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RESEARCH ARTICLE

CO-ADMINISTRATION OF GOKO HERBAL CLEANSER AND PARACETAMOL: A HERB-DRUG INTERACTION STUDY

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Abstract

Aim: The present study aimed to evaluate the effects of co-administering paracetamol and Goko cleanser®on the liver.
Method: Twenty rats divided into four different groups were used for this Study. Group one (control group) received distilled water only; Group two received paracetamol only (100mg/kg), Group three received Goko cleanser®only (2 mL/kg) and Group four received paracetamol and Goko cleanser®concomitantly for 3 days. Blood and liver samples were analyzed for biochemical and histopathological parameters respectively.
Results: Data obtained revealed a significant decrease ($p<0.05$) in the levels of the liver enzymes (ALT, AST, and GGT) in the Goko cleanser®-only group compared to control. A significant decrease in AST was also observed in paracetamol + Goko cleanser®group. No significant change in ALT, ALP and GGT levels in the paracetamol + Goko cleanser®groups was observed. Results of histology examination showed normal liver tissues with normal hepatocytes, sinusoids and central vein for both treated and control groups.
Conclusion: The significant reductions in the liver enzymes by observed in the Goko cleanser®-only group indicated potential hepato-protective effects which could be due to the presence of phenolic compounds which acted as antioxidants. The short-term co-administration of paracetamol and Goko cleanser®produced no liver toxicity. However, this is subject to further studies using pharmacokinetic analysis and also, a long-term study is strongly advocated.
Keywords: Goko cleanser, hepatotoxicity, herb-drug interaction, paracetamol.

INTRODUCTION

Phytochemicals in foods and herbs have been proven to be beneficial to human health[1,2,3]. However, the heightened use of herbal medicines in recent times has come with growing concerns associated with the safety and toxicity profile[4]. Phytochemical constituents can modulate the efficacy and toxic effects of drugs by influencing their metabolism and absorption by interacting with drug transporters and metabolizing enzyme[2,5]. Co-morbidities of certain diseases have favoured polypharmacy thence posing an increased risk of drug interaction[6]. This has resulted in the rise in the utilization of herbal medicines in combination with conventional drugs[7]. The concurrent intake of herbal and orthodox medicines raises concerns about herb-drug interactions and potential patient safety owing to unclear pharmacokinetic and pharmacodynamic mechanisms of these herbal medicines[8]. Certain herbal and dietary supplements may produce potentially dangerous herb-drug interaction as they can alter the pharmacokinetics and/or pharmacodynamics of certain medications[9]. This could be due the presence of adulterants or phytochemicals which could interfere with these processes[2,10]. Such herb-drug interactions may be beneficial or detrimental. Interference (induction/inhibition) with CYP isozymes and phase II metabolizing enzymes or drug transporters by phytochemicals is the major mechanisms of drug/herb/nutrient interactions[2].

Acetaminophen-induced hepatotoxicity is due to the decreased levels of glutathione due to conjugation with NAPQI (N-acetyl-p-benzoquinone imine)[11] a metabolite of acetaminophen metabolism via cytochrome P450 enzyme in the liver[12]. However, the concentration of NAPQI produced at therapeutic doses are quite little to result in an adverse reaction but when overdosed, it's concentration increases which results in the depletion of glutathione resulting in hepatotoxicity and necrosis[11,12,13]. In view of this, an overdose of

acetaminophen results to hepatotoxicity amongst other side effects[14].

Goko cleanser®isa herbal mixture claimed to be effective for various kinds of disease conditions such as, diabetes, infertility, blood clots, hepatitis, erectly dysfunction. Its contents include: *Vernonia amygdalina*, *Cajanuscajan*, *Zingiberofficinale*, *Allium sativum*, *Saccharum officinarum* and caramel[15]. A recent study has identified nephrotoxic effect of Goko cleanser in wistar rats[15,16]. Current study aims to probe the effects of a co-administration of Goko cleanser® and paracetamol on the histology and biochemical parameters of the liver.

MATERIALS AND METHODS

Chemicals and Reagents

Distilled water, methylated spirit (JHD, China), Xylene, Diethyl ether(JHD Guagdong Guanghua Sci-Tech. co. Ltd. Shantou, Guandong, China), 10% formalin, Goko cleanser® (Kayfahd herbaceuticals), Paracetamol 500 mg tablets BP (Panadol® from Glaxo Smith Kline). All chemicals and reagents used in this study were of analytical grade.

Source of herbal formulation

The herbal formulation under study was obtained in August 2020, from Choba open market, Port Harcourt, Rivers State. The herbal formulation was manufactured by Kayfahd herbaceuticals. Exclusively for: Purity biz.com FCT Abuja, Nigeria.

Animals

A previous experimental design described by Ewing *et al*.,[14] was used for this study with little modifications. Twenty (20) healthy adult male rats (152.6±20.6 g) were used for the experiment. The animals were kept in the animal house of the Department of Experimental Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Nigeria for a period of two weeks and fed with standard feed (Broiler finisher- Guinea feeds) *ad libitum* with free access to water before experiment. Animal ethics and proper handling methods following during experiments.

Animal experiment

The dosage for Goko cleanser® herbal mixture was chosen using its prescription label. Animals were randomly assigned to four groups (1-4) of five animals each. Group I received 0.3mL of distilled water orally daily for 3 days (control group). Group II animals received oral dose of paracetamol (100 mg/kg daily for 3 days). Dose of paracetamol was chosen based on results of LD50 previously determined by Ewing *et al*[14]. Animals in group III received oral dose of Goko cleanser® (2mL/kg daily for 3 days). Group IV animals received both paracetamol and Gokocleanser® orally at a dosage of 100 mg/kg and 2 mL/kg respectively concurrently daily for 3 days. A conventional/therapeutic usage of paracetamol and Goko cleanser® was mimicked with this experimental setup. Animals were then fasted overnight on the third day of treatment and sacrificed using ether anaesthesia on the fourth day.

Blood sampling and biochemical analysis

Samples of blood were collected via cardiac puncture and kept for 6 hours at a temperature of 4℃. Prior to biochemical analysis, blood samples were centrifuged at 3000 rpm for 10 minutes. Liver function was probed with commercial diagnostic kits (Randox laboratory kit, England) using serum levels of Glutamyl transferase (GGT), Alkaline phosphatase (ALP), Alanine amino transferase (ALT) and Aspartate amino transferase (AST).

Histopathological Examination

Liver sections were fixed in 10% formalin for 6-12 hours. They were processed and examined for histological changes at the college of Health Sciences pathology facility. For light microscopy examination, liver tissues fixed in formalin were dehydrated using increasing grades of alcohol embedded in paraffin. Serial sections were taken and stained with H and E as per standard protocol. Stained sections were morphologically evaluated, and the pictures of the slides were taken for comparison.

Ethical issues

The study protocol was designed in line with the ethical principles of the International Committees for the Protection of Animal Rights Laboratory and approved by the research ethics Committee of the University of Port Harcourt, Rivers State, Nigeria.

Statistical analysis

Statistical analysis involved use of the Microsoft Excel. Results were expressed as the Mean ± SD. Analysis were done using one-way Anova and *t*-tests. *P* values below 5% were considered statistically significant ($p < 0.05$).

RESULTS

Biochemical Analysis

In this study, enzyme concentrations were all within normal ranges. The rats treated with Goko cleanser® alone showed a significant ($p<0.05$) decrease in the concentrations of liver function markers, ALT, AST, and GGT enzymes compared to the control group, paracetamol-only group and Goko®-paracetamol group. However, there was a mild increase in the concentration of ALP in the Goko cleanser®-only and the paracetamol/Goko cleanser® groups when compared with the control. However, this increase was not statistically significant. Similarly, there was a non-significant increase in ALP, ALT and GGT in the Goko®-paracetamol interaction group compared to the control group. These results are shown in Figure 1.

Histopathology

Results of the histopathology analysis revealed no apparent distortions in the liver tissues from both control and treated groups. The liver tissues were histologically normal showing normal hepatocytes, sinusoids, central vein and portal triad.

Effects of Paracetamol-Goko Cleanser® interaction on Rat Body Weights

The body weights of the rats were determined and are shown in Table 1. All animals exhibited increased body weights at the end of the experiment with significant difference (*p<0.05) between both control and Goko cleanser® groups.

DISCUSSION

Drug-herb interaction is a matter of concern especially in the developing countries, as herbal remedies are linked with complications such as liver toxicities with high incidence of mortalities and morbidities[4]. The clinical presentation could range from asymptomatic cases with distorted liver function tests to more severe liver failure[4]. Herbal remedies have become popular across the globe in primary healthcare, and some have been erroneously regarded as safe just because they are of natural source[5]. In addition, these therapeutic products from medicinal plants are claimed to be safe without any toxic health effects, and thus widely utilized as self-medications[17]. However, there are little or no proven scientific studies on the toxicity and adverse effect of these remedies[18].

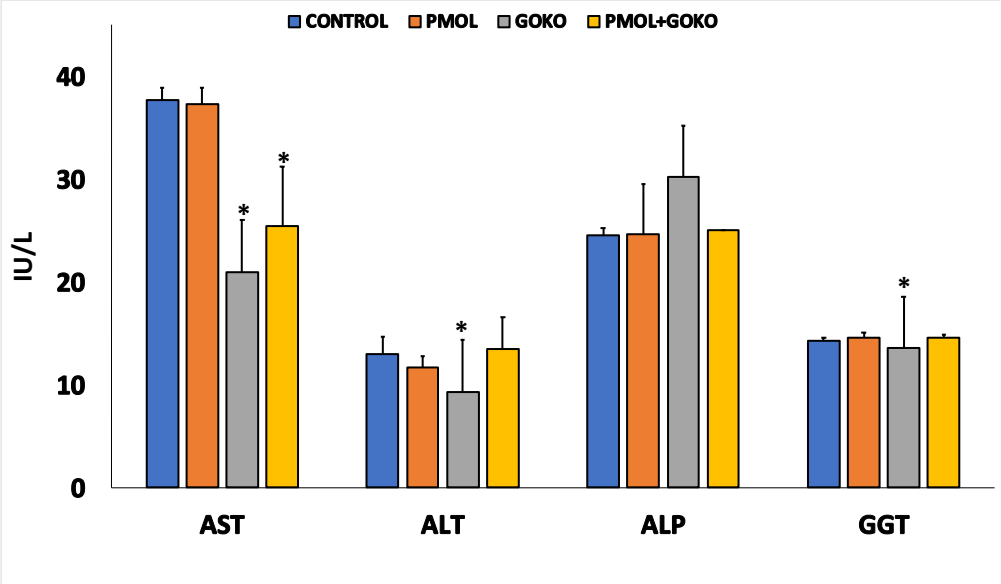

Figure 1: Effect of Paracetamol + Goko® interaction on liver enzymes; n=5, values are expressed as mean±SEM. * p<0.05 compared to control group.

Recent studies have reported that certain herbs have the potential to induce drug metabolizing enzymes and transporters[19]. For example, a herbal preparation containing *Kaempferia parviflora* have been shown to induce CYP2E1 which is an enzyme that metabolizes paracetamol. Paracetamol (acetaminophen) is metabolized to give the major hepatotoxic product known as *N*-acetyl-*p*-benzoquinone imine (NAPQI)[20]. In view of this, Mekjaruskul and Sripanidkulchai[19] investigated the combined use of *K. parviflora* extract with CYP2E1 paracetamol. Results obtained from that study provided a possible drug-herb interaction between *K. parviflora* and paracetamol leading to increased metabolism and possible enhanced levels of the metabolite NAPQI[19].

Besides the negative effects of drug-herb interaction, some studies have highlighted beneficial effects. For example, certain herbs have been shown to possess ameliorative effects against some drug-induced toxicity. In a study by Hamid *et al*., *Zingiber zerumbet* was documented to have protective activity against paracetamol-induced acute hepatotoxicity in rat model[21]. Further to this, *Curcuma longa* extract was shown to protect the liver against carbon tetrachloride-induced liver injury[22].

Table 1: Showing the effects of paracetamol and Goko cleanser® interaction on rat body weights.

Groups	Initial Weight (g)	Final Weight (g)	% Body Weight Change
Control	125.6±5.8	138.4 ±8.4	10.2
Paracetamol	134± 1.6	138.8 ± 2.9	3.6
Goko cleanser®.	145.6 ±3.4	151.8 ±4.7	4.1

In addition, some herbs such as *Ginkgo biloba* have demonstrated beneficial synergistic effects that enhance the efficiency of haloperidol[23].

In the present study, the results obtained from biochemical analysis produced a reduction in the levels of liver enzymes in the Goko cleanser®-paracetamol group compared to control. These results are in agreement with the data obtained from histopathological examination, which showed normal liver tissues with normal hepatocytes, sinusoids, central

vein and portal triad (portal vein, portal artery and bile duct). Goko cleanser® when administered alone and in combination with paracetamol reduced the concentrations of ALT, AST and GGT significantly (p<0.05) compared to control and paracetamol-only groups. While AST levels were significantly reduced in group that received Goko cleanser® alone and paracetamol + Goko cleanser® concurrently, the AST level in the paracetamol- Goko cleanser® group was higher than the Goko cleanser® -only group suggestive of an elevation accruing from an interaction between paracetamol and Goko cleanser®. Furthermore, increased body weights of the animals across all treatment groups were suggestive of the absence of toxicities from the co-administration of paracetamol and Goko cleanser®.

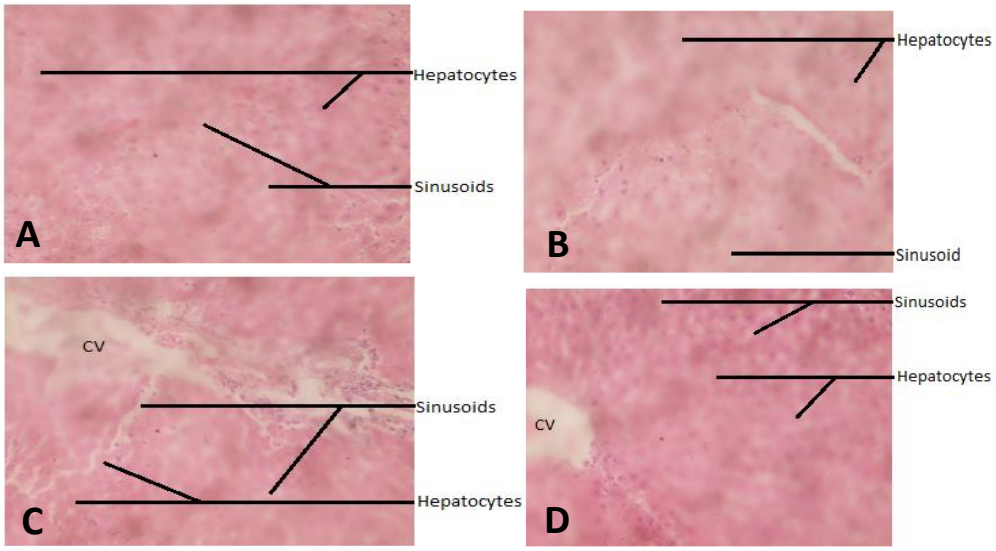

Figure 2: Photomicrograph (400x magnification) of A). Liver from rats in the control group that received distilled water only; B). Liver tissue of rats that received paracetamol only; C). Liver from rats that received Goko cleanser® only; D). Liver from rats that received paracetamol + Goko cleanser®.

Taken together, the significant reductions in the liver enzymes by Goko cleanser® indicated potential hepato-protective effects; this provides some level of support to the claims made by the manufacturer about Goko cleanser® being hepato-protective. The potential hepato-protective effect of Goko cleanser® could be attributable to the presence of flavonoids and other phenolics like tannins contained in some of its constituent herbs[15]. Flavonoids and tannins are plant-based antioxidants known to reduce the risk of occurrence of numerous human disease related to oxidative stress[24]. Oxidative stress is known to play a foremost role in the progress of liver diseases[25]. Earlier studies have highlighted the potential hepato-protective effects of flavonoids and other plant-based antioxidants in herbs. For instance, a study by Kim *et al.*, demonstrated that extracts of *Alnus japonica* alleviated the acetaminophen induced hepatic injury in rats[26]. These findings are in agreement with data obtained from our study.

CONCLUSION

From the results obtained from this study, no hepatotoxic effects were observed with short-term administration of paracetamol and Goko cleanser® at therapeutic doses in rats. Therefore, the study hypothesizes that a short-term co-administration of the duo poses no potential health risk, however this is subject to further studies. Specifically, pharmacokinetics studies and long-term co-administration studies are strongly advocated.

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AUTHOR'S CONTRIBUTION

Amadi CN: writing original draft, methodology. **Edevbie OR:** investigation, conceptualization, literature survey. Both authors revised the article and approved the final version.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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