Biochemistry and Biophysics Reports 26 (2021) 100927

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

A time course study on dose-response relationship between alcohol exposure and its effects on lipid profile and biomarkers of tissue damage

Dorcas Ibukun Akinloye [a,*], Regina Ngozi Ugbaja [a], Oluwatosin Adebisi Dosumu [a], Samson Adisa Rahman [a,b], Emmanuel Ifeanyichukwu Ugwor [a], Adewale Segun James [a], Olushola Oladapo Oyesile [a], Mary Bunmi Bada [a]

[a] Department of Biochemistry, Federal University of Agriculture, Abeokuta, P.M.B 2240, Ogun State, Nigeria
[b] College of Veterinary Medicine, Federal University of Agriculture, Abeokuta, P.M.B 2240, Ogun State, Nigeria

ARTICLE INFO

Keywords:
Alcohol
Tissue damage
Dose-response relationship
Time course
Lipid profile

ABSTRACT

This present research investigated variations in lipid profiles and important biomarkers of tissue damage in response to graded concentrations of alcohol administration in male Wistar rats. Group A (control) received distilled water while group B, C and D received 30%, 40% and 50% (v/v) alcohol respectively. Five rats each from groups A-D were sacrificed after day(s) 1, 7, 14, 21 and 28 of administration. A significant increase was observed at day 28 for serum cholesterol by 79% (group B), 78% (group C) and 47% (group D) together with serum phospholipid 58% (group B), 50% (group C) and 92% (group D). Serum triacylglycerol increased by 71% (group B), 43% (group C) and 16% (group D) at day 21, while concentration of serum albumin decreased at day 28 by 40.9% (group B), 50.2% (group C), 53.3% (group D) respectively when compared with control (group A). Serum aminotransferases and alkaline phosphatase specific activities, as well as creatinine and uric acid concentration increased in a concentration-dependent manner, following alcohol administration. Though most of these effects induced by alcohol were time- and concentration-dependent, 40% alcohol appear to be more stable, giving results consistent with alcohol-induced damages, with minimal mortality. This study therefore further validated dyslipidemia and imbalance in clinical biomarkers as hallmarks of tissue damage induced by excessive alcohol consumption with an insight on the time- and concentration-response relationship between alcohol consumption and its toxicity.

1. Introduction

The consumption of alcohol has long been part of everyday life in many societies and it still remains so currently [1,2]. More than ever before, there is an upsurge in alcohol abuse and as a result, alcohol-related disorders are becoming increasingly important causes of morbidity and mortality globally [3,4]. Several reports on the association between chronic alcohol consumption and variety of pathological conditions varying from simple intoxication to severe life-threatening pathological states have been published [4–6].

Toxicity of alcohol consumption in the body involves the liver and kidneys, and heavy consumption of alcohol is associated with these tissues damage which ultimately affects the metabolism of lipids, carbohydrates and protein [2,6,7]. Alcohol toxicity results in hepatic derangement due to the fact that approximately 80% of ingested alcohol is metabolized in the liver by a process that generates many reactive oxygen species [5,6,8]. Also, evidences are emerging in support of the hypothesis that habitual consumption of large amounts of alcohol has a variety of deleterious effects on the kidney that are independent of chronic liver disease [9]. Alcohol has been reported to have a strong effect on lipid component causing various disease conditions such as coronary heart disease, brain damage, cirrhosis, diabetes and ischemic stroke [10–12].

Interestingly, epidemiological data from the general population have shown that the effect of alcohol on many diseases has a biphasic pattern, depending on the amount of alcohol consumed [13]. Moderate alcohol consumption has been known to lower the incidence of coronary heart disease while high alcohol consumption increases its incidence, although the detailed mechanism of these biphasic effects remains to be determined [13,14]. In addition, number of stringent prospective

* Corresponding author.
E-mail addresses: akinloyedi@funaab.edu.ng, yinkaukachi2@gmail.com (D.I. Akinloye).

https://doi.org/10.1016/j.bbrep.2021.100927
Received 11 August 2020; Received in revised form 9 January 2021; Accepted 19 January 2021

observational studies had documented that moderate alcohol consumption has a beneficial effect both on the decline in renal function with age and on the evolution of primary kidney disease [14–17]. At lower doses, alcohol can act as a stimulant inducing feelings of euphoria and talkativeness [18] but drinking too much alcohol at one session can lead to drowsiness, respiratory depression (where breathing becomes slow, shallow or stops entirely), coma or even death [19].

The abuse of alcohol has been noticed in large per cent of drinkable age and has been well studied, but without putting into consideration the right dose that could be beneficial or detrimental to health [19]. Previous studies have shown that excessive alcohol consumption caused damage to the organs and tissues [1,6], however, to the best of our knowledge, the exact concentration of alcohol causing these damage, particularly on clinically important biomarkers are not well established. Therefore, this present study investigates variations in some lipid profiles and clinically important biomarkers of tissue damage over a period, in response to different concentrations of alcohol administration in male rats, with the aim of proffering the most efficient concentration, with lesser mortality, for animal models of alcohol toxicity studies.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals and reagents used were of analytical and purified grade. Chemicals used were purchased from Sigma Chemical Co., Saint Louis, MO, USA and British Drug House (BDH) Chemical Ltd., Poole, UK. All reagent diagnostic kits used were purchased from RANDOX Laboratories, Crumlin, UK.

2.2. Experimental animals

The approval of the departmental animal ethical committee (FUNAAB- BCH) was taken prior to the experiment with ethical no FUNAAB- BCH- DI 016. All the protocols and the experiments were conducted in strict compliance according to the guidelines approved by the committee. Male albino rats (170–185g) were purchased from the Department of Veterinary Physiology and Biochemistry, College of Veterinary Medicine, Federal University of Agriculture, Abeokuta (FUNAAB) Nigeria. They were housed and allowed free access to water and animal feed throughout the period of experiment in the animal care unit of the Department of Pure and Applied Zoology, Federal University of Agriculture, Abeokuta (FUNAAB) with adequate lighting and ventilation. The animals were acclimatized for two weeks and observed on daily basis throughout the period of experiment.

2.3. Experimental design

The animals were divided into baseline (day 0, n = 5) and other groups, which included;

- ➢ Group A - Control (distilled water),
- ➢ Group B- 30% Alcohol (4 ml/kg body weight)
- ➢ Group C – 40% Alcohol (4 ml/kg body weight) and
- ➢ Group D – 50% Alcohol (4 ml/kg body weight)

On day(s) 1, 7, 14, 21 and 28, blood samples were collected from the animals (five rats per group), periorbitally, under a slight anesthesia, by ocular puncture into a plain tube, allowed to stand for 15 min for the blood to clot and then centrifuged at 3000 rpm for 10 min. The serum (supernatant) was then carefully collected and stored at -20 °C until further analyses.

2.4. Isolation of HDL and VLDL + LDL

The high density lipoprotein (HDL) fraction was isolated after precipitation of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) from the serum, by heparin-$MnCl_2$ solution, as described by Gidez*et al.* [20]. The supernatant (HDL fraction) was carefully collected and stored at −20 °C until further analyses. The precipitate, which contains the VLDL + LDL fraction, was reconstituted to with 10 mM Tris-HCl buffer, pH 7.4, and stored at −20 °C.

2.5. Biochemical analysis

The serum, HDL and VLDL + LDL concentrations of total cholesterol, triacylglycerol and phospholipid were determined spectrophotometrically using commercial diagnostic kits.

The activities of alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) as well as levels of albumin, creatinine, uric acid and urea were assayed using standard commercial assay kits (RANDOX).

2.6. Statistical analysis

Values are expressed as mean ± standard error mean (S.E.M). The level of homogeneity among the results of groups was tested using one way Analysis of Variance (ANOVA), with $p < 0.05$ considered significant. Where heterogeneity occurred, the groups were separated using Duncan Multiple Range Test (DMRT). All analyses were done using Statistical Package for Social Sciences (SPSS) version 16.0.

3. Results

During the study, up to 48% mortality (12 out of 25) was observed in the group administered 50% alcohol, while 12% mortality (3 out of 25) was observed in the 30% and 40% alcohol-treated groups.

Fig. 1 shows the effects of alcohol administration on triacylglycerol concentration (mg/dl) in control and experimental rats. In the serum (Fig. 1A), a significant ($p < 0.05$) increase of 5% (group B) and 21% (groups C and D) was observed as compared to control after day 1 of administration. After day 14, a significant ($p < 0.05$) increase of 10% (groups B and C) and 8% (group D) was observed. A significant ($p < 0.05$) increase of 71%, 43% and 16% was observed in 30%, 40% and 50% alcohol groups respectively after day 21. However, there was no significant difference after day 28 of alcohol administration for 30% concentration while 40% and 50% concentrations showed an increase of 34% and 13% respectively when compared to control (group A). In the HDL (Fig. 1B), a significant ($p < 0.05$) increase of 3% was observed for 30% alcohol concentration while a decrease of 15% and 12% were observed at 40% and 50% alcohol respectively when compared to control after day 1 of administration. After day 14 of alcohol administration, there was a significant ($p < 0.05$) increase of 26% for 50% alcohol, while other groups (B and D) showed no significant difference. After 21 days, 40% and 50% alcohol showed a significant ($p < 0.05$) increase of 82% and 100% respectively while 30% alcohol showed no significant difference. Meanwhile, a significant ($p < 0.05$) decrease was observed after day 28 of administration for groups C and D (25% and 38% respectively) with no significant difference for group B. In VLDL + LDL (Fig. 1C), after day 7, there was a significant ($p < 0.05$) increase of 3% and 11% for 30% and 40% alcohol concentration. After day 21, there was significant ($p < 0.05$) increase of 8% for both 30% and 40% alcohol and 16% increase for 50% alcohol (group D).

Fig. 2 shows the effects of alcohol administration on cholesterol concentration (mg/dl). In the serum (Fig. 2A), there was a significant ($p < 0.05$) increase of 36%, 82% and 82% after day 7 for 30%, 40% and 50% alcohol respectively. After day 14, a significant ($p < 0.05$) increase of 44%, 50% and 88% was observed for 30%, 40% and 50% alcohol treated groups respectively. There was also a significant ($p < 0.05$) increase of 23%, 77% and 86% for 30%, 40% and 50% alcohol respectively at day 21. In HDL (Fig. 2B), there was no significant difference after day 1 of administration in all alcohol treated groups (B, C and D)

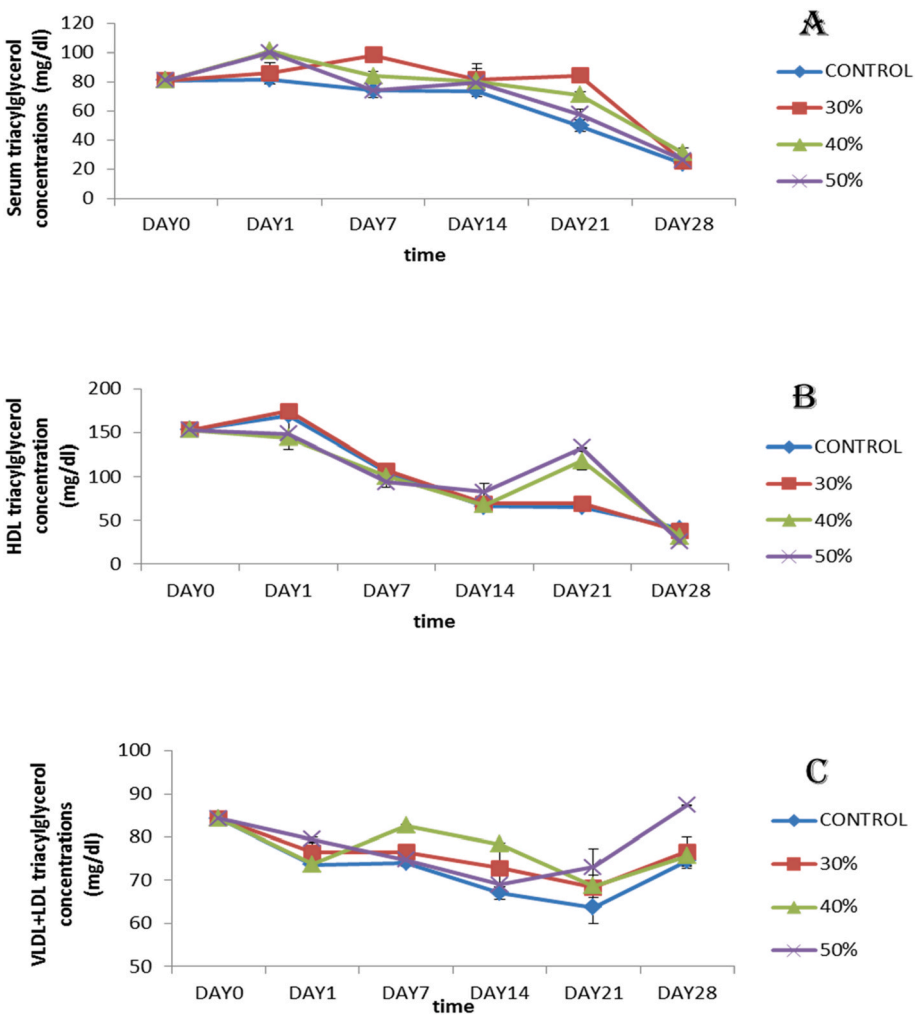

Fig. 1. Time-course effects of graded doses of alcohol on triacylglycerol concentrations of control and experimental rats. **A –** Serum; **B –** HDL; **C -** VLDL + LDL. Data were expressed as mean ± SEM. Significant difference is indicated at $p < 0.05$.

when compared to control (group A). There was no significant ($p < 0.05$) increase for both 30% and 40% alcohol when compared to control while a 33% significant ($p < 0.05$) increase was observed for 50% alcohol after day 14. At day 21, a significant ($p < 0.05$) increase of 30%, 28% and 21% was observed for 30%, 40%, 50% alcohol treated groups respectively. In VLDL + LDL (Fig. 2C), after day 7 of treatment, 16%, 11% and 58% increase was observed for 30%, 40% and 50% alcohol groups respectively, compared to control. At day 21, there was no significant difference for 30% alcohol, but a significant ($p < 0.05$) increase of 7% and 37% was observed in group C and D.

Fig. 3 shows the effects of alcohol administration on phospholipid concentration (mg/dl). In the serum (Fig. 3A), there was a significant ($p < 0.05$) increase of 11% (group B), 22% (group C) and 12% (group D) after day 1 of alcohol administration when compared to control (group A), while an increase of 9% (group B), 27% (group C) and 77% (group D) was observed after day 21 of alcohol administration. After 28 days, there was a significant ($p < 0.05$) increase of 70%, 58% and 98% for 30%, 40% and 50% alcohol concentrations respectively as compared to control. In HDL (Fig. 3B), after day 1, phospholipid concentration was significantly increased by 2 fold and 4 fold respectively in 40% and 50% alcohol treated groups while 30% treated group showed no significant difference when compared to control (group A). After 21 days, a significant increase of 35%, 85%, and 100% was observed for group B, C and D respectively when compared to group A. In VLDL + LDL (Fig. 3C), phospholipid concentration was significant decreased by 8% after day 1 for both 40% and 50% alcohol treated groups while 30% alcohol showed a significant increase. After day 7, a significant ($p < 0.05$) increase of 12%, 37% and 79% was observed in 30%, 40% and 50% alcohol treated groups respectively as compared to control. Alcohol administration for 21 days caused a significant ($p < 0.05$) increase of 24% (group B), 54% (group C) and 51% (group D) for all alcohol treated groups.

Time-course effects of graded doses of alcohol on some biomarkers of hepatic damage in rats are shown in Fig. 4. After day 1, serum AST specific activity increased in 30%, 40%, 50% alcohol groups respectively by 32.8%, 1 fold, 1.5 folds when compared to control group (Fig. 4A). There was an increase in AST specific activity after day 7, in group B, C and D by 20.6%, 35.5%, 39.8% respectively. AST specific activity increased in 30%, 40% and 50% alcohol groups after day 14 administration by 30.7%, 42.3% and 82.6% respectively. At day 21, AST specific activity increased by 87% (group B), 1.5 folds (group C) and 2 folds (group D) respectively. There was an increase in AST specific activity in 30%, 40% and 50% alcohol after day 28 administration by 60.8%, 1.5 folds and 2 folds respectively when compared to control group.

Serum ALT specific activity of the alcohol groups (30%, 40%, and 50%), after day1, increased by 67.7%, 1.4 folds and 2 folds respectively, when compared to control group (Fig. 4B). Also, the specific activity of ALT increased in all alcohol treated groups after day 7 administration by 10.17% (group B), 61.17% (group C), 1.2 folds (group D) respectively. There was 1.5 folds increase in ALT specific activity after day 14 administrations in all alcohol treated groups when compared to control group. An increase of 2 folds was observed in all alcohol groups' ALT specific activity, after 21 days of treatment. After day 28 alcohol

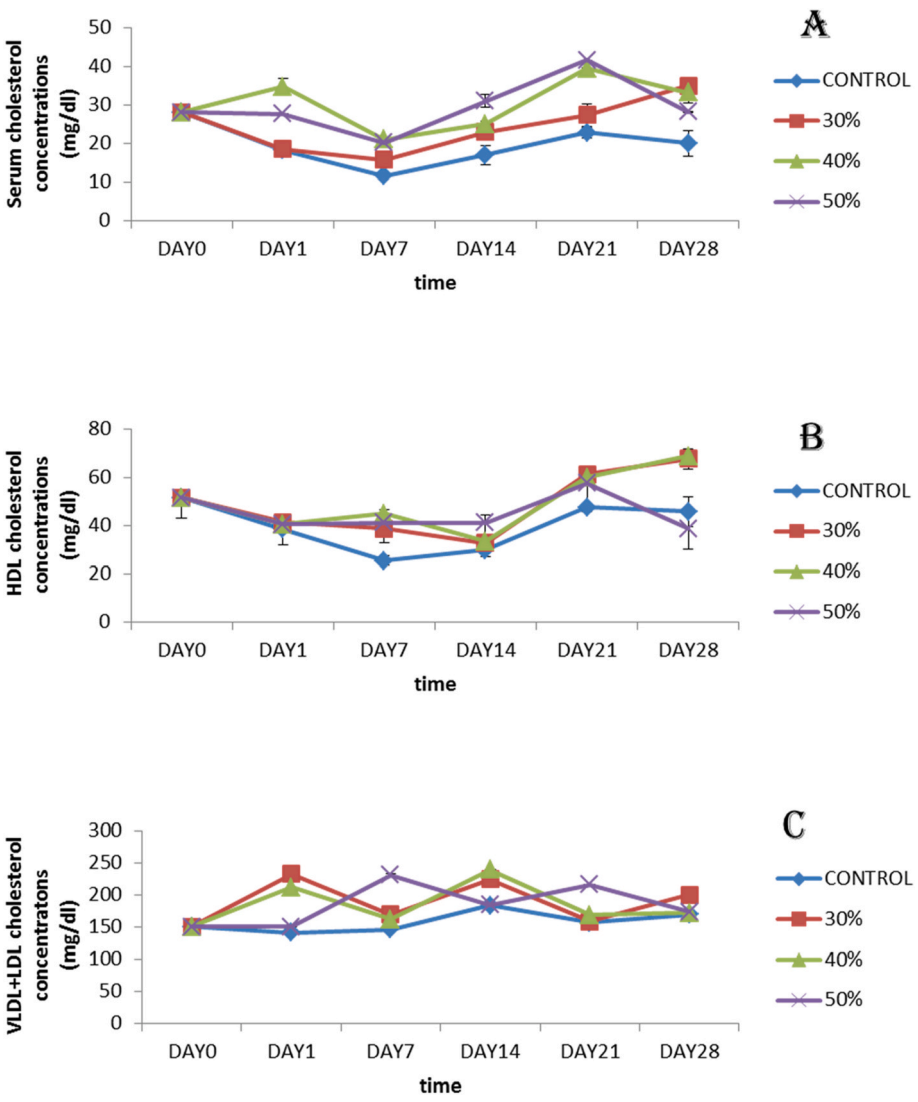

Fig. 2. Time-course effects of graded doses of alcohol on cholesterol concentrations of control and experimental rats. **A –** Serum; **B –** HDL; **C -** VLDL + LDL. Data were expressed as mean ± SEM. Significant difference is indicated at $p < 0.05$.

administration, AST specific activity increased by 2 folds (group B and C) and 3.5 folds (group D) when compared to control (group A).

After day1 of alcohol administration, an increase of 26.23% (group B), 53.95% (group C) and 64.9% (group C) respectively was observed in serum ALP specific activity when compared to control group (Fig. 4C). ALP specific activity increased after day 7 of alcohol administration in group B (52.85%), C (1 fold) and D (1 fold) respectively. A significant ($p < 0.05$) increase ($p < 0.05$) was observed in the specific activity of ALP in all alcohol treated groups (B, C and D) after day 14 of administration by 75.2% (group B), 1 fold (group C) and 2 fold (group D) respectively. After day 21 of alcohol administration, ALP specific activity increased by 71.5%, 1 fold and 2 fold respectively in group B, C and D. There was also an increase in ALP specific activity after day 28 of administration by 65.59% (group B), 1 fold (group C) and 2 fold (group C) respectively, when compared to control group.

A decrease in albumin concentration was observed after day 7 of administration in all alcohol treated groups (B, C and D) by 5%, 10% and 20% respectively, when compared to group A (Fig. 4D). After day 14 of alcohol administration albumin concentration decreased by 24.94%, 33.91% and 50.24% respectively in group B, C and D. There was a decrease in serum albumin concentration after day 21 of alcohol administration for 30%, 40% and 50% alcohol dose by 20.90%, 33.71% and 43.95% respectively. Also a decrease in albumin concentration was observed in group B, C and D after day 28 of alcohol administrations by respective 40.9%, 50.1% and 54.6%, when compared to control group.

Fig. 5 shows the time-course effects of graded doses of alcohol on some biomarkers of renal damage in control and experimental rats. After day 1 of administration, an increase was observed in serum uric acid concentration for rats administered 30%, 40% and 50% dose of alcohol, by 2.44%, 12.74% and 21.48% respectively when compared to the control group (Fig. 5A). The concentration of uric acid increased after day 7 administrations by 25.2% and 42.5% respectively in group C and D. Treatment with alcohol at 30%, 40% and 50% concentrations increased uric acid levels after day 14 administration by respective 0.9%, 20% and 46%. There was an increase in uric acid concentration after 21 days of alcohol administration by 1.27%, 23.32% and 56.65% respectively in group B, C and D. Serum uric acid concentration increased at 30%, 40% and 50% dose of alcohol administration by 13.68%, 30.97% and 57.74% respectively, when compared to control group, after 28 days of administration.

Urea concentration in the serum (Fig. 5B) increased by 17.9% and 24.7% in group B and C respectively while group D showed 15.6% decrease after day 1 administrations. After day 7 administrations, urea concentration at 30% and 40% alcohol dose decreased by 2.4% and 2.6% respectively while 50% alcohol caused 1.5% increase. Alcohol administrations for 14 days at 30%, 40% and 50% dose caused increased

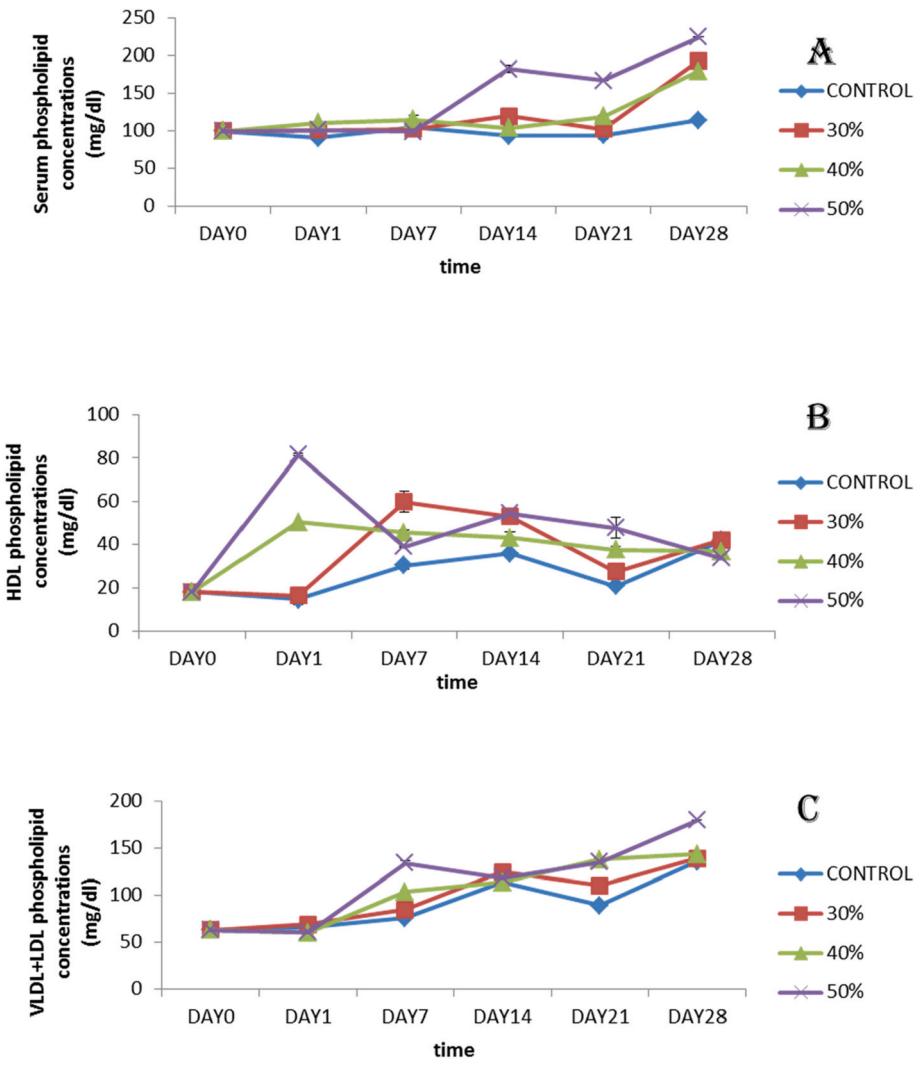

Fig. 3. Time-course effects of graded doses of alcohol on phospholipid concentrations of control and experimental rats. **A –** Serum; **B –** HDL; **C -** VLDL + LDL. Data were expressed as mean ± SEM. Significant difference is indicated at $p < 0.05$.

in urea concentration by 2.57%, 5.76% and 6.35% respectively. Serum creatinine concentration (Fig. 5C) after day 7 of alcohol administration was decreased when compared to control. Also, the concentration of creatinine increased in group B, C and D after day 14 of alcohol administration by 16.7%, 44.4% and 55.5% respectively. Alcohol administration at 30% and 40% concentrations increased creatinine levels by 4.2% and 18.8% respectively when compared to control group after 21 days of alcohol administrations.

4. Discussion

Alcohol affects virtually every organ and tissue in the body, with multi-factorial actions on cellular and molecular functions by altering biological function either via direct interaction with cellular components, or direct biochemical effect of alcohol metabolism on the systemic oxidative and inflammatory state of the body system [6,21]. Direct interactions of alcohol with molecular components affect physiological function, such as modification of signal transduction at multiple sites through its interaction with cell membranes [22,23] as well as with signaling proteins [24–26] and ion channels [27] of multiple signaling pathways that mediate many essential processes. Characterization of the cellular and molecular processes that are disrupted after exposure to alcohol is therefore necessary in understanding and treating or preventing its pathophysiological effects [6,21]. Evaluations of the toxic effects and treatments of alcohol exposure are clearly relevant areas of research in the alcohol field, because insights gotten from such researches may be of great therapeutic importance in the design of newer, better and more specific drugs and therapies capable of ameliorating the toxic effects of alcohol. Indeed, most researches have focused on the toxic effects of alcohol, and less on the dose-response relationship of these effects, hence the need for this study.

The consumption of alcoholic beverages is associated with an elevated incidence of many diseases, including metabolic syndrome and cardiovascular disease [28,29]. Additionally, the associations between alcohol consumption and the risk of cardiovascular disease, including myocardial infarction and coronary heart disease, are mediated, in large part, by the differential influence on the levels lipid profiles, especially HDL-cholesterol and LDL-cholesterol [10,11]. This study therefore, investigated the time-course effects of graded concentrations of alcohol on lipid profiles (triacylglycerol, cholesterol and phospholipids) in control and experimental rats. The results of the present study revealed a time- and dose-dependent relationship between alcohol exposure and the assayed lipid profiles, though this was not consistent across all groups. These inconsistency in the lipid profile ensued from alcohol administration agreed with the reports of other researchers in respect of associated inconsistencies between alcohol consumption and lipid concentrations [29–31]. More so, various studies have shown that ethanol consumption is often associated with disruptions in concentration of

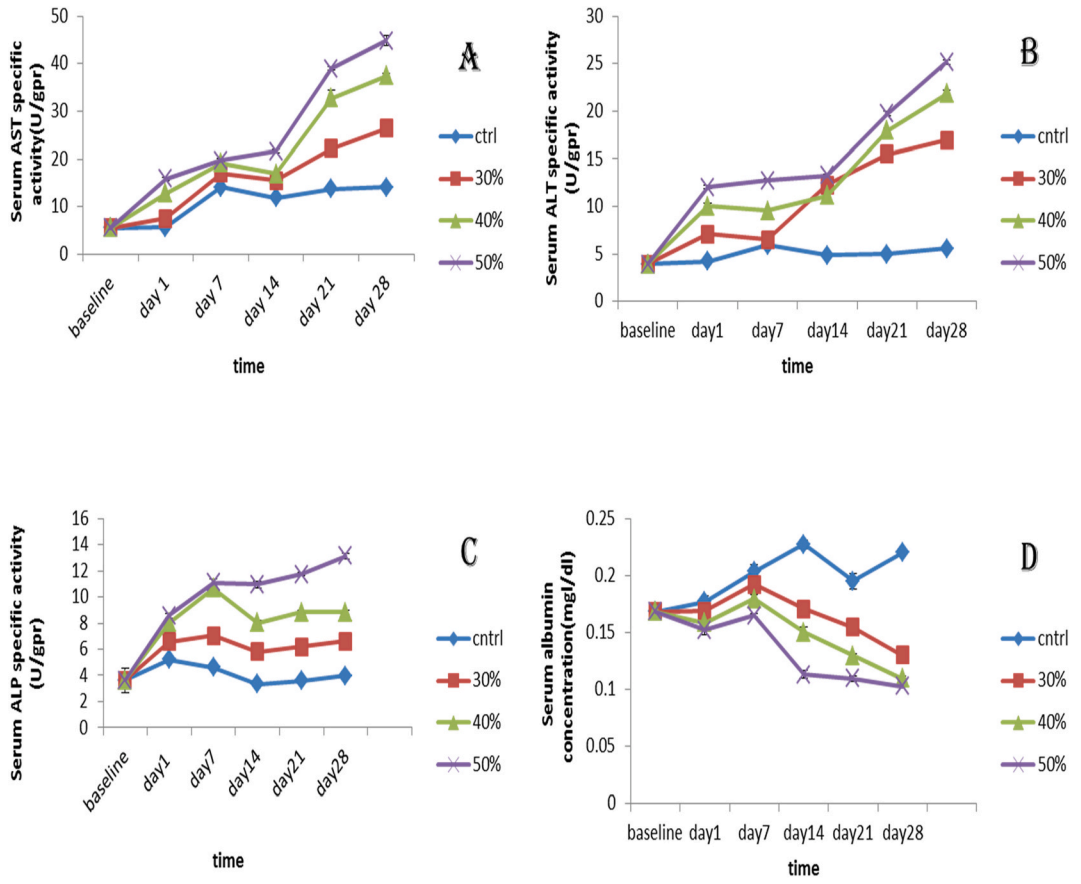

Fig. 4. Time-course effects of graded doses of alcohol on some biomarkers of hepatic damage in control and experimental rats. **A -** Aspartate transaminase (AST) specific activity (U/g protein); **B -** Alanine transaminase (ALT) specific activity (U/g protein); **C -** Alkaline phosphatase (ALP) specific activity (U/g protein); **D -** Albumin concentration (mg/dl). Data were expressed as mean ± SEM. Significant difference is indicated at $p < 0.05$.

plasma lipids [6,32,33]. The increase in concentration of triacylglycerol in serum and lipoprotein (HDL and VLDL + LDL) observed in this study could be implicated as or attributed to one of the reasons for the development of cardiovascular diseases among alcoholics [19,32]. An increase in serum and lipoprotein (VLDL + LDL) cholesterol concentration could be as a result of alcohol contributing to development of cholesteronaemia which is in agreement with previous reports by Reynolds et al. [34], Rehm et al. [19] and Akinloye et al. [6] that excessive consumption of alcohol causes high concentrations of cholesterol in the blood. Phospholipids are a class of lipids that are a major component of all cell membranes [19] as they play a role in the formation of lipid bilayers [35]. Alcohol showed significant effect on phospholipid concentration in serum, HDL, VLDL + LDL at the various time courses (day 1, 7, 14, 21, 28) by increasing the levels of phospholipid in a concentration dependent manner. The increased and high concentration of phospholipid in serum, HDL, VLDL + LDL may be due to tissue damage induced by alcohol administration which could have affected the membrane integrity of the tissues hence releasing more phospholipid into the blood stream and some bounded to lipoproteins (HDL and VLDL + LDL) [7,35]. Excessive alcohol consumption has been documented to increase the output of triacylglycerol-carrying lipoproteins from the liver as one of the major mechanisms for the alcoholic hyperlipemia [6,11,13]. Moreover, light alcohol consumption has been suggested to be helpful for hypertensive men to alleviate the risk of dyslipidaemia [10], but this risk is increased by high alcohol consumption, and the harmful effects of alcohol may be attributable to increased serum lipid concentrations as amount and period of consumption increases [6,13,33], corroborated with the findings of this present study on effects of graded doses of excess alcohol administrations to rats on blood lipid profiles.

This research work also evaluated the time course effects on some clinically important hepatic biomarkers in rats administered with graded concentrations of alcohol. The liver is the main site of alcohol metabolism and a major target organ of alcohol-induced injury. The susceptibility of the liver to alcohol-induced toxicity is due to both the high concentrations of alcohol found in the portal blood (versus systemic), as well as the metabolic consequences of ethanol metabolism [36]. The exposure of the liver to a variety of hepatotoxins, such as excessive alcohol intake, result in excessive generation of free radicals which leads to hepatotoxic lesions [2,37]. Liver status can be monitored by activities of some biomarker enzymes which are normally abundantly present in hepatocytes or bound to their membranes and may leak into the blood in response to both effect xenobiotic intake and liver diseases. Findings from this study revealed a progressive increase in the activities of aminotransferases (AST, ALT) and ALP in the serum (most consistent in the 40% alcohol administered groups) when compared to control with the amount and duration of ethanol exposure, indicating a time- and concentration-dependent relationship between alcohol consumption and its toxicity effects. These observations are in agreement with the reports of Sankaran et al. [38] that increased levels of serum enzymes such as AST, ALT and ALP observed in alcohol treated rats was as a result of liver damage which leads to leakage of cellular enzymes into the serum.

Albumin is the most abundant serum protein representing 55–65% of the total protein [38]. As albumin is synthesized in the liver, it can also be used as a biomarker to monitor liver function [38]. Administration of graded concentration of alcohol (30%, 40% and 50%) caused reduction of serum albumin in a concentration and time-dependent manner, which may be attributed to alcohol-induced liver damage, altering the rates of

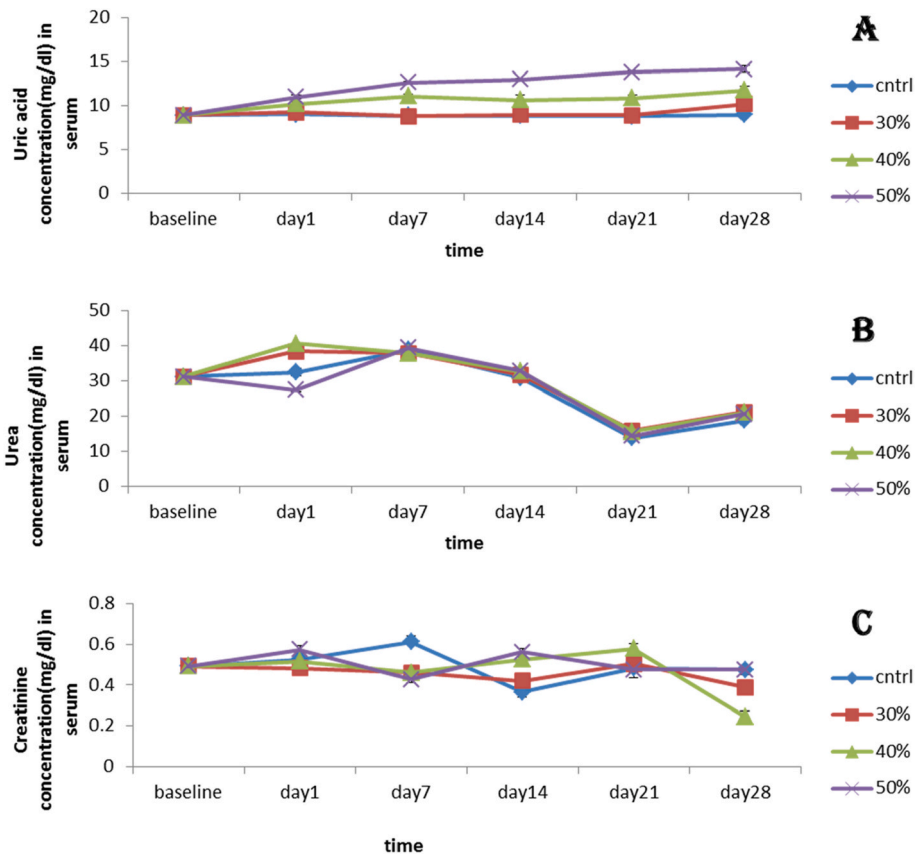

Fig. 5. Time-course effects of graded doses of alcohol on some biomarkers of renal damage in control and experimental rats. **A -** Uric acid concentration (mg/dl); **B -** Urea concentration (mg/dl); **C -** Creatinine concentration (mg/dl). Data were expressed as mean ± SEM. Significant difference is indicated at $p < 0.05$.

protein synthesis. Uric acid (UA) a product of purine metabolism and is a normal component of urine. It is produced in conditions where there is cellular destruction and thus, degradation of the nuclear material and is efficiently excreted by the kidney, thus increased concentrations of blood uric acid may indicate onset of kidney failure [39]. In this study, it was discovered that administration of all graded concentrations of alcohol increased uric acid concentration. The increased uric acid concentrations in the alcohol treated groups may also be partly due to alterations in the catabolism of purines, as it has been documented that serum uric acid concentrations could increase via alcohol-induced activation of adenine nucleotide turnover, which was triggered by the acetate formed from excessive alcohol metabolism [9,40]. A similar finding was also observed by Abdrabo et al. [41] that excessive alcohol intake increased uric acid production by increasing ATP degradation to AMP (a precursor of uric acid). Since the nineteenth century, it has been known that alcoholism is associated with a higher risk of glomerulonephritis, and has been documented that alcoholism remains a risk factor for post-infectious glomerulonephritis, acute kidney injury, and kidney graft failure [14]. Considering information gathered from literature and data from this study, one could suggest that the observed hyperuricemia in rat administered graded doses of excess alcohol might be due to impaired glomerular function of the kidneys. Creatinine is the by-product of muscle metabolism that is excreted unchanged by the kidney out of the serum, while urea, a waste product from dietary protein is also filtered into the urine by the kidneys. Hence, they serves as an important indicator of kidney function and elevated or irregular creatinine and urea concentrations may thus signify impaired kidney function or kidney damage [39]. The administration of graded doses of alcohol in this study that causes elevations as well as irregularity of creatinine and urea concentration could be attributed to poor clearance due to progressive kidney dysfunction, with loss of kidney filtration and less excretion of wastes, resulting in imbalance of creatinine and urea in the blood.

5. Conclusion

This study validated that alcohol exposure disrupts lipid homeostasis (lending credence to the fact that it a risk factor for development of cardiovascular diseases) and induces tissue (renal and hepatic) dysfunctions. Our findings also indicated that some of these effects were in dose-as well as time-dependent manner. However, 40% alcohol dose represent the most stable and consistent of all the graded doses used in this study, with evident toxic effects and yet minimal mortality in the animals.

Funding

This research work was not funded by grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2021.100927.

Authors' contributions

The research work was designed by the corresponding author

(Akinloye D.I.) under the major supervision of Ugbaja R. N. and Dosumu O. A. Conceptualization, investigation, methodology, writing, reviewing, editing and approving of the manuscript was also carried out by all the authors (Akinloye D. I., Ugbaja R. N., Dosumu O. A., Rahman S. A., Ugwor E.I., James A. S., Oyesile O.O. and Bada M.B.).

References

[1] O.O. Dosumu, A.A. Osinubi, F.I. Osinubi, Duru, Alcohol induced testicular damage can abstinence equal recovery, Middle East Fertil, Soc. J. 19 (2014) 221–228.
[2] M.A. Mahgoub, Rosmarinic acid attenuates the hepatotoxicity induced by ethanol in rats, Am. J. Biochem. 6 (2016) 82–90.
[3] R. Rukkumani, K. Aruna, P. Suresh Varma, V.P. Menon, Influence of ferulic acid on circulatory peroxidant-antioxidant status during alcohol and PUFA- induced toxicity, J. Physiol. Pharmacol. 55 (2004) 551–561.
[4] L.C. Saalu, B. Ogunlade, G.O. Ajayi, A.O. Oyewopo, G.G. Akunna, O. S. Ogunmodede, The Hepato-protective Potentials of *Moringa oleifera* leaf extract on alcohol-induced hepato-toxicity in wistar rat, Am. J. Biotechnol. Mol. Sci. 2 (2012) 6–14.
[5] I.O. Macdonald, O.J. Olusola, U.A. Osaigbovo, Effects of chronic ethanol administration on body weight, reduced glutathione (GSH), malondialdehyde (MDA) levels and glutathione-S-transferase activity (GST) in rats, Nucl. Sci. J. 3 (2010) 39–47.
[6] D.I. Akinloye, R.N. Ugbaja, O.A. Dosumu, Appraisal of the antioxidative potential of *aloe barbadensis* M. On alcohol-induced oxidative stress, Folia Vet. 63 (2019) 34–46.
[7] C.S. Lieber, Medical disorders of alcoholism, N. Engl. J. Med. 333 (1999) 1058–1065.
[8] A. Venkatraman, S. Shiva, A. Wigley, E. Ulasova, D. Shhieng, S.M. Bailey, The role of iNOS in alcohol-dependent hepatotoxicity and mitochondrial dysfunction in mice, Hepatology 40 (2004) 565–573.
[9] K.R. Shanmugam, C.H. Ramakrishna, K. Mallikarjuna, K. Sathyavelu-Reddy, Protective effect of ginger against alcohol-induced renal damage and antioxidant enzymes in male albino rats, Indian J. Exp. Biol. 48 (2010) 143–149.
[10] J.M. Gaziano, J.E. Buring, J.L. Breslow, S.Z. Goldhaber, B. Rosner, M. Van-Denburgh, W. Willett, C.H. Hennekens, Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction, N. Engl. J. Med. 329 (1993) 1829–1834.
[11] M.J. Savolainen, Y.A. Kesäniemi, Effects of alcohol on lipoproteins in relation to coronary heart disease, Curr. Opin. Lipidol. 6 (1995) 243–250.
[12] H. Campose, C. Khoo, F.M. Sacks, Diurnal and acute pattern of postprandial apolipoprotein B-48 in VLDL, IDL and LDL from normolipidemic human, Atherosclerosis 181 (2005) 345–351.
[13] H. Park, K.K. Kisok, Association of alcohol consumption with lipid profile in hypertensive men, Alcohol Alcohol 47 (2012) 282–287.
[14] E. Schaeffner, E. Ritz, Alcohol and kidney damage: a Janus-faced relationship, Kidney Int. 81 (2012) 816–818.
[15] E.S. Schaeffner, T. Kurth, P.E. de Jong, R.J. Glynn, J.E. Buring, J.M. Gaziano, Alcohol consumption and the risk of renal dysfunction in apparently healthy men, Arch. Intern. Med. 165 (2005) 1048–1053.
[16] K. Reynolds, D. Gu, J. Chen, X. Tang, C.L. Yau, L. Yu, C.S. Chen, X. Wu, L.L. Hamm, J. He, Alcohol consumption and the risk of end-stage renal disease among Chinese men, Kidney Int. 73 (2008) 870–876.
[17] S.L. White, K.R. Polkinghorne, A. Cass, J.E. Shaw, R.C. Atkins, S.J. Chadban, Alcohol consumption and 5-year onset of chronic kidney disease: the AusDiab study, Nephrol. Dial. Transplant. 24 (2009) 2464–2472.
[18] T. Roehrs, T. Roth, Sleep, sleepiness, and alcohol use, Alcohol Res. Health 25 (2001) 101–109.
[19] J. Rehm, C. Mathers, S. Popova, M. Thavorncharoensap, Y. Teerawattananon, J. Patra, Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders, Lancet 373 (2009) 2223–2233.
[20] L.I. Gidez, G.J. Miller, M. Burtein, S. Slagle, Separation and quantification of subclasses of human plasma high density lipoprotein procedure, J. Lipid Res. 23 (1982) 1206–1223.
[21] K.M. Jung, J.J. Callaci, K.L. Lauing, J.S. Otis, K.A. Radek, M.K. Jones, E.J. Kovacs, Alcohol exposure and mechanisms of tissue injury and repair, Alcohol Clin. Exp. Res. 35 (2011) 392–399.
[22] A. Dolganiuc, G. Bakis, K. Kodys, P. Mandrekar, G. Szabo, Acute ethanol treatment modulates toll-like receptor-4 association with lipid rafts, Alcohol Clin. Exp. Res. 30 (2006) 76–85.
[23] G. Szabo, A. Dolganiuc, Q. Dai, S.B. Pruett, TLR4, ethanol, and lipid rafts: a new mechanism of ethanol action with implications for other receptor-mediated effects, J. Immunol. 178 (2007) 1243–1249.
[24] K. Higashi, M. Hoshino, T. Nomura, K. Saso, M. Ito, J.B. Hoek, Interaction of protein phosphatases and ethanol on phospholipase C-mediated intracellular signal transduction processes in rat hepatocytes: role of protein kinase A, Alcohol Clin. Exp. Res. 20 (1996) 320A–324A.
[25] K. Saso, G. Moehren, K. Higashi, J.B. Hoek, Differential inhibition of epidermal growth factor signaling pathways in rat hepatocytes by long-term ethanol treatment, Gastroenterol. 112 (1997) 2073–2088.
[26] J. Goral, E.J. Kovacs, In *vivo* ethanol exposure down-regulates TLR2-, TLR4-, and TLR9-mediated macrophage inflammatory response by limiting p38 and ERK1/2 activation, J. Immunol. 174 (2005) 456–463.
[27] A.M. Dopico, Ethanol sensitivity of BK (Ca) channels from arterial smooth muscle does not require the presence of the beta 1-subunit, Am. J. Physiol. Cell Physiol. 284 (2003) C1468–C1480.
[28] O. Clerc, D. Nanchen, J. Cornuz, P. Marques-Vidal, G. Gmel, F. Daeppen, F. Paccaud, V. Mooser, G. Waeber, P. Vollenweider, N. Rodondi, Alcohol drinking, the metabolic syndrome and diabetes in a population with high mean alcohol consumption, Diabet. Med. 27 (2010) 1241–1249.
[29] I. Wakabayashi, Associations between alcohol drinking and multiple risk factors for atherosclerosis in smokers and nonsmokers, Angiology 61 (2010) 495–503.
[30] M. Foerster, P. Marques-Vidal, G. Gmel, F. Daeppen, J. Cornuz, D. Hayoz, A. Pecoud, V. Mooser, G. Waeber, P. Vollenweider, F. Paccaud, Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption, Am. J. Cardiol. 103 (2009) 361–368.
[31] B. Hansel, F. Thomas, B. Pannier, K. Bean, A. Kontush, M.J. Chapman, L. Guize, E. Bruckert, Relationship between alcohol intake, health and social status and cardiovascular risk factors in the urban Paris-Ile-De-France Cohort: is the cardioprotective action of alcohol a myth? Eur. J. Clin. Nutr. 64 (2010) 561–568.
[32] E. Barrett-Connor, L. Suarez, A community study of alcohol and other factors associated with the distribution of high density lipoprotein cholesterol in older vs. younger men, Am. J. Epidemiol. 115 (1982) 888–893.
[33] K.J. Mukamal, S.E. Chiuve, E.B. Rimm, Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles, Arch. Intern. Med. 166 (2006) 2145–2150.
[34] K. Reynolds, L.B. Lewis, J.D.L. Nolan, G.L. Kinney, B. Sathya, J. He, Alcohol consumption and risk of stroke: a meta-analysis, J. Am. Med. Assoc. 289 (2003) 579–588.
[35] K.J. Mukamal, E.B. Rimm, Alcohol's effects on the risk for coronary heart disease, Alcohol Res. Health 25 (2001) 255–261.
[36] G.E. Arteel, Acute alcohol-induced liver injury, Front. Physiol. 3 (2012) 193–235.
[37] R. Nakagiri, E. Hashizume, S. Kayahashi, Y. Sakai, T. Kamiya, Suppression by *Hydrageaedulcis folium* of D-galactosamine-induced liver injury *in vitro* and *in vivo*, Biosci. Biotechnol. Biochem. 67 (2003) 2641–2643.
[38] M. Sankaran, A. Vadivel, A. Thangam, Curative effect of garlic on alcoholic liver disease patients, Jordan J. Biol. Sci. 3 (2010) 147–152.
[39] C.M. Burns, R.L. Wortmann, Gout therapeutics: new drugs for an old disease, Lancet 377 (2011) 165–177.
[40] J.G. Puig, I.H. Fox, Ethanol-induced activation of adenine nucleotide turnover: evidence for role of acetate, J. Clin. Invest. 74 (1984) 936–941.
[41] A.A. Adbrabo, Y.S. Mohamed, S.A. Ahmed, S.B. Mohamed, Evaluation of Alcoholic consumption on serum uric acid, urea and creatinine levels, Eur. J. Pharm. Med. Res. 3 (2016) 577–579.