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Methotrexate Induced Hepatotoxicity and its Management

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Abstract: ***Liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Commonly used drugs such as anti cancer drugs, certain antibiotics, antituberculer agents, paracetamol and various other toxic chemicals such as carbon tetrachloride (CCL_4), thioacetamide (TAA), excessive alcohol consumption, arsenic and microbes reported to cause hepatotoxicity. In addition to this, genetics, metabolism and immunology also played important role in hepatotoxicity. Methotrexate is commonly used as anticancer and immunosuppressant drug. Its major side effects are bone marrow depression and hepatotoxicity. In the present review, we discuss about the mechanism of methotrexate induced hepatotoxicity and its herbal based treatment. Mechanism of methotrexate induced hepatotoxicity includes oxidative stress which increase the generation of reactive oxygen (ROS) and nitrogen species, inhibits cytosolic NADP-dependent dehydrogenase and NADP malic enzyme, which reduce the levels of glutathion, superoxide dismutase, catalase and ultimately reducing the effectivity of the antioxidant defence system protecting the cell against ROS. Herbal medicines may serve as a vital source of potentially useful for the development of effective therapy to combat a variety of liver problems. Developing a satisfactory herbal therapy to treat severe liver diseases requires systematic investigation of properties like anti-hepatotoxicity and stimulation of liver regeneration.***

Keywords: Hepatotoxicity; Methotrexate; Mechanism; Hepatoprotective Plants

1. Introduction

Liver is considered to be one of the most vital organs that functions as a centre of metabolism for nutrients such as proteins, carbohydrates and lipids with excretion of waste metabolites. It also carries out the metabolism, fight against disease, nutrient supply, energy provision and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them [1]. As we know that, liver can metabolizes xenobiotics which can leads to the drug-induced liver injury (DILI) and is a potential complication of many drugs. DILI broadly classified into two types: intrinsic and idiosyncratic types; intrinsic DILI generally is dose-dependent and predictable (eg,acetaminophen toxicity), whereas idiosyncratic DILI is unpredictable and does not depend directly on dose [2]. Liver injury is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies [3]. The rate of hepatotoxicity has been reported to be much higher in developing countries like India (8% - 30%) compared to that in advanced countries (2% - 3%) with a similar dose schedule [4]. Drug induced liver injury is one of the main reason of withdrawal of many drugs from the market and most of the time severe case of liver dysfunction required liver transplant or some time death [5]. Mechanism of hepatotoxicity can be investigated through mitochondrial dysfunction and DNA damage [6]. This imperial function caused by drug itself or its cytochrome P450 mediated metabolite. Recent reports on hepatotoxicity suggest that suggest that oxidative stress, microvacular steatosis, imbalance energy storage are major outcome of mitochondrial dysfunction [7].

2. Risk Factors of Hepatotoxicity

Different risk factors which lead to hepatotoxicity like genetic, non genetic or environmental etc [8]. In addition to this, there are number of drugs whose metabolites leads to liver injury i.e. anticancer drug, antiretroviral drug, alcohol and certain health condition such as age, sex, and diseases eg. TB, HIV are coupled with each other. Some recent research on hepatic injury shown that the risk of hepatotoxicity is increased in various diseased conditions like HIV,diabetic or tuberculosis, cancerous patients [9].

A. Genetic factors

Drug-induced liver injuries (DILI) with different genetic traits and studies conducted till date are hypothesis-driven only. Genetic variations in thioredoxin reductase 1 gene leads to DILI. Moreover, changes in the activity of drug metabolizing phase - I enzyme such as CYPS3A, CYP2C9 and CYP2C19 lead to pathogenesis of DILI [10].

In addition to this polymorphism of bioactivities pathway through phase II enzyme i.e. CYP450, detoxification reactions and excretion/transport reaction together with immunological factors i.e. HLA class II antigen, cytokines are major genetic factors which can leads to hepatotoxicity [11].

B. Non -genetic factors

Different environmental and others host factors like age, drug dose ,gender, alcohol abuse and some disease condition like cancer, HIV also associate with hepatotoxicity. Age is an important risk factor for hepatotoxicity such as use of aspirin in younger age increase risk to liver injury. Women and men have different susceptibility for drug induced hepatotoxicity. For example according to Hyman and Zimmermanin in 1978 women are more susceptible for drugs like isoniazid, nitrofurantoin, chlorpromazine etc where as men are mostly affected azathioperine induced hepatotoxicity [9]. Obesity is also responsible for liver injury. Acute and chronic alcohol consumption is also one of the important causes of liver injury. Some disease condition like HIV tuberculosis, Hepatitis B and C associate disease always increase of liver injury [12].

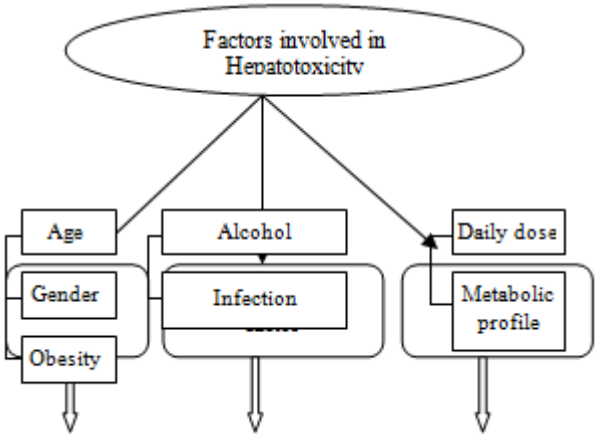

Figure 1: Non genetic factors that involved in hepatotoxicity

3. Methotrexate Induced Hepatotoxicity

Methotrexate is a folic acid antagonist, widely used as a chemotherapeutic agent in the treatment of various cancerous stages such as acute lymphoblastic leukaemia and in the treatment of various inflammatory diseases [13]. It is also used for the treatment of multiple sclerosis, dermatomyositis, sarcoidosis, psoriasis, and rheumatoid arthritis, disorders causing inflammation. Its side effects include hypersensitivity pneumonia, central and peripheral nervous system toxicity, liver and gastrointestinal system dysfunctions, and hematologic failure [14]. MTX exerts its primary toxic effects against the rapidly replicating cells of the bone marrow and gastrointestinal epithelium producing leucopoenia and thrombocytopenia. Both low and high-dose therapy can cause hepatotoxicity. Methotrexate at very low dosage affects the liver and causes changes in histology of liver. Other frequently reported adverse toxic effects are malaise, nausea, vomiting, diarrhoea, headache, mild alopecia and fever. Low dose therapy produces a different type of hepatotoxicity which includes cirrhosis. Long term administration of the same causes anaemia. Kidney damage is a frequent complication of high-dose therapy. High-dose therapy results in elevated liver enzymes. However, the use of high-dose methotrexate (as in leukaemia) or prolonged use may result in hepatotoxicity that may lead to progressive fibrosis and cirrhosis. Methotrexate seems to be hepatotoxic, nephrotoxic and toxic to respiratory and reproductive system at very low doses for continuous therapy [15]. On the other hand, substantial evidence supports the concept that MTX was mutagenic and carcinogenic in animals, and the efficacy of this compound is often limited by its severe hepatotoxicity [16].Toxic side effects of methotrexate have been demonstrated in various animals including rat, mice, rabbit and dog. Clinically, hepatotoxicity, which occurs in long-term use of methotrexate, remains one of the significant restrictions on its use in the doses desired. The inhibition of tetrahydrofolate formation is responsible for both the therapeutic and toxic effects of methotrexate. Although these deleterious toxic effects of methotrexate can theoretically be reduced or prevented with the addition of folic acid to the treatment. On the contrary, there are studies showing that with the addition of folic acid, the therapeutic effectiveness of methotrexate decreases [17]. MTX induced toxicity appears to be a consequence of the interaction of many factors that includes the dosing schedule, length of treatment, patient risk factors, type of disease, and the presence of genetic and molecular apoptotic factors.

4. Mechanism of Methotrexate Induced Hepatotoxicity

MTX has been shown to lead to a reduction in methionine synthesis, antioxidant enzymes such as catalase, glutathione peroxidase, superoxide dismutase and a decrease of SAM (S-adenosyl methionine) in cerebrospinal fluid of patients on MTX treatment. Due to its antioxidant effects, a deficiency of SAM caused by MTX may be a reason for increased reactive oxygen species (ROS). Effects of MTX are partly due to its direct toxicity by increasing ROS production. Altered balance between ROS production and antioxidant defenses leads to the “oxidative stress” and could be lead to various pathological conditions [13]. The mechanisms of MTX hepatotoxicity could be related to the cellular pathway of the drug [18].Methotrexate enters the stellate cell bound to folate trasporter 1 and is pumped out by the ATP-binding cassette (ABC) family of transporters. Methotrexate is retained within the cell as a polyglutamate that inhibits dihydrofolate reductase(DHFR T’ase, thymidylate synthase(TS) and AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) transformylase, leading to impaired pyrimidine and purine synthesis.

Moreover, methotrexate indirectly affects MTHFR (methylene-tetrahydro folate reductase) and hence the generation of methionine from homocysteine. Excess homocysteine can generate oxidative stress or sensitize the cell to its cytotoxic effects. Homocysteine has been shown to induce endoplasmic reticulum (ER) stress, which when unresolved, leads to fatty infiltration of the liver. In addition to this, it can also activate proinflammatory cytokines. The combination of these insults could contribute to the activation of hepatic stellate cells, which leads to liver fibrosis [19, 20]. Lipid peroxidation plays an essential role in damage to the cell membrane through reactive oxygen radicals. In experimental studies, MTX toxicity has been shown to increase malondialdehyde (MDA), an important index of lipid peroxidation, and this increase has been shown to be suppressed by antioxidant therapies [21, 22].So it consider a good marker of free radical mediated damage and oxidative stress .This blocking in the synthesis of nucleic acids, certain amino acids and consequently proteins might lead to damage of organelles and plasma membranes of the hepatic parenchymal cells, interfering with their function and allowing leakage of enzymes. Studies have demonstrated that various anti-oxidants are protective against methotrexate hepatotoxicity [23].

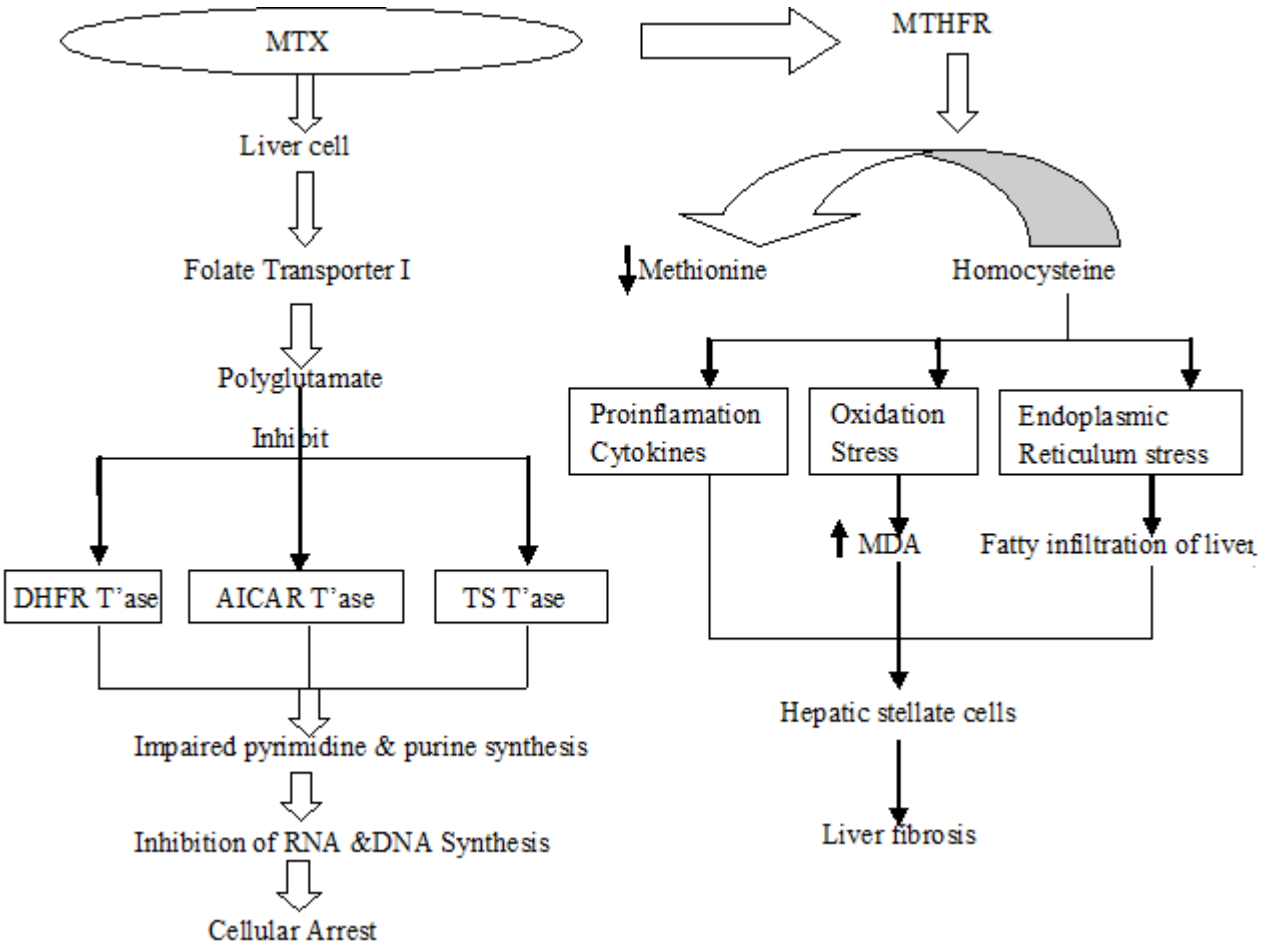

Figure 2: Mechanism Of Mtx Induced Hepatotoxicity related to cellular Pathway; MTHFR:Methylenetetrahydro folate reductase, AICAR:5-aminoimidazole-4-caboxamide ribonucleotide, DHFR:dihydrofolate reductase; TS:thymidylate synthetase ; ABC:ATP-binding cassette; MDA: Malondialdehyde;

5. Herbal treatment for methotrexate induced hepatotoxicity

A lot of medicinal plants, traditionally used for thousands of years are present in group of herbal preparation of the Indian traditional health care system. In India, millions of polyherbal commercial formulations reputed to have hepatoprotective action are being used. Scrutiny of the literature indicates that 160 phyto-constituents from 101 plant families have antihepatotoxic activity. Silymarin; a phytoconstituent from (Silybum Marianum) has been widely used from ancient times because of its excellent hepatoprotective action [24] .Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases [1].There are many herbs, which have been proven to be as hepatoprotective agents while many more are claimed to be hepatoprotective but lack any such scientific evidence to support such claims. Developing a satisfactory herbal therapy to treat severe liver diseases requires systematic investigation of properties like anti-hepatotoxicity (antioxidants), stimulation of liver regeneration. Formulation of herbal drugs with standards of safety and efficacy can revitalize treatment of liver disorders [25] .There are some of the plants which have hepatoprotective activity against methotrexate induced hepatotoxicity.

Table 1: List of plants used as Hepatoprotective

Biological Name	*Common Name*	*Family*	*Dose Of MTX*	*Animal Used*	*Reference*
Curcuma longa	Turmeric	Zingiberaceae	20mg/kg/ip/single dose	Albino rats	[16]
Flacourtia indica	Batoka plum	Flacourtiaceae	1750mg/kg/1 days	Albino Mice	[26]
Thymus vulgaris	Thyme	Lamiacea	20mg/kg/ip/3 days	Rabbits	272222 [27]
Silybum marianum	Milk thistle	Compositae	100µg/kg/45 days	Wistar rats	[28]
Camellia sinensis	Green tea	Theaceae	20mg/kg/single dose	Sprague-dawley rats	[29]
Olea europea	Olive	Oleaceae	20mg/kg/12 days	Wistar rats	[30]
Spinach oleracea	Spinach	Chenopodiac	20mg/kg/5 days	Wistar rats	[31]
Vitis vinifera L	Grape	Vitaceae	20mg/kg/single dose	Wistar rats	[32]
Opuntia ficus-indica	Cactus	Cactaceae	20mg/kg/10days	Wistar rats	[33]
Arachis hypogaea	Peanuts	Fabaceae	20mg/kg/5days	Wistar rats	[34]
Passiflora coerula	Chrysin	Passifloraceae	20mg/kg/7days	Wistar rats	[35]
Prunus armeniaca	apricot	Rosaceae	20mg/kg/10days	Wistar rats	[36]

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