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Full Length Research Paper

In vivo analyses of the effects of co-administration of *Carica papaya* leaf extract with ciprofloxacin

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Carica papaya **leaf extract is an antisickling phytomedicine reported to inhibit the polymerisation of defective hemoglobin S molecules in sickle cell individuals. In this research, the biochemical effects of ciprofloxacin, a wide spectrum antibiotic, co-administered with** ***C. papaya*** **leaf extract was studied. Using standard methods for biochemical, hematological and antioxidant assays, results showed that ciprofloxacin administration gave rise to increase in oxidative stress markers, which lowered considerably during co-administration with** ***C. papaya*** **leaf extract, whereas administration of** ***C. papaya*** **leaf extract alone did not produce any of such side-effects. Co-administration of both drugs was found to have no deleterious effects on body organs and erythrocytes. This suggests that the presence of** ***C. papaya*** **leaf extract had a palliative effect on the free radicals produced during ciprofloxacin administration.**

Key words: *Carica papaya*, ciprofloxacin, antisickling agents, antibiotics, antioxidants.

INTRODUCTION

Sickle cell disorder is a genetic disorder involving abnormal hemoglobin in red blood cells. Orthodox medication, hydroxyurea is administered to aid in stimulation of fetal hemoglobin to stabilize the individual. Herbal therapies have also been used to help prevent the frequent sickling crisis phenomenon experienced during oxidative stress. Though the aberrant gene is not corrected, the individual can live a stable life if well managed. Sickle cell individuals often suffer excruciating pain during crisis and various herbal therapies with analgesic and antiinflammatory activities could be used to alleviate the pain and inflammation (Nasri et al., 2012). Among the herbal therapy employed in the management of sickle cell disease is *Carica papaya*. *C. papaya* (pawpaw) is a member of the small family "Caricaceae" allied to the "Passifloraceae". It is regarded as a wholesome fruit, the daily requirements of some of the essential nutrients like proteins, minerals and vitamins can be met from this fruit. *C. papaya* leaf extract was reported to contain alkaloids, flavonoids, glycosides, cardiac glycosides, tannins, saponins and anthraquinones and proximate analysis of the plants showed that all the macronutrients were present (Imaga et al., 2009). Thomas and Ajani (1987) established both antisickling and reversal of sickling activities of an extract of unripe pawpaw with the aqueous extract of unripe *C. papaya* documented to possess antisickling properties. Oduola et al. (2006) and Reiser et al. (1992) confirmed this property and established the minimum concentration of the aqueous extract of unripe *C. papaya* fruit that achieved maximum antisickling to be 1 g/ml in physiological saline. Solvent partitioning further revealed that the antisickling agent also resides in the ethyl acetate fraction of the extract (Reiser et al., 1992). Also, pre-treatment of

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sickle cell suspensions with *C. papaya* leaf extract inhibited the formation of sickle cells under severe hypoxia, with only 0 to 2% sickle cells at 40 min incubation time when compared with untreated sickle cell suspensions which had over 60% sickle cells when compared with the controls (Imaga et al., 2009).

Ciprofloxacin is a second-generation fluoroquinolone antibacterial agent. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops DNA and protein synthesis. It has limited use in veterinary medicine. It can alter and be altered by the metabolism and effects of other drugs, resulting in some significant drug-drug interactions that may affect the musculoskeletal, central nervous, renal, and other systems. Ciprofloxacin interacts with other drugs, herbal and natural supplements, and thyroid medications (Frost et al., 1992*)*.

In this research, we studied the drug-drug interaction of ciprofloxacin co-administered with *C. papaya* leaf extract from a biochemical point of view, bearing in mind that sickle cell individuals, who are susceptible to infections, may at one point in their lives need to take an antibiotic drug to treat any onset of infection while in treatment with *C. papaya* leaf extract. Many medicinal plants have been reported to possess phytotoxic properties, enabling them act as anti-fungal agents (Alam et al., 2012) and others have been reported to possess antibacterial, antitumour, antidiabetic, antiviral effects. It is therefore necessary to evaluate any possible interactions the herbal drugs may have when co-administered with orthodox medications and thus regulate its usage, especially as multidrug-resistant (MDR) bacterial pathogens has become a worldwide health hazard (Asgarpanah and Ramezanloo, 2012).

The aim of this study is to evaluate the biochemical effect of the co-administration of ciprofloxacin and *C. papaya* leaf extract *in vivo* using standard methods of assay for liver function, kidney function, hematological parameters and antioxidant enzymes in normal rat models.

MATERIALS AND METHODS

All experimentation was carried out in accordance with the International, National and Institutional rules concerning animal experiments, clinical studies and biodiversity rights.

Chemicals and drugs

Drugs (Ciprogem ®Ciprofloxacin 500 mg/Tablet) were obtained from a reputable pharmacy store in Lagos, Nigeria. All chemicals used were of analytical grade, obtained from the Sigma chemical company, USA and used without further purification.

Collection of plant

Dried leaves of *C. papaya* were collected from a reputable herbal market in Mushin, Lagos State, Nigeria and blended into powdered form using a mechanical blender after authentication by a Botanist at the University of Lagos, Akoka, Nigeria.

Aqueous extraction of plant

Powdered *C. papaya* leaves (400 g) was weighed into a clean bowl and 2.5 L of hot distilled water was poured and covered. This was allowed to infuse for 3 h and then cooled at room temperature. The mixture was sieved with a clean muslin cloth. The resultant aqueous extract was stored in freeze-dried form and kept in the refrigerator at 4°C till use.

Animals

White albino Sprague-Dawley rats (180 to 210 g mean ± standard deviation (STD) weight) from the Laboratory Animal Center of the Nigerian Institute of Research (NIMR), Yaba, Lagos, Nigeria were used for the study. The animals were kept in a well-ventilated animal house at the annex of the Laboratory Animal Center of the College of Medicine, University of Lagos, and were acclimatized for 14 days before commencement of the study. They were fed each day with standard rabbit chow (Pfizer Feeds, Ibadan, Nigeria Plc.) and water *ad libitum.*

Drug administration

The rats were grouped into three categories A, B and C. Groups A and B were given varying doses of ciprofloxacin and *C. papaya* leaf extract , respectively as outlined subsequently.

Group A_1, A_2, A_3 with 4 rats in each according to their body weight, were dosed orally with different concentrations of only ciprofloxacin according to their body weight for a period of 5 days. A_1 was given the underdose (3.61 mg/kg), A_2 was given the normal dose (7.22 mg/kg) and A_3 was given the overdose of 14.35 mg ciprofloxacin/kg of rat.

Group B_1, B_2, B_3 with 4 rats in each were dosed orally with 0.28 mg of *C. papaya* leaf extract/kg body weight and then immediately followed by a single dose of ciprofloxacin per body weight of different concentrations (as outlined for Group A rats) for a period of 5 days: B_1 were given *C. papaya* leaf extract with underdose of ciprofloxacin, B_2 were given *C. papaya* leaf extract and normal dose of ciprofloxacin, B_3 were given *C. papaya* leaf extract and overdose of ciprofloxacin.

Group C with 4 rats were orally administered distilled water (1 ml/body weight) only for a period of 5 days.

Blood collection

At the end of the 5 days, the rats were euthanized by cervical dislocation and blood samples collected. Standard biochemical, hematological and antioxidant evaluations were then carried out on the collected blood samples. For the hematological studies EDTA bottles were used to collect the blood samples. For the antioxidant assay, liver function test and kidney function test heparin bottles were used for the blood collection.

Biochemical analysis

All biochemical analysis (test for albumin, tests for liver function, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), tests for kidney function, creatinine, total bilirubin, urea, total lipid tests, triglyceride (TG), cholesterol) were done using the Roche/Hitachi 902 automated analyzer.

Determination of total protein

This was determined using biuret method (Gonall et al., 1949). Absorbance was read at 540 nm. The concentration of protein was calculated using optical density for standard × concentration of standard.

Antioxidant assay

The antioxidant enzymes activity was determined spectrometrically as follows.

Determination of superoxide dismutase (SOD) activity

SOD activity was determined as described by Sun and Zigma (1978). The reaction mixture (3 ml) contained 2.95 ml 0.05 M sodium carbonate buffer pH 10.2, 0.02 ml of the serum and 0.03 ml of epinephrine in 0.005 N HCl was used to initiate the reaction. The reference cuvette contained 2.95 ml buffer, 0.03 ml of substrate (epinephrine) and 0.02 ml of water. Enzyme activity was calculated by measuring the change in absorbance at 480 nm for 5 min.

Determination of catalase

Serum catalase activity was determined according to the method of Beers and Sizer as described by Usoh et al. (2005) by measuring the decrease in absorbance at 240 nm due to the decomposition of H_2O_2 in ultraviolet (UV) recording spectrophotometer. The reaction mixture (3 ml) contained 0.1 ml of serum in phosphate buffer (50 mM, pH 7.0) and 2.9 of 30 mM H_2O_2 in phosphate buffer pH 7.0. An extinction coefficient for H_2O_2 at 240 nm of 40.0 $M^{-1}cm^{-1}$ (Aebi1984) was used for the calculation; the specific activity of catalase was expressed as moles of H_2O_2 reduced per min mg protein.

Reduced glutathione (GSH) determination

The reduced GSH content of tissue as non-protein sulphydryls was estimated according to the method described by Sedlak and Lindsay (1960).

Lipid peroxidation (MDA)

Malondialdehyde (MDA), an index of lipid peroxidation was determined using the method of Bluege and Ausl (1978). MDA was calculated using the molar extinction coefficient for malondialdehyde-thiobarbituric acid (MDATBA)-complex of $1.56 \times 10^5\ M^{-1}cm^{-1}$.

Hematological analysis

All hematological analyses (white blood cells, red blood cell, hemoglobin, hemoglobin count, platelet, lymphocyte, neutrophils (%), lymphocytes (%) neutrophils absolute) were performed using standard procedures with the Sysmex Automated Analyzer (Model:KN-21N).

Statistical analysis

Data from the various studies are presented as mean ± standard error of mean (SEM). Students' t-test and Satterwhaites' method of one way analysis of variance were used to compare mean values between groups. $P<0.05$ was taken to indicate a statistical significance.

RESULTS

Table 1 shows that the orally administered papaya leaf extract and ciprofloxacin manifest some effects on liver function when administered separately and together. Ciprofloxacin when administered alone increased the activities of the liver enzymes (AST, ALT and ALP) and the level of bilirubin and albumin progressively from the underdose group (A_1) to the overdose group (A_3). This shows that the effects could be dose dependent. There is a statistically significant increase at $P<0.05$. Also, it was observed that Group B_1 which was administered under dose of ciprofloxacin and normal dose of *C. papaya* leaf extract had slightly elevated liver enzyme activities when compared with Group B_3 which was given overdose of ciprofloxacin and normal dose of the antisickling plant extract. This observation is contrary to the dose dependent effect exerted by ciprofloxacin on the liver enzyme.

The effect of the combined therapy on serum triglyceride and cholesterol is presented in Table 2. The results obtained indicates a slight disruption of lipid metabolism when ciprofloxacin was administered alone resulting in a progressive increase in the level of triglyceride and cholesterol from the underdose group to the overdose group, when compared with the control at $P<0.05$. On the contrary, the elevated levels of triglyceride and cholesterol were suppressed when combined therapy was adopted.

Table 3 shows the effects of ciprofloxacin administered alone and in combination with the antisickling plant elicit on kidney function through their effects on serum urea and creatinine level. The underdose, normal dose and overdose of this drug as observed in groups A_1, A_2, and A_3, respectively, caused increase in serum creatinine and urea level, when compared with the control at $P<0.05$. Group A_3 is the most affected which showed marked elevated level of creatinine (295.67 ± 3.73) and slightly elevated level of urea (9.93 ± 0.26) when compared with the control (52.45 ± 13.33 and 4.5 ± 0.17, respectively).

Table 4 presents the result of antioxidant assay. The most affected being the overdose group A3. On the contrary, there was a slight decrease in the antioxidant enzyme activities when ciprofloxacin was co-administered with *C. papaya* in the underdose (B_1), normal dose (B_2) and overdose group (B_3).

The result of hematological assay presented in Table 5 reveals that there was progressive increase in the level of red blood cells, hematocrit, platelets, lymphocyte and neutrophils from the underdose group (A_1) to the overdose group (A_3) when compared with the control at $P<0.05$. Ciprofloxacin in combination with *C. papaya* (B_1, B_2, B_3) shows a slight decrease in the level of these blood cells when compared with the group given ciprofloxacin alone (A_1, A_2, A_3).

Table 1. Effects of co-administration of ciprofloxacin and *C. papaya* leaf extract on liver function parameters.

Parameter	Alanine amino transferase (U/l) (Mean ± SEM)	Alkaline phosphatise (U/l) (Mean ± SEM)	Aspartate amino transferase (U/l) (Mean ± SEM)
A_1	51.93* ± 3.19	204.28* ± 31.68	205.37* ± 8.52
A_2	60.73* ± 2.03	224.88* ± 31.19	264.87* ± 8.55
A_3	73.067* ± 9.44	274.17* ± 22.10	357.07* ± 61.69
B_1	64.10 ± 16.07	256.36 ± 17.10	239.4 ± 21.04
B_2	42.60 ± 8.12	132.92 ± 21.46	226.4 ± 18.34
B_3	43.36 ± 4.98	121.31 ± 13.94	207.96 ± 19.21
Control	33.57 ± 2.63	97.72 ±0.70	130.00 ± 10.00

*Significant difference at P<0.05 in the concentration level of alanine amino transferase (ALT), alkaline phosphatase (ALP), and aspartate amino transferase (AST).

Table 2. Lipid and protein profile of rats administered *C. papaya* leaf extract in combination with ciprofloxacin.

Parameter	Triglyceride (mg/ml)	Cholesterol (mg/ml)	Total bilirubin (mg/ml)	Albumin (mg/ml)	Total protein (mg/ml)
A_1	0.45 ± 0.04	1.56 ± 0.32	0.24 ± 0.06	19.50* ± 3.21	142.13* ± 7.97
A_2	1.62* ± 0.12	3.35* ± 0.13	0.40* ± 0.02	35.97 ± 9.83	178.93* ± 1.16
A_3	3.07* ± 0.22	6.47* ± 0.47	1.33* ± 0.3	77.90* ± 3.97	240.96* ± 10.75
B_1	0.67 ± 0.003	2.13 ± 0.17	0.26 ± 0.03	30.2667 ± 2.68	106.66 ± 14.66
B_2	0.75 ± 0.079	2.31 ± 0.21	0.31 ± 0.02	35.80 ± 0.76	120.36 ± 11.28
B_3	0.67 ± 0.14	2.67 ± 0.04	0.2800 ± 0.03	34.73 ± 1.32	133.73 ± 9.43
Control	0.54 ± 0.08	1.82 ± 0.11	0.26 ± 0.01	36.13 ± 0.64	99.47 ± 3.21

Values are Mean ± SEM. *Significant difference at P<0.05 in the concentration level of triglyceride, cholesterol, total bilirubin (T.BIL), albumin (ALB), and total protein (TP).

Table 3. Effect of co-administration of *C. papaya* extract and ciprofloxacin on kidney function parameters.

Parameter	Creatinine (mg/ml) (Mean ± SEM)	Urea (mg/ml) (Mean ± SEM)
A_1	74.08 ± 2.26	5.57 ± 1.11
A_2	83.36 ± 10.25	7.43* ± 0.52
A_3	70.62 ± 5.78	9.93* ± 0.26
B_1	68.34 ± 12.10	6.53 ± 0.37
B_2	65.08 ± 2.93	6.00 ± 0.40
B_3	66.70 ± 3.60	5.80 ± 0.55
Control	52.45 ± 13.66	4.50 ± 0.17

*Significant difference at P<0.05 in the concentration level of creatinine and urea.

DISCUSSION

A variety of antisickling plants are used by Nigerians in the management of sickle cell disease. Any of these medicinal plants may at one time or the other be administered alone or in combination with other orthodox or herbal drugs. In the management of microbial infection in the sickle cell patient, antisickling plant extracts may be co-administered with antimicrobial drugs such as ciprofloxacin. In this research, aqueous extract of *C. papaya* leaf was administered with ciprofloxacin in albino rats and the effect on liver function (Serum ASP, ALT, albumin, total protein, ALP and total bilirubin), kidney function (urea and creatinine), lipid profile (cholesterol and triglyceride), blood cells (red blood cell, hemoglobin, hematocrit, lymphocyte (%), lymphocyte absolute, neutrophils (%), neutrophils absolute) and antioxidant enzymes were evaluated.

The observed dose-dependent increase effect of ciprofloxacin on liver marker enzymes, is in conformity with previous reports on the drug (Snider, 2002). This signifies that overdose of ciprofloxacin could result to acute liver damage, because the observed elevated level of these liver marker enzymes is an index used in checking for liver damage. Also, it could result to jaundice due to the increased level of total bilirubin. However, in combination with the antisickling plant (*C. papaya* leaf extract), there was decrease in the level of the activities of these enzymes (in groups B_1, B_2 and B_3) when compared with that of ciprofloxacin alone (A_1, A_2 and A_3) at P<0.05. This observed decrease could be attributed to the therapeutic effect of *C. papaya* leaf extract on the liver as previously

Table 4. Effect of the co-administration of ciprofloxacin and ciprofloxacin on antioxidant enzymes.

Antioxidant enzyme	GSH (µm/mg) (Mean ± SEM)	CAT (µm/mg) (Mean ± SEM)	SOD (µm/mg) (Mean ± SEM)	MDA (µm/mg) (Mean ± SEM)	TP (µm/mg) (Mean ± SEM)
A_1	1.87 ± 0.059	112.09* ± 1.82	24.34* ± 0.43	0.10 ± 0.001	31.82 ± 0.83
A_2	1.96 ± 0 .03	111.56* ± 1.29	24.73* ± 0.26	0.079 ± 0.007	32.01 ± 0.28
A_3	2.65* ± 0.64	356.03* ± 5.44	55.42* ± 1.17	0.77* ± 0.09	31.63 ± 0.94
B_1	1.88 ± 0.040	218.74 ± 7.58	49.24 ± 0.19	0.058 ± 0.003	32.32 ± 0.84
B_2	1.17* ± 0.40	73.34* ± 4.20	42.45 ± 5.72	0.54* ± 0.000027	40.56* ± 0.60
B_3	1.37 ± 0.12	114.43* ± 12.31	40.84 ± 4.10	0.61 ± 0.0089	38.78 ± 3.34
Control	2.005 ± 0.0101	237.74 ± 0.243	51.57 ± 0.56	0.087 ± 0.0088	30.77 ± 0.16

*Significant difference at P<0.05 in the concentration level of catalase (CAT), glutathione (GSH), sodium dismutase (SOD), total protein (TP) and malondialdehyde (MDA).

reported (Adeneye et al., 2009). Ciprofloxacin chelates with the metals present in the *C. papaya* and as such not readily available to cause the increase observed where ciprofloxacin was administered alone (Li et al., 1994; Yukinori et al., 1996). It could also be attributed to possible drug-drug interaction that could occur between the medications causing reduction in the amount of ciprofloxacin which is eventually absorbed by the body from the gastro-intestinal tract.

The effect of ciprofloxacin on lipid metabolism, with increased the levels of triglyceride and cholesterol is in conformity with previous reports (Snider, 2002). This indicates that overdose of ciprofloxacin could increase the possibility of patients having possible cardiovascular disease due to the increase level of cholesterol. Elevated levels of triglyceride and cholesterol were suppressed when combined therapy was adopted, showing that *C. papaya* may have cholesterol and triglyceride lowering effect as previously reported (Powell et al., 2008; Kamal et al., 2009).

Ciprofloxacin administered alone and in combination with the antisickling plant elicited some effects on kidney function through their effects on serum urea and creatinine level, which are an index for checking kidney function. This affirms that overdose of ciprofloxacin could cause renal dysfunction and lead to kidney damage as reported earlier (Başaran et al., 1993). In combination with *C. papaya*, there was great decrease in the level of creatinine and slight decrease of urea when compared with those given ciprofloxacin alone. This decrease could be as a result of the corrective effect *C. papaya* has on kidney function as reported (Adeneye et al. 2009) and/or the interaction between the two medications which causes reduction in the amount of ciprofloxacin absorbed, hence, reducing the amount of the drug available in the body to elicit its effect on kidney function.

The result of the antioxidant assay indicated that increased dosage of the antibiotic (ciprofloxacin) causes an increase in the level of these antioxidant enzymes-catalase and superoxide dismutase activities, and MDA level. This suggests that there is a progressive increase in the level of free radicals produced as drug dosage is increased. As a result, anti-oxidant enzyme's activities would increase to prevent the damaging effect of these free radicals on the body cells. The slight decrease in the antioxidant enzyme activities when ciprofloxacin was co-administered with *C. papaya* could be as a result of the antioxidative property of *C. papaya* complementing the activities of those antioxidant enzymes produced by the body as reported earlier (Marotta et al., 2007). It could also be due to interaction that occurred between these medications causing reduction in the amount of ciprofloxacin absorbed (Chan and Tak, 2002).

The progressive increase in the level of hematological parameters indicates that increasing the drug dosage could lead to elevated blood cell count as reported in literature (Snider, 2002). It is also an index of increased presence of foreign materials in the body due to the increased level of lymphocyte and neutrophils in the blood. The observed increase could be that the rats had an infection or the presence of the drug triggers their release. The slight decrease in the level of blood cells by the ciprofloxacin-*C. papaya* combination could be attributed to the effect of *C. papaya* on blood cells especially on lymphocyte and neutrophils.

This study on the effect of co-administration of *C. papaya* leaf extract and ciprofloxacin has shown that there could be an interaction between these two medications when co-administered in sickle cell patients. The observed lowering effect of the activities of AST, ALT, ALP, catalase, superoxide dismutase and the level of cholesterol, triglyceride, urea, creatinine, red cell, hemoglobin, hematocrit, lymphocyte and neutrophil count when combination therapy was administered as compared to ciprofloxacin alone proves it. Also, co-administering the herbal plant extract with ciprofloxacin has the tendency of preventing the likely side effects exhibited by patients on ciprofloxacin treatment alone. This could be as a result of the interaction that exists between the drugs causing reduction in the amount of ciprofloxacin absorbed by the body and/or the therapeutic effect of *C. papaya* leaf extract in the body.

Table 5. Effect of co-administration of *C. papaya* extract and ciprofloxacin on hematological parameters.

Test	Red blood cell (Mean ± SEM)	Hemoglobin (g/dl) (Mean ± SEM)	Hematocrit (Mean ± SEM)	Platelets (Mean ± SEM)	Lymphocyte absolute (Mean ± SEM)	Neutrophil (%) (Mean ± SEM)	Lymphocyte (%) (Mean ± SEM)	Neutrophil absolute (Mean ± SEM)
A1	6.77 ± 0.41	12.8 ± 0.55	41.87 ± 2.42	953.33 ± 71.14	7.10 ± 1.16	33.17 ± 3.91	66.50 ± 3.68	3.60 ± 0.69
A2	5.51 ± 0.84	10.60 ± 1.85	34.07 ± 5.92	602.33 ± 233.27	4.70 ± 2.23	38.23 ± 8.20	61.77 ± 8.20	2.27 ± 0.18
A3	5.08 ± 0.84	9.20 ± 1.50	30.30 ± 5.30	841.50 ± 740.50	2.50 ± 0.90	58.55 ± 1.25	41.45 ± 1.25	3.45 ± 1.15
B1	6.66 ± 0.50	11.47 ± 0.43	37.53 ± 2.12	1032.66 ± 66.78	5.60 ± 1.23	34.90 ± 1.23	65.10 ± 1.23	2.93 ± 0.55
B2	6.83 ± 0.36	12.80 ± 0.51	40.87 ± 2.65	1102.00 ± 89.72	6.27 ± 0.52	25.90 ± 2.75	74.10 ± 2.75	2.17 ± 0.15
B3	6.15 ± 0.28	12.13 ± 0.90	38.33 ± 2.64	1166.67 ± 232.74	5.47 ± 1.70	27.83 ± 13.12	72.17 ± 13.12	1.77 ± 0.74
Control	4.20 ± 0.12	6.35 ± 0.55	8.03 ± 0.12	692.80 ± 72.56	692.80 ± 72.56	3.43 ± 0.67	27.00 ± 0.72	1.33 ± 0.22

*Significant difference at P<0.05 in the concentration of level red blood cell (RBC), hemoglobin (HB), hematocrit (HCT), platelet (PLT), lymphocyte (LYMP), neutrophil (NEUT, %), lymphocyte (LYMP, %), and Neutrophil absorbance (Neut Abs).

Conclusion

From this study, ciprofloxacin administration gave rise to increase in oxidative stress markers, which lowered considerably during co-administration with *C. papaya* leaf extract, without any deleterious effects on body organs and erythrocytes. Therefore, administration of *C. papaya* leaf extract may have had a palliative effect on the free radicals produced during ciprofloxacin administration.

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