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A Review on the Role of *Rosa Damascene* in Drug-Induced Liver Injury

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ABSTRACT

Drug-induced liver injury is a frequent cause of liver dysfunction. Damage to the hepatic cells is a known adverse effect of many drugs. The drug or its metabolite might often trigger an immune-mediated response against the hepatocytes or cause direct disruption of the hepatocytic membrane leading to the loss of its physiological functions. Free radicals and reactive oxygen species produced after the metabolism of various drugs might also be involved in the initiation and progression of liver disorders. Treatment options for liver disorders such as drug-induced hepatitis, fatty liver, hepatitis of different origins and cirrhosis are limited and, in most cases, only supportive. A large number of natural formulations claim to have hepatoprotective activity. So, there is a worldwide initiative to develop an efficacious hepatoprotective agent derived from natural phytoconstituents.

Keywords: Drug-induced liver injury, Hepatoprotective, Isoniazid, Rosa damascene

INTRODUCTION

The liver is an essential organ required to sustain life. It performs a host of essential biochemical and metabolic functions, including plasma protein synthesis, production of biochemicals necessary for digestion and detoxification of substances, which, if allowed to accumulate, would be harmful to the living organism. Though the liver regulates the internal chemical environment of an organism efficiently, it is susceptible to a wide variety of diseases like hepatitis of different etiologies, cirrhosis, alcohol-related disorders and carcinomas. Also, the functioning of the liver as a clearance organ makes it susceptible to injury by the substances which are either degraded or eliminated by the liver [1]. So, the study of liver disorders and the development of drugs for various liver diseases has become one of the essential objectives of biomedical research as there is a rapid escalation in the number of patients suffering from hepatic disorders worldwide.

Drug-induced liver injury is a frequent cause of liver dysfunction [2]. Damage to the hepatic cells is a known adverse effect of many drugs, but the exact mechanism by which these agents cause hepatic injury is unknown in the majority of the cases. The offending drug or its metabolite might often trigger an immune-mediated response against the hepatocytes or cause direct disruption of the hepatocytic membrane leading to the loss of its physiological functions [3]. Free radicals and reactive oxygen species which are produced after the metabolism of various chemicals, might also be involved in various steps that initiate and regulate the progression of liver disorders [4].

Treatment options for liver disorders such as drug-induced hepatitis, fatty liver, hepatitis of different origins and cirrhosis are limited and, in most cases, only supportive. Also, the effectiveness of the available drugs such as interferons, colchicine, penicillamine and corticosteroids are inconsistent with a broad spectrum of side effects [5].

So, despite the recent advances in modern medicine, the options for medical management of patients suffering from liver ailments are limited and, at best inconsistent also with the rapidly increasing rate of liver disease due to enhanced exposure to drugs and environmental toxins, there is a compelling need for the development of potent hepatoprotective agent.

Tuberculosis is one of the most prevalent microbial diseases worldwide. According to the WHO, India had the highest TB burden worldwide, with approximate 23% out of the global estimate of new incidences [6]. The drugs which serve as the first-line agents for the management of TB are

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rifampicin, isoniazid, pyrazinamide and ethambutol. Hepatoxicity is a well-reported and documented adverse effect of the 1st line antitubercular drugs, which often leads to discontinuation and relapse or failure of the therapy.

The first line antitubercular drugs which have the highest reported hepatoxicity are isoniazid and pyrazinamide, and concomitant use of these drugs might lead to fulminant hepatitis with lethal consequences [7]. According to the study conducted by Hayashi [8] isoniazid continues to be a leading cause of drug-induced hepatic injury in the United States, and its hepatotoxicity has often been significantly under-reported.

Plant derivatives with purported hepatoprotective activity have been used in folk medicine and traditional systems of medicine around the world for centuries. In the last few years, there has been rampant growth in herbal medicine research. These drugs are also gaining popularity in both developing and developed countries because of their lesser side effects and natural origin [9,10].

A huge number of natural formulations claim to have hepatoprotective activity. Approximately 160 phytoconstituents derived from 101 plants claim to possess hepatoprotective activity. In India alone, over 33 patented and proprietary multi-ingredient plant formulations are available for liver ailments [11]. Despite the advancement in medical science in recent years, there is still no safe and effective drug for treating liver ailments. So, there is a worldwide initiative to develop an efficacious hepatoprotective agent derived from natural phytoconstituents.

ROSA DAMASCENA

Rosa damascena Mill. is a well-known flowering plant and cultivated in gardens in several places in Kashmir, Bengal and Punjab [12] This plant contains flavonoids such as caempferol and quercetin and their glycoside derivatives [13,14], carboxylic acids [15], terpene, myrcene, tannins and vitamin C [16]. Along with its perfuming effect, flowers and petals of *Rosa damascene* possess medical properties. It has been used as an anti-inflammatory [15], cardiotonic [17], mild laxative [18], cough suppressant [16] and also for the treatment of menstrual bleeding and digestive problems [19]. Recent studies demonstrated anti-HIV [13], anticonflict [20], antibacterial [21], antitussive [22] and respiratory smooth muscle relaxant properties for this plant [23,24]. *R. damascena* protects against CCl_4 induced hepatotoxicity by its free radical scavenging activity [25]. Alam [12] demonstrated the hepatoprotective and antioxidant effect of ethanolic extract of *Rosa damascene* (RDEE) flowers at 1.5g/kg and 3g/kg doses in paracetamol-induced hepatotoxicity.

Therefore, the therapeutic benefits of RDEE in isoniazid induced hepatic damage in rats were explored by me. Results of the biochemical parameters demonstrated that 15 days of treatment with RDEE in both doses (1.5g/kg and 3g/kg) resulted in improvement of liver enzymes. The percentage of hepatoprotection offered by RDEE was almost similar to the standard drug silymarin. The findings of histopathological examination supported the hepatoprotective activity of RDEE shown in the parameters. Liver sections of animals treated with RDEE exhibited significant liver protection against INH, which was evident by the presence of regenerating and lesser degenerating hepatocytes, fibrotic bridges and necrotic foci. The protection offered by RDEE 3g/kg dose though somewhat lesser than the standard drug silymarin but was considerable compared to the liver slices of the rats treated with isoniazid (INH) alone [26].

Oxidative stress is one of the major mechanisms by which isoniazid (INH) and rifampicin cause damage to the hepatocytes. During combined treatment, glutathione and related thiols, which prevent tissue from oxidative damage, get reduced in blood and liver tissue. This results in micro vesicular deposition of fats in the hepatocytes and inflammation of the portal triad [27]. The likely reason for RDEE's protection against INH induced hepatotoxicity may be due to its antioxidant activity. RDEE improved CAT, glutathione and MDA significantly. Alam [12] also described the antioxidant effect of RDEE in their study.

CONCLUSION

RDEE administration demonstrated improvement in the liver parameters. Therefore, *Rosa damascene* is beneficial against Drug-induced liver injury.

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