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Original Article

Alterations in the biochemical indices in Wistar rats exposed to an overdose of codeine and dextromethorphan

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الملخص

أهداف البحث: دراسة تأثير التعرض المتكرر عن طريق الفم لنوعين من شراب السعال تحتوي على الكودبين وديكستروميثورفان على الفئران ويستار الذكور.

طرق البحث: قسمنا ٣٥ جرذا إلى سبع مجموعات من خمسة فئران لكل منها. المجموعة "أ" أعطيت ٠.٥ مل من الماء المقطر، وأعطيت المجموعات "ب " و"ج" و" د" ١.٠ و٠.٢ و ٠.٤ مل/كغ وزن الجسم من شراب السعال الذي يحتوي على الكودبين، على التوالي، بينما أعطيت المجموعات" ه" و" و" و" ز" ٠.١ و ٠.٢ و ٠.٤ مل/كغ من شراب السعال الذي يحتوي على ديكستروميثورفان، على التوالي. واستمر العلاج لمدة ٢٨ يوما. تم التضحية بالجرذان تحت تخدير الإثير الخفيف. وتم فحص الكلى والكبد والدم للفئران لإجراء المزيد من التحاليل.

النتائج: لوحظت تغييرات كبيرة في اختبارات وظائف الكبد؛ ناقلة أمين الأنين، ناقلة أمين الأسبارتات، الفسفاتاز القلوي، الزلال والبيليروبين الكلي. وزادت جميع جرعات شراب السعال التي تحتوي على الكودبين وديكستروميثورفان بشكل كبير مستويات ناقلة أمين الأنين. وعلاوة على ذلك، لوحظت تغيرات كبيرة مماثلة لعلامات وظائف الكلى مثل الكرياتينين واليوريا وحمض اليوريك. تسبب جميع جرعات ديكستروميثورفان ارتفاعات كبيرة في مستويات اليوريا. كما أظهرت التقييمات الهستولوجية تغيرات طفيفة في بنية أنسجة الكبد والكلى والدماغ.

الاستنتاجات: تشير النتائج الواردة في دراستنا إلى أن الجرعة الزائدة من شراب السعال قد تهيئ المستهلكين للإصابات الكبدية والكلوية.

الكلمات المفتاحية: التعديلات؛ الكودبين؛ شراب السعال؛ ديكستروميثورفان؛ جرعة زائدة

Abstract

Objective: This study investigates the impact of repeated oral exposure to two cough syrups containing codeine and dextromethorphan (DXM) on male Wistar rats.

Methods: We divided 35 rats into seven groups of five rats each. Group A was given 0.5 mL of distilled water, Groups B, C, and D were given 0.1, 0.2 and 0.4 mL/kg body weight (*b. w*) of cough syrup containing codeine (CSC), respectively, and Groups E, F, and G were administered 0.1, 0.2 and 0.4 mL/kg *b. w* of cough syrup containing DXM, respectively. The treatment was continued for 28 days. The rats were euthanised under mild diethyl ether anaesthesia. The kidney, liver, and blood of the rats were examined for further analyses.

Results: Significant ($p < 0.05$) alterations were observed in the liver function tests: ALT, AST, ALP, albumin, and total bilirubin. All doses of CSC and DXM significantly increased the ALT levels ($p < 0.05$). Furthermore, similar significant alterations were observed for the kidney function parameters such as creatinine, urea, and uric acid ($p < 0.05$). All doses of DXM caused significant elevations in the levels of urea ($p < 0.05$). The histopathological evaluations also showed slight changes in the architecture of the liver, kidney, and brain tissues.

Conclusion: The findings of this study suggest that overdose of these cough syrups may predispose the consumer to hepatic and renal injuries.

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Keywords: Alterations; Codeine; Cough syrup; Dextromethorphan; Overdose

Introduction

Cough syrup is a medication produced for suppressing cough or cold symptoms in those experiencing such conditions. The drug is usually sold as an over-the-counter (OTC) drug.[1] There are different forms of cough syrups with different components used for a wide array of different forms of cough and cold symptoms. Dextromethorphan (DXM) can easily be purchased by anyone as OTC cold and cough mixtures and has the potential for abuse because it is a narcotic agent.[2,3] DXM is a cough suppressant substance that was initially sold as antitussive. Daily allowable dosage is approximately 120 mg/day.[4] Codeine (3-methylmorphine) is among the most consumed opiates globally, and is often used for its analgesic, antitussive, and antidiarrheal properties.[5] It has the potential for misuse and abuse or dependence despite the fact that many consider it a weak opiate.[6] Continuous exposure and overdose of combination products containing codeine may lead to side effects such as nephrotoxicity, hepatotoxicity, and gastric ulcers.[6,7] Drug addiction could be a long-term and recurring disorder that confers dependence on its victim, the terrible and negative consequences notwithstanding. Substance dependency causes positive emotions and feelings of euphoria in the initial stage or helps to reduce negative emotions such as anxiety, sadness, and pain. Persistent use stimulates adaptive changes in the central nervous system, which may result in tolerance, physical dependence, sensitisation, craving, and relapse.[8] Although the spread and increase in the abuse of cough syrup in Nigeria is becoming alarming, there is little or no documented evidence on the likely side effects of the misuse of cough syrups, and as such, there is no scientific knowledge on its biochemical implications. This study investigated cough syrups, which contain the antitussive or cough suppressants, as they are usually the active ingredients in most of the cough syrups that are abused. Some of the active ingredients include DXM and codeine. This work examined the impact of oral administration and repeated exposure of Wistar rats to two cough syrups on selected biochemical indices and organs. A total of two cough syrups, namely Tutolin containing codeine and Greenlin containing DXM as active ingredients, were orally and daily administered to male Wistar rats for a period of four weeks (28 days).

Materials and Methods

Animal grouping and administration of drug

Tutolin with codeine produced by Tuyil Pharm Industry Limited and Greenlin produced by Greenlife Pharmaceuticals Limited were purchased from a registered pharmacy store. The normal approved dosage of the cough syrup is 10 mL, which is taken four times a day. From this data, any dosage above this quantity can be considered an abuse.

A total of 35 Wistar rats were randomly distributed into seven groups.

Group A: Control (0.5 mL of distilled water)
Group B: Cough syrup containing codeine (CSC-1) (0.1 mL)
Group C: Cough syrup containing codeine (CSC-2) (0.2 mL)
Group D: Cough syrup containing codeine (CSC-3) (0.4 mL)
Group E: Cough syrup containing dextromethorphan (DXM-1) (0.1 mL)
Group F: Cough syrup containing dextromethorphan (DXM-2) (0.2 mL)
Group G: Cough syrup containing dextromethorphan (DXM-3) (0.4 mL)

Biochemical assays and analyses

The determination of creatinine was carried out according to the method described by Tietz et al.[9] Veniamin and Vakirtzi–Lemonias'[10] method was used to determine urea concentration. The dimethyl sulphoxide method described by Tietz et al.[9] was used for bilirubin determination. Trinder's[11] CHOD-PAD enzymatic colorimetric method was used to measure the levels of total cholesterol, triglyceride, and HDL and LDL cholesterol. Wright et al.'s[12] method was employed for the determination of alkaline phosphatase (ALP). Determination of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were realised following the principle described by Reitman and Frankel.[13]

Statistical analysis

Data generated were expressed as means ± standard error of means (SEM). The significant difference was calculated using one way ANOVA with the level of significance set at $P \leq 0.05$.

Results

During the course of the experiment, observations were carried out to check how the administration of overdose of cough syrup affects the behavioural patterns of the animals. Their level of activities hours after the administration of the drug and the effect on their weight were also observed. All the animals in Groups D, F, and G slept more frequently when compared to the control group. A high level of activity was also observed in Groups F and G, with an increase in agitation and aggressiveness. A steady weight gain was observed after 15 days of administration (an average of 0.02 kg (20 g)) and also after 28 days of administration (an average of 0.03 kg (30 g)), indicating that the administration of cough syrup did not affect or diminish the rats' appetites.

The results of the effect of oral exposure of CSC and DXM on the haematological parameters of Wistar rats are

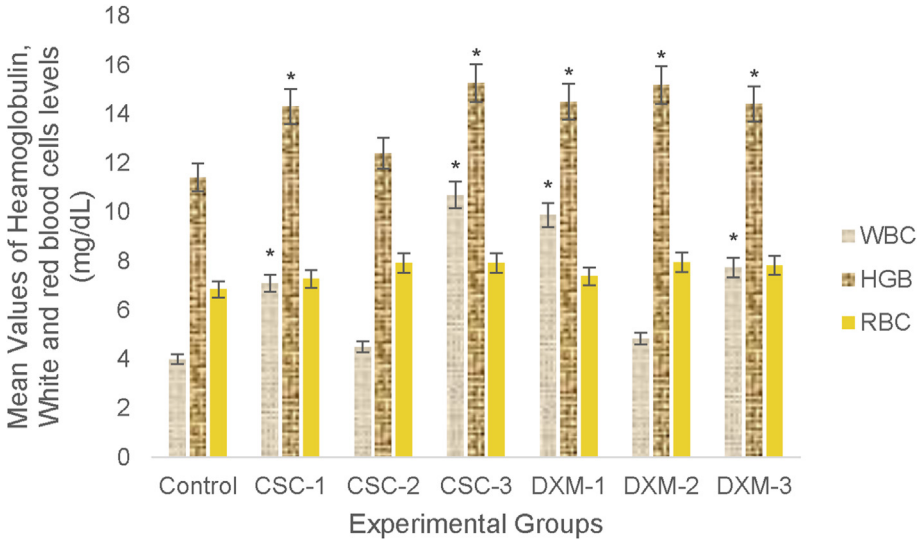

Figure 1: Effect on White Blood Cells (WBC), heamoglobulin (HGB) and Red Blood Bell (RBC).

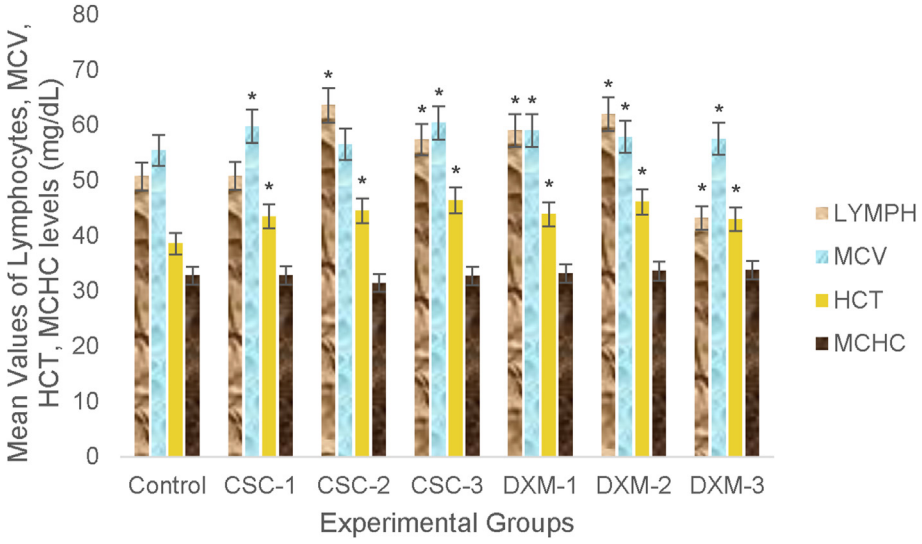

Figure 2: Effect on lymphocytes, Mean Corpuscular Volume (MCV), haematocrit (HCT) and Mean Corpuscular Haemoglobin Concentration (MCHC).

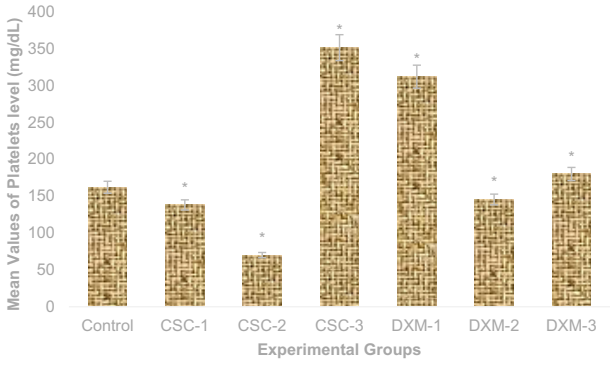

Figure 3: Effect on platelets.

presented in Figures 1–3. The levels of white blood cells (WBC) increased significantly ($p \leq 0.05$) in the CSC-1, CSC-3, DXM-1 and DXM-3 groups (Figure 1). In addition, heamoglobulin (HGB) levels were also significantly ($p \leq 0.05$) elevated in the CSC-1, CSC-3, DXM-1, DXM-2, and DXM-3 groups (Figure 1). However, there was no significant ($p \leq 0.05$) change in the levels of red blood cells (RBC) in the groups treated with the cough syrups (Figure 1). The cough syrups caused varying degrees of alterations in the levels of lymphocytes, mean corpuscular volume (MCV), and haematocrit (HCT), except mean corpuscular haemoglobin concentration (MCHC), which showed no significant change (Figure 2). Platelets levels were significantly ($p \leq 0.05$) depleted in the CSC-1, CSC-2, and DXM-1 groups while they were

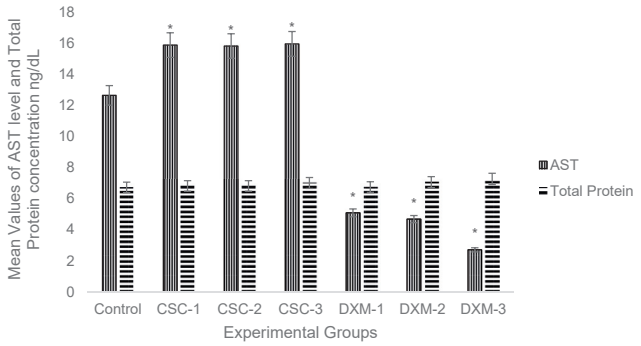

Figure 4: Effect on Aspartate Transaminase (AST) and total protein.

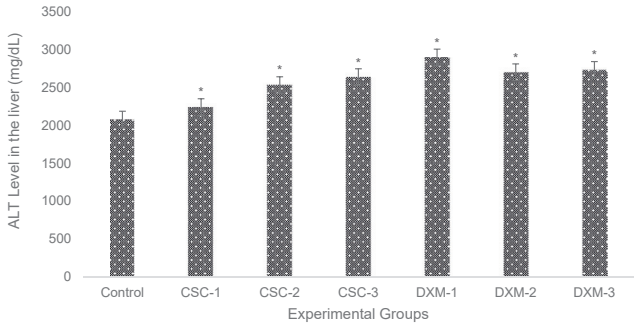

Figure 5: Effect on Alanine Aminotransferase (ALT).

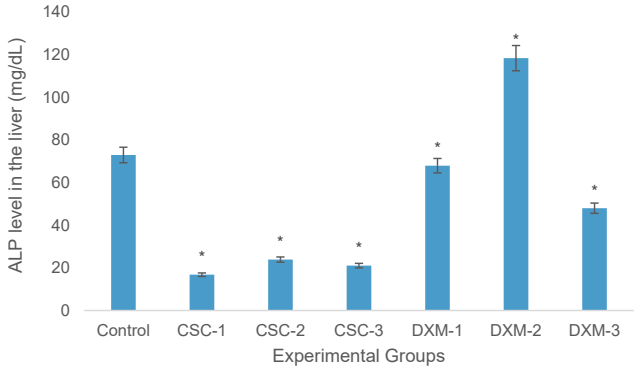

Figure 6: Effect on Alkaline Phosphatase (ALP).

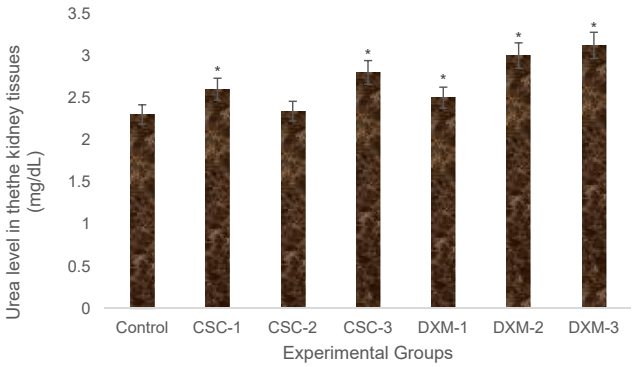

Figure 8: Effect on urea.

significantly ($p \leq 0.05$) elevated in CSC-3, DXM-1 and DXM-3 groups (Figure 3).

The effect of the cough syrups on the liver function parameters, which include AST, ALT, ALP, albumin, and total bilirubin are depicted in Figures 4–7, respectively. The AST levels were significantly ($p \leq 0.05$) increased in the animals treated with CSC (CSC-1, CSC-2, and CSC-3) but the reverse was the case with those treated with cough syrup containing DXM (DXM-, DXM-2, and DXM-3) when compared with the control group (Figure 4). There was a significant ($p \leq 0.05$) increase in the ALT levels in all the treatment groups (Figure 5). The ALP levels were significantly ($p \leq 0.05$) increased in the DXM-1 and DXM-2 groups but were reversed in the CSC-1, CSC-2, CSC-3, and DXM-3 groups when compared with the control group (Figure 6). Albumin levels were significantly ($p \leq 0.05$) higher in the CSC-1 and CSC-3 groups but were significantly ($p \leq 0.05$) lowered in the CSC-2, DXM-2, and DXM-3, whereas there was no significant ($p \leq 0.05$) change in albumin level in DXM-1 (Figure 7).

The effect of the cough syrups on kidney function, such as urea, creatinine, and uric acid are shown in Figures 8–10, respectively. Urea levels are significantly ($p \leq 0.05$) elevated in the CSC-1, CSC-3, DXM-1, DXM-2, and DXM-3 groups but no significant ($p \leq 0.05$) change in CSC-2 group (Figure 8). No significant ($p \leq 0.05$) change was observed in the creatinine levels in the treatment groups

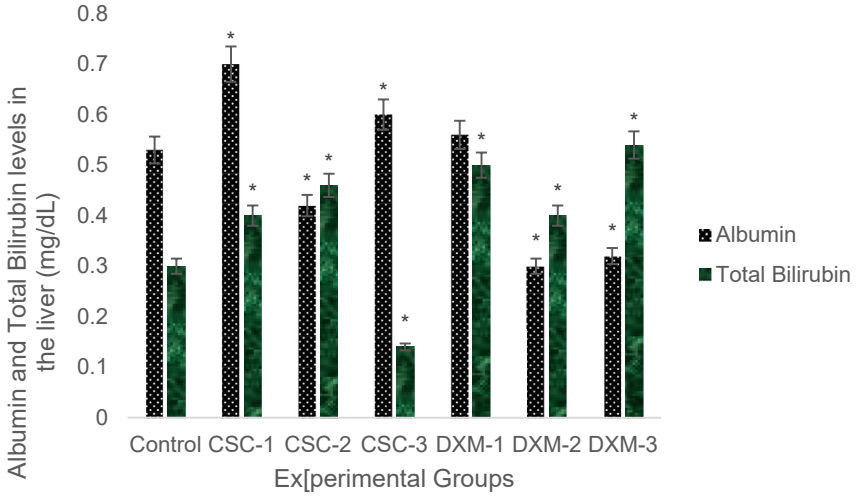

Figure 7: Effect on albumin and total bilirubin.

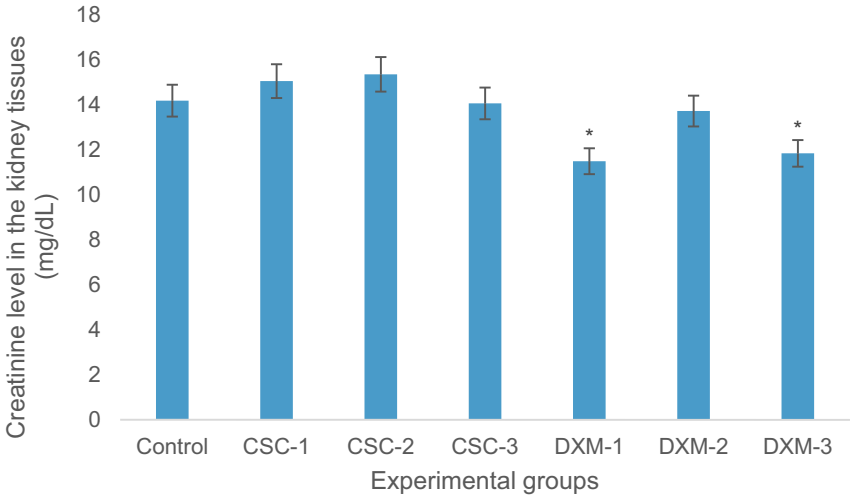

Figure 9: Effect on creatinine.

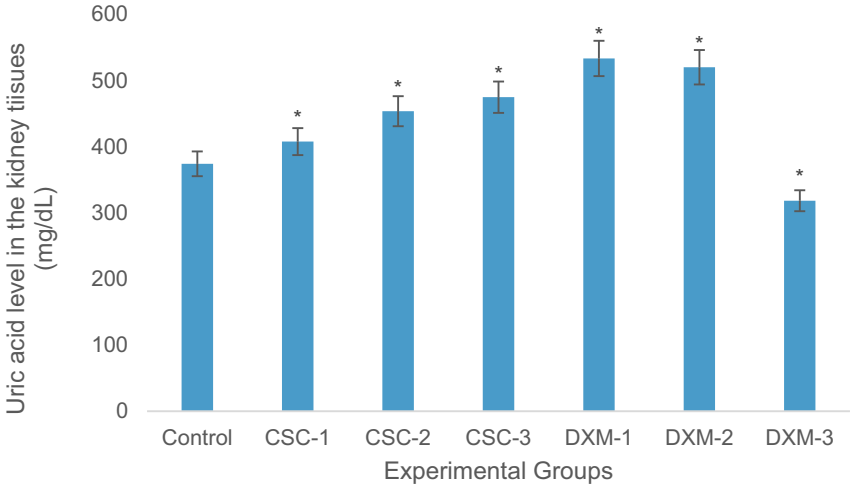

Figure 10: Effect on uric acid.

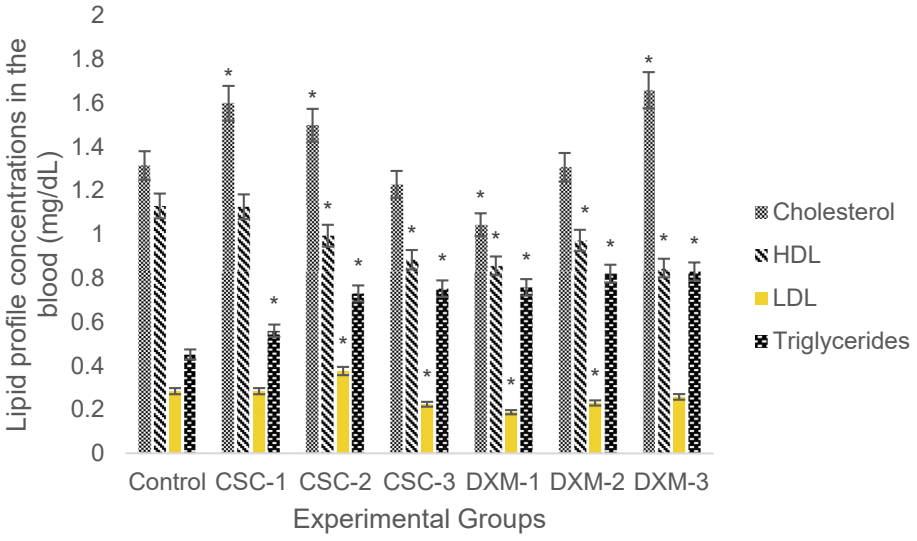

Figure 11: Effect on lipid profile.

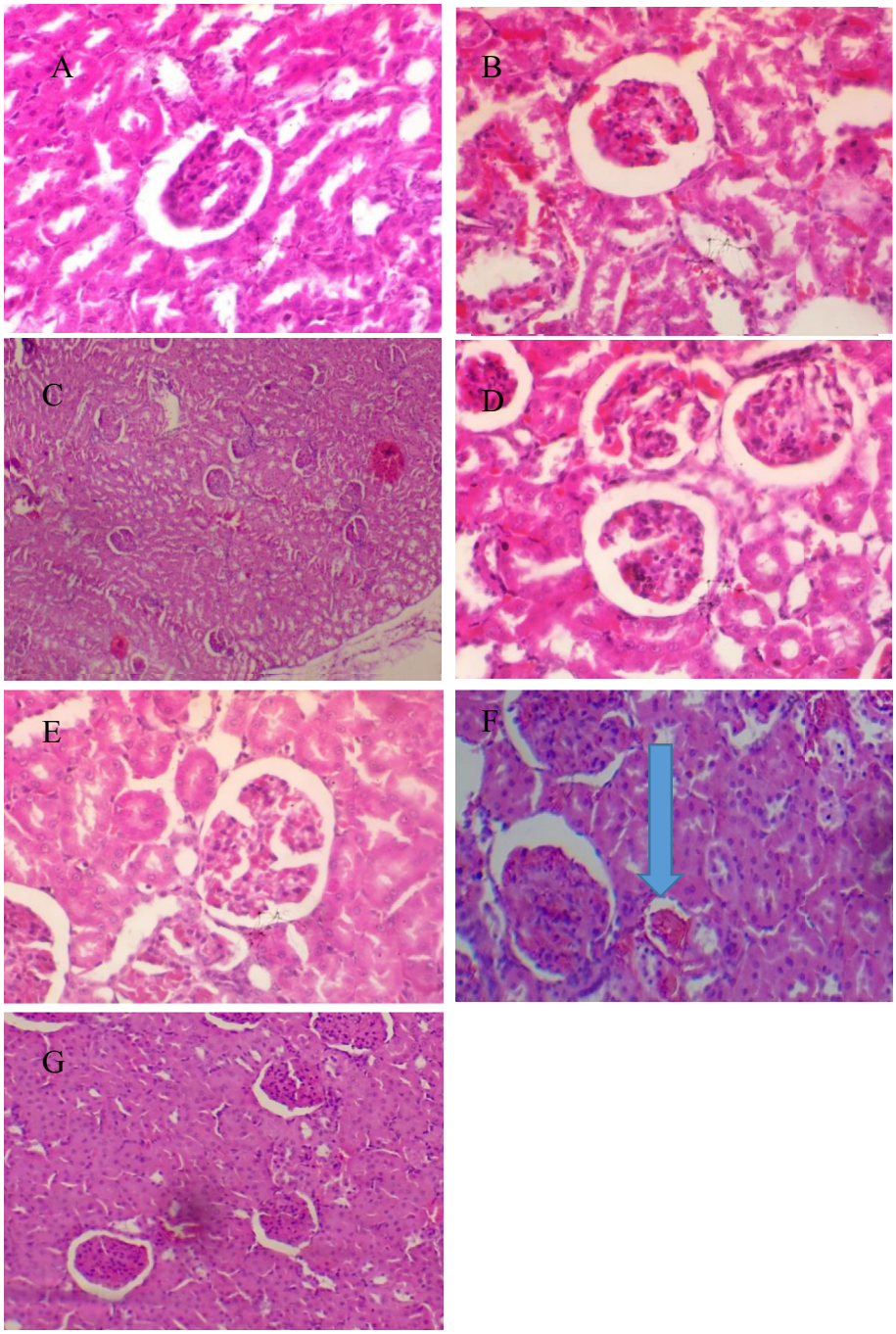

Figure 12: The effect of oral administration of cough syrup on kidney tissues at X400 magnification. **A** = control, **B**= CSC-1, **C**= CSC-2, **D** = CSC-3, **E** = DXM-1, **F** = DXM-2 (blue arrow indicating congestion), **G** = DXM-3.

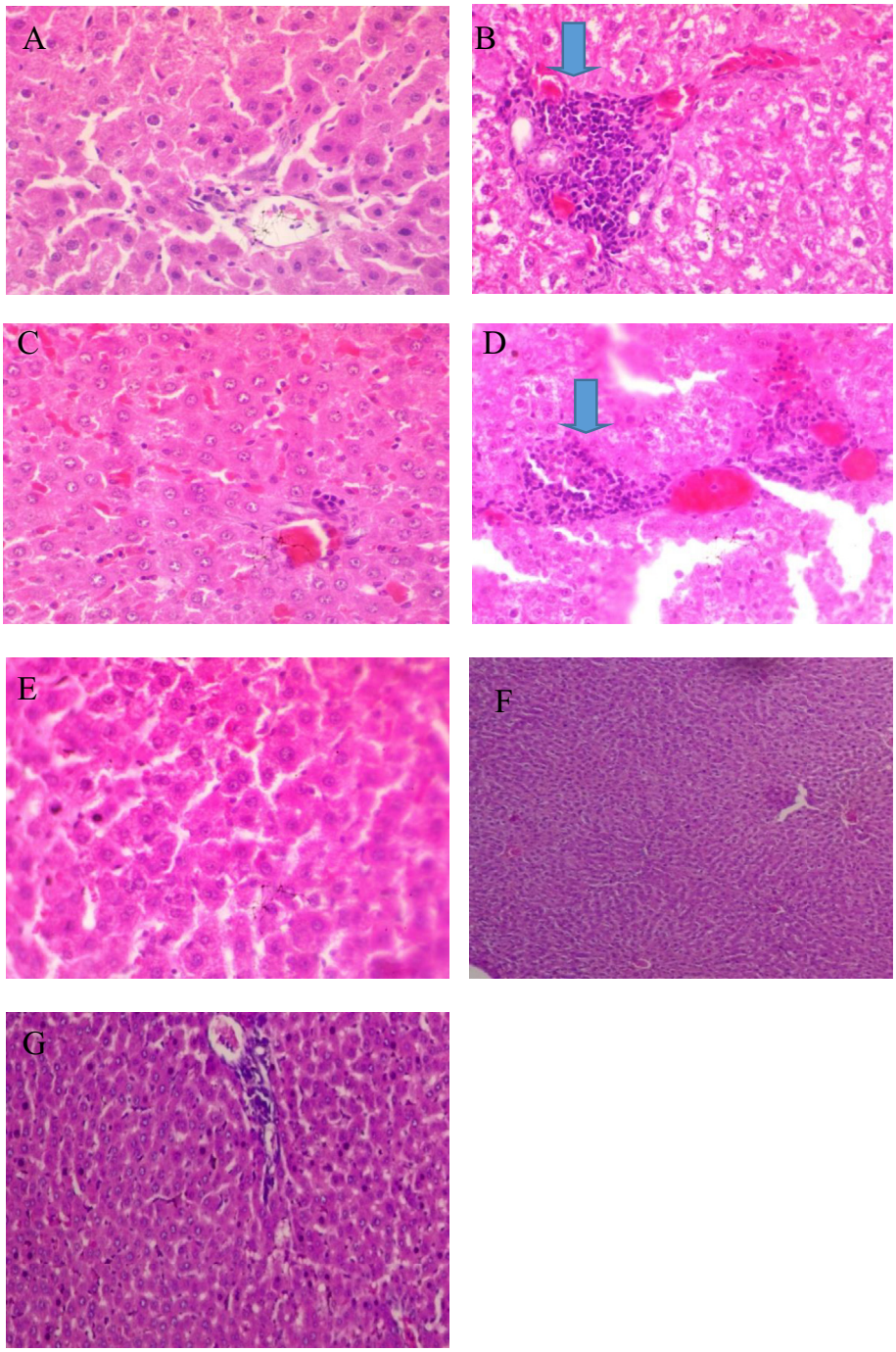

Figure 13: The effect of oral administration of cough syrup on liver tissues at X400 magnification. **A** = control, **B**= CSC-1 (arrow indicating portal inflammation), **C** = CSC-2, **D** = CSC-3 (arrow indicating lobular inflammation), **E** = DXM-1, **F** = DXM-2, **G** = DXM-3.

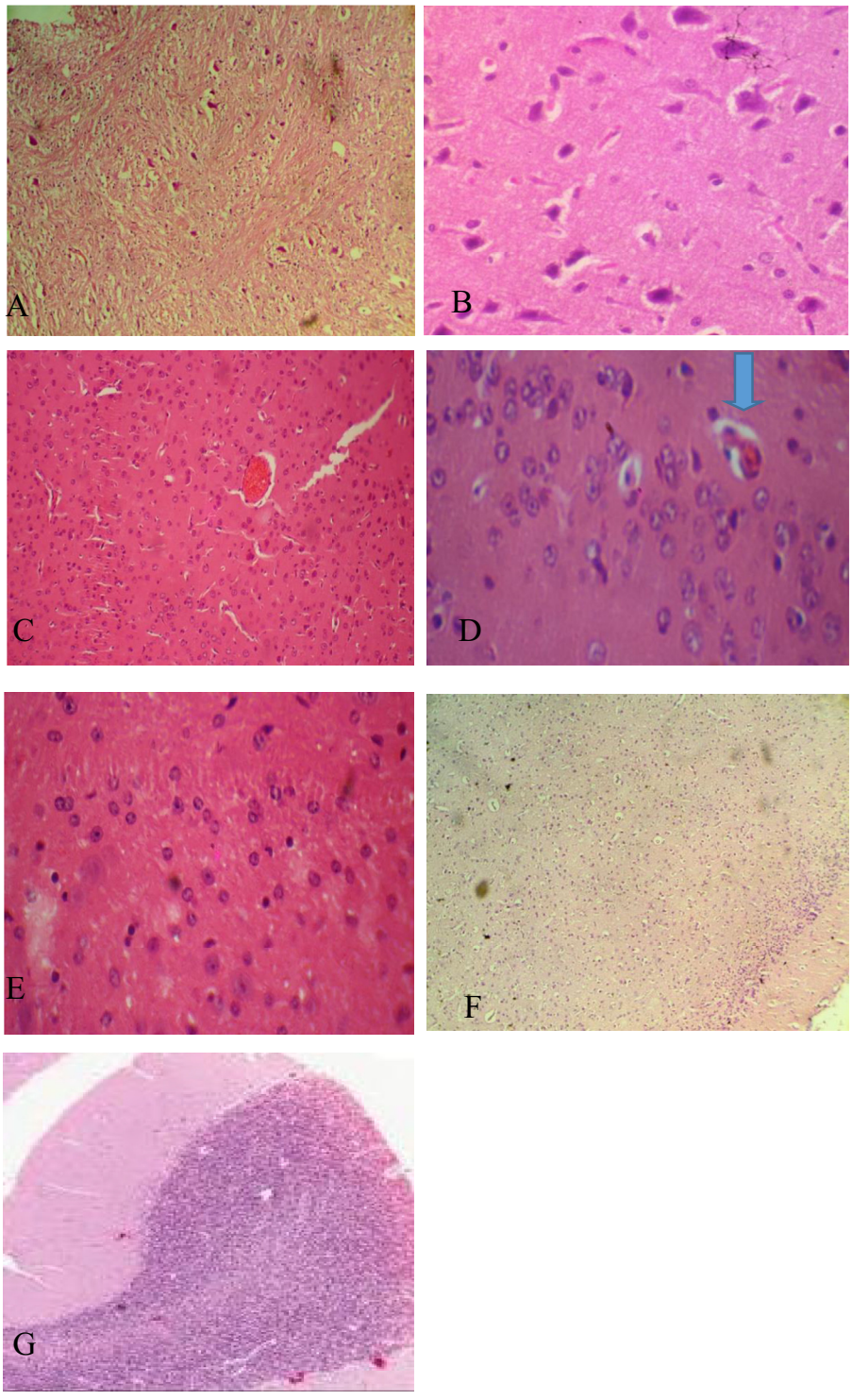

Figure 14: The effect of oral administration of cough syrup on brain tissues at X400 magnification. **A** = control, **B**= CSC-2, **C**= CSC-2, **D** = CSC-3 (arrow indicating mild oedema), **E** = DXM-1, **F** = DXM-2, **G** = DXM-3.

except the DXM-1 and DXM-3 groups, which showed significant ($p \leq 0.05$) depletion in creatinine levels (Figure 9). Uric acid concentrations were significantly ($p \leq 0.05$) higher in the cough syrups treated groups except the DXM-1 group with lower uric acid level (Figure 10).

The results of the effect of oral administration of cough syrups containing codeine and DXM on the lipid profile of the Wistar rats are presented in Figure 11. There was a significant ($p \leq 0.05$) increase in the cholesterol level in CSC-1 and DXM-3 groups and a significant ($p \leq 0.05$) decrease in DXM-1, but no significant ($p \leq 0.05$) change was observed in CSC-3 and DXM-2. The high-density lipoprotein (HDL) levels were significantly ($p \leq 0.05$) depleted in the cough syrup treated groups except the CSC-1, in which there was no significant ($p \leq 0.05$) change. The cough syrups caused varying degrees of alterations in the levels of LDL. In addition, there was significant ($p \leq 0.05$) elevations in the triglycerides level in the groups orally exposed to both cough syrups without exceptions (see Figure 11).

The histopathologic assessment of the kidney, liver, and brain tissues of Wistar rats treated with cough syrups containing codeine and DXM are illustrated in Figures 12–14, respectively. There were alterations in architectures and normal structure in the following: the kidney tissue in DXM-2, liver tissue in CSC-2 and CSC-3, and the brain tissue in CSC-3.

Discussion

There is a relative lack of research on the effect of cough syrup overdose on metabolic profiles. It is important to investigate and understand the effects of cough syrup on these metabolic profiles. When cough syrups are taken within the normal dosage, the common publicised short-term effects are drowsiness, dizziness, weakness, and urinary retention, among others. This research investigated the extended effects when cough syrups are taken in amounts that exceed the stipulated doses. Abuse of cough syrups containing codeine and DXM is an emergent global public health concern. Abuse occurs when they are used for recreational and excessive dose purposes as opposed to medical purposes. Codeine is a drug used in some prescription pain medicines. It is in the class of drugs known as opioids, which refers to any synthetic, semisynthetic, or natural drug that has morphine-like properties. Codeine overdose occurs when someone takes more than the normal or recommended amount of this medicine. This can be by accident or on purpose. Codeine can be poisonous in large amounts.[14] Codeine pharmacokinetics may be altered in patients with renal failure; clearance may be decreased, and metabolites may accumulate much higher plasma levels in patients with renal failure as compared to those with normal renal function.[15] Codeine is one of the natural plant alkaloids found in extracts of opium and is commonly used to treat mild-to-moderate pain and coughs. Despite wide use for many years, codeine, like other opioids, has not been linked to serum enzyme elevations during therapy and there have been no convincing cases of idiosyncratic acute, clinically apparent liver injury attributed to its use.[16] Increased blood cell indices may increase risk of nonhematologic diseases.[17] Elevated WBC (leukocytosis) is suggestive of metabolic disorder and is a risk factor of certain diseases such as leukaemia.[18,19] Excessive ingestion of DXM via cough syrup brought about high levels of haematologic molecules such as WBC, heamoglobulin (HGB), RBC, lymphocytes, MCV, haematocrit (HCT), and MCHC. However, low dose of DXM has been reported to help maintain hematologic molecules in patients with bipolar disorder.[20] Hyperdosing with DXM causes intoxicating, hallucinogenic, and dissociative effects. It has been reported that five teenagers who purposefully ingested large doses of DXM obtained over the internet for recreational purposes died as a result of the direct toxic effects of the drug. Investigation of the deaths led to a federal prosecution.[21] Other biochemical indices alterations observed include lowered platelets level, elevated liver function enzymes, and high levels of cholesterol and triglycerides. Depletion of platelet levels may lead to impaired function of coagulation factors and increased bleeding times during injury.[22] Misuse of DXM products containing acetaminophen can cause liver damage.[23] An increase in liver enzymes such as AST, ALT, and ALP levels may indicate liver damage or disease.[24–26] The aforementioned results indicate that there was probably significant damage to the liver of the rats that were administered CSC, this could be attributed to the fact that the liver is the main organ involved in the biotransformation of xenobiotics, and is therefore the site of multiple oxidative reactions, with free radical formation.[27] DXM, a non-prescription antitussive is found in some guaifenesin-containing preparations. Guaifenesin is a common non-prescription medication that has been implicated in drug-induced nephrolithiasis. Renally excreted medications known to have poor solubility in urine have the potential to precipitate when ingested in large quantity, leading to acute obstruction of the ureters and renal failure. Small and Sandefur (2014)[28] described the case of a 22-year-old male who developed severe bilateral flank pain, haematuria, and oliguria after an isolated recreational ingestion of guaifenesin and DXM. The patient was found to have bilateral ureteral obstruction and acute renal failure, suspected to be secondary to precipitation of medication metabolites in the urine. This case highlights the potential for acute renal failure secondary to guaifenesin and DXM abuse.[28] In 2013, more than 50 deaths were reported in two incidents in Pakistan after victims ingested cough syrup containing DXM. Shafi et al. (2016)[29] reported the deaths of 19 subjects who purposefully ingested cough syrup containing DXM for recreational purposes in combination with other drugs including benzodiazepines, opiates, cannabinoids, chlorpheniramine, and ethanol. They died as a result of direct toxic effects of DXM as well as lethal synergistic effects of co-ingested drugs of abuse.[29] Elevated triglyceride levels are associated with adverse outcomes such as coronary heart disease.[30] Elevated levels of cholesterol is among the foremost risk factor for human cardiovascular disease such as coronary heart disease and stroke.[31–33] Hypertriglyceridemia is one of the most common lipid abnormalities and has been known to be associated with other metabolic derangements.[34] Patients with overdose of certain opiates like cocaine and codeine usually present with muscle pain and tenderness. Laboratory tests detect an increase of creatinine and urea, potassium, phosphorus, and creatine kinase levels. Myoglobin and granular casts are also detected in urine. Due to the frequency of acute renal failure, users are aware of the risk

when dehydration coexists and often consume large quantities of water, so they may present hyponatraemia and/or cerebral oedema. Hyponatraemia on dilution due to excessive fluid intake can coexist with inappropriate antidiuretic hormones. The significant increase in the levels of urea is also an indicator of probable kidney damage.[35,36]

Conclusion

This study suggests that overdose of cough syrup may predispose the consumers to hepatic and renal injuries in addition to their consequences on behavioural patterns. These observations are also supported by the results of the histological assessments. Alterations in architectures and normal structures were observed in the tissues. The findings only depict the short-term effects of overdose of these cough syrups. These short-term toxic effects may have major implications in the long run, which may be severe. It is therefore essential that information on the likely effects of overdose be made available on many platforms to reduce abuse of such syrups especially among teenagers and young adults.

Recommendations

Research to investigate the long-term effect and impact on other vital organs is recommended.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This research was approved in December, 2014 (BUTACC-2014-12A) by the Department of Chemical Sciences, Bells University of Technology, Ota.

Authors' contributions

AKA and OKT conceived and designed the study, conducted research, provided research materials, and collected and organised data. OOJ analysed and interpreted data. AKA wrote initial and final draft of article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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