Nuclear Factor Erythroid-2 Linked Factor (Nrf2) as a Potential Mediator of Hepatotoxicity
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Abstract:
Hepatotoxicity is a term used to describe serious health complications of liver disease caused by a variety of factors. Nuclear factor erythroid-2 linked factor (Nrf2) as a potential mediator of hepatotoxicity via inflammatory and induction of oxidative stress, oxidation produces more toxic compounds caused more pathogenic cases; therefore, to maintain sufficient homeostasis, involve antioxidant materials and detoxification factors. Controlling cytokine activity in normal cells is a useful way to regulate the signaling pathway of Nrf2. Recent studies found a relation between each Nrf2 and NF-κB activation and drug-induced liver injury. This review presents a detailed and conformation update of Nrf2 roles in hepatotoxicity which considers that drug-induced liver injury is the main problem to draw attention in medical clinics and to develop new drugs with less harmful to the liver. In addition to that. Kept each of normal oxidation and cytokines levels is crucial responses for cells alteration and remaining to survive.

Key words: Nrf2, Hepatotoxicity, drug-induced liver injury.

Background
Nrf2-Keap1 Signaling Pathway
Nrf2-Keap1 is a protein responsible of transcribed and regulating the Nuclear factor erythroid-2 linked factor (Nrf2) expression, it is found in the cytoplasm and accumulates in the nucleus, where it functions as a transcription activator released by Keap1, belongs to the family of a transcription

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factor called Cap'n'collar (CNC), which
divided into seven domain (Neh1-Neh7)
(Figure-1), the N-terminal domains
influenced the stabilities and predominant
of Nrf2 by Keap1 binding, while the Neh5
domains are managing the localization of
cytoplasm for Nrf2’s transcription and
regulation Nrf2 expression [1]

![Figure (1): A surface presentation of the Kelch domain (carton) with peptide from Neh2 domain of Nrf2[1]](image)
Kelch repeats, on the other hand, are
responsible for accelerating the binding of
Keap1’s to p62 and Nrf2, as shown in
Figure 2. [2]

![Figure (2): Mediator associated the binding of Keap1 to protein (p62) and Nrf2[2]](image)

Hepatotoxicity produces by different
mechanisms.
One of the most remarkable biomarkers of
hepatic injury is lipid peroxidation since
certain hepatotoxicants need metabolic
activation to generate reactive
intermediates involved in liver disease [3]
therefore activated or induced by certain
genes involved antioxidant protection is very
necessary, glutathione (GSH) system is the
most essential process that defends against
hepatotoxicity [3] and oxidative stress [4].
Nrf2 acts as an important part of this
process. [5].
Also, the complication of liver injury is characterized by exacerbating inflammatory responses such as cytokine and chemokine production, as well as changes in the extracellular matrix composition. Excessive levels of reactive oxygen species are more harmful to cells; it involves molecules that have unpaired electrons obtained from the reduction of oxygen which is unstable and become more reactive when reacted with adjacent molecules. Superoxide radicals, hydroxyl radicals, and peroxy radicals are examples of oxygen-centered radicals, while H2O2 and singlet oxygen are examples of oxygen-centered non-radicals.

Antioxidants are substances that delay or prevent free radicals from damaging the cell by scavenging reactive oxygen species, the human system has a variety of process ways to combat oxidative stress. Oxidation and cytokines are survival responses to adverse drug reactions that are dependent on an active transcription factor (Nrf2). Tumour necrosis factor (TNFα) mediates intracellular signaling through activating the Nuclear Factor Kappa B (NF-κB) transcription factors. (Nrf2) mediates oxidation responses and death receptors signaling.

Drugs induce liver injury to activate TNF-α which mediates NF-κB signaling. Nrf2 enhances the effect of the TNFα signal pathway as synergistic toward oxidative which amplified TNFα sensitization. All these mediators are part of some important physiological functions like the signal transduction pathway and protect microorganisms (neutrophil, eosinophil, and macrophage) during inflammations. Inflammation can be classified as either acute or chronic. Acute inflammations describe the rapid response of innate immune components to a challenge.

The role of Nrf2 overexpression on liver enzymes
Hepatocellular toxicities markers, such as increased levels of aspartate and alanine transaminase (AST, ALT) or total bilirubin, are associated with suppression of (NF-κB) activation by intrinsic hepatotoxicity drugs that stimulate the (Nrf2) response and sensitize toward Tumour necrosis factor (TNFα) which induce cytotoxicity. Although elevated liver enzymes can reflect glutathione depletion, lipid peroxidation, and increase production of reactive oxygen species, increased levels of Alanine Aminotransferase enzyme upon normal ranges related to acute hepatocellular injury can lead to liver failure. Tissue distribution of Nrf2 is in kidneys, muscles, lungs, heart, liver, and brain, Nrf2 expressions in high concentrations in these sites add them to show the tissue distribution in tumor overexpression of Nrf2 induced 6-phosphogluconate dehydrogenase and glucose -6-phosphate dehydrogenase which involve stimulating cell proliferation. Furthermore, promote Nrf2 associate with increased levels of hepatocellular carcinoma and metastasis.

Respective pathology
Genetic pathways of Nrf2 can demonstrate via de novo malignant tumor that similar to the mechanism of atherosclerosis which involve synthesis in the liver.

Therapeutic Strategies
Drug-induced liver injury increases levels of (Nrf2) targeting usually correlate with Nuclear Factor Kappa B (NF-κB) such as diclofenac, carbamazepine, and ketoconazole, making people more sensitive to TNF-mediated cytotoxicity. The hepatocyte has a complex protection mechanism against damage, one of which is the antioxidant enzyme such as Superoxide dismutase.

Most drugs derived from plants like turmeric, resveratrol, and plant pigment quercetin, as well as synthetic compounds like Esbriet (pirfenidone) and oltipraz, may be an excellent choice for treating oxidative diseases.
studies have shown the abilities of these drugs to prevent liver injury. [21-23]

**Conclusion**
This review showed that Nuclear Factor Erythroid-2 Linked Factor (Nrf2) has a strong role in hepatotoxicity which considers drug-induced liver injury.

**Recommendation**
Because of the significant potential function of the (Nrf2) transcription factor, further clinical trials are required to investigate the impact of (Nrf2) as a potential mediator of hepatotoxicity.

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**References**
4- Tang, W. Jiang, Y.F. Ponnumasy, M.; Diallo, M. Role of Nrf2 in chronic liver disease. World J. Gastroenterol. 2014; 20: 13079–13087
8- Bram Herpers, Steven Wink, Lisa Fredriksson . Activation of the Nrf2 response by intrinsic hepatotoxic drugs correlates with suppression of NF-κB activation and sensitizes toward TNFα-induced cytotoxicity. Archives of Toxicology volume. 3016; 90:1163–1179.