IJPSR (2016), Vol. 7, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 September, 2015; received in revised form, 22 November, 2015; accepted, 17 December, 2015; published 01 March, 2016

EFFECT OF *ALOE VERA* EXTRACT ON THE HEPATOTOXICITY INDUCED BY ISONIAZID AND RIFAMPICIN DRUG IN MALE WISTAR RATS

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Keywords:

Wistar rats, *Aloe vera*, Isoniazid, Rifampicin, Hepatotoxicity

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ABSTRACT: Male Wistar rats were procured from 'The Bombay Veterinary College', Parel, Mumbai. The animals were maintained and housed in cages and were acclimatized in laboratory conditions for ten days prior to the experiment. The experimental rats were fed orally with isoniazid 300 mg/ 70 kg body weight / day; rifampicin 450 mg / 70 kg body weight / day and Aloe *vera* extract 50 mg/ kg body weight / day for 30 days. Blood samples of the above groups (A to H) were taken after 30th day from cardiac puncture for estimation of mean concentration serum of AST, ALT, ALP, and ACP, bilirubin, total proein, total albumin and total globulin in serum of rats treated with *Aloe vera,* Isoniazid and Rifampicin independently as well as in combinations. In our study the more commonly measured 'liver' enzymes are showing significant increase in the levels of AST, ALT, ALP, and ACP, bilirubin total proein, total albumin and total globulin in serum of rats treated with Isoniazid and Rifampicin individually and in combination when compared with control rats, whereas the levels of AST, ALT, ALP, and ACP, bilirubin, total protein, total albumin and total globulin in serum were found somewhat decreased in rat treated with *Aloe vera* independently as well as in combination with Isoniazid and Rifampicin drug.

INTRODUCTION: Liver is one of the largest and vital organs of human body and is vulnerable for tissue insult continuously. Liver regulates various important metabolic functions, the distortion of which causes hepatic damage [1]. Liver disease is still a worldwide health problem. Drug-induced hepatotoxicity is one of the major concerns which limit the therapy and drug use. About 2% of all causes of jaundice in hospitalized patients are drug induced.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(3).1314-20

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (3).1314-20

Approximately quarter of cases of fulminant hepatic failure are thought to be drug related. More than 900 drugs have been implicated in causing liver injury [2] and it is the most common reason for a drug to be withdrawn from the market.

Conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects. This is one of the reasons for many people in the world including those in developed countries, turning to complementary and alternative medicine. Many traditional remedies employ herbal drugs for the treatment of liver ailments [3, 4, 5, 6].

Aloe vera has been used for many centuries for its curative and therapeutic properties and although over 75 active ingredients from the inner gel have

been identified, the therapeutic effects have not been correlated well with each individual component[7]. Many of the medicinal effects of aloe leaf extracts have been attributed to the Polysaccharides found in the inner leaf parenchymatous tissue [8, 9], but it is believed that these biological activities should be assigned to a synergistic action of the compounds contained therein rather than a single chemical substance [10].

In the pharmaceutical industry, *Aloe vera* has been used for the manufacture of tropical products such as ointments and gel preparations, as well as in the production of tablets and capsules [11, 12]. Important pharmaceutical properties that have recently been discovered from both the *Aloe vera* gel and whole leaf extracts include the ability to improve bioavailability of co-administered vitamins in human subjects [13]. The biological activities include promotion of wound healing, antifungal activity, hypoglycemic or anti diabetic effects, anti inflammatory, anticancer, hepatoprotective, immunomodulatory and gastroprotective properties.

In recent years study has shown that both *Aloe vera* gel and whole leaf extracts have been investigated for their drug absorption enhancing properties and some of these extracts have been associated with cytotoxic effect and some others were not efficient enough to ensure that therapeutic levels of poorly absorbable drugs are achieved [14].

a)

Isoniazid drug is used for the treatment of tuberculosis and diabetes. Isoniazid induces generalized convulsions, coma and metabolic acidosis. Death may occur from acute respiratory failure or hypertension, liver and peripheral nervous and hematologic system is the main target organs of isoniazid chronic toxicity. Over dosage of Isoniazid has produced nausea, vomiting dizziness, slurred speech, blurred vision and visual hallucinations. Symptoms of over dosages usually occur within 30 minutes to 3 hours following ingestion of the drug [15, 16].

b)

Rifampicin or rifampin (USAN) is a bacteriostatic antibiotic drug of the Rifampicin group. It is a semisynthetic compound derived from Streptomyces mediterranei. Rifampicin may be abbreviated RIF, RMP, RD or R. Rifampicin was introduced in 1967 as a major addition to the cocktail-drug treatment of tuberculosis and inactive meningitis, along with isoniazid, ethambutol, pyrazinamide and streptomycin. It must be administered regularly daily for several months without break; otherwise, the risk of drug-resistant tuberculosis is greatly increased [17].

c)

Rifampicin is typically used to treat Mycobacterium infections, including tuberculosis and leprosy. It also has a role in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) in combination with fusidic acid. It is used in prophylactic therapy against *Neisseria meningitidis* (meningococcal) infection. It is also used to *treat Listeria species, Neisseria gonorrhoeae, Haemophilus influenzae* and *Legionella pneumophila*. The most common effects are fever, gastrointestinal disturbances, rashes and immunological reactions. Liver damage, associated with jaundice, has also been reported and in some rare cases has led to death [18, 19].

MATERIALS AND METHODS:

Fresh *Aloe vera* leaves were brought from the botanical garden and sample was identified and was brought to the laboratory in the Department of Zoology S.S & L.S. Patkar College Goregaon (west), Mumbai India.

Extraction:

Aloe vera leaves were rinsed 2-3 times in the tap-water. 50 grams of leaves were then grounded with 50ml of distilled water in sterilized pestle and mortar. The homogenized mixture was filtered twice through a cotton cloth and centrifuged at 5,000 rpm for 10 minutes. Supernatants were collected and diluted with 50 ml of distilled water to obtain a concentration of 50mg /day / kg body wt. of male Wistar rat. As per the body weight, Isoniazid tablets (Macleods Pharmaceuticals, Andheri, Mumbai) and Rifampicin capsules (Lupin Ltd, Kartholi, Jammu & Kashmir) were dissolved in sterile distilled water and given orally.

Experimental Design:

Forty eight (48) male Wistar rats (age 60-100 days, weighing 175-260 mg) were purchased and procured from 'The Bombay Veterinary College',

Parel, Mumbai. The animals were maintained and housed in cages in the Department of Pharmacology, The Bombay Veterinary College, Departmental animal house and were fed on commercial rat pallets brought from the market. The rats were acclimatized in laboratory conditions for ten (10) days prior to the experiment. The rats were divided into eight (8) groups containing Six (6) rats in each group. The experiments were carried out according to the guidelines and prior approval of Institutional Animal Ethics Committee (CPCSEA No. MCV/IAEC/19/2014) for the present experimental study.

Group A: Control i.e. male albino wistar rats fed with rat pellets and ordinary water.

Group B: Male albino wistar rats fed orally with *Aloe vera* extract 50 mg / kg body weight / day for 30 days.

Group C: Male albino wistar rats fed orally with *Aloe vera* extract 50 mg / kg body weight / day and Isoniazid drug (LD) the dose will be decided on the basis of human consumption, 300 mg / 70 kg body weight / day for 30 days

Group D: Male albino wistar rats fed orally with *Aloe vera* extract 50 mg / kg body weight / day and rifampicin drug (LD) the dose will be decided on the basis of human consumption, 450 mg / 70 kg body weight / day for 30 days

Group E: Male albino wistar rats fed orally with isoniazid drug (LD) the dose will be decided on the basis of human consumption, 300 mg / 70 kg body weight / day for 30 days.

Group F: Male albino wistar rats fed orally with rifampicin drug (LD) the dose will be decided on the basis of human consumption, 450 mg / 70 kg body weight / day for 30 days.

Group G: Male albino wistar rats fed orally with isoniazid + rifampicin drug (LD) the dose will be decided on the basis of human consumption, 300 mg (isoniazid) + 450 mg (rifampicin) / 70 kg body weight / day for 30 days

Group H: Male albino wistar rats fed orally with *Aloe vera* extract 50 mg / kg body weight / day and with isoniazid+ rifampicin drug (LD) the dose will be decided on the basis of human consumption, 300 mg (isoniazid) + 450 mg (rifampicin) / 70 kg body weight / day for 30 days.

Analysis of the blood samples:

Blood samples of the above groups were taken after 30th day from cardiac puncture and was analyzed at the Unique Bio Diagnostics Enterprises (UBE)Veterinary Pathology Laboratory, B-20, Bhuvaneshwar, Dr. V. K. Valimbe Road, Near Gururani Nagkanya Chowk, Parel Village, Mumbai, for estimation of of Serum bilirubin, Serum aspartate aminotransferase (serum AST) serum alanine aminotransferase (serum ALT) serum alkaline phosphatase (serum ALP), serum acid phosphatase (serum ACP), Serum total protein, Serum Total Albumin and Serum Total Globulin.

RESULTS AND DISCUSSIONS:

TABLE 1: SHOWING THE MEAN CONCENTRATION OF SERUM BIOCHEMISTRY IN MALE WISTAR RATS .

Sample code	BILI Mg/dl	SGOT IU/L	SGPT IU/L	Alk Phosphatase IU/L	Acid Phosphatase IU/L	Pro. g/dl	Alb. g/dl	Glb g/dl
A	4.5	257.8	74.3	727.6	0.06	8.8	4.3	4.4
B	5.1	270.5	98.3	946.6	0.04	8.8	4.4	4.2
C	4.5	284.6	89.6	969.1	0.06	9.1	4.6	3.7
D	4.6	282.2	94.6	967.1	0.06	8.9	4.6	4.3
E	5.3	305.5	95.0	1042.8	0.06	8.2	4.8	4.7
F	5.3	274.8	94.0	1033.6	0.07	9.2	4.8	4.4
G	4.8	309.1	104.5	986.6	0.05	8.1	4.6	3.5
H	5.1	286.0	87.1	909.6	0.05	7.9	4.6	3.4

*Each value is the average of 6 determinations.

Bili: Serum Bilirubin mg / dl

SGOT: Serum Glutamic Oxaloacetic Transaminase IU / L, SGPT: Serum Glutamic Pyruvic Transaminase IU / L

ALP: Serum Alkaline Phosphatase IU / L, ACP: Serum Acid Phosphatase IU / L

PRO: Serum Total Proteins g / dl, ALB: Serum Total Albumin g / dl, GLO: Serum Total Globulin g / dl

Table 1. The mean concentration of Serum Biochemical investigations of Serum bilirubin, Serum aspartate aminotransferase (serum AST), serum alanine aminotransferase (serum ALT), serum alkaline phosphatase (serum ALP), serum acid phosphatase (serum ACP), Serum total protein, Serum Total Albumin and Serum Total Globulin.

There was no mortality in any of the groups. The body weight and relative liver weights of the experimental animals calculated at the end of the study had no statistically significant difference observed when compared to the control animals.

The mean concentration of serum bilirubin was found in control group A is (4.5mg/dI). With respect to experimental groups the minimum concentration of serum bilirubin was found in group C rats fed orally with *Aloe vera* extract and Isoniazid drug (4.5 mg/dI) whereas maximum concentration of serum bilirubin was found in group E and group F rats fed orally with isoniazid as well as fed orally with rifampicin drug extract and rifampicin drug (5.3 mg/dI).

The mean concentration of serum AST was found in control group A is (257.8 IU/L). With respect to experimental groups the minimum concentration of serum AST found in group B (270.8 IU/L) rats fed orally with *Aloe vera* extract, whereas maximum concentration of serum AST was found in group G (309.1 IU/L) rats fed orally with isoniazid + rifampicin drug.

The mean concentration of serum ALT was found in control group A is (74.3 IU/L). With respect to experimental groups the minimum concentration of serum ALT found in group H(87.1 IU/L) rats fed orally with *Aloe vera* extract with isoniazid+ rifampicin drug, whereas maximum concentration of serum ALT was found in group G (104.5 IU/L) rats fed orally with isoniazid + rifampicin drug.

The mean concentration of serum ALP was found in control group A is (727.6 IU/L). With respect to experimental groups the concentration of serum ALP found minimum in group B (946.6 IU/L) rats fed orally with *Aloe vera* extract, whereas concentration of serum ALP was found maximum in group E (1042.8 IU/L) rats fed orally with isoniazid drug and group F (1033.6 IU/L) rats fed orally with rifampicin drug.

The mean concentration of serum ACP was found in control group A is (0.06 IU/L). With respect to experimental groups the concentration of serum ACP found minimum in group B (0.04 IU/L) rats fed orally with *Aloe vera* extract whereas, Concentration of ACP was found maximum in group F (0.07 IU/L) rats fed orally with rifampicin drug.

The mean concentration of serum total proteins was found in control group A is (8.8 g / dl). With respect to experimental groups the concentration of serum total proteins found minimum in group H(7.9 g / dl) rats fed orally with *Aloe vera* extract with isoniazid+ rifampicin drug, whereas concentration of serum total proteins was found maximum in group F (9.2 g / dl) rats fed orally with rifampicin drug.

The mean concentration of serum total albumin was found in control group A is (4.3 g / dl). With respect to experimental groups the concentration of serum total albumin found minimum in group B (4.4 g / dl) rats fed orally with *Aloe vera* extract, whereas concentration of serum total albumin was found maximum in group E (4.8 g / dl) rats fed orally with isoniazid drug and group F (4.8 g / dl) rats fed orally with rifampicin drug.

The mean concentration of serum total globulin was found in control group A is (4.4 g / dl). With respect to experimental groups the concentration of serum total globulin found minimum in group H (3.4 g / dl) rats fed orally with *Aloe vera* extract with isoniazid+ rifampicin drug, whereas concentration of serum total globulin was found maximum in group E (4.7 g / dl) rats fed orally with isoniazid drug.

Rifampicin and Isoniazid are the most important first line drugs, used for the treatment of tuberculosis. Isoniazid can cause hepatotoxicity in 20% of patients and is usually associated with an inflammatory response [20]. Rifampicin and Isoniazid are reported to induce hepatotoxicity judged by elevated serum AST, ALT, ALP and total bilirubin

levels, presence of focal hepatocytic necrosis and portal triaditis [21]. Rifampicin and isoniazid, alone or in association, are still widely used in most antitubercular chemotherapeutic regimens. However, these drugs are also well known as hepatotoxic agents [22, 23]. Oxidative stress is one of the mechanisms with a central role involved in the pathogenesis of antitubercular drugs (isoniazid and rifampicin)-induced hepatitis [24]. Administration of Isoniazid and Rifampicin individually and in combination, showed a significant derangement of liver function as assessed by change in serum enzymes (AST, ALT, ALP and ACP) as well as bilirubin, total proein, total albumin and total globulin also liver histopathology.

In our study the more commonly measured 'liver' enzymes are showing significant increase in the levels of AST, ALT, ALP, and ACP, bilirubin total proein, total albumin and total globulin in serum of rats treated with Isoniazid and Rifampicin individually and in combination when compared with control rats, whereas the levels of AST, ALT, ALP, and ACP, bilirubin, total protein, total albumin and total globulin in serum were found somewhat decreased as the rat were treated with *Aloe vera* independently as well as in combination with Isoniazid and Rifampicin drug. Pretreatment of rats with *Aloe vera* extract caused a significant reduction in the levels of enzymes, and bilirubin leading to a significant reversal of hepatotoxicity. The similar results were also found by [25, 26, 27 a, b]. increased levels of ALT, AST, and SDH are usually associated with damage to hepatocytes. In their study, they mention that, the hepatic injury induced by Isoniazid and Rifampicin (I+R) combination is evident by an increase in the levels of serum enzymes.

This is in agreement with the results obtained in other previous investigations [28]. The increased levels of AST and ALT are indicative of cellular damage and loss of functional integrity of the cell membrane in the liver [29]. The increase in ALP in liver disease is the result of increased synthesis of the enzyme by cells lining the canaliculi, usually either intra- or extra hepatic, which reflects the pathological alteration in biliary flow [30]. An abnormal increase in the levels of bilirubin in serum indicates hepatobiliary disease and severe disturbance of hepatocellular function [31]. Reversal of the bilirubin level to near normal upon administration of *Aloe vera* extract clearly indicates improvement of the functional status of the liver cells.

The hepatoprotective potential of cimetidine in hepatotoxicity induced by isoniazid- rifampicin combination in albino rabbits has also been evaluated by many researchers and compared with the hepatoprotective and immunomodulatory effects of Curcuma longa (CL), Ocimum sanctum (OS), Tinospora cordifolia (TC) and Zizyphus mauritiana (ZM) on liver injury and immunosuppression induced by Isoniazid (INH), Rifampicin (RIF) and Pyrazinamide (PZA) [32]. Hepatotoxin is mainly responsible for increased bile secretion in the serum [33]. Experimental studies on animals suggest that administration of antitubercular drugs results in the rise of ALT, AST and ALP in serum, affecting hepatocellular membrane integrity and its organelles [34, 35]. Increased activity of hepatocytes leads to hyperbillirubinaemia which helps to determine integrity of liver [36]. It has been reported that sub acute or chronic treatment with isoniazid induced hepatotoxicity in man [37,] rat [38], and guinea pigs[39].resulting in the rise of serum transaminases and phosphatase activities. Isoniazid-induced hepatitis is associated with ballooning degeneration, focal hepatocyte necrosis with minimal cholestasis [40].

In our previous study, it was found that *Aloe vera* at the higher dose levels prevented an increased in ALT, AST, ALP, ACP, Bilirubin, total proteins (albumin and globulin) levels as well as the histological changes associated with *Aloe vera* – isoniazid combination [41].

Our present studies revealed the Co-administration of *Aloe vera* extract along with antituberculosis drugs protected liver from hepatotoxicity due to isoniazid and rifampicin. Administration of *Aloe vera* extract consecutively for 30 days resulted in restoration of hepatic function as evident from normalization of serum markers of liver function. The study further suggests that *Aloe vera* juice supplementation with isoniazid and rifampicin drug

can be used in the pharmaceutical industry for the manufacture of multi- drugs therapy.

CONCLUSION: *Aloe vera* has been reported to have a hepatoprotective effect in animals. There was a significant increase in the levels of AST, ALT, ALP, and ACP, bilirubin total proein, total albumin and total globulin in serum of rats treated with Isoniazid and Rifampicin independently as well as in combination when compared with control rats. In the current study, pretreatment of rats with *Aloe vera* extract caused a significant reduction in the levels of enzymes, AST, ALT, ALP, and ACP, bilirubin, total protein, total albumin and total globulin. It was also found that *Aloe vera* extract at the higher dose in combination with Isoniazid and Rifampicin drug prevented an increased in the levels of enzymes leading to a significant reversal of hepatotoxicity.

ACKNOWLEDGEMENT: Authors are thankful to the Head, Department of Pharmacology, The Bombay Veterinary College, Parel, Mumbai, for providing the facilities of procurement of male Wistar rats and providing departmental animal house for the present experimental study. Authors are also thankful to the Unique Bio Diagnostics Enterprises (UBE) Veterinary Pathology Laboratory, B-20, Bhuvaneshwar, Dr. V. K. Valimbe Road, Near Gururani Nagkanya Chowk, Parel Village, Mumbai. Thanks are also due to the Principal, S.S. & L.S. Patkar College of Arts and Science & V.P. Varde College of Commerce and Economics, S.V. Road, Goregaon (West), Mumbai-400 062, for providing laboratory and infrastructure for the above work.

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How to cite this article:
Zodape GV and Bhise PP: Effect of *Aloe Vera* Extract on the Hepatotoxicity Induced by Isoniazid and Rifampicin Drug in Male Wistar Rats. Int J Pharm Sci Res 2016; 7(3): 1314-20.doi: 10.13040/IJPSR.0975-8232.7(3).1314-20.