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Research Article

Effect of co-administered lopinavir/ritonavir and sulfamethoxazole/ trimethoprim on cardiac function and architecture of albino rats

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ABSTRACT

Background: Lopinavir/ritonavir (LPV/r) could be associated with adverse cardiac event. Antiretroviral drugs containing LPV/r are used concurrently with sulfamethoxazole/ trimethoprim (SMX/TMP) which may also be associated with adverse cardiac events in the management of human immunodeficiency virus and co-infection. The concurrent use of these drugs may precipitate synergistic adverse cardiac events. This work, therefore, evaluates the possible toxicological interaction of co administered LPV/r and SMX/TMP on cardiac function and architecture of albino rats.
Methods: Seventy five (75) animals which were divided into five groups (A-E) of fifteen (15) animals each were used in this study. Animals in Group A, which served as the control, were treated with 1% ethanol orally. Animals in Group (B-E) were treated with oral doses of SMX/TMP (11.2/2.3 mg/kg), LPV/r (11.4/2.9 mg/kg), and combine doses of SMX/TMP+LPV/r for 2-8 weeks, respectively. Blood sample was collected and evaluated for pack cell volume, hemoglobin, red blood cell and white blood cell. Cardiac tissues were evaluated for malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase ($GSHP_X$), and histopathological changes.
Results: Treatment with SMX/TMP LPV/r and their combine doses produced no significant effect on cardiac weight. SMX/TMP significantly decreased red blood cell and hemoglobin while LPV/r produced no significant hematologic effect. Combine doses of these agents produced no synergistic hematologic effects. Treatment with a single and combine doses of these agents produced time-dependent decrease in SOD, $GSHP_X$ and increase in MDA, but no synergistic effects were produced by their combine doses. Normal cardiac myocytes with patchy collection of mononuclear inflammatory cells infiltration of the interstitium were observed after treatment with single and combined doses of these agents but without any synergistic effect when agents were co-administered.
Conclusion: In this study, the co-administration of SMX/TMP and LPV/r did not produce any significant synergistic effects on all the evaluated parameters; hence, the concurrent use of these agents in the management of HIV and co-infections may be safe on cardiac function and structure.

Keywords: Cardiac, Lopinavir/Ritonavir, Rats, Sulfamethoxazole/Trimethoprim, Toxicity

INTRODUCTION

In 2012, report showed that 1.8 million deaths were recorded among 34 million people infected with human immunodeficiency virus (HIV). But the availability of highly active antiretroviral therapy has tremendously reduced scourge and death associated with HIV/acquired immunodeficiency syndrome (AIDS).[1] Lopinavir (LPV) is a protease inhibitors used for the management of HIV/AIDS. Due to its poor bioavailability, it is co-formulated with ritonavir a potent inhibitor of cytochrome p450 3A4.[2] In the management of HIV/AIDS, LPV/ritonavir (LPV/r) is always co-administered with other classes of antiretroviral drugs to maximize clinical and therapeutic benefits. Despite the clinical success achieved with the use of protease inhibitors, they are reported to be associated with toxicological effects which include cardio-metabolic effects.[3]

Sulfamethoxazole/trimethoprim (SMX/TMP) is an inexpensive antibacterial agent that is universally available and with a wide spectrum of use. This combination has a wide spectrum of action against Gram-negative organism, Gram-positive organism, fungi and protozoa.[4] Probably due to its spectrum of action, WHO recommends the use of SMX/TMP as prophylaxis in HIV-positive adults with WHO clinical Stage 2, 3, or 4 especially in settings where the health-care infrastructure is limited. However, if morbidity is high, it is recommended that all HIV-positive adults should be treated with SMX/TMP because it reduces mortality irrespective of clinical disease stage or CD4 cell count.[5]

Therapy with SMX/TMP has been reported to be associated with some toxicological effects which include cardiotoxic effect[6] while antiretroviral medications containing LPV/r have been linked with adverse cardiac effects including cardio-metabolic effects.[7,8] The presence of HIV/AIDS-associated co-morbidity and co-infections have necessitated the concurrent use of SMX/TMP and antiretroviral medications containing LPV/r which have been shown to be of clinical benefits.[9] The concurrent use of LPV/r with SMX/TMP may possibly place more toxicological burden on the heart which pumps blood that serves as a means of drug transportation. This work, therefore evaluates possible effect of the co-administration of SMX/TMP and LPV/r on cardiac function and architecture of albino rats.

METHODS

Drugs

Drugs used in this work are LPV/r manufactured by Myland Laboratories Limited India, and SMX/TMP manufactured by CSPC Ouyi Pharmaceuticals Ltd. No. 276 Zhongshen West Road Shijiazhuang, China. Both drugs were of analytical grade.

Animals

The animals used in this research work were obtained from the Animal House of the Department of Pharmacology and Toxicology, Madonna University, Elele, Rivers State. The animals were allowed free access to food and water *ad libitum* and were allowed to acclimatize for 14 days. Animals were handled according to Helsinki declaration on the handling and use of animals.

Dose selection

22.4/4.6 mg/kg of SMX/TMP and 22.8/5.8 mg/kg of LPV/r were used in this study.[10,11]

Preparation of drug

LPV/r tablets were crushed and dissolved in 1% ethanol while SMX/TMP tablets were also crushed and suspended in water.[12]

Grouping of animals

Seventy five (75) healthy male rats of average weight 320±5 g were used in this study. The rats which were divided into five Groups A, B, C, D and E were housed in a large mesh cage.

Drug administration

Group A: This which contained 15 animals served as the control. Animals in this group were treated with 1% ethanol orally throughout the duration of the study.

Group B: This group contained 15 animals which were further divided into three subgroups (B1-B3). Animals in subgroup B1 were treated with 22.4/4.6 mg/kg of SMX/TMP. Animals in subgroup B2 were treated with 22.8/5.8 mg/kg of LPV/r. Animals in subgroup B3 were treated with combined doses of SMX/TMP+LPV/r. All animals in this group were treated for 2 weeks.

Group C: This group contained 15 animals which were further divided into four subgroups (C1-C3). Animals in subgroup C1 were treated with 22.4/4.6 mg/kg of SMX/TMP. Animals in subgroup C2 were treated with 22.8/5.8 mg/kg of LPV/r. Animals in subgroup C3 were treated with combined doses of SMX/TMP+LPV/r. All animals in this group were treated for 4 weeks.

Group D: This group contained 15 rats which were further divided into four subgroups (D1-D3). Animals in subgroup D1 were treated with 22.4/4.6 mg/kg of SMX/TMP. Animals in subgroup D2 were treated with 22.8/5.8 mg/kg of LPV/r. Animals in subgroup D3 were treated with combined doses of SMX/TMP+LPV/r. All animals in this group were treated for 6 weeks.

Group E: This group contained 15 animals which were further divided into four subgroups (E1-E3). Animals in subgroup E1 were treated with 22.4/4.6 mg/kg of SMX/TMP. Animals in subgroup E2 were treated with 22.8/5.8 mg/kg of LPV/r. Animals in subgroup E3 were treated with combined doses of SMX/TMP+LPV/r. All animals in this group were treated for 8 weeks.

Collection of sample for analysis

Animals were sacrificed using chloroform anesthesia at the end of 2, 4, 6, and 8 weeks of treatment, respectively. Blood sample was collected from the common carotid artery. The sample was allowed to clot and centrifuged at 1000 rpm for 5 mins using Uniscope centrifuge and serum separated for analysis. About 2 ml of blood was collected into ethylenediaminetetraacetic acid (EDTA) sample bottles, and this was carefully mixed with the anticoagulant (EDTA) to prevent clotting. Rats were

dissected heart was collected, weighed, and analyzed for histopathological changes.

Preparation of tissue homogenate

Cardiac tissues were homogenized in ice-cold 10 mmol/L tris-HC1, pH 8.2, containing 0.25 mol/L sucrose, 2 mmol/L 2-mercaptoethanol, 10 mmol/L sodium azide, and 0.1 mmol/L phenylmethylsulfonyl fluoride with a polytron (4 vol/wt), and centrifuged at 50,000 g (20 mins, 4°C). The supernatants were lyophilized and stored at −20°C.[13]

Evaluation of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSHPX)

Cardiac MDA concentrations, SOD activity, and glutathione peroxidase were evaluated using the methods reported by Ahmed and Hassanein, 2013.[13]

Evaluation of hematologic parameters

The Automated Hematologic Analyzer, Sysmex, KX-21 (Japan) was used to analyze the hematological parameters white blood cell, red blood cell, hemoglobin, and pack cell volume.

Statistical analysis

Results were expressed as mean ± S.E.M. Statistical analysis was done with the aid of SPSS for windows; SPSS Inc., Chicago, Standard version 14.0 to determine the difference between mean using one-way analysis of variance.

RESULTS

Effects on cardiac weight and hematologic parameters

Treatment with SMX/TMP, LPV/r, and their combination for 2, 4, 6, and 8 weeks, respectively did not produce any significant ($p>0.05$) change in cardiac weight with respect to the control (Table 1). Animals exposed to SMX/TMP for 8 weeks produced significant ($p<0.05$) decrease in red blood cell (RBC) and hemoglobin (Hb) level which represents 42 and 49%, respectively when compared with the control. No significant ($p>0.05$) changes in red blood cells and hemoglobin were observed with respect to the control in animals treated with LPV/r (Table 2). Exposure of animals to combine doses of SMX/TMP+LPV/r significantly ($p<0.05$) decreased red RBC and Hb by 44 and 51%, respectively, when compared with the control. Single and combine doses of these agents did not produce any significant ($p>0.05$) change in packed cell volume and white blood cell when compared with the control (Table 2).

Effects on cardiac MDA, SOD and GSHPX

Treatments with LPV/r for 2-8 weeks produced time-dependent decrease in SOD, which becomes significant ($p<0.05$) in week 8 when compared with the control. SMX/TMP produced time-dependent decrease in cardiac SOD with significance (47%, $p<0.05$) in week 8 with respect to the control (Table 3). Exposure of animals to co-administered SMX/TMP+LPV/r produced a time-dependent decrease in cardiac SOD levels from the control values to 8.18±2.35, 7.95±2.14, 6.75±1.40, and 4.30±3.20 in week 2-8, respectively. Decrease in SOD which represents 48% was found to be significant ($p<0.05$) in week 8 when compared with the control (Table 3).

SMX/TMP produced a time-dependent increase in MDA level with significant increases (44%; 60%, $p<0.05$) in week 6 and 8, respectively, when compared with the control. Time-dependent increase in cardiac MDA was noted in animals exposed to LPV/r which becomes significant (67%, $p<0.05$) in week 8 with respect to the control. Combine doses of these agents increased MDA time-dependently with observed significance (47%; 69%, $p<0.05$) in week 6 and 8, respectively, when compared with the control (Table 4). Cardiac $GSHP_X$ level was time decreased dependently by SMX/TMP with significance (50%, $p<0.05$) in week 8 while LPV/r also produced significant (51%, $p<0.05$) decrease in cardiac $GSHP_X$ in week 8 with respect to the control (Table 5). Combine doses of these agents time-dependently decreased cardiac $GSHP_X$ level with observed significance (52%, $p<0.05$) in week 8 when compared with the control (Table 5).

Effects on histopathology of the heart

Hearts of animals treated with SMX/TMP, LPV/r, and combine doses of these agents showed normal cardiac myocyte with patchy collection of mononuclear inflammatory cells infiltration of the interstitium (Figures 1-4).

Table 1: Effects of LPV/r, SMX/TMP, and their combination on cardiac weight (g) in rats.

Dose (mg/kg)	Week 2	Week 4	Week 6	Week 8
Control	1.25±2.51	1.17±2.42	1.22±3.10	1.18±1.50
SMX/TMP (22.4/4.6)	1.23±2.11	1.11±0.21	1.22±3.22	1.19±3.10
LPV/r (22.8/5.8)	1.12±4.00	1.24±3.10	1.22±2.51	1.19±2.11
SMX/TMP+LPV/r	1.19±2.04	1.18±2.15	1.21±1.10	1.22±2.10

Results are express as mean± SEM. SMX/TMP: Sulfamethoxazole/trimethoprim, LPV/r: Lopinavir/ritonavir, SEM: Standard error of the mean

Table 2: Effects of LPV/r, SMX/TMP, and their combination for 8 weeks on hematologic parameters of rats.

Dose (mg/kg)	PCV (%)	WBC ($\times 10^3$ mm^{-3})	RBC ($\times 10^6$ mm^{-3})	Hb (g/L)
Control	35.00±3.16	6.85±3.16	7.85±4.27	10.25±2.75
SMX/TMP (22.4/4.6)	33.50±3.30	5.93±2.51	4.55±4.20	5.23±3.21
LPV/r (22.8/5.8)	34.62±1.41	6.84±1.55	7.15±3.10	11.10±2.00
SMX/TMP+LPV/r	33.30±2.00	6.74±1.10	4.40±2.32	5.11±4.40

Results are express as mean±SEM, *Means significant difference with respect to the control at p<0.05, analysis of variance. SMX/TMP: Sulfamethoxazole/trimethoprim, LPV/r: Lopinavir/ritonavir, SEM: Standard error of the mean, RBC: Red blood cell, WBC: White blood cell, PCV: Packed cell volume, Hb: Hemoglobin

Table 3: Effects of LPV/r, SMX/TMP, and their combination on cardiac SOD (units/g protein) in rats.

Dose (mg/kg)	Week 2	Week 4	Week 6	Week 8
Control	8.31±1.20	8.25±1.20	8.33±1.20	8.26±1.20
SMX/TMP (22.4/4.6)	8.20±2.10	8.18±3.21	6.89±2.03	4.37±1.24*
LPV/r (22.8/5.3)	8.27±4.12	7.99±2.25	6.80±2.41	5.07±2.10*
SMX/TMP+LPV/r	8.18±2.35	7.99±2.14	6.75±1.40	4.30±3.20*

Results are express as mean±SEM, *Means significant difference with respect to the control at p<0.05, analysis of variance, SMX/TMP: Sulfamethoxazole/trimethoprim, LPV/r: Lopinavir/ritonavir, SEM: Standard error of the mean, SOD: Superoxide dismutase

Table 4: Effects of LPV/r, SMX/TMP, and their combination on cardiac MDA (nmol/mg protein) in rats.

Dose (mg/kg)	Week 2	Week 4	Week 6	Week 8
Control	1.53±2.10	1.61±3.15	1.67±1.15	1.63±3.20
SMX/TMP (22.4/4.6)	1.58±5.41	1.65±4.50	2.40±2.15*	2.60±2.60*
LPV/r (22.8/5.8)	1.62±2.14	1.69±4.25	1.75±3.11	2.71±2.34*
SMX/TMP+LPV/r	1.75±3.21	1.84±1.35	2.45±5.20	2.75±4.13*

Results are expressed as mean±SEM, *Means significant difference with respect to the control at p<0.05, analysis of variance. MDA: Malondialdehyde, SMX/TMP: Sulfamethoxazole/trimethoprim, LPV/r: Lopinavir/ritonavir, SEM: Standard error of the mean

Table 5: Effects of LPV/r, SMX/TMP, and their combination on cardiac $GSHP_X$ (µm/mg protein) in rats.

Dose mg/kg	Week 2	Week 4	Week 6	Week 8
Control	8.30±3.25	8.25±2.18	8.20±1.17	8.21±2.15
SMX/TMP (22.4/4.6)	8.10±3.30	8.05±2.51	6.90±4.20	4.03±3.21*
LPV/r (22.8/5.8)	8.02±1.41	7.90±1.55	7.81±3.10	4.10±2.00*
SMX/TMP+LPV/r	7.90±2.00	7.89±1.10	6.80±2.32	4.00±4.40*

Results are expressed as mean±SEM, *Means significant difference with respect to the control at p<0.05, $GSHP_X$: Glutathione peroxidase, analysis of variance, SMX/TMP: Sulfamethoxazole/trimethoprim, LPV/r: Lopinavir/ritonavir, SEM: Standard error of the mean

DISCUSSION

It is reported that organ weights are an essential part of toxicological and risk assessment of drugs, chemicals, and other biologicals.[14] In this study, rats treated with LPV/r, SMX/TMP, and their combination showed no significant change in cardiac weight. Changes in hematological parameters observed in rats treated with SMX/TMP are in agreement with some observations.[15,16] Mallolas et al.,[17] in their study reported some cases of LPV/r associated impairments in hematological function which disagrees with observations in this study.[18] Concurrent use of these agents may not have any deleterious effects on hematologic parameters as observed in this study. Decrease in hemoglobin level observed with respect to SMX/TMP might be due to increased catabolism and degradation of hemoglobin. Observed decrease in hemoglobin content can be related with decrease in RBC level which may precipitate anemic condition.[19]

Enzymatic antioxidants such as catalase, $GSHP_X$, and SOD protect organs from drug-induced oxidative stress and decreases in their levels connote organ injury.[20] In this study, observed decrease in enzymatic antioxidants levels in animals treated with LPV/r is consistent with some reported observations.[21]

Some scholars have reported antibiotics induced decrease in cardiac $GSHP_X$ and SOD level which is consistent with the observation in SMX/TMP treated animals in this study.[12,22]

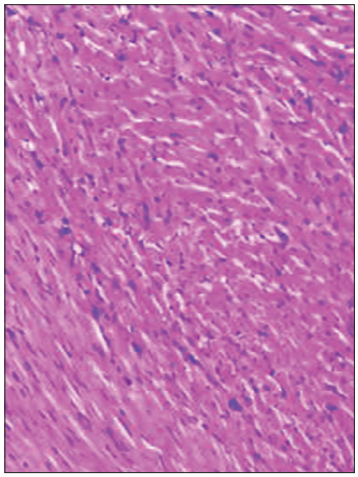

Figure 1: This is the photomicrograph of hematoxylin and eosin section of the heart of control rats treated with 1% ethanol showing normal cardiac myocyte and interstitium (×400).

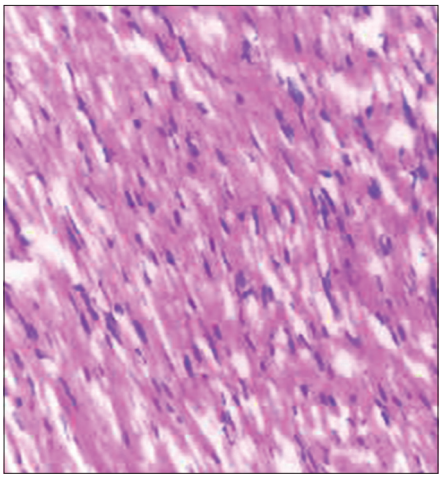

Figure 2: This is the photomicrograph of the hematoxylin and eosin section stained of the heart of rats treated with 22.8/5.8 mg/kg of lopinavir/ritonavir for 8 weeks showing normal cardiac myocyte with patchy collection of mononuclear inflammatory cells infiltration of the interstitium (×400).

The inability of these agents to induced synergistic decrease in enzymatic antioxidants level when co-administered may connotes lack of toxicity on the heart.

Increased in cardiac MDA levels in rats treated with SMX/TMP observed in this work is in resonance with some reports.[23,24] Increase in cardiac MDA level observed in animals treated with LPV/r is consistent with some reported observations.[25] Elevation in cardiac MDA level observed with respect to treatment with these single agents could be attributed to cardiac injury induced by oxidative stress.[26,27] No synergistic elevation in cardiac MDA level was observed when these agents were co-administered which shows concurrent use may not be deleterious to cardiac function.

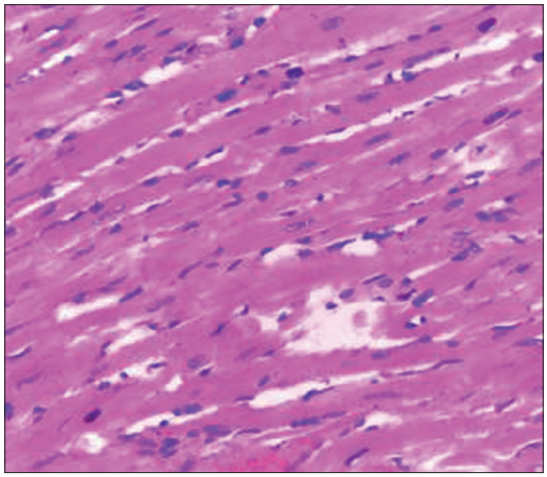

Figure 3: This is the photomicrograph of the hematoxylin and eosin section stained of the heart of rats treated with 22.4/4.6 mg/kg of sulfamethoxazole/ trimethoprim for 8 weeks showing normal cardiac myocyte with scanty mononuclear inflammatory cells infiltration of the interstitium (×400).

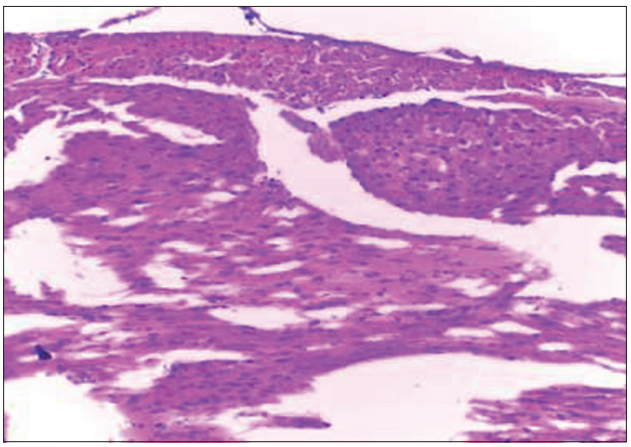

Figure 4: This is photomicrograph of the hematoxylin and eosin section stained of the heart of rats treated with lopinavir/ritonavir and sulfamethoxazole/ trimethoprim for 8 weeks showing normal cardiac myocyte with scanty mononuclear inflammatory cells infiltration of the interstitium (×400).

Mononuclear inflammatory cells infiltration of the interstitium observed in this study in SMX/TMP treated animals have also been reported.[28] Tanuma et al. 2003,[29] reported a case of cardiac histopathological changes induced by antiretroviral drugs which is in agreement with the mononuclear inflammatory cells infiltration of the interstitium observed in this study in animals treated with LPV/r.

Evidence indicates that oxidative stress and cardiac inflammation are involved in drug-induced cardiotoxicity. Earlier studies have illustrated that drugs can cause inflammatory reactions in the vicinity of heart tissues, induced inflammatory effects in the vasculature, the myocardium and elevated the levels of proinflammatory

cytokines.[30] This supports the report that SMX/TMP is associated with the production of reactive metabolites, reactive oxygen species processing, and binding of reactive metabolites to proteins/DNA, resulting in inflammation, cell damage, and neo-antigen formation.[31] Furthermore, previous studies suggested that protease inhibitors are associated with endoplasmic reticulum stress response which could stimulate activation of unfolded protein response. This mechanism has been reported to be an important cellular signaling pathway of protease inhibitors induced cardio-metabolic syndromes.[32,33]

CONCLUSION

In this study, the co-administration of SMX/TMP and LPV/r did not produce any significant synergistic effects on all the evaluated parameters; hence, the concurrent use of these agents in the management of HIV and co-infection may be safe on cardiac function and structure.

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REFERENCES

1. UNAIDS. UNAIDS Report on the Global AIDS Epidemic. Geneva: Joint United Nations Programme on HIV/AIDS; 2011.
2. Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: A review. Ther Clin Risk Manag. 2008;4(5):1023-33.
3. Teply R, Goodman M, Destache C. Lopinavir/ritonavir. A review for 2011 clinical medicine insight. Therapeutics. 2011;3(3):93-102.
4. Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of co-trimoxazole for treatment and prevention of *Plasmodium falciparum* malaria: A systematic review. PLoS One. 2013;8(2):e56916.
5. World Health Organization. Guidelines on Co-Trimoxazole Prophylaxis for HIV-Related Infections among Children, Adolescents and Adults: recommendations for a Public Health Approach. Geneva: World Health Organization Department of HIV/AIDS; 2006.
6. Letsas KP, Efremidis M, Filippatos GS, Sideris AM. Drug-induced long QT syndrome. Hellenic J Cardiol. 2007;48(5):296-9.
7. Mondy KE, Gottdiener J, Overton ET, Henry K, Bush T, Conley L, et al. High prevalence of echocardiographic abnormalities among HIV-infected persons in the era of highly active antiretroviral therapy. Clin Infect Dis. 2011;52(3):378-86.
8. Becker AC, Sliwa K, Stewart S, Libhaber E, Essop AR, Zambakides CA, et al. Acute coronary syndromes in treatment-naïve black South Africans with human immunodeficiency virus infection. J Interv Cardiol. 2010;23(1):70-7.
9. Suthar AB, Granich R, Mermin J, Van Rie A. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta-analysis. Bull World Health Organ. 2012;90(2):128C-38.
10. Kielhofner MA. Trimethoprim- sulfamethoxazole: pharmacokinetics, clinical uses, and adverse reactions. Tex Heart Inst J. 1990;17(2):86-93.
11. Hull MW, Harris M, Lima V, Guillemi S, Harrigan PR, Montaner JS. Lopinavir/ritonavir pharmacokinetics in a substitution of high-dose soft-gelatin capsule to tablet formulation. J Clin Pharmacol. 2009;49(2):155-61.
12. Reyskens KM, Fisher TL, Schisler JC, O'Connor WG, Rogers AB, Willis MS, et al. Cardio-metabolic effects of HIV protease inhibitors (lopinavir/ritonavir). PLoS One. 2013 30;8:e73347.
13. Ahmed AM, Hassanein KMA. Cardioprotective effects of nigella sativa oil on lead induced cardiology; antiinflammatory and antioxidant mechanism. J Physiol Pathol. 2013;4(5):72-80.
14. Michael B, Yano B, Sellers RS, Perry R, Morton D, Roome N, et al. Evaluation of organ weights for rodent and non-rodent toxicity studies: a review of regulatory guidelines and a survey of current practices. Toxicol Pathol. 2007;35(5):742-50.
15. Bapani S, Epperla N, Kasirye Y, Mercier R, Garcia-Montilla R. ADAMTS13 deficiency and thrombotic thrombocytopenic purpura associated with trimethoprim-sulfamethoxazole. Clin Med Res. 2013;11(2):86-90.
16. Lee JS, Owshalimpur D, Schofield C. Trimethoprim/sulfamethoxazole induced multiorgan dysfunction. BMJ Case Rep. 2012;2012.
17. Mallolas J, Pich J, Peñaranda M, Domingo P, Knobel H, Pedrol E, et al. Induction therapy with trizivir plus efavirenz or lopinavir/ritonavir followed by trizivir alone in naive HIV-1-infected adults. AIDS. 2008;22(3):377-84.
18. Hasson H, Galli L, Gallotta G, Neri V, Blanc P, D'Annunzio M, et al. HAART simplification with lopinavir/ritonavir monotherapy in HIV/HCV co-infected patients starting anti-HCV treatment: a randomised pilot study (KaMon study). New Microbiol. 2012;35(4):469-74.
19. Guptar R, Anwar F, Khosa RL. The effect of sulfamethoxazole and selenium on antioxidant defence system in blood of rats treated with DEN. J Pharm Biol Sci. 2013;8(6):29-37.
20. Izunya AM, Nwaopara AO, Anyanwu LC, Odike MAC, Oaikhena GA, Bankole JK, et al. Effect of chronic oral administration of chloroquine on the histology of the heart in Wistar rats. Biol Med. 2011;3(4):01-6.
21. Zhang SH, Wang WQ, Wang JL. Protective effect of tetrahydroxystilbene glucoside on cardiotoxicity induced by doxorubicin *in vitro* and *in vivo*. Acta Pharmacol Sin. 2009;30(11):1479-87.
22. El-Boghdady NA. Increased cardiac endothelin-1 and nitric oxide in adriamycin-induced acute cardiotoxicity: protective effect of Ginkgo biloba extract. Indian J Biochem Biophys. 2013;50(3):202-9.
23. Mohammad B, Aharis NR, Yousif MG, Alkefae Z, Hadi NR. Effect of caffeic acid on doxorubicin induced cardiotoxicity in rats. AJBM. 2013;1(2):23-37.

24. Swamy AV, Gulliaya S, Thippeswamy A, Koti BC, Manjula DV. Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian J Pharmacol. 2012;44(1):73-7.
25. Adaramoye OA, Adesanoye OA, Adewumi OM, Akanni O. Studies on the toxicological effect of nevirapine, an antiretroviral drug, on the liver, kidney and testis of male Wistar rats. Hum Exp Toxicol. 2012;31(7):676-85.
26. Ogbuehi I, Adikwu E, Oputiri D. Effect of *Acalypha wilkesiana* MuellArg leaf extract on the oxidative indices, liver enzymes and liver integrity of rats infected with *Plasmodium berghei.* Br J Pharmacol Toxicol. 2014;5(2):68-74.
27. Elias A, Ogbuehi I, Edikpo NJ, Oputiri D, Oru-Bo PS. Tenofovir renal toxicity: evaluation of cohorts and clinical studies – Part 2. Pharmacol Pharm. 2014;5:97-111.
28. Sari FR, Aroza W, Watanabe K, Harima M, Veeravedu PT. Carvedilol attenuates inflammatory-mediated cardiotoxicity in daunorubicin-induced rats. Pharmaceuticals. 2011; 4(3):551-6.
29. Tanuma J, Ishizaki A, Gatanaga H, Kikuchi Y, Kimura S. Dilated cardiomyopathy in an adult human immunodeficiency virus type 1 – Positive patient treated with a zidovudine-containing antiretroviral regime. *Clin Infect Dis.* 2003;37(7):e109-11.
30. Mercuro G, Cadeddu C, Piras A, Dessì M, Madeddu C, Deidda M, et al. Early epirubicin-induced myocardial dysfunction revealed by serial tissue Doppler echocardiography: correlation with inflammatory and oxidative stress markers. Oncologist. 2007;12(9):1124-33.
31. Wang D, Curtis A, Papp AC, Koletar SL, Para MF. Polymorphism in glutamate cysteine ligase catalytic subunit (GCLC) is associated with sulfamethoxazole-induced hypersensitivity in HIV/AIDS patients. BMC Med Genomics. 2012 23;5:32.
32. Scull CM, Tabas I. Mechanisms of ER stress-induced apoptosis in atherosclerosis. Arterioscler Thromb Vasc Biol. 2011;31(12):2792-7.
33. Ozcan L, Tabas I. Role of endoplasmic reticulum stress in metabolic disease and other disorders. Annu Rev Med. 2012;63:317-28.

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