot;Oxidative stress potentiated by diallylsulfide, a selective CYP2E1 inhibitor, in isoniazid toxic effect on rat primary hepatocytes&quot;, Toxicology Letters, 20081215</td>
</tr>
<tr>
<td></td>
<td>Author(s)</td>
<td>Title</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>25</td>
<td>Masubuchi, Y.</td>
<td>&quot;Involvement of mitochondrial permeability transition in acetaminophen-induced liver injury in mice&quot;</td>
</tr>
<tr>
<td>30</td>
<td>David W. Haas.</td>
<td>&quot;Pharmacogenomics of antiretroviral therapy&quot;</td>
</tr>
<tr>
<td>31</td>
<td>Teixeira, R.L.F.</td>
<td>&quot;Genetic profile of the arylamine N-acetyltransferase 2 coding gene among individuals from two different regions of Brazil&quot;</td>
</tr>
<tr>
<td>32</td>
<td>Jean, P C Kengne, M Nji Akindeh, M Ali Innocent, Olivia, M Aristid</td>
<td></td>
</tr>
</tbody>
</table>
Ekollo, and F Mbacham Wilfred. "Predominance of N-acetyl transferase 2 slow acetylator alleles in children less than ten years experiencing adverse treatment events following artemisinin-based combination therapy in North and South West Regions of Cameroon", AFRICAN JOURNAL OF BIOTECHNOLOGY, 2016.


"Patent Issued for Low Side Effect Pharmaceutical Composition Containing Isoniazid.", Drug Week, Nov 23 2012 Issue


Guruprasad P. Aithal. "Hepatic ADRs", Pharmacovigilance, 01/01/2006


