

A Review on Hepatotoxic Effects of Methotrexate Therapy with Possible Strategies that May Counteract Hepatotoxicity

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ABSTRACT

Methotrexate, inhibitor of a dihydrofolate reductase, is a chemotherapeutic treatment applied in many kinds of tumors as an anti-metabolite. also, Methotrexate applied to treat different other disorders, including diseases of autoimmunity, such as psoriasis, rheumatism, vasculitis and ulcerative colitis and Crohn's disease. However, Methotrexate induces toxic effects on neurons, kidney toxicity, and liver damage, also Methotrexate have been associated with elevation risk of hepatic injury, fibrosis and cirrhosis. Methotrexate work as a dihydrofolic acid analog that binds to the dihydrofolate reductase enzyme that prevent the synthesis of tetrahydrofolic acid, that is essential synthesis of DNA. Although folic acid combine with Methotrexate therapy to prevent hepatotoxic effects, folic acid may reduce therapeutic effects of Methotrexate so recent research focus incorporation of new agent to counteract Methotrexate induced hepatotoxicity that include vitamin B12, vitamin E, N-acetylcysteine, melatonin, Erdosteine, inulin, Ferulic acid, Human placental extract, Natural plant extract (flavonoids). These agents are promising to counteract Methotrexate induced hepatotoxicity.

Materials and methods: A comprehensive literature review on different published articles hepatotoxic effects of methotrexate and was carried out by electronic research on Medline, PubMed, Google scholar, and Cochrane Libran data bases using different searching terms related to prevention of methotrexate induced hepatotoxicity. The article focusses on clinical studies in different regions in the period of 2018-2022.

Objective: To search for new update modality preventive therapy for methotrexate induced liver damage Results: Recent study oriented for the prevention and treatment of methotrexate associated with hepatotoxicity.

KEYWORDS: Methotrexate induced hepatotoxicity, antioxidant.

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INTRODUCTION

Methotrexate inhibitor for dihydrofolate reductase, is an anti-metabolite applied as a chemotherapy for many kinds of tumors¹. Methotrexate involved in treatment of other disease involving diseases of autoimmunity, like psoriasis, rheumatism, vasculitis and ulcerative colitis and Crohn's disease⁽²⁻⁵⁾. However, Methotrexate may cause neurotoxicity⁶, nephrotoxicity⁷, and hepatotoxicity^(8,9), Methotrexate have been linked to increase risk of liver damage, fibrosis and cirrhotic damage. Methotrexate work as a dihydrofolate analog which binds to the dihydrofolate reductase enzyme by preventing the production of tetrahydrofolic acid, that essential for production of DNA.

Many factors that may increase risk of methotrexate induced hepatotoxicity, involving alcohol consumption, aging, timing

for doses with Methotrexate and its amount of drug consumed by patient, medical history for liver disease, obesity, diabetic disease, hepatitis B or C virus infection and taking medicine associated with liver injury⁸. Moreover, non-alcoholic fatty injury, were liver steatosis is detected without heavy alcohol consumption¹⁰ which has been similarly associated with Methotrexate therapy¹¹. As dangerous adverse effects also low doses, Methotrexate may cause liver fibrotic damage and even cirrhosis. Minimum Methotrexate doses in chronic plaque psoriatic lesion was detected to have a 7% increase risk for development of cirrhotic liver injury, and aminotransferase rises up to triple times than standard level that found in 8% of the patients examined¹³. The incidence of Methotrexate-induced hepatic fibrosis and cirrhosis¹⁴.

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1. Vitamin B12

This Vitamin is an vital vitamin that possess essential function in numerous activities in the human organ, involving DNA methylation and DNA biosynthesis, production of erythrocytes, with neuronal function¹⁵. Vitamin B12 belong to cobalamins compounds, mainly stored in the hepatic tissue, many studies have shown that vitamin B12 protect against numerous liver diseases such as acute hepatitis, cirrhosis¹⁶. Derya *et al* investigate the protective activity of vitamin B12 on the necrosis induced by methotrexate, a antagonist for folic acid. Vit B12 showed supplied experimental group appear improvement in all of the negative laboratory liver enzyme and histological finding. Therefore, Vitamin B12 is an essential supplement that applied for necrosis in tissue after methotrexate hepatotoxicity¹⁷.

2. Vitamin E:

is a type of lipid-soluble vitamin, and found as eight different forms, were tocopherol is the main active form. vitamin E is very important physiological antioxidant, tocopherol also proposed to have the main cellular binding antioxidant utilized via human tissue¹⁸. Vitamin E consider the main protection to prevent peroxidation of cellular membrane that essential for the cellular immunity. Vitamin E has been approved to reduce and manage hepatic inflammatory response and tissue fibrosis through modulating inflammation and signaling cascade by reducing the production of interleukin-6, tumor growth factor- β 1, tumor necrosis factor- α , and further inflammation cytokines¹⁹. On other hand Binit *et al* show in his study prophylactic doses with vitamin E had preventive potential against hepatotoxicity induced by methotrexate in this experimental research showed that vitE in combination with folic acid superior to folic acid alone therefore the study results seem to be effective in ameliorating the hepatotoxicity of methotrexate therefore assists to fix the therapeutic dosing in patients²⁰.

3. N-acetylcysteine:

is a classical antioxidant, usually included in experimental research and a cellular protective agent which effective for drug-induced hepatotoxicity. In the lab study, displayed that N-acetylcysteine maintain the hepatocyte from oxidation by preventing the production of peroxide free radical. N-acetylcysteine may also display its antioxidant effects on hepatocytes by preventing expression of adhesive materials, decreasing inflammatory cytokines and reduction-oxidation system inside cellular cytoplasm. However, Tuba *et al* reveal in his study that there is a valuable preventive effect of N-acetylcysteine against methotrexate-induced hepatic damage. The ameliorated action of N-acetylcysteine based on its potency to improve antioxidant cellular mechanism, and its capability to decrease inflammatory and apoptotic molecular cascade²¹.

3-Melatonin (N-acetyl-5-methoxytryptamine):

Ayat *et al*²² concluded in her study that melatonin is promising in the protecting liver tissue from methotrexate toxic effect by their radical scavenging activities and antioxidant²². Melatonin is produced mainly through the pineal gland and is suggested to have antioxidant and defensive potential in opposit to oxidative stress²³. It has potent antioxidant action thus safing cellular tissue against oxidative stress of DNA molecule, proteins, and lipids that involved in disease pathogenic pathway^{24,25}. Melatonin maintains the hepatocyte from oxidative stress induced by pathological hypoxia formation²⁶. Since melatonin has potent antioxidative potential, therefore melatonin has the ability to prevent the patients against MTX induced hepatotoxicity.

4. Erdosteine: is a mucolytic agent that applied for the management of subacute lung disorder to improve bronchial clearance²⁷. currently, a many experimental studies has emphasized the antioxidant potential of erdosteine, also to its approved mucolytic action²⁸. however, erdosteine prevent oxidative tissue damage in many laboratory models studies that induced tissue damage by injecting animal with hepatotoxic drug²⁹. study finding display that use of erdosteine in animal result improvement in liver damage by oxidation, inflammation, programmed cell death, and pathological change, in comparison with methotrexate treated animal³⁰.

5. Inulin (IN): a plant fructan-type polysaccharide, is commonly present naturally. The main wild sources of Inulin involve dahlia, chicory. Studies have establish that Inulin broad spectrum of biological activities, e.g. as a probiotic to enhance the intestinal flora environment, controlling glucose level, controlling cholesterol profile, antioxidant, antitumor, immunomodulatory action and new study show that Inulin with antioxidant action has hepatoprotective effects that mediated by the regulation of apoptosis and oxidative damage³¹.

6. Ferulic acid: as a polyphenolic drug, is produced through tyrosine and phenylalanine metabolic pathway and is mainly present in rice, barely, wheat, banana, tomato, citrus fruits and vegetables³². Ferulic acid established to be a potent cellular protective against oxidative stress, also effective for dermatological malignancy, viral infection, atrophy of muscular tissues, and fatigue³³. On other hand Ferulic acid show many therapeutic actions, including anti-nociceptive, anti-inflammatory, anti-tumor, hypoglycemic, hypolipidemic, neuroprotection and hypotensive action³⁴. Ferulic acid, possess polyphenolic nucleus with long side chain, which produce stabilization against phenoxy radicals, that are function as free radical scavenger ability³⁵. However, Mozhdéh R *et al* found Ferulic acid in 100 mg/kg dose could can reduce oxidative damage, inflammatory response and enhance the internal cellular defense against oxidation by

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methotrexate. So Ferulic acid would be a good treatment to inhibit methotrexate associated hepatotoxicity³⁶.

7. Human Placental Extract:

It has approved that maternal placental supply is the major organ of a huge number of biological effective growth factors³⁷.like transforming growth factor- α (TGF- α)³⁸, hepatocyte growth factor (HGF) and epidermal growth factor (EGF)³⁹. Human placental extract also has Tryptophan as a major antioxidant content⁴⁰. also, Human placental extract applied for numerous useful pharmacological indications, involving healing of wound⁴⁰. Human placental extract was mentioned to improve hepatic regeneration after induction liver injury⁴¹ and to inflammatory damage with apoptotic damage⁴². Mamdooh G approved in his study that Human placental extract will prevent methotrexate induced hepatotoxicity in animals. Human placental extract show ability to improve and protect liver tissue against hepatotoxic agent by enhancing

The endogenous antioxidant liver markers with reduction lipid peroxidation, with anti-inflammatory action.

8. Natural plant extract (flavonoids):

Include (Apigenin, Zingerone, Silibinin, Ellagic acid, Naringin) all of them are extract from natural plant, and approved by experimental studies to prevent and attenuate methotrexate induced hepatic injury by antioxidant, anti-inflammatory and free radical scavenging properties^(44,45,46,47,48).

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