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The Precautionary Role of Ajwa Date on Hepatotoxicity Induced by Anti-Tubercular Drugs

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ABSTRACT

Background: Anti-tubercular drugs are known to causes hepatic injury, leading to stop the medical treatment by people globally. Ajwa data as herbal medicine may help in hepatic recovery. **Objective:** To find the precautionary of Ajwa date on hepatotoxicity induced by anti-tubercular drugs in rabbits. **Study Design:** Experimental study. **Settings:** Department of Pharmacology, Post Graduate Medical Institute, Lahore Pakistan. **Duration:** One year from June 2018-June 2019. **Methods:** Thirty rabbits were divided into five groups (A, B, C, D & E). Two groups (A, B) were on normal diet and drugs. Three groups (C, D & E) were on drug + Ajwa(seed/flesh) for 14 days. Hepatotoxicity was confirmed by liver enzymes (ALT & AST) and by histopathology of liver tissue. **Results:** Level of ALT and AST were in normal limits in all groups at the start of experiment. Significant hepatotoxicity was seen after 2 weeks of orally given INH and rifampicin in group B as compared to healthy control group A. Using of Ajwa date during the same period decreased the high levels of enzymes in groups C, D and E and brings liver function normal like healthy controls. Histological findings showed that after the administration of Ajwa, its flesh and powder, the changes of liver structure like degeneration, steatosis, necrosis etc. are relieved. **Conclusion:** Co-administration of Ajwa date along with its constituents are parallel and effective in reducing isoniazid and rifampicin induced hepatotoxicity.

Keywords: *Anti-tubercular drug, Ajwa date, Liver enzymes, Liver injury.*

INTRODUCTION

Tuberculosis (TB) is the main cause of mortality from infectious disease in adults globally with greater 10 million people suffered from tuberculosis every year.[1] In Pakistan the prevalence of tuberculosis was 3.1 %, more in male as compare to female and augmented with age.[2]

Drugs used for treatment of TB are usually rifampicin (prevent regimen) and isoniazid in combination with ethambutol and pyrazinamide used to prevent the progression of infection to the TB problem.[1] Side effects of these anti-tuberculous drugs were nausea, anorexia[3]along with drug-induced liver injury including acute hepatocellular, cholestatic and mixed type liver injury.[4,5]

The advantageous effect of INH is to inhibit the cell wall formation of *Mycobacterium tuberculosis,* however it produces hepatotoxicity via its metabolites.[6,7] It is proposed that INH binds to and inhibits *InhA*, an enzyme take part in the synthesis of mycolic acids, an important part of cell wall mycobacterium resulting in the death of mycobacterium.[8]

Liver injury by INH is mainly due to metabolic idiosyncratic drug reactions. Study stated that INH is metabolized by the liver, initially by acetylation to acetyl-isoniazid which is further metabolized to give metabolites of hydrazine. The effects of rate of acetylation on hepatotoxicity are contrary; it is thought that free radical produces from metabolites of hydrazine

covalently bonding to macromolecules of liver and cause injury of liver cells.[9]

Rifampin (rifampicin) used in combination with INH and give anti-tuberculous effects. Rifampin blocks the growth of mycobacterium via an inhibition of bacterial DNA-dependent RNA polymerase. Like INH it induces hepatoxicity with transient increase in the values of liver enzymes that can be fatal. Rifampin also induces liver injury due to idiosyncratic drug metabolic products that give toxicity either directly or via an immunologic response. Along with INH, rifmapin also persuade oxidative stress, inflammatory reactions, and impaired antioxidant defense scheme in liver cells.[10,11]

Phoenix dactylifera palm date (Awja) is an appreciated herbal medicine against many diseases including TB. The herb fruit contains alkaloids, fatty acid, carbohydrate, protein, vitamins, minerals, tannins, flavonoids and phenolic compounds.[12,13] Among these the phenolic compounds act as antioxidant and shows robust activities against many pathogenic bacteria.[14,15] It is proposed that seeds of Phoenix dactylifera reinstated the function of antioxidant enzymes of liver that were reduced after the usage of anti-tuberculous drugs. Besides, histopathological reports of liver showed that the seeds of Awja prevent against the carbon tetra-chloride persuade lesions of liver lesions (vacuolization / fibroblast proliferation).[16]

Significant adverse effect of medicine rifampicin and isoniazid are hepatotoxicity with increased levels of aminotransferase that may results failure of liver. The levels of aspartate (AST) or alanine transaminase (ALT) of 2-3 times higher than normal values with nausea, abdominal pain etc. The values of AST and ALT 4-5 times higher than normal levels label hepatotoxicity.[17,18] Risk Factors of related with anti TB drugs induced hepatotoxicity are increased age, gender female, malnutrition and previous liver problem.[19]

METHODS

Study was carried out in Post Graduate Medical Institute, Lahore with a time period of one Year vide Ethical Review letter No. CMC-IRB/25/2020. 30 male rabbits with weight range 1200 to 1500 gm were taken for study. These rabbits were divided into groups A, B, C, D and E by lottery technique having 06 rabbits in each group. Rabbits were given usual diet and water before starting the study. Isoniazid and Rifampicin were purchased from Schazoo Zaka Pharmaceutical CO, while dates of Ajwas were purchased from local market.

Formation of powder of seed of Ajwa dates: The seeds were washed, dried and ground properly to get seed powder which was mixed in 1000 gm pellet diet. It was based on seven Ajwa dates / day for human adult.

Formation of Ajwa date + flesh diet pellet: Ajwa date flesh (1.0) mixed with pellet diet.

Formation of Ajwa date+ seed powder + diet pellet: 100g diet mixed with one date seed powder

Initiation of Hepatotoxicity: 50mg/kg of isoniazid and 100 mg /kg of rifampicin were given orally to rabbits for fourteen days.[20]

Preparation of solution of Isoniazid: 21.0 g of drug isoniazid was added in D/w and make the volume upto350 ml and kept in dark bottle at 4°C.

Preparation of Rifampicin solution: 42.0 g of rifampicin was added in distilled water to make volume up-to 350 ml and kept in dark bottles at 4°C.

Calculation of dose of Isoniazid: 21000.0 mg in 350.0 ml of solution.50.0 mg drug in 0.83ml of solution. For 1000gm rabbit weight, quantity was = 0.83ml. Calculation of dose of Rifampicin: 42000.0 mg in 350.0 ml of solution. 100mg in 0.83ml of solution for 1000gram rabbit weight, quantity was = 0.83ml.

Groups of Rabbits:

Group A (Negative control): Six rabbits used standard diet for 14 days.

Group B (Positive control): Six rabbits used orally normal diet along with 50 mg/kg Isoniazidand 100 mg/kg of rifampicinfor 14 days.[20]

Group C (Ajwa date with drugs): Six rabbits were given one Ajwa date /100gm of diet along with 50 mg/kg Isoniazid and 100 mg/kg of rifampicin dose for 14 days.

Group D (flesh of Ajwa plus drugs): Six rabbits were given one Ajwa date flesh /100gm of diet along with 50 mg/kg Isoniazid and 100 mg/kg of rifampicin dose for 14 days.

Group E (Ajwa seed powder with drugs): Six rabbits were given one Ajwa date seed powder /100gm of diet along with 50 mg/kg Isoniazid and 100 mg/kg of rifampicin dose for 14 days.

About 2.0 ml of Blood sample was drawn from vein of ear vein oc rabbits on zero day and fourteenth day for estimation of enzymes AST and ALT and determined by Auto-Analyzer using standard kits.

Data was entered and analyzed by SPSS 20. The quantitative variable (ALT and AST) was given as mean ±SD. The levels of ALT and AST were compared by One way ANOVA at zero day and 14th day. For finding the significant difference between variables AST and ALT among different groups, paired student t-test was

applied. P value<0.05 = significant. Fischer's exact test was applied for changes in the liver that may cause injury.

RESULTS

Thirty adult healthy male rabbits weighing 1200 – 1500 grams were used in this study. They were divided into five groups (A, B, C, D and E). Each group contained 6 animals.

Effect of Ajwa date on serum ALT level (IU/L) of ATT induced hepatotoxic rabbits was tabulated (table 1). Non-significantly raised levels of ALT in group A and group C from zero day - 14th day. Significant increase values of ALT were observed in groups B, group D and group from zero day to 14th day. The levels of ALT among groups were compared by One way ANOVA at zero day and 14th day. It was found that at start of the experimentation the mean values of ALT of all groups are significantly different. However, significant difference was observed in mean values of ALT among groups at 14th day (< 0.001). One way ANOVA displayed that significant difference in levels of ALT levels from 0 day to day 14 among groups. Significant difference in the levels of ALT was seen in Group B and higher in comparison to other groups like A, C, D and E.

Effect of Ajwa date on serum AST level (IU/L) of ATT induced hepatotoxic rabbits was tabulated (table 2). According to paired t-test an insignificant increase in the levels of AST levels from zero day to 14th day. However, the level of AST was significantly rises in groups B, C, D and E from zero day to 14th day. One way ANOVA showed that at the beginning of the testing the mean values of AST levels showed no significant difference. However, significant difference was observed in the mean values of AST at the 14th day of experiment among groups at 14th day.

Effect of Ajwa date on ALP (IU/L) of ATT induced hepatotoxic rabbits was tabulated (table 3). According to paired t-test an insignificant increase in the levels of Alkaline phosphatase (ALP) from zero day to 14th day. However, the level of ALP was significantly rises in groups B, C, D and E from zero day to 14th day. One way ANOVA showed that at the beginning of the testing the mean values of ALP levels showed no significant difference. However, significant difference (p-value < 0.001) was observed in the mean values of ALP at the 14th day of experiment among groups at 14th day.

Thirty adult healthy male rabbits weight range 1200 to 1500 grams were included in the study. Rabbits were comprised into 5 groups (A, B, C, D & E), with 06 animals in each group.

Table 1 showed the outcomes of Ajwa on level of serum ALT of ATT induced hepatotoxicity in rabbits. Study found in-significant increased values of ALT in group A & group C from zero day to 14th day. Significantly high values of ALT were seen group B, group D & group E from zero day to 14th day. The levels of ALT among all groups were compared by using one way ANOVA at zero day and 14th day. It was found that at start of the experiment the mean levels of ALT of all groups showed in-significantly difference. One way ANOVA showed that significant difference in levels of ALT levels from 0 day to day 14 among groups. Significant difference in the values of ALT was observed in Group B and it is higher in comparison to other groups.

Table 1: Results of Ajwa date on level of serum ALT (IU/L) of ATT induced hepatotoxicity in six groups of rabbits

Groups	Start time (Zero day)	After 14 days	P value Using 't' test
Group A (Negative control)	46.5± 7.0	47.3± 6.5	0.612
Group B (Positive control)	51.8± 5.6	202.2± 19.7	0.001
Group C	51.5± 6.3	56.7± 4.6	0.075
Group D	49.0± 5.1	88.7 ±6.0	0.002
Group E	48.0± 6.2	84.6± 8.4	0.002
P value via ANOVA	>0.05	< 0.001	-

Group A: Negative Control, Group B: Anti-tuberculous drugs, (ATT)Group C: full Ajwa Date + ATT Group D: ATT + Flesh of Ajwa Date, Group E: ATT + Seed powder of Ajwa

Table 2 showed the outcomes of Ajwa date on levels of serum AST of ATT induced hepatotoxicity in rabbits. According to paired student t-test in group A, in-significant rise in the levels of AST levels from zero day - 14th day. However, the values of AST were significantly rises in groups B, C, D and E from zero day - 14th day. One way ANOVA showed that at the starting time the mean levels of AST levels showed no significant difference. However, significant difference (p < 0.001) was observed in the mean values of AST at the 14th day of testing among groups at 14th day.

Table 2: Results of Ajwa date on level of serum AST (IU/L) of ATT induced hepatotoxicity in six groups of rabbits

Groups	Start time (Zero day)	After fourteen days	P value Using 't' test
Group A	42.5± 9.7	43.0 ± 9.7	<0.203
Group B	43.8 ±5.5	139.0±22.6	< 0.001
Group C	47.7 ±14.4	59.0 ± 15.3	< 0.001
Group D	50.0±8.5	73.7±8.3	0.003
Group E	41.2±2.8	57.5±5.3	< 0.001
P value via ANOVA	>0.05	<0.001	-

Group A: Negative Control, Group B: Anti-tuberculous drugs, (ATT)Group C: full Ajwa Date + ATT Group D: ATT + Flesh of Ajwa Date, Group E: ATT + Seed powder of Ajwa

Table 3 shows the histological Findings: It was observed that administration of antitubercular drugs for 14 days to group B causes degeneration, steatosis, necrosis, Triaditis and fibrosis on liver cells of rabbit. However, after administration of full Ajwa date, flesh of Ajwa and seed powder of Ajwa to group C, D and E respectively the changes in liver were reduced and structure of liver is saved. Fischer's exact test revealed that there was significant difference among groups for each findings.

Table 3: Distribution of histological findings among experimental groups of rabbit (normal and ATT groups with ajwa).

Histological findings	Group A (Normal)	Group B (ATT)	Group C (ATT with whole date)	Group D (ATT with date flesh)	Group E (ATT with powder ofseed)	P-value
Degeneration	0 (0.0%)	6.0 (100.0%)	1 (16.9%)	2.0 (33.3%)	2.0 (33.3%)	0.00 4
Necrosis	0 (0.0%)	5.0 (83.3%)	1.0 (16.9%)	1.0 (16.7%)	2.0 (33.3%)	0.0 23
Steatosis	0 (0.0%)	6.0(100.0%)	1.0 (16.9%)	2.0 (33.3%)	2.0(33.3%)	0.00 4
Fibrosis	0 (0.0%)	6.0(100.0%)	1.0(16.9%)	2.0 (33.3%)	2.0(33.3%)	0.00 4
Triaditis	0 (0.0%)	5.0 (83.3%)	0(0.0%)	2.0 (33.3%)	2.0(33.3%)	0.00 1
Regeneration	0 (0.0%)	0(0.0%)	0(0.0%)	0 (0.0%)	0 (0.0%)	-

DISCUSSION

Antitubercular drugs are the known reason of liver damage. It may be challenge to protect liver from toxic effect of these drugs during the treatment of tuberculosis. The usage of these drugs may interrupt the treatment and reason of recurrence of disease. Herbs including Ajwa date may be use as an alternative mean for drug induced hepatotoxicity.[21]

According to our study before starting the experiment the mean values of AST and ALT are insignificantly different. However, significant difference was observed in mean values of ALT among groups at 14th day (< 0.001) when compared with -ve controls. We agreed with some studies. One of the study is reported that the damage of liver is based on the level of liver enzymes (ALT& AST). According to the international consensus of the Council related with medical sciences, damage of liver is definite when the values of enzymes of liver are two times more than the normal values. However, it is reported that the types of liver injuries may be congregated into 2. a) Cells damage of liver is confirmed with values of ALT is two times greater than the normal values. b) Mixed damage is confirmed when the values of ALT/alkaline phosphatase are > than two times the upper normal limits.[22,23]

Another study is stated that dates of Ajwa exhibit therapeutic effect in hepatotoxicity and may aid to reduced the values of liver enzymes ALT and AST due to its vitamins and antioxidants.[24] Besides, flesh of dates / pit may stop the fibrosis of liver by repress genotoxicity and inflammation.[25] The extract of date pits also help to protect oxidative liver damage.[16]

We observed that administration of anti-tuberculous drugs for 14 days results in degeneration, necrosis, steatosis, triaditis and fibrosis of liver tissue of rabbit. However, the administration of Ajwa date whole, flesh and seed powder to groups of rabbit preserved the histological structure of liver by significantly reducing these changes. According to a study the administration of INH along with RMP to mice cause activation of hepatic stellate cell activation related with alterations in matrix along with high content of collagen of liver and periportal fibrosis along with apoptosis of the liver cells and may help in progression of oxidative stress.[26] INH-RMP induced hepatotoxicity is described by variable amounts of hepatic necrosis / inflammation results in increase death of liver cells.[27] INH induces micro-vesicular steatosis in many experimental animal including rabbits, mice and rats,[28] but these phenotypes are usually not observed in patients with INH-induced liver injury. It is proposed that metabolites of INH, hydrazine and acetyl-hydrazineare oxidized to reactive metabolites and cause hepatocellular injury, results in inflammation and scar tissue formation.[7]

Experimental studies also demonstrated the cytoprotective role of Ajwa date against ochratoxin induced hepatotoxicity[29] in albino rats. Another study found that extract of Ajwa date provide noteworthy protection against injury of liver cells which may be due to antiapoptotic, antioxidant and antifibrotic actions.[30]

CONCLUSION

Ajwa dates along with its seeds and pit reduced the increased levels of liver enzymes, and liver injury due to Anit-TB drugs. It is concluded that Ajwa date is an effective herb against Isoniazid and rifampicin that bring histopathological changes in hepatic cells.

LIMITATIONS

Small sample size and Budget restraints.

SUGGESTIONS / RECOMMENDATIONS

Further studies are needed to assess the response of treatment giving Ajwa dates. Need of awareness of benefits of Ajwa in treating tuberculosis

CONFLICT OF INTEREST / DISCLOSURE

None.

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