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The aqueous extract of *Leptadenia pyrotechnica* Decne enhances the innate immune response and inhibits the acquired immune response, while the aqueous extract of *Capparis cartilaginea* Decne does the exact opposite in Healthy Rats

Elham H Algahdali[1], Sawsan H Mahassni[1]

[1] Biochemistry Department, King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT

Leptadenia pyrotechnica (Forssk.) Decne. (LP) and *Capparis cartilaginea Decne*. (CC) are plants used in local folk medicine, although there are no published studies on their physiological, hematological, and immune system effects. This study is the first to determine and compare the effects of aqueous LP and CC extracts on body weight parameters, consumptions of feed and water, and the differential complete blood counts in blood samples of healthy Wister albino rats. Six groups of rats (3 rats/group) were orally gavage separately with the aqueous extracts of LP (groups LP1, LP2, and LP3, respectively) and CC (groups CC1, CC2, and CC3, respectively) at concentrations of 30, 100, and 200 mg/kg body weight, while three control rats were gavage with water, daily for two weeks. Body weights were measured daily. The mean total body weights were not significantly different between all groups, between the experimental groups and the control group, and between the equal concentrations of LP and CC groups. The mean total and daily body weight gains and percent relative total body weight gain for the LP3 group were significantly lower compared with the control group. The mean feed and water intakes were highly significantly lower for the LP2, LP3, CC2, and CC3 groups compared with the control group, and for the LP3 group it was significantly lower compared with the CC3 group. The FER for the LP3 group was significantly lower compared with the control group. The mean lymphocyte percent for CC1 was significantly higher and the mean lymphocyte count for LP1 was significantly lower compared with the control. The mean neutrophil percent for LP1 was significantly higher than for CC1 and the mean lymphocyte percents for LP1 and LP2 were significantly lower than for CC1 and CC2. In conclusion, the LP extract enhances the innate immune response and inhibits the acquired immune response, while the CC extract does the exact opposite. Thus, the extract may be used for modulating the immune response.

Keywords: *Leptadenia pyrotechnica* (Forssk.) Decne., *Capparis cartilaginea* Decne., folk medicine, differential complete blood count, Wister albino rats, aqueous extract, orally gavage.

INTRODUCTION

One of the most important systems in the body is the immune system which protects the body from pathogens. Various exogenous and endogenous agents contribute to the efficiency and function of the immune system and lead to immunosuppression or immunostimulation [1]. The two main types of immune response, the innate and acquired immunity, function through diverse white blood cells (WBC), molecules, and organs. The neutrophils, basophils, eosinophils, and monocytes are the main cells of the innate (or natural) immunity, while the lymphocytes are the major cells of the acquired (adaptive) immunity [2]. Many diseases and conditions that afflict humans, such as cancer, autoimmune diseases, inflammation, and organ transplant rejection are due to a dysfunction or malfunction of the immune system [3]. Therefore, it is essential to strive to maintain a healthy and strong immune system for an efficient immune response. The immune response and its activity may be modified by different factors, some of which are unmodifiable, such as age and genetics, while others are modifiable, such as lifestyle factors like nutrients, types of foods consumed, stress levels, and hours of sleep. In addition, it is possible to modulate the activity of the immune response by affecting the counts of WBC. This may be achieved by different ways, including by the use of natural plants and seeds that have been used as alternatives to conventional medications for the treatment of different diseases that may enhance the immune system [4].

Plants and plant products have been used since prehistoric times in alternative and folk medicines to enhance health, treat many different diseases, and to enhance different systems in the body including the immune system to help the body avoid and fight diseases. According to the World Health Organization

***Corresponding author:**
Dr. Sawsan H Mahassni
Biochemistry Department, King Abdulaziz University, Jeddah, Saudi Arabia
Email: sawsanmahassni@hotmail.com

(WHO), up to 88% of people worldwide utilize plants to treat illnesses and ailments [5]. Furthermore, a lot of the drugs used in conventional medicine have ingredients made from plants and their parts. The use of plants and seeds offers many benefits, some of which are few or no side effects, the low or no cost for the plants, and ease of obtaining these plants and seeds. Many medicinal plants and seeds are harmless to humans and possess anti-inflammatory, immunomodulatory, and other medicinal properties, such as moringa oleifera, garden cress seeds, black seeds, and soybean [6-8].

Leptadenia pyrotechnica (Forsk.) Decne. (LP), known as markh in Arabic, is a shrub of the Asclepiadaceae family that grows in different parts of Africa, Asia, the Mediterranean region and in the Western Gulf countries including Saudi Arabia. It is found in sandy planes, forests, farms and on the sides of roads [9]. The LP plant contains many different components, such as phenolic compounds, terpenes, flavonoids, tri-terpenoids, alkaloids, cardiac glycosides, pregnane glycosides, free fatty acids, and amino acids, leading to different effects and activities [10-12]. A previous study showed that the LP aqueous methanolic extract has the ability to stimulate the immune system [1]. LP is used traditionally for the treatment of a variety of inflammatory diseases, including rheumatism, asthma, gout, wound healing, and tumors [1]. Several studies [13, 14] have reported that it has antispasmodic, antihistaminic, antibacterial, hypoglycemic, diuretic, expectorant, laxative, hypolipidemic, and antiatherosclerotic actions.

Capparis is the largest genera of the plant family Capparidaceae, commonly named caper family, which includes between 250 and 400 species of woody climbers, shrubs, and trees. The Capparidaceae plants are found in the Middle East, including Saudi Arabia, southwest Asia, north and east Africa, Europe, southern America, Australia, the Pacific Islands, and Madagascar [15]. *Capparis cartilaginea Decne*. (CC), named lattssaf, laşaf or nişaf in Saudi Arabia, is a perennial species that produces edible oval fruits [15]. CC is used in folk medicine in the Arab world for a variety of ailments, including the treatment of tendinitis, earaches, headaches, paralysis, edema, and skin and joint inflammation, and for the treatment of snakebites [16]. In Saudi Arabia, it is used to treat knee discomfort, head colds, tumors, shortness of breath, head itching, and head colds [17]. In addition it is used as a disinfectant, wound wash, antitumor medicine, tonic, and purgative [18]. The CC plant contains isothiocyanates, saponins, alkaloids, tannins, triterpenes, sterols, and protein, polyphenols, flavonoids, and carbohydrates[19, 20]. These active components are responsible for the immunostimulant, anti-inflammatory, and immunomodulatory activities and other effects of the CC plant. Previous investigations have shown that various Capparis species extracts, including those from Saudi Arabia's *C. spinosa* and *C. decidua*, have a strong anti-inflammatory action [21] and some effects on cytokines [22]. CC has been shown [15, 19] to have antioxidant, cytotoxic, larvicidal, antibacterial, hypotensive, and bradycardic properties.

Previous studies showed that the botanically-derived phytochemicals found in both LP and CC have anti-inflammatory and immunomodulating properties [23]. However, there is no published research demonstrating the immunomodulatory activity of the aqueous extracts of LP and CC in healthy rats. Nevertheless, the extensive traditional uses of LP and CC, such as healing of wounds, allergic skin diseases, rheumatism, pain, and their use as stimulants and general tonics [24], show that the plants affect certain aspects of the immune system. Therefore, it is highly advantageous to scientifically investigate the effects of both plants on the immune system and its cells for possible therapeutic use and as home remedies.

The RBC and platelet counts, and hemoglobin concentrations are effected by general health and studies have shown that they have some roles in immune functions [25]. Platelets are an acute phase reactant to infection or inflammation. The CBC determines some indices that are related to the different cells in the blood and some diseases and conditons. Plateletcrits (PCT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet-large cell ratio (PLCR) are platelet indices [26] and they are used to diagnose some disease some of which are immune diseases. In addition, the RBC and hemoglobin help assess anemia and erythropoiesis. The mean red blood indices, which describe size and volume of RBC, and hemoglobin content of RBC, are the hematocrit (HCT), red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Finally, the nucleated RBC (NRBC) measure the nucleated RBC, which are found in certain disease. These indices are related to anemia, polycythemia, and other medical conditions. The reticulocyte percent (RET) and reticulocyte hemoglobin content (RET-He) measure the percentage of total reticulocytes in red blood cells and their hemoglobin content. They diagnose diseases related to the RBC indices and other blood cells. A high immature granulocyte (IG) may indicate that the immune system is fighting an infection, the presence of inflammation, and autoimmune and other conditions. Low fluorescence ratio (LFR%), medium fluorescence ratio (MFR), and high fluorescence ratio (HFR) are used to classify white blood cells [27]. These indices are used to diagnose some immune related disease and some cancers. Immature reticulocyte fraction (IRF) is a the combination of HFR and MFR and it is used to study the pathology of red blood cell formation and to test the effectiveness of anemia treatments [28].

Research studies on LP and CC are limited [29, 30]. There is only one study [31] that determined the effects of aqueous LP extracts on the immune system, leading to suppressed innate immune responses and enhanced adaptive immune responses. However, to our knowledge, there are no studies that investigated the immunomodulatory effects of the oral intake of each of the aqueous extracts of LP and CC in healthy rat models and this study does just that. As the use of aqueous extracts, rather than the alcoholic extracts, is the preferred approach in local (Saudi Arabian) traditional medicine and is the one that the average person can easily acquire at home, it was chosen in the present study. Therefore, the purpose of this study was to determine the effects of the aqueous extracts of LP and CC separately on the body weights, amount of water and feed consumed; and the counts of immune system cells, RBC, and platelet; hemoglobin levels; and other hematological parameters. If LP and CC do really impact the counts of immune system cells and red blood cells, this might help in determining the appropriate amount of extracts for human usage to treat various illnesses.

METHODOLOGY

Collection of plant materials

The young stems of LP, not containing any leaves or flowers and only plump stems, were collected during the month of March 2022, from Jeddah and, Makkah, Saudi Arabia. The CC leaves (only dark green and complete leaves) were collected from Taif, Saudi Arabia. LP stems and CC leaves were confirmed by a taxonomist. The LP stems and CC leaves were cut to small pieces, cleaned with distilled water, dried in the shade, and then thoroughly screened to eliminate any foreign objects. Subsequently, they were stored at -20 °C for later use.

Preparation of aqueous extracts

After being sliced into small pieces, 500 g of LP stems were boiled in 1200 L of water for 10 minutes to create the aqueous extract of LP stems which is a modification of a previous study [32]. To prepare the aqueous extract of CC leaves, the same amount used for LP were tried but it was found to produce a very concentrated extract. Thus, after several different amounts were used, the method was modified to better suit the CC leaves. Therefore, the CC extract was prepared by boiling 250 g of CC leaves in 1500 L of water for 10 minutes. The extracts were filtered using filter papers and subsequently administered to the rats. Fresh extracts were used every two to four days. After four days any remaining extracts were discarded.

Experimental animals and groups

In this study, 21 healthy male Wister albino rats, 9 weeks old, weighing 200-265 g, were used. The rats were kept at room temperature and exposed to artificial light for 8 to 10 hours each day. Water and food were freely available. The rats were brought into the lab seven days before to the experiment's start to acclimatize to the laboratory conditions. Rats were then randomized into seven groups and orally gavaged with water or plant extract, depending on their group, for 14 days. Three groups were orally gavaged with three different doses of LP aqueous extracts (LP1 = 30, LP2 = 100, and LP3 = 200 mg/kg). Another three groups of rats were gavaged with three different doses of CC aqueous extracts (CC1 = 30, CC2 = 100, and CC3 = 200 mg/kg). Finally, 3 ml of water were gavaged orally to the control group. This study was reviewed and approved by the Animal Care and Use Committee Office (ACUC) at King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia (approval number ACUC-23-01-03). Animal welfare standards and all laws governing the ethical treatment of experimental animals were followed.

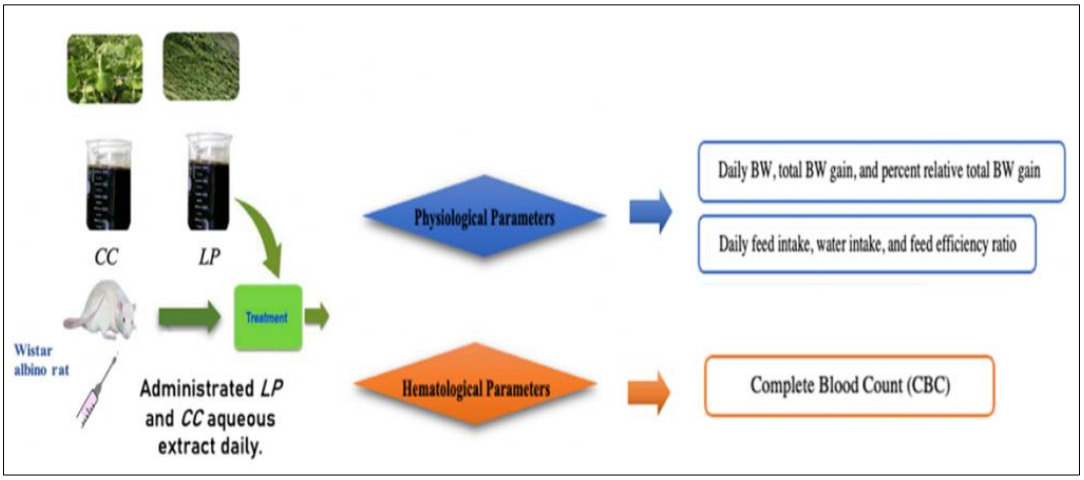

Figure 1: The experimental design for the determination of the effects of the aqueous extracts of LP and CC in Wister albino rats

MEASUREMENT OF PHYSIOLOGICAL PARAMETERS

Calculation of the mean total, daily and weekly body weights

For the physiological evaluation of the rats, the mean total, daily, and weekly body weights for each group were calculated. The mean total body weight for each rat was calculated by taking the mean of the daily body weights for the entire experimental period. Subsequently, the mean daily body weight for all rats in each group were calculated. The mean weakly body weight for each rat was calculated by taking the mean of the body weights for the rat for each week separately. The mean weekly body weight, for weeks 1 and 2 separately, for all rats in each group were then calculated.

Calculation of the mean total and daily body weight gain and percent relative total body weight gain

The mean total body weight gain for each group was calculated by subtracting the initial body weight for each rat from its final body weight and then calculating the mean for the group. The daily body weight gain for each rat was calculated by subtracting the body weight for the previous day from the current body weight. Subsequently, the mean of the weight gains for the rats in each group was calculated. The mean percent relative total body weight gain for each rat was calculated using the following equation:

$$\% \text{ Relative total body weight gain} = (\text{final weight- initial weight})/(\text{inital weight}) \times 100$$

Subsequently, the mean percent relative total body weight gain was calculated for each group.

Calculation of the mean total, daily, and weekly feed intake, water intake, and feed efficiency ratio

The mean total feed and water intakes for the experimental period were calculated by taking the mean of the daily feed and water intakes for all the rats in each group separately. The daily feed intake for each group was calculated by subtracting the weight of the remaining feed from the weight of the feed placed in the cages the day before. The

daily mean water intake for each group was calculated as done above for the feed intake, using the volume of water consumed daily. Subsequently, the mean feed and water intakes for each group were calculated. The daily feed efficiency ratio (FER) for each group was calculated using the following equation:

Daily FER = daily body weight gain for the group/daily feed intake for the group

Blood collection and complete blood count

Blood was drawn from the retro-orbital plexus at the end of the experimental period under ether anesthesia into heparinized tubes to determine the total blood count (CBC). The differential CBC and other hematological parameters were determined for all rats at the end of the experimental period by using an Automated Hematology Analyzer MYTHIC 22 OT [C2 Diagnostics, Montpellier, France]. The total white blood cell counts were determined for all rats on days 7 and 14.

Statistical analysis

The MegaStat statistical program (Version 9.4, Butler University, Indianapolis, Indiana, USA) was used for the statistical analysis. The one-way ANOVA test was used for the comparisons between all groups for all the parameters. On the other hand, the pairwise t-test was used for the significance testing between the experimental groups and the control, and between the LP and CC groups of the same dose for all parameters. The statistical difference was considered significant for $P < 0.05$, highly significant for $P < 0.01$ and non-significant for $P \geq 0.05$.

RESULTS

Percentage yield of the LP and CC extracts

To calculate the yield for the extracts, the LP and CC extracts were air dried, separately, for two days to produce semisolid precipitates that were green for LP and brown for CC The semisolid extracts of LP and CC were then weighed, and the percent yield of the extracts were calculated. The mean of three LP and CC extract preparation and evaporation were used for the determination of the yield. The mean percent yield for LP and CC were 1.28% and 9.64%, respectively.

Determination of the of physiological parameters

Using the one-way ANOVA test, shown in Table 1, there were no significant differences between the groups for the mean total body weights. In addition, for the post hoc analysis, using the t-test, there were no significant differences between the mean total body weights for each of the experimental groups and the control group. Finally, there were no significant differences for the mean total body weights between the LP1 and CC1, LP2 and CC2, and LP3 and CC3 groups. The effects of the LP and CC extracts on the mean total and daily body weight gains and percent relative total body weight gains compared to the control group are shown in Table 1. The one-way ANOVA showed no significant differences between all the groups. As for the comparisons between each experimental group and the control, using the t-test, the mean total and daily body weight gains and percent relative total body weight gain for the LP3 group were significantly lower compared to the control group. All other comparisons were not significantly different. Finally, for the post hoc comparisons between the same dose of LP and CC (Tables 1), there were no significant differences for the mean total and daily body weight gains and percent relative total body weight gains.

The one-way ANOVA test showed (Table 1) highly significant differences between all groups for the mean total feed and water intakes. As for the post hoc analysis between the experimental groups and the control, using the t-test, the mean feed and water intake for the LP2, LP3, CC2, and CC3 groups were significantly lower compared to the control group. Finally, the post hoc comparisons between the same concentrations of the LP and CC groups showed significantly lower mean total feed and water intakes for the LP3 group compared to the CC3 group. In addition, the one-way ANOVA test (Table 1) showed no significant differences for the FER between all groups. As for the post hoc analysis between the experimental groups and the control, using the t-test, the FER for the LP3 group was significantly lower compared to the control group. All other comparisons were not significantly different. Finally, there were no significant differences for the FER between the LP1 and CC1, LP2 and CC2, and LP3 and CC3 groups.

Using the one-way ANOVA test and t-test (Table 2), there were no significant differences for the mean weekly body weights between all groups, between the experimental groups and the control group, and between the equal concentrations of LP and CC groups for each of the first and second weeks separately. Using the one-way ANOVA test (Table 2), there were highly significant differences between the groups for the mean feed and water intakes for each of the first and second weeks. As for the post hoc analysis between the experimental groups and the control, using the t-test, the mean feed intakes for the LP2, LP3, CC2, and CC3 groups only were significantly lower compared to the control in the first week, while for the second week only the LP2, LP3 groups were significantly lower compared to the control. In addition, the post hoc (Table 2) showed significantly lower mean water intakes only for the LP3, CC2, and CC3 groups compared to control group in the first week, while for the second week all groups except for CC1 were significantly lower compared to the control group. Finally, the only significant differences for the post hoc comparisons for the feed intakes between the same dose of LP and CC groups (Table 2), were a significantly lower intake for the LP2 group compared to the CC2 and for the LP3 group compared to the CC3 group in the second week. In addition, the only significant differences for the water intake between the same doses of CC and LP were significantly lower water intakes for the LP2 group compared to the CC2 in the first week and for the LP3 group compared to the CC3 group in the second week.

Table 1: Statistical analysis for the mean total body weights, mean total and daily body weight gains, percent relative total body weight gain (%), mean total feed and water intake, and FER using the one-way ANOVA test.

Parameter	Group	Mean ± SD	P-value	Post hoc P-value	
				P-value a	P-value b
Mean total body weight (g)	C	260 ± 36.35	0.879	-	
	LP1	252 ± 13.74		0.656	0.871
	LP2	243 ± 23.46		0.325	0.989
	LP3	240 ± 24.29		0.263	0.639
	CC1	255 ± 15.45		0.777	
	CC2	242 ± 14.59		0.319	
	CC3	248 ± 10.65		0.502	
Mean total body weight gains (g)	C	23 ± 20.03	0.148	-	
	LP1	10 ± 5.03		0.518	0.447
	LP2	-3 ± 7.51		0.195	0.789
	LP3	-26 ± 25.36		0.025*	0.606
	CC1	26 ± 12.10		0.907	
	CC2	2 ± 42.46		0.294	
	CC3	-15 ± 30.86		0.066	
Mean daily body weight gain for each rat (g)	C	1.79 ± 1.54	0.205	-	
	LP1	0.79 ± 0.39		0.797	0.762
	LP2	-0.26 ± 0.58		0.599	0.916
	LP3	-8.15 ± 11.53		0.0207*	0.090
	CC1	1.97 ± 0.93		0.963	
	CC2	0.15 ± 3.27		0.674	
	CC3	-1.21 ± 2.37		0.445	
Percent relative total body weight gain (%)	C	9.09 ± 7.17	0.186	-	
	LP1	4.14 ± 1.92		0.789	0.737
	LP2	-1.19 ± 2.86		0.579	0.867
	LP3	-38.97 ± 53.76		0.019*	0.089
	CC1	10.36 ± 4.62		0.945	
	CC2	1.91 ± 18.15		0.698	
	CC3	-5.85 ± 11.79		0.423	
Mean total feed intake (feed /day (500g)	C	82 ± 7.41		-	
	LP1	83 ± 21.71		0.862	0.303

	LP2	61 ± 11.49		0.000**	0.093
	LP3	52 ± 26.36	0.000**	0.000**	0.002**
	CC1	77 ± 5.18		0.391	
	CC2	71 ± 7.49		0.046*	
	CC3	71 ± 12.92		0.041*	
Mean total water intake (water /day (500ml)	C	115 ± 8.43		-	
	LP1	101 ± 8.42		0.058	0.695
	LP2	97 ± 11.39		0.014*	0.119
	LP3	71 ± 36.29		0.000**	0.020*
	CC1	104 ± 9.17	0.000**	0.130	
	CC2	86 ± 21.65		0.000**	
	CC3	89 ± 20.89		0.000**	
FER	C	0.022 ± 0.019		-	
	LP1	0.010 ± 0.005		0.865	0.825
	LP2	-0.004 ± 0.009		0.719	0.930
	LP3	-0.156 ± 0.221		0.025*	0.070
	CC1	0.025 ± 0.012	0.222	0.959	
	CC2	0.002 ± 0.046		0.786	
	CC3	-0.017 ± 0.034		0.592	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg).

* Significant, **Highly significant; FER (Feed efficiency ratio).

Table 2: Statistical analysis for the mean weekly body weight, feed, and water intake, using the one- way ANOVA test.

Parameter	Group	Week	Mean ± SD	P-value	Post hoc P-value	
					P-value a	P-value b
Weekly body weight	C		256 ± 32.56	0.958	-	
(g)	LP1		250 ± 12.89		0.707	0.948
	LP2	1	244 ± 25.53		0.467	0.734
	LP3		248 ± 25.48		0.618	0.882
	CC1		248 ± 12.23		0.660	
	CC2		238 ± 7.19		0.292	
	CC3		250 ± 13.24		0.726	
	C		265 ± 40.38	0.604	-	

	LP1		255 ± 14.60		0.624	0.722
	LP2	2	242 ± 21.52		0.240	0.785
	LP3		231 ± 23.22		0.100	0.434
	CC1		262 ± 18.71		0.892	
	CC2		247 ± 21.98		0.359	
	CC3		247 ± 10.30		0.356	
Weekly feed intake	C		88 ± 5.88	0.002**	-	
(feed /day (500g)	LP1		84 ± 20.14		0.531	0.302
	LP2	1	69 ± 5.32		0.001**	0.743
	LP3		75 ± 8.24		0.015*	0.785
	CC1		79 ± 4.93		0.101	
	CC2		67 ± 8.86		0.000**	
	CC3		76 ± 4.73		0.030*	
	C		77 ± 4.16	0.000**	-	
	LP1		82 ± 24.76		0.476	0.387
	LP2	2	54 ± 11.24		0.003**	0.006**
	LP3		29 ± 16.25		0.000**	0.000**
	CC1		76 ± 5.30		0.877	
	CC2		75 ± 2.63		0.757	
	CC3		65 ± 16.39		0.110	
Weekly water intake	C		121 ± 9.32	0.001**	-	
(water /day (500ml)	LP1		107 ± 7.56		0.096	0.859
	LP2		106 ± 9.76		0.067	0.002**
	LP3	1	101 ± 15.74		0.020*	0.859
	CC1		109 ± 9.00		0.135	
	CC2		79 ± 29.54		0.000**	
	CC3		103 ± 10.75		0.030*	
	C		110 ± 0.00	0.000**	-	
	LP1		96 ± 4.50		0.029*	0.501
	LP2	2	89 ± 3.78		0.002**	0.501
	LP3		41 ± 22.49		0.000**	0.000**
	CC1		100 ± 7.64		0.121	
	CC2		93 ± 4.88		0.010**	

	CC3		74 ± 18.80		0.000**	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, **Highly significant.

Determination of the differential complete blood counts

Using the one-way ANOVA test (Table 3), there were no significant differences between the groups for the mean WBC counts for each of the first and second blood samples. For the post hoc analysis, using the t-test, there were no significant differences between the mean WBC counts for the experimental groups and the control for each of the blood samples. On the other hand, there were no significant differences for the WBC counts between the LP1 and CC1, LP2 and CC2, and LP3 and CC3 groups for the first and second blood samples separately. Finally, the comparison between the first and second blood samples for the mean WBC counts for each group (Figure 1) showed that there were no significant differences between the first and second blood samples for all groups except for the CC2 that showed a significant decrease (P= 0.029) in the mean WBC for second sample compared to first sample.

The mean lymphocyte percents were highly significantly different between the groups, using the one-way ANOVA test (Table 4). The remaining comparisons (Tables 4-5) between the groups for the white blood cells counts and percents, and the comparisons for the mean platelets and RBC counts, and hemoglobin concentrations were not significantly different between the groups, using the one-way ANOVA. As for the comparisons between the experimental groups and the control, using the t-test, the mean lymphocyte percent for the CC1 group was significantly higher and the mean lymphocyte count for the LP1 was significantly lower. All other comparisons were not significantly different. Finally, the post hoc comparisons between the same dose of LP group and CC group (Tables 4), the only significant differences were found between the LP1 and CC1 groups for the mean neutrophil percent and between the LP1 and CC1, and the LP2 and CC2 groups for the mean lymphocyte percents.

Tables 6 shows the effects of the LP and CC extracts on the mean HCT, MCV MCH, MCHC, IG (counts), IG (%), RET (counts), RET (%), RET-HE, IPF, MPV, PCT, RDW-SD, RDW-CV, PDW, and P-LCR compared to the control group. The one-way ANOVA and t-test showed that there were no significant differences between all the groups and between the experimental groups and the control group for the mean HCT, MCV MCH, MCHC, IG (%), RET (counts), RET (%), IPF, MPV, PCT, PDW, and P-LCR. On the other hand, the mean IG, RET-HE, RDW-SD, and RDW-CV were not significantly different between the groups, using the one-way ANOVA test (Table 5). As for the post hoc comparisons for these parameters, using the t-test, compared with the control, the only significant differences were as follows: the mean IG for the LP1 group was significantly lower, mean RET-HE was significantly higher, mean RDW-SD for the LP2 and CC1 were significantly lower, and the mean RDW-CV was significantly lower for the CC1 group. Finally, the only significant differences for the post hoc comparisons between the same dose of LP and CC groups (Table 6), were a significantly higher MCHC for the LP1 group compared to the CC1, a significantly higher RET-HE for the LP3 group compared to the CC3 group, and a significantly lower RDW-SD for the LP3 group compared to the CC3 group.

The one-way ANOVA test showed (Table 7) highly significant differences between all groups for the mean IRF, LFR, MFR, HFR, NRBC (counts), and NRBC (%). As for the post hoc analysis between the experimental groups and the control, using the t-test, the mean IRF for the LP2 and CC3 groups were significantly higher, the mean LFR for the LP2 and CC3 groups were significantly lower, the mean MFR was significantly lower for the LP2, LP3, and CC3 groups, the mean HFR was significantly higher for the LP2, LP3, and CC3 groups, the mean NRBC (counts) and NRBC (%) were significantly higher for the CC1 and CC2 groups, comparing each to control group. Finally, the post hoc comparisons between the same concentrations of the LP and CC groups showed higher mean IRF and HFR for the LP2 group compared to the CC2 group, and higher mean LFR and MFR for the LP2 group compared to the CC2 group. In addition, the post hoc (Table 7) showed significantly lower mean NRBC (counts) and NRBC (%) for the LP1 and LP2 groups compared to the CC1 and CC2 groups, respectively.

The one-way ANOVA test and t-test (Table 8) showed no significant differences for the neutrophil/lymphocyte and monocyte/lymphocyte ratio for the cell counts and percents between all groups, between the experimental groups and the control group, and between the equal concentrations of LP and CC groups.

Table 3: Statistical analysis for the mean total WBC counts for the LP and CC extract groups after 7, and 14 days, using the one-way ANOVA test.

		at 7 days (First blood sample)				**at 14 days (Second blood sample)**			
Parameter	Group	Mean ± SD	P-value	Post hoc P-value		Mean ± SD	P-value	Post hoc P-value	
				P-value (a)	P-value (b)			P-value (a)	P-value (b)
WBC (10^3/µL)	C	19.00 ± 2.65	0.426	-		18.33 ± 1.37	0.457	-	
	LP1	18.76 ± 1.15		0.934	0.868	14.07 ± 2.80		0.075	0.320
	LP2	23.00 ± 7.55		0.327	0.459	17.46 ± 2.50		0.696	0.959

	LP3	21.00 ± 1.00		0.619	0.459	14.31 ± 4.15		0.126	0.549
	CC1	19.33 ± 4.51		0.934		16.34 ± 4.14		0.382	
	CC2	26.00 ± 4.36		0.097		17.57 ± 0.61		0.734	
	CC3	18.00 ± 7.55		0.803		15.96 ± 1.48		0.352	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg).

* Significant, **Highly significant; White blood cells (WBC)

Table 4: Statistical analysis for the differential mean WBC counts and percents for the LP and CC extract groups, using the one-way ANOVA test.

Parameter	**Group**	**Mean ± SD**	**P-value**	**Post hoc P-value**	
				P-value (a)	**P-value (b)**
Neutrophil (10^3/µL)	C	3.13 ± 1.53	0.516	-	
	LP1	3.04 ± 0.71		0.913	0.251
	LP2	3.03 ± 0.76		0.907	0.481
	LP3	1.99 ± 1.29		0.215	0.798
	CC1	2.10 ± 0.74		0.212	
	CC2	2.47 ± 0.58		0.414	
	CC3	1.74 ± 0.80		0.136	
Neutrophil (%)	C	16.8 ± 7.3	0.146	-	
	LP1	21.6 ± 2.6		0.191	0.025*
	LP2	17.4 ± 1.7		0.879	0.357
	LP3	13.2 ± 5.4		0.357	0.572
	CC1	12.8 ± 2.7		0.264	
	CC2	14.1 ± 3.8		0.437	
	CC3	10.7 ± 3.9		0.137	
Lymphocyte (10^3/µL)	C	13.91 ± 0.70	0.274	-	
	LP1	10.30 ± 1.92		0.046*	0.059
	LP2	12.48 ± 1.64		0.394	0.275
	LP3	11.75 ± 2.76		0.256	0.590
	CC1	13.67 ± 3.30		0.884	
	CC2	14.32 ± 1.05		0.801	
	CC3	12.85 ± 1.34		0.568	
Lymphocyte (%)	C	76.2 ± 4.9	0.007 **	-	
	LP1	73.6 ± 4.0		0.381	0.004**

	LP2	71.5 ± 2.3		0.126	0.005**
	LP3	83.1 ± 4.4		0.052	0.480
	CC1	83.8 ± 2.6		0.021*	
	CC2	81.5 ± 3.2		0.090	
	CC3	80.6 ± 0.8		0.199	
Monocyte (10^3/µL)	C	0.24 ± 0.12	0.624	-	
	LP1	0.32 ± 0.27		0.857	0.814
	LP2	0.72 ± 0.97		0.274	0.383
	LP3	0.19 ± 0.07		0.916	0.172
	CC1	0.22 ± 0.07		0.956	
	CC2	0.34 ± 0.10		0.814	
	CC3	0.93 ± 1.00		0.163	
Monocyte (%)	C	1.3 ± 0.8	0.618	-	
	LP1	2.2 ± 1.9		0.747	0.738
	LP2	4.4 ± 6.2		0.277	0.376
	LP3	1.3 ± 0.1		0.991	0.171
	CC1	1.3 ± 0.1		0.990	
	CC2	1.9 ± 0.6		0.829	
	CC3	6.2 ± 6.9		0.139	
Eosinophil (10^3/µL)	C	0.40 ± 0.02	0.321	-	
	LP1	0.25 ± 0.10		0.234	0.958
	LP2	0.48 ± 0.20		0.526	0.244
	LP3	0.17 ± 0.16		0.107	0.421
	CC1	0.26 ± 0.12		0.254	
	CC2	0.33 ± 0.08		0.578	
	CC3	0.29 ± 0.33		0.424	
Eosinophil (%)	C	2.2 ± 0.1	0.643	-	
	LP1	1.9 ± 0.6		0.605	0.672
	LP2	2.7 ± 0.8		0.512	0.269
	LP3	1.4 ± 1.6		0.302	0.686
	CC1	1.6 ± 0.4		0.353	
	CC2	1.9 ± 0.4		0.638	
	CC3	1.8 ± 1.9		0.543	

Basophil (10^3/µL)	C	0.09 ± 0.02	0.510	-	
	LP1	0.06 ± 0.01		0.173	0.753
	LP2	0.06 ± 0.03		0.222	0.753
	LP3	0.09 ± 0.06		0.944	0.445
	CC1	0.05 ± 0.02		0.102	
	CC2	0.05 ± 0.02		0.133	
	CC3	0.07 ± 0.01		0.367	
Basophil (%)	C	0.5 ± 0.1	0.188	-	
	LP1	0.4 ± 0.1		0.761	0.146
	LP2	0.4 ± 0.2		0.369	0.545
	LP3	0.6 ± 0.3		0.288	0.153
	CC1	0.3 ± 0.1		0.087	
	CC2	0.3 ± 0.1		0.146	
	CC3	0.4 ± 0.0		0.588	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, ** Highly significant.

Table 5: Statistical analysis for the mean total RBC counts, platelet counts, and hemoglobin concentrations for the LP and CC extract groups, using the one-way ANOVA test.

Parameter	**Group**	**Mean ± SD**	**P-value**	**Post hoc P-value**	
				P-value (a)	**P-value (b)**
RBC (10^6/µL)	C	8.28 ± 0.45	0.992	-	
	LP1	8.22 ± 0.76		0.925	0.850
	LP2	8.43 ± 1.39		0.810	0.829
	LP3	8.30 ± 0.60		0.983	0.913
	CC1	8.10 ± 0.45		0.777	
	CC2	8.57 ± 0.62		0.650	
	CC3	8.38 ± 0.08		0.888	
Platelet (10^3/µL)	C	915 ± 267	0.762	-	
	LP1	651 ± 170		0.359	0.659
	LP2	895 ± 622		0.945	0.787
	LP3	1182 ± 538		0.404	0.337
	CC1	776 ± 91		0.625	

	CC2	819 ± 180		0.735	
	CC3	844 ± 162		0.822	
Hemoglobin (g/dl)	C	15.1 ± 0.4	0.627	-	
	LP1	16.0 ± 0.5		0.226	0.183
	LP2	14.9 ± 1.4		0.823	0.276
	LP3	15.0 ± 0.6		0.936	0.418
	CC1	15.0 ± 0.8		0.893	
	CC2	15.7 ± 0.3		0.379	
	CC3	15.8 ± 1.9		0.419	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, ** Highly significant.

Table 6: Statistical analysis for the HCT, MCV, MCH, MCHC, IG (counts and percents), RET (counts and percents), RET-HE, IPF, MPV, PCT, RDW-SD, RDW-CV, PDW, and PLCR for the LP and CC extract groups, using the one-way ANOVA test.

Parameter	**Group**	**Mean ± SD**	**P-value**	**Post hoc P-value**	
				P-value (a)	**P-value (b)**
HCT (%)	C	44.6 ± 1.3	0.748	-	
	LP1	46.6 ± 2.7		0.450	0.657
	LP2	44.9 ± 5.5		0.919	0.312
	LP3	44.1 ± 1.1		0.842	0.243
	CC1	45.4 ± 2.1		0.750	
	CC2	47.6 ± 0.6		0.269	
	CC3	47.9 ± 5.5		0.276	
MCV (fL)	C	54.0 ± 1.6	0.578	-	
	LP1	56.9 ± 2.3		0.245	0.771
	LP2	53.5 ± 2.2		0.835	0.367
	LP3	53.2 ± 2.6		0.766	0.195
	CC1	56.2 ± 1.0		0.374	
	CC2	55.7 ± 3.8		0.483	
	CC3	57.2 ± 6.0		0.253	
MCH (pg)	C	18.2 ± 0.6	0.676	-	
	LP1	19.5 ± 1.4		0.184	0.296
	LP2	17.8 ± 1.3		0.680	0.538

	LP3	18.2 ± 0.6		0.963	0.585
	CC1	18.5 ± 0.4		0.756	
	CC2	18.4 ± 1.2		0.836	
	CC3	18.8 ± 2.1		0.581	
MCHC (g/dl)	C	33.8 ± 0.2	0.097	-	
	LP1	34.4 ± 1.1		0.297	0.0154*
	LP2	33.3 ± 1.0		0.355	0.662
	LP3	34.1 ± 0.5		0.675	0.071
	CC1	32.9 ± 0.3		0.109	
	CC2	33.1 ± 0.2		0.184	
	CC3	32.9 ± 0.2		0.128	
IG (10^3/µL)	C	0.12 ± 0.04	0.184	-	
	LP1	0.03 ± 0.03		0.020*	0.255
	LP2	0.11 ± 0.08		0.697	0.137
	LP3	0.05 ± 0.01		0.086	0.410
	CC1	0.07 ± 0.02		0.161	
	CC2	0.05 ± 0.01		0.070	
	CC3	0.09 ± 0.04		0.368	
IG (%)	C	0.7 ± 0.2	0.467	-	
	LP1	0.3 ± 0.3		0.091	0.459
	LP2	0.7 ± 0.6		1.000	0.152
	LP3	0.4 ± 0.0		0.295	0.714
	CC1	0.4 ± 0.2		0.305	
	CC2	0.3 ± 0.1		0.152	
	CC3	0.5 ± 0.1		0.507	
RET (10^6/µL)	C	0.32 ± 0.03	0.439	-	
	LP1	0.22 ± 0.02		0.164	0.676
	LP2	0.30 ± 0.05		0.826	0.233
	LP3	0.35 ± 0.23		0.649	0.535
	CC1	0.25 ± 0.05		0.313	
	CC2	0.22 ± 0.02		0.164	
	CC3	0.30 ± 0.08		0.820	
RET (%)	C	3.85 ± 0.51	0.533	-	

	LP1	2.72 ± 0.12		0.193	0.339
	LP2	3.59 ± 0.25		0.757	0.306
	LP3	4.34 ± 3.08		0.601	0.422
	CC1	3.53 ± 0.59		0.706	
	CC2	2.72 ± 0.12		0.192	
	CC3	3.32 ± 0.00		0.655	
RET-HE (%)	C	20.8 ± 0.3	0.056	-	
	LP1	22.3 ± 0.4		0.041*	0.219
	LP2	21.0 ± 1.0		0.697	0.173
	LP3	21.9 ± 0.4		0.172	0.019 *
	CC1	21.4 ± 1.1		0.338	
	CC2	22.0 ± 0.9		0.090	
	CC3	19.7 ± 1.1		0.161	
IPF (%)	C	0.3 ± 0.1	0.259	-	
	LP1	1.2 ± 1.1		0.105	0.084
	LP2	0.2 ± 0.1		0.837	0.099
	LP3	0.7 ± 0.0		0.519	0.449
	CC1	0.2 ± 0.2		0.878	
	CC2	1.1 ± 0.8		0.102	
	CC3	0.2 ± 0.1		0.837	
MPV (fL)	C	7.4 ± 0.5	0.484	-	
	LP1	7.5 ± 0.4		0.847	0.445
	LP2	7.5 ± 0.4		0.700	0.072
	LP3	7.6 ± 0.5		0.698	0.482
	CC1	7.2 ± 0.2		0.564	
	CC2	6.9 ± 0.4		0.140	
	CC3	7.3 ± 0.6		0.698	
PCT (%)	C	0.48 ± 0.27	0.857	-	
	LP1	0.51 ± 0.06		0.844	0.784
	LP2	0.59 ± 0.36		0.533	0.906
	LP3	0.75 ± 0.17		0.172	0.489
	CC1	0.56 ± 0.06		0.639	
	CC2	0.57 ± 0.14		0.611	

	CC3	0.61 ± 0.06		0.514	
RDW-SD (fL)	C	27.8 ± 0.3	0.082	-	
	LP1	25.6 ± 2.5		0.207	0.360
	LP2	24.0 ± 0.9		0.049*	0.874
	LP3	24.5 ± 2.4		0.102	0.039 *
	CC1	24.0 ± 2.3		0.041 *	
	CC2	24.3 ± 0.7		0.057	
	CC3	29.2 ± 4.2		0.467	
RDW-CV (%)	C	19.2 ± 1.0	0.268	-	
	LP1	17.6 ± 0.6		0.135	0.517
	LP2	17.8 ± 2.1		0.168	0.719
	LP3	18.3 ± 0.1		0.396	0.291
	CC1	17.0 ± 0.6		0.042*	
	CC2	18.1 ± 1.7		0.292	
	CC3	19.6 ± 0.3		0.748	
PDW (fL)	C	7.9 ± 1.0	0.660	-	
	LP1	7.9 ± 0.8		1.000	0.512
	LP2	8.0 ± 0.6		0.912	0.128
	LP3	8.0 ± 0.7		0.921	0.686
	CC1	7.5 ± 0.3		0.512	
	CC2	7.0 ± 0.4		0.154	
	CC3	7.7 ± 1.1		0.731	
P-LCR (%)	C	7.1 ± 4.1	0.815	-	
	LP1	6.5 ± 0.5		0.776	0.713
	LP2	7.1 ± 1.9		0.973	0.223
	LP3	7.5 ± 2.6		0.846	0.541
	CC1	5.8 ± 1.1		0.517	
	CC2	4.6 ± 1.6		0.235	
	CC3	6.0 ± 3.5		0.633	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, ** Highly significant

Hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), immature granulocytes (IG),a reticulocyte count (RET), reticulocyte hemoglobin equivalent (RET-HE), platelet Fraction percent

(IPF), mean platelet volume (MPV), procalcitonin (PCT), red cell distribution width (RDW-SD), red cell distribution width (RDW-CV), platelet distribution width (PDW),and platelet-large cell ratio (PLCR).

Table 7: Statistical analysis for the IRF, LFR, MFR, HFR, and NRBC (counts and percents) for the LP and CC extract groups, using the one-way ANOVA test.

Parameter	Group	Mean ± SD	P-value	Post hoc P-value	
				P-value (a)	P-value (b)
IRF (%)	C	31.3 ± 1.9	0.008**	-	
	LP1	28.8 ± 1.4		0.487	0.409
	LP2	43.0 ± 2.5		0.007**	0.002**
	LP3	37.1 ± 13.4		0.175	0.234
	CC1	31.8 ± 2.1		0.891	
	CC2	29.1 ± 1.8		0.545	
	CC3	42.6 ± 3.4		0.016*	
LFR (%)	C	68.8 ± 1.9	0.009**	-	
	LP1	71.2 ± 1.4		0.484	0.484
	LP2	56.9 ± 2.5		0.006**	0.002**
	LP3	62.9 ± 13.4		0.172	0.376
	CC1	68.7 ± 2.5		1.000	
	CC2	71.2 ± 1.4		0.484	
	CC3	58.9 ± 2.7		0.030*	
MFR (%)	C	20.6 ± 0.9	0.003**	-	
	LP1	19.1 ± 0.3		0.252	0.216
	LP2	15.5 ± 0.6		0.002**	0.009**
	LP3	14.8 ± 4.4		0.001**	0.247
	CC1	20.8 ± 1.9		0.918	
	CC2	19.4 ± 0.3		0.365	
	CC3	16.7 ± 0.4		0.017 *	
HFR (%)	C	10.7 ± 1.0	0.000**	-	
	LP1	9.7 ± 1.9		0.687	0.814
	LP2	27.4 ± 3.0		0.000**	0.000**
	LP3	22.3 ± 9.1		0.001**	0.122
	CC1	10.3 ± 1.3		0.865	
	CC2	9.9 ± 0.5		0.754	
	CC3	27.4 ± 2.0		0.000**	

NRBC (10^3/µL)	C	0.02 ± 0.01	0.000**	-	
	LP1	0.01 ± 0.01		0.295	0.000**
	LP2	0.01 ± 0.01		0.295	0.000**
	LP3	0.01 ± 0.00		0.167	0.205
	CC1	0.05 ± 0.01		0.000**	
	CC2	0.06 ± 0.01		0.000**	
	CC3	0.02 ± 0.01		1.000	
NRBC (%)	C	0.1 ± 0.1	0.000**	_-	
	LP1	0.1 ± 0.0		0.389	0.000**
	LP2	0.1 ± 0.0		0.390	0.000**
	LP3	0.1 ± 0.0		0.439	0.295
	CC1	0.3 ± 0.1		0.000**	
	CC2	0.3 ± 0.1		0.000**	
	CC3	0.2 ± 0.1		0.696	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, ** Highly significant

Immature reticulocyte fraction (IRF), reticulocytes low fluorescence ratio (LFR), reticulocytes medium fluorescence ratio (MFR), reticulocytes high fluorescence ratio (HFR), and nucleated RBCs (NRBC).

Table 8: Statistical analysis for the neutrophil/lymphocyte ratio and monocyte/lymphocyte ratio for the LP and CC extract groups, using the one-way ANOVA test.

Parameter	**Group**	**Mean ± SD**	**P-value**	**Post hoc P-value**	
				P-value (a)	**P-value (b)**
Neutrophil/lymphocyte ratio (10^3 cell/µL)	C	0.23 ± 0.11	0.107	-	
	LP1	0.29 ± 0.05		0.202	0.892
	LP2	0.24 ± 0.03		0.774	0.943
	LP3	0.16 ± 0.07		0.284	0.962
	CC1	0.15 ± 0.04		0.188	
	CC2	0.18 ± 0.05		0.346	
	CC3	0.13 ± 0.05		0.135	
Neutrophil/lymphocyte ratio (%)	C	0.23 ± 0.11	0.107	-	
	LP1	0.29 ± 0.05		0.207	0.991
	LP2	0.24 ± 0.03		0.741	0.949
	LP3	0.16 ± 0.07		0.282	0.962

	CC1	0.15 ± 0.04		0.190	
	CC2	0.17 ± 0.05		0.339	
	CC3	0.13 ± 0.05		0.135	
Monocyte/lymphocyte ratio (10^3 cell/µL)	C	0.02 ± 0.01		-	
	LP1	0.03 ± 0.02		0.758	0.858
	LP2	0.06 ± 0.09	0.628	0.241	0.937
	LP3	0.02 ± 0.00		0.971	0.917
	CC1	0.02 ± 0.00		0.961	
	CC2	0.02 ± 0.01		0.868	
	CC3	0.08 ± 0.09		0.175	
Monocyte/lymphocyte ratio (%)	C	0.02 ± 0.01		-	
	LP1	0.03 ± 0.03		0.719	0.934
	LP2	0.06 ± 0.09	0.639	0.242	0.947
	LP3	0.02 ± 0.00		0.972	0.983
	CC1	0.02 ± 0.00		0.965	
	CC2	0.02 ± 0.01		0.865	
	CC3	0.08 ± 0.09		0.179	

Pairwise t-test was used for the post hoc significance testing: P-value (a) is between groups and control; P-value (b) is between LP1 and CC1, LP2 and CC2, and LP3 and CC3, respectively.

C (Control), LP1 (LP 30 mg/kg), LP2 (LP 100 mg/kg), LP3 (LP 200 mg/kg), CC1 (CC 30 mg/kg), CC2 (CC 100 mg/kg), CC3 (CC 200 mg/kg). * Significant, ** High significant.

DISCUSSION

This study is the first to investigate the effects of the oral administration of the aqueous extracts of LP and CC separately and the differences in these effects between the two plant extracts on body weight parameters, consumptions of feed and water, and the differential CBC in healthy rats. The LP and CC aqueous extracts were each administered daily at three different doses (30, 100 and 200 mg/kg) for 14 days. The extracts were administered by oral gavage since oral gavage delivers the specific amount of extracts directly into the gastrointestinal tract of rats resembling the normal ingestion of foods and liquids. Published studies using the aqueous LP extracts in healthy laboratory animals are very few, while there are none on aqueous CC extracts of any kind. On the other hand, there are many published studies on the effects alcoholic extracts of LP and CC. Only one previous study [33] used the aqueous extract of LP for the determination of the body weight, body weight loss, feed and water intake, and the counts and percents of total and differential WBC counts and RBC counts. Moreover, previous studies used different preparations and amounts of LP and CC than the ones used in the current study. Furthermore, most studies on laboratory animals using medicinal plants used animals with induced medical conditions or diseases, while very few used healthy animals. Therefore, we were not able to compare all our results with those of others, and studies on other medicinal plants and seeds were used for the comparison with the present results.

Results of the present study showed that both the extract of LP and CC resulted in non-significantly ($P \geq 0.05$) lower body weights and percent relative body weight gains for the groups, which was linked to, and probably due to, significantly lower feed and water consumptions in these groups. Another explanation for these results may be due to the fact that phenolic compounds, such as tannin that is naturally present in vegetables and plants including LP and CC [34], has been shown to reduce weight and feed intake in rats [35, 36].

The findings of this study showed no significant differences between the LP and CC groups and between the same concentration groups of the LP and CC groups for the mean total body weight, total and daily body weight gains, and percent relative total body weight gains. On the other hand, results of the present study showed significantly lower ($P < 0.01$) feed and water consumptions for the LP and CC groups compared to the control and for the LP3 compared to the CC3 groups. The current results agree with previous studies [37-39] that found no significant differences in the mean body weights for rats consuming *Lepidium sativum* seeds powder mixed with the regular diet compared to the

control. Additionally in agreement is a study [40] that found no effects on body weights in rats consuming LP alcoholic extracts for two months. Moreover, one study [41] reported no significant differences in weight gain among buffaloes consuming Lepidium sativum seeds and those that did not for 5 months. In agreement with these results, previous studies found lower feed intake in rats that consumed an aqueous Lepidium sativum extract administered for two weeks compared to the control [42]. Additionally, findings of a previous study [43] in rats administered with Cinnamomum cassia for 30 days showed a reduction in body weight gain, feed intake, and food efficiency ratio compared to control rats. Moreover, the results are in agreement with the findings of lower feed and water consumptions in rats consuming LP aqueous extract [33] and ground Lepidium sativum seeds mixed with the regular diet [7].

On the other hand, some previous studies were in disagreement with the current results. A previous study [7] on rats consuming ground Lepidium sativum seeds mixed with the regular diet for 39 days showed significantly higher overall body weight gain percent compared to the control. The current results are also in disagreement with a previous study [31] found significantly higher mean body weight loss and feed inefficiency ratio in rats consuming ground LP and higher mean body weight loss, feed inefficiency ratio, and lower mean daily body weight in rats consuming aqueous LP, both for 14 days. Additionally, in contrast to our results, [42] oral administration of *Lepidium sativum* aqueous extract given to normal rats for 15 days caused a significant decrease in body weight. A previous study [44] using alcoholic extracts of Maerua psuedopetalosa administered to rats for a week showed a significant reduction in body weights. Moreover, previous studies showed a significant increase in body weights of rats using puncturevine plant extract [45], aqueous extract of *Lepidium sativum* seeds in mice [8], and methanolic extract of *Ganoderma lucidum* in rats [46], comparing each with its control. Also in disagreement with the current findings, is the significantly higher percent overall body weight gain found in rats consuming ground Lepidium sativum seeds [7, 8]. A significant increase in the body weights of rats following oral administration of methanol extract of ganoderma lucidum for 21 days was found in a previous study [46].

Hematological parameters give a good overview of the health of the host and the efficiency of the immune system. The mean WBC counts for days 7 and 14 for the LP and CC extracts were not significantly different ($P \geq 0.05$) between the groups and when comparing each experimental group with the control. Studies on other medicinal plants show similar results to the results of the current study. The present findings agree with a study on rats that showed no significant differences between the mean WBC counts for different concentrations of aqueous LP extract and the control after 7 and 14 days [47]. The current results also agree with previous studies [37-39] in rats consuming Lepidium sativum seeds powder mixed with the regular diet that did not find any significant differences in the mean WBC counts compared to the control. On the other hand, a study on different concentrations of the ethanolic extract of Bougainvillea spectabilis leaves showed a significantly reduced WBC count in rats consuming the leaves compared with the control [48], in disagreement with the current study. Moreover, studies in disagreement with the current findings, found increased WBC counts in rats consuming varying doses of the methanolic extracts of Carissa edulis leaf, and the ethanolic root extract of Gonglonema latifolium [49, 50].

The findings of this study showed no significant differences ($P \geq 0.05$) between the LP and CC groups each compared with the control group for the mean neutrophil, lymphocyte, monocyte, eosinophil, basophile counts and percents, except for the mean lymphocyte percents for the LP1 group that was significantly higher than the mean percent for the control group. The lymphocyte is the main type of effector cell in the acquired immunity and thus the higher percent for the LP in the present study may indicate an enhanced immune response. The current results are in agreement with a previous study in rats consuming Lepidium sativum seeds powder mixed with the regular diet of rats for 14 days that did not find any significant differences in the mean lymphocyte, neutrophil, monocyte, eosinophil, and basophile counts compared to the control 39]. Also,in agreement with the current findings, increased counts and percents for lymphocytes were found in normal rats that consumed alcoholic leaf extracts of Carissa edulis (Forssk.) Vahl [50]. On the other hand, the current results are in disagreement with a previous study in rats consuming ground LP and its extracts for 14 days that resulted in significantly higher neutrophil and monocyte counts and percents, and lower lymphocyte percent and eosinophil counts and percents [47]. The current results are in disagreement with a previous study in rats consuming aqueous extract of Ocimum gratissimum for 28 days that found higher neutrophil counts and lower lymphocyte counts [51]. A study [50] using varying doses of the alcoholic leaf extracts of Carissa edulis (Forssk.) Vahl in normal rat models, for different time periods up to 21 days, found significant increases in the monocyte, neutrophil, and basophil cell counts and increased counts for lymphocyte and eosinophil cells, which disagrees with the present findings for eosinophil and basophil counts but agrees with our higher counts and percent of lymphocyte cells.

The findings of this study showed no significant differences ($P \geq 0.05$) between the LP and CC groups and the control nor between the same concentration groups of the LP and CC groups for the mean hemoglobin concentrations, RBC, HCT, platelets count, PCT, MPV, PDW, P-LCR, and IPF. RBC counts are related to anemia while hemoglobin concentration is related to RBC, iron, and anemia. HCT is related to the volume of RBC and the degree of anemia. Platelets are an acute phase reactant to infection or inflammation. Plateletcrit (PCT) is used to determine the degree of acute blood loss while the mean platelet volume (MPV) is used to evaluate the effectiveness of therapies to enhance blood clotting. MPV, PDW, and P-LCR provide a simple method of indirect assessment of platelet stimulation and IPF gives the percentage of immature platelets in peripheral blood.

The current results are in agreement with a previous study in rats consuming ethanolic extract of the Azadirachta indica leaf, for 14 days, that found that the mean hemoglobin concentration and total RBCs counts were not significantly different for the experimental groups compared to the control group [52]. Moreover, previous studies in rats consuming Lepidium sativum seeds powder mixed with the regular diet of rats for experimental periods ranging from 2 to 6 weeks, rats consuming various doses of stem extract of Fadogia agresis, and rats consuming Azadirachta Indica leaf did not show any significant differences for the mean hemoglobin concentration [37, 39, 52, 54] and RBC counts [37, 39, 52] compared to the control, in agreement with the current

study. In agreement with the current findings, a previous research study [48] on the ethanolic extract of Bougainvillea spectabilis leaves, given to rats for 14 days, resulted in no significant effect on platelet counts when compared with the control. Moreover, there was no significant difference for the PDW and hemoglobin levels of D. tripetala extract in rats compared to the control [54].

On the other hand, in disagreement with the current results, rats consuming aqueous LP extracts for 7 and 14 days showed significantly higher mean RBC counts compared with the control [47]. A previous study [51] in rats consuming aqueous extract of *Ocimum gratissimum* for 28 days found higher RBC counts, in disagreement with the current results. The current results are in disagreement with a previous study [55] that found a significant reduction in RBC levels and HCT levels in the groups administered alcohlic Nauclea latifolium leaves extract for 2 weeks when compared with the control group. A previous study [56] reported that aqueous extract of Hibiscus rosa sinensis flowers and Bougainvillea spectabilis leaves for a period of 30 days resulted in a significant increase in the levels of hemoglobin and RBC counts in mice. Another study [50] found significant increases in platelets and RBC counts, hemoglobin concentration, MPV, PCT, and PDW after oral administration of alcoholic leaf extracts of Carissa edulis to rats for 14 and 21 days.

The results show that the mean MCH, MCHC, and MCV were not significantly different ($P \geq 0.05$) for the LP and CC extracts compared with the control group. HCT, MCHC, MCH, and MCV are related to individual red blood cells while hemoglobin and RBC are related to the total population of red blood cells in the blood. MCV is used to define the size of red blood cells while MCH and MCHC are used to define hemoglobin content of red blood cells. Thus, the results imply that the extract may neither affect the incorporation of hemoglobin (MCH and MCHC) into red blood cells nor the morphology and osmotic fragility (MCV) of the produced red blood cells. However, the absence of a significant change in the hemoglobin concentrations and RBC counts implies that the extract does not affect the number of red blood cells produced from the bone marrow. In addition, since the MCH, MCHC and MCV were not affected, the extract does not affect the oxygen carrying capacity of each red blood cell.

The current results are in agreement with previous studies in rats consuming ethanolic extract of the leaf of Azadirachta indica (Koofreh et al., 2010) and the ethanolic extract of Bougainvillea spectabilis leaves for 14 days (Adebayo et al., 2005) [3] that found that the mean MCV, MCH and MCHC values were not significantly different between the experimental groups and the control. On the other hand, in disagreement with the current results, rats consuming ethanol extract of Nauclea latifolium for two weeks had significantly higher MCV and MCH levels when compared with the control group (Edet et al., 2013). Additionally, in disagreement with the current results, rats consuming methanolic leaf extracts of Carissa edulis had significant increases in the levels of MCH, MCV, and MCHC both after 14 and 21 days (Jorum et al., 2016) [26]. Another study [56] showed that the aqueous extracts of Hibiscus rosa sinensis flowers and Bougainvillea spectabilis leaves administered to mice for a period of 30 days resulted in a significant decline in the levels of MCH and MCV.

In the current study, no significant differences were found for RET (counts and percents), RET-He, IG (counts and percents), RDW-SD, and RDW-CV for the LP and CC groups compared with the control. RET measures the percentage of total reticulocytes in red blood cells. RET-He is a measure of the amount of hemoglobin in reticulocytes and it is used as an indicator of iron-deficient and iron-restricted erythropoiesis. IG are white blood cells that are immature and are the precursors of neutrophil cells. RDW measures the amount of variation in the volume and size of red blood cell. A normal RDW level indicates that the red blood cells are all about the same size, while a high RDW means that they vary widely in size [56]. In addition, a normal count and perecents of IG indicates that the subjects have no infections nor inflammation. The findings of a previous study [26] showed a significant increase in the levels of RDW after oral administration of alcoholic leaf extracts of Carissa edulis in normal rats, for 14 and 21 days, in disagreement with the current study results.

The findings of this study showed highly significant differences ($P < 0.01$) for the mean IRF, LFR, MFR, HFR and NRBCs (counts and percents) between the LP and CC groups each compared with the control group. LFR% is the percent of red blood cells, the MFR is the percent of erythrocytes of the embryo, and HFR is the percent of embryonic red blood cells in the blood. IRF is a value consisting of the HFR and MFR groups, the result can be used to study the pathology of red blood cell formation [57]. NRBC are red blood cells with a nucleus which are usually not present in the circulation of healthy adults. The LP2 and CC3 groups had significantly higher IRF and lower LFR compared with the control. The LP2, LP3, and CC3 groups had significantly lower mean MFR and higher HFR compared with the control. The mean NRBC (counts) and NRBC (%) were significantly higher for the CC1 and CC2 groups compared with the control group. The mean IRF and HFR for the LP2 group were significantly higher compared to the CC2 group and the mean LFR and MFR for the LP2 group were significantly higher compared to the CC2 group. The mean NRBC (counts) and NRBC (%) for the LP1 and LP2 groups were significantly lower compared to the CC1 and CC2 groups, respectively.

In situations where there is bleeding, IRF will increase despite no change in hemoglobin levels. In the current study more than one sample of blood was collected from some rats and some showed some bleeding after blood sample collection. This may explain the resulting higher IRF for some groups. A previous study in humans [58] that found that the mean LFR, MFR, HFR values were highly significantly increased in individuals with iron deficiency. This study suggested that the MFR and HFR are high in iron deficiency, suggesting increased erythropoietic activity in anemic individuals, thus MFR and HFR may potentially be used as early diagnostic markers for iron deficiency and anemia [58]. On the other hand, the possible causes of high level of NRBCs in the blood include anemia, low oxygen, spleen dysfunction, and bone marrow damage and disorders. The results cannot lead to any conclusions regarding the presence of these conditions in the experimental rats.

CONCLUSION

The results show that the aqueous extracts of LP and CC had minimal effects on the counts of white blood cells. Both LP and CC extracts affect lymphocyte cell counts with LP leading to lower counts while CC leading to higher counts. On the other hand, comparing the LP and CC groups, the LP extract resulted in higher counts of neutrophil cells and lower counts of lymphocyte cells. Finally, only the LP1 and LP2 groups showed differences when compared with CC1 and CC2 groups for the

counts of white and red blood cells and platelet, and hemoglobin concentrations, while the LP3 and CC3 did not show any differences. The other indices determined by the CBC showed some differences. Therefore, in conclusion, the LP extract enhances the innate immune response and inhibits the acquired immune response, while the CC extract does the exact opposite. Thus, the extract may be used for modulating the immune response. Based on the current findings, it is recommended that lower concentrations of the LP and CC extracts be used in rats and for a longer experimental period. In addition, it is recommended to use both female and male rats to determine if they react differently to the extracts.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORCID ID

Sawsan Mahassni: https://orcid.org/0000-0003-2730-164X
Elham Algahdali: https://orcid.org/0009-0005-9014-3375

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