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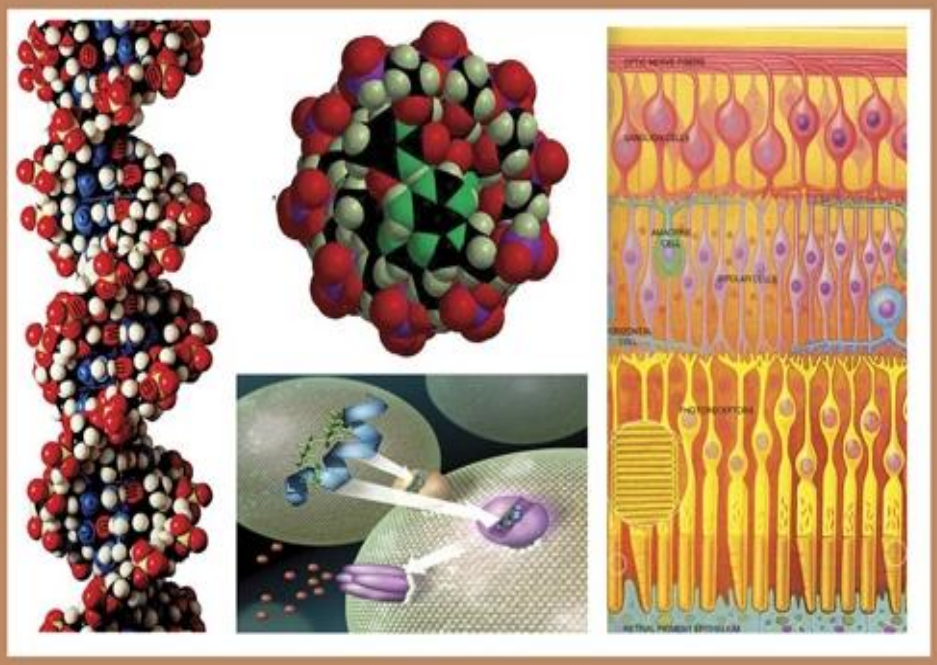

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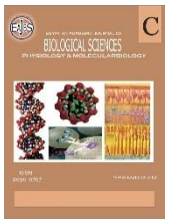

A Novel Study on the Hematological and Physiological Disturbance of Ivermectin-COVID 19 Treatment Abuse in Male Wistar Rats

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ABSTRACT

Background: During COVID-19 and reported prevalence of self-medication practices dup to 88.35 % of the overall population which included mainly acetaminophen, antibiotics, chloroquine and ivermectin. Pointless prophylaxis, prevention and treatment protocols for COVID-19 pushed people to adopt self-medication and more concerning, self-dosing without prescription. The present study was designed to detect the therapeutic effect of COVID-19 treatment protocols (ivermectin) followed by the administration of lactoferrin on biochemical as well as haematological parameters in experimental Albino rats. **Material and Methods:** Thirty adult male albino rats were carried out in the present study; rats were randomly assigned to different control and treatment groups. The experimental groups in common were divided into three groups (Each group have10 rats) as the following: **Group I:** Rats received saline solution orally); **Group II:** Rats Ivermectin intraperitoneal (ip) at (15 mg/kg B.W) at a single dose weekly for 6 weeks; **Group III:** Rats administrated to Ivermectin intraperitoneal (ip) at (15 mg/kg B.W) followed by treatment of Lactoferrin per orally for 6 weeks. Blood samples were collected under diethyl ether anaesthesia for further determination of hematological and biochemical parameters. **Results:** Following the present results, the administration of therapeutic ivermectin produced alterations in some biochemical parameters which correlated with hematological parameters in the positive untreated group as compared to the normal control group. In contrast, a group of rats administrated lactoferrin caused a reduction in urea, and creatinine levels in the positive treated group in comparison to the positive untreated group. **Consequently**, it could be concluded that it is not preferable to use ivermectin, particularly without any recommendation or evidence of parasitic exposure while lactoferrin need to be used for prophylaxes prior to oral intake in need.

INTRODUCTION

The year 2020 was demarcated by COVID-19, the worst pandemic in the past 100 years. COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had a major impact on human health globally; infecting about 75 million people and affecting 1.6 million deaths worldwide and associated with long-term health sequelae. Covid -19 has disrupted lifestyles, including work, education, trade, travel, sports, routine healthcare services and social activities. This had a great impact on people's physical and mental health (WHO, 2020a).

According to WHO reports, the estimated number of confirmed cases of SARS-CoV-1 in Egypt from Jan. 2020 to June 2021 was 276,756 with 15,829 deaths (WHO, 2021).

Since the beginning of this pandemic, researchers and doctors have searched for medications and vaccines to treat covid 19. Although there is no specific curative treatment till now, many drugs such as tocilizumab, heparin, remdesivir, chloroquine and ivermectin have been introduced in the treatment protocols. Also, symptomatic treatment for fever and pain relief by paracetamol as a safer drug rather than NSAID has been introduced in almost all treatment protocols (NIH, 2021). In Egypt, The Ministry of Health protocol included ivermectin and paracetamol for the treatment of mild cases which required to be isolated as well as followed treatment at home and in moderate cases which may require hospitalization (MOHP, 2020).

Ivermectin is considered a anthelmintic broad-spectrum and frequently reflected as a macrocyclic lactone, is commonly used to control parasitic infestations against parasitic diseases in both animals and human beings approved by the Food and Drug Administration (FDA) as an antiparasitic drug used for the treatment of onchocerciasis, helminthiases, and scabies where it is well tolerated in such conditions (Yang *et al.,* 2020). Although its anti-parasitic activity is well known, there is a lack of studies on its effect according to the host (Qureshi, 2013). Nevertheless, the efficacy of these considered worthwhile to study the biochemical effects of drugs depends on the toxic concentrations presented to the parasite for a certain duration to cause irreversible damage that may cause harm to the host as well (Prichard, 1985). While many papers have been published on the antiparasitic activity of ivermectin, little is known about its toxicity to the host.

Furthermore, Ivermectin-induced adverse side effects have highlighted its oxidative nature with an increasing load of toxic oxygen intermediates causing activation of neutrophils (Njoo *et al.,* 1993) and the burst of eosinophilic granulocytes (Tischendorf *et al.,* 1993). However, *in vitro*, studies suggested that ivermectin inhibits the replication of SARS-CoV-2 in cell cultures (Caly *et al.,* 2020) and interferes with the attachment of (SARS-CoV-2) spike protein to the human cell membrane (Lehrer and Rheinstein, 2020). Although, insufficient clinical trials or observational studies to confirm the clinical effectiveness of ivermectin for COVID-19 treatment (NIH, 2021), it was proposed in some treatment protocols including that of Egypt where it is used as one of the treatment and prophylactic drugs (Hellwig and Maia., 2021) against covid19 (MOHP, 2020). However, it can be toxic to the liver especially when used with some other medications or in patients with existing liver problems, malnourished, underweight, or old age.

However, some studies reported that liver injury associated with the administration of therapeutic doses of ivermectin and for short durations (3-7 days) such as in mild and moderate cases of covid-19 is mild and self-limited (Veit *et al.,* 2006; Hanafy & Abd-Elsalam, 2020). However, not enough studies have been carried out to evaluate the risk of toxicity of both ivermectin and paracetamol when used in combination as in some protocols of covid-19 treatment especially since home management of such drugs doesn't guarantee the use of therapeutic doses and/or recommended duration. Also, ivermectin can diffuse to all tissue compartments except the central nervous system after being taken orally or in other ways (Lankas, *et al*., 1989).

Despite there are several studies on the toxicity of ivermectin, there is a lack of studies on repeated subcutaneous injection of ivermectin in therapeutic and double therapeutic doses. Ivermectin's unfavorable efficacy is influenced by the dosage and time of treatment (Prichard, 1985).

However, Ivermectin overdose may be produced variable side effects ranging from mild to extremely severe (Epstein and Hollingsworth, 2013). In addition to, either therapeutic or toxic doses of ivermectin in albino rats had a marked effect on some liver function parameters (Utu-Baku, 2009). Furthermore, regenerative changes in the brain and kidney as well as in liver were established in rainbow trout organs that indicate a direct toxicity of ivermectin (Jencic, *et al.,* 2006). Although permanent liver damage is not revealed immediately, intoxication of ivermectin may affect may impair hepatocyte function (Hsu, *et al*. 2001).

These animal models are well suited for evidence-of-concept studies into the efficacy of potential vaccines, antiparasitic and antivirals. However, each model system has limitations, and as of this writing (April 2020), no documented animal model of SARS-CoV-2 infection entirely reproduces every critical trait of severe COVID-19 infection. Recently, it has been reported that IVM is widely used for prophylaxis and associated with a reduction of SARS-CoV-2 infection among healthcare workers for weeks (Al-Zharani *et al.*, 2022). Hence, the present study aimed to assess the pathophysiological effects of Ivermectin on the Hematological and biochemical parameters in normal albino rats after six weeks.

MATERIALS AND METHODS

Iversine tablets, each containing 6 mg of ivermectin and manufactured by Uni Pharma company, Egypt. Bovine Lactoferrin (LF) was provided by Jarrow Formulas (Superior Nutrition and Formulation, Los Angeles). LF was prepared to give a required dose concentration of (100mg/Kg bw) by dissolving LF in distilled water (SH, 2018).

Experimental Design:

Thirty (12 weeks old) adult male albino rats (*Rattus norvegicus*) were carried out in the present study. The animals were randomly assigned to control and different treatment groups and were divided into five groups (10 rats in each group) as the following: Group I: Rats received saline solution orally; Group II: Rats administrated Ivermectin intraperitoneal (ip) at (15 mg/kg B.W) dissolved in saline solution as single dose weekly for 6 weeks according to Qureshi (2013); Group III: Rats administrated to Ivermectin followed by treatment of Lactoferrin per orally at (100 mg/Kg b.w) by dissolving in distilled water according to SH (2018). The experimental period was designated to be 6 weeks for drug administration while rats stand for one week to acclimatize prior to starting the experiment.

Blood Sample Collection:

At the end of the experiment, rats were fasted for 12 hr weighed and the blood samples were collected under diethyl ether anesthesia from retro-orbital venous plexus puncture using blood capillary tubes from each animal. One part of the blood samples was collected on EDTA (Ethylene Diamine Tetra Acetic Acid) for hematological study. The other part was left to clot at room temperature for 45 minutes. Sera were separated by centrifugation at 3000 rpm at 20°C for 15 minutes where the clear serum was obtained and kept frozen at -20°C for various physiological and biochemical analyses.

Biochemical Analysis:

Liver enzymes were assessed. Serum levels of alanine transaminase (ALT), and aspartate transaminase (AST) determined according to (Reitman and Frankel,1957). Serum albumin concentration was determined according to the colorimetric method described by Doumas *et al.* (1971). Serum urea level was estimated according to the colorimetric method described by Fawcett & Soctt (1960). Serum creatinine level was determined according to the colorimetric method described by Larsen (1972).

TSH, FT3, and FT4 levels were measured with the electrochemiluminescence method (Roche Diagnostics, Mannheim, Germany). Increased and decreased thyroid hormone (Serum FT_3 & FT4) levels were defined according to age-specific reference limits established by Kratzsch *et al.* (2008).

Estimation of serum testosterone level was adopted using enzyme-linked immune-sorbent assay (ELISA) kit according to Tietz, (1995).

Hematological Studies:

Hematological parameters include Red Blood Corpuscles (RBCs), White Blood Cells (WBCs) and Differential leucocytes count as well as Erythrocytes Indices were measured in a part of the blood collected in EDTA by using a haematological cell counter (Sino thinker. sk9000, U.S), Physiology research lab in the faculty of science, Al-Azhar university, Nasr city, Cairo. Egypt.

Statistical Analysis:

Data were presented as means (±SEM). Statistical analysis was concluded by using One-way ANOVA followed by Dunnett's test for comparison of treated groups with the corresponding values in control group. At $p < 0.05$ differences were measured as significant.

Aim of the Work:

The aim of this work is to evaluate the side effects to using the COVID-19 treatment protocol, especially Ivermectin in normal albino rats' model in relation to their clinical presentation in humans during medication abuse. In addition, we discuss the pathophysiological changes related to the administration of COVID-19 treatment. However, lactoferrin used as a prophylaxis against prospective adverse side effects related to administration.

RESULTS

Biochemical Parameters:

Biochemical parameters include Liver Function tests (ALT, AST, and Albumin) and Kidney Function tests (Urea & Creatinine). One-way ANOVA followed by Dunnett's test for comparison of treated groups with control group were represented in Table (1).

Table 1: Mean±S.E Values of Liver function (ALT & AST) activities as well as Albumin level and kidney Function (Urea & Creatinine) levels in all subject groups.

Biochemical Parameters	Liver Function Tests						Kidney Function Tests			
	ALT (IU/ml)		AST (IU/ml)		Albumin (g/dl)		Urea (mg/dl)		Creatinine (mg/dl)	
Experimental groups	**Mean±S.E**	***P-value***	**Mean±S.E**	***P-value***	**Mean±S.E**	***P-value***	**Mean±S.E**	***P-value***	**Mean±S.E**	***P-value***
Group I	48.4±3.3		20.8±4.9		4.2±0.1		45.5±2.1		0.5±0.0	
Group II	112.5±7.4	*P<0.001* [a]	110.4±6.1	*P<0.001* [a]	3.4±0.4	*P<0.05* [a]	66.8±4.3	*P<0.001* [a]	1.8±0.1	*P<0.001* [a]
% Change	132%		430%		-19%		272%		431%	
Group III	51.3±2.5	*P<0.001* [b]	40.0±3.9	*P<0.01* [a]	4.1±0.2	*P<0.05* [b]	51.5±4.1	*P<0.001* [b]	1.4±0.0	*P<0.001* [a]
% Change	-54%		-64%	*P<0.001* [b]	21%		-19%		-64%	
F-Probability	*P<0.001*		*P<0.001*		*P<0.001*		*P<0.001*		*P<0.001*	

Mean value represents mean of 8 records ± SE.

Percent of changes (%) are calculated by comparing Group II with negative control group (GI); whereas (%) are calculated by comparing Group III with Positive control group (GII).

Means with dissimilar superscript letter are significantly different at $P < 0.05$; Where, Means, which have the same superscript symbol (N.S.), are not significantly different. Symbol [a] represent that P-value significant when compared to Negative control group (I). Whereas Symbol [b] represent that P-value significant when compared to positive control groups (II).

Liver Functions:

The represented data of ALT activity showed a highly significant increase in positive control groups administrated to ivermectin when compared to the mean corresponding values negative control group respectively. Furthermore, ALT activity showed a highly significant decrease in positive group treated with ivermectin in combination with Lactoferrin as compared to the mean value in positive untreated group. The results of the present study showed that ivermectin induced a significant increase in liver function enzymes (AST and ALT) in comparison to control group, which is dose-dependent that confirms the hepatotoxicity of ivermectin. Moreover, AST showed a significant increase in positive untreated and treated control groups when compared with the mean value in negative control group. Whereas AST activity showed a significant decrease in positive groups treated with ivermectin in combination with Lactoferrin as compared to the mean value in positive

untreated control group. On the other hand, the results of serum albumin levels in positive untreated group showed a significant decrease as compared to the mean values in negative control group. However, the albumin level in positive-treated group showed a significant increase compared to positive-untreated group.

Kidney Functions:

The results of serum Urea and creatinine levels showed a highly significant increase in the positive-untreated group when compared to negative control group. Also, serum creatinine levels reported a significant increase in positive treated group as compared to the negative control group. On the other hand, serum Urea levels in positive treated group showed a highly significant decrease when compared with the corresponding values of positive untreated group.

Hematological Parameters:

The data of Hematological parameters were represented in Tables (2 & 3) after One-way ANOVA followed by Dunnett's test for comparison of treated groups with the control group. According to hemoglobin which is related to RBC.s and Erythrocytes indices (MCV & MCH) there are no significant changes found between all subject groups. However, the percentage of Hematocrit (%) showed a highly significant increase in positive untreated group when compared to negative control group. However, Hct (%) in positive treated group showed a significant decrease compared to positive untreated group. Furthermore, the Mean Corpuscular Hemoglobin Concentration (MCHC) level significantly declined in positive untreated group when compared to negative control group. However, MCHC level in the positive treated group was significantly elevated near to store in normal level in comparison to positive untreated group.

On the other hand, total leucocytes count and its differential (Lymphocyte, Monocytes, Neutrophil and Basophil) showed a highly significant increase in the positive untreated group when compared to negative control group. Nevertheless, Platelets Count, in positive untreated group showed a highly significant decrease when compared to negative control group. However, total leucocytes count, and its differential significantly declined near to store normal level in comparison to positive untreated group. Yet, Platelets Count, in positive treated group was significantly elevated compared to positive untreated group.

Table 2: Mean±S.E Values of Hb %, RBC.s, Hct and Erythrocytes indices (MCV, MCH and MCHC) in all subject groups.

Hematological Parameters	**RBCs (10^6/mm^3)**		**Hb (g/dl)**		**Hct (%)**		**Erythrocyte indices**					
							MCV (fl)		**MCH (pg)**		**MCHC g/dl**	
Experimental groups	Mean ±SD	*P- value*	Mean ±SD	*P- value*	Mean ±SD	*P- value*	Mean ±SD	*P- value*	Mean ±SD	*P- value*	Mean ±SD	*P- value*
Group I: (Normal)	6.48±1.19		13.75±0.69		41.25±2.07		71.34±7.22		23.78±2.41		33.3±0.00	
Group II: (Ivermectin)	6.79±0.40	*N.S.*	13.98±0.98	N.S.	50.85±3.21	*P<0.01* [a]	75.14±0.85	*N.S.*	24.25±0.27	*N.S.*	28.4±2.53	*P<0.05* [a]
% Change	4.79%		3.47%		23.27%		5.33%		1.98%		-14.83%	
Group III: (Ivermectin + Lactoferrin)	6.23±0.12	*N.S.*	14.55±0.19	N.S.	43.65±0.58	*P<0.05* [b]	70.08±0.52	*N.S.*	23.38±0.16	*N.S.*	33.0±0.00	*P<0.05* [b]
% Change	-8.12%		4.11%		-14.16%		-6.74%		-3.61%		16.4%	
F-Probability	*N.S.*		*N.S.*		*P<0.01*		*N.S.*		*N.S.*		*P<0.05*	

Mean value represents mean of 8 records ± SE.

Percent of changes (%) are calculated by comparing Group II with negative control group (GI); whereas (%) are calculated by comparing Group III with Positive control group (GII).

Means with dissimilar superscript letter are significantly different at $P < 0.05$; Where, Means, which have the same superscript symbol (N.S.), are not significantly different.

Symbol [a] represent that P-value significant when compared to Negative control group (I). Whereas Symbol [b] represent that P-value significant when compared to positive control groups (II).

Table 3: Mean±S.E Values of WBC.s and Differential leucocytes (Lymphocytes, Monocytes, Neutrophils, Eosinophiles and Basophils) as well as Platelets in all subject groups.

Hematological Parameters	T. WBCs (10^3/mm^3)		Differential leucocytes										Platelets (10^3/mm^3)	
			Lymphocyte (%)		Monocyte (%)		Neutrophil (%)		Basophil (%)		Eosinophil (%)			
Experimental groups	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***	**Mean ±SD**	***P- value***
Group I: (Normal)	6.9±0.52		78.25±2.02		5.9±0.90		12.75±1.92		0.50±0.19		2.63±0.18		486±56.3	
Group II: (Ivermectin)	16.4±2.75	*P<0.001 a*	65.3±3.19	*P<0.001 a*	10.5±0.73	*P<0.001 a*	19.88±2.72	*P<0.001 a*	0.75±0.37	*N.S.*	3.6±0.32	*P<0.05 a*	241±30.5	*P<0.01 a*
% Change	137.07%		-16.61%		78.72%		55.88%		50.00%		38.10%		-50.32%	
Group III: (Ivermectin + Lactoferrin)	4.03±0.23	*P<0.001 b*	80.9±1.76	*P<0.001 b*	6.8±0.86	*P<0.001 b*	8.63±0.98	*P<0.001 b*	0.88±0.35	*N.S.*	2.9±0.30	*N.S.*	714 ±45.6	*P<0.01 a* *P<0.001 b*
% Change	-75.44%		23.95%		-35.71%		-56.60%		16.67%		-20.69%		196.11%	
F-Probability	*P<0.001*		*P<0.001*		*P<0.001*		*P<0.001*		*N.S.*		*P<0.05*		*P<0.001*	

Mean value represents mean of 8 records ± SE.

Percent of changes (%) are calculated by comparing Group II with negative control group (GI); whereas (%) are calculated by comparing Group III with Positive control group (GII).

Means with dissimilar superscript letter are significantly different at $P < 0.05$; Where, Means, which have the same superscript symbol (N.S.), are not significantly different.

Symbol [a] represent that P-value significant when compared to Negative control group (I). Whereas Symbol [b] represent that P-value significant when compared to positive control groups (II).

DISCUSSION

Since the beginning of this pandemic, researchers and doctors have searched for medications and vaccines to treat covid 19. Although there is no specific curative treatment till now, many drugs such as tocilizumab, heparin, remdesivir, chloroquine and ivermectin have been introduced in the treatment protocols. Also, symptomatic treatment for fever and pain relief by paracetamol as a safer drug rather than NSAID has been introduced in almost all treatment protocols (NIH, 2021). In Egypt, the Ministry of Health protocol included invermectin for treatment of mild cases which required only isolation and treatment at home and in moderate cases which may require hospitalization. (MOHP, 2020). Ivermectin is a Food and Drug Administration (FDA) approved antiparasitic drug used for the treatment of onchocerciasis, helminthiases, and scabies where it is well tolerated in such conditions (Yang *et al.*, 2020). On the other hand, it is not FDA-approved for the treatment of viral infections since pharmacokinetic and pharmacodynamics studies stated that 100-fold higher doses than those approved for use in humans are needed to get anti-viral efficacy (Chaccour *et al.*, 2020). Although, insufficient clinical trials or observational studies to confirm the clinical effectiveness of ivermectin for COVID-19 treatment (NIH, 2021), it was proposed in some treatment protocols including that of Egypt where it is used as one of the treatment and prophylactic drugs (Hellwig and Maia, 2021) against covid19 (MOHP, 2020).

Antiparasitic drugs are critical for animal husbandry development and animal health safety, however, they must be supplied regularly due to their short half-life and insolubility, which limits bioavailability (Ceylan *et al.*, 2021). Because of the potent antiparasitic activity of ivermectin, its therapeutic dosage is low and ranges from 0.2 to 0.3 mg/Kg B.W in most animal species. A wide range of physiological and metabolic activities impacting target organ identification and tissue injury evaluation are assessed using various biochemical markers. (Akhtar *et al.*, 2012). Biochemical parameters including enzymes such as ALT and AST are considered an important indicator of liver damage in clinical studies, while urea and creatinine for glomerular dysfunction (Evans, 1996). Therefore, the present study was designed to investigate the therapeutic dose effect of ivermectin on the changes in biochemical parameters of the liver and kidneys as well as haematological parameters of albino rats.

The increased activity of liver enzymes (ALT and AST) could be attributed to hepatotoxicity, which causes an increase in the permeability of the hepatic cell membrane or its rupture, resulting in leakage of lysosomal enzymes, which increases the release of liver enzymes into the bloodstream (Shrivastava *et al.*, 1989). Several studies have reported an elevation of

transaminase activity as a result of hepatocellular injury, as in death or damaged cells, these enzymes leak into the bloodstream (Choudhary *et al.*, 2003; Mansour and Mossa, 2010), which is consistent with the current study's findings. Furthermore, previous studies had shown that the electrophilic and oxidative properties of ivermectin may be responsible for a variety of metabolic alterations (Bloomquist, 2003). However, several studies indicated that hepatic and renal alterations frequently occur after administration.

Also, the present study demonstrated that the level of urea and creatinine were significantly increased following ivermectin injection was matched with the findings of Homeida *et al*. (1988) and Ragab, (1994). This elevation may be due to a direct effect of ivermectin or its metabolites on the renal tissue. The elevation in creatinine in a positive untreated group with ivermectin may be attributed to the reduction in glomerular filtration in the kidney, as well as dysfunction of the renal tubules (Walmsley and White, 1994).

Hematological parameters are reported as an integral part of toxicity and safety measurement in animal models (Evans, 2008). Slight pathological changes in tissues, or organs can cause changes in blood composition, so the results of hematology examination are of great help to understanding the diseases of the body (DeBonis and Pierre, 2011). The results suggested that high doses of ivermectin can cause hematological variations. Some studies have suggested that the observed alterations in hematopoietic system parameters may indicate interference with the hematopoietic function of the bone marrow system by exogenous substances (Adeoye *et al.,* 2015).

Previous studies on ivermectin have shown a reduction of hemoglobin levels, but the results are not significant (Hosseini Omshi *et al.,* 2018). In addition to that, there are no significant differences between R.B. Cs, MCV and MCH besides Hemoglobin level between all experimental groups. Although there is insufficient evidence to prove that the decline in hematological parameters is due to ivermectin suppression of the hematopoietic system, it is still noteworthy. According to the results of hematological parameters, rats were more sensitive to the toxicity of ivermectin, and these results are in accordance with the study of Dong *et al.* (2020). However, the percentage of Hematocrit (%) showed a highly significant increase in positive untreated group when compared to negative control group. While Hct (%) in positive treated group showed a significant decrease compared to positive untreated group. Furthermore, the Mean Corpuscular Hemoglobin Concentration (MCHC) level significantly declined in positive untreated group when compared to negative control group. However, the MCHC level in positive treated group was significantly elevated near to store in normal level in comparison to positive untreated group.

In this experiment, male rats showed leukocytosis and its differential leucocytes were significantly elevated in positive untreated group when compared to negative control group. This alteration of leukocytosis and its differential leucocytes count occurred due to the disturbance in the haematopoiesis of the bone marrow system. The results agree with the study of Adeoye *et al.* (2015). Nevertheless, Platelets Count, in the positive untreated group showed a high significant decrease when compared to the negative control group. However, total leucocytes count, and its differential significantly declined near to store normal level in comparison to the positive untreated group. Yet, the Platelets Count, in positive treated group was significantly elevated compared to the positive untreated group.

Declaration of Conflicting Interests:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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