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Enhancement of Colchicine in the Management of Paracetamol-Induced Hepatotoxicity with Cysteine and Vitamine E.

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Abstract: This paper reports on the enhancement of cysteine and vitamin E in Colchicine management of Paracetamol-induced Hepatoxicity.
Sixty four experimental male albino rats were divided into nine groups with the first group as control, eight groups were treated with colchicines except group three, four, five and six were treated with the combination with 80, 90 and 100mg /dl of cysteine per day respectively while group seven, eight and nine were treated with 0.1, 0.2 and 0.3ml/day of vitamin E respectively for four weeks.
Paracetamol caused an increase in the plasma concentration of the liver enzymes; AST, ALT, ALP, GGT, Total and direct Bilirubin. Combine therapy of colchicine and cysteine caused slight decrease in the concentration of these enzymes while combination therapy of colchicine and Vitamine E caused a significant decrease in the concentration of the enzymes and this further reduces as the concentration of vitamin E increases. SOD and catalase increased significantly in liver disease while total protein decreased and this was reversed by the combined therapy.
The combined administration of colchicine and Vitamin E (0.3ml/day) was most suitable therapy in the treatment of paractamol induced hepatoxicity.
Keywords: Enhancement, Colchicine, Paracetamol-induced, cysteine, Vitamin E, Liver damage.

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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 (3000 to 4000mg a day for a year) can cause liver damage (Hepatoxicity), especially if alcohol is involved [1].It is implicated in acute liver failure, hepatic necroses, renal tubular necrosis and hypaglycaemiccoma[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 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 such as vitamin E have been shown to play very important roles in reducing the hepatoxicity of paracetamol[11]. Several vitamins, including C, E, and B_{12}, have been recognized as antioxidants and have shown hepatoprotective effects against the hepatotoxicity caused by acetaminophen (APAP) overdose.[4]. vitamin E or *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

2.1 Animals

72 albino rats obtained from the department of veterinary science university of Nigeria, Nsukka served as the subject for this project work. The rats were 6-8 weeks old and weighed between 120g-290g at the beginning of the experiment and were fed with grower pelleted feed and water.

2.2 Proximate Composition of Rat Diet

The rats were fed with palletized Guinea Grower's mash from Bendel Feed and Flour mill Limited, Nigeria. The proximate composition of rat diet was:
Crude protein -14.5%, Crude Fat-4.8%, Crude Fibre-7.2%, Crude Ash -8%, Calcium-0.8%, Phosphorus -0.62%, Lysine-0.60%, Methionine-0.31%, Cystine-0.31%, Vitamin A, -8,000 I.U,Vitamin D- 2,400 I.U.,Vitamin E-15mg, Vitamin B-4mg, Vitamin C-50mg, Manganese -30mg, Zinc-30mg, Sodium-0.15%.

2.3 Drug Used

Paracetamol and Colchicines.

2.4 Antioxidants Used

Cystine and Vitamin E

2.5 Animal Treatment and Dosage of Drug Administered

The 72 rats were housed in nine cages containing eight rats each. They were fed and the cages were cleaned at 12 hour intervals.Normal Rats, No Treatment; Group A, Paracetamol only (640mg/kg) for 4 days; Group B, Colchicine only (0.03mg/kg), GroupC, Colchicine + Cystine (80mg); Group D, Colchicine + Cystine (90mg); Group E, Colchicine + Cystine (100mg); Group F, Colchicine + Vitamin E (0.1ml); Group G, Colchicine + Vitamin E (0.2ml); Group H, Colchicine + Vitamin E (0.3ml).

2.6 Collection of Blood samples

The rats were sacrificed under chloroform anaesthetics. Blood was collected by cardiac puncture allowed to stand for 10 minutes and centrifuged at 3000rpm for 10minutes. Serum was collected for further analysis.

2.7 Determination of biochemical variables

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

2.8 Statistical Analysis

The mean and standard deviation was gotten using the graph prism pad version 5.1. Turkey's Multiple Composon was used to test the statistical significant difference among the variables. $P<0.05$ was taken as a significant value.

III. RESULTS

Table 3.1 shows the effect of Colchicine, Cysteine and Vitamine E on Akaline Phosphatase in Paracetamol-induced liver damage after four weeks of treatment. Table 3.2 Effects of Colchicine, Cysteine and Vitamin E on Alanine Transferase Level (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats. Table 3.3 Effects of Colchicine, Cysteine and Vitamin E on Aspartate TransferaseLevel(U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats. Table 3.4 Effects of Colchicine, Cysteine and Vitamin E on Gama- GT Level (U/L) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.Table 3.5 Effects of Colchicine, Cysteine and Vitamin E on Total BiliruinLevel(mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats. Table 3.6 Effects of Colchicine, Cysteine and Vitamin E on Direct Bilirubin(mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats. Table 3.7 Effects of Colchicine, Cysteine and Vitamin E on Hemoglobin Level (mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.Table 3.8 Effects of Colchicine, Cysteine and

Vitamin E on PCV Level (%) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

Table 3.1 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.

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}
COLCH-VIT E(0.1ml/kg)	29.8267	29.1500	28.4867	27.8767
	$\pm$0.14723	$\pm$0.10263	$\pm$0.02603	$\pm$0.20086
COLCH-VIT E(0.2ml/kg)	29.3267	28.5867	28.1500	27.4333
	$\pm$0.02603	$\pm$0.28521	$\pm$0.06928	$\pm$0.35244
COLCH-VIT E(0.3ml/kg)	28.7767	27.6267	27.0900	26.1600
	$\pm$0.1761^{cba}	$\pm$0.0895^{cba}	$\pm$0.0519^{cba}	$\pm$0.1113^{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.

Table 3.2 Effects of Colchicine, Cysteine and Vitamin E 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}
COLCH-VIT E(0.1ml/kg)	18.5500	17.6500	16.0500	14.6667
	$\pm$0.20207	$\pm$0.2598^{cba}	$\pm$0.08660	$\pm$0.35277
COLCH-VIT E(0.2ml/kg)	17.9500	17.0500	16.0500	15.7500

	.3175^{cba}	±0.60622	±0.54848	±0.43301
COLCH-VIT E(0.3ml/kg)	17.0500	16.2500	15.7000	14.4500
	±0.4907^{cba}	±0.4907^{cba}	±0.4618	±0.3752^{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.

Table 3.3 Effects of Colchicine, Cysteine and Vitamin E on Aspartate TransferaseLevel(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}
COLCH-VIT E(.1ml/kg)	22.5800	21.9500	21.5067	20.2767
	±0.8140^{cba}	±0.6697^{cba}	±0.7592^{cba}	±0.40168
COLCH-VIT E(0.2ml/kg)	21.2767	20.5400	20.4267	19.8800
	±0.47632	±0.34064	±0.34930	±0.48497
COLCH-VIT E(0.3ml/kg)	20.6467	20.2667	19.5700	19.3967
	±0.7245^{cba}	.±05225^{cba}	±0.5196^{cba}	±0.5629^{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.

Table 3.4 Effects of Colchicine, Cysteine and Vitamin E 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}
COLCH-VIT E(0.1ml/kg)	24.8233	24.1900	23.6100	23.1367
	±.0352^{bac}	±.10392	±.2193^{bac}	±.0033^{bac}
COLCH-VIT E(0.2ml/kg)	24.0233	23.8900	23.6267	23.3500
	±.07265	±.06351	±.00882	±.08083
COLCH-VIT E(0.3ml/kg)	23.6000	23.3567	23.0500	22.5900
	±.0057^{bac}	±.0664^{ba}	±.1124^{ba}	±.1732^{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 3.5 Effects of Colchicine, Cysteine and Vitamin E 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}
COLCH-VIT E(80mg/kg)	.9600	.9567	.9267	.8800
	±.01155	±.00667	±.00882	±.00577
COLCH-VIT E(90mg/kg)	.9067	.8700	.8067	.7700
	±.00667^{ba}	±.0115^{ba}	±.0202^{ba}	±.0346^{ba}
COLCH-VIT E(100mg/kg)	.8500	.7700	.7467	.6900
	±.0152^{cba}	±.0230^{ba}	±.0260^{bac}	±.0288^{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.

Table 3.6 Effects of Colchicine, Cysteine and Vitamin E 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]
COLCH-VIT E(0.1ml/kg)	.6067	.6733	.6200	.5700
	±.0088[ba]	±.1344[ba]	±.14012	±.1150[ba]
COLCH-VIT E(0.2ml/kg)	.5967	.5167	.4600	.4400
	±.0371[ba]	±.01453	±.01528	±.0230[ba]
COLCH-VIT E(0.3ml/kg)	.4633	.4300	.4000	.3467
	±.0176[bac]	±.01732	±.0173[ba]	±.0240[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.

Table 3.7 Effects of Colchicine, Cysteine and Vitamin E on Hemoglobin Level (mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	14.6667	16.6667	13.3333	16.6667
	±.8819[ab]	±.8819[ab]	±.3333[ab]	±.3333[ab]
PARA-INDUCED	6.6667	8.6667	8.6667	8.6667
	±.3333[ab]	±.3333[ab]	±.3333[ab]	±.3333[ab]
COLCH-ALONE	7.6667	8.6667	8.6667	11.3333
	±.3333[ab]	±.3333 [a]	±.3333 [a]	±.3333[ab]
COLCH-CYS(80mg/kg)	8.6667	10.3333	10.0000	13.6667
	±.3333[ca]	±.3333[ab]	±.5773[ca]	±.3333[abc]
COLCH-CYS(90mg/kg)	11.0000	11.3333	13.6667	12.6667
	±.5773 [cab]	±.3333[ab]	±.3333 [cab]	±.3333[abc]
COLCH-CYS(100mg/kg)	10.0000	8.6667	12.0000	10.3333
	±.5773[ab]	±.3333 [a]	±.5773[cb]	±.3333[abc]
COLCH-VIT E(80mg/kg)	10.3333	9.6667	11.6667	12.0000
	±.6666[ab]	±.3333[ab]	±.3333[ab]	±1.1547[abc]
COLCH-VIT E(90mg/kg)	10.0000	10.6667	11.3333	16.0000
	±.5773[ab]	±.3333[ab]	±.8819 [cab]	±.5773 [b]
COLCH-VIT E(100mg/kg)	10.0000	11.0000	13.0000	17.3333
	±.5773[ab]	±.5773[ab]	±.5773[cb]	±.666[cb]

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 3.8 Effects of Colchicine, Cysteine and Vitamin E on PCV Level (%) in Paracetamol – Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	42.0000	40.6667	43.0000	41.6667
	±.5773^{ab}	±.3333^{ab}	±.5773^{ab}	±.3333^{ab}
PARA-INDUCED	21.0000	22.6667	23.0000	21.0000
	±.5773^{ab}	±.3333^{ab}	±.57735	±.5773^{ab}
COLCH-ALONE	30.6667	27.3333	32.6667	31.6667
	±.8819^{ab}	±2.1858^{ab}	±.6666^{ab}	±.8819^{ab}
COLCH-CYS(80mg/kg)	33.0000	32.6667	33.6667	33.0000
	±.5773^{ab}	±1.4529^{ab}	±1.20185	±.5773^{ab}
COLCH-CYS(90mg/kg)	34.6667	34.3333	34.3333	34.3333
	±2.1858^{ab}	±.3333^{ab}	±.33333	±.8819^{ab}
COLCH-CYS(100mg/kg)	33.6667	35.0000	35.6667	36.3333
	±.3333^{ab}	±.5773^{ab}	±.3333^{ab}	±.3333^{ab}
COLCH-VIT E(80mg/kg)	34.0000	33.3333	35.3333	36.3333
	±.0000^{ab}	±.3333^{ab}	±.33333	±.3333^{ab}
COLCH-VIT E(90mg/kg)	34.6667	34.3333	35.0000	36.3333
	±.3333^{ab}	±1.2018^{ab}	±.5773^{ab}	±.3333^{ab}
COLCH-VIT E(100mg/kg)	34.6667	35.3333	36.3333	38.0000
	±.3333^{ab}	±.3333^{ab}	±.3333^{ab}	±.5773^{ab}

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.

IV. DISCUSSION

4.1 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.

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. Vitamin E (0.3ml/kg) significantly decreased the ALP level more than cystiene and colchicine alone. The decrease was 28.77 +0.17 to 26.16 +0.176 in the 1st week and 26.16 +0.114 in the fourth week which is highly significant (p<.05).This consistent to the report of Videla [18] reporting that a rapid mobilization of liver-ALP in blood, resulting increase serum levels at early stages of liver damage.

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

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. Vitamin E (0.3ml/kg) significantly decreased the ALT level from 17.05 +.49 to 14.45 +.37 U/L in the fourth week. Colchicine decreased ALT level than in combination with cysteine and vitamin especially after four weeks. 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 [19].This finding is was consistent with the reports of Li et al. [20] .

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

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. Vitamin E (0.3ml/kg) significantly decreased the AST level from 20.64 +.72 to 19.39 +.56 U/L in the fourth week. Vitamin E and cysteine significantly decreased AST level in combined therapy than when colchicines was administered alone. 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. Vitamin E (0.3ml/kg) significantly decreased the AST level from 20.64 +.72 to 19.39 +.56 U/L in the fourth week. Vitamin E and cysteine significantly decreased AST level in combined therapy than when colchicines was administered alone. 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 [19].This finding is was consistent with the reports of Li et al. [20] .

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

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. Vitamin E (0.3ml/kg) significantly decreased the GT level from 23.60 +0.0057 to 22.59 +0.123 U/L in the fourth week. Vitamin E and cysteine significantly decreased GT level in combined therapy than when colchicines was administered alone.This study is consistent with the report on the gamma-glutamyltransferase elevation [21] and the antioxidant effect on hepatotoxicity[5].

*4.5 and 4.6 Effects of Colchicine, Cysteine and Vitamin E on Total and Direct Bilirubin Level in Paracetamol – induced Liver Diseaseafter 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]. The normal level for total bilirubin was between 0.34$\pm$0 .035mg/dl to 0.3367 $\pm$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 $\pm$0.035 to 1.256 $\pm$0.008 in the 1st week to 1.16 $\pm$0.0033 (Mean $\pm$SEM) in the fourth week. Colchicine decreased the total bilirubin level from 1.256 $\pm$0.008 to 1.19 v0.011 after 1st week and to 1.143 $\pm$0.02 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together,bilirubin level was significantly decreased to 1.0167 $\pm$0.21 in the first week and to 0.966 $\pm$0.0038 in the fourth week. Vitamin E (0.3ml/kg) significantly decreased the total bilirubin level from 0.85 $\pm$0.01 to 0.69 $\pm$0.028 in the fourth week. Vitamin E and cysteine significantly decreased total bilirubin level in combined therapy than when colchicines was administered alone.The observations could be attributed to theincreased presence of the various treatments over the daration of the study, which is consistent the the report of Tripathi [22]

4.7 Effects of Colchicine, Cysteine and Vitamin E on Hemoglobin Level (mg/dl) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

The normal level of Hb was between14.6667 $\pm$.88192mg/dl (Mean $\pm$SEM) from the first week to 16.6667$\pm$ .33333 inthe last week which did not show any significant change. Paracetamol -induced liver disease significantly (p< 0.05) decreased the Hb level after four days and decreased the level from 14.6667$\pm$ .88192 to 6.6667 $\pm$ 33333 in the 1st week to 8.6667$\pm$ 33333 in the 4th week. Colchicine increased the Hb level from 7.6667

±33333 after 1st week and to 11.3333 333 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together, the Hb level was significantly decreased to 10.0000± .88192 in the first week and to 10,333 ±33333 in the fourth week. Vitamin E (0.3ml/kg) significantly increased the level from 10.0000± .88192 in the first week to 17.3333±.57735 in the fourth week. Vitamin E and cysteine significantly increased the Hb level in combined therapy than when colchicines was administered alone.

4.8 Effects of Colchicine, Cysteine and Vitamin E on PCV Level (%) in Paracetamol –Induced Liver Disease, After Four Weeks of Treatment in Albino Rats.

The normal level of PCV was between 42.0000 ± .57735 % ((Mean ±SEM)). to 41.6667± .33333 % from the first to the last week which did not show any significant change. Paracetamol -induced liver disease significantly ($p< 0.05$) decreased the PCV level after four days and decreased the level from 42.0000 ± .57735. to 21.0000 ±.57735 in the 1st week and remained the same till 4th week. Colchicine decreased the PCV level from 30.6667±.88192 after 1st week and to 31.6667 ±88192 after 4th week. When colchicine and cysteine (100mg/kg body weight) were given together, the PCV level was significantly decreased to 33.6667± .33333 in the first week and to 36.3333±33333 in the fourth week. Vitamin E (0.3ml/kg) significantly increased the level from 34.6667 ±33333 in the first week to 38.0000 ±.57735 in the fourth week. Vitamin E and cysteine significantly decreased the PCV level in combined therapy than when colchicines was administered alone. This is similar to the report of study of Videla[18].The correlation observed in this study and the cited references is evident of the restoration enhancement of Cysteine, Vitamins E in the effect of Colchicine in hepatotoxicity.

V. CONCLUSION

From the results in the above tables it can be concluded that the combined therapy of Cysteine and Vitamin E will enhance the efficacy of Colchicine management of 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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