ARTICLE / INVESTIGACIÓN

Chemotherapy's impact on a few blood parameters

Qasim Al-Shibli*, Mohammed Jawad Al-Haidarey

DOI. 10.21931/RB/2022.07.04.7

University of Knfa, Iraq.
Corresponding author: qasim2019nn@gmail.com

Abstract: Cyclophosphamide (CP), Ifosfamide (IFO), Paclitaxel (PTX) and Doxorubicin (DOX) are commonly used cytostatic drugs. The present study investigates the ecotoxicity and genotoxicity of CP, DOX, and PTX, their human metabolites/ transformation products (TPs) cyclophosphamide (NCP) as individual compounds and as a mixture. The three-parent compounds (Further ecotoxicity studies of metabolites. The measured toxicity of the cross was lower than the toxicity predicted by the concentration addition model indicating potentiating effects of the CPCOOH toxicity. Revealed genotoxic activity of CP and the mixture in the presence The degradation study with UV irradiation of samples containing (CP, cyclo, and DOX) showed efficient degradation of compounds and remained toxic. They are suggesting that no stable with adverse effects was formed. This is the first study describing the ecotoxicity and genotoxicity of the commonly used cytostatics CP, cyclo, and DOX, their known metabolites, and their mixture. The results indicate the importance of toxicological evaluation and monitoring drug metabolites as they may be more hazardous to humans than parent compounds.

Key words: Paclitaxel, Doxorubicin, Cyclophosphamide, toxicity.

Introduction

The most common reason cancer patients experience low blood counts is as a side effect of chemotherapy. Chemotherapy involves the use of drugs to destroy cancer cells. Chemotherapy works by destroying cells that proliferate, a characteristic of cancer cells. Unfortunately, chemotherapy also affects normal cells that overgrow, such as cells in the bone marrow that produce red blood cells, white blood cells, and platelets.Cancer is the second leading cause of death worldwide, with approximately 9.6 million cancer-related deaths in 2018[1]. Cancer is a generic term for a large group of diseases that can affect any body part. Other terms used are malignant tumors and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, which can invade adjoining body parts and spread to other organs; the latter process is referred to as metastasis. Metastases are the primary cause of death from cancer[2]. In compliance with this trend of increasing cancer prevalence, new ANP drugs are also being designed, tested, and manufactured at an increasing rate[3]. More than over the past few years, 70 new ANPs (antineoplastic drugs) drugs have been released to treat 20 variants of tumors (cancerous growths), and the number of antineoplastic drugs (ANP) drugs has expanded by more than 60%. More than 500 companies are currently pursuing ANP drug development, with 300 companies having cancer drugs under clinical development stages[4], so the chemotherapy or antineoplastic agents are designed to interact directly or indirectly with DNA by damaging its structure, inhibiting, altering and disrupting mechanisms of its transcription, replication, and synthesis. Derivatives of nitrogen mustards were developed, including the DNA alkylating agents cyclophosphamide, chlorambucil, and melphalan, widely used in clinical therapeutics[6,7], and chemotherapy may be administered to cancer patients through usual routes of intravenous, intramuscular or subcutaneous injection. In general, the fate of chemical biotransformation includes the generation of metabolites, which may be desired for the therapeutic purpose or not, due to toxicity. Briefly, drug pharmacokinetics occurs in two phases of biotransformation, comprised of the functionalization (Phase I) and conjugation (Phase II) of the compound load, to increase its polarity and facilitate its elimination through excretion[8]. Phase I relies on an enzymatic system of defense against most of the xenobiotic compounds, composed of members of the cytochrome 450 gene family (CYP 450), flavin-containing monooxygenases (FMO), monoamine oxidases (MAOs), and xanthine oxidase/aldehyde oxidase. Those enzymes are differentially expressed in tissues but broadly distributed in the liver, kidney, and intestine, employing introducing, modifying, or unmasking reactive functional groups at the parent drug. and the Phase II reactions occur with the introduction of acetyl, sulfate, glucuronide acid, glutathione, and amino acids functional groups, either in the parent molecule or in a phase I metabolite structurally changed, enabling binding sites for conjugation. These reactions are mostly catalyzed by the enzyme uridine 5'- diphosphate (UDP)-glucuronosyltransferase (UGTs), sulfotransferases (SULTs), glutathione S-transferase (GSTs), and N-acetyltransferases (NATs). Biotransformation mechanisms present low specificity to pharmaceuticals and, in general, enhance the polarity of compounds, thus favoring excretion. Nevertheless, this change is often incomplete, with parent compounds excreted together with the metabolites in a variable proportion[14]. So The pharmaceuticals elected for the toxicity assessment in the present thesis were: cisplatin, cyclophosphamide, and tamoxifen. They were chosen according to a combi-

Citation: Al-Shibli Q, Al-Haidarey M. Chemotherapy's impact on a few blood parameters.Revis Bionatura 2022;7(4) 7. http://dx.doi.org/10.21931/RB/2022.07.04.7

Received: 20 July 2022 / **Accepted:** 15 October 2022 / **Published:** 15 November 2022

Publisher's Note: Bionatura stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

nation of 50 criteria regarding their consumption and environmental occurrence. Despite the increase in the number and quality of innovative new drugs currently released in the pharmaceutical market[5], the first drug(CP), The advent of chemotherapy fundamentals, emerged in the first four decades of the 20th century. Breakthrough advances undertaken in World War II after an accidental spill of sulfur mustards led to the marked depletion of bone marrow and lymph nodes in men exposed to those chemicals, following discoveries of potential anticancer therapeutic[9]. In this course, cyclophosphamide (CP) was developed as a mustard prodrug with cytotoxic and alkylating purposes[10]. The CP dosage commonly administered in humans varies widely depending on the clinical indication, and can be defined as low (1–3 mg kg^{-1} or 40–120 mg m-2), daily orally administered; intermediate (15–40 mg kg^{-1} or 600–1,500 mg m-2), via intravenous, every 3 to 4 weeks; and high (> 120 mg kg^{-1} or > 5,000 mg m-2), every two days. After consumption, CP undergoes subsequent activation and transformation by the CYP 450 enzymes to yield the major cytotoxic species activation, the phosphoramide mustard (PAM) and acrolein. These species form labile covalent DNA adducts and inter-strand crosslinks, accountable for blocking DNA replication and avoiding cell proliferation[11]. According to Bagley *et al.*[12], not more than 20% of injected CP is excreted intact in urine at any dose level. Chemotherapy-induced alterations and incomplete blood count may cause significant problems in clinical practice. Anemia, neutropenia, and thrombocytopenia induced by chemotherapy regimens may cause life-threatening complications such as severe infections and hemorrhagic complications. Moreover, these side effects may also necessitate dose reduction and delay in schedules of chemotherapy treatment[13], and the reason for choosing this study is to know the toxicity of chemotherapy drugs and their effect on some blood parameters (WBC, HB, PLT) Table1

Materials and methods

In this study, samples were collected from the Middle Euphrates cancer center in Al-Najaf city, Iraq collected 40 samples were from patients 20 patients treated with different types of chemotherapy-treated withe(Cyclophosphamide, DOX rubicin, paclitaxel) take the sample in (Nov and Dec -2021) Serum hemoglobin Table 6 (HGB) levels, white blood cell Table4 (WBC), platelet Table5 (PLT) count, and 20 patients considered as control (Table 1,2). And work (UV) to know the wavelength of three drugs (figure 1, 2,3)

Results

After working in UV spectrophotometer measure, the wavelength of each drug is taken urine and serum after and before taking drugs so camper between this process the rate before took drugs and this test show the percentage of drugs in the patient's body like this (figure 1) after and before taking the drugs and measure samples by (UV) to know the wavelength to three drugs.

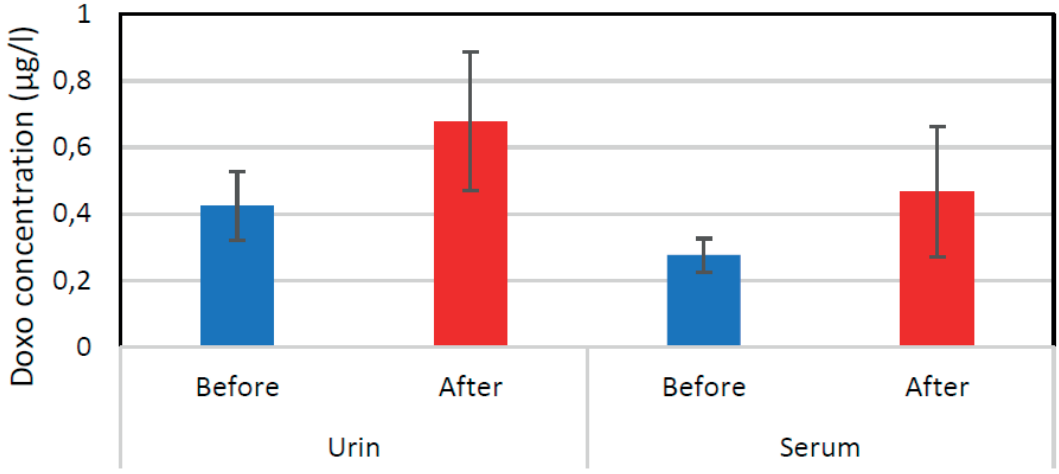

Figure 1. Shows the process of measuring serum and urine samples by (UV) spectrophotometer to know the wavelength of drugs and, after learning the wavelength according to published research, the toxicity percentage for each drug.

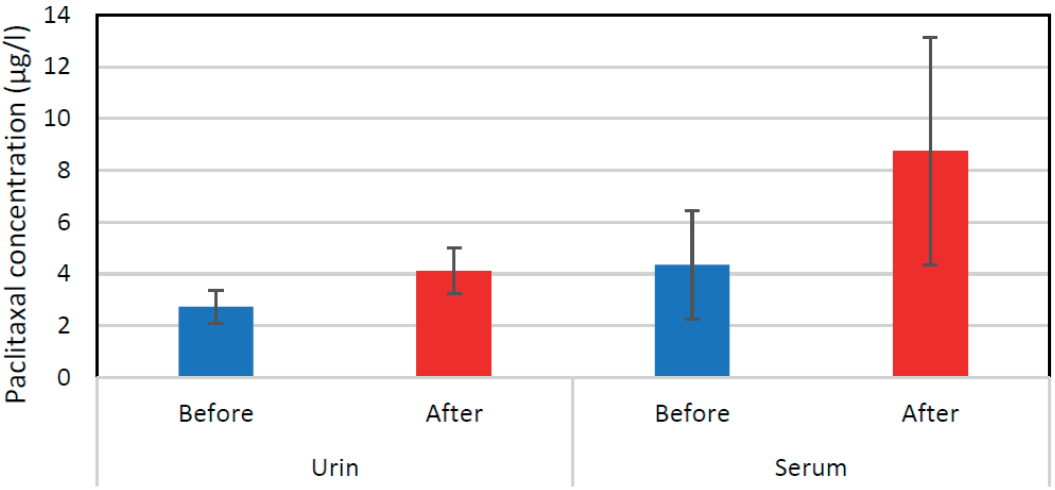

Figure 2. Paclitaxel drugs(urine, serum) after and before taking the drugs show an increased rate of drugs after taking the drug as a result of the difficulty of breaking down these compounds inside the patient's body.

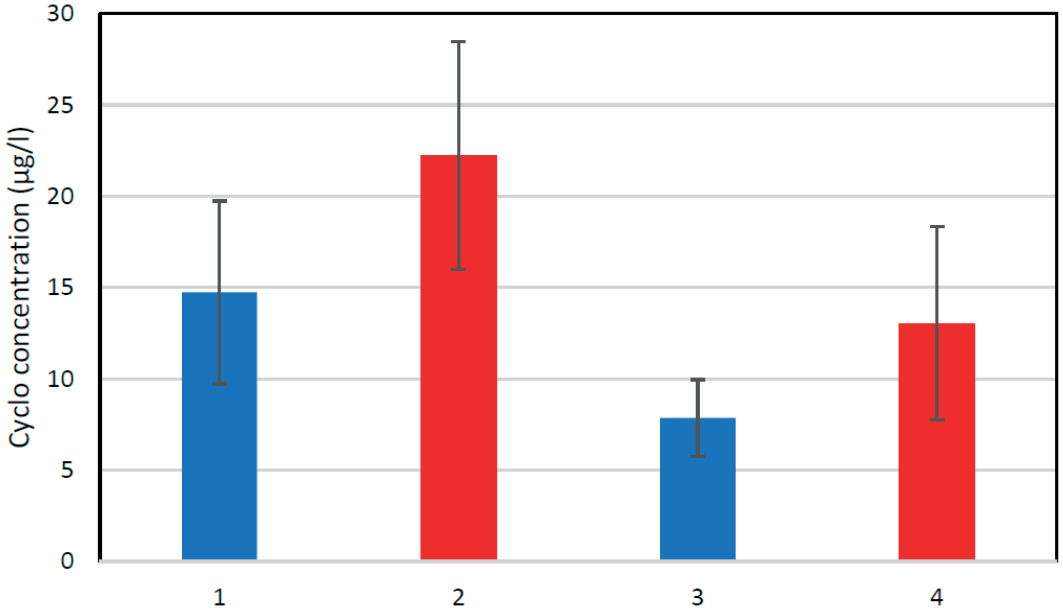

Figure 3. Cyclophosphamide drugs (urine, serum) after and before taking the drugs.

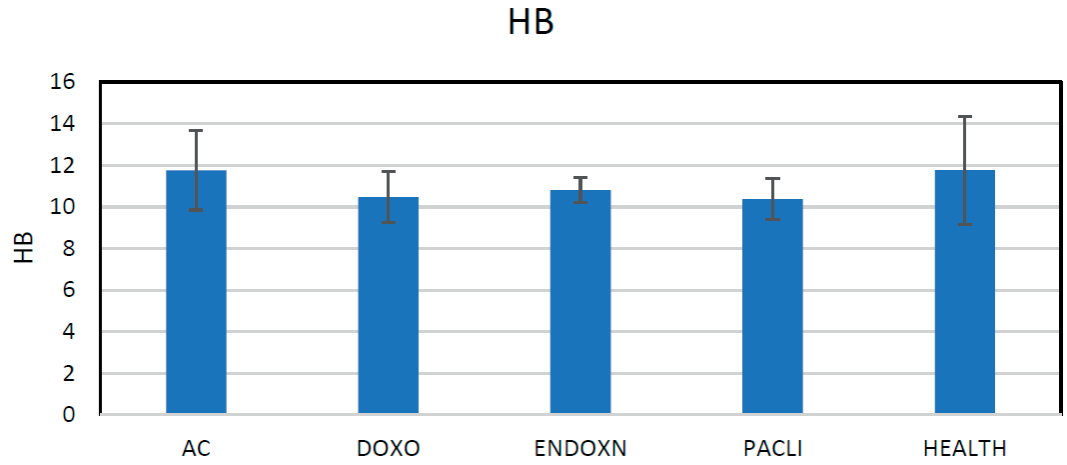

Figure 4. Shown patients receiving (AC) drugs, meaning (endoxan and DOX rubicin drugs) and influence or minimize the percentage of hemoglobin.

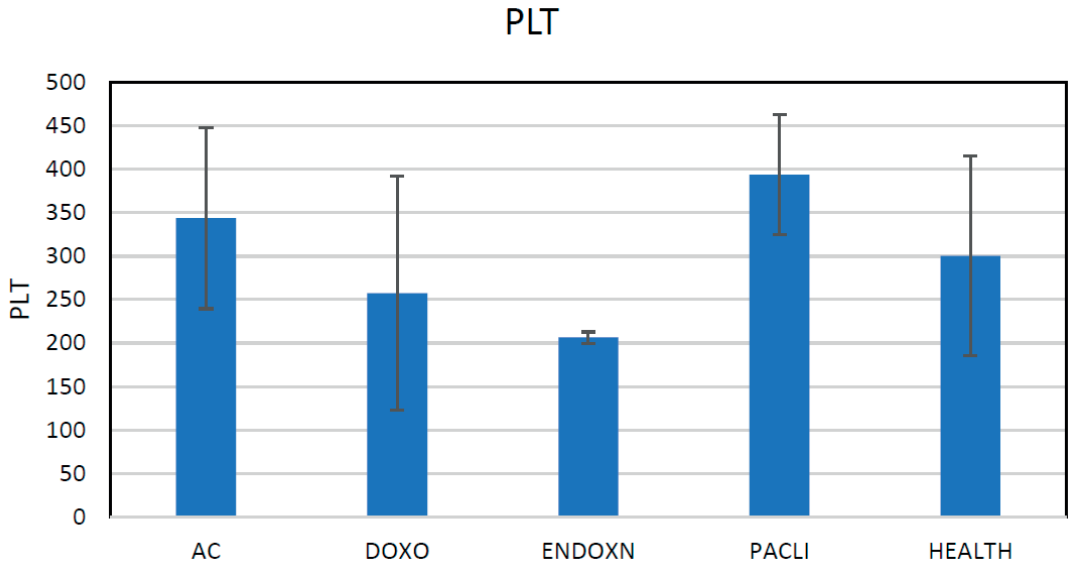

Figure 5. Shows the rate of platelet is increased in chemotherapy drugs.

ANOVA		
	Sum of Squares	Df
WBC	Between Groups	127.340
data	Within Groups	748.945
data	Total	876.285
HB	Between Groups	14.674
data	Within Groups	172.245
data	Total	186.919
PLT	Between Groups	89632.067
data	Within Groups	427438.907
data	Total	517070.974
	Sum of Squares	Df

Table 1. Explain the sum and mean square between the WBC, HB, PLT.

Descriptives									
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
WBC	AC	6	7.2500	3.41921	1.39589	3.6618	10.8382	4.40	13.90
	DOX	4	12.7100	7.59897	3.79949	.6183	24.8017	4.20	20.60
	ENDOXN	2	11.1000	1.55563	1.10000	-2.8768	25.0768	10.00	12.20
	PACLI	7	6.8314	2.47437	.93522	4.5430	9.1198	3.84	10.20
	No Medication	20	9.8700	5.01630	1.12168	7.5223	12.2177	.00	24.10
	Total	39	9.2759	4.80210	.76895	7.7192	10.8326	.00	24.10
HB	AC	6	11.7500	2.17509	.88798	9.4674	14.0326	8.80	14.10
	DOX	4	10.4750	1.43149	.71575	8.1972	12.7528	8.40	11.60
	ENDOXN	2	10.8000	.84853	.60000	3.1763	18.4237	10.20	11.40
	PACLI	7	10.3714	1.05469	.39864	9.3960	11.3469	9.00	12.20
	No Medication	20	11.7600	2.66604	.59615	10.5123	13.0077	5.90	15.20
	Total	39	11.3282	2.21786	.35514	10.6093	12.0472	5.90	15.20
PLT	AC	6	344.0000	106.75205	43.58134	231.9706	456.0294	213.00	509.00
	DOX	4	257.5000	155.44024	77.72012	10.1599	504.8401	26.00	352.00
	ENDOXN	2	206.5000	9.19239	6.50000	123.9097	289.0903	200.00	213.00
	PACLI	7	393.8571	74.22809	28.05558	325.2076	462.5067	307.00	527.00
	No Medication	20	300.3500	118.06121	26.39929	245.0957	355.6043	92.00	545.00
	Total	39	314.6410	116.64961	18.67889	276.8276	352.4545	26.00	545.00

Table 2. Explains the descriptives statistics between the three drugs and other drugs, not chemotherapy.

Discussion

The Ministry of Health should import cancer treatments from internationally accredited companies. With this study, it was possible to analyze cancer treatments to know their effect on patients and the degree of benefit to the patient after taking medicine. It also allowed us to see the influence of antitumor drugs and to reduce them by combining them with a special diet for patients to increase their immunity. Cancer patients should take the necessary preventive measures (wear masks and do not enter crowded places. The arrangement is made By comparing these concentrations with a set of experiments. The measured toxicity of the crossover was lower than predicted by the concentration addition model, indicating potentiating effects of CPCOOH toxicity. They revealed the genotoxic activity of CP and the mixture. UV irradiation degradation study of the samples containing (CP, cyclo, and DOX) showed efficient degradation of the compounds and they remained toxic.The results of the current study were estimated, as they revealed the effect of these treatments on a decrease in WBC, as well as a decrease in PLT as a result of taking this treatment and its effect on the patient's immunity because it is classified as toxic solid chemotherapy as in the table of WBC, PLT, and HB.

Multiple Comparisons								
Dependent Variable		(I) Factors	(J) Factors	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
							Lower Bound	Upper Bound
WBC	LSD	AC	DOXO	-5.46000-	3.02956	.080	-11.6168-	.6968
			ENDOXN	-3.85000-	3.83213	.322	-11.6378-	3.9378
			PACLI	.41857	2.61115	.874	-4.8879-	5.7251
			No Medication	-2.62000-	2.18465	.239	-7.0597-	1.8197
		DOXO	AC	5.46000	3.02956	.080	-.6968-	11.6168
			ENDOXN	1.61000	4.06459	.695	-6.6502-	9.8702
			PACLI	5.87857	2.94173	.054	-.0997-	11.8569
			No Medication	2.84000	2.57067	.277	-2.3842-	8.0642
		ENDOXN	AC	3.85000	3.83213	.322	-3.9378-	11.6378
			DOXO	-1.61000-	4.06459	.695	-9.8702-	6.6502
			PACLI	4.26857	3.76307	.265	-3.3789-	11.9161
			No Medication	1.23000	3.48070	.726	-5.8436-	8.3036
		PACLI	AC	-.41857-	2.61115	.874	-5.7251-	4.8879
			DOXO	-5.87857-	2.94173	.054	-11.8569-	.0997
			ENDOXN	-4.26857-	3.76307	.265	-11.9161-	3.3789
			No Medication	-3.03857-	2.06112	.150	-7.2273-	1.1501
		No Medication	AC	2.62000	2.18465	.239	-1.8197-	7.0597
			DOXO	-2.84000-	2.57067	.277	-8.0642-	2.3842
			ENDOXN	-1.23000-	3.48070	.726	-8.3036-	5.8436
			PACLI	3.03857	2.06112	.150	-1.1501-	7.2273
HB	LSD	AC	DOXO	1.27500	1.45287	.386	-1.6776-	4.2276
			ENDOXN	.95000	1.83776	.609	-2.7848-	4.6848
			PACLI	1.37857	1.25222	.279	-1.1662-	3.9234
			No Medication	-.01000-	1.04768	.992	-2.1391-	2.1191
		DOXO	AC	-1.27500-	1.45287	.386	-4.2276-	1.6776
			ENDOXN	-.32500-	1.94924	.869	-4.2863-	3.6363
			PACLI	.10357	1.41075	.942	-2.7634-	2.9706
			No Medication	-1.28500-	1.23280	.305	-3.7904-	1.2204
		ENDOXN	AC	-.95000-	1.83776	.609	-4.6848-	2.7848
			DOXO	.32500	1.94924	.869	-3.6363-	4.2863
			PACLI	.42857	1.80464	.814	-3.2389-	4.0960
			No Medication	-.96000-	1.66923	.569	-4.3523-	2.4323
		PACLI	AC	-1.37857-	1.25222	.279	-3.9234-	1.1662
			DOXO	-.10357-	1.41075	.942	-2.9706-	2.7634
			ENDOXN	-.42857-	1.80464	.814	-4.0960-	3.2389
			No Medication	-1.38857-	.98844	.169	-3.3973-	.6202
		No Medication	AC	.01000	1.04768	.992	-2.1191-	2.1391
			DOXO	1.28500	1.23280	.305	-1.2204-	3.7904
			ENDOXN	.96000	1.66923	.569	-2.4323-	4.3523
			PACLI	1.38857	.98844	.169	-.6202-	3.3973

Table 3. The difference between the three drugs means the difference. *. The mean difference is significant at the 0.05 level.

PLT	LSD	AC	DOXO	86.50000	72.37556	.240	-60.5848-	233.5848
			ENDOXN	137.50000	91.54865	.142	-48.5492-	323.5492
			PACLI	-49.85714-	62.37989	.430	-176.6283-	76.9140
			No Medication	43.65000	52.19076	.409	-62.4144-	149.7144
		DOXO	AC	-86.50000-	72.37556	.240	-233.5848-	60.5848
			ENDOXN	51.00000	97.10201	.603	-146.3350-	248.3350
			PACLI	-136.35714-	70.27727	.061	-279.1777-	6.4635
			No Medication	-42.85000-	61.41270	.490	-167.6556-	81.9556
		ENDOXN	AC	-137.50000-	91.54865	.142	-323.5492-	48.5492
			DOXO	-51.00000-	97.10201	.603	-248.3350-	146.3350
			No Medication	-93.85000-	83.15319	.267	-262.8376-	75.1376
		PACLI	AC	49.85714	62.37989	.430	-76.9140-	176.6283
			DOXO	136.35714	70.27727	.061	-6.4635-	279.1777
			ENDOXN	187.35714*	89.89899	.045	4.6604	370.0539
			No Medication	93.50714	49.23970	.066	-6.5600-	193.5743
		No Medication	AC	-43.65000-	52.19076	.409	-149.7144-	62.4144
			DOXO	42.85000	61.41270	.490	-81.9556-	167.6556
			ENDOXN	93.85000	83.15319	.267	-75.1376-	262.8376
			PACLI	-93.50714-	49.23970	.066	-193.5743-	6.5600

*. The mean difference is significant at the 0.05 level.

Table 3. The difference between the three drugs means the difference. *. The mean difference is significant at the 0.05 level.

HB			
	Factors	N	Subset for alpha = 0.05
			1
Duncan[a,b]	PACLI	7	10.3714
	DOX	4	10.4750
	ENDOXN	2	10.8000
	AC	6	11.7500
	No Medication	20	11.7600
	Sig.		.417
Means for groups in homogeneous subsets are displayed.			
a. Uses Harmonic Mean Sample Size = 4.506.			
b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.			

Table 4. Shows the rate of HB in three drugs.

Conclusions

This study suggests that no stable compounds with adverse effects were formed. This is the first study to describe the ecotoxicity and genotoxicity of the commonly used cytostatics CP, Cyclo and DOX, their known metabolites and their mixture. The results indicate the importance of toxicological evaluation and monitoring drug metabolites, as they may be more hazardous to humans than the parent compounds.

Funding

This research received no external funding.

PLT				
	Factors	N	Subset for alpha = 0.05	
			1	2
Duncan[a,b]	ENDOXN	2	206.5000	
	DOX	4	257.5000	257.5000
	No Medication	20	300.3500	300.3500
	AC	6	344.0000	344.0000
	PACLI	7		393.8571
	Sig.		.101	.103
Means for groups in homogeneous subsets are displayed.				
a. Uses Harmonic Mean Sample Size = 4.506.				
b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.				

Table 5. Different rates of PLT between three drugs.

Institutional Review Board Statement

The study was conducted according to the guidelines (or Ethics Committee) of the university of Kufa (protocol code 58799and 2021/12/16.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

At the tumors hospital in the middle Euphrates, Iraq.

Acknowledgments

In this study, three types of chemotherapy were used, which are Doxorubicin, paclitaxel and cyclophosphamide. The devices include (ultraviolet rays and centrifuges), and samples include blood, urine, and sewage.

Conflicts of Interest

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Bibliographic references

1. International Agency for Research on Cancer . On the International Agency for Research on Cancer classification of glyphosate as a probable human carcinogen. European Journal of Cancer Prevention.2018, 27(1), 82-87.) 2
2. Cancer I A R, Goodman, J. E., Mayfield, D. B., Becker, R. A., Hartigan, S. B., & Erraguntla, N. K.. Recommendations for further revisions to improve the International Agency for Research on Cancer (IARC) Monograph program. Regulatory Toxicology and Pharmacology.2020, 113, 104639).
3. Sun J, Von Tungeln LS, Hines W, Beger RD. Identification of metabolite profiles of the catechol-Omethyl transferase inhibitor tolcapone in rat urine using LC/MS-based metabonomics analysis. J Chromatogr B Analyt Technol Biomed Life Sci 2009;877:2557–2565
4. Aitken,Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, Elbert A, Petren KM, Marshall BC. Teh Cystic Fibrosis Foundation patient registry: design and methods of a national observational disease registry. Ann Am Thorac Soc 2016;13:1173–1179.
5. Aitken and Kleinrock,.Murray Aitken, executive director, Ernst R. Berndt., Medicines use and spending in the US—a review of 2015 and outlook to 2020. Parsippany (NJ): The Institute; 2015. IMS Institute for Healthcare Informatics.
6. Cheung-Ong .Cystic Fibrosis Foundation. Cystic Fibrosis Foundation patient registry: 2013 annual report.
7. Xie. Bethesda, MD: Cystic Fibrosis Foundation; 2015. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: A randomized trial. JAMA. 2012;307:1383–93.
8. Al-Enzy, A. F. M., Saed, Z. J. M., Naser, A. S., Mohammed, Th. T., Abdulateef, S. M., Al- Khalani, F. M. H. & Abdulateef, F. M. The role of adding sodium chloride in broiler chicks diets to improve production performance and antioxidant status during heat stress. Annals of Tropical Medicine and Public Health. 2020, 23(16): 231- 612. Doi: 10.36295/ASRO.2020.231612
9. Huang and Li, H.T., Kathrein, K.L., Barton, A., Gitlin, Z., Huang, Y.H., Ward, T.P., Hofmann, O., Dibiase, A., Song, A., Tyekucheva, S., Hide, W., Zhou, Y., and Zon, L. 2013
10. Emadi, A., Jones, R. J., and Brodsky, R. A. Cyclophosphamide and Cancer: golden Anniversary. Nat. Rev. Clin. Oncol. 6 (11), 638–647. doi:10.1038/nrclinonc.2009.146
11. Lawley P.D. and Phillips,D.H. Mutat. Res., 355, 13–40.1996
12. Bagley A prospective study of 22,707 men in Taiwan. Lancet;2:1129 –33. 1973
13. Lopes, MD Serrao, SM Gressert Ussery, RG Hall II , etal: Evaluation of chemotherapy-induced severe myelosuppression incidence in obese patients with capped dosing J Clin Oncol 7: 13– 17,2011 Google Scholar (Williston Park. 2009.
14. Kümmerer, Nakamura, E. F., & Kessler, R. C. Epidemiology of mental disorders in children and adolescents. Dialogues in Clinical Neuroscience.2010, 11, 7.