IJPSR (2018), Volume 9, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 January, 2018; received in revised form, 16 April, 2018; accepted, 11 June, 2018; published 01 October, 2018

EFFECT OF *ALOE VERA* EXTRACT AND ISONIAZID - RIFAMPICIN DRUG ON LIVER HISTOLOGICAL STUDIES OF MALE WISTAR RATS

G. V. Zodape * and P. P. Bhise

Departments of Zoology, S. S. and L. S. Patkar College of Arts and Science, V.P. Varde College of Commerce and Economics, S. V. Road, Goregaon (West), Mumbai - 400062, Maharashtra, India.

Keywords:

Liver histology, SEM-microscopy, *Aloe vera*, INH-RIF drugs, Hepatoprotection

Correspondence to Author:
G. V. Zodape

Departments of Zoology, S. S. and L. S. Patkar College of Arts and Science, V.P. Varde College of Commerce and Economics, S. V. Road, Goregaon (West), Mumbai - 400062, Maharashtra, India.

E-mail: gautamvz5@yahoo.com

ABSTRACT: The study carried out to find the effect of *Aloe vera* extract on the toxicity induced by INH - RIF in male Wistar albino rats. We have perform the experiments on rats for 30 days and found the effect on histological alternations of liver by two different method. Firstly, by Compound microscopy and the same tissues were further process through SEM microscopy. We have found the effect of *Aloe vera* extract and isoniazid and rifampicin on histological architecture of liver. We found that there is partial restoration of hepatic function as evident from normalization of serum markers of liver function, and we were able to show hepatoprotection against INH+RIF induced hepatotoxicity, as evidenced by the partial reversal of increased serum transaminases showed trend towards returning to normal (but partially) by supplementation of *Aloe vera* indicating partial hepatoprotective effect. Co-administration of *Aloe vera* extract along with anti-tuberculosis drugs showed hepatoprotection in some extent against INH-RIF drugs.

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. Hepatic damage is associated with distortion of these metabolic functions [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. About quarter of cases of fulminant hepatic failure thought to be drug related. More than 900 drugs has implicated in causing liver injury.

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.9(10).4318-25

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

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(10).4318-25

Drug induced liver damage is responsible for 5% of all hospital admissions and 50% of all acute liver failures. It is the most common reason for a drug to be withdrawn from the market [2]. Liver diseases are still a worldwide health problem. Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects [3]. In the absence of a reliable liver protective drug in modern medicine, there are a number of medicinal preparations in Ayurveda recommended for the treatment of liver disorders [4].

In allopathic medicinal practices, reliable liver protective drugs are not available but herbs play an important role in management of liver disorders [5]. In view of severe undesirable side effects of synthetic agents, there is growing focus to follow systematic research methodology and to evaluate the scientific basis for the traditional herbal medicines that claimed to possess hepatoprotective

activity [6]. The use of plants in medicine is an age-long practice in various parts of the globe for both preventive and curative. Today, it has estimated that about 80% of the world population relies on botanical preparations as medicine to meet their health needs [7].

Hepatotoxicity: Hepatotoxicity implies chemically driven liver damage. Certain medicinal substance which taken in overdose and sometimes even when introduced within hepatic ranges may injure the organ. Other chemical substance such as those used in the labs like carbon tetrachloride, paracetamol and industrial substances such as lead and arsenic as well as neutral chemicals like microcystin, agrotoxins and herbal remedies such as cascara sagrada, ephedrine *etc*., induce hepatotoxicity.

The chemicals that cause the liver damage called as hepatotoxins. These substances convert into chemically reactive metabolites in the liver, which have the ability to interconnect with cellular macromolecules such as protein, lipids and nucleic acids leading to protein dysfunction, lipid peroxidation, DNA damage and oxidative stress. Thus, hepatotoxicity may be defined as the damage in the liver caused by chemical substance, which includes herbal preparations, medicinal drugs or dietary supplement. Hepatotoxicity or liver injury introduced by drug substances called as drug-induced hepatotoxicity.

Isoniazid Drug (INH): INH has been introducing in 1952 for treatment of TB. Later it also recommended using for primary prophylaxis of tuberculosis infection and treatment of latent infection to prevent active TB. INH induced injury is usually acute hepatocellular in type, though a mixed hepatocellular-cholestatic picture also been reported. Liver biopsy of patients reveals bridging and multilobular necrosis. An individual receiving INH may experience severe hepatic injury which may be fatal [8, 9, 10].

Simultaneous use of RIF and INH increases the risk of hepatic injury [11]. The incidence of impaired liver function tests in patients receiving INH, with raised transaminases, varies from 10-25% [12, 13, 14, 15, 16]. Over dosage of isoniazid has produced nausea, vomiting dizziness, slurred speech, blurred vision and visual hallucinations. Symptoms of over dosages usually occur within 30 min to 3 h following ingestion of the drug [17, 18].

Rifampicin Drug (RIF): Rifampicin (RIF) is a potent inducer of the hepatic CYP450 system in the liver and intestine, thereby increasing metabolism of many other compounds. Hepatitis and deaths due to liver failure have been observed rarely in patients receiving rifampicin. Chronic liver disease, alcoholism, and old age increase the risk of severe hepatitis when rifampin given alone or concurrently with isoniazid.

RIF may cause transient hyperbilirubinaemia, due to interference with bilirubin excretion, and a rise in gamma-glutamyl transferase. RIF induced liver injury is associated with zone 3centrilobular necrosis [19]. RIF increases the hepatotoxicity of isoniazid. This effect is thought to be due to enzyme induction, leading to an increase in hepatotoxic metabolites of isoniazid [20, 21]. Rifampicin induces isoniazid hydrolase, increasing hydrazine production; when rifampicin is combined with isoniazid (especially in slow acetylators), which may explain the higher toxicity of the combination [22, 23]. Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity [24].

Role of Medicinal Plants in Hepatotoxicity: Medicinal plant play a role in the human health care system pharmacological medicinal plants and there taxonomical health era system. Herbal medicines are great demand in various diseases. Many drugs cause hepatic injury and are a great concern of the world for primary health. To overcome these effects drugs, now a day's many herbal preparations are in use to cure the disease because of their efficiency, safety, lesser side effects and narrow therapeutic window.

Therefore, the use of herbal drug is much safer then synthetic products available in the market. Herbal remedies support natural healing phenomena through blocking the progression of degenerative pathological process. Ayurveda has a clinical speciality called Rasayana, which prevents diseases and control the drug process by means of optimization of homeostasis. There are many herbal medicinal plants having antioxidant properties, which show hepatoprotective activity [25].

Hepatic injury leads to disturbances in transport function of hepatocytes resulting in leakage of plasma membrane thereby causing an increased enzyme level in serum. This leads to depletion of antioxidants status of hepatic tissue and induced lipid peroxidation degradation of membrane. Administration of antioxidant, which can scavenge the free radical, could reduce the hepatic injury. There are many herbal medicinal plants having antioxidant properties, which show hepato-protective activity [26].

***Aloe vera* Plant and its Applications:** *Aloe vera* is succulent plant species of the genus Aloe. It grows wild in tropical climates around the world and is cultured for agriculture and medicinal uses. *Aloe vera* contains many ingredients such as vitamins, minerals, sugars, enzymes, lignin's, antibiotics, anthraquinones, saponins, fatty acids, salicylic acid *etc*. which are useful for growth process and healthy functions of the all body system. *Aloe vera* gel has therapeutic properties such as prevention of radiation damage effect, antibacterial, antiviral and neoplastic activation and stimulation of haematoma process.

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 [27, 28]. 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 [29]. The biological activities include promotion of wound healing, antifungal activity, hypoglycemic or antidiabetic effects, anti-inflammatory, anticancer, immunomodulatory and gastro protective 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 [30]. An aqueous extract of dried areal parts of *Aloe vera* significantly reduced hepatic damage induced by carbon tetrachloride in mice and reversed certain biochemical parameters [31].

MATERIALS AND METHODS:

Collection and Identification of *Aloe vera* Plant: Fresh *Aloe vera* plant leaves were brought from botanical garden of Mahim Nature Park, Mumbai and brought to the laboratory of Department of Zoology, S. S. and L.S. Patkar - Varde College, Goregaon (W), Mumbai - 400062. The identification of *Aloe vera* plant was done at the Department of Zoology by referring standard literature and final identification was done at the "Government of India, Ministry of Environment, Forest and Climate change, Botanical Survey of India, Western Regional Centre, 7, Koregaon, Road, Pune - 411001. No.BST/WRC/IDEN.CER./2016/551.

After identification, *Aloe vera* leaves were rinsed 2-3 times in the tap water. 50 grams of leaves were, then grounded with 50 ml 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 min. The supernatant collected and diluted with 50 ml of distilled water to obtain a concentration of 50 mg /day / kg body wt. of male Wistar rat.

Isoniazid and Rifampicin Drugs: Isoniazid tablets (Macleods Pharmaceuticals, Andheri, Mumbai) and Rifampicin capsules (Lupin Ltd, Kartholi, Jammu & Kashmir) were dissolved in sterile distilled water.

Animals: Forty eight (48) male wistar rats (age 60-100 days, weighing 175-260 gm) 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 acclimatizedin the laboratory conditions for ten days prior to the experiment. The rats divided into eight groups containing six rats in each group. The experiments carried out according to the guidelines and prior approval of Institutional Animal Ethics Committee (CPCSEA No. MVC/ IAEC/29/2014) for the present experimental study.

Experimental Protocol:

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.

Histological Studies of Liver:

Processing of Isolated Liver: After 30th day, the animals sacrificed and dissected to isolate the liver of each animal. After isolation, the liver placed in the Petri dishes, cut into small pieces with the help of sharp seizer, and fixed in 10% formalin for two days in polypropylene bottles. After two days, the liver pieces removed from the polypropylene bottles and washed in running water for about 12 h. The pieces of liver further processed for dehydration with isopropyl alcohol of increasing strength (70%, 80% and 90%) for 12 h each. The final dehydration carried out using absolute alcohol with about three changes for 12 h each. The clearing of the tissues done by using chloroform with two changes for 15 to 20 min each. The liver pieces further subjected to paraffin infiltration in automatic tissue processing unit. The liver pieces washed with running water to remove formalin completely. For the removal of water, The alcohol of increasing grades were used to removed water and finally alcohol was removed by using chloroform and chloroform was removed by paraffin infiltration. The further procedure followed as proposed by [32].

Scanning Electron Microscopy: Scanning electron microscopy is a well-known non-destructive technique that uses an electron beam probe to analyse surface details down to nano-scale. The scanning electron microscopes produce high magnification images with high resolution, feature of which makes them suitable tools for a wide range of applications in numerous fields of science and industry.

RESULTS AND DISCUSSION: The histo-pathology study of liver was also performed which showed hepatoprotective effect. The hepatoprotective effect of *Aloe vera* confirmed by histopathological examination of the liver tissue of control and treated animals. The histological architecture of liver sections of healthy rats showed normal cellular architecture with distinct hepatic cells and sinusoidal space (Group A: **Fig. 1a** and **b**). The structural changes of the liver are normal and hepatocytes show no symptoms of necrosis and degeneration (Group B: **Fig. 2a** and **b**). The animals treated with *Aloe vera* extract and isoniazid drug shows that mild degenerative effect of liver (Group C: **Fig. 3a** and **b**). The animals treated with *Aloe vera* extract and rifampicin drug showed mild degenerative effect of liver (Group D: **Fig. 4a** and **b**). In the liver section of the rats intoxicated with isoniazid drug, (Group E: **Fig. 5a** and **b**), there was disarrangement and degeneration of normal hepatic cells with intense centrilobular necrosis, while rats treated with rifampicin showed necrosis and somewhat less disarrangement and degeneration of hepatocyte (Group F: **Fig. 6a** and **b**). The profile of the rat treated with isoniazid and rifampicin showed necrosis and hepatocyte degeneration. The animals administered with isoniazid and rifampicin drug alone or in combination showed mildly multifocal mild degree periportal mononuclear cell infiltration.

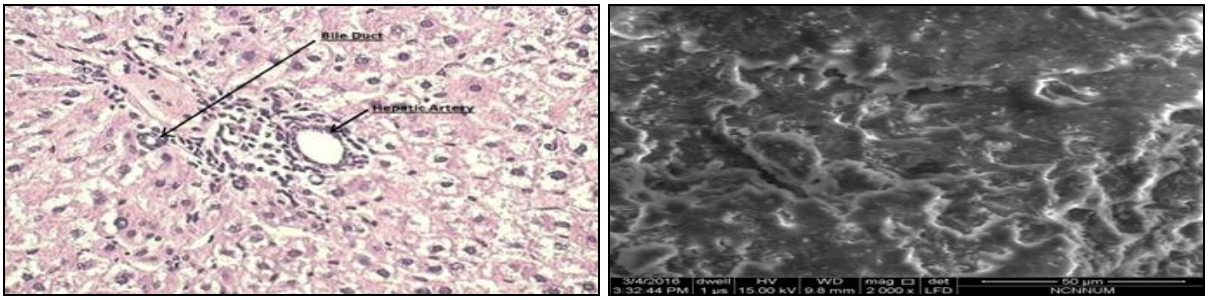

FIG. 1a AND b: GROUP A: THE HISTOLOGICAL ARCHITECTURE OF LIVER SECTIONS OF HEALTHY RATS SHOWED NORMAL CELLULAR ARCHITECTURE WITH DISTINCT HEPATIC CELLS AND SINUSOIDAL SPACE

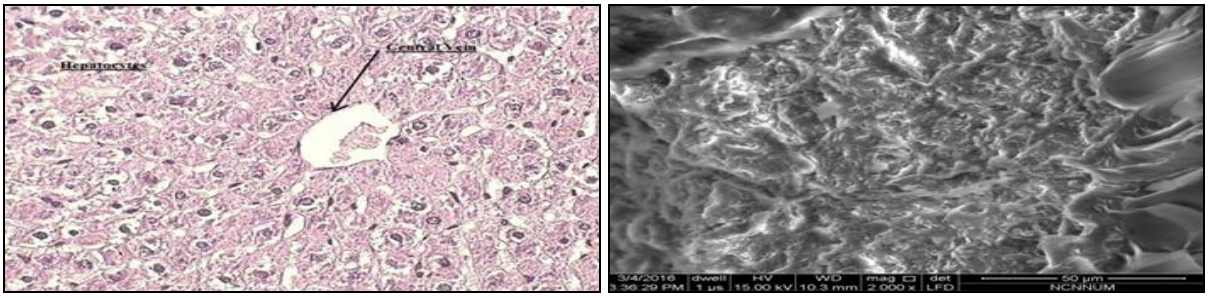

FIG. 2a AND b: GROUP B: THE STRUCTURAL CHANGES OF THE LIVER ARE NORMAL AND HEPATOCYTES SHOW NO SYMPTOMS OF NECROSIS AND DEGENERATION

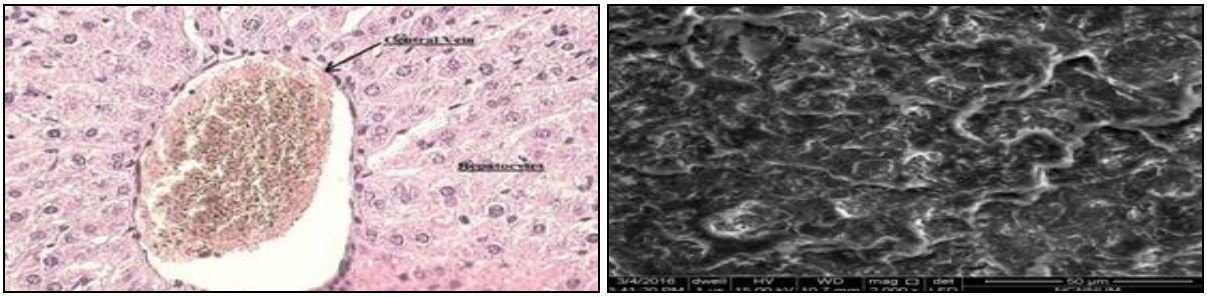

FIG. 3a AND b: GROUP C: THE ANIMALS TREATED WITH *ALOE VERA* EXTRACT AND ISONIAZID DRUG SHOWS THAT MILD DEGENERATIVE EFFECT OF LIVER

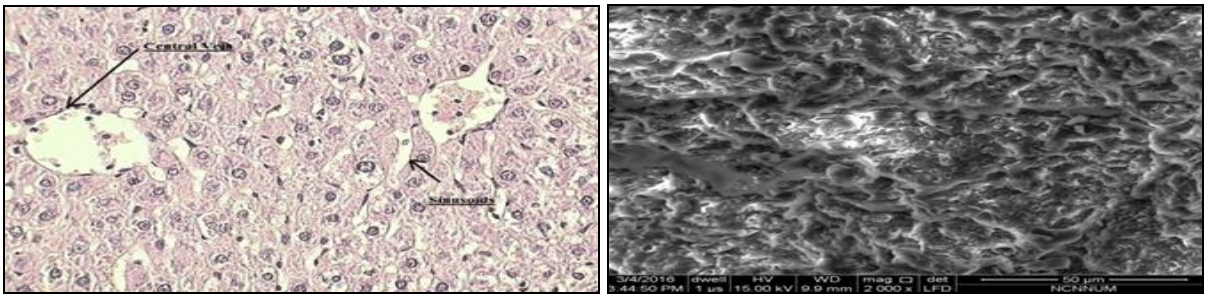

FIG. 4a AND b: GROUP D: THE ANIMALS TREATED WITH *ALOE VERA* EXTRACT AND RIFAMPICIN DRUG SHOWED MILD DEGENERATIVE EFFECT OF LIVER

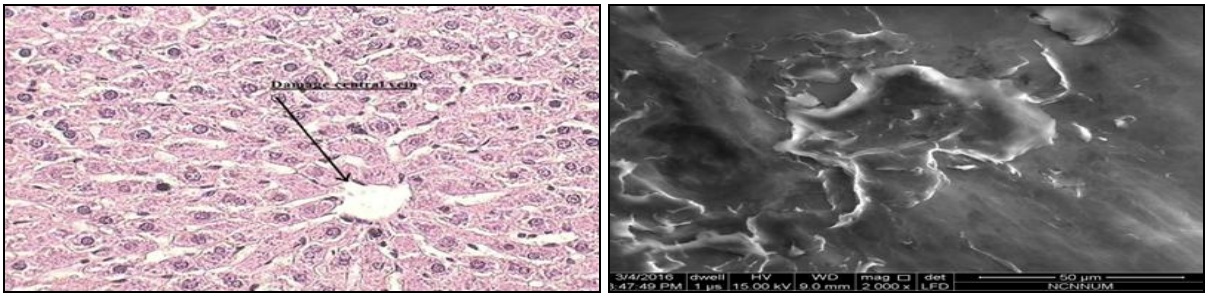

FIG. 5a AND b: GROUP E: IN THE LIVER SECTION OF THE RATS INTOXICATED WITH ISONIAZID DRUG, THERE WAS DISARRANGEMENT AND DEGENERATION OF NORMAL HEPATIC CELLS WITH INTENSE CENTRILOBULAR NECROSIS

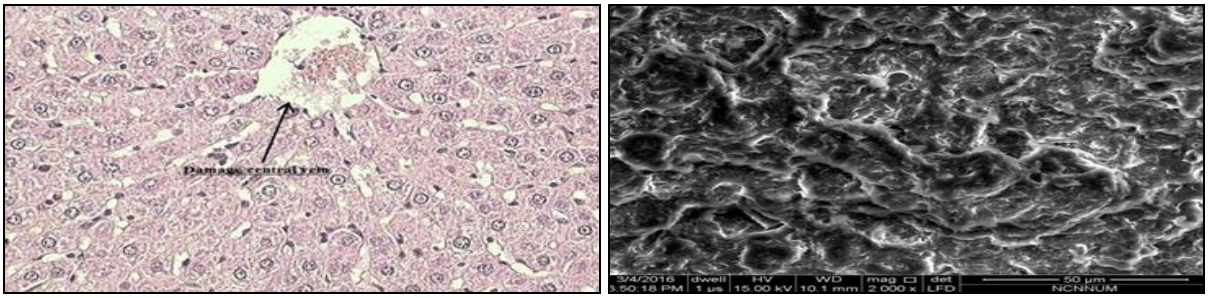

FIG. 6a AND b: GROUP F: RATS TREATED WITH RIFAMPICIN SHOWED NECROSIS AND SOMEWHAT LESS DISARRANGEMENT AND DEGENERATION OF HEPATOCYTE

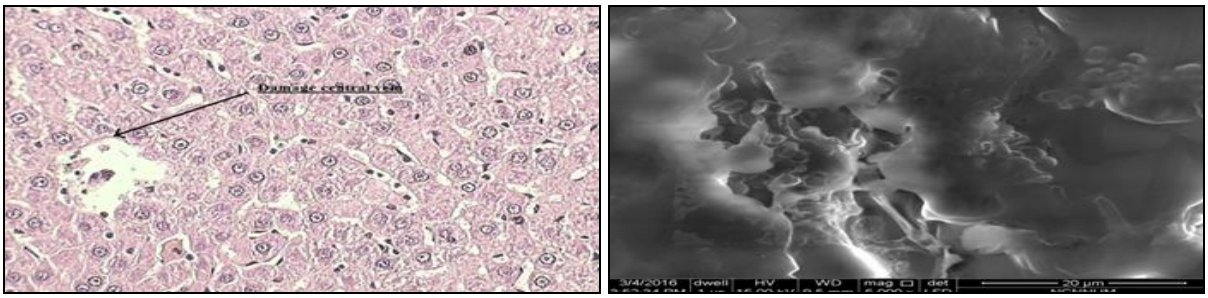

FIG. 7a AND b: GROUP G: THE PROFILE OF THE RAT TREATED WITH ISONIAZID AND RIFAMPICIN SHOWED NECROSIS AND HEPATOCYTE DEGENERATION. The animals administered with isoniazid and rifampicin drug alone or in combination showed mildly multifocal mild degree periportal mononuclear cell infiltration. Histological lesions ranged from hepatocellular disintegration and vacuolation in the peri-central vein area to marked proliferation of the rough endoplasmic reticulum.

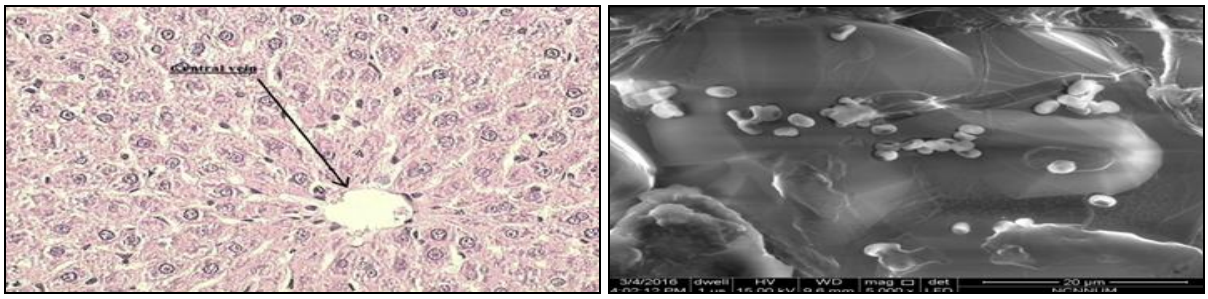

FIG. 8a AND b: GROUP H: THE HISTOPATHOLOGICAL PROFILE OF THE RAT TREATED WITH *ALOE VERA* EXTRACT + ISONIAZID +RIFAMPICIN SHOWED THAT THERE ARE FEW DEGENERATING CELLS INDICATING *ALOE VERA* EXTRACT REDUCED THE HEPATOTOXICITY (MODERATE HEPATOPROTECTIVE ACTIVITY)

Histological lesions ranged from hepatocellular disintegration and vacuolation in the peri-central vein area to marked proliferation of the rough endoplasmic reticulum. (Group G: **Fig. 7a** and **b**), whereas the histopathological profile of the rat treated with *Aloe vera* extract + Isoniazid + Rifampicin showed that there are few degenerating cells indicating *Aloe vera* extract reduced the hepatotoxicity (moderate hepatoprotective activity) (Group H: **Fig. 8a** and **b**), hence it acts as hepato-protective agent for hepatotoxicity induced by isoniazid and rifampicin alone or in combination.

Histopathological studies carried out by [33], confirmed the curative efficacy of the water extract of *Aloe vera* against carbon tetrachloride induced liver damage as indicated by reversal of centrilobular necrosis, macro-vascular fatty changes and scattered lymphomono-nuclear cell infiltrate in hepatic parenchyma. The hepatoprotective action of the plant attributed to the preservation of the liver enzymes through the antioxidant properties of the gel. The histopathological changes observed by [34] and [35] in their study were piecemeal necrosis, portal triaditis and focal lobular inflammation in INH+RIF treated rats. In the animals treated *Carica papaya* or silymarin, the hepatocytes showed restoration or preservation of the normal tissue architecture. This proved the ameliorative effect of *Carica papaya* leaves against ethanol-induced and anti-tubercular drugs induced hepatotoxic changes.

Previous studies have also shown that INH-RMP treatment lead to inhibition of bile secretion resulting cholesterol accumulation in liver [36] and [37]. Normally, cholesterol gets secreted as bile acid in

liver. Other authors have also observed increased plasma cholesterol in hepatotoxicity conditions [38] (Pari, 2003) and in chronic liver diseases [39].

CONCLUSION: In our previous studies on "effect of *Aloe vera* extract on the hepatotoxicity induced by isoniazid and rifampicin drug in male wistar rats". In addition, "effect of *Aloe vera* extract on the toxicity induced by isoniazid and rifampicin drug on complete blood count in male Wistar rats [40] and [41]". We found the hepatoprotective effect of *Aloe vera* extract against toxicity induced by isoniazid and rifampicin drugs by reversal of biochemical and haematological parameters.

In the present study we found that, the effect of *Aloe vera* extract on the hepatotoxicity induced by INH-RIF with respect to histopathological study. It showed that, the administration of *Aloe vera* extract consecutively for 30 days resulted in partial restoration of hepatic function. It was evident from normalization of serum markers of liver function tests. So we were able to show hepatoprotection against INH+RIF induced hepatotoxicity, as evidenced by the partial reversal of increased serum transaminases showed trend towards returning to normal (but partially) by supplementation of *Aloe vera* indicating partial hepatoprotective effect. Co-administration of *Aloe vera* extract along with antituberculosis drugs showed hepatoprotection in some extent against INH-RIF drugs.

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. We 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. Authors are also thankful to the Head, Department of Nanoscience and Nanotechnology, University of Mumbai, for providing the SEM facilities. Thanks are also due to the Principal, S. S. and L.S. Patkar College of Arts and Science & V.P. Varde College of Commerce and Economics, S.V. Road, Goregaon (West), Mumbai - 400062, for providing laboratory and infrastructure for the above work.

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Wolf PL: Biochemical diagniosis of liver diseases. Indian J. Cli 1999; 14: 59-90.
2. Friedman S, Grendell E, James H, McQuaid and Kenneth, R: Current. Diagnosis and treatment in gastroenterology. New York. Lang Medical books/McGraw- Hill 2003; 664-679.
3. Guntupalli M: Hepatoprotective effects of rubiadin, a major constituent of *Rubia cordifolia* Linn. J. Ethnopharmacol 2006; 103: 484-90.
4. Chatterjee TK: Medicinal plants with hepatoprotective properties. In: Herbal Options. Calcutta: Books and Allied (P) Ltd. Edition 3rd, 2000; 135.
5. Pingale SS, Pokharkar RD and Pingale MS: Standardization of herbal drug as a potent liver tonic. Pharmacology -online 2008; 1: 13-19.
6. Manokaran S, Jaswanth A and Sengottuvelu S: Hepatoprotective activity of Aervalanata Linn. against paracetamol induced hepatotoxicity in rats. Res J Pharm Tech 2008; 1: 398-400.
7. Ogbera AO, Dada O, Adeyeye F and Jewo PI: Complementary and alternative medicine use in diabetes mellitus. West Afr. J. Med 2010; 29(3): 158-162.
8. Black M, Mitchell JR, Zimmerman HJ, Ishak KG and Epler GR: Isoniazid-associated hepatitis in 144 patients. Gastroenterology 1975; 69: 289-302.
9. Garibaldi RA, Drusin RE, Ferbee SH and Gregg MB: Isoniazid associated hepatitis. Am Rev Respir Dis 1972; 106: 357-65
10. Mitchell JR, Zimmerman HJ and Ishak KG: Isoniazid liver injury: clinical spectrum, pathology and probable pathogenesis. Ann Intern Med 1976; 84: 181-92.
11. Pessayre D, Bentata M, Degott C, Nouel O, Miguet JP and Rueff B: Isoniazid-Rifampin fulminant hepatitis, A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. Gastroenterology 1977; 72: 284-9.
12. Chadha VK: Tuberculosis epidemiology in India: a review. International Journal of Tuberculosis and Lung Disease 2005; 9(10): 1072-82.
13. Brayden DJ and O'Mahony DJ: Novel oral drug delivery gateways for biotechnology products: Polypeptides and vaccines. Pharm. Sci. Technol 1998; 291-299.
14. Bailey WC, Weill H, De Roen TA, Ziskind MM, Jackson HA and Greenberg HB: The effect of isoniazid on transaminase levels. Ann Intern Med 1974; 81: 200-202.
15. Scharer L and Smith JP: Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 1969; 71: 1113-1120.
16. Yasuda K, Sato A and Chida K: Pulmonary tuberculosis with chemotherapy related liver dysfunction. Kekkaku 1990; 65: 407-13.
17. Gurnani A: Anaesthesia 1992; 47 (9): 781-783.
18. Gilhotra R: Int J. ClinPharmacolTherToxicol 1987; 25(5); 259-261
19. Stricker BH: Drug-induced hepatic injury. In: Dukes MNG. Drug-induced Disorders. Amsterdam, Elviser Edition 2nd, 1992; 212.

20. Yasuda K, Sato A and Chida K: Pulmonary tuberculosis with chemotherapy related liver dysfunction. Kekkaku 1990; 65: 407-13.
21. Wu JW, Lee SD and Yeh P: Isoniazid-rifampicin induced hepatitis in hepatitis B carriers. Gastroenterology 1990; 98: 502-4.
22. Blair IA, Mansilla TR and Brodie MJ: Plasma hydrazine concentrations in man after isoniazid and hydralazine administration. Hum Toxicol 1985; 4: 195-202.
23. Sarma GR, Immanuel C, Kailasam S, Narayana AS and Venkatesan P: Rifampin-induced release of hydrazine from isoniazid. A possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. Am Rev Respir Dis 1986; 133: 1072-5.
24. Kwara A, Flanigan TP and Carter EJ: Highly active antiretroviral therapy (HAART) in adults with tuber-culosis: current status. Int J Tuberc Lung Dis 2005; 9: 248-57.
25. Krinsky NI, Mathews-Roth MM, Welankiwar S, Sehgal PK, Lausen NCG and Russett M: The metabolism of [14 C] β-carotene and the presence of other carotenoids in rats and monkeys. J Nutr 1990; 120: 81-87.
26. Krinsky NI, Mathews-Roth MM, Welankiwar S, Sehgal PK, Lausen NCG and Russett M: The metabolism of [14 C] β-carotene and the presence of other carotenoids in rats and monkeys. J Nutr 1990; 120: 81-87.
27. Eshun K and He Q: *Aloe vera*: A valuable ingredient of the food, Pharmaceutical and Cosmetic industries- A review. Crit. Rev. Food Sci. Nutr; 44: 91-96 Ethnopharmacology 2004; 68: 3-37.
28. He Q, Changhong L, Kojo E and Tiah Z: Quality and safety assurance in the processing of *Aloe vera* gel juice. Food Control 2005; 16: 95-104.
29. Vinson JA, Al Kharrat H and Andreoli L: Effect of *Aloe vera* preparations on the human bioavailability of Vitamins C and E. Phytomedicine 2005; 12: 760-765.
30. Brayden DJ and O'Mahony DJ: Novel oral drug delivery gateways for biotechnology products: Polypeptides and vaccines. Pharm. Sci. Technol 1998; 291-299.
31. Chandan BK, Saxena AK, Shukla S, Sharma N, Gupta DK, Suri KA, Suri J, Bhadauria M and Singh B: Hepatoprotective potential of *Aloe barbadensis* Mill. against carbon tetrachloride induced hepatotoxicity. Journal of Ethnopharmacolog 2007; 22: 560-6.
32. Davidson CS: Guidelines for detection of hepatotoxicity due to drugs and chemicals. NIH publication, U.S. Department of Health and Education and Welfare NIH U.S.A 1979.
33. Hamman JH: Composition and applications of *Aloe vera* leaf gel. Molecules 2008; 13: 1599-1616.
34. Tasduq SA, Kaisar P, Gupta DK, Kapahi BK, Maheshwari HS and Jyotsna S: Protective effect of 50% hydroalcobolic fruit extract of *Emblica officinalis* against anti-tuberculosis drug induced liver toxicity. Phytotherapy Research 2005; 19: 193-7.
35. Santamaria L, Bianchi-Santamaria A and Dell' Orti M: Carotenoids in cancer, mastalgia and AIDS: prevention and treatment an overview. J Environ Pathol Toxicol Oncol 1996; 15: 89-95.
36. Shakun NP and Tabachuk OP: The comparative action of isoniazide, rifampicin and ethambutol on liver function. EKSP. Klin. Farmakol 1992; 55: 45.
37. Bugianesi E, Leone N and Vanni E: Expanding the natural history of non-alcoholic steatohepatitis from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002; 123: 134-40.
38. Pari L and Uma A: Protective effect of *Sesbania grandiflora* against erythromycin estolate induced hepato-toxicity. Therapie 2003; 58: 439-43.
39. Byrd RB, Horn BR, Solomon DA and Griggs GA: Toxic effects of isoniazid in tuberculosis chemoprophylaxis. J Am Med Assoc 1979; 241: 1239-41.
40. Zodape GV and Bhise PP: Effect of *Aloe vera* extract on the hepatotoxicity induced by isoniazid and rifampicin drug in male Wistar rats. IJPSR 2016; 7(3): 1314-1320.
41. Bhise PP and Zodape GV: Effect of *Aloe vera* juice on the toxicity induced by isoniazid and rifampicin drugs on complete blood count in male Wistar rats. IJPSR 2016; 7(9): 3728-3733.

How to cite this article:
Zodape GV and Bhise PP: Effect of *Aloe vera* extract and isoniazid - rifampicin drug on liver histological studies of male Wistar rats. Int J Pharm Sci & Res 2018; 9(10): 4318-25. doi: 10.13040/IJPSR.0975-8232.9(10).4318-25.