Efficacy of a herbal-based medication for treatment of paracetamol-induced hepatotoxicity in dogs

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ABSTRACT

This study aimed to evaluate the therapeutic efficacy of a herbal-based formula as an adjunct to silymarin in mitigating paracetamol-induced hepatotoxicity in dogs. Fourteen dogs were experimentally induced with toxicity and divided into two equal groups (n=7). Group 1 (Herbal) was treated with silymarin plus a herbal formula, while Group 2 (Control) received only silymarin. Paracetamol induction caused a significant ($P < 0.05$) decline in erythrogram parameters (RBCs, HGB, HCT) and a significant elevation in liver enzymes (ALT, AST, ALKP), platelets, total cholesterol, and triglycerides. Treatment with the herbal formula significantly restored hematological values and led to a marked reduction in all elevated biochemical markers, showing superior restorative and hepatoprotective effects compared to the control group. Ultrasonography confirmed a near-complete resolution of hepatic lesions in the herbal-treated group. It is concluded that the tested herbal-based formula is a potent and beneficial adjunctive therapy for accelerating recovery from paracetamol-induced hepatotoxicity in dogs.

Keywords: Paracetamol, Hepatotoxicity, Herbal medicine, Silymarin, Liver enzymes

المستخلص

هدفت هذه الدراسة إلى تقييم الفعالية العلاجية لتركيبة عشبية كعلاج مساعد مع السيليمارين في تخفيف السمية الكبدية الناجمة عن الباراسيتامول في الكلاب. تم إحداث التسمم تجريبياً في أربعة عشر كلباً، ثم قُسّمت إلى مجموعتين متساويتين (ن=٧). عولجت المجموعة الأولى (المجموعة العشبية) بالسيليمارين بالإضافة إلى التركيبة العشبية، بينما تلقت المجموعة الثانية (المجموعة الضابطة) السيليمارين فقط. أدى إحداث التسمم بالباراسيتامول إلى انخفاض معنوي ($P < 0.05$) في مؤشرات الدم الحمراء (عدد كريات الدم الحمراء، الهيموجلوبين، والهيماتوكريت)، وارتفاع

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)، والصفائح الدموية، ALT, AST, ALKPمعنوي في إنزيمات الكبد (والكوليسترول الكلي، والدهون الثلاثية. وقد أدى العلاج بالتركيبة العشبية إلى استعادة المؤشرات الدموية بشكل ملحوظ، كما أدى إلى انخفاض واضح في جميع المؤشرات البيوكيميائية المرتفعة، مما يُظهر تأثيرات علاجية وواقية للكبد تفوق تأثيرات المجموعة الضابطة. وأكد الفحص بالموجات فوق الصوتية زوالاً شبه كامل للآفات الكبدية في المجموعة التي عولجت بالأعشاب. يُستنتج من ذلك أن التركيبة العشبية المختبرة تمثل علاجًا مساعدًا فعالاً ومفيدًا في تسريع التعافي من السمية الكبدية الناجمة عن الباراسيتامول في الكلاب.

الكلمات المفتاحية: الباراسيتامول، السمية الكبدية، الطب العشبي، السيليمارين، إنزيمات الكبد.

INTRODUCTION

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is readily available without prescription in most countries **(Brune et al., 2015).** It is listed on the World Health Organisation's **(WHO, 2021)** essential medicines list**.** It is recommended as a first-line treatment for most cases of pain and fever and is safe to use in children as young as one-month old as well as women who are pregnant. It comes in a variety of forms and strengths including oral tablets, capsules, and liquid formulations as well as rectal suppositories **(Acheampong et al., 2016).**

The mechanism of action of paracetamol is still not entirely understood. Antipyretic effects are thought to be due to the inhibition of prostaglandin production **(Anderson et al., 2008).** However, it does not display any anti-inflammatory effects (cf. non-steroidal anti-inflammatory drugs (NSAIDs)), suggesting that it only acts centrally rather than peripherally **(Anderson et al., 2008).**

Analgesic effects may also be due to interference with descending serotonergic pain pathways through their activation. As such these analgesic effects can be inhibited by serotonin antagonists **(Graham et al., 2013).** Paracetamol is generally

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regarded as a first-line analgesic and is preferred over NSAIDs in certain patient groups. Despite this, a recent systematic review found there was sufficient evidence for the use of paracetamol in only 4 of 44 painful conditions and evidence it was not effective for some common indications **(Abdel Shaheed et al., 2021).**

In therapeutic use, paracetamol is rapidly absorbed reaching therapeutic levels after 30 min and peak plasma concentrations within 2 h **(Agrawal and Khazaeni, 2022).** Immediate release paracetamol can be taken every 4–6 h and modified/extended release (MR/ER) every 8 h to maintain therapeutic concentrations (Paracetamol, 2022). Most paracetamol is metabolized by glucuronidation and sulfation and these metabolites are then renally excreted **(Hodgman and Garrard, 2012).** The remaining small amounts are converted into N-acetyl-p-benzoquinoneimine (NAPQI),a toxic metabolite, or excreted unchanged in the urine **(Abdel Shaheed et al., 2021).**

The toxic mechanism of paracetamol and mechanism of action of acetylcysteine. Paracetamol is primarily detoxified by glucuronide and sulfate conjugates which are then excreted in the urine. A small percentage is metabolized by CYP2E1 to the reactive intermediate NAPQI. Under normal conditions, NAPQI can be detoxified by reaction with glutathione to form cysteine and mercaptopuric acid conjugates. If glutathione is depleted (e.g. in paracetamol overdose), NAPQI binds to cell macromolecules causing hepatocyte cell death. The antidote acetylcysteine replenishes cysteine, which is the rate-limiting factor for glutathione synthesis.

The main toxic effect of paracetamol is hepatoxicity. Paracetamol is a ‘pro-poison’ that exerts its toxic effect through the toxic reactive metabolite, NAPQI. This metabolite is formed by cytochrome P−450 (CYP) enzymes, primarily CYP2E1 and

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CYP3A4. NAPQI is formed in small amounts in therapeutic doses where it is readily detoxified by conjugation with glutathione **(Hodgman and Garrard , 2012).** In overdose, there may be insufficient glutathione to detoxify NAPQI, causing it to bind to cellular proteins (adduct formation) **(Bunchorntavakul and Reddy, 2013).**

NAPQI primarily binds to cysteine residues but can potentially also damage proteins at methionine, tryptophan, and tyrosine residues **(Leeming et al., 2015).** The mitochondria are a key target for NAPQI adduct formation. Formation of reactive oxygen species causes oxidative stress and leads to activation of c-jun N-terminal kinase (JNK) **(Hinson et al., 2010).** The JNK enzyme translocates to the mitochondria, leading to mitochondrial dysfunction, cessation of ATP formation, and mitochondrial membrane rupture **(Hinson et al., 2010).** This leads to cellular necrosis. The role of mitochondria in paracetamol hepatotoxicity has been reviewed extensively **(Ramachandran and Jaeschke , 2019** and Ramachandran et al., 2020). Severe liver injury leads to loss of hepatic synthetic function and coagulopathy and hypoglycemia. Loss of hepatic metabolic functions leads to encephalopathy and lactic acidosis **(Saccomano et al., 2019).** The clinical manifestations of hepatotoxicity are delayed, with peak serum transaminase levels occurring two to three days after the overdose **(Bunchorntavakul and Reddy , 2013).** Approximately 12–13% of acute overdoses result in hepatotoxicity even with treatment **(Green et al., 2013),** with 2–5% progressing to liver failure and 0.2–0.5% resulting in death **(Buckley et al., 2002).**

Acute kidney injury can also occur, even in the absence of liver failure, and may be delayed. Nephrotoxicity may be direct due to tubular necrosis from renal NAPQI production or indicate hepatorenal syndrome **(Waring et al., 2010).**

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Paracetamol is also a direct mitochondrial toxin and at very high concentrations can result in central nervous system (CNS) depression. Coma may occur in the absence of hepatotoxicity or other drugs causing CNS depression and may lead to delayed diagnosis and treatment of paracetamol overdose **(Wiegand et al., 2010).**

Herbal medicines (HMs) have gathered increasing recognition in recent years, as one of the treatment options. Nearly 65% of the rural population in India depends on the HMs and about 40%–50% of people in Germany, 42% in the USA, 48% in Australia and 49% in France are using traditional medicine. **(Sen et al., 2015).** HMs originated from natural sources such as medicinal plants, minerals, animal products and their combinations are sometime presumed to be devoid of adverse effects **(Devi et al., 2007).**

Herbal medicines are naturally occurring, plant-derived substances, containing phytochemical compounds used for treatment or medicinal purposes **(Woerdenbag et al., 2014).** Since the market of herbal medicine is increasing every year, to date there have still been reports that found chemical adulterants in herbal medicines, thereby containing an undeclared synthetic drug. In Indonesia, in 2020, The Food and Drug Administration issued a press release regarding herbal medicine that contains undeclared synthetic drugs **(Porn, 2020).**

Based on their regulation, herbal medicine should not contain synthetic chemicals or medicinal isolation results. Some examples of adulterated herbal medicines are undeclared ingredients, such as sildenafil in the herbal extract **(Minh et al., 2019),** sibutramine phenolphthalein in slimming, dietary capsule supplements **(Wu et al., 2020),** and dexamethasone and prednisolone in herbal medicine pellets**.** Adulteration with synthetic drugs can be life-threatening, especially when those

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medications cause potential interactions or can cause other medical conditions. Therefore, detecting the presence of undeclared synthetic drugs in herbal medicine is important **(Primpray et al., 2019)**.

"Therefore, this study was designed to evaluate the efficacy of a herbal-based medication in mitigating paracetamol-induced hepatotoxicity in dogs."

Materials and methods

Ethical Statement

This study was conducted following the approval of the Institutional Animal Care and Use Committee (IACUC) at the Faculty of Veterinary Medicine, Cairo University. Informed consent was obtained from the owners of the dogs included in this study.

Animals

A total of fourteen clinically affected mongrel dogs (males and females), aged 4-5 years, were included. The animals were housed in a private clinic under standard conditions.

Experimental Design

The dogs were randomly allocated into two equal groups (n=7):

Group 1 (Herbal Group): Treated with paracetamol followed by a combination of Silymarin and a herbal-based formula.

Group 2 (Control Group): Treated with paracetamol followed by Silymarin only.

Treatment Protocol

The hepatic herbal solution consisted of choline (5 g), silymarin (5g), inositol (100mg), betaine (5mg), arginine (10mg), ornithine (3.5mg), citrulline (3mg), metacresol (1mg), D-L-Methionine (500mg), Lysine (500mg), and Glycine

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(500mg). It was administered at a dose of 1 ml/kg bodyweight once daily for 30 days via oral drench.

Ultrasonographic Examination

Ultrasonography was performed on each fasted dog (24 hrs) using a Pie Medical Scanner with a 5.0-7.5 MHz sector transducer. Transverse and longitudinal scans of the liver were conducted.

Sample Collection and Analysis

Blood samples were collected at three time points: baseline (before any treatment), 7 days post-paracetamol administration, and after the 30-day treatment period. Hematological analysis was performed using an automated cell counter. Biochemical parameters (ALT, AST, ALKP, triglycerides, total cholesterol) were measured using a clinical chemistry analyzer.

Statistical Analysis

Data were expressed as Mean ± Standard Deviation (SD). A two-way analysis of variance (ANOVA) was used to analyze the data, followed by Tukey's post-hoc test for multiple comparisons using SPSS software (Version 24). A P-value of < 0.05 was considered statistically significant.

RESULTS

Effect of different treatments on RBCs and hemoglobin parameters at different period of experiment.:

The results obtained in Table 1 cleared that, the paracetamol decreased significantly ($P < 0.05$) the level of RBCs, HGB, MVC HCT MCH , MCHC and RDW levels than the control samples that collected from the dogs before paracetamol treatment. While the level of the previous parameters using the Silymarine with herbal base improve the level of RBCs, HGB, MVC HCT MCH , MCHC and RDW that reached to its level in control groups.

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By comparison of the level of this parameters with the group that treated with Silymarin only the group that take the herbal base of a higher improvement in this hematological parameters than those treated without herbal base (Table, 1).

Table 1: Effect of different treatments on RBCs and hemoglobin parameters at different period of experiment.

Group		Treated by silymarin plus only + Herbal base			Treated by silymarin plus only			P-value (F-test)
Time		Control	After paracetamol treatment -7 days	Paracetamol + silymarin plus + Herbal base	Control	After paracetamol treatment -7 days	Paracetamol + silymarin plus	
N		7	7	7	7	7	7	
RBCs	Mean± SD	A 7.23± 1.06	C 6.11± 1.12	B 6.61± 0.84	C 6.19± 2.03	D 5.72± 1.01	D 5.70± 0.82	3.14 *
HGB	Mean± SD	A 15.80± 3.86	B 14.31±2.83	A 15.53±1.48	A 15.05± 3.44	B 14.89±2.15	C 13.63±1.89	2.45 *
MVC	Mean± SD	D 65.43± 9.61	B 71.57± 9.73	A 72.43± 2.23	E 62.24± 21.15	C 70.37± 4.74	B 71.57± 6.78	2.80 *
HCT	Mean± SD	B 48.57± 13.49	D 44.19± 9.35	C 47.86± 6.52	A 51.00± 10.92	E 40.29± 7.43	E 40.57± 6.43	2.55 *
MCH	Mean± SD	D 23.58± 4.89	D 23.39± 2.43	D 23.54± 1.85	A 27.29± 7.11	B 26.10± 1.48	C 24.01± 2.67	2.55 *
MCHC	Mean± SD	B 34.47± 2.87	C 32.97± 4.30	D 32.21± 2.86	C 32.81± 3.87	A 37.20± 2.50	B 34.23± 1.26	2.60 *
RDW	Mean± SD	A 14.60± 1.37	C 0.00	B 6.20± 8.77	A 15.53± 1.29	C 0	C 0	2.55 *

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Means within the same column of different litters are significantly different at ($P < 0.05$)

* = significant at ($P < 0.05$)

Effect of different treatments on WBCs and differential leucocyte parameters at different period of experiment.

The results obtained in Table 2 cleared that, the paracetamol increased significantly the level of WBCs than its level in control group and the level of differential leucocytic counts that includes lymphocytes, monocytes, neutrophils , eosinophils and basophils its level increased than its level in control group. While, the level of WBCs and its differential leucocytic counts in Silymarin treated dogs with herbal base showed decreased and returned to its normal level than the control and paracetamol treated groups

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Table 2: Effect of different treatments on WBCs and differential leucocyte parameters at different period of experiment.

Group		Treated by silymarin plus only + Herbal base			Treated by silymarin plus only			P-value (F-test)
Time		Control	After paracetamol treatment -7 days	Paracetamol + silymarin plus	Control	After paracetamol treatment -7 days	Paracetamol + silymarin plus	
N		7	7	7	7	7	7	
WBCs	Mean±SD	B 14.16±5.31	B 14.87±4.07	C 11.87±2.45	B 14.57±5.23	C 11.37±4.70	A 18.44±8.85	2.45*
Lymphocyte	Mean±SD	B 1.67±0.80	B 1.79±0.39	A 3.00±1.67	B 1.89±1.27	C 1.35±0.77	C 1.17±0.74	2.67*
MONO	Mean±SD	B 1.79±0.73	B 1.79±0.68	C 1.30±0.49	C 1.46±0.98	C 1.21±0.68	A 1.91±0.72	2.89*
Neu	Mean±SD	B 10.47±5.10	B 10.63±4.21	E 6.79±3.02	C 9.24±4.96	D 7.94±3.59	A 14.89±8.97	2.59*
EOs	Mean±SD	D 0.33±0.26	C 0.51±0.46	B 0.64±0.44	A 0.86±1.32	C 0.53±0.38	E 0.17±0.15	2.58*
Baso	Mean±SD	B 0.13±0.08	A 0.19±0.17	A 0.16±0.08	A 0.17±0.13	B 0.10±0.06	A 0.20±0.06	2.63*

Means within the same column of different litters are significantly different at ($P < 0.05$)

* = significant at ($P < 0.05$)

3- Platelets, ALT, ALKp and AST levels at different period in different group of experiment.

The results obtained in Table 3 cleared that, the paracetamol increased significantly the level of platelet level, ALT, ALKP and AST level than the control group while, the group treated with Silymarin + herba; base showed a lower level in platelets counts, ALT, ALKP and AST and its level reached to its normal level in control dogs. While, the level of platelet ,

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ALT, ALKP and AST in the group treated with Silymarin and paractamol its level reached to its level in the group treated with paracetamol only.

Table 3: Platelets, ALT, ALKp and AST levels at different period in different group of experiment.

Group		Treated by silymarin plus only + Herbal base			Treated by silymarin plus only			P-value (F-test)
Time		Control	After paracetamol treatment -7 days	Paracetamol + silymarin plus	Control	After paracetamol treatment - 7 days	Paracetamol + silymarin plus	
N		7	7	7	7	7	7	
Platelet	Mean±SD	D 312.57± 160.92	A 341.86±168.71	B 333.00±152.24	E 289.57±135.57	E 288.43±80.37	C 314.57±61.66	2.49*
ALT	Mean±SD	F 65.80±11.36	C 125.57±41.66	D 100.21±43.56	E 69.97±10.16	A 202.01±92.15	B 172.99±80.66	6.83**
ALKp	Mean±SD	F 64.86±23.98	C 104.30±45.05	D 77.00±33.79	E 72.39±14.03	A 127.14±44.33	B 117.46±32.35	4.05**
AST	Mean±SD	E 38.43±10.29	C 135.86±58.50	D 93.34±72.23	F 34.10±9.15	A 231.43±95.08	B 163.43±74.35	10.48**

Means within the same column of different litters are significantly different at ($P < 0.05$)

* = Significant at ($P < 0.05$) ** = Significant at ($P < 0.01$)

4- Triglyceride and total cholesterol levels at different period in different group of experiment.

The results obtained in Table 4 cleared that, the paracetamol increased significantly the level of triglycerdes and total cholesterol level than its level in control group , while, in the group treated with herbal base and Silymarin showed a lower level in triglycerides and total cholesterol level. The results also

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cleared that, the group treated with Silymarin showed a higher level in total cholesterol and triglycerides level that reached to its level in group treated with paracetamol only.

Table 4: Triglyceride and total cholesterol levels at different period in different group of experiment.

Group		Treated by silymarin plus only + Herbal base			Treated by silymarin plus only			P-value (F-test)
Time		Control	After paracetamol treatment - 7 days	Paracetamol + silymarin plus	Control	After paracetamol treatment - 7 days	Paracetamol + silymarin plus	
N		7	7	7	7	7	7	
TG	Mean±SD	F 76.27±30.15	C 103.03±44.45	E 92.14±34.37	D 99.17±5.84	A 143.71±49.51	B 127.14±51.31	2.55*
TCHO	Mean±SD	F 158.24±71.94	C 215.09±57.67	D 204.00±61.02	E 179.27±79.34	A 248.43±132.73	B 230.71±130.25	2.83*

Means within the same column of different litters are significantly different at ($P < 0.05$)

* = Significant at ($P < 0.05$) ** = Significant at ($P < 0.01$)

5- Ultrasonographic Findings

Prior to treatment (Baseline), ultrasonographic examination of all affected canines revealed severe, diffuse hepatic abnormalities. The liver parenchyma consistently exhibited marked hyperechogenicity and a coarse, heterogeneous echotexture (Scan A). Portal vein walls were distinctly

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hyperechoic and prominent, creating a "starry sky" appearance (Scan B). Subjective hepatomegaly with rounded hepatic margins was also frequently observed (Scan C). These findings were in agreement with Lakshmi and Padmaja (2022), who reported hepatomegaly characterized by increased size of liver The gallbladder wall was generally within normal limits to minimally prominent, with predominantly anechoic bile, though occasional mild sludge was noted. These baseline findings were indicative of severe, acute diffuse hepatopathy.

Following conventional therapy, a moderate improvement in hepatic appearance was noted. The diffuse hyperechogenicity, while still present, was subjectively less pronounced (Scan D). The hepatic echotexture remained somewhat coarse, though a slight trend towards improved homogeneity was observed. Portal vein wall prominence appeared mildly reduced. There was a suggestion of reduced hepatic size with slightly less rounded margins. Overall, conventional therapy resulted in a partial resolution of sonographic abnormalities.

Subsequent to the addition of the novel herbal supplement, a striking and substantial improvement in hepatic ultrasonographic architecture was observed. The hepatic parenchyma demonstrated a significant further reduction in echogenicity, approaching an isoechoic state (Scan E; Scan F). The echotexture became notably smoother and more homogeneous, closely resembling normal hepatic tissue. Portal vein walls normalized, and the "starry sky" appearance resolved. Hepatic margins appeared sharper, consistent with a return towards normal liver size (Scan G). The gallbladder generally

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appeared unremarkable. These findings indicated a marked and near-complete resolution of the ultrasonographic signs of hepatopathy following combined conventional and herbal therapy.

Conclusion of Ultrasonographic Findings:

Ultrasonography proved to be a valuable, non-invasive tool for monitoring the course of paracetamol-induced hepatotoxicity and the response to therapeutic interventions. The findings from this study demonstrate that while conventional therapy provides partial benefit, the addition of the novel herbal supplement was associated with a significantly more pronounced and comprehensive improvement in the ultrasonographic appearance of the liver, suggesting a potent hepatoprotective and restorative role in this canine model of toxic liver injury. These results highlight the potential of this herbal formulation as an effective adjunctive therapy for accelerating and enhancing hepatic recovery from paracetamol toxicosis."

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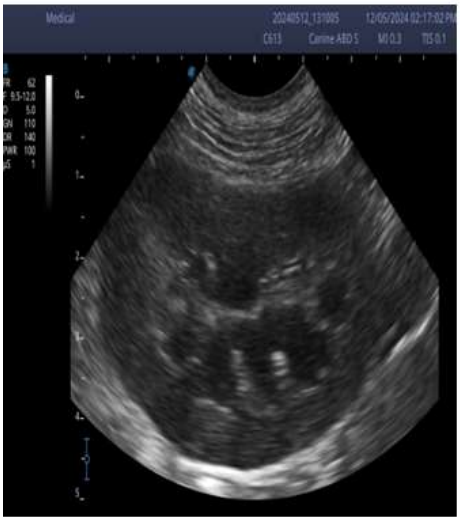

Fig(A)

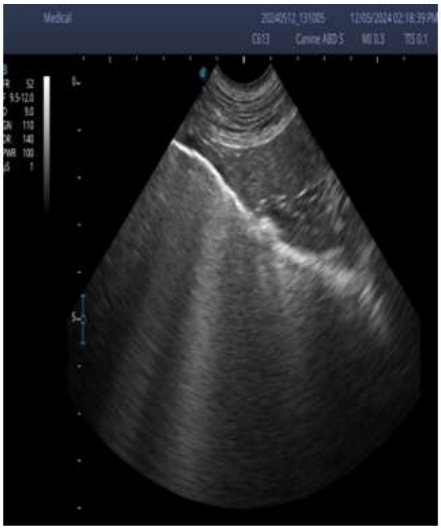

Fig (B)

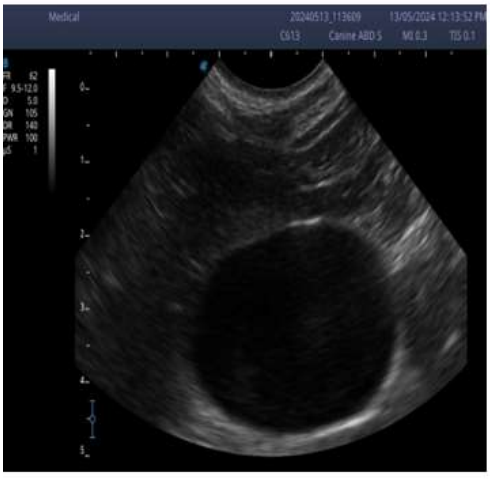

Fig (C)

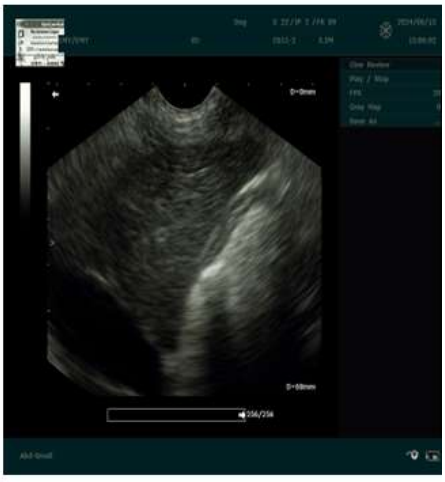

Fig (D)

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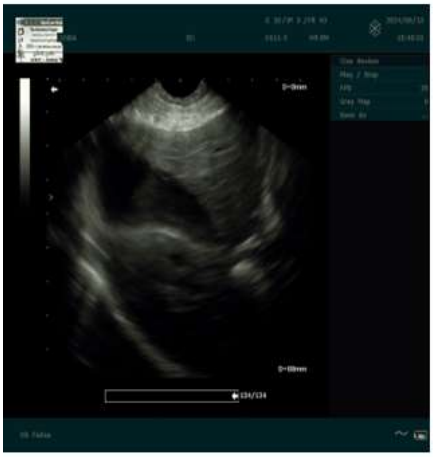

Fig (E)

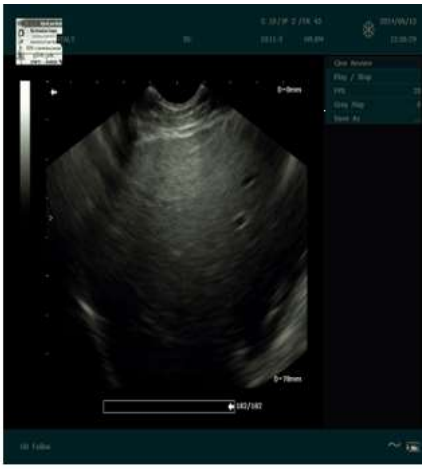

Fig (F)

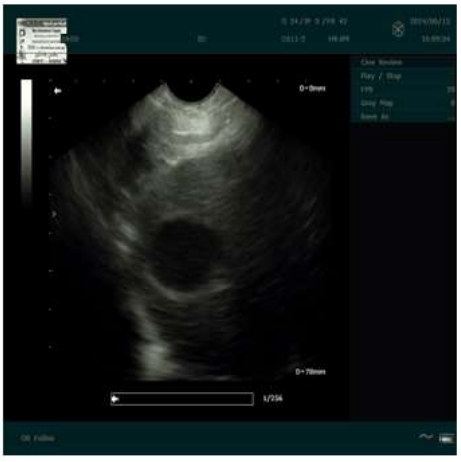

Fig (G)

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DISCUSSION

Paracetamol (acetaminophen) was marketed in the 1950s as a nonprescription analgesic/antipyretic without any preclinical toxicity studies. It became used increasingly for self-poisoning, particularly in the UK and was lately found to cause acute liver damage, which could be fatal. Management of poisoned patients was difficult as maximum abnormalities of liver function were delayed for 3 days or more after an overdose. There was no treatment and the mechanism of hepatotoxicity was not known **(Prescott et al., 2023).**

Management of poisoned patients was difficult as maximum abnormalities of liver function were delayed for 3 days or more after an overdose. There was no treatment and the mechanism of hepatotoxicity was not known. The paracetamol half-life was prolonged with liver damage occurring when it exceeded 4 h and the Rumack-Matthew nomogram was an important advance that allowed stratification of patients into separate zones of risk **(Proudfoot and Prescott, 2009).** It is used to guide prognosis and treatment and its predictive value could be increased by combining it with the paracetamol half-life **(Rumack et al., 2002).** The problems of a sheep farmer in Australia in the early 1970s led to the discovery of the mechanism of paracetamol hepatotoxicity, and the first effective treatment of overdosage with intravenous (IV) cysteamine. This had unpleasant side effects and administration was difficult. N-acetylcysteine soon became the treatment of choice for paracetamol overdose and given early it was very effective when administered either IV or orally. N-acetylcysteine could cause

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anaphylactoid reactions, particularly early during IV administration when the concentrations were highest. Simpler and shorter regimes with slower initial rates of infusion have now been introduced with a reduced incidence of these adverse effects. In addition, there has been a move to use larger doses of N-acetylcysteine given over longer periods for patients who are more severely poisoned and those with risk factors **(Mutsaers et al., 2019).**

So, this study was planned to study the using of herbal base treatment for treatment of paracetamol toxicity in dogs

Our results on the effect of different treatments on RBCs and hemoglobin parameters at different period of experiment cleared that, the paracetamol decreased significantly ($P < 0.05$) the level of RBCs, HGB, MVC HCT MCH , MCHC and RDW levels than the control samples that collected from the dogs before paracetamol treatment. While the level of the previous parameters using the Silymarine with herbal base improve the level of RBCs, HGB, MVC HCT MCH , MCHC and RDW that reached to its level in control groups and By comparison of the level of this parameters with the group that treated with Silymarine only the group that take the herbal base of a higher improvement in this hematological parameters than those treated without herbal base.

This results agreed with those of **(Mallet et al., 2018 and Pom, 2020),** where they reported that the herbal base treatment improve the RBCs level and the other blood parameters.

The decrease in RBC count which could indicate that there were destruction of matured RBC and reduction in the rate

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of erythropoiesis. This could also imply that paracetamol has the potential to inhibit erythropoietin release from the kidneys. Similar report was given by **Daniel and Clement (2008)** in rats treated with Dennettia tripetala extract. Paracetamol caused significant decrease in haemoglobin (Hb) concentration which suggest a reduction in the oxygen-carrying capacity of blood and the amount of oxygen-carrying capacity of blood and the amount of oxygen delivered to the tissues. Similar report was given by **Adedapo et al., (2007)** in rats treated with A. cordifolia and S. Virosa extracts. Paracetamol also caused significant decrease in PCV value which could indicate the induction of anemia. Similar report was given by **Biu et al. (2009)** and **Aronoff et al. (2002)** in rats treated with aqueous Neem extract.

While, our results on the effect of different treatments on WBCs and differential leucocyte parameters at different period of experiment. cleared that, the paracetamol increased significantly the level of WBCs than its level in control group and the level of differential leucocytic counts that includes lymphocytes, monocytes, neutrophils , eosinophils and basophils its level increased than its level in control group. While, the level of WBCs and its differential leucocytic counts in Silymarin treated dogs with herbal base showed decreased and returned to its normal level than the control and paracetamol treated groups.

This results agreed with those of ***(Mukazayire et al., 2010),*** *where they reported that, the herbal base treatment improve the immunity and WBCs level in toxicated guinea pigs*.

This results disagreed with those of **(Oyedeji et al., 2013 and Brune et al., 2015)** where they reported that, Paracetamol

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caused non-significant changes in total WBC, neutrophil, eosinophil, monocyte and lymphocyte counts, which suggest that the immune system have not been compromised. It also caused non-significant change in platelet count which probably indicates its inability to stimulate haemostasis.

There is an effective antidote to paracetamol (N-acetylcysteine or NAC); however, despite this, paracetamol toxicity is still the leading cause of acute liver failure (ALF) in most high-income countries **(Wei et al., 2007).** Severe cases may require liver transplantation or result in death **(Bunchorntavakul and Reddy , 2013).**

While, our results on the platelets, ALT, ALKp and AST levels at different period in different group of experiment cleared that, the paracetamol increased significantly the level of platelet level, ALT, ALKP and AST level than the control group while, the group treated with Silymarin + herba; base showed a lower level in platelets counts, ALT, ALKP and AST and its level reached to its normal level in control dogs. While, the level of platelet , ALT, ALKP and AST in the group treated with Silymarin and paractamol its level reached to its level in the group treated with paracetamol only. Also, **While, our results on the Triglyceride and total cholesterol levels at different period in different group of experiment, cleared that,** cleared that, the paracetamol increased significantly the level of triglycerdes and total cholesterol level than its level in control group , while, in the group treated with herbal base and Silymarin showed a lower level in triglycerides and total cholesterol level. The results also cleared that, the group treated

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with Silymarin showed a higher level in total cholesterol and triglycerides level that reached to its level in group treated with paracetamol only.

This results attributed to the effect of paracetamol toxicity on the liver function that causes damaged and fibrosis to the liver with increasing level of ALT, ALKp, and AST. This results agreed with those of **(Prescott , 2023)** where they reported that, acute centrilobular hepatic necrosis was the primary manifestation of paracetamol toxicity following an overdose and renal failure could also occur, usually, but not always, in patients with severe liver damage. Also, .paracetamol can cause severe hepatotoxicity with as little as 10 g (or 200 mg/kg for patients under 50 kg) in an acute overdose. Repeated supratherapeutic ingestion can cause toxicity in doses only slightly above the maximum daily therapeutic dose **(Larson et al., 2005).**

The improvement of paracetanol toxicity after admistration of herbal base extract attributed to its contents on enzymes, that improve the hematological, immunological and biochemical changes resulted from paracetamol toxicity **(Green et al., 2013).**

This results agreed with those of **(Change et al., 2024)** where they reported that, recently, herbal medicine was found to be a promising therapeutic approach for associated liver injury (ALI). Several herbal components were reported to have the same therapeutic effect as NAC. In a previous study, the effectiveness of the treatment was significantly noticed when it was administered after Acetaminophen (APAP), but not as a pretreatment. These underlying limitations regarding the

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applicability and effectiveness of herbal therapy have been modified and improved in recent years by direct application in an APAP overdose setting **(Chen et al., 2009; Mukazayire et al., 2010 and Tien et al., 2014).**

conclusion

In conclusion, the findings of this study provide strong evidence that the investigated herbal-based formula serves as a highly effective adjunctive therapy in the management of paracetamol-induced hepatotoxicity in dogs, offering superior restorative and hepatoprotective effects compared to silymarin alone.

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