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Research article

Pharmaco-epidemiologic Survey and Experimental Study of Co-administration of Three Herbal Products with Paracetamol

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ABSTRACT

Pharmacoepidemiological survey of the use of herbal products and orthodox drugs was carried out within a university community using structured questionnaires. Three commonly used herbal products; Oroki Herbal Mixture® (OH), Mama Decoction® (MD) and Alomo Bitters® (AB) and co-administration with paracetamol were investigated based on the dosage instructions. Analgesic activity was evaluated using Hotplate method to determine the pain reaction time (PRT), while haematological and biochemical analysis and histopathological evaluation of the organs were carried out at the end of the study using standard procedures. All the herbal products showed significant analgesic activity, co-administration with paracetamol resulted in slight reduction in the PRT of AB and OH, while MD showed a significant reduction in time to reach peak PRT from 120 minutes to 30minutes. There was no significant effect on PCV, RBC and Hb level, while varied effect on other haematological parameters was observed by the co-administration with paracetamol. Co-administration of AB and MD increased alanine aminotransferase (ALT), while reduction was observed in OH. All the herbal products and their combination with paracetamol showed various stages of liver damage. Marked testicular degeneration was observed with co-administration of the herbal products with paracetamol, while kidney morphology was normal in all the treatments. All the herbal products investigated showed analgesic activities with synergistic enhancement of analgesic activity of paracetamol by Mama Decoction. However, their effect and their co-administration with paracetamol on some of the biochemical and haematological parameters as well as the damage to the liver and testes call for caution.

Keywords: *Paracetamol, Analgesic activity, Herbal products, Haematological parameters, Biochemical parameters*

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INTRODUCTION

World Health Organization (WHO) reported that about 80% of the world population in developing and developed countries use herbal medicines (WHO, 2008). The use of herbal products with orthodox medicines is on the increase with the risk of herb-drug interactions which could be beneficial or harmful to the body. Herbs can be potent products which can affect body functions; therefore, when taken concurrently with drugs, interactions are possible (Hussain and Alzubaidi, 2015).

Herb-drug interactions may exhibit synergistic, potentiating or antagonistic activities, sometimes result in adverse drug reactions (ADR), and cause emergency admissions leading to increase morbidity and mortality (Fakeye *et al.*, 2007). These interactions may be

pharmacodynamics or pharmacokinetic in nature (Hooda, 2016). Some herbal products have been reported to be toxic at high doses, while some others were associated with potential adverse effects after prolonged usage (Park *et al.*, 2010). Oreagba *et al.*, (2011) reported mild to moderate adverse effects in 20.8% of respondents using herbal medicines. The herbal products regarded as safe can however interact with orthodox medicine and cause adverse effects either by potentiating the pharmacological action or reducing the therapeutic efficacy (Woodward, 2005).

Furthermore, in recent times, herb-drug interactions studies have been receiving more attention (Van den Berg, 2011). For instance, Esimone, (2011) reported increased in cardiac activity when *Aloe vera* interacts with digoxin and thiazides resulting in serious herb-drug interactions and fatal hypersensitivity. Also, *Zingiber officinale* (ginger) increases

bleeding time when concurrently used with heparin (Shalansky *et al.*, 2007). Similarly, irreversible inhibition of platelet aggregation was observed when *Allium sativum* (garlic) interacts with aspirin and warfarin (Hooda, 2016). Grapefruit juice was also reported to increase oral bioavailability of calcium channel blockers and many other drugs (Adibe *et al.*, 2009).

Generally, herbal mixtures including bitters are used for maintaining body functions as well as treatment of varied diseased conditions. Bitters are traditionally alcoholic preparations flavoured with botanical matters blended in water or alcohol (tincture) base (Ales, 2002). They are originally sold as a digestive aid because of their ability to increase the production of saliva and digestive juices, thus, are used primarily as digestive stimulants, detoxifiers, and antibacterial agents.

Three herbal mixtures including a bitter (Alomo bitter, Oroki herbal mixture and Mama Decoction) were selected for this study based on their wide consumption within the South-western states of Nigeria. Alomo Bitters® (AB), a digestive bitter is an herbal drink containing 42% v/v alcohol, which originated from Ghana and is widely consumed in Nigeria as a social drink. It is reportedly made from carefully-selected tropical plant extracts consisting *Khaya ivorensis*, *Capparis arthrocarpus*, *Lecaniodiscus cupanoides*, *Dialium guineense*, and *Treulia africana*. It is advertised to enhance vitality and general wellbeing, clean the bowel and relieves body pain, ease of menstrual pains/cramps in women with antimalarial and aphrodisiac properties.

Similarly, Oroki herbal mixture® (OH) is an herbal product made in Nigeria which is indicated for pile, dysentery, constipation, diarrhoea, blood stooling, waist and stomach pain, menstrual problems, deworming and turgidity. It is reportedly made from the stem bark of *Khaya grandifolia* A.Chev. (African mahogany) tree bark, *Alstonia congensis* Engl (pattern wood) bark, *Mangifera indica* L. (mango) leaves, *Sorghum bicolor* Moench (Sorghum stem), *Securidaca longipedunculata* root, *Cynthula prostrate* leaves, *Cassia sieberiana* root, *Ocimum basilicum* leaves and *Seccharum officinarum* stem.

Also, Mama Decoction® (MD) is a traditional multicomponent herbal antimalarial preparation formulated from four components plant parts; *Mangifera indica*, *Alstonia boonei*, *Morinda lucida*, and *Azadirachta indica* leaves in a particular ratio based on previous clinical observational experiences which supported the ethnomedical records (Odeiran *et al.*, 2014). Oroki herbal mixture (OH) and AB are duly registered for consumption.

However, paracetamol is a commonly used and widely abused analgesic drug with antipyretic activity which is predisposed to co-administration with herbal products. Hence, this study evaluated the possible biological implication of the co-administration of the three herbal products with paracetamol using animal model based on the outcome of a pharmacoepidemiologic survey

MATERIALS AND METHODS

Reagents: Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine assay kits (RANDOX®) were purchased from Randox Laboratories

Limited (Autrium, U.K). All other chemicals and reagents were of analytical grade.

Pharmacoepidemiological survey of the use of herbal products: Structured questionnaire was used to assess the herbal medicines and orthodox drugs commonly consumed within the study population of Obafemi Awolowo University community, Ile-Ife, Osun State, Nigeria. Three hundred questionnaires were randomly administered among the workers (both skilled and unskilled) and students of the University community.

Procurement of herbal products and paracetamol pure powder: Alomo Bitters® (AB) (batch number ALM350141) and Oroki Herbal Mixture® (OH) were purchased at open market in Ibadan Oyo State respectively, while Mama Decoction® (MD) with (batch number FP15001) and paracetamol powder were supplied by the Drug Research and Production Unit (DRPU), Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.

Identification and assay of paracetamol pure: The quality of the paracetamol powder was ascertained using official identification and assay methods (B. P. 2013).

Qualitative phytochemical screening of the herbal products: The herbal product samples were subjected to qualitative phytochemical screening using standard methods (Sofowora, 2008).

Experimental animals: Forty (40) healthy Wistar albino rats of both sexes (150-225g) obtained from the animal house of the Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, were used for this study. The rats were allowed to acclimatize for about two weeks, housed under a 12-h light/dark cycle with free access to water and commercial food pellets (Vital Feed Nig. Ltd, Jos, Nigeria). The study was carried out in accordance with the National Institute of Health (NIH) "Guide for the Care and Use of Laboratory Animals" 1985.

Research design: The Wistar albino rats were randomly divided into eight groups of both sexes each (n=5). Groups 1 and 2 were administered with distilled water (negative control) and Paracetamol (PA) respectively, while groups 3 to 8 were administered Alomo Bitter® (AB); PA and Alomo Bitter® (PAB); Mama Decoction® (MD); PA and Mama Decoction® (PMD); Oroki Herbal Mixture® (OH); and PA and Oroki Herbal Mixture® (POH) respectively.

Drug and herbal products administration: Paracetamol was administered at 15mg/kg 8 hourly daily for three days (Brayfield, 2014) and herbal products administration was twice daily for Mama decoction® at 1mL/kg for 4 days and Oroki herbal mixture® at 0.7mL/kg for 6 days and once daily for Alomo bitters® at 3.3mL/kg for 4 days respectively based on dosage instruction. The co-administration doses were based on the individual dosage instructions of the herbal products while paracetamol was administered at 15mg/kg. Paracetamol and the herbal products were administered orally using oral cannula and the treatment was repeated after one week of completion of the first phase. The animals were sacrificed 24 hours after the last dose treatment.

Hotplate method for analgesic activity assay: Shethy and Anika (1982) method as modified by Franzotti *et al.*, (2000) was used. The rats were subjected to 12 hours fast with adequate clean water provided *ad libitum*. Each of the rats in the groups was placed on a Hotplate Analgesia Meter (Columbus, OHIO 43204, USA) maintained at the temperature of $55 \pm 1^{\circ}\text{C}$. Pain Reaction Time (PRT) was determined as the time taken for the rat to react to the pain stimulus; jumping, raising and licking of hind foot. The cut-off time was fixed at 20 seconds which served as control pain reaction time. The rats were treated as described in the research design above accordingly. The timing of each rat started immediately after oral administration taken as 0 minute, and subsequently at 30, 60, 120 and 180minutes respectively post administration.

Haematological and biochemical analyses: At the end of the experiment, the animals were anaesthetized with chloroform, carefully dissected and blood was obtained using cardiac puncture technique. Blood (5ml) each was transferred into the pre-labelled heparinised bottles and ethylenediaminetetraacetic acid (EDTA) sample bottles respectively, which were gently rolled to allow the blood to mix thoroughly with the respective anticoagulants. The heparinised blood was evaluated for packed cell volume (PCV), haemoglobin level (Hb), red blood cell count (RBC), white blood cells count (WBC), platelets count, neutrophils and lymphocytes counts using standard methods (Baker, *et al.*, 1998). On the hand, the EDTA blood samples were centrifuged at 3,000 rpm to obtain the plasma which was analysed for ALT, AST and Creatinine using the commercially available RANDOX[®] kits.

Histopathology: The liver, kidney, and testes were removed, stored in sample bottles containing 10% buffered formalin

solution and preserved for histopathological evaluation using standard procedures (Soujanya, *et al.*, 2013).

Statistical analysis: The results were presented as mean \pm SEM and analysed using Student t-test and ANOVA with the Duncan's Multiple Comparison test (DMC) used for the post-test where appropriate. Differences were considered significant at $p < 0.05$.

RESULTS

Pharmacoepidemiological survey: Two hundred and sixty-three (87.7%) of the respondents reported the use of herbal products with 16% co-administering with orthodox medicines of which paracetamol was the most common orthodox medicine used with herbal products with 21 (50%) respondents (Table 1).

Table 1: Pharmacoepidemiological survey outcome of the use of herbal preparations with orthodox medicine within the study population

Herbal drugs use	Types of herbal preparation	Respondents (%)
Yes 263 (87.7%)	Yoyo Bitter [®]	26.1
No 37 (12.3%)	Oroki Herbal Mixture [®]	19.1
	Mama Decoction [®]	3.6
	Alomo Bitter [®]	8.6
	Osomo [®]	8.6
	Others	39.0
		Number (%)
	- Without orthodox drug	221 (84)
	- With orthodox drug	42 (16)
	• With paracetamol	21 (50.0)
	• With Ibuprofen	2 (4.7)
	• With antimalarials	4 (9.3)
	• With Cold & Catarrh drugs	2 (4.7)
	• Other drugs	8 (31.0)

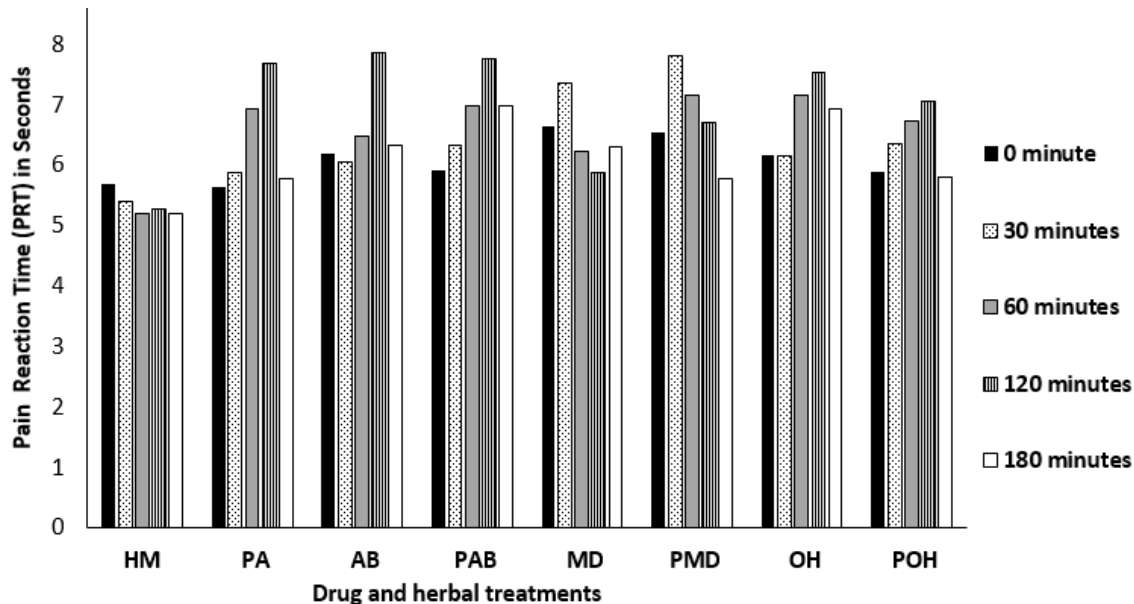


Figure 1: Pain reaction time following the various treatment schedules of Mama Decoction[®] (MD), Oroki Herbal Mixture[®] (OH), Alomo Bitters[®] (AB), paracetamol (PA) and their co-administrations with PA, in Wistar rat model using hotplate method.

Table 2:

Effects of Mama Decoction® (MD), Oroki Herbal Mixture® (OH), Alomo Bitters® (AB), paracetamol (PA) and their co-administrations with PA on haematological parameters following analgesic evaluation in Wistar rats model

Code	PCV (%)	Hb (g/dL)	RBC ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Platelet ($\times 10^9/L$)	NEU (%)	LYM (%)
HM	45.80 \pm 3.92	15.26 \pm 1.31	5.100 \pm 0.43	9.04 \pm 0.26	305 \pm 6.22	28.8 \pm 3.63	71.2 \pm 3.63
PA	50.40 \pm 1.89	16.80 \pm 0.62	5.600 \pm 0.21	8.06 \pm 0.35	338 \pm 14.42	60.4 \pm 0.93 ^c	39.6 \pm 0.93 ^c
AB	50.00 \pm 1.10	16.68 \pm 0.36	5.560 \pm 0.13	8.36 \pm 0.27	389 \pm 8.45 ^a	63.4 \pm 4.20 ^a	36.6 \pm 4.20 ^a
PAB	50.00 \pm 2.74	16.68 \pm 0.91	5.575 \pm 0.30	7.25 \pm 0.42 ^a	371 \pm 12.53 ^a	57.3 \pm 2.21 ^a	42.8 \pm 2.21 ^a
MD	48.60 \pm 1.70	16.20 \pm 0.56	5.380 \pm 0.19	8.82 \pm 0.21	404 \pm 6.62 ^a	56.2 \pm 1.39 ^a	43.8 \pm 1.39 ^a
PMD	48.80 \pm 1.50	16.26 \pm 0.51	5.420 \pm 0.17	7.62 \pm 0.42 ^a	356 \pm 16.63	39.2 \pm 1.88	60.8 \pm 1.88
OH	43.60 \pm 2.94	14.54 \pm 0.99	4.740 \pm 0.26	7.92 \pm 0.35	339 \pm 28.24	33.0 \pm 2.24	67.0 \pm 2.24
POH	47.00 \pm 1.30	15.66 \pm 0.44	5.240 \pm 0.15	5.22 \pm 0.24 ^{a, b}	362 \pm 8.28 ^a	43.0 \pm 4.15 ^a	57.0 \pm 4.15 ^a

Data are expressed as mean \pm S.E.M., (n= 5), (p<0.05),

a = significant when compared with PA; b = significant when OH was compared with POH;

c = statistically significant when compared with control

Physicochemical properties of the herbal products: All the herbal products were acidic; pH 2.52, 4.70 and 5.5 for Oroki, Mama Decoction and Alomo bitters respectively with varied colours; dark brown, brown and golden orange respectively and difference in taste (slightly to very bitter).

Qualitative phytochemical screening of the herbal products: Qualitative phytochemical screening results revealed that the three herbal products contained saponins, flavonoids terpenoids, reducing sugar and anthraquinones. Tannins and cardiac glycosides were observed in MD and AB, while only MD contained alkaloids.

Analgesic activity: the peak PRT (pPRT) for AB and OH (7.86 \pm 0.84 and 7.52 \pm 0.66 seconds respectively) at 120minutes was comparable with PA of 7.68 \pm 0.51 seconds, which was significantly higher than MD (5.88 \pm 0.54 seconds) at the same time (p= 0.028) (Figure 1). However, the time for pPRT for MD (5.88 \pm 0.54 seconds) was significantly lower than all the other treatments. There was no significant difference in the pPRT values for herbal products compared to PA, although the time to attain the pPRT was different. Furthermore, AB increased the pPRT of paracetamol (PAB) while OH (i.e. POH) caused a reduction at 120minutes. On the other hand, MD reduces the time to attain pPRT of PA to 30minutes which was sustained at 60 minutes, this indicates synergistic enhancement of the analgesic activity of MD and PA (Figure 1).

Effect on haematological parameters: There was no significant difference in PCV, RBC and Hb values in all the treated groups (Table 2). However, significant decrease in WBC (p<0.0001) was observed in the co-administration of the three herbal products with paracetamol (PAB, PMD and POH groups). Similarly, platelet and neutrophils counts were decreased with co-administration of MD and AB with PA,

while significantly increased by OH (p= 0.0011). The reverse was observed with lymphocytes counts.

Liver enzyme levels: Plasma AST showed no significant difference in all the groups. Two of the herbal preparations; MD and OH significantly increase the ALT levels. However, co-administration of AB and MD or PA (PAB and PMD) significantly increase the ALT compared with PA (p<0.001), while the high ALT observed with OH was reduced by the co-administration with PA (Table 3). Plasma creatinine which was significantly increased (p< 0.001) by AB and MD was however reduced by their co-administration with PA, although the values were significantly higher than PA and healthy control. On the other hand, no significant effect was observed with OH and its co-administration with paracetamol (Table 3).

Table 3:

Effects of Mama Decoction® (MD), Oroki Herbal Mixture® (OH), Alomo Bitters® (AB), paracetamol (PA) and their co-administrations with PA on biochemical parameters following analgesic evaluation in Wistar rats model

Code	AST (IU/L)	ALT (IU/L)	CREATININE (μ mol/L)
HM	25.6 \pm 6.74	2.90 \pm 0.13	57.71 \pm 3.26
PA	22.4 \pm 5.18	3.00 \pm 0.32	60.71 \pm 2.65
AB	24.4 \pm 2.40	3.00 \pm 0.00	75.95 \pm 2.15 ^a
PAB	24.0 \pm 4.08	5.00 \pm 0.41 ^{a, b}	65.11 \pm 6.48
MD	25.2 \pm 4.03	5.00 \pm 0.00 ^a	81.99 \pm 5.40 ^a
PMD	23.6 \pm 2.11	6.40 \pm 0.75 ^{a, c}	69.89 \pm 3.43
OH	21.6 \pm 6.00	4.22 \pm 0.26	57.57 \pm 6.77
POH	25.2 \pm 4.16	2.76 \pm 0.20 ^d	58.83 \pm 1.14

Data are expressed as mean \pm S.E.M., (n= 5).

One-way ANOVA followed by Dunnett's Multiple Comparisons Test. (p<0.05)

a = statistically significant when compared with the control,

b = statistically significant when AB was compared with PAB,

c = statistically significant when MD was compared with PMD,

d = statistically significant when OH was compared with POH

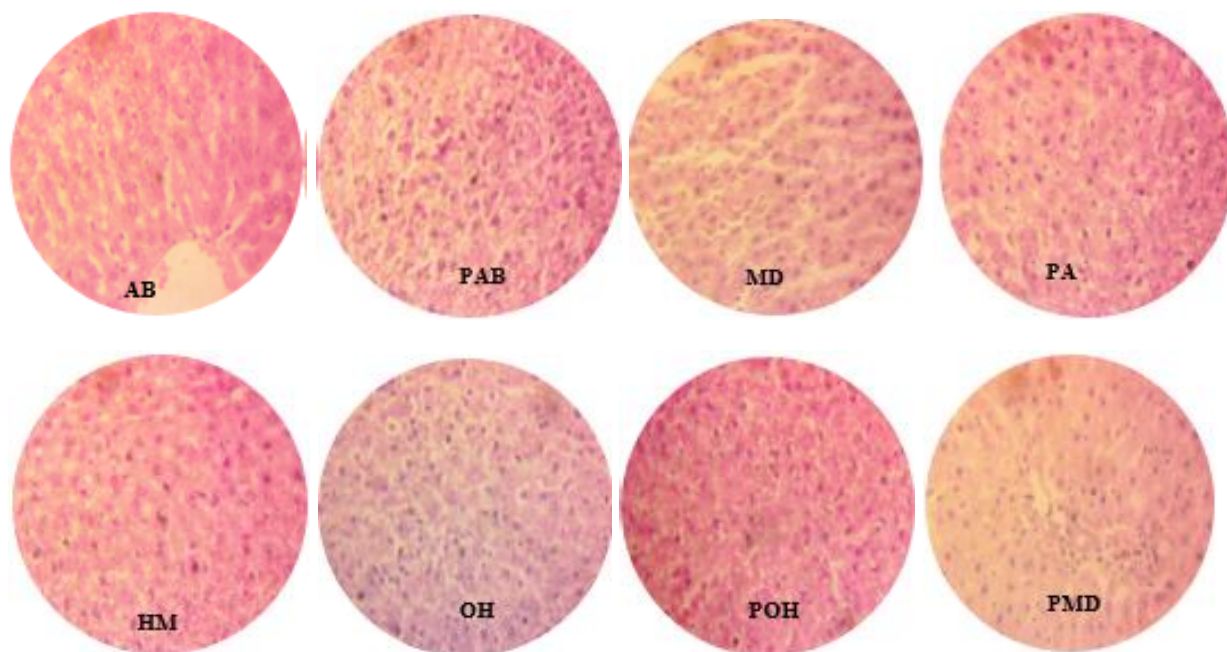


Plate 1:

Photomicrograph sections of liver tissues after the different treatment conditions of the herbal preparations with paracetamol showing normal morphology in healthy liver (HM), moderate zonal degeneration of hepatocytes in PA, multifocal hepatocellular degeneration and necrosis in AB, diffuse degeneration of hepatocytes in PAB, focal degeneration of periacinar hepatocytes in MD, single cell necrosis of hepatocytes in PMD, diffuse degeneration and necrosis of hepatocytes in OH and hepatocellular degeneration in POH treated groups

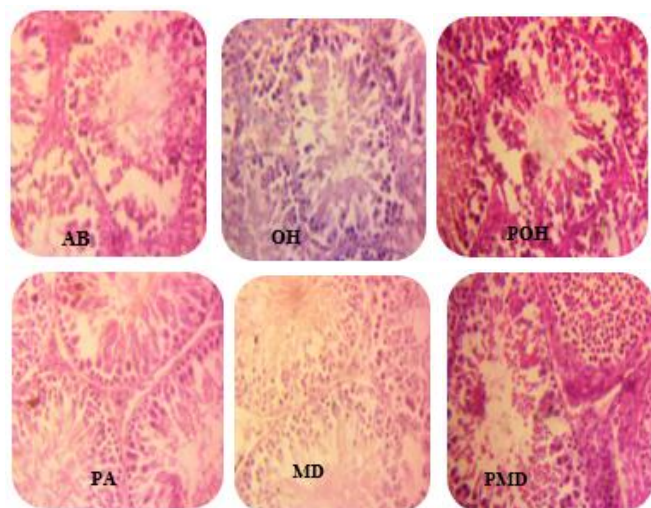


Plate 2:

Photomicrograph sections of testes of the treated groups showing normal morphology in PA and MD, moderate testicular degeneration in PMD, marked testicular degeneration in AB, OH and their co-administration with paracetamol (PAB and POH).

Histopathological evaluation: All the herbal products and their combination with paracetamol showed various stages of liver damage; ranging from multifocal hepatocellular degeneration and necrosis to diffused degeneration of hepatocytes (Plate 1). Marked testicular degeneration was observed in the OH and AB groups (Plate 2). Kidney morphology was normal in all the treatments

DISCUSSION

The practice of co-administration of orthodox medicines with herbal products in hope of hastening recovery is a common practice in different populations globally, especially in developing and low-income communities. This may sometimes result in adverse drug reactions (ADR), and cause emergency admissions leading to increase morbidity and mortality (Fakeye *et al.*, 2007). Many drugs; antihypertensives, analgesics, antidiabetics have been implicated in such herb-drug co-administration. This study reported the prevalence of co-administration of paracetamol with herbal medicines within a population in Southwestern Nigeria, and the implication of its co-administration. Paracetamol is a widely abused analgesic agent with the likelihood of its being co-administered with herbal products. Following the pharmacoepidemiological survey, two hundred and sixty-three (87.7%) respondents reported the use of herbal products; 16% practice co-administration with orthodox medicines of which paracetamol was the most common with 50% respondents. Yoyo Bitters®, Oroki Herbal Mixture® (OH), Alomo Bitters® (AB) and Mama Decoction® (MD) constitute 26.1, 19.3, 8.6 and 3.6% of respondents respectively.

The paracetamol pure powder used for the study at 99.9%w/w complied with the official specification (B.P. 2013). All the herbal products were acidic; pH 2.52, 4.70 and 5.5 for Oroki, Mama Decoction and Alomo bitters respectively and varied colours; dark brown, brown and golden orange respectively with difference in taste (slightly to very bitter). Phytochemical screening revealed the presence of saponins, flavonoids, terpenoids, reducing sugar and

anthraquinones in the three herbal products, while tannins and cardiac glycosides were absent in Oroki, and only Mama decoction contains alkaloids.

All the herbal products showed analgesic activities, with comparable peak Pain Reaction Time (pPRT) to paracetamol by AB and OH at 120 minutes post administration, while the pPRT for MD was achieved at a significantly earlier time of 30 minutes, although no significant difference in the PRT ($p > 0.05$) (Figure 1). Although, co-administration of MD with PA (PMD group) gave a non-significant increase in pPRT at 30 minutes post administration ($p > 0.05$), there was a significant reduction in the time to reach pPRT, indicating synergistic enhancement of analgesic activity by PA and MD i.e. reduced onset of action when compared with the PA alone at 30 minutes. On the other hand, there was no significant difference in the analgesic activity with the co-administration of paracetamol with OH and AB, although the analgesic activities of the herbal products were reduced by paracetamol. The analgesic activities observed in these herbal products could be attributed to the presence of flavonoids, tannins and alkaloids which have been reported to possess analgesic properties (Khadem et al., 2012; Faujdar et al., 2016).

Haematological parameters are valuable tools for assessing the injuries caused by certain substances. Outcome of this study showed that there was no significant effect on PCV, RBC and Hb in all the treated groups when compared with the paracetamol and healthy control groups (Table 2). This implies that the herbal products and paracetamol have no effect on these parameters at the normal recommended doses and treatment period.

However, white blood cell counts (WBC) were generally reduced in all the treated groups. There was no significant difference observed with the administration of PA, AB, MD and OH, but the reduction observed with their co-administration with paracetamol was only significant for OH (POH) ($p < 0.001$) (Table 2). The reduction in WBC count which is medically referred to as leucopenia indicates a need for caution by the co-administration of paracetamol with the herbal products investigated in this study. White blood cell produced in the bone marrow is an important part of the immune system and body's natural weapon to fight infections (Chung, et al., 2015). Such reduction in WBC could be linked to bone marrow problems and the inability to make enough white blood cells. Hence, it can be deduced that prolong use of the herbal products with paracetamol can have a deleterious effect on the immune system as a result of the decreased production of WBC. Similarly, the increased platelet counts by all the groups though only significant with AB and MD ($p < 0.01$) and ameliorated by their co-administration with paracetamol (Table 2), was however not clinically significant as the obtained values were within the normal reference range (150-460 x 10⁹/L) (Johnson-Delaney, 1996).

Furthermore, the increase in neutrophils observed with PA, AB and MD was reduced by co-administration with MD and OH ($p < 0.001$) although OH alone had no effect when compared with the healthy groups. The significant increase in the neutrophils by AB and MD possibly suggest the ability of the herbal products to enhance blood component to phagocytose (Odeghe, et al., 2012). On the other hand, the significant decrease in lymphocytes by paracetamol, AB and

MD was increased by the co-administration of MD and OH (PMD and POH respectively) ($p < 0.001$) indicating that MD and OH ameliorates the effect of PA on the lymphocytes (Table 2).

The blood level of aminotransferases is a measure of the concentration of intracellular hepatic enzymes leaked into the circulation, thus serving as a marker of hepatocyte injury (Shelli, et al., 2013). Liver contains aspartate aminotransaminases (AST) and alanine aminotransaminases (ALT) as hepatobiliary enzymes in high concentrations which are released into the blood circulation following hepatic damage and necrosis. This results in raised serum concentration of these enzymes as a result of cellular breakage and loss of functional integrity of cell membranes in liver tissues, making both enzymes indicators of possible liver damage/toxicity (Attiah et al., 2013). Aspartate aminotransaminases (AST) was not significantly affected by all the treatment groups. Similarly, paracetamol and all the herbal products alone had no significant effect on ALT, however, co-administration of AB and MD with paracetamol (PAB and PMD) significantly increase ALT level ($p < 0.05$). The observed non-significant effect of paracetamol on the ALT level though at variance with an earlier report of increased ALT indicating a biochemical evidence of significant liver damage and induced hepatotoxicity in rats (Kanchana and Sadiq, 2011) was corroborated by the moderate hepatocyte degeneration observed in this study. Furthermore, histopathological results showed varied degrees of hepatocellular degeneration and cell necrosis by AB, MD and OH and their co-administration with paracetamol (Plate 1). This indicates that AST and ALT levels may not be conclusive of possible hepatotoxicity. An earlier study by Akanmu et al., (2013) reported a significant increase in plasma ALT, AST and ALP in rats by sub-chronic administration of dried extract of MD. This was corroborated by the hepatocellular degeneration by MD obtained in this study indicating a need for caution with the use of MD at the recommended doses and treatment duration.

Also, the increased plasma creatinine levels by AB and MD ($p < 0.05$) was reduced by the co-administration with paracetamol to a comparable level of paracetamol and healthy groups. This was confirmed by the normal kidney morphology observed with histopathological evaluation of the kidney in the groups. Creatinine is one of the parameters to diagnose functionality of the kidney as it is the most frequently used marker of renal function and often thought to reflect glomerular filtration rate (GFR), notwithstanding some limitations (Dirk, et al., 2016; Jacek, et al., 2017). Herb-drug interactions have been associated with variety of deleterious effect on the body vital organs such as liver and kidney which are important in the elimination of waste products and toxic substances.

Interestingly, normal testicular morphology was observed with paracetamol and MD, while varied degree of testicular degeneration was observed with AB and OH groups and the co-administration of the three herbal products with paracetamol (Plate 2). This indicates a need for caution by the consumer of these products.

In conclusion, all the herbal products investigated showed analgesic activities with the synergistic enhancement of

analgesic activity of paracetamol by Mama Decoction i.e. reduced onset of action. The effect of these herbal products and their co-administration with paracetamol on some of the biochemical and haematological parameters as well as the damage to the liver and testes calls for caution.

Conflict of interest statement

The authors declare that there is no conflict of interests in this study.

Acknowledgement

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