Advances in Biological Research 14 (2): 52-59, 2020
ISSN 1992-0067

DOI: 10.5829/idosi.abr.2020.52.59

Hepatoprotective Effect of *Ruta graveolens* and *Artemisia judaica* Extracts against Intoxication Liver in Rats

Khulud Mohammad Alshehri

Department of Biology, Al-Baha University, Baljurashi, Saudi Arabia

Abstract: One of the most common international public health disease and pharmaceutical field problem is a hepatic disease. Various toxic chemicals are caused Hepatic-cell injury, the carbon tetrachloride (CCl_4) is the commonly administered toxic liver injury in animals Lab which caused hepatotoxicity. Therefore, the present study aimed to investigate the hepatoprotective effect of *Ruta graveolens* and *Artemisia judaica* aqueous extracts against intoxication liver in rat induced with Ccl_4. The liver injury was measured by determined the activities of liver enzymes, Lipid profile and histopathological examination before and after treatments. Results show an increase in the levels of liver enzymes including aspartate transaminase (AST, alanine transaminase (ALT), alkaline phosphatase (ALP) and the lipid profile including total cholesterol (TC, triglycerides (TAG), high-density lipoprotein cholesterol (HDL, low-density lipoprotein cholesterol (LDL) and very low density lipoprotein cholesterol (VLDL). *A. judaica* aqueous extracts (400 mg/kg) showed a greater reduction in all treatment groups. The results of histopathological examination section in livers were supported the biochemical test result via hepatocytes recovery with inhibition of necrosis and no inflammatory appearance. The treatments with different concentration of *Ruta graveolens* and *Artemisia judaica* aqueous extracts were improvement of liver functions and serum biomarkers, add to ameliorated liver injury caused by CCl_4 induced.

Key words: Hepatoprotective · *Ruta graveolens* · *Artemisia judaica* · Intoxication liver and Ccl_4

INTRODUCTION

The biological functions in the body including synthesis of proteins, secretion of biochemical enzymes, metabolism of substances and detoxification are regulated by the liver [1, 2]. One of the most common international public health disease and pharmaceutical field problem is a hepatic disease, which is united term for an entire group of trouble that afflict the tissues, structures and cells of the human liver [3]. The complications of liver injury usually involve the participation of a toxic drug or metabolite that either elicits an immune response or directly affects the biochemistry of the cell. In either case, the resultant cell death is the event that leads to the clinical manifestation of hepatitis [4, 5]. The many factors can be affected metabolism function of the liver such toxic chemicals, drugs, drug-drug interactions or pathogen infections [6, 7] various toxic chemicals are caused Hepatic-cell injury, the carbon tetrachloride (CCl_4) is the commonly administered toxic liver injury in animals Lab which caused hepatotoxicity [8]. Various efficiency of pathological influence of carbon tetrachloride (CCl_4) and hepatoprotective influence of Chlorophytum comosum hydrolizate during the different age periods of rats have appeared in different biochemical parameters in liver [9].

The alternative medicines for the treatment of Hepatic disease has been a considerable interest in developing therapeutically effective agents from natural products may reduce the risk of toxicity [10]. The chemical components of plants had biological activities against various diseases like a hepatoprotective and fibrosis. Several medicinal plants have been used for the management of liver disorder, such as *Melastoma malabathricum* L. (Family; *Melastomaceae*) has been reported as antioxidant properties & presence of flavonoids [11]. *Feijoa sellowiana* showed increasing the reduced level of blood Glutathione (GSH), *Acacia nilotica* Linn reducing the oxidative stress & elevating the total protein and GSH level [12] and *Andrographis paniculata* is reducing the elevated SGOT, SGPT, ALP, TB level, *Swertia*

Corresponding Author: Khulud Mohammad Alshehri, Department of Biology, Al-Baha University, Baljurashi, Saudi Arabia.

chirayitais decreasing ALT, AST and bilirubin levels [13]. The enzymes marker indicate significantly decreased of oxidative stress to minimize the harmful effects of CCl_4 in rats treated with the *Paederia foetida* leaves ethanolic extract [14].

Fennel (*Foeniculum vulgare*) and propolis improve liver functions and liver with decreases ALAT, ASAT and ALP levels and increases albumin and total protein on liver in alloxan diabetic rats [15].

The phenolic compounds are the major components of different parts of Conocarpus erectus extracts; leaves, stems, flowers and fruits which are effective treatment of intoxicated mice and acted as antioxidant activity that improved the enzymes liver activities [16].

Artemisia judaica L. belongs to the family *Compositae*. Phytochemical analysis of *A. judaica* shows that it is a rich source of flavonoids including apigenin, cirsimaritin and various novel compounds [17]. *A. judaica* L. is a perennial fragrant, strongly aromatic, covered by woolly hairs, leaves grayish, which grow widely in the Kingdom of Saudi Arabia [18]. *Artemisia judaica* L. has been traditionally medicinal used to treat gastrointestinal disorders, poor eye sight, cardiovascular disease, skin disorders and weak immune systems as well as to decrease the risk of atherosclerosis, cancer and arthritis [19]. *Ruta graveolens* L. (*Rutaceae*) commonly known as rue is known as a medicinal plant since ancient times and currently used for the treatment of various disorders such as aching pain-eye problems, rheumatism and dermatitis [16, 17]. Rue is a native of the Mediterranean region but cultivated in many Asian countries, The plant contains more than120 compounds of different classes of natural products such as acrid one alkaloids, coumarins, essentialoils, flavonoids and furquinolines [22]. The present study aimed to investigate the hepatoprotective effect of *R. graveolens* and *A. judaica* extracts against intoxication liver in rat induced with Ccl_4.

MATERIALS ANDMETHODS

Plants Collection and Extracts Preparation: The tested plants in this investigation were (*R. graveolens* and *A. judaica*). These plants were selected to study their effects against hepatoprotective effect against intoxication liver in rat induced with CCl_4. These plants were collected from Al-Makhwah Governorate, Al-Baha Region, Kingdom of Saudi Arabia.

The leaves of *R. graveolens* and *A. judaica* were collected, washed and then dried at room temperature to obtain a fine powder from each plant. The aqueous extracts of these plants were done. 100gms of the plant powder were mixed with 500 ml of distilled water and then magnetically stirred in a container overnight at room temperature according to Applequist [23] with some modified. The plant extracts kept in a cool, dry and dark location.

Experimental Animals: Sixty young at (14-16 week-old) (weighing 150-160 g) male albino rats of Sprague - Dawley strain. All animals were allocated in plastic cages and kept under the controlled conditions of light (12 hours light and 12 hours dark) at temperature (25±2°C). The rats were feed pellet diet and water was provided ad libitum for one week. The study was conducted on rats in accordance with experimental animal ethics approved by Al-Baha University.

Experimental Design: After one week, the rats divided into six groups, the first group (n=10 rats) were fed on the pellet diet only as a control negative (G1: C -ve group) normal rats for 2 months. The rats of other groups were injected s/c by CCl_4 to induce liver damage according to Zhang *el al*., [24] by modified. Rats with liver intoxication were disported into five groups (n=10 rats) as follow:

Group (2): Was kept without any treatment as a control positive (C +ve group) and fed on pellet diet for 2 months.

Group (3): Was fed on a pellet diet and oral treatment (200 mg/kg of *R. graveolens* extract for 8 weeks.

Group (4): Was fed on a pellet diet and oral treatment (400 mg/kg of *R. graveolens* extract for 8 weeks.

Group (5): Was fed on a pellet diet and oral treatment (200 mg/kg. of *A. judaica* extract for 8 weeks.

Group (6): Was fed on a pellet diet and oral treatment (400 mg/kg. of *A. judaica* extract for 8 weeks.

Blood Sampling and Biochemical Analysis: Blood samples were collected at the end of the experiment and obtained from retro-orbital plexus veins. Samples were collected in a clean dry centrifuge tube and left to clot by standing at room temperature for 20 minutes. The serum was separated by centrifugation at 1500 r.p.m for 15 minutes,then used to determine the biochemical parameters of liver enzymes and serum lipid profile.

Activities of liver enzymes including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and serum total bilirubin (TB) were determined according to Reitman and Frankel [25].

Lipid profile including total cholesterol (TC), triglycerides (TAG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and very low density lipoprotein cholesterol (VLDL) was determined according to Ratliff and Hall; Eggstein and Kuhlmann, Patel *et al.* [22-24], respectively.

Histopathological Examination: After 8 weeks, the rats were sacrificed and fresh livers were collected and fixed in formalin solution (10% v/v) according to methods described by Drury *et al.* [29]. For fixation for histopathological investigation of liver injury.

Statistical Analysis: Effects of different treatments were analyzed by one way ANOVA (Analysis of variance) test using Duncan's multiple range test and $p<0.05$ was used to indicate significance between different groups, the following formulas were used [30]. All statistical analyses were performed using computerized SPSS (Statistic Program Sigmastat, statistical soft-ware, SAS Institute, Cary, NC).

RESULTS

In the current study the carbon tetrachloride (CCl_4) was used to causes liver intoxicated to determine the hepatoprotective effect of different concentrations of (*R. graveolens* and *A. judaica*) aqueous extracts on liver tissue and function.

Biochemical Analysis

Effect on Liver Enzymes (AST, ALT and ALP): The hepatoprotective effect of different concentrations of (*R. graveolens* and *A. judaica*) aqueous extracts on liver enzymes including aspartate amino transaminase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) enzymes in Ccl_4 intoxicated rats was showed in Table (1) Rat in the group (2) were induced of Ccl_4 with no reserved any treatment recorded 130.6±2.1, 70.5±2.4 and 159.4±2.7 which is a significant increase in AST, ALT and ALP serum level respectively. The effect of (G6) *Arteemisia judaica* extract in 400 mg/kg concentration were showed a slight improvement in AST level compared to (G2) intoxicated group. While the significant decreased of ALT enzyme activity observed in (G5) *Arteemisia judaica* extract in 200 mg/kg concentration with 35.5±1.9 compared to the intoxicated group. High levels of ALP enzyme were illustrated in all groups compared to (G1) C-ve normal rat.

Effect on Total Protein and Total Bilirubin: The total protein and total bilirubinin serum of CCl_4 intoxicated rats were recorded in different concentrations of *R. graveolens* and *A. judaica* extracts. Table (2) showed normally level of protein and total bilirubin in serum of all treatment group with high significant compared to (G2) intoxicated group.

Table 1: Effect of different concentrations of *R. graveolens* and *A. judaica* aqueous extracts on serum levels of aspartate amino transaminase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) enzymes in CCl_4 intoxicated rats

		Parameters		
Groups	Extract Concentration (g/kg)	AST (U/L)*	ALT (U/L)*	ALP (U/L)*
Group 1		65.6±1.8 e	36.5±1.6 e	84.5±1.9 e
Group 2		130.6±2.1 a	70.5±2.4 a	159.4±2.7 a
Group 3	(200 mg/kg)	124.6±2.3 b	65.5±2.8 b	154.7±2.5 b
Group 4	(400 mg/kg)	118.3±2.4 c	46.7±2.2 c	146.3±2.8 c
Group 5	(200 mg/kg)	113.5±1.6 c	35.5±1.9 c	135.5±1.2 c
Group 6	(400 mg/kg)	94.7±2.4 d	30.3±2.7 d	114.2±2.9 d

(U/L)* means unit per liter. Values denote arithmetic means±Standard error of the mean. Means with different letters (a, b,c,d) in the same column differ significantly at $p \leq 0.05$ using one way ANOVA test, while those with similar letters are non-significant.

Table 2: Effect of different concentrations of *Ruta graveolens* and *Arteemisia judaica* aqueous extracts on serum levels of total protein and total bilirubin

	Parameters		
Groups	Extract Concentration (g/kg)	Total protein (mg/dl)	Total bilirubin (mg/dl)
Group 1		6.68±1.3 a	0.66±0.011 b
Group 2		4.65±1.6 b	0.99±0.012 a
Group 3	(200 mg/kg)	6.54±1.8 a	0.83±0.013 b
Group 4	(400 mg/kg)	6.55±1.2 a	0.80±0.012 b
Group 5	(200 mg/kg)	6.54±1.5 a	0.70±0.014 b
Group 6	(400 mg/kg)	6.53±1.1 a	0.69±0.015 b

Values denote arithmetic means±Standard error of the mean. Means with different letters (a, b,c,d) in the same column different significantly at $p \leq 0.05$ using one way ANOVA test, while those with similar letters are non-significant

Table 3: Effect of different concentrations of *R. graveolens* and *A. judaica* aqueous extracts on lipid profile parameters of CCl_4 intoxicated rats

Groups	Extract Concentration (g/kg)	Parameters				
		Total cholesterol (mg/dl)	Triglycerides (mg/dl)	HDLc	LDLc	VLDLc
Group 1		88.98±1.4 d	43.35±1.5 d	63.96±1.1 e	16.35±1.2 b	8.67±1.1 d
Group 2		105.95±1.6 a	56.60±1.9 a	75.99±1.2 a	18.64±1.4 a	11.32±1.6 a
Group 3	(200 mg/kg)	101.97±1.8 b	52.60±1.4 b	74.75±1.3 b	16.70±1.3 b	10.52±1.8 b
Group 4	(400 mg/kg)	98.90±1.2 c	49.50±1.2 c	72.10±1.3 c	16.90±1.3 b	9.90±1.1 c
Group 5	(200 mg/kg)	95.90±1.5 c	46.50±1.3 c	70.10±1.2 c	16.50±1.4 b	9.30±1.1 c
Group 6	(400 mg/kg)	90.45±1.1 d	40.50±1.4 d	68.85±1.6 d	13.50±1.3 c	8.10±1.2 d

Values denote arithmetic means±Standard error of the mean. Means with different letters (a, b,c,d) in the same column different significantly at $p \leq 0.05$ using one way ANOVA test, while those with similar letters are non-significant.

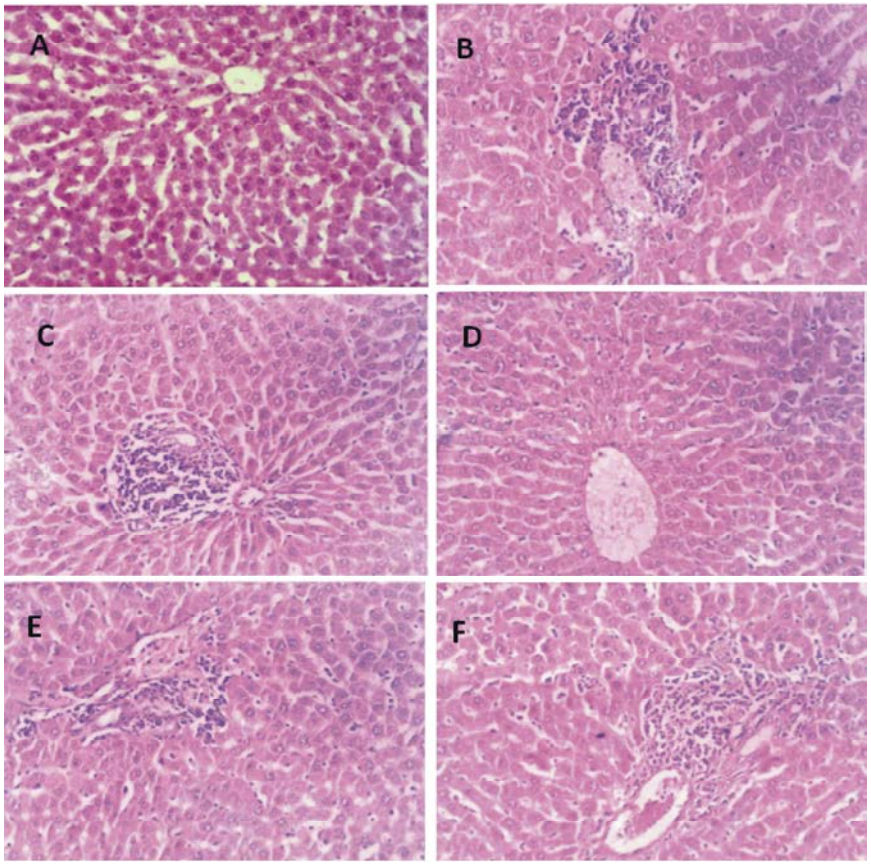

Fig. 1: A- Control- showing normal histopathological appearance in liver. B- Control+ CCl_4 intoxicated liver without treatment showing disturbance of the normal appearance in the hepatic lobule with multiple areas of collagen fiber. C- liver of CCl_4 intoxicated rat treated with (200 mg/kg *R. graveolens*) showing decreasing in areas of necrosis and most areas appear to have recovered. D- liver of CCl_4 intoxicated rat treated with (400 mg/kg *R. graveolens*) showing improvement in liver histology with no necrosis or inflammatory appearance. E- liver of CCl_4 intoxicated rat and treatment with (200 mg/kg *A. judaica*) showing mild changes in hepatocytes. F- liver of CCl_4 intoxicated rat and treatment with (400 mg/kg *A. judaica*) showing hepatocytes recovery with no necrosis or inflammatory appearance.

Effect on Lipid Profile Parameters: The lipid profile parameters, total cholesterol, triglycerides and lipoprotein fractions (HDLc, LDLc and VLDLc were increased in intoxicatedrats (G2) positive control Table (3). The lipid profile parameters were markedly decreased in (G6) (400 mg/kg) of *Arteemisia judaica* extracts, with 90.45±1.1 and 40.50±1.4, 68.85±1.6 and 8.10±1.2 of total cholesterol, triglycerides, HDLc and VLDLc, respectively compared to control negative group (G2). The LDLc levels were decreased in all treatment groups (G3), (G4), (G5) and (G6) compared to intoxicated group (G2).

Histopathological Results: Microscopically liver examination of rat from control -ve normal group revealed the normal histological structure of hepatic lobules (Fig. 1-A). On the other hand, liver of Ccl_4 intoxicated rat without treatment (C +ve) group disturbance of the normal appearance in the hepatic lobules with multiple areas of collagen fiber and local area of hepatic necrosis completely replaced by leucocytic cells infiltration (Fig. 1-B). Examined liver of CCl_4 intoxicated rat and treated with (200 mg/kg *Ruta graveolens*) showed decreasing in areas of necrosis of sporadic hepatocytes and most areas appear to have recovered (Fig. 1-C). Meanwhile, examined liver sections of CCl_4 intoxicated rat and treated with (400 mg/kg *Ruta graveolens*) revealed improvement in liver histology with no necrosis or inflammation appearance (Fig. 1-D). Meanwhile, examined liver of CCl_4 intoxicated rat and treatment with (200 mg/kg *A. judaica*) showed mild changes in hepatocytes (Fig. 1-E). While, examined liver of CCl_4 intoxicated rat and treatment with (400 mg/kg *A. judaica* showed hepatocytes recovery with no necrosis and few inflammation appearance (Fig. 1-F).

DISCUSSION

The investigation of hepatoprotective effect of *R. graveolens* and *A. judaica* extracts against intoxication livers in rats indicated that all concentrations of *R. graveolens* and *A. judaica* aqueous extracts showed significant protection against CCl_4 induced intoxication liver in rats. In this study CCl_4 induced intoxication in the livers of experimental animal that leads to an increased level of serum enzymes AST, ALT and ALP and increased lipid profile parameters including total cholesterol, triglycerides and lipoprotein fractions (HDLc, LDLc and VLDLc). This increased are an indication of cellular leakage and loss of functional integrity of cell membrane in the liver. Damage to the liver cells cause leakage of cellular enzymes into serum [31]. Also, CCl_4 is used xenobiotic to cause chemical liver injury, wherein CCl_4 is metabolized by liver microsomal cytochrome P450 to free radicals including trichloromethyl (CCl_3) and proxy trichloromethyl ($OOCCl_3$) radicals [28,29]. While, the treatment with *R. graveolens* and *A. judaica* extracts were prevented these harmful effects with significant improvement level of serum enzymes AST, ALT and ALP and lower level of lipid profile parameters [34]. Seeram *et al*. [31] reported that, there has been significant interest in the application of phenolics to treat liver diseases. An inverse relation between the consumption of phenolics-rich products and the risk of several diseases. The antioxidant traits of phenolics and their ability to modulate the activity of enzymes were studied *in vitro* and believed to be a primary mechanism for their biological impacts [35].

In accordance with the present study, different concentrations of *R. graveolens* L. extract showed influences in biochemical parameters and prevented these harmful effects. This may be due to the presence of flavonoids which are a group of naturally occurring phenolic compounds that are a part of primary chemical components of *R. graveolens* L. [36]. Phytochemical analysis of *Artemisia judaica* shows that it is a rich source of flavonoids including apigenin, cirsimaritin and various novel compounds [17].

Phenolic compounds show strong hepatoprotective impacts and may prevent inflammatory response, dyslipidemia and mitochondrial oxidative damage of animals hepatocytes. Therefore, bioactive phytochemicals with high antioxidant potential, superior free radical-scavenging ability and inhibition of oxidation is contributed to the hepatoprotective traits in animal models [37].

Many of the biological action of flavonoids have been attributed to their powerful hypolipidemic properties [38]. Several clinical trials have documented beneficial modifications of the LDL/HDL ratio after intake of flavonoid containing food products [39]. Independent Studies have confirmed the presence of antioxidant phenolic compounds in the aerial part of *R. graveolens* L. [40].

Flavonoids exhibit several biological effects such as anti-inflammatory, antihepatotoxic and anti-ulcer actions. They also inhibit enzymes such as aldose reductase and xanthine oxidase [41]. Moreover, it has been suggested that the protective effects of *A. judaica*is attributed to the existence of active compounds such as flavonoids [42]. They reported that the flavonoids compounds found in this extract were flavonoid glycosides and cirsimaritin as well as apigenin. These flavonoids exhibited antioxidant activity and anti- hypoglycemic action. The antioxidant activity of *A. judaica* extract decreased the oxidative stress caused by the free radicals and subsequently suppressed the formation of the pro-inflammatory intermediate factors such as tumor necrosis factor-α, interleukins-12 and interleukins-2 cytokines which have coincided with tumor pathway [43].

The present study revealed a Liver injury caused by CCl_4 in histopathological sections with multiple areas of collagen fiber and area of necrosis. The damage in

hepatocytes was caused enzymes residing in the cytoplasm were released into the bloodstream. While, the decreasing in areas of collagen fiber in treated with different concentrations of *R. graveolens* and *A. judaica* aqueous extracts in liver sections compering to control -ev. These results indicated that aqueous extracts have a hepatocytes protective effect and improving liver function. This may be due to the presence of flavonoids (apigenin, cirsimaritin, flavonoid glycosides) which have a hypoglycemic action as well as to a potent antioxidant action attenuating the oxidative stress induced by free radicals, so they can ameliorate the functions of the liver by protecting the hepatocytes and inhibiting the production proinflammatory mediators which has been associated with inflammatory diseases [44]. Eze-Steven *et al.,* interpret the influenced of liver tissue by assessment of liver function, estimating the activities of serum AST, ALT and ALP as the elevation of the levels of serum maker enzymes is generally regarded of the most sensitive index of the liver [45].

CONCLUSIONS

In conclusion, the present study revealed that different concentrations of *R. graveolens* and *A. judaica* aqueous extracts have a preservative effect on intoxication liver in rat induced with CCl_4. Therefore, this study suggests that aqueous extracts may be helpful for hepatotoxic treatment according to improvement of liver functions and serum biomarkers.

ACKNOWLEDGEMENT

The gratefully acknowledge to Biology department at Albaha University, Baljurashi for providing research facilities.

REFERENCES

1. Meyer, S.A. and A. P. Kulkarni, 2001. Hepatotoxicity. Introduction to biochemical toxicology. Edited by E Hodgson & RC Smart (A John Wiley and Jons, Inc, New York), pp: 487.
2. Wang, Y., C. Tang and H. Zhang, 2015. Hepatoprotective effects of kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside from *Carthamus tinctorius* L. on CCl4-induced oxidative liver injury in mice. Journal of Food and Drug Analysis, 23: 310-7.
3. Ahsan, M.R., K.M. Islam, I.J. Bulbul, M.A. Musaddik and E. Haque, 2009. Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride-induced hepatotoxicity in rats. European Journal of Scientific Research, 37: 302-10.
4. Zimmerman, H.J., 1999. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. Lippincott Williams & Wilkins.
5. Kaplowitz, N., 2002. Biochemical and cellular mechanisms of toxic liver injury. Seminars in Liver Disease, pp: 137-44.
6. Wang, J., M.F. Rahman, H.M. Duhart, G.D. Newport, T.A. Patterson, R.C. Murdock, S.M. Hussain, J.J. Schlager and S.F. Ali, 2009. Expression changes of dopaminergic system-related genes in PC_{12} cells induced by manganese, silver, or copper nanoparticles. Neurotoxicology, 30: 926-33.
7. Baer-Dubowska, W. and H. Szaefer, 2013. Modulation of carcinogen-metabolizing cytochromes P450 by phytochemicals in humans. Expert Opinion on Drug Metabolism & Toxicology, 9: 927-41.
8. Halliwell, B. and J.M.C. Gutteridge, 1990. Role of free radicals and catalytic metal ions in human disease: an overview. Methods in Enzymology, pp: 1-85.
9. Areshidze, D.A., L.D. Timchenko, A.I. Klimenko, M. Gulyukin and M. Kozlova, 2013. Influence of an Enzymatic Hydrolyzate of *Chlorophytum comosum* (L.) on Morphofunctional Integrity of a Liver of White Rats at Experimental Toxic Damage During Various Periods of Ontogenesis. Global Veterinaria, 11: 794-802.
10. Shen, X., Y. Tang, R. Yang, L. Yu, T. Fang and J. Duan, 2009. The protective effect of *Zizyphus jujube* fruit on carbon tetrachloride-induced hepatic injury in mice by anti-oxidative activities. Journal of Ethnopharmacology, 122: 555-60.
11. Mamat, S.S., M.F.F. Kamarolzaman, F. Yahya, N.D. Mahmood, M.S. Shahril, K.F. Jakius, N. Mohtarrudin, S.M. Ching, D. Susanti, M. Taher and A.Z. Zakaria, 2013. Methanol extract of *Melastoma malabathricum* leaves exerted antioxidant and liver protective activity in rats. BMC Complementary and Alternative Medicine, 13: 326.
12. Karami, M., S. Saeidnia and A. Nosrati, 2013. Study of the hepatoprotective activity of methanolic extract of *Feijoa sellowiana* fruits against MDMA using the isolated rat liver perfusion system. Iranian Journal of Pharmaceutical Research, 12: 85.

13. Nagalekshmi, R., A. Menon, D.K. Chandrasekharan and C.K.K. Nair, 2011. Hepatoprotective activity of *Andrographis paniculata* and *Swertia chirayita*. Food and Chemical Toxicology, 49: 3367-73.
14. Uddin, B., T. Nahar, M.A. Basunia and S. Hossain 2011. *Paederia foetida* protects liver against hepatotoxin-induced oxidative damage. Advances in Biological Research, 5: 262-72.
15. El Araby, B., D.F.I. Ahmed and S.A. Zahkouk, 2017. Effect of *Foeniculum vulgare* and Propolis on Liver in Alloxan Diabetic Rats. Advances in Biological Research, 11: 311-8.
16. Abdel-Hameed, E.S.S., S.A. Bazaid and A.N.A. Sabra, 2013. Protective effect of *Conocarpus erectus* extracts on CCl4-induced chronic liver injury in mice. Glob J. Pharmacol., 7:52-60.
17. Saleh, N.A.M., S.I. El-Negoumy and M.M. Abou-zaid, 1987. Flavonoids of *Artemisia judaica*, A. monosperma and A. herba-alba. Phytochemistry, 26: 3059-64.
18. Abu-Darwish, M.S., C. Cabral, M.J. Gonçalves, C. Cavaleiro, M.T. Cruz, A. Zulfiqar, I.A. Khan, T. Efferth and L. Salgueiro, 2016. Chemical composition and biological activities of *Artemisia judaica* essential oil from southern desert of Jordan. Journal of Ethnopharmacology, 191: 161-8.
19. Abd-Elhady, H., 2012. Insecticidal activity and chemical composition of essential oil from *Artemisia judaica* L. against *Callosobruchus maculatus* (F.)(*Coleoptera*: Bruchidae). Journal of Plant Protection Research, 52(3): 347-352.
20. Conway, G.A. and J.C. Slocumb, 1979. Plants used as abortifacients and emmenagogues by Spanish New Mexicans. Journal of Ethnopharmacology, 1: 241-61.
21. San Miguel, E., 2003. Rue (*Ruta L., Rutaceae*) in traditional Spain: frequency and distribution of its medicinal and symbolic applications. Economic Botany, 57: 231-44.
22. Kuzovkina, I., I. Al'terman and B. Schneider, 2004. Specific accumulation and revised structures of acridone alkaloid glucosides in the tips of transformed roots of Ruta graveolens. Phytochemistry, 65: 1095-100.
23. Applequist, W., 2001. Handbook of Psychotropic Herbs. A Scientific Analysis of Herbal Remedies for Psychiatric Conditions. JSTOR.
24. Zhang, Y., J. Li, Z. Wu, E. Liu, P. Shi, L. Han, L. Guo, X. Gao and T. Wang, 2014. Acute and long-term toxicity of mango leaves extract in mice and rats. Evidence-Based Complementary and Alternative Medicine, 2014.
25. Reitman, S. and S. Frankel, 1957. Colorimetric methods for aspartate and alanine aminotransferase. American Journal of Clinical Pathology, 28: 55-60.
26. Ratliff, C.R. and F. Hall, 1973. A new method for direct colorimetric determination on serum cholesterol. Cited in Laboratory Manual of Clinical Biochemistry, Scoot and White Memorial Hospital Publication, Texas, USA.
27. Eggstein, M. and E. Kuhlmann, 1974. Triglycerides and glycerol determination after alkaline hydrolysis. Methods of Enzymatic Analysis, pp: 1825-31.
28. Patel, D.A., B. Gillespie, J.D. Sobel, D. Leaman, P. Nyirjesy, M.V. Weitz and B. Foxman, 2004. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy?: Results of a prospective cohort study. American Journal of Obstetrics and Gynecology, 190: 644-53.
29. Drury, R.A. and E.A. Wallington, 1980. Carton's. Histological Technique 5th ed Oxford Univ.,
30. Snedecor, G.W. and W.C. Cochran, 1969. Statistical methods 6th ed The Iowa State University Press Ames lowa USA.
31. Protman, R.B. and G.T. Lawhorn, 1978. Serum enzymes are indicators of chemical induced liver damage, drug chem. Toxicol, 1: 163.
32. Lee, K.J., E.R. Woo, C.Y. Choi, D.W. Shin, D.G. Lee, H.J. You and H.G. Jeong, 2004. Protective effect of acteoside on carbon tetrachloride-induced hepatotoxicity. Life Sciences, 74: 1051-64.
33. Eidi, A., M. Eidi, M. Al-Ebrahim, A.H. Rohani and P. Mortazavi, 2011. Protective effects of sodium molybdate on carbon tetrachloride-induced hepatotoxicity in rats. Journal of Trace Elements in Medicine and Biology, 25: 67-71.
34. Arts, I.C.W. and P.C.H. Hollman, 2005. Polyphenols and disease risk in epidemiologic studies. The American Journal of Clinical Nutrition, 81: 317S-325S.
35. Seeram, N.P., L.S. Adams, S.M. Henning, Y. Niu, Y. Zhang, M.G. Nair and D. Heber, 2005. *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. The Journal of Nutritional Biochemistry, 16: 360-7.
36. Chen, C.C., Y.L. Huang, F.I. Huang, C.W. Wang and J.C. Ou, 2001. Water-soluble glycosides from *Ruta graveolens*. Journal of Natural Products, 64: 990-2.

37. Yeh, Y.H., Y.L. Hsieh and Y.T. Lee, 2013. Effects of yam peel extract against carbon tetrachloride-induced hepatotoxicity in rats. Journal of Agricultural and Food Chemistry, 61: 7387-96.
38. Koshy, A.S. and N.R. Vijayalakshmi, 2001. Impact of certain flavonoids on lipid profiles-potential action of *Garcinia cambogia* flavonoids. Phytotherapy Research, 15: 395-400.
39. Weggemans, R.M. and E.A. Trautwein, 2003. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis. European Journal of Clinical Nutrition, 57: 940-6.
40. Saieed, P., R.M. Reza, D. Abbas, R. Seyyedvali and H. Aliasghar, 2006. Inhibitory effects of *Ruta graveolens* L. extract on guinea pig liver aldehyde oxidase. Chemical and Pharmaceutical Bulletin, 54: 9-13.
41. Ratheesh, M., G.L. Shyni, G. Sindhu and A. Helen, 2011. Inhibitory effect of Ruta graveolens L. on oxidative damage, inflammation and aortic pathology in hypercholesteromic rats. Experimental and Toxicologic Pathology, 63: 285-90.
42. Kratz, F., G. Ehling, H.M. Kauffmann and C. Unger, 2007. Acute and repeat-dose toxicity studies of the (6-maleimidocaproyl) hydrazone derivative of doxorubicin (DOXO-EMCH), an albumin-binding prodrug of the anticancer agent doxorubicin. Human & Experimental Toxicology, 26: 19-35.
43. Sharma, V.J. and U.D. Shah, 2010. Antihyperglycemic activity of flavonoids from methanolic extract of aerial parts of *Scoparia dulcis* in streptozotocin induced diabetic rats. International Journal of ChemTech Research, 2: 214-8.
44. Rao, Y.K., S.H. Fang and Y.M. Tzeng, 2005. Anti-inflammatory activities of flavonoids isolated from *Caesalpinia pulcherrima.* Journal of Ethnopharmacology, 100: 249-53.
45. Eze-Steven, P.E., I.P. Udeozo, O. Emmanuel and O. Farida, 2014. The effects of ethanol exract of *Desmodium velutinum* stem on liver markers of albino wistar rats fed with high fat diet. World Applied Science Journal, 31: 1684-8.