EJTAS ISSN 2786-7447
EUROPEAN JOURNAL OF THEORETICAL AND APPLIED SCIENCES
OPEN ACCESS
PEER REVIEWED

Therapeutics of *L. Lanceolata* and *V. Doniana* on Alcohol Induced Hepatic Pathology

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Suggested Citation
Ujah, F.O., Nenge, P.H., Kassar, R.T., Okafor, J.O. & Abeda, I.T. (2023). Therapeutics of *L. Lanceolata* and *V. Doniana* on Alcohol Induced Hepatic Pathology. *European Journal of Theoretical and Applied Sciences, 1*(6), 958-969.
DOI: 10.59324/ejtas.2023.1(6).92

Abstract:

Additive and stimulative properties of alcohol encourage large intake. Notwithstanding, chronic alcohol consumption causes severe hepatic damage, that alters normal biological function of the liver. The aim of this research was to assess the effects of *Lophira lanceolata* and *Vitex doniana* extracts on alcohol induced hepatotoxicity using rat model by examining liver serum enzymes (AST, ALT, ALP), lipid peroxidation level, antioxidant enzyme activity and haematological parameters. Thirty Wister rats weighing 70 to 120g were placed in six groups of fives per group. The negative control and treatment groups were familiarized with alcohol (42%) in drinking water before oral administration of 42% consumable alcohol (v/v, 1ml/100g body weight) for nine days. Afterward, the treatment groups were administered 600mg/kg body weight extracts of *Lophira lanceolata*, *Vitex doniana* and Vitamin C (as standard drug). Body weight and behavioural characters were monitored during the period. It was observed that, rats in the negative and treatment groups showed significant depletion in weight and negative changes in behaviour. Furthermore, biochemical assessment revealed significant elevated levels of liver serum enzymes (ALT, AST, ALP) activity, total and direct bilirubin, MDA, SOD and CAT while GSH and haematological parameters were significantly depleted at $p<0.05$. However, the treated groups revealed significant reduction in the liver enzymes, MDA, SOD and CAT while GSH activity and haematological parameters were significantly increased. In conclusion, both extracts have ameliorative and antioxidant properties that could mitigates chronic alcohol hepatotoxicity.

Keywords: *Alcohol, Antioxidant, Hepatotoxicity Lophira lanceolata, Vitex doniana.*

Introduction

Generally, in Africa the first line of treatment is the traditional medicine practitioner who uses plants believed to contain certain properties in curing an ailment. And with knowledge of modern science, there is now vast information on plants' rich bioactive natural compounds of therapeutic and nutritional usefulness to man (Ujah & Hough, 2020). These Phytocompounds majorly act as oxidant scavenger or inducers of endogenic antioxidants (glutathione etc) against radicals generated during metabolic reactions in biocellular environments. They play vital role in xenobiotic metabolism for easy elimination of toxic products from the system (Ujah, et al., 2021).

Alcohol is the most used and abused psychoactive drug in the world (Angela, 2015). Often consumed as beverages in the form of beers, wines and spirits. Its misuse has

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devastating effects and accounts for 5.9% deaths and 5.1% of global burden of disease injury thereby imposing a significant social and economic burden on society (Angela, 2015; WHO, 2015). Chronic alcohol consumption is often associated with alcohol induced hepatotoxicity, but there is no consume level known to initiate hepatotoxicity. This is because there are different factors that affect the rate of alcohol metabolism in the system, these maybe genetic such as variations in the enzymes that break down alcohol, environmental factors, such as the amount of alcohol an individual consumes and his or her overall nutrition, gender, body composition, health status of the liver etc (Samir, 2006; Arthur, 2012; Angela, 2015). The National Institute of Alcohol Abuse and Alcoholism (2015) stated that, chronic alcohol consumption like binge or heavy drinking are category of people whose consumption of alcohol is such that their blood alcohol concentration is above 0.08% while according to Centre for Disease Control-CDC (2014), binge drinking are consumers of 5 or more bottles of alcohol per day for men and 4 or more bottles per day for women and a consumption rate at least 15-18 bottles a week.

Chronic alcohol consumption generates excessive free radical species which could interact with cellular components causing cellular damages, the excessive free radicals generated is regarded as key factor in the development of alcohol-induced liver injury (Zhou et al., 2017). The most important characteristic impact of free radicals is the peroxidation of membrane lipids resulting in tissue damage and death of affected cells (Bandyopadhyay, 1999). Despite the significant progress made in understanding the pathogenesis of alcohol liver disease, current therapies for the disease has not been effective as abstinence from alcohol is the only effective method (Zhou et al., 2003; Gupta et al., 2005; Dahiru et al., 2007). It becomes imperative to source alternative but natural ways to unravel active component(s) that could serve as model for drugs that can mitigate the chronic effect of alcohol with no side pathological effect and less cost effective. Natural products of plant origin are known to contain abundant antioxidants and are reported to possess the power to scavenge free radicals and protect the liver and other internal organs from damage (Li et al., 2015; Wang et al., 2016). Common among these tradomedicinal plants are *Lophira lanceolata* and *Vitex doniana*.

Brief Description of *Lophira lanceolata* and *Vitex doniana* Plants

Lophira lanceolata is commonly known as the 'dwarf red ironwood' in English (Plant Resources of Tropical Africa PROTA, (Grubben, 2008). It is a multipurpose tree valued for its oil, timber and many medicinal applications due to its rich phytochemicals (Collins et al., 2021); it is native to the tropics of Central and West Africa, ranging from Senegal, Uganda, Democratic Republic of Congo and Nigeria. It grows at altitudes of up to 500m (5000ft.) on wooden savannah, and at forested areas where it may grow thickly (Plant Resources of Tropical Africa PROTA, 2007). *Lophira lanceolata* is a specie in the Ochnacaea family represented by three genera; *Ochna, Ouratea,* and *Lophira*. It is a small medium sized tree of about 16-24m tall that loses its leaves in the dry season (Tropical Plants Database, Fern, 2021). The plant has narrow crown and branches that are ascending with prominent leave-scars; the leaves alternate on the branch but cluster at the branch end, and they are simple and entire. The trunk is usually branchless for about 8m (26ft) and can reach a diameter of 70cm (28inch). The bark is grey and coarsely flaking in small pieces. The inflorescence takes the form of a loose pinnacle at the end of the stem; individual flowers are bisexual, scented and white with parts in fives. This is followed by a winged calyx, containing a single, large seed (Tropical Plants Database, Fern, 2021).

It is known in different parts of Nigeria by different names; Nmijinkande in Hausa, Okpopia in Igbo, Ikponhon in Yoruba and Horkula in Tiv. The qualitative phytochemical analysis of *L.* lanceolata confirmed the presence of saponins, tannins, flavonoids, terpenoids, glycosides, alkaloids, steroids, phenolic compounds and antraquinones (Lohlum, 2010).

The tree resembles *Lophira alata* morphologically but differs mainly in their habitat with the *alata* specie growing in thick dense forests. Other difference includes size, leaves and seeds (Lemmens and Siemonsma, 2008).

Vitex doniana is commonly known as 'black plum' in English. It is a plant valued mostly for its black drupe fruit eaten by children amidst other uses, for industrial production of jellies and medicinal use of the bark or leaf. It is native to the tropics (Africa, spreading from Senegal east to Somalia, South Africa and West Africa) (Hounkpèvi, 2016). It is a deciduous flowering tree that grows up to 20m (65ft), with a heavy rounded crown, the trunk can be up to 1m across with a bark coloured pale brown or gray white that looks cracky. It has leaves that look leathery and slippery, arranged like finger on a hand with five leaflets. The fruits of the plant are plum; which are smooth and roundish, and green with white spots when unripe but turns black when ripe while sometimes maintaining the white spots (Martin et al., 1987). The natives of Logo LGA in Benue state use both *Lophira lanceolata* and *Vitex doniana* to treat viral hepatitis. Below is the pictorial identification of *Lophira lanceolata* and *Vitex doniana.*

Figure 1. *Lophira lanceolata*

Figure 2. *Vitex doniana*

Materials and Methods

Materials

The stem of *Lophira lanceolata* and *Vitex doniana* were collected from Logo local government area of Benue state Nigeria and were dried at room temperature (25°C) for 7 days. The barks were peeled and crushed using a mortar and pestle into fine coarse particles. The pulverized form of both samples were weighed separately and soaked in 99.7% absolute ethanol and allowed to stand for 72 hours with mechanical shaking at regular intervals. The extracts were filtered twice using a sieve cloth and then Whatman No 1 filter paper. The filtrate was evaporated using water bath at 50°C to obtain crude extracts.

Experimental Design

Thirty Wistar rats were obtained from the Department of small animal unit, Central Diagnostic Division of National Veterinary Research Institute (NVRI) Vom, Plateau State. The animals were kept under standard condition of 12/12 hours dark-light cycle and were fed with standard feed (chicken feed) and water *ad libitum*. Animals were allowed to acclimatize for two weeks prior to distribution into six groups of five; the animals were intoxicated and treated in accordance to the experimental design in table 1.

Table 1. Experimental Design and Treatment Schedule for Effect of *Lophira lanceolata* and *Vitex doniana* Extracts on Alcohol Induced Hepatotoxicity

Group	Number of animals	Administration	Dosage
Positive	5	Feed + Water	-
Negative	5	Feed + Water + Alcohol for 9days	1ml/100g B.W
Lophira lanceolata	5	Feed + Water + Alcohol + *Lophira lanceolata* for 9days	600mg/Kg B.W
Vitex doniana	5	Feed + Water + Alcohol + *Vitex doniana* for 9days	600mg/Kg B.W
Vitamin C	5	Feed + Water + Alcohol + Standard Drug (Vitamin C tablets) for 9days	600mg/Kg B.W
Binge Drinker	5	Feed + Water + Continuous Alcohol for 7 more days	1ml/100g B.W

Note: Alcohol and extracts were administered orally. B.W –Body weight; 42% consumable alcohol

Methods

Biochemical and Haematological Estimations

The animals were sacrificed following the guidelines of the European convention for the protection of vertebrate animals and other scientific purposes ETS-123 (European treaty series, 2005). Blood samples were collected via the terminal blood collection technique into plain tubes and allowed to clot, centrifuged and separated using a pipette while those for haematological analysis were collected in EDTA tubes. Liver biochemical parameters (GSH, ALT, AST, ALP, Total and Direct Bilirubin) were assayed using Randox assay kits (Randox laboratories ltd., Antrim, United Kingdom), whereas haematological parameters (RBC, WBC, Hb and PCV) were examined using Sysmex (SYSMEX XE-2100D) automated blood analyser. The levels of SOD, and CAT were measured using the commercial detection kits following the manufacturer's instructions. Levels of MDA (Malondialdehyde) were measured by thiobarbituric acid (TBA) method using the commercial detection kits and the results were expressed as nmol MDA equivalent/mg protein.

Statistical Analysis

Results were presented as Mean ± Standard Deviation, analysed using one-way analysis of variance (ANOVA) on statistical package for social sciences (SPSS) version 23, Chicago, II, USA. Mean values were compared using Post Hoc Multiple Comparison (Duncan's test) at 95% confident limit ($p<0.05$) as significant in comparison with appropriate groups.

Results

Table 2 shows the result of body weight changes in rats administered with alcohol in drinking water for three days followed by oral administration of 42% consumable alcohol for additional six days. An increase in rats' weight was observed during the first three days, after which there was consistent decline in weight gain from day six in the negative, *V. doniana* group, Vit. C group and binge drinker's group. Rats in positive and those administered with *L. Lanceolata* maintained weight gain.

Table 2. Effect of Alcohol and Extracts on Body Weight of Rat

GROUP	Day One	Day Three	Day Six	Day Nine
Positive Control	85.62±7.19^{a}	141.42±18.12^{b}	143.78±18.12^{b}	145.46±17.23^{b}
Negative Control	87.52±9.32^{a}	88.96±8.7^{a}	88.96±7.5^{a}	72.94±7.53^{b}
L. lanceolata	124.04±1.5^{a}	134.14±4.31^{b}	135.13±5.14^{b}	134.1±3.58^{b}
V. doniana	71.96±1.1^{a}	89.02±6.3^{b}	85.88±9.4^{b}	80.4±16^{c}

Vitamin C	73.98±1.7[a]	82.8±5.8[b]	77.72±1.9[c]	74.18±6.6[c]
Binge Drinker	70.96±1[a]	75.18±1.4[a]	71.7±1.2[a]	69.12±1.6[b]

Note: Results are Mean ± S.D (n=5). Values in the same row having different superscripts differ significantly at $p<0.05$

Table 3, highlights the behavioural attitude exhibited by rats with alcohol administration. There were changes in natural behaviour of rats administered with alcohol compared with those in the normal group. This difference in natural behaviour confirms that alcohol has an effect on the natural lifestyle of the animals, and though this effect varies for group to group based on specific chemistry not studied in this work.

Table 3. Effect of Alcohol on Behavioural Attitude in Wistar Rats

Behavior	Positive Control	Negative Control	*Lophira Lanceolata*	*Vitex Doniana*	Vitamin C
Nocturnal Activity					
(Day 1-3)	H	H	H	H	H
(Day 4-9)	H	L	sL	L	sL
Feeding					
(Day 1-3)	H	H	H	H	H
(Day 4-9)	H	sL	H	L	sL
Mood					
(Day 1-3)	N	C	N	N	C
(Day 4-9)	N	C&D	D	D	A&C

Key: H=high, sL=slightly low, L=low, N=normal, C=confused, D=dull, A=aggressive

Table 4 shows the effect of extracts on alcohol administered rats as compared to the positive control group. The level of serum enzymes was significantly ($p<0.05$) elevated in both negative and binge drinker groups, but were significantly ($p<0.05$) depleted in groups treated with extracts and standard drug.

Table 4. Effect of Alcohol and Extracts of *L. lanceolata* and *V. doniana* on Liver Serum Enzymes and other Biochemical Parameters

GROUP	AST	ALT	ALP	Total Bilirubin	Direct Bilirubin	Conjugated Bilirubin
Positive Control	138.86±3.83[a]	36.02±6.44[a]	77.38±12.43[a]	1.27±0.32[a]	0.75±0.17[a]	0.52±0.01[a]
Negative Control	147.02±8.42[b]	47.4±3.59[b]	87.33±1.55[b]	1.21±0.31[a]	0.84±0.16[a]	0.37±0.03[b]
L. lanceolata	120.07±6.75[c]	40.7±1.27[c]	72.49±8.12[c]	1.15±0.32[a]	0.68±0.15[a]	0.47±-0.01[a]
V. doniana	92.03±1.27[d]	32.07±1.34[c]	75.46±1.17[a]	1.29±0.14[a]	0.76±0.03[a]	0.53±0.10[a]
Vitamin C	92.06±1.95[d]	35.4±0.83[a]	70.58±1.53[c]	1.21±0.22[a]	0.69±0.04[a]	0.52±0.11[a]
Binge Drinker	156.60±0.91[b]	46.6±1.14[b]	91.32±1.57[b]	1.50±0.21[b]	1.01±0.22[b]	0.49±0.01[c]

Note: Results are Mean ± S.D (n=5). Values in the same column having different superscripts differ significantly at $p<0.05$.

Table 5 shows the effect of both extracts on serum biomolecules such as malondialdehydate (MDA), glutathione (GSH), superoxide (SOD) and catalase (CAT) activity in alcohol administered rats. Antioxidant (GSH) levels across treatment groups showed no significant difference. The negative and binge drinker groups showed significant elevated levels of MDA, CAT, SOD and significant depletion in levels of GSH. Treatment groups showed significant depletion in MDA levels, while SOD and CAT levels were significantly depleted in *Lophira lanceolata* group, but in *Vitex doniana* group, there was no significant difference in these indices at ($p<0.05$).

Table 5. Effect of Alcohol and Ethanol Extracts of *L. lanceolata* and *V. doniana* on Antioxidant Markers

GROUP	MDA	GSH	SOD	CAT
Positive Control	10.8 ± 6.38^{a}	4.44 ± 0.77^{a}	18.04 ± 4.43^{a}	5.91 ± 2.47^{a}
Negative Control	17.28 ± 3.25^{b}	2.66 ± 0.36^{b}	24.55 ± 2.12^{b}	11.5 ± 1.35^{b}
L. lanceolata	8.3 ± 0.74^{c}	4.04 ± 0.54^{a}	15.02 ± 2.44^{c}	7.88 ± 1.74^{c}
V. doniana	7.56 ± 0.52^{c}	3.99 ± 0.72^{a}	22.11 ± 1.37^{a}	5.84 ± 1.14^{a}
Vitamin C	8.61 ± 1.18^{c}	3.88 ± 0.81^{a}	20.25 ± 1.21^{a}	7.49 ± 0.63^{c}
Binge Drinker	22.87 ± 0.91^{b}	3.88 ± 0.52^{b}	28.59 ± 1.92^{b}	14.44 ± 12^{b}

Note: Results are Mean ± S.D (n=5). Values in the same column having different superscripts differ significantly at $p<0.05$

Table 6 reveals the effect of alcohol, and *L. lanceolata* and *V. doniana* on rat's haematological indices. All the groups showed no significant difference in PCV levels. However, in the negative and binge drinker group, there is significant decrease in levels of blood components such as RBC, WBC and Hb and were increased significantly in treatment groups at ($p<0.05$).

Table 6. Effect of Alcohol and Extracts of *L. lanceolata* and *V. doniana* on Haematological Indices in Wistar Rats

GROUP	PCV	RBC	Hb	WBC
Positive Control	42.6 ± 2.18^{a}	9.54 ± 0.28^{a}	14.44 ± 0.93^{a}	8.22 ± 2.75^{a}
Negative Control	37.0 ± 5.42^{a}	7.64 ± 1.43^{b}	11.74 ± 0.11^{b}	3.40 ± 1.93^{b}
L. lanceolata	42.8 ± 2.28^{a}	9.70 ± 0.95^{c}	14.20 ± 0.84^{c}	8.82 ± 0.67^{c}
V. doniana	46.2 ± 0.85^{a}	10.08 ± 1.22^{c}	14.96 ± 0.12^{c}	8.36 ± 0.61^{c}
Vitamin C	44.8 ± 4.43^{a}	9.70 ± 0.52^{c}	13.94 ± 0.74^{c}	7.82 ± 0.35^{c}
Binge Drinker	40.8 ± 0.62^{a}	6.78 ± 0.63^{b}	9.28 ± 1.82^{b}	2.32 ± 1.23^{b}

Note: Results are Mean ± S.D (n=5). Values in the same column having different superscripts differ significantly at $p<0.05$

Discussion

Excessive alcohol consumption is becoming a trend among younger generations (McKetta & Keys, 2019). This is encouraged by its additive and stimulative properties, predisposing large population of youth to chronic hepatic damage by altering normal biological function of the liver (Osna et al., 2017). Many synthetic drugs and related substances used in liver diseases inflict side effect on the liver physiology, thus Scientist are faced with the imperative demand to research on drug with no side effect, less cost and active physiotherapeutic property. This

encourages research into herbology. Many medicinal plants contain dozens of active constituents that together gives the plant a therapeutic value (Jeeva et al., 2012). These plants are widely used in the management of disease all over the world (Adewunmi, 2004). In Nigeria, thousands of plant species have been claimed to possess medicinal properties and are employed in treatment of many ailments (Adeleye et al., 2021).

Chronic consumption of alcohol which is rich in energy (7.1cal/g) does not produce gain in body weight (Lieber 1991 and Dahiru et al., 2007). The observed weight loss in alcohol induced groups over 9 days' period agrees with previous literature on alcohol and body weight. Asides the clinical characters studied in the research, behavioural patterns of rats related with alcohol consumption further confirms claim of the world health organisation that chronic alcohol consumption is a global problem with social, economic and clinical consequences (Marshall, 2014).

Alcohol induced impairment in liver of rats was evident with increased serum enzymes (AST, ALT and ALT) and direct bilirubin levels in both Binge and Negative control groups. Treatment with *Vitex doniana* significantly lowered the levels of AST and ALT to amounts similar to the group treated with standard drug compared to those with *Lophira lanceolata*. However, there is significant depletion in levels of direct bilirubin and ALP in group treated with *Lophira lanceolata* than those of *Vitex doniana*. These results are in agreement with previous research that *Lophira lanceolata* and *Vitex doniana* might have hepatoprotective properties (Ladeji & Okoye, 2008; Patrick et al., 2014; James et al., 2014; Raphael et al., 2020) but in contrast to Abdulrahman et al., (2007) who suggested that *Vitex doniana* might possess toxic characteristics.

One of the major concerns of chronic alcohol consumption is the accumulation of reactive oxygen species that causes lipid peroxidation in hepatocytes, the common product of this process is MDA which accumulates in hepatocytes and is a good factor for estimating total oxidative stress (Cao et al., 2015; Zhang et al., 2016). The elevation of MDA and depletion of GSH levels and other hepatic antioxidants in alcohol induced groups confirms the damage of hepatocytes. This finding is in concord with the concept of Stickel and Osterreicher (2006) and Dahiru et al. (2007). Treatment groups had lowered MDA levels, increased GSH levels, indicating amelioration of the hepatocytes. Similar findings were made about the antioxidant property of *Lophira lanceolata* and *Vitex doniana* by Agbafor et al., (2011); Adetoro et al., (2013) and Collins (2014).

There are controversies from several researches in literatures relating to the physiological assessment of the effect of alcohol on liver, as touching on activity/level of antioxidant enzymes (SOD/CAT), that is to say, an increase, no changes or a decrease (Kanbagli *et* al., 2002). This non concurrency may be due to diet, duration and amount of alcohol administered or consumed. For instance, Ignatowicz et al., (2013) and Cheng et al., (2014) stated in their respective studies that, CAT activity increased in chronic alcohol consumption while Das et al., (2009) indicated decreased. Zhou et al. (2017) reported increase and decrease in activity of SOD and CAT respectively and treatment lowered activities of both enzymes. However in this study, it is observed that, the activity of both SOD and CAT were increased in alcohol intoxicated groups but their activities were depleted in the treatment groups. The elevation of SOD activity in alcohol intoxicated group reflects the activation of compensation mechanism which tries to counteract free radicals. Normally, SOD is considered the first line among antioxidant enzymes in the defence against free radicals (Zhou et al., 2017). SOD catalyses the dismutation of two superoxide anions to hydrogen peroxide and oxygen, then hydrogen peroxide is degraded into water and oxygen by CAT (Li et al., 2012). Thus, this elevation can be explained as an induction due to the presence of increased imbalance of radicals generated by the metabolism of the alcohol administered. But interestingly, the both plant extracts reversed the biochemical anomaly.

Furthermore, a look at the haematology of the rats indicated alterations in levels of PCV, RBC,

Hb and WBC in the Binge and Negative control groups. These shows that chronic consumption of alcohol may disrupts neural stem cell growth and division, causing cells to progress more slowly through the cell cycle and might reduce the number of blood cell precursors in the bone marrow and may cause a characteristic structural abnormalities in these cells and further impair oxygen circulation. Interestingly, treatment with both extracts had similar effects of restoring blood cell counts. This finding agrees with that of Etuk et al., (2010), and Abdulrahman et al., (2010) on the same plant extracts.

Conclusion

Conclusively, it was observed from physical and biochemical parameters that chronic alcohol affects the body negatively and as such should be consumed at a controlled rate. *Lophira lanceolata* and *Vitex doniana*, has proved to have ameliorative and antioxidant effect as indicated by low serum ALT, AST, ALP, direct bilirubin, and MDA levels while increasing the amount of blood cells, antioxidant enzymes and GSH at different amounts and thus can be used in treating alcohol-induced liver disease.

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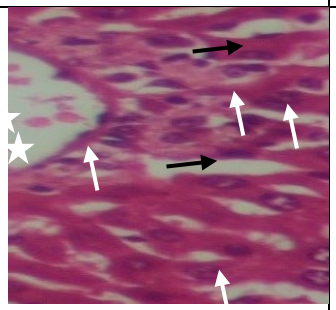
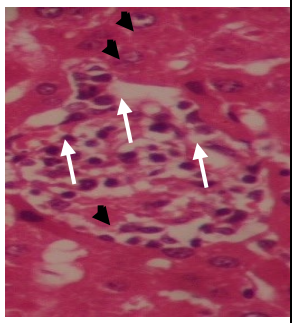
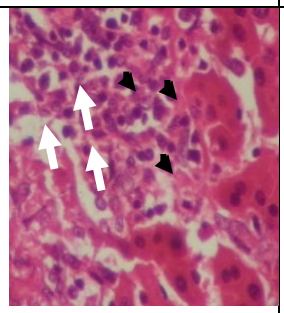
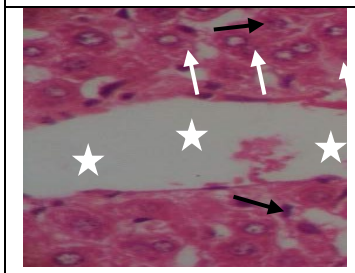
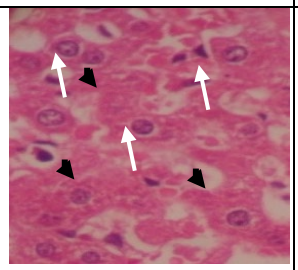
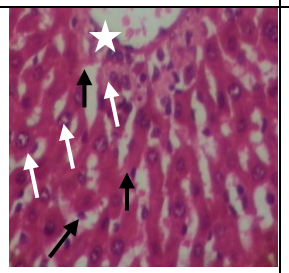
Appendix 1

Plate 1. Histology of Liver after Alcohol Administration and Treatment with Extracts of *L. lanceolata* and *V. doniana* in Wistra Rats

Normal Group	Interpretation	Negative Group	Interpretation	Binge Drinker	Interpretation
 **Plate 1**	Plate.1 showed normal morphology as characterized by the presence of hepatocytes with characteristic polygonal shapes and interspersed by hepatic sinusoids (**black arrowheads**) which are linked to the central vein (**white stars**). **White arrows** represent cell nuclei. H&E: **X400**	 **Plate 2**	Plate.2 showed inflammation evidently proven by presence of inflammatory cells (**white arrows**) within the tissue and necrosis as seen by the degradation (**black arrowheads**) of cellular components. H&E: **X400**.	 **Plate 3**	Plate.3 showed inflammation evidently proven by presence of inflammatory cells (**white arrows**) within the tissue and necrosis as seen by the degradation (**black arrowheads**) of cellular components. H&E: **X400**.
Treatment Phase					
Lophira lanceolata	**Interpretation**	*Vitex doniana*	**Interpretation**	**Standard Drug**	**Interpretation**
 **Plate 4**	Plate 4 of rat treated with *Lophira lanceolata* showed normal liver morphology similar to the normal group. H&E: X400	 **Plate 5**	Plate.5 showed normal liver histology after treatment with Vitex *doniana,* intact nuclei (**white arrows**) and surrounded by intact hepatic sinusoids (**black arrowheads**). H&E: X400	 **Plate 6**	Plate.6 normal liver morphology similar to normal group after treatment with vitamin C. H&E: X400