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Medical plant extracts and natural compounds with a hepatoprotective effect against damage caused by antitubercular drugs: A review

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ABSTRACT

Drug-induced liver injury encompasses a spectrum of diseases ranging from mild biochemical abnormalities to acute liver failure; example of this scenery is hepatotoxicity caused by the first-line antituberculous drugs isoniazid, rifampin and pyrazinamide, which are basic for treatment of drug-sensible and drug-resistant tuberculosis. In the search for pharmacological alternatives to prevent liver damage, antitubercular drugs have been the subject of numerous studies and published reviews, a great majority of them carried out by Asian countries. At the same time, hepatoprotectors from plant source are now emerging as a possible alternative to counteract the toxic effects of these therapeutic agents. The present review aims to highlight the most recent studies on the subject, based information published in scientific databases such as Scopus and PubMed.

1. Introduction

Tuberculosis (TB) is a disease that affects one third of the world's population; in 2014, nearly 9.6 million cases were reported and close to 2 million deaths [1–3]. At present, there is an alarming increase of multidrug-resistant-TB (MDR-TB) and of extended drug-resistant-TB (XDR-TB) cases; the former are resistant to RIF, PZA and INH (basic drugs) and XDR cases are resistant to RIF, INH, fluoroquinolones and to a second-line injectable drug (amikacin, capreomycin or kanamycin). The World Health Organization (WHO) TB Report 2012 indicates that 4% of new cases and 20% of retreated cases are MDR and that <20% receive adequate treatment [2,4]. On the other hand, around 60% of the patients with MDR-TB are cured and 10% become XDR-TB; of the latter, only 10% are cured [2–5].

RIF, INH and PZA are basic for treating sensitive or mono-resistant TB, and these mainly cause liver damage, as well as neuropathy, hypersensitivity, nephrotoxicity, nausea, vomiting and gastritis. The hepatotoxicity incidence depends on the population studied, treatment time and factors such as age, malnutrition, alcoholism, diabetes mellitus, arthritis, HIV/AIDS, host genetic, exposure to other drugs, *etc* [2,4,6–8]. For the treatment of sensitive TB, a multi-therapy is used, based on four first-line drugs (RIF, INH, PZA, EMB or STR) for 2 months and a mixture of RIF/INH for 8 months. For latent TB, RIF/INH is administered for 3 months or RIF/PZA for 4 months; this treatment causes 2.5%–13% of liver damage, respectively. When the INH is administered alone for 9 months, the hepatotoxicity increases to 1.6% and it increases to 2.6% when RIF/INH mixture is used [8–10].

MDR-TB is treated with up to eight drugs, including first and second line (amikacin, capreomycin, fluoroquinolones, cycloserine, ethionamide, *etc*), for a period of 8–30 months; in this case, the treatment causes severe liver damage in >69% of patients. Subsequently, secondary effects provoke non-adherence to treatment and contribute to treatment failure, propitiating the appearance of drug resistance (DR) [8,9]. It is noteworthy that for contacts of MDR-TB cases, the PZA/EMB combination or fluoroquinolones are employed for treatment [4,11,12].

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Most xenobiotics, such as drugs, are biotransformed in the liver; this organ is the most affected when the substance is metabolized and generates more toxic products, such as free radicals (FR). This alters the structural integrity and functionality of the liver, generates inflammation, steatosis, induces hepatitis, liver fibrosis, nonalcoholic cirrhosis, necrosis and even hepatocellular carcinoma, and these are among the causes of drug withdrawal from the market [13–16].

The majority of epidemiological studies on hepatotoxicity have been conducted in Europe, Asia and the U.S., and incidence varies among the different regions of the world. The proportion is higher in developing countries as compared with developed countries; for example, it has been reported that in India there is a higher incidence of adverse effects, the mixture of RIF/INH/PZA causing up to 30% of hepatotoxicity, while in other countries this percentage is 23% [17,18]. This type of study has also been carried out in Sub-Saharan Africa, but the incidence of hepatotoxicity has not been reported [8,12].

Since the discovery of INH (1952), the incidence of hepatotoxicity is present in 2% of patients and 20% of these show an increase in the values of hepatic enzymes, such as glutamic oxaloacetic transaminase (GOT) or aspartate aminotransferase (AST) and glutamic pyruvic transferase (GPT) or alanine aminotransferase (ALT) and alkaline phosphatase (ALP) [19]. With the introduction of RIF (in 1963), cases of hepatitis were more frequent, but the increase was greater when the mixture INH/RIF was employed for TB treatment [11]. In the decade of the 1950s, PZA was introduced, being the most active drug against MDR *Mycobacterium tuberculosis* strains, but it is more hepatotoxic, and cases of hepatotoxicity increased when the mixture of INH/RIF/PZA was used, reaching values of up to 60% [8,11,12,20].

The pathogenesis of the hepatotoxicity caused by the INH/RIF mixture is not yet very clear. It generates very reactive compounds such as FR, these favoring the development of oxidative stress (OS), lipid peroxidation and choline deficiency. Phospholipoprotein synthesis and integrity of the cellular membrane of the hepatocytes are altered. Moreover, the levels of glutathione present in them are reduced [11,12,20].

Although the mechanism by which anti-TB drugs induce hepatotoxicity is not yet fully elucidated, it is known that INH and RIF are metabolized by diverse hepatic enzymes of the P_{450} cytochrome family [12]. RIF is an inducer of CYP2D6 and CYP3A4 isoforms of the cytochrome while INH induces CYP2E1 [20–22]. These generate toxic metabolites, such as hydrazine (toxic metabolite of INH), giving rise to OS in humans as well as in animals, and also generate hepatic necrosis. Likewise, INH inhibits cytochrome P_{450} 1A2 reductase, which is involved in the detoxification of its metabolite (hydrazine); therefore, the hepatotoxicity of this drug increases [12,17,23]. Moreover, it has been asserted that RIF increases the biotransformation of INH by stimulating the liver's enzymatic system; in turn, affecting the toxic metabolites of the INH and increasing OS. Furthermore, PZA, once metabolized, becomes pyrazinoic acid (PA), which causes granulomatous hepatitis [12]. In addition, there is strong evidence that host genetic factors influence individual susceptibility to develop hepatotoxicity by anti-TB, such as polymorphisms in *NAT2*, *CYP2E1* and *GST* genes, this is a topic that is getting much attention. Similarly, the effects of GST polymorphisms on genetic susceptibility to anti-TB damage have been reported, particularly for *GSTM1* and *GSTT1* genes [24].

Due to the fact that the three main anti-TB drugs (RIF, INH, and PZA) are those that cause the greatest liver damage and cannot be substituted today, research is being conducted aimed at preventing or reducing the adverse side effects by using herbal extracts and/or natural compounds isolated from these, with a hepatoprotective effect. Among natural products, we can mention silymarin, resveratrol, vitamins E and C, polyphenols and garlic, among others, which do not interfere with the anti-TB effect of the drugs. It is noteworthy that the inhibition of cytochrome P_{450} in its isoform CYP2E1, together with the antioxidant effect of these substances, is beneficial and is the most common mechanism of herbal remedies and isolated natural compounds. Therefore, they are the most frequently recommended substances for protection from the hepatotoxicity induced by anti-TB drugs [17,21,25–27].

In the present paper, an exhaustive search was carried out on the hepatoprotective effect of extracts and/or compounds obtained from medicinal plants against liver damage induced by anti-TB drugs (RIF/INH or RIF/INH/PZA mixture) in preclinical models, *in vivo* and *in vitro*. The main scientific sources consulted were the Scopus and PubMed databases. In this manuscript we describe 101 references published from the year 2000 to date. The key words employed included medicinal plants, hepatoprotective effect, antitubercular drugs-induced hepatotoxicity and natural compounds.

It is noteworthy that in the literature there are numerous papers concerned with the hepatoprotective effect of extracts and compounds obtained from medicinal plants against the liver damage induced by several chemical substances, such as carbon tetrachloride (CCl_4), ethanol (EtOH), acetaminophen (or paracetamol), among others; but there is a scarcity of research that describes this effect against the damage generated by the administration of anti-TB drugs -RIF/INH/PZA- [26].

2. Plants extract with hepatoprotective effect

The ethanol (EtOH) extract from the leaves of *Cnidoscolus chayamansa* administered orally demonstrated a protective effect in Wistar rats against the hepatotoxicity induced by the mixture of RIF/INH (100 mg/kg each), this extract diminishing AST, ALT and ALP levels. The observed effect was similar to that of the positive control (silymarin, 2.5 mg/kg), the authors attributing this protection to the flavonoids present in the plant extract [27].

The aqueous extract of *Allium sativum* bulbs (fresh garlic homogenate, 0.25 g/kg/d) generates a hepatoprotective effect against the sub-acute liver damage induced by the mixture of INH/RIF (50 mg/d, each) administered by oral via, half an hour before anti-TB drugs over a period of 28 d in Wistar rats. The results showed that ALT, AST and total bilirubin levels were reduced in animals receiving the garlic extract and RIF/INH, with respect to the group where only RIF/INH was administered. The authors also observed an increase in the glutathione level and a low level of lipid peroxidation; the effect observed was attributed to the presence of thiosulfinates, steroids, terpenes, flavonoids and other phenols present in garlic [17]. *Allium sativum* (250 mg/kg, oral via), administered by 28 days also protects from liver injury caused only with INH (50 mg/kg); the effect observed was similar to that of silymarin (200 mg/kg) employed as a positive control [28].

Another scientific paper report the evaluation of four extracts [petroleum ether, Chloroform ($CHCl_3$), Methanol (MeOH) and

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