

A Preliminary Study of Comparison of Preventive and Therapeutic Effect of Green and White Tea Against Rifampicin-Induced Chronic Hepatotoxicity in Rats

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Abstract: Many different dietary supplements are currently marketed for the management of hepatic illness, but the evidence for effectiveness is mixed. The aim of this study was to evaluate the effect of white and green tea extracts in a rifampicin-induced hepatic damage model of rats. In this study 55 male wistar albino rats were divided into 11 groups of 5 animals, named: normal control, hepatotoxic control with rifampicin (150 mg/kg), hepatotoxic with silymarin, hepatotoxic treated with green tea (250 and 500 mg/kg aqueous extract), hepatotoxic treated with white tea (250 and 500 mg/kg aqueous extract) and preventive groups of green and white tea with mentioned above doses. After 3 weeks treatment with green and white tea, a significant reduction in total cholesterol, triglyceride, LDL cholesterol, malondialdehyde and liver enzymes was observed. In the cases of white tea these changes were notable and dose-dependently improved liver function compared with green tea. The results obtained in this study suggest white tea is much more effective than green tea for prevention and treatment of drug-induced liver injury.

Keywords: Green Tea, White Tea, Rifampin, Chronic Hepatotoxicity

1. Introduction

Rifampicin, also known as Rifampin, is an antibiotic used to treat several types of bacterial infections and also as an anti-tuberculosis drug, usually administered with other anti-tuberculosis agents. Some patients experience hepatotoxic reaction after using this drug [1].

Medicinal plants have been used for the treatment of the diseases since ancient times. More attention has been paid to the protective effect of the natural antioxidants against chemically induced toxicities [2]. Tea is the most commonly consumed beverage worldwide and has been used in traditional medicine for centuries. Black and green teas are

the most popular types. Different types of tea are produced from fresh tea leaf (*Camellia sinensis*): Green, black, white, and red tea which is different in terms of production methods. Each type of tea has its own characteristics including a different taste and different pharmacological activities [3-5].

Tea contains a wide range of phenolic compounds such as flavanols, flavandiol, flavonoids, and phenolic acids and other ingredients are alkaloids (caffeine, theophylline, and Theobromine), amino acids, carbohydrates, proteins, chlorophyll, volatile compounds, minerals, and trace elements. Polyphenols are the main bioactive molecules in tea [6].

Polyphenol compounds which comprise epigallocatechin-

3- gallate (EGCG) (the most abundant catechin in GT¹), epigallocatechin (EGC), epicatechin- 3-gallate (ECG) and epicatechin (EC), are the main constituents of green tea. [5-7]. Health benefits of tea are related to catechins, which account for up to 30% of the weight of dry tea. Therefore, the antioxidant capacity of green tea is greater than that of other types [8, 9]. The tea beverage is considered as a medicine because of its polyphenol content [10]. Although green tea has been considered safe, emerging reports regarding the liver injury should not be ignored [5, 11, 12]. Although some in vivo studies have shown that green tea consumption could be hepatoinvasive [13, 14], other studies have demonstrated that green tea consumption is quite safe [3, 4, 15].

White tea is very similar to green tea, but in contrast to Green and Black Tea, WT² Tea is manufactured only from the first leaves of *Camellia Sinensis* that are dried with minimal processing. Therefore, the concentrations of epigallocatechin-3-gallate (EGCG) catechin, antioxidant activity and also methylxanthines (like caffeine) in WT are more than Green or Black Tea [16, 17].

In some studies, tea has been associated with anti-allergic actions and antimicrobial properties. Further studies have associated the consumption of tea with a lower risk of several types of cancer, cardiovascular disease, liver disease, diabetes and improvement in the blood lipid profile and, etc [2, 18, 19]. Therefore, tea appears to be an effective chemopreventive agent for toxic chemicals and carcinogens. Moreover, it has antioxidant properties that are even much stronger than vitamins E or C [20].

The aim of this paper is to investigate the physiochemical effect of green and white tea on lipid profile, hepatic lipid peroxidation activity, antioxidant enzyme and liver enzyme as a marker for hepatic injury in hepatotoxic rat model induced by rifampin to determine which tea could have potentially more beneficial effect on liver status.

2. Material and Methods

2.1. Green and White Tea Extracts Preparation

Air-dried green and white tea grounded into fine powder by a grinder. The herbal powder was mixed with distilled water at a ratio of 1:9 (50 g powder in 450 ml of distilled water) and boiled for 10 to 15 min to prepare the extract. After centrifuging at 2000 rpm for 3 min; it was filtered using #1 Whatman filter paper (Sigma-Aldrich, USA) and dried at 37°C. The extracts were stored in colored glass away from moisture until further use.

2.2. Animal and Basal Diet

55 adult male *Wistar Albino* rats weighing 200-220g, were used all of which were weighed and housed in individual polypropylene cages (12 h light/ dark cycle). The rats were kept in a room at a temperature of 22 ± 2°C with free access

to water and food.

The animals were randomly divided into 11 experimental groups: control group (n = 5) administered distilled water, and 10 groups with 5 members in each exposed to rifampicin, silymarin and supplemented with tea extracts (green tea and white tea) with different doses (250 and 500 mg/kg/day). At the end of the 3-week treatment, blood samples were collected carefully from anesthetized fasted overnight rats. The serum was immediately separated by centrifugation and stored at -20°C for further analysis.

2.3. Plasma Biochemical Analysis

The Serum level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC) and triglyceride (TG) were measured using desired kits (Pars Azmoon, Tehran) based on the protocol.

2.4. Estimation of Malondialdehyde

The malondialdehyde was assayed with Elisa kit (zellbio, Germany) and total serum antioxidant power was measured with the FRAP assay of Benzie & Strain (1996) based on ferric reducing potential.

2.5. Ethics Statements

The experimental procedures used throughout this study were approved by the Local Ethics Committee on Animal Experimentation of University of medical Sciences of Birjand, Iran. The experiment complied with the Guiding Principles for Research on Animals. All the efforts were made to minimize their suffering.

2.6. Statistical Analysis

All statistical analyses were carried out as the mean ± standard deviation in each group. Statistics differences of green and white tea intake between groups were evaluated by student t-test. One-way analysis of variance (ANOVA) was used for examining differences among groups followed by Turkey's post hoc test. A p-value below 0.01 was considered statistically significant.

3. Result

3.1. Effects of Green Tea and White Tea on Biochemical Parameters

Effect of green tea and white tea administration on serum cholesterol (TC), triglyceride (TG) and low density lipoprotein (LDL) levels were summarized in Tables 1 and 2, respectively. Based on the results, TC, TG and LDL-C increased among hepatotoxic group while high density lipoprotein (HDL) concentration was decreased compared to control group (p<0.01). Interestingly, white tea supplementation improved lipid profile in treated rats in dose dependent manner more effectively than green tea. Increase

¹Green tea

²White tea

in HDL level was observed in the treatment group which is a good indicator of improvement in hepatotoxic patients.

Table 1. The effect of green tea on blood lipid profile in rifampicin-induced hepatotoxic rats.

Experimental groups	Triglyceride	Cholesterol-LDL	Cholesterol-HDL	Total Cholesterol-
Normal control	67±3.2 [†]	65.1±5.3 [†]	32.2±2.2 [†]	104.6±3.2 [†]
Hepatotoxic group	185±4.3	131±2.6	13.5±4.8	158.9±6.3
Hepatotoxic + silymarin	97±6.3 [†]	98.7±4.3 [†]	28±4.5 [†]	125.5±5.2 [†]
Hepatotoxic + 250 mg green tea (treatment group)	128±4.1 [†]	110±4.2 [†]	21±3.2 [†]	124.7±5.2 [†]
Hepatotoxic + 500 mg green tea (treatment group)	117±3.5 [†]	97±2.3 [†]	24±4.5 [†]	121.6±3.9 [†]
Hepatotoxic + 250 mg green tea (preventive group)	119±3.4 [†]	95±4.3 [†]	23±1.3 [†]	118.6±4.6 [†]
Hepatotoxic + 500 mg green tea (preventive group)	106±2.5 [†]	87±4.2 [†]	29±5.3 [†]	114.5±4.2 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

Table 2. Effect of white tea on blood lipid profile in rifampicin-induced hepatotoxic rats.

Experimental groups	Triglyceride	Cholesterol-LDL	Cholesterol-HDL	Total Cholesterol-
Normal control	67±3.2 [†]	65.1±5.3 [†]	32.2±2.2 [†]	104.6±3.2 [†]
Hepatotoxic group	185±4.3	131±2.6	13.5±4.8	158.9±6.3
Hepatotoxic + silymarin	97±6.3 [†]	98.7±4.3 [†]	28±4.5 [†]	125.5±5.2 [†]
Hepatotoxic + 250 mg white tea (treatment group)	125±4.1 [†]	78±4.2 [†]	29±3.2 [†]	104.7±5.2 [†]
Hepatotoxic + 500 mg white tea (treatment group)	109.7±3.5 [†]	70±2.3 [†]	30±4.5 [†]	99.9±3.9 [†]
Hepatotoxic + 250 mg white tea (preventive group)	114±3.4 [†]	69±4.3 [†]	30±1.3 [†]	92.6±3.5 [†]
Hepatotoxic + 500 mg white tea (preventive group)	99.6±2.5 [†]	59±4.2 [†]	31±5.3 [†]	86.5±3.2 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

3.2. Lipid Peroxidation

Lipid peroxidation was measured as MDA in the experimental rats. MDA of rifampin-treated rats increased significantly compared to control group.

MDA level of white tea supplementation in combination

with rifampin was significantly (P < 0.01) lowered compared to the hepatotoxic group, but no significant decrease was observed, in hepatotoxic group using green tea (data are shown in Tables 3 and 4).

Table 3. The effect of green tea on malondialdehyde and the antioxidant capacity in rifampicin-induced hepatotoxic rats.

Experimental groups	malondialdehyde	Antioxidant capacity
Normal control	1.2±0.1 [†]	860±18.9 [†]
Hepatotoxic group	5.5±0.4	515±10.9
Hepatotoxic + silymarin	3.1±0.11 [†]	680±12.5 [†]
Hepatotoxic + 250 mg green tea (treatment group)	4.1±0.12	620±10.2
Hepatotoxic + 500 mg green tea (treatment group)	3.7±0.2 [†]	635±12.3 [†]
Hepatotoxic + 250 mg green tea (preventive group)	3.6±0.11 [†]	640±11.5 [†]
Hepatotoxic + 500 mg green tea (preventive group)	2.8±0.13 [†]	715±10 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

Table 4. Effect of white tea on malondialdehyde and antioxidant capacity in rifampicin-induced hepatotoxic rats.

Experimental groups	malondialdehyde	Antioxidant capacity
Normal control	1.2±0.1 [†]	860±18.9 [†]
Hepatotoxic group	5.5±0.4	515±10.9
Hepatotoxic + silymarin	3.1±0.11 [†]	680±12.5 [†]
Hepatotoxic + 250 mg white tea (treatment group)	3.9±0.12	620±10.2
Hepatotoxic + 500 mg white tea (treatment group)	3.6±0.2 [†]	635±12.3 [†]
Hepatotoxic + 250 mg white tea (preventive group)	3.1±0.11 [†]	709±11.5 [†]
Hepatotoxic + 500 mg white tea (preventive group)	2.3±0.13 [†]	735±10 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

3.3. Assessment of Hepatic Parameters

Several markers are involved in determining the liver function such as ALT, AST, ALP and LDH. As shown in Tables 5 and 6, ALT, AST, ALP and LDH activities in

rifampicin hepatotoxic group were significantly higher than normal control group. Administration of green and white tea decreased liver enzyme activities.

According to the results, there was progressive decrease in the level of liver enzyme in preventive group consuming white

tea compared to the ones using green tea (Tables 5 and 6).

Table 5. The effect of green tea on liver enzymes in rifampicin-induced hepatotoxic rats.

Experimental groups	Lactate dehydrogenase	Alkaline phosphatase	Aspartate transaminase	Alanine transaminase
Normal control	350±15 [†]	110±12 [†]	75±5.2 [†]	55±11.1 [†]
Hepatotoxic group	1220±17	980±22	470±4.7	265±12.2
Hepatotoxic + silymarin	420±9.5 [†]	426±13 [†]	230±5.6 [†]	129±13.2 [†]
Hepatotoxic + 250 mg green tea (treatment group)	810±13	615±9.7	345±11	212±11
Hepatotoxic + 500 mg green tea (treatment group)	705±21	587±5.8	310±13	157±10.5 [†]
Hepatotoxic + 250 mg green tea (preventive group)	595±16 [†]	567±11 [†]	298±8.7 [†]	142±8.9 [†]
Hepatotoxic + 500 mg green tea (preventive group)	490±9.8 [†]	438±23 [†]	241±11 [†]	131±6.5 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

Table 6. The effect of white tea on liver enzymes in rifampicin-induced hepatotoxic rats.

Experimental groups	Lactate dehydrogenase	Alkaline phosphatase	Aspartate transaminase	Alanine transaminase
Normal control	350±15 [†]	110±12 [†]	75±5.2 [†]	55±11.1 [†]
Hepatotoxic group	1220±17	980±22	470±4.7	265±12.2
Hepatotoxic + silymarin	420±9.5 [†]	426±13 [†]	230±5.6 [†]	129±13.2 [†]
Hepatotoxic + 250 mg white tea (treatment group)	740±13	595±9.7	342±11	172±11
Hepatotoxic + 500 mg white tea (treatment group)	690±21	558±5.8	276±13 [†]	157±10.5 [†]
Hepatotoxic + 250 mg white tea (preventive group)	567±16 [†]	518±11 [†]	265±8.7 [†]	102±8.9 [†]
Hepatotoxic + 500 mg white tea (preventive group)	476±9.8 [†]	442±23 [†]	237±11 [†]	97±6.5 [†]

Data are expressed as mean ± SD (mg/100ml) of 5 rats in each group. In each column, [†]was considered significant at P< 0.01 when compared with the hepatotoxic control group.

4. Discussion

A large body of evidence indicates that certain plant extracts and their bioactive component might have direct effect on hepatotoxicity. The Toxic effects of rifampicin on animals and plants are well documented [1]. Based on these data, green and white tea extracts were tested in this study for their effects on rifampin induced hepatic injuries in male rats through assessment of lipid profile, liver enzyme and antioxidant capacity [16].

We have selected white tea beside green tea, because it is yet to be comprehensively studied. White tea is composed of immature leaves so it represents high-priced tea. The caffeine content of white tea is obviously much higher [17]. Theogallin might be higher in white tea compared with green tea. White tea also contains a newly discovered myricetin triglyceride, which is absent in the other tea. Hence, the mechanism of hepatoprotection of WT may be attributed to the antioxidants and high concentration of catechins present in WT that scavenge a wide range of free radicals including the most active hydroxyl radical which may initiate lipid peroxidation. Several structures appear to be important for these antioxidant activities of tea polyphenols including the ortho-3', 4'-dihydrox-yl (catechol) group in the B-ring, that promotes the formation of a stable phenoxyl radical due to effective electron delocalization or the 3', 4', 5'-trihydroxyl (gallate) group in the B-ring, a gallate group esterified at the 3 position of the C-ring, and hydroxyl groups at the 5 and 7 positions of the A-ring [21, 22].

A large body of evidence indicates that certain plants component might have direct effect on the adipose tissue. As other researches have shown the green tea extract is an effective adjunct to reduce LDL and it is well tolerated [16], the results of the current study demonstrated highly significant (p<0.01) hypolipidemic effect in treated groups compared to the control group, while its level was significantly improved in GT+ rifampin treated rats compared to the rifampin group. Our results showed that the effect of WT on blood lipid profile was more efficient than green tea in dose dependent manner. These results are in complete accordance with the previous studies [19, 23-25]. Some studies indicate that lipolytic activity of white tea might not be mediated by EGCG; on the other hand methylxanthines in white tea might have lipolysis activity [16]. Despite the evidence from epidemiological and animal studies, several experiments on humans have attributed no lipid-lowering effects to green or black tea drinking [26].

One possible explanation in attenuation of triglyceride could be the ability of white tea in stimulating the lipolytic activity. The main attraction of tea as a lipolytic agent is that it is a safer and more natural alternative. Laboratorial studies using animal models have largely demonstrated reducing lipid profile effects of GT, the effectiveness of WT on the other hand has not been fully elucidated.

Lipid profile alteration is a factor for excessive lipid peroxidation and oxidative stress that resulted from increase in ROS production and reduction in antioxidant enzymes, resulted from increased MDA in rifampin group [27]. The

effect of rifampin could be reversed by GTE that ameliorates hepatotoxicity, lipid peroxidation and oxidative stress on hepatic tissue [21, 28].

Preventive group with white tea showed lower levels of MDA than rifampin+ white tea treatment rats, suggesting that WT reverses the elevation of lipid peroxidation. Previous studies have shown that there is a higher content of polyphenol and antioxidant activity in white tea than green tea [17] but our result did not show any significant difference in total antioxidant capacity between white tea and green tea [15, 29].

Tea has a positive effect on hepatocytes, which are susceptible to damage. More polyphenols, especially catechins, are present in white and green teas compared to black and red teas [15, 30]. It is known that rifampin reduces the LDH fraction in the liver tissue and leads to release thereof into the bloodstream after the cell damage. Further, aminotransferase enzymes are normally inside the cells, so elevated level of AST and ALT in all rats exposed to rifampin can suggest substantial liver damage. ALT is more specific to liver while AST is found in cardiac and skeletal cells [7, 30]. Our study showed elevated LDH, ALP, ALT and AST activities in hepatotoxic group. In our study there was a significant decrease ($P < 0.01$) in the level of liver enzyme in the preventive group treated with WT compare to those group treated with GT. This result could be attributed to the more effective anti-inflammatory effect of white tea compared to green tea in controlling the progression of hepatic disease.

5. Conclusion

In summary, the available evidence of this study suggests that the aqueous extract of white tea is more effective in reducing most of the hepatic associated parameters in rifampicin-induced hepatic models of rats. Hence, WT can be used as an adjunct therapy to ameliorate the hepatotoxicity associated abnormalities.

Further studies are needed to clarify the precise mechanisms of GT and WT actions and to confirm the most effective dose of WT in terms of reducing hepatotoxicity related abnormalities.

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