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Review Article

Hepato-Protective Effect from Natural Compounds, Biological Products and Medicinal Plant Extracts on Antitubercular Drug-Induced Liver Injuries: A Systematic Review

Oscar Abelardo Ramírez-Marroquín[1], María Adelina Jiménez-Arellanes[2]*

[1]Instituto de Química Aplicada, Universidad del Papaloapan, Tuxtepec, Oaxaca, Mexico; [2]Unidad de Investigación Médica en Farmacología, Hospital de Especialidades, Centro Médico Nacional Siglo XXI (CMN-SXXI), Instituto Mexicano del Seguro Social (IMSS), Mexico

ABSTRACT

Tuberculosis is mainly treated with rifampicin, pyrazinamide, isoniazide, ethambutol and/or streptomycin; however, the first three cause hepato- and nephro-toxicity, then the patient abandons therapy. This cause contributes to the failure of the treatment and favors the appearance of drug-resistant strains. Currently, alternatives are being sought to counteract this hepatic-damage, and medicinal plants, natural compounds and/or biological products are of great interest. In this manuscript we describe current data on the hepato-protective effect from extracts of medicinal plants, compounds isolated from them and biological products that protect against liver damage caused by anti-tubercular (anti-TB) drugs caused by therapy in patients with tuberculosis (TB).

The main consulted databases were: PubMed, Worldwidescience.org, and Scopus, including records between 2000 and 2018 years. Thus, we found many articles about hepatoprotective effect from medicinal plants and polyherbal preparations (Hepatoplus and Liv 52), the majority of these have an important effect (on preclinical study) due to their antioxidant compounds content. In addition, the hepatoprotective activity of biological products and/or natural compounds has been discussed and it should be noted that the quercetin (natural antioxidant compound)/polyvinylpyrrolidone mixture protects against hepatic damage caused by therapy in patients with TB. Another interesting compound with good effect in TB patients is *N*-acetylcysteine (an oral marketed mucolytic drug) which could be repurposed as an hepatoprotective drug. We consider that these findings are of great interest for researchers and clinicians, also for the development of new agents as well as for the therapeutic use of hepatoprotective substances in patients with TB, which helps reduce the toxic effects that drugs cause.

Keywords: Hepato-protective activity; Medicinal plants; Pure compounds; Biological products; Anti-tubercular drugs

INTRODUCTION

Tuberculosis (TB) is a disease that affects one third of the world population, and is a health problem in various developing countries, being one of the nine top causes of death by infectious processes. In 2016, 1.7 million people died and approximately 10.4 million developed the disease; of the latter, about 10-12% were HIV-positive. This co-infection being one of the main causes of death worldwide [1,2]. It is estimated that 95% of the deaths occurred in developing countries (India, China, Pakistan, and South Africa) and 40% of the deaths were from a co-infection HIV/TB.

Currently, there has been an increase in the cases of Multidrug-Resistant (MDR-TB) and extensively drug-resistant strains (XDR-TB). MDR cases are resistant to Rifampicin (RIF), Pyrazinamide (PZA) and Isoniazide (INH), basic drugs for the treatment of TB. On the other hand, XDR cases are resistant to RIF, INH, fluoroquinolones, and second-line injectable drugs (amikacin, capreomycin or kanamicin) [3,4].

In a global TB report was described that in 2016, approximately 6.3 million new TB cases appeared, of which 600,000 were resistant to RIF and approximately 490,000 was MDR cases, and only 111,000 cases were adequately treated [3,4]. In contrast, about

Correspondence to: María Adelina Jiménez-Arellanes, Unidad de Investigación Médica en Farmacología, Hospital de Especialidades, Centro Médico Nacional Siglo XXI (CMN-SXXI), Instituto Mexicano del Seguro Social (IMSS), Av. Cuauhtémoc 330, Col. Doctores 06720, Delegación Cuauhtémoc, México, Tel: 56276900, Ext: 21367; E-mail: adelinajim08@prodigy.net.mx

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60% of the MDR-TB cases were cured and it is suspected that 10-20% developed XDR-TB [1,4,5]. In Mexico, around 21,600 cases are registered each year, between new and relapses and by 2016, 16.820 new cases of pulmonary TB were reported [6]. RIF, INH and PZA are basic drugs for the treatment of TB, and this mixture cause mainly hepatic damage, also neuropathy, hypersensitivity, nephro-toxicity, nausea, vomiting and gastritis. The incidence of hepato-toxicity (HPT) depends on the population studied, treatment time, and factors such as age, malnutrition, alcoholism, diabetes mellitus, arthritis, HIV/AIDS, cancer, and other [1,4,7,8].

For sensitive TB, multitherapy is used, based on four first-line drugs: RIF, INH, PZA and Ethambutol (Et) or Streptomycin (St) for two months, and the combination RIF/INH up to 8 months. For latent TB, RIF/INH is administered for 3 months, or RIF/PZA for 4 months, generating around 2.5% and 13% hepatic damage, respectively, while INH administered for 9 months induce hepatic damage in 1.6% of cases [8,9].

The main manifestation of HPT consists in increase of hepatic enzymes until fulminant hepatic failure [10]. Treatment of MDR-TB requires a mixture of at least 8 first- and second-line drugs (amikacin, capreomycin, fluoroquinolones, cycloserine, ethionamide, among others) for a period of 8 up to 30 months; in these cases, the treatment provokes severe hepatic damage in more than 69% of patients. These secondary effects induce lack of adherence and contribute to treatment failure, favoring the appearance of drug-resistance (DR). In addition, the contacts of MDR-TB cases are treated with PZA/Et plus a fluoroquinolone [1,10,11].

The bio-transformation of antitubercular (anti-TB) drug is carried out mainly in the liver, which is why it is the most affected organ when these substances are metabolized and generate very reactive products such as Free Radicals (FR). These FR alter the functional and structural integrity of the liver, generating inflammation, chronic hepatitis, hepatic fibrosis, non-alcoholic cirrhosis and even hepato-cellular cancer, being one of the main causes for which drugs are withdrawn from the market [12-15]. The most of epidemiological studies on HPT induced by anti-TB drugs have been carried out in Europe, Asia and USA, and the incidence varies between the different regions of the world, being higher the percentage of cases in developing countries. For example, it has been reported that in India there are greater incidence of adverse effects, where multitherapy with RIF/INH/PZA causes HPT in around 30% of patients, and in other countries this percentage is 23%, therefore, the incidence of HPT depends on the population studied [16-18].

INH (discovered in 1952) causes HPT in 1 to 2% of patients, and 20% of them show elevated levels of hepatic enzymes, such as Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT), as well as alkaline phosphatase (ALP) [18].

When RIF was introduced the hepatitis cases were more frequent; however, the presence of hepatitis increased when using the mixture of both (INH/RIF) in TB treatment [10]. In the 1950s, PZA was introduced, this drug is the most active against MDR *Mycobacterium tuberculosis* strains, but it is the most HPT because when it is metabolized generates pyrazinoic acid. PZA increases the metabolism of INH, and the latter produces iso-nicotine acid and hydrazine, which are more HPT. It has been well documented that the combination of INH/RIF/PZA increases the incidence of hepatic damage by up to 60% [19].

Although the mechanism by which the INH/RIF/PZA mixture causes HPT is still not entirely clear, the main explanation is: metabolism of these drugs produces very reactive FR that favors Oxidative Stress (OS), peroxidation of Lipids (LPO) and proteins, induce choline deficiency, reduce the synthesis of phospholipoproteins, and alter the integrity of the cell membrane of hepatocytes. Additionally, reduce hepatocytes' glutathione levels and activate some isoforms of the cytochrome P450 system (CYP2E1) [19-21]. It is well known that INH and RIF are metabolized by various hepatic enzymes of the cytochrome P450 family [10]. RIF induces isoforms CYP2D6, CYP3A4, CYP2C18, CYP2B6, CYP2C9, CYP2C19 of the cytochrome, while INH induces CYP2E1. INH also generates toxic metabolites such as hydrazine, favoring OS in humans and in animal models; hydrazine causes hepatic necrosis. Likewise, INH inhibits cytochrome P450 1A2 reductase, an enzyme involved in the de-toxification of hydrazine, it leads to an increase in HPT [9,16,22]. In addition, it has been described that RIF enhances INF bio-transformation and subsequently this increases concentration of INH toxic metabolites, and increases OS.

On the other hand, PZA, upon being metabolized, becomes pyrazinoic acid, which causes granulomatous hepatitis [11]. Also, there exist evidence that genetic factors influence the development of HPT generated by anti-TB drugs; for example, the polymorphism in the genes *NAT2, CYP2E1, GST* M1 and GSTT1 alters the metabolism of INH and RIF [23].

The most important anti-TB drugs (RIF, INH and PZA) mainly cause HPT and cannot be substituted. In this sense, current research is focused on preventing or reducing this secondary effect through the use of medicinal plants, natural compounds or biological products with Hepatoprotective (HPP) effects. Among these, we could mention silymarin (Sil), resveratrol, vitamins E and C, polyphenols and garlic, among others. It is important to note that the inhibition of the cytochrome P450, in its isoform CYP 2E1, together with an antioxidant effect, are the main beneficial mechanisms and are most common in herbal remedies (extracts, biological products and natural compounds), so these are the most recommended treatments against HPT caused by anti-TB drugs [16,20,24-27].

The objective of the present work was to continue with the exhaustive search and analysis of scientific literature on the HPP effect of medicinal plant extracts, the compounds isolated from these, and biological products that protect against the hepatic damage caused by anti-TB drugs. In this review we addressed the following question: ¿what efforts have been made during the last two decades (from 2000 to 2018) for to discover or to develop new or alternative HPP therapies, and how these findings can be useful for biomedical researchers and clinicians? We hope the next pages contribute to the answer.

LITERATURE SEARCH

Search strategies and inclusion and exclusion criteria

An exhaustive search was made on the HPP effect of the biological products, extracts and/or compounds obtained from medicinal plants used against the HPT caused by anti-TB drugs in clinical,

preclinical, *in vivo* and *in vitro* models. We use the methodology described by Liberati [28], the chemical name of natural compounds and the commercial name as well as a duration of treatment and the anti-TB drug used to induce damage liver were included. Only English language published articles and just a few trusted web pages were included in the present work. In this respect, the main scientific portals consulted were PubMed, Web of Science, worldwidescience.org, and Scopus, and the search period between 2000 to December 2018. Validation of the scientific names of the plants described was performed, as well as the families they belong to, at the website http://www.tropicos.org. The key words used in the search were: medicinal plants, hepatoprotector effect, antitubercular drugs, natural compounds, biological product, and HPP activity.

Data extraction

We selected all the articles that describe the evaluation of medicinal plants, natural compounds and biological products in *in vitro* and *in vivo* models as hepatoprotectors against damage induced with anti-TB drugs (RIF, INH and PZA) and we exclude those articles that describe the hepatoprotective (HPP) effect of the substances against damage induced with other types of substances (such as CCl_4, thioacetamide, EtOH and other). We review the title, the abstract and the complete text of the articles on the subject. From the reviewed articles we select the scientific name of the plant, the composition of the herbal mixtures, the chemical name of the natural compounds, the commercial and/or chemical name of the biological product. In addition, we include the type of extract (organic or aqueous) evaluated, the dose administered, biological model (*in vitro* and *in vivo*) used, administration route, duration of treatment, anti-TB used to induce hepatic damage, and control positive used, as well as, the parameters used to determine the hepatoprotective effect of the assayed products.

RESULTS AND DISCUSSION

This review is a second part of a previous one; we considered 90 additional articles to update the state of the art in the HPP effect studies between 2000 to December, 2018. In the next pages we present the most important contributions to the field divided in: a) HPP effects derived from medicinal plant extracts, classified by solvent used for extraction: aqueous extracts, ethanolic and methanolic extracts, and finally essential oils; b) HPP effect by polyherbal mixtures, especially those commercial ones; c) HPP effects found in pure natural or synthetic organic compounds; and finally d) Biological products with HPP effect.

In a previous work was described some plant species and some polyherbal preparations from medicinal plants that shown an important HPP activity against the HPT caused by INH/RIF/PZA and a mixture of them [27,29-34]. In order to update the information on this subject, in this manuscript we describe important additional data. We found 30 manuscripts describing the HPP effect of the extracts of medicinal plants, one describing the effect of the essential oil, two articles describing the HPP effect of organic extracts, 4 articles describing the HPP activity from polyherbal preparation, 16 articles describing pure compounds and three describing the HPP effect for biological products.

Aqueous (H_2O), Ethanolic (EtOH) and Methanolic (MeOH) extracts from medicinal plants

In a study carried out in male Wistar rats with damage caused by INH (50 mg/kg) treated for eight weeks with *Rosmarinus officinalis* leaves extract (Lamiaceae, 440 mg/kg) and *Petroselinum crispum* (Apiaceae, 250 mg/kg) by oral via (O.V.), it was found that both extracts reduced the hepatic enzyme values (ALT, AST, γ-glutamyltransferase -GGT- and ALP), glutathione (GSH), nitric oxide (NO), and malonaldehyde (MDA) values. The HPP effect was confirmed by histological analysis. In spite of the values of hepatic enzymes evaluated were lower in the group that received *P. crispum*, upon analysing all the results, it was concluded that the aqueous extract of *R. officinalis* showed a better HPP activity, due to its antioxidant property against the damage caused by INH [35].

The HPP effect of *Tinospora cordifolia* stem (Menispermaceae) and the *Phyllanthus emblica* fruit (Phyllanthaceae) was evaluated. The treatments were administered separately (at 100 and 300 mg/kg, respectively) and mixed together (at doses of 100+300 mg/kg and 50+150 mg/kg) against the damage caused by the INH/RIF/PZA (31.5, 54, 189 mg/kg) in male Wistar rats during 90 days, using carboxymethylcellulose (CMC) at 0.5% as vehicle and Sil (50 mg/kg) as positive control (PC). The results did not show significant differences in hepatic enzymes activity. In the histological analysis, it was noted that there was necrosis and cell degradation in the group that only received the anti-TB drugs; however, the groups treated with the mixture of *T. cordifolia* and *P. emblica* at both doses showed less histological damage, lower liver weight variability and less cell degeneration, with little evidence of necrosis. The mixture of both extracts reduced the HPT caused by the anti-TB drugs [36].

The protector effect of the *Tamarindus indica* fruit (Fabaceae) (250 and 500 mg/kg) has also been described. This extract was administered O.V. during 14 days in rats with injury caused by the INH/RIF (50/100 mg/kg). This treatment significantly reduced concentrations of ALT, AST, ALP, bilirubin and TBARS (substances reactive to thiobarbituric acid), and increased the levels of antioxidant enzymes (superoxide dismutase -SOD-, catalase -CAT- and GSH), showing a dose-dependent effect, being 500 mg/kg the best dose [37].

In another study, the HPP effect of the *Azadirachta indica* (Meliaceae) leaves collected in six bimesters (January-February, March-April, May-June, July-August, September-October, and November-December), was evaluated on Wistar rats (both sexes) against the damage caused by INH/RIF/PZA mixture (27, 54, 135 mg/kg, each one); the sample was administered by O.V. during a month and the aqueous extract (prepared by decoction proccess) was administered at 1 mL/kg (1 g/kg). The results obtained showed that the collection of March-April had the best HPP effect, by reducing the levels of ALT and bilirubin while increasing total serum protein levels, compared with the group that only received the anti-TB drug; the authors noted that the collection season directly influenced the accumulation of bio-active compounds in the leaves, roots, and stem, which may be responsible for this activity [38].

Artemisia vulgaris L. leaves (Asteraceae) collected at six bimester at a dose of 1 mL/kg (1 g of leaves/mL), was evaluated against the HPT caused by anti-TB drugs (INH/RIF/PZA mixture, 27, 54

and 135 mg/kg, each one) in male Wistar rats over one month by O.V. The best HPP effect was observed in the leaf extract collected in May-June, due to the maximum accumulation of bio-active compounds in the leaves of *A. vulgaris*, probably due to climatic or environmental factors [39].

The HPP effect of the tea extract from *Camellia sinensis* (family Theaceae, at green tea 1.5 with dose 100 mg/kg/day by O.V.) was evaluated in male Wistar rats with liver injury caused by the INH/RIF mixture (50:50 mg/kg each one, administered during 28 days by O.V). The extract was administered 3 days before treatment with anti-TB drugs, and all through treatment. At the end, values of AST, ALT, ALP, LDH and bilirubin were determined, as well as SOD, CAT and malonaldehyde (MDA). The results showed a statistically significant reduction of enzyme values in the group co-treated with the extract, being very close to the control group (without any treatment) in all the parameters evaluated; likewise, an increase was noted in levels of SOD and CAT and a reduction in MDA values very close to controls. Regarding microscopic findings, a necrosis reduction and hepatocytes with low fat content and clear cytoplasm, moderately congested central vein, liver cells with conserved cytoplasm and prominent nucleus, was observed; this extract has hepatoprotective activity against the damage caused by INH/RIF [40].

In other instance, the EtOH (90%) extract of *Mentha piperita* L. (Labiatae) leaves, *Origanum vulgare* L. leaves (Lamiaceae) and *Pimpinella anisum* (Apiaceae) seeds (100 mg/kg), alone and in combination (polyherbal mixture) were evaluated against the liver injury caused by INH/RIF/PZA/Et mixture (6.75/13.5/36/24.8 mg/kg, each one) administered by O.V. for 30 days on Sprague-Dawley rats, using Sil (100 mg/kg) as PC. In the co-administered groups (anti-TB drugs plus extracts) was observed a reduction of levels of hepatic enzymes (AST, ALT and ALP) in the following order: Sil ≥ polyherbal mixture >*M. piperita* >*O. vulgare* >*P. anisum*. The results of total antioxidant capacity, GSH and markers of OS (conjugated dienes, total hydroperoxide, lipids and proteins oxidized) showed an increase in the groups treated with the extracts, suggesting that the mechanism of action of these extracts is through antioxidant activity. Also, these extracts have the ability to reverse or prevent OS caused by the anti-TB drug [41]. The *Crocus sativus* stigma (Iridaceae) at 40 and 80 mg/kg was evaluated for the damage caused by RIF (500 mg/kg) in male Wistar rats using Sil (50 mg/kg) as PC. Sample was administered by O.V. for one month. *C. sativus* at 80 mg/kg showed a better effect; this effect was very similar to Sil, reducing significantly biomarkers of hepatic damage (ALT, AST and ALP) and total bilirubin (TotBil) in serum [42].

The EtOH extract from *Euphorbia fusiformis* Buch. Ham.ex D. Don tubers (Euphorbiaceae) at 250 mg/kg showed an HPP effect against the damage caused by RIF (100 mg/kg/o.v.) in Wistar rats administered for 15 days, using Sil (100 mg/kg) as PC. A reduction in the biochemical parameters analyzed (AST, ALT, ALP, γ-GTP, TotBil and total protein) was observed respect to the anti-TB drug group, upon re-establishing values to levels similar to the PC group [43]. EtOH extract of the *Leucas cephalotes* (Lamiaceae) whole plant at 200 and 400 mg/kg/orally was evaluated against injury induced by INH/RIF (100:100 mg/kg each one) in Sprague Dawley rats administered for 21 days, and Sil (200 mg/kg, PC). A reduction in ALT, AST, ALP, lipid peroxidated (LPO) levels, and an increase in SOD, GSH and CAT levels, at both doses was observed; the better dose was 400 mg/kg of extract and also showed protection against CCl_4 induced damage [44]

EtOH (50%) extract of the *Solanum xanthocarpum* Linn fruit (Solanaceae) was evaluated in Wistar rats at 100, 200 and 400 mg/kg, against harm caused by INH/RIF/PZA mixture (7.5:10:35 mg/kg, each one), using Sil (100 mg/kg) as PC. All treatments were administered by O.V. for 35 days. The results showed that co-treated groups with the extract showed a dose-dependent response, being 400 mg/kg the best dose. The LPO value was lower in the group treated with extract, and the activity of GSH, SOD and CAT was increased; these data was confirmed by liver histological analysis [46]. In another study, this extract from *S. xanthocarpum*, whole plant at 125 and 250 mg/kg were administered by O.V. in Wistar rats for 28 days with injury caused by INH/RIF (50 mg each). A better effect was observed at higher extract dose (250 mg/kg); in this group was observed a reduction in hepatic enzyme levels and CAT, MDA and GSH levels showed similar behavior to Sil. Histological analysis showed no alterations in extract group [46]. The HPP effect of *Cucumis trigonus* Roxb. fruit (Cucurbitaceae) at 100, 250 and 500 mg/kg was evaluated against the injury induced by RIF/INH (50:50 mg/kg, each one) in male Wistar rats, by intraperitoneal administration for 21 days, using Sil (2.5 mg/kg) as PC. The extract at 500 mg/kg exhibited a better effect than Sil in hepatic enzyme levels (ALT, AST, ALP and GTP); likewise, upon evaluating the same biochemical parameters in liver homogenate, a dose-dependent effect was observed on the LPO values. Addittionally, GPx, GRD, SOD and CAT values were increased, suggesting a protector effect. In histopathological analysis, it was observed that the groups treated with extract showed minimal changes [47].

The protector action of the EtOH (70%) extract form *Cissampelos pareira* roots (Menispermaceae) at 100, 200 and 400 mg/kg) was investigated against the HPT caused by INH/RIF (50 mg/kg each) in Sprague-Dawley rats, the sample was administered by O.V. for 28 days. The results showed significant differences between groups, with a dose-dependent effect. This extract can be considered as an alternative to reduce the damage caused by INH/RIF for 28 days [48].

In addition, the protector activity of EtOH (95%) extract from the *Barleria montana* leaves (Acanthaceae) at 250 and 500 mg/kg has been reported against the toxicity caused by INH/RIF/PZA/Et (27, 250, 500, 53 mg/kg), administered for 35 days by O.V. in rats. The results showed that pre-treatment with the EtOH extract significantly reduced levels of ALT, AST, ALP, TotBil, total cholesterol and total HDL. This extract also reduced LPO values and increased antioxidant activity (SOD, CAT, GSH), being 500 mg/kg the best dose. Microscopic observations of the liver cyto-architecture for the group treated with *B. montana* extract did not show significant changes; the HPP effect has been attributed to the antioxidant activity [49].

In another experiment, the protector effect of the *Boerhaavia diffusa* var. *hirsuta* (Nyctaginaceae) root at 150 and 300 mg/kg alone and enriched with piperine (10 and 20 mg/kg) were evaluated in Wistar rats with liver damage caused by RIF/INH (50 mg/kg each), administered for 30 days, using Sil (100 mg/kg) as control. The results showed that the extract at highest dose had the best effect, and the dose of 150 mg/kg enriched with piperine had a dose-dependent effect, the levels of ALT, AST and ALP, were lower respect to anti-TB group [50].

The HPP effect of the EtOH (70%) extract from *Jasminum grandiflorum* (Oleaceae) leaves at 200 mg/kg were evaluated against the injury caused by INH (54 mg/kg) in Wistar rats, using Sil (50 mg/kg) as PC. The extract and Sil were administered by O.V. for 30 days. Levels of ALT and AST were reduced in the group that received the EtOH extract respect to INH group. The effect was similar to the group treated with Sil. Likewise, it was observed that the LDL and HDL levels were very close to the healthy group; on the other hand, LPO levels dropped significantly and antioxidant activity increased in the group co-treated with extract [51].

A study was designed to evaluate the HPP effect of the EtOH (95%) extract of *Chelidonium majus* L. aerial parts (Papavaraceae) (500 mg/kg) against the harm caused by INH/RIF mixture (100:100 mg/kg, each one) in Wistar rats over 21 days. The group that received the extract showed a significant reduction in the enzymatic biomarkers of hepatic damage, and re-established levels of SOD, CAT and GPx while decreasing levels of MDA [52]. EtOH (70%) extract of the *Ocimum sanctum* L. (Lamiaceae) leaves was evaluated at 200 mg/kg by O.V. on Wistar rats with hepatic harm induced by INH/RIF/PZA mixture (27, 54, 135 mg/kg, each one); two experiments were performed, one of which was administered concomitantly, the extract plus anti-TB drugs, and in the second experiment the extract was administered from day 31 to 50. The results showed that the concomitant treatment (extract plus drugs) prevented the damage observed in the anti-TB group. Likewise, a significant reduction was observed in ALT and bilirubin levels for extract group after treatment with anti-TB drug (second experiment). The concomitant administration of the extract did not alter liver histology, and significantly reduced necrosis and fibrosis, with evidence of regeneration of hepatocytes. In the later treatment, significant changes and fibrosis with regenerative changes were observed. In conclusion, the best effect was observed when extract and anti-TB drugs were administered together. The authors suggest that UrAc (main component of *O. sanctum*) is responsible for inhibiting the peroxidation of lipids, showing HPP action [53].

Pollen obtained from the hive *Apis mellifera* L. (compound with 50-70% resins, 10-15% essential oil, 30-50% wax and 5-10% pollen; also contains with vitamins, folic acid, nicotinic acid and some minerals: calcium, magnesium, manganese, vanadium, iron, copper, strontium, aluminium and silicon) showed HPP effect against the harm caused by alcohol and CCl_4. The protector effect of EtOH extract from pollen (150 mg/kg) was evaluated against the harm produced by INH (100 mg/kg) in male albino mice (administered by 40, 50 and 60 days). The results showed that the EtOH extract administered before the INH reduced of ALT, AST, ALP and serum bilirubin levels, showing a better effect in the group that received the extract for 30 days. Histological liver analysis showed regeneration in some hepatocytes in the group previously treated with the extract, being more pronounced in the group at 60 days, since normal structure of the sinusoid space, rounded or polyhedral hepatocytes with simple nucleus and some bi-nucleates with prominent nucleolus were observed, which indicate regeneration [54].

The HPP activity of the EtOH (70%) extract of *Luffa acutangula* (Cucurbitaceae) fruit was evaluated against injury caused by RIF in Wistar rats (both sexes) using Sil as PC. RIF (100 mg/kg) was administered by O.V./30 days, Sil (200 mg/kg) was administered for 15 days (from day 16 to 30) together with RIF (administered from day 1); the extract was administered at 3 doses (100, 200 and 400 mg/kg) for 15 days (from day 16 to 30) plus RIF (all period of treatment, daily for 30 days). The AST, ALT, ALP, LDH and total proteins in serum levels was determined, and the liver homogenate MDA, GSH, SOD and CAT; likewise, histological cuts of the liver were analyzed. The results showed a dose-dependent response, and the extract of *L. acutangula* at 400 mg/kg showed better results than Sil group. In the histological analysis, the groups treated with the extract showed a moderate centrio-lobular fat and infiltration of lymphocytes, as well as regeneration of hepatocytes with prominent nuclei and a very low infiltration of inflammatory cells. Regarding biochemical results the same tendency was observed, the highest dose of the extract was the better. Author concluded that this extract has an HPP effect against the harm caused by RIF [55].

The HPP effect of the EtOH extract from *Cassia fistula* (Fabaceae) leaves at 400 and 500 mg/kg were evaluated in male Wistar rats with hepatitis caused by INH/RIF (50 mg/kg each), the treatments were administered by O.V./30 days. At the end, levels of ALT, AST, ALP and TotBil were determined. The results showed that the groups co-administered with both doses of *C. fistula* presented low levels of ALT, AST and ALP; and the liver histological analyses from *C. fistula* group with lower dose showed slight regeneration in some hepatocytes and a slight recovery; but in the group with high dose of EtOH extract vascular congestion and evidence of regeneration were observed, with some apoptotic bodies. The authors concluded that the *C. fistula* at high dose (500 mg/kg) shows a better effect on hepatitis caused by anti-TB drug in rats [56].

Also, has been reported that the EtOH extract from *Picrorhiza kurroa* (Plantaginaceae) roots and rhizomes has protector effect against hepatitis caused by INH/RIF (200 mg/kg each) in male Wistar rats administered during 45 days by O.V. Next, levels of LPO, GSH (baseline and in the presence of promoters such as ascorbate, $FeSO_4$ and *tert*-butylhydroperoxide), and the activity of antioxidant enzymes were determined in the liver mitochondria. Administration of anti-TB drugs significantly raised LPO values, reduced GSH levels and antioxidant activity of GSH, glutathione peroxidase (GPx), glutathione *S*-transferase (GST), SOD and CAT. Concomitant administration of the EtOH extract of *P. kurroa* (50 mg/kg for 45 days) significantly prevented the alterations caused by anti-TB drugs, and kept the rats in a near-normal state; the authors concluded that the HPP effect of this extract is probably due to the stimulation of antioxidant enzymes or the neutralization of FR by the presence of electrophilic components such as picroside I, picroside II and kutkoside (main compounds in *P. kurroa*) [57].

In another experiment, the potential HPP effect of the EtOH extract from *Ixora pavetta* (Rubiaceae) leaves and stem at 200 and 400 mg/kg were evaluated against the toxicity caused by INH/RIF (100 mg/kg, each one) in male Wistar rats, using Sil (2.5 mg/kg) as PC and the treatments were administered by O.V. for 21 days. After that, ALT, AST, ALP, TotBil, direct bilirubin, total cholesterol levels were quantified, and liver histopathological analysis was made. The results showed a significant reduction in biochemical parameters evaluated in the groups that received the extract at both doses respect to anti-TB group. Histopathological analysis of the liver from extract groups showed signs of protection, with an absence of necrosis and regenerative changes in the central vein of the hepatic tissue. The authors concluded that *I. pavetta* protects against the oxidative damage in the liver caused by RIF/INH [58].

The extracts from *Achyranthes aspera* Linn. (Amarantaceae) aerial parts were evaluated against the HPT induced with RIF (1 g/kg/O.V.) in Wistar rats of both sexes. The extract was administered every 12 hrs/two days at 50, 100, 200, 400 and 800 mg/kg and Sil (100 mg/kg, PC). The results showed a dose-dependent effect and the HPP effect of extract at higher dose, the effect was comparable to Sil. Therefore, the authors concluded that this extract has a protector effect against injury caused by RIF [59].

The MeOH extract *Cuscuta reflexa* (Convolvulaceae) aerial parts at 100, 200 and 400 mg/kg by intraperitoneal administration in male rats were evaluated against the harm induced by INH/RIF (50 mg/kg each) for 21 days, and Sil was PC. The results of the biochemical parameters (ALT, AST, ALP, TotBil and γ-GT) were lower in the groups treated with Sil and with the *C. reflexa* MeOH extract, and the effect was dose-dependent (being best at 400 mg/kg). In addition, histological liver analysis of the animals that received Sil and *C. reflexa* did not show alterations; it was therefore concluded that the MeOH extract of *C. reflexa* is a good candidate for using as HPP agent, against the injury caused by INH/RIF [60].

The MeOH extract of the *Bombax ceiba* L. (Malvaceae) flower at 150, 300 and 450 mg/kg administered by O.V. for 10 and 21 days was evaluated in rats with harm caused by INH/RIF (100 mg/kg, each), using Sil (2.5 mg/kg, PC). The extract reduced the levels of hepatic enzymes and OS markers; the protector effect is attributed to the presence of flavonoids and sesquiterpenes [61]. Among studied medicinal plants, pharmacological properties and medicinal uses of *Oxalis corniculata* Linn (Oxalidaceae) remain in doubt due to the high content of oxalates. In 2014, Sohail et al. [62] developed an extraction method with different solvents to reduce the oxalates amount present in this plant. The MeOH extracts of the stem and leaves with a low oxalate content showed a good antioxidant activity *in vitro* (DDPH and β-carotene linoleate), and showed HPP activity compared against the hepatic damage caused by thioacetamide (aqueous and EtOH extracts) and against CCl_4 (MeOH) [63,64]; therefore, they evaluated the HPP activity *in vivo* against the OS caused by INH/RIF (100 mg/kg, each) in Wistar rats. The MeOH extract (stems and leaves) was administered orally for 21 days, at 400 mg/kg, using Sil (2.5 mg/kg) as PC. In this study, a reduction of the enzyme levels (AST, ALT, ALP) and bilirubin was reported, the result being greater in the group that received the leaf extract, although none of the groups showed levels below those with Sil. Regarding the histological analysis, in the groups treated with both extracts and with Sil, peri-portal and centri-zonal inflammation was observed, with normal lobular architecture of the hepatic cells. With these results, the protection of the extracts with low oxalate content was proven against the damage caused by anti-TB drugs [62].

The hepato-therapeutic role of the aqueous and EtOH extract from *Embelia tsjeriam-cottam* (Primulaceae) berries at 200 mg/kg were evaluated in rats with injury caused by INH (50 mg/kg) for 30 days administered by O.V., using Liv 52™ as PC. Liv 52 is a mixture of 8 plants [*Capparis spinosa* (Capparaceae) 32 mg, *Cichorium intybus* (Asteraceae) 32 mg, *Mandur bhasma* (iron oxide) 32 mg, *Solanum nigrum* 32 mg, *Terminalia arjuna* (Combretaceae) 32 mg, *Cassia occidentalis* 16 mg, *Achillea millefolium* (Asteraceae) 16 mg and *Tamarix gallica* (Tamaricaceae) 16 mg (5 mL/kg)]. After that, the ALT, AST, bilirubin and MDA were determined, these values were lower in the groups co-administered with the extract, and the SOD, CAT and GSH levels increased. With these results, it was concluded that both extracts of *E. tsjeriam-cottam* and Liv52 protect from the hepatic toxicity caused by the intake of INH, observing better effect in the EtOH extract [65].

Evaluation of essential oil (EO) and other organic extracts from medicinal plants

The EO from *Citrus reticulata* (Rutaceae) (200 mg/kg) was evaluated in Wistar rats with injury was caused by INH (50 mg/kg/O.V.) for 30 days, using Liv 52 as PC. The animals treated with the *C. reticulata* EO and Liv52 showed a reduction in all biochemical parameters (ALT, AST, bilirubin), suggesting that the plant protects against the liver damage caused by INH [66].

In another experiment, HPT damage was induced with INH/RIF/PZA (50:100:350 mg/kg) in Wistar rats and the organic extract of *Plectranthus amboinicus* (Lamiaceae) aerial parts at 600 and 900 mg/kg was evaluated during 14 days and Sil (50 mg/kg v.o) was used as PC. In the groups administered with *P. amboinicus* extract and Sil, the levels were significantly lower compared with the anti-TB group. Also, in these groups, MDA levels decreased significantly, but there was an increase in levels of GSH; however, there were no significant differences in the data at either dose. The benefic effect of the *P. amboinicus* is due to the presence of flavonoids and tannins, which may be responsible for the HPP activity [67].

The petroleum ether extract (60-80%) of the *Ficus carica* (Moraceae) leaves at 200 mg/kg administered over 10 days against the hepatic harm caused by RIF (50 mg/kg), also reduced ALT and AST in the extract group and re-established liver cytostructure, being very similar to the healthy control, suggesting it as a good alternative as hepato-regenerator agent [68].

Evaluation of polyherbal mixtures from medicinal plants

A clinical study was performed with 48 TB patients recently diagnosed between 18-60 years old, in the intensive treatment phase (RIF, 450 mg; INH, 300 mg; PZA, 1500 mg; Et, 800 mg) for 4 months and RIF+ INH for two more months, the patients was divided into two groups: one received anti-TB therapy plus placebo, and the other received anti-TB therapy plus two capsules twice a day of Livina™ [polyherbal mixture of 11 plants extracts, capsule with 50 mg each of the following: *Picrorhiza kurrooa* (Plantaginaceae), *Phyllanthus niruri, Andrographis paniculata* (Acanthaceae), *Cichorium intybus* (Asteraceae), *Tephrosia purpurea* (Fabaceae), *Crinum asiaticum* (Amaryllidaceae), *Astonia seholanis* (Alismataceae), and 25 mg of *Holarrhena antidysenterica* (Apocynaceae), *Tinospora cordifolia, Terminalia chebula, Asteracantha longifolia*]. In this study, the levels of hepatic enzymes at the start of treatment, and at 4th and 8th week were quantified to evaluate differences between groups. The group that received Livina showed low levels of ALT, AST and ALP respect to placebo group. With this experiment, the safety and efficacy of this polyherbal mixture was confirmed, mixture which can be combined with anti-TB drugs to reduce the problems caused by this therapy and also to avoid cases of drug-resistance [69].

On the other hand, the *in vitro* effect of Hepatoplus™ [HP, capsules with polyherbal formula: *Phyllanthus amarus* (complete plant) 100 mg, (*Eclipta alba* leaves) 50 mg, *Tephrosia purpurea* (leaves) 30 mg, *Curcuma longa* (rhizomes) 30 mg, *Picrorhiza kurrooa* (root) 20 mg, *Withania somnifera* (root, 100 mg), *Pinus succinifera* (amber, 37.5 mg), *Pistacia lentiscus* (resinous sap, 25 mg), *Orchis mascula* (seeds,

25 mg) and *Cycas circinalis* (flowers, 62.5 mg) was evaluated. This investigation was performed on the cellular line Chang (human), which were treated with INH+RIF (30 ng/mL) and HP at 50, 100 and 200 ng/mL, for 24 h. Viability and cellular proliferation were evaluated by MTT [through dependent reduction of mitochondria of bromide 3-(4,5-dimethyltiazol-2-yl)-2, 5-diphenyl tetrazolium and formazan)]; evenly, levels of AST, ALT, ALP and HDL, and antioxidant profile, (CAT, SOD and GSH) were measured, and by means of RT-PCR, sequences were sought for genes GAPDH, apoptosis and CYP2E1. In regard to the function of hepatic markers, the results showed an increase in the ALT, AST and ALP levels for group treated only with the anti-TB drug and in groups co-treated was observed a reduction on these levels dependent on dose. For antioxidant enzyme levels, a reduction was observed in the group that received HP respect to anti-TB group; also, was described an increase for SOD, CAT and GSH values ingroup that received HP at 100 and 200 ng/mL, showing a dose-dependent effect. In HP group was observed a reduction of apoptotic activity respect to anti-TB group. In conclusion, HP™ (50 and 100 ng/mL) is an alternative to protect against the hepatic harm produced by anti-TB therapy [70]. In addition, the HPP activity of HP at 50 and 100 mg/kg was evaluated on Sprague Dawley rats with liver harm caused by INH/RIF (50 mg/kg each) and Liv 52 (100 mg/kg) was used as PC. The sample was administered for 30 days by O.V. Parameters of hepatic function (ALT, AST, total protein, albumin, TotBil, ALP, lactate dehydrogenase, GGT and C-reactive protein, clotting time, isocitrate dehydrogenase, α-cetoglutarate dehydrogenase, malate dehydrogenase and NADH dehydrogenase) were determined; as well as antioxidant enzymes (CAT, MDA, SOD, GPx and GSH) were determined; hepatic liposomal enzymes, cathepsin D, β-galactosidase; also gene expression studies were performed by RT-PCR for CYP2E1, β-actin, BAX, Bcl-2, caspase 3 and p53 (anti-apoptotic genes), as well as comet assays and histological analyses. In groups co-treated with Liv 52 or HP at 100 mg/kg, showed ALP, LDH, GGT, PT, CRP and albumin levels similar to healthy group. Likewise, it was noted that HP and Liv 52 increased GSH, GPx, CAT and SOD levels, and significantly reduced levels of MDA compared with the anti-TB group. In the anti-TB group, the β-galactosidase and cathepsin D activity was increased; these values were similar to normal levels in the group treated with HP in dose-dependent manner, and in the group co-treated with Liv 52, normal enzymatic liposomal activity was reported. The results of the comet assay showed that groups co-treated with Liv 52 and HP had less DNA injury compared with the anti-TB group; the effect was dose-dependent. These same results were observed in the expression of CYP2E1 and apoptotic genes, being less this expression in groups co-administered with Liv 52 or HP. Respect to the histopathological findings, in the groups co-treated with HP and Liv 52 showed similar architecture to the healthy group. The authors concluded that the use of HP effectively protects hepatic cells, which may be due to the presence of active antioxidant ingredients, such as fillantin, hypofillantin, withaferin, amber and curcumin, among others, which are present in the polyherbal formula [70-73]. In literature there are numerous vegetable species that have been evaluated as possible HPP agents against the damage caused by CCl_4, EtOH, D-galactosamin, nitrobenzene, morphine, methotrexate, diclofenac and/or acetaminophen, mainly, but their effect is unknown against the damage caused by anti-TB drugs [73,74].

Compounds (natural and synthetic) with HPP effect in pre-clinical evaluation

To date, a few studies have been performed for determine the HPP effect of some compounds obtained from medicinal plants against the harm caused by anti-TB drugs. Some compounds are: Sil, curcumin, resveratrol, ursolic acid (UrAc), oleanolic acid (OlAc), *N-trans*-caffeoyldopamine, vitamin C and vitamin E; which have been shown to have a protector effect, mainly through antioxidant activity [27,75]. Sil is mixture of flavonoids and is one of the most studied and most employed (both *in vivo* and clinical studies) as PC against the damage caused by anti-TB drugs. Sil also presents other biological activities, such as: antioxidant, antiinflammatory, immunomodulator, antiproliferative, antiviral, anti-fibrotic and other [20-27].

In one experiment, the HPP role of Sil (50 mg/kg) was evaluated against the damage caused by INH in rabbits, administered by O.V. for 19 days and ALT and bilirubin were analyzed. The INH group had an increase in bilirubin and a decrease in ALT values respect to healthy group; the group treated with Sil + INH, maintained levels very close to the healthy group. With these results, the HPP effect of Sil was confirmed [76].

The *N*-acetylcysteine (NAC, 100 mg/kg, a precursor of GSH) was investigated against the harm caused by INH/RIF (50 mg/kg, c/u) in Wistar rats. All treatments were administered by intraperitoneal route for 3 weeks. Histological analysis showed protection, since no lesions were observed in the group that received NAC; this prevents the onset of OS caused by INH/RIF, due to an increase in SOD, CAT and GSH levels [77].

A clinical study was carried out in 60 patients (60 years old) recently diagnosed with TB, who were divided into two groups and treated for two weeks. All patients received anti-TB treatment [INH (5 mg/kg), RIF (10 mg/kg), PZA (25 mg/kg) and Et (15 mg/kg)] and one group was NAC co-administered (600 mg/kg twice a day). Upon evaluating hepatic enzymes (ALT and AST) and bilirubin, it was reported from the first week of treatment, NAC avoided raise of hepatic enzymes, an effect that was maintained through the second week, maintaining levels very close to baseline (start of treatment); the authors concluded that NAC is an alternative to avoid the HPT cause by this therapy [78]. Other clinical study was performed on 85 patients (>50 years), recently TB diagnosed and treated with INH, RIF, PZA and Et; these were divided into a placebo group and one treated with NAC (600 mg/kg, twice/day) with follow-up for two months, with blood samples taken every 14 days. The results showed a reduction in ALT, AST and CRP, from the start of treatment. The authors concluded that NAC is a coadjuvant in the TB treatment, since it prevents and reduced the incidence, duration and severity of HPT, in addition, improved the quality of life of patients [79].

Curcumin (natural compound) with an important HPP effect against the damage caused by CCl_4 (acute and subacute damage, attenuated by OS, suppressed inflammation and fibrogenesis caused by this agent), paraquat, EtOH (*in vivo* and *in vitro*), dimethylnitrosamine, D-galactosamin, thioacetamide, aflatoxine, nicotine; however, to date, its beneficial effect against the damage caused by anti-TB drugs is unknown; there is only one work that describes the HPP effect of a mixture of Sil, curcumin and NAC [80-87].

Punicalagin (ellagitannin, isolated from *Punica granatum*), showed a protector effect against the CCl_4, acetaminophen and cyclophosphamide damage, but its effect against anti-TB drugs has not been reported [88]. The protector effect of ursodeoxycholic acid (UDCA at 15, 50 and 150 mg/kg) was analyzed against liver harm caused by INH/RIF (75 and 150 mg/kg) in female CD-1 mice during a week. Pre-treatment with UDCA significantly attenuated the onset of OS in the livers of the UDCA treated, in addition to reducing apoptosis. The anti-apoptotic effect seems to be related with regulation of genes Bcl-2 and Bax, which are expressed in the liver. The best results were observed at 50 mg/kg. These findings suggest that UDCA may protect against the INH/PZA injury caused by antioxidant and anti-apoptotic effects. UDCA, also has a HPP effect shown against amoxycilin with clavulanic acid in rats [89].

N-trans-caffeoyldopamine, a phenylpropenic acid amide clovamide-type, isolated from *Capsicum annuum* (Solanaceae), *Theobroma cacao* (Malvaceae) and *Lycium chinense* (Solanaceae), was tested against the oxidative injury caused by INH and RIF (100 mg/kg each) in male Wistar rats. *N-trans*-caffeoyldopamine was administered by O.V. at 2.5 mg/kg, caffeic acid (2.5 mg/kg) and Sil (2.5 mg/kg) as PC. The results showed that the groups co-treated with the caffeic acid or Sil, significantly reduced .AST, ALT and ALP levels, as well as showing a good antioxidant activity, since they increased levels of SOD and GSH in hepatic tissue and reduced levels of LPO; however, a better effect was observed with *N-trans*-caffeoyldopamine and caffeic acid was less active, and its effect is probably due to inhibition of $CYP_{450}2E1$ [75].

On the other hand, OlAc and UrAc have important hepatoprotector effect against the damage caused by EtOH, CCl_4, D-galactosamine, acetaminophen, cadmium, bromobenzene, phalloidin, thioacetamide and other hepatotoxic substances. HPP effect was shown against the damage caused by RIF/INH/PZA (10/10/30 mg/kg), administered subcutaneously at 100 and 200 µg/mouse/day, in BALB/c mice for 11 weeks. The groups treated with OlAc/UrAC mixture showed a significant reduction in AST and ALT levels; likewise, few histological changes were observed in the livers of these groups compared with anti-TB group, being 100 µg the best doses [90].

The modulator and HPP effect of vitamins C (8 mg/kg) and E (5 mg/kg) were evaluated against the hepatic damage caused by RIF (9 mg/kg/O.V.) in Wistar rats over 90 days. The results showed a significant reduction in AST level in group co-administered with vitamin E, and non-significant but lower levels of ALT in the same group. The group co-administered with vitamin C showed a non-significant reduction in levels of ALT. However, both vitamins reduced abnormality in the rat's sperm, since it has been noted that RIF also damages this kind of cell. In conclusion, both vitamins protect sperm cells, and only vitamin E showed an HPP effect against RIF, although for vitamin C, the effect is questionable [91].

Yulangsan (YLSPS) a polysaccharide obtained from *Millettia pulchra* (Fabaceae) is used as a HPP, and was evaluated at 100, 200 and 400 mg/kg/O.V. against the harm induced with INH or RIF (100 mg/kg) and the mixture of both (INH/RIF, 100 mg/kg each), in Kunming mice over 10 days, using diphenyl-dimethyl-bicarboxylate (DDB) as PC. The results showed that YLSPS has a beneficial effect by reducing ALT and AST levels, and increasing SOD, GSH, and GPx values; however, the most important finding was the protection at histological level, the effect was dose-dependent, suggesting YLSPS as a good co-treatment alternative in cases of TB [92].

In cases of TB/HIV/AIDS, antiretroviral therapy (zidovudine 300 mg/tablet) plus a mixture of anti-TB drugs may increase liver damage, which could become fatal. A study was performed in rats, which were treated with zidovudine (8.5 mg/kg/day) plus 25 mg of anti-TB mixture (RIF/INH/PZA/Et, 150, 75, 400 and 275 mg, each), in addition was administered Neutrosec™ liquid (0.4 mL/kg/day), which contains (DL)-methionine, choline, vitamin B1, dexpantenol, folic acid, (DL)-α-tocopherol acetate, biotine, vitamin B6, nicotinamide, vitamin B2, and cyanocobalamin. This sample was administered by O.V. for 60 days. Significant differences were observed on AST and ALP levels in the group treated with zidovudine (8.5 mg/kg/day) plus Neutrosec® respect to zidovudine plus anti-TB group. The authors concluded that the HPT effect of zidovudine combined with anti-TB drugs was due to the generation of FR, which may be modulated by Neutrosec®, in spite of not showing significant differences in levels of GSH, CAT or MDA [93].

Thymoquinone, main active compound of *Nigella sativa* (Ranunculaceae) seeds, was evaluated in female Sprague-Dawley rats, for its HPP activity against the injury caused by PZA/Et/INH/RIF (175, 140, 70, 52 mg/kg, each). Thymoquinone was administered at 10, 20 and 40 mg/kg dissolved in 5 mL of olive oil, and Sil (40 mg/kg) was used as PC. The anti-TB mixture, thymoquinone and Sil were administered every third day by O.V. Upon ending the treatments, ALT, AST, haemoglobin, ALP, albumin, cholesterol, urea, uric acid and creatinine levels were determined. In addition, LPO, SOD, CAT, adenosine triphosphatase (ATPase) and glucose-6-phosphatase (G-6-Pase) in liver and kidney tissue were quantified, along with histological analysis. The results showed a dose-dependent effect, observing a decrease in liver damage at 10 mg/kg dose, although at 40 mg/kg results were statistically significant, which was comparable to the PC (Sil). The same effect was observed in LPO and SOD levels, and in enzymatic activity in liver and kidney tissues (CAT, ATPase and G-6-Pase). The histological analyses showed that the thymoquinone at 10 mg/kg showed slight recovery, with evidence of regeneration in some hepatocytes; the treatment with 20 mg/kg showed some inflammatory cells, absence of necrosis, rearrangement of hepatocytes in string and the treatment with 40 mg/kg showed a reduction in necrosis and inflammation with regenerated hepatocytes. Treatment with Sil showed normal hepatocytes and normal lobular architecture. With these results, the HPP and antioxidant activity of thymoquinone against the harm caused by anti-TB drugs was confirmed but the effect was minor than Sil [94].

The efficacy and safety of quercetin (antioxidant) combined with polyvinylpyrrolidone (capillary agent stabilizing) was evaluated in 124 TB patients recently diagnosed (20-79 years old). All patients received the standard therapy: INH (0.3 g), RIF (0.6 g), PZA (2 g), Et (1.2 g) and an injection of St (1 g). The mixture of quercetin-polyvinylpyrrolidone (QP) was administered by O.V. at 0.5 g/100 mL of NaCl 0.9%, during 10 days from hospital admission. Patients co-treated with QP showed weight gain, this parameter is crucial, since patients with treatment TB lose weight. They also showed a reduction in adverse effects such as cardiac disorders, toxic hepatitis and allergic dermatitis; QP raised the tolerance (20.42%) towards

the treatment of TB. Likewise, upon analyzing transaminase data, a reduction was observed in the group co-treated with QP for two months. Therapy with QP did not cause adverse events [95].

3,5-dicloro-salicylaldehyde isonicotinoyl hydrazone (SH7, INH analogue), can protect against hepatic harm caused by INH, so it was the object of evaluation in white mice. Animal groups were treated by O.V. with INH (7.5 and 15 mg/kg), SH7 (7.5 and 15 mg/kg), mixture of INH + SH7 (7.5 mg/kg, each), and mixture of INH + SH7 (7.5 and 15 mg/kg). Groups that received the combination INH + SH7 (both doses) showed low levels of MDA respect to INH group. Also, SOD and CAT activity increased significantly in these groups. At the histological level, different degrees of karyopyknosis (hepatocyte nucleus reduced with condensed chromatin) were observed in some parts of hepatocytes and isolated cases of infiltration of leukocytes in some lobes. In the group that received the combination of INH (7.5 mg/kg) + SH7 (7.5 mg/kg) and the group that received the combination at higher dose of SH7, showed more pronounced vascular hyperaemia than the other groups. There was no cellular perivascular infiltrate, cytoplasm showed small granules. In conclusion, SH7 reduced the OS caused by INH administration for 30 days, since it showed that it reduces levels of MDA and re-establishes levels of SOD and CAT; however, more studies are needed to confirm the HPP activity [96].

Biological products with HPP effect

Nong et al. [97] described the hepatoprotective effect of mesenchyme bone marrow stem cells administered by intraperitoneal via (1×10^6 cells/0.5 mL/rat) at day 30 of experimentation (last day of treatment) against the damage caused by INH/RIF (200 mg/kg each, administered by O.V. for 30 days) in male Wistar rats. The results showed that the stem cells reduced the damage caused by anti-TB drugs, by maintaining or reducing levels of albumin, urea, creatinine, and hepatic enzymes (ALT and AST); likewise, a reduction was observed in the levels of the parameters of OS (TBARS and NO), along with a slight change in levels of GSH, SOD and CAT. This indicates that the stem cells of mesenchyme bone marrow increased the levels of SOD and CAT and reduced levels of ROS, thus protecting the liver and kidneys of rats treated with the mixture of anti-TB drugs.

The HPP effect of co-enzyme Q10 (10 mg/kg) was evaluated against the damage caused by INH/RIF (50 mg/kg each) in Wistar rats for 28 days, using Sil (25 mg/kg) as PC. Evaluation of the biochemical parameters showed that the treatment with co-enzyme Q10 caused a statistically significant reduction ($p<0.05$) in levels of the markers of hepatic function (ALT, AST and ALP), and re-established the normal levels of antioxidant enzymes, reduced GSH level and peroxidation of lipids [98].

The processes of liver repair, after damage, are directed by growth factors, released in response to the damage. Hepatocyte Growth Factor (HGF) and its receptor, c-Met, represent the first line of defense against the hepato-toxic factors, and were identified as a potent mitogen in rat hepatocytes. The role of HGF/c-Met in the regulation of cellular redox state and OS in the liver was described. The results show that HGF/c-Met regulates the activation of key transcription factors that govern the expression of antioxidant and survival genes, such as nuclear factor κB (NF-κB) or the protein C delta kinase (PKCδ), dependent on the transcription factor Nrf2, helping the cell survive under OS, such as in the damage from alcohol metabolism. An experiment was carried out in BALB/c mice with damage caused by RIF/INH (150/75 mg/kg/O.V. for 7 days) to evaluate the HPP effect of HGF (10 mg/kg). The livers of co-treated mice with HGF showed scare apoptotic cells, significantly reducing the cellular death induced by drugs. The HGF group showed ALT and AST levels very similar to the healthy control; OS was reduced in HGF group and induced an increase in ERK ½ and PKCδ which are signaling pathways for the production of liver protective proteins [99].

CONCLUSION

The basic drugs for TB treatment are RIF, INH, PZA mixture; this treatment mainly causes HPT, this side effect favors the abandonment of treatment and induces the occurrence of cases of MDR-TB or XDR-TB. For this reason, it is necessary to seek alternatives to reduce or prevent this effect. To date, are few medicinal species and scare number of pure compounds or biological products investigated for their possible use as hepatoprotective substances. In this context,it is worth to mentioning polyherbal mixtures such as Liv 52™, Livina™, Heptoplus™, the mixture of *Phyllanthus niruri/Curcuma xanthorrhiza/C. longa* and the mixture of *Curcuma longa/Tinospora cordifolia*, that have been shown an important HPP effect in TB patients. Likewise, the solution of the mixture of quercetin with polyvinylpyrrolidone has been evaluated in clinical studies (patients with TB) and has been reported to have a beneficial effect against the liver damage provocate with anti-TB drugs.

Another compound that has been evaluated for its hepatoprotector effect on patients with tuberculosis is NAC. The rest of the pure compounds and/or biological products have been tested in preclinical studies (mainly in rats), and may be candidates for evaluation in clinical studies. These findings could orientate further research for both, biomedical researchers and clinicians.

In other instance, this systematic review indicates the limited progress in the discovery and development of HPP treatments. Thus, we conclude that is urgent to investigate extensively more medicinal plants, especially those used by traditional medicine all around the world. Another important area of opportunity is the synthesis of HPP agents based on the molecular structure of NAC or quercetin, for example.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest statement.

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