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Colchicine and Cysteine in the management of Paracetamol-induced Liver damage.

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ABSTRACT: *Colchicine has found its place in the management of liver damage with blood disease as side effects.This paper reports on the use ofColchicine and Cysteine in the management of paracetamol-induced hepatoxicity.Seventy-two experimental male albino rats were divided into 6 groups, Groupone served as Normal control and was not induced with paracetamol; the other groups (2-6) weregiven intra peritoneal injection of 640 mg/kg body weight of paracetamoland was allowed to develop hepatotoxicity for 72 hours. After 72 hrs, Groups 2-6 were treated for four weeks with water, Colchicine only (0.03), Colchicine/Cysteine (0.03/80), Colchicine /Cystine (0,03/90) and Colchicine /Cystine (0,03/100) in mg/Kg body weight of ratrespectively. Blood was collected at weekly intervals and liver markers were assayed using standard methods and reagent kits. Paracetamol caused an increase in the plasma concentration of the liver enzymes; AST, ALT, ALP, GGT, Total and Direct Bilirubin. Paraceutamol grossly induced liver damage and raised the levels of AST, ALT, ALP, GGT, Total and Direct bilirubin, for example, AST level(U/L) was increased from 10.72± 0.3 to 33. 93± 0.16 and to 37.57± 0.64 at the fourth week, for ALT (U/L) from 6.80 ±0.11to 27.10± .06 in the first week and increased to 29.10± 0.12 in the fourth week , Colchicine alone reduced these parameters essentially as the weeks increased for example, on the fourth weekALT level was reduced from 22.00 0.23 to 15.46 0.37. Colchicine and cysteine (100mg/Kg body weight) reduced it to 15.40 1.38 after the fourth week. The reduction of the liver makers was observed as the concentration of Cysteine increased from 80 to 100mg.This work shows that Colchicine at low dose of 0. 03 mg/kg body weight or in combination with Cysteine could be used to manage effectively, liver damage.*

KEYWORDS*:Colchicine, Paracetamol-induced, Cysteine, Liverdamage(Hepatotoxicity).*

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I. INTRODUCTION

Paracetamol (acetaminophen) is usually used to relieve pain and fever associated with cold, flu, viral infections or other disorders where pain or fever may occur. However, overdose can cause liver damage (Hepatoxicity), especially if alcohol is involved [1]. It is implicated in acute liver failure, hepatic necroses, renal tubular necrosis and hypyglycaemiccoma[2]. At therapeutic levels, most of the administered dose is normally metabolized by glucuronidation and sulfonation (Phase II) to produce inactive nontoxic metabolites that are easily excreted by kidney **[**3].However, a small portion is metabolized by oxidation (Phase I) through CYP2E1, to N-acetyl-p-benzoquinoneimine (NAPQI), a highly toxic and reactive metabolite that depletes glutathione (GSH) and covalently binds to mitochondrial proteins which is efficiently detoxified by conjugation with GSH. However, at toxic doses, GSH is depleted by the conjugation reaction, and NAPQI covalently binds to proteins to produce reactive oxygen species (ROS) which induce oxidative stress leading to lipid peroxidation, mitochondrial dysfunction, disruption of calcium, nitric oxide homeostasis, and finally, cell death by apoptosis and necrosis. [4,5] This is a leading cause of liver failure in the United States[5].

Colchicine was officially approved for use in the United States in 1961 and it is still widely used. It has always been reported to be safe, but could be toxic at a prolonged use of more than seven days and at higher dose. It has antifibrotic and anti-inflammatory effects and hence proposed as a treatment for liver disease. Long-term colchicine treatment in patients with hepatic fibrosis appears to exert an anti-inflammatory, anti-fibrotic and immunomodulatory effect [6]. It demonstrates the greatest anti-mitotic activity on rapidly dividing tissues, so toxicity initially presents with gastrointestinal (GI) symptoms, but patients can develop bone marrow hypoplasia, cardiac arrhythmias, cardiovascular collapse, respiratory distress, and shock, which can lead to multisystem organ failure.[6] The report stated that its association with hepatotoxicity was with cases of overdose in which the hepatic injury has been self-limited and overshadowed by the other toxicities. It is also implicated to prevent the development of hepatocellular carcinoma in virally-related liver cirrhosis Colchicine is

an effective and safe antifibrotic drug for long-term treatment of chronic liver disease in which fibrosis progresses towards cirrhosis. It was shown not only to arrest, but even to reverse this process [7].

Protection against paracetamol-induced toxicity by Cysteine has been reported as measured by the prevention of mortality, fall in hepatic non-protein sulphydryls (NPSH) and the decrease in elevation of serum transaminases[8]. N-acetylcysteine (NAC) is the treatment of choice for acetaminophen poisoning; standard 72-h oral or 21-h intravenous protocols are most frequently used[9]. The administration of N-acetylcysteine was also reported to partly restored enzyme activities[10].

Antioxidants play very important roles in reducing the hepatoxicity of paracetamol[4,11] N- acetylcystein (NAC) are protective against AA toxicity in mice[12]. This has been shown by means of histological examination, analysis of serum parameters and biochemical evaluation of collagen content [13].

II. MATERIALS AND METHODS

Animals: Seventy- two male Wistar albino rats weighing 120g-290g and about 6-8 weeks old were obtained from the department of Veterinary Science, University of Nigeria, Nsukka and kept in cages in the animal house of Madonna University, Elele Campus, where the research work was done. Colchicine , cysteine, and paraceutamol were purchased fromQauli-kems, Jonkins Chemicals and Emzor Pharmacy respectively . The animals were treated according to the ethical guidelines of the University; They were kept in well ventilated room with ambient temp, with water and food ad libitum.

Animal Treatment and Dosage of Drug Administered

The 72 experimental rats were divided into six groups of 12 rats each. Group one served as Normal control, received normal feed (palletized Guinea Grower's mash from Bendel Feed and Flour mill Limited, Nigeria), water and was not induced with paracetamol, nor treated with Colchicine and cysteine. The other groups (2-6) were given intra peritoneal injection of 640 mg/kg body weight of paracetamol and was allowed to develop hepatotoxicity for 72 hours. After 72 hrs, Groups 2-6 were treated for four weeks with water, Colchicine only (0.03), Colchicine/Cysteine (0.03/80), Colchicine /Cystine (0,03/90) and Colchicine /Cystine (0,03/100) in mg/Kg body weight of rat respectively

Collection of Blood samples

The rats were sacrificed painlessly under chloroform anesthesia. Blood was collected at weekly intervals by cardiac puncture, centrifuged at 3000rpm for 10minutes and serum was collected for further analysis.

Determination of Liver Markers

The serum activities of the liver makers were determined by spectrophotometric methods of Reitman and Frankel [14] for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), GSCC (15) for Alkaline phosphatase (ALP), Jendrassik and Grof [16] for direct and total bilirubin, and Szasz method [17] for gama-glutamyltransferase.

Statistical Analysis

The data obtained were expressed as mean + SEM. The significance of difference among the various treated groups and control group were analyzed by means of one-way analysis of variance ANOVA followed by Dunnett's multiple comparison test using Graphat instant Software(San Diego, CA.USA). The level of significance was set at $p<0.05$.

III. RESULTS AND DISCUSSION

Colchicine overdose and long time effect has been a burden as a result of multi-organ failure including liver damage. [18-19]. Overdose of colchicine (30 mg) lead to bilirubin level of bilirubin 1.7 mg/dL, AST 152 U/L with normal ALP [20], Other cases 30 mg of colchicine led to rapid development of fever, diarrhea, vomiting, dehydration and hypotension with renal failure, acidosis, septicemia, and liver test abnormalities of bilirubin 0.7 rising to 6.6 mg/d, AST 58 to 333 U/L, ALP 91 to 667 U/L. [21], 2.4 mg of colchicine rapidly leads to very high bilirubin, AST 481 U/L, ALP 595 U/L [22].

Effects of Colchicine, Cysteine on Aspartate Transferase Level (U/L) in Paracetamol–induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

Table 1 show that the normal AST level was between 10.72 +.30 to 11.15+ .034 from the first to the last week which did not show any significant change. Paracetamol -induced liver disease significantly ($p<,0.05$) raised AST level after four days and raised the level from 10.72+ .30 to 33.90 +3.16 in the 1st week to 37,56+ .63 U/L(Mean +SEM) in the fourth week . Colchicine decreased the AST level from 33.90 +3.16 to 30.18 +0.05 after 1st week and to 28.56 +0.199 after 4th week. When colchicine and cysteine(100mg/kg body weight) were

given together, AST level was significantly decreased to 27.58 +0 .81 in the first week and to 24. 73 +.039 in the fourth week. Colchicine decreased the AST level from 33.90 +3.16 to 30.18 +0.05 after 1st week and to 28.56 +0.199 after 4th week. When colchicine and cysteine(100mg/kg body weight) were given together, AST level was significantly decreased to 27.58 +0 .81 in the first week and to 24. 73 +.039 in the fourth week. This is attributed to the to the ability of the antioxidant supplement to balance off free radicals generated hence preventing peroxidation of the lipid components of the cell membrane. Disruption of membrane integrity is a common causative factor attributed to increase release or leakage of cellular contents [23].This finding is was consistent with the reports of Li et al. [24] .

Effects of Colchicine, Cysteine on Alanine TransferaseLevel(U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

Table 2 shows the normal ALT level was between 6.8+ .115 and 6.5 +0.34 from the first to the last week which did not show any significant change. Paracetamol -induced liver disease significantly (p<,0.05) raised ALT level after four days and raised the level from 6.8+ .115 to 27.1 +057 in the 1st week to 29.1 +0.115 U/L(Mean +SEM) in the fourth week . Colchicine decreased the ALT level from 27.1 +057 to 22.00 +.23 after 1st week and to 15.46 +.37 after 4th week. When colchicine and cysteine(100mg/kg body weight) were given together, ALT level was significantly decreased to 19.43 +.17 in the first week and to 15.40 +1.38 in the fourth week. Colchicine decreased ALT level than in combination with cysteine especially after four weeks. This is attributed to the ability of the antioxidant supplement to balance off free radicals generated hence preventing peroxidation of the lipid components of the cell membrane. Disruption of membrane integrity is a common causative factor attributed to increase release or leakage of cellular contents [23].This finding is was consistent with the reports of Li et al. [24] .

Table 1 Effects of Colchicine and Cysteine on Alanine Transferase Level (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	6.8000	6.3500	5.8500	6.5000
	$\pm$0.1154 [a]	$\pm$0.0866 [a]	$\pm$0.2020 [a]	$\pm$0.3464 [a]
PARA-INDUCED	27.1000	28.3500	29.1000	28.1667
	$\pm$0.0577[ba]	$\pm$0.0288[ba]	$\pm$0.1154[ba]	$\pm$0.3844[ba]
COLCH-ALONE	22.0000	21.3500	18.9500	15.4667
	$\pm$0.2309[ba]	$\pm$0.3752 [a]	$\pm$0.43301	$\pm$0.3711[ba]
COLCH-CYS(80mg/kg)	21.8700	21.3000	19.3500	13.4000
	$\pm$0.3117 [a]	$\pm$0.40415	$\pm$0.7794 [a]	$\pm$0.2309 [a]
COLCH-CYS(90mg/kg)	20.0500	19.1000	16.8500	13.4000
	$\pm$0.0288[ba]	$\pm$0.0577[ba]	$\pm$0.31754	$\pm$0.2309[ba]
COLCH-CYS(100mg/kg)	19.4333	18.9500	17.5000	15.4000
	$\pm$0.17638[cba]	$\pm$0.02887	$\pm$0.3461[cba]	$\pm$1.38564[cba]

Result Represents Mean $\pm$SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same column with the same letters are not significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

Effects of Colchicine, Cysteine and Vitamin E on Alkaline Phosphatase (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

Table 3 show the normal ALP level was between 11.43+ .08 and 11.126 +0.03 from the first to the last week which did not show any significant change I ALP level. Paracetamol induced liver disease significantly (p<,0.05) after four days and raised ALP level from 11.1267 +0.003 to 39.00 +0.57735 U/L(Mean +SEM). Colchicine decreased the ALP level from 39.00 +0.57735 U/L to 35.15 +0.044 after 1st week and to 34.176 +0.089 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together, ALP level was significantly decreased to 33.7+ .03 in the first week to 31.8 +0.026 in the fourth week. This consistent to the report of

Table 2: Effects of Colchicine and Cysteine on Aspartate Transferase Level(U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	10.7233	11.1100	9.8600	11.1500
	±0.300[a]	±0.6524[a]	±0.5658[a]	±0.0346[a]
PARA-INDUCED	33.9300	36.3100	37.7500	37.5667
	±0.1616[ba]	±0.2367[ba]	±1.125[ba]	±0.6359[ba]
COLCH-ALONE	30.1800	29.6867	29.3967	28.5667
	±0.0519[ba]	±0.2396[ba]	±0.2280[ba]	±0.19953
COLCH-CYS(80mg/kg)	28.2567	28.0200	27.6567	26.2267
	±0.1356[cba]	±0.05774	±0.07796	±0.0088[cba]
COLCH-CYS(90mg/kg)	27.8767	27.3367	27.0267	26.4600
	±0.12991	±0.04910	±0.08950	±0.20207
COLCH-CYS(100mg/kg)	27.0367	26.5500	26.1767	24.7300
	±0.4936[cba]	±0.3117[cba]	±0.3723 [cba]	±0.3983[cba]

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same column with the same letters are not significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

Videla [18] reporting that a rapid mobilization of liver-ALP in blood, resulting increase serum levels at early stages of liver damage.

Effects of Colchicine and Cysteine on Gama- GT Level (U/L) in Paracetamol –Induced Liver disease, After Four Weeks of Treatment in Albino Rats.

Table 4 show the normal GT level was between 7.38 +0.223 U/L to 6.84 +0.21 U/L from the first to the last week which did not show any significant change. Paracetamol -induced liver disease significantly (p<, 0.05) raised GT level after four days and raised the level from 29.75 +0.16U/L in the 1st week to 32.00 +1.15 U/L(Mean +SEM) in the fourth week . Colchicine decreased the GT level from 29.75 +0.16U/L to 29.61 +0.98 after 1st week and to 27.96 +0.10 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together, GT level was significantly decreased to 25.64 +0.086 in the first week and to 24.4 +0.129 in the fourth week. This study is consistent with the report on the gamma-glutamyltransferase elevation [21] and the antioxidant effect on hepatotoxicity[5].

Effects of Colchicine and Cysteine on Total and Direct Bilirubin Level in Paracetamol – induced Liver Disease after four weeks of Treatment in Albino Rats.

Biluribin is a product of the breakdown of the heme component of the heamoglobin. Its elevation is a function of the rate of red cell destruction and the capacity of the liver to excrete the newly formed biluribin [22]. Table 5 show the normal level for total bilirubin was between 0.34±0 .035mg/dl to 0.3367 ±0.031 from the first to the last week which did not show any significant change. Paracetamol -induced liver disease significantly (p< 0.05) raised total bilirubin level after four days and raised the level from 0.34 ±0.035 to 1.256 ±0.008 in the 1st week to 1.16 ±0.0033 (Mean ±SEM) in the fourth week. Colchicine decreased the total bilirubin level from 1.256 ±0.008 to 1.19 v0.011 after 1st week and to 1.143 ±0.02 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together, bilirubin level was significantly decreased to 1.0167 ±0.21 in the first week and to 0.966 ±0.0038 in the fourth week. The observations could be attributed to the increased presence of the various treatments over the daration of the study, which is consistent the report of Tripathi [22]

Table 3: Effects of Colchicine and Cysteine on Alkaline Phosphatase (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	11.4300	12.0367	10.4167	11.1267
	$\pm$0.080[a]	$\pm$0.0166[a]	$\pm$0.1010[a]	$\pm$0.0033[a]
PARA-INDUCED	36.0867	36.5500	37.7400	39.0000
	$\pm$0.0895[ba]	$\pm$0.2136[a]	$\pm$0.6458[a]	$\pm$0.5773[a]
COLCH-ALONE	35.1533	34.8900	34.8367	34.1767
	$\pm$0.044[ca]	$\pm$0.0692[ca]	$\pm$0.0606[cba]	$\pm$0.0895[cba]
COLCH-CYS(80mg/kg)	34.8300	33.9467	33.1433	31.9400
	$\pm$0.0230[ba]	$\pm$0.03480[ba]	$\pm$0.0779[ba]	$\pm$0.0404[ba]
COLCH-CYS(90mg/kg)	34.3867	33.6200	32.8067	31.5000
	$\pm$0.026[cba]	$\pm$0.2193[cba]	$\pm$0.0491[cba]	$\pm$0.1501[cba]
COLCH-CYS(100mg/kg)	33.7000	32.6967	32.2167	31.8167
	$\pm$0.0346[cba]	$\pm$0.0837[cba]	$\pm$0.12414	$\pm$0.0260[cba]

Result Represents Mean $\pm$SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same row with the same letters are significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

Table4: Effects of Colchicine and Cysteine on Gama- GT Level (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	7.3800	7.9500	8.7133	6.8467
	±.2251[a]	±.1616[a]	±.5565[a]	±.2107[a]
PARA-INDUCED	29.7533	30.3600	30.5667	32.0000
	±.1637[ba]	±.3348[ba]	±.3897[ba]	±1.1547[ba]
COLCH-ALONE	29.6100	29.1167	28.5567	27.9667
	±.0981[ba]	±.0606[ba]	±.1934[ba]	±.1010[ba]
COLCH-CYS(80mg/kg)	27.3500	26.7967	26.2567	25.8700
	±.1212[bac]	±.1183[ba]	±.0433[ba]	±.0519[bac]
COLCH-CYS(90mg/kg)	27.0967	26.3767	26.1700	25.8500
	±.0145[ba]	±.0260[ba]	±.0404[ba]	±.0305[ba]
COLCH-CYS(100mg/kg)	25.6400	25.4767	24.9467	24.4167
	±.0866[bac]	±.09528	±.09528	±.1299[bac]

Result Represents Mean $\pm$SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same column with the same letters are not significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

Table 5: Effects of Colchicine and Cysteine on Total BiliruinLevel(mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	.3400	.2967	.1900	.3367
	±.0346[ba]	±.1010[ba]	±.0230[ba]	±.0318[ba]
PARA-INDUCED	1.2567	1.3100	1.3267	1.1633
	±.0088[ba]	±.0173[ba]	±.0935[ba]	±.0033[ba]
COLCH-ALONE	1.1900	1.1467	1.1233	1.1433
	±.0115[ba]	±.0033[ba]	±.0166[ba]	±.0240[ba]
COLCH-CYS(80mg/kg)	1.1200	1.0967	1.0767	1.0600

	±.0057^{bac}	±.00333	±.00333	±.0057^{bac}
COLCH-CYS(90mg/kg)	1.0700	1.0567	1.0267	1.0167
	±.01155	±.00882	±.00882	±.00882
COLCH-CYS(100mg/kg)	1.0167	1.0200	.9933	.9667
	±.0218^{bac}	±.0057^{bac}	±.00333	±.0033^{bac}

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same column with the same letters are not significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

Table 6: Effects of Colchicine and Cysteine on Direct Bilirubin(mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	.1800	.1600	.1500	.1267
	±.0230^{ba}	±.0100^{ba}	±.0230^{ba}	±.0033^{ba}
PARA-INDUCED	1.1200	1.1567	1.1900	1.1800
	±.0173^{ba}	±.0088^{ba}	±.0057^{ba}	±.0057^{ba}
COLCH-ALONE	1.0867	1.0600	1.0567	1.0400
	±.0033^{ba}	±.0057^{ba}	±.0088^{ba}	±.0057^{ba}
COLCH-CYS(80mg/kg)	1.0500	1.0167	1.0067	.9867
	±.00577	±.00882	±.00333	±.00882
COLCH-CYS(90mg/kg)	1.0167	1.0000	.9667	.9233
	±.00882	±.00577	±.00882	±.01202
COLCH-CYS(100mg/kg)	1.0100	.9567	.8733	.8667
	±.0057^{bac}	±.0233^{bac}	±.0233^{bac}	±.0145^{bac}

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts in the same row with the same letters are not significant.

[a] = Significant Difference when each Concentration is considered with Normal Level first control

[b] = Significant Difference when each Concentration is considered with Normal Level first control

[c] = Significant increase when the concentrations are compared with each other.

IV. CONCLUSION

The combination therapy of Colchicine and Cysteine in the management of liver damage will provide bitter outcome in hepatotoxic patients.

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Conflict of interest

No conflict of interest associated with this work.

Contribution of authors

The authors declare that work was done by the authors named in this article and all liabilities pertaining to the claims relating to the content of this article will be borne by the authors.

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