

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/etap](http://www.elsevier.com/locate/etap)

## Review

# Models of hepatotoxicity and the underlying cellular, biochemical and immunological mechanism(s): A critical discussion



Deepa K. Ingawale<sup>a</sup>, Satish K. Mandlik<sup>b</sup>, Suresh R. Naik<sup>a,\*</sup>

<sup>a</sup> *Sinhgad Technical Education Society's, Sinhgad Institute of Pharmaceutical Sciences, S. No. 309/310, Off Mumbai-Pune Expressway, Kusgaon (Bk.), Lonavala, Pune 410 401, Maharashtra, India*

<sup>b</sup> *Sinhgad College of Pharmacy, S. No. 44/1, Vadgaon (Bk.), Off Sinhgad Road, Pune 411 041, Maharashtra, India*

## ARTICLE INFO

## Article history:

Received 24 April 2013

Received in revised form

27 August 2013

Accepted 31 August 2013

Available online 21 November 2013

## Keywords:

Hepatotoxic agents

Models of hepatotoxicity

Hepatotoxicity risk factors

Cytochrome P<sub>450</sub>

Oxidative stress

Biochemical and cellular markers

## ABSTRACT

Liver is a primary organ involved in biotransformation of food and drugs. Hepatic diseases are a major worldwide problem. Hepatic disorders are mainly caused by toxic chemicals (alcohol), xenobiotics (carbon tetrachloride, chlorinated hydrocarbons and gases CO<sub>2</sub> and O<sub>2</sub>) anticancer (azathioprine, doxorubicin, cisplatin), immunosuppressant (cyclosporine), analgesic anti-inflammatory (paracetamol, thioacetamide), anti-tubercular (isoniazid, rifampicin) drugs, biologicals (Bacillus-Calmette-Guerin vaccine), radiations (gamma radiations), heavy metals (cadmium, arsenic), mycotoxin (aflatoxin), galactosamine, lipopolysaccharides, etc. Various risk factors for hepatic injury include concomitant hepatic diseases, age, gender, alcoholism, nutrition and genetic polymorphisms of cytochrome P<sub>450</sub> enzymes have also been emphasized.

The present review enumerates various *in vivo* animal models and *in vitro* methods of hepatic injury using diverse toxicants, their probable metabolic pathways, and numerous biochemical changes viz. serum biomarkers enzymes, liver function, oxidative stress associated events like free radicals formation, lipid peroxidation, enzyme antioxidants and participation of cytokines (tumour necrosis factor- $\alpha$ , transforming growth factor- $\beta$ , tumour necrosis factor-related apoptosis inducing ligand), and other biomolecules (Fas and C-jun N-terminal kinase) are also discussed. The underlying cellular, molecular, immunological, and biochemical mechanism(s) of action responsible for liver damage (toxicity) are also been discussed. This review should be immensely useful for researchers especially for phytochemists, pharmacologists and toxicologists working on hepatotoxicity, hepatotoxic chemicals and drugs, hepatoprotective agents and drug research organizations involved especially in phytopharmaceuticals and other natural products.

© 2013 Published by Elsevier B.V.

\* Corresponding author. Tel.: +91 9960977198; fax: +91 02114 270258.

E-mail address: [srnaik5@rediffmail.com](mailto:srnaik5@rediffmail.com) (S.R. Naik).

1382-6689/\$ – see front matter © 2013 Published by Elsevier B.V.

<http://dx.doi.org/10.1016/j.etap.2013.08.015>

## Contents

1. Introduction	120
1.1. Risk factors for hepatotoxicity	120
1.1.1. Age	120
1.1.2. Gender	120
1.1.3. Concomitant medication	120
1.1.4. Nutrition	120
1.1.5. Alcohol	120
1.1.6. Hepatitis B and hepatitis C	120
1.1.7. Genetic factors	120
1.1.8. Drug dose and varied adverse triggering factors	120
1.1.9. Non steroidal anti-inflammatory drugs (NSAIDs)	120
2. Experimental models of hepatotoxicity	121
2.1. Chemical induced hepatotoxicity	121
2.1.1. Alcohol	121
2.1.2. CCl <sub>4</sub>	121
2.1.3. D-Galactosamine and lipopolysaccharides	121
2.2. Drug induced hepatotoxicity	121
2.2.1. Paracetamol	121
2.2.2. Thioacetamide	122
2.2.3. Azathioprine	122
2.2.4. Doxorubicin	122
2.2.5. Cyclosporine-A	122
2.2.6. Anti-tubercular drug	122
2.2.7. Cisplatin	122
2.3. Heavy metal induced hepatotoxicity	122
2.3.1. Cadmium	122
2.3.2. Arsenic	122
2.4. Other models of hepatotoxicity	123
2.4.1. Bile duct ligation	123
2.4.2. Aflatoxin B <sub>1</sub>	123
2.4.3. Gamma radiation	123
2.4.4. Xenobiotics	123
2.4.5. Bacillus-Calmette–Guerin–lipopolysaccharide	123
3. Hepatotoxicity evaluation model (in vitro)	124
3.1. Isolated liver cell model (Bakala et al., 2003)	124
3.2. Isolated perfused organs (Carraro et al., 2007)	124
3.3. Liver slices studies (Mukazayire et al., 2010)	124
4. Cellular, molecular, biochemical and immunological alterations in hepatic damage	124
4.1. Cellular alterations	124
4.1.1. Mitochondria	124
4.1.2. Lysosomes	125
4.1.3. Endoplasmic reticulum	125
4.1.4. Lipid peroxidation	125
4.1.5. Oxidative stress	125
4.1.6. Disturbance of calcium homeostasis	126
4.2. Molecular alterations during hepatic damage and their relevance	126
4.2.1. Cytokines	126
4.2.2. Tumour necrosis factor alpha	126
4.2.3. Tumour necrosis factor-related apoptosis inducing ligand (TRAIL)	126
4.2.4. C-jun N-terminal kinase (JNK)	126
4.2.5. Fas	127
4.3. Immunobiological alterations	127
4.3.1. Osteopontin (OPN)	127
4.4. Biochemical alterations	127
5. Conclusion	128
Appendix A. Supplementary data	128
References	128

Download English Version:

<https://daneshyari.com/en/article/2583969>

Download Persian Version:

<https://daneshyari.com/article/2583969>

[Daneshyari.com](https://daneshyari.com)