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EVALUATION THE SAFETY OF A POLYHERBAL FORMULATION OF *Artemisia monosperma* AND *Mentha piperita* IN MALE ALBINO RATS

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ABSTRACT

Even though some polyherbal combinations have been used traditionally, there is limited scientific research on their safety and effectiveness. To address this gap, this study sets out to explore the potential synergies and safety of a polyherbal formulation that contains *A. monosperma* and *M. piperita*. Specifically, the study examined the impact of this formulation on certain biochemical and hematological parameters *in vivo*. The study involved organizing the animals into eight groups, each comprising five animals. Group1, served as control group, received distilled water. Groups 2, 3, and 4, referred to as AL, AM, and AH received *A. monosperma* in doses of 1000, 3000, and 5000 mg/kg body, respectively. Group5 received 290 mg/kg of *M. piperita* extract. The remaining three groups, ALM, AMM, and AHM, received a mixture of *A. monosperma* and *M. piperita* in a polyherbal formulation (PF) at the same doses for 14 days, once daily. The results showed that none of the treated animals died or showed signs of toxicity. Additionally, the polyherbal formulation did not cause any notable shifts in body weight or blood-related parameters, when compared to the control groups. Furthermore, the hepatic and renal functions remained unaffected using this formulation. Therefore, it can be concluded that the polyherbal formulation is harmless and non-poisonous, even at high doses of 5000 mg/kg, and has the potential to be employed as a diabetes remedy.

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INTRODUCTION

The practice of herbalism involves utilizing plants and extracts for medicinal purposes, as a form of traditional medicine. For many years, people have relied on natural remedies to treat and prevent various ailments. In fact, these remedies have been more popular than modern medicine. The field of traditional medicine encompasses various forms of treatments, comprising vitamins, minerals, herbal remedies, nutritional supplements, and homeopathic remedies, which can interact with each other. 80% of people all over the world were estimated by the world health organization using this herbal medicine (**WHO, 2005**), either in individual or in combination (**Parasuraman *et al.*, 2014; Kaur *et al.*, 2019**), which considered being without side effects (**Karakoca *et al.*, 2013**). In Ayurveda, combinations containing two herbs or more (polyherbal formulations), oils, or infusions (**Che *et al.*, 2013**). Polyherbal formulations have therapeutic potential which is not found in drugs allopathic medicine (**Parasuraman *et al.*, 2014; Kaur *et al.*, 2019**). Nonetheless, the application of numerous amalgamations is based on trial and error as there is no empirical proof to support their advantages. For instance, it is uncertain whether the ratios of these mixtures are suitable, if the type of interaction they produce is favorable, or if their negative impacts are mitigated. Two such plants with a long history of use

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are *Artemisia monosperma* (commonly known as Aader as a local name) (**Migahid and Hammouda, 1978**) and *Mentha piperita* (peppermint). While these plants possess distinct characteristics, we are interested in exploring their potential synergy when used in combination.

Artemisia has a presence in Egypt through four wild species: *Artemisia judaica* L., *Artemisia monosperma* Delile, *Artemisia scoparia* Waldst, and *Artemisia verlotiorum* Lamotte. A fifth species, *A. vulgaris* L., is grown through cultivation. (**Boulos, 2002**). *Artemisia monosperma* (*A. monosperma*) is a sweet-smelling perennial shrub found in the deserts of Africa, China (**Migahid and Hammouda, 1974; Bora and Sharma, 2011; Abad *et al.*, 2012**), and the Middle East. It can grow in desert plains and wadis, both inland and along the Mediterranean coast, and is often spotted near the northern Sinai coast (**Badr *et al.*, 2012**). Traditional medicine employs *A. monosperma* to treat illnesses such as gastrointestinal problems (**Dabe and Kefale, 2017**), rheumatism, fever, hypertension, and parasitic worm infections (**Hijazi and Salhab, 2010**).

A. monosperma contains many beneficial compounds like coumarins (**Hammoda *et al.*, 2008**), acetylenes (**Saleh, 1985**), sesquiterpenoids (**Zaki *et al.*, 2004**), alkaloids (**Zaki *et al.*, 1984**), flavonoids (**Elgamal *et al.*, 1997**), triterpenoids (Lupeol and β-amyrin) (**Elgamal *et al.*, 1997; El Sayed *et al.*, 2017)**, α-terpinolene, α-pinene, β-Pinene, shyobunone, and limonene (**Khan *et al.*, 2012**).

Peppermint is a common name for *Mentha piperita* (*M. piperita*) and is used widely in folk medicine (**Liu *et al.*, 2006; Trevisan *et al.*, 2017; Anwar *et al.*, 2019**). *M. piperita* is a hybrid plant that is cultivated by crossing two species, *M. spicata* and L *M. aquatica*. Peppermint is originally native to the Mediterranean region but has been widely distributed and utilized for its fragrance, flavoring, cosmetics, medicine, and pharmaceuticals (**Balakrishnan, 2015**).

Dried peppermint aerial parts were discovered in the Egyptian pyramids, indicating that this fragrant plant has been in use for more than a millennium. Peppermint has been shown to possess a variety of biological activities. Due to its cancer-fighting properties, potential to prevent cancer, effects on the kidneys, and ability to alleviate digestive issues such as anorexia, cramping, diarrhea, and nausea, this natural remedy has been widely used in traditional medicine for treating nervous system disorders and digestive complaints (**Loolaie *et al.*, 2017**).

Interestingly, both *A. monosperma* and *M. piperita* share some documented medicinal uses, hinting at potential synergistic effects when combined.

Both *A. monosperma* and *M. piperita* possess a range of interesting medicinal properties. *A. monosperma* has been explored for its antimicrobial, anti-inflammatory (**El Zalabani *et al.*, 2017; El Sayed *et al.*, 2017)**, antioxidant (**Al- Soqeer, 2011; El Zalabani *et al.*, 2017; Salih *et al.*, 2023**), and antidiabetic potential (**Hijazi and Salhab, 2010; Badawy *et al.*, 2022**), while also showing promise in managing rheumatism (**Hijazi and Salhab, 2010**), spasms properties (**Wagner and Wolff, 1977**), and even cancer (**Stavri *et al.*, 2005**). Similarly, *M. piperita* boasts antifungal, antimicrobial, antiviral, (**Kamatou *et al.*, 2013; Loolaie *et al.*, 2017; Chumpitazi *et al.*, 2018**) and anti-inflammatory properties (**Ghasemi-Pirbaluti *et al.*, 2017; Chumpitazi *et al.*, 2018; Anwar *et al.*, 2019; Kehili *et al.*, 2020**), alongside potential applications in diabetes (**Angel *et al.*, 2013; Chandirasegaran *et al.*, 2014; Abdellatief *et al.*, 2017**) and as an antioxidant (**Schuhmacher *et al.*, 2003**). This shared focus on inflammation and potentially even blood sugar regulation suggests that combining these two herbs

could lead to a synergistic effect, enhancing their overall therapeutic efficacy.

While the individual properties of *A. monosperma* and *M. piperita* offer a promising therapeutic arsenal, the potential benefits of their combined use remain largely unexplored. In our previous investigation into male reproductive health, we discovered that when given separately to rats, *A. monosperma* and *M. piperita* caused harm to the testicles and a decrease in sperm quality, which might result in infertility. Interestingly, the combination of both herbs seemed to counteract this damage (**Mohammed *et al.*, 2021**). However, no published research has investigated the impact of this specific combination on hematological and biochemical parameters. This knowledge gap necessitates a safety evaluation of the *A. monosperma* and *M. piperita* combination before human use.

MATERIALS AND METHODS

Chemicals

Isoflurane was bought from Adwic-El Nasr Pharmaceutical Co. (Cairo, Egypt). The biochemical assays were performed using assay kits that were products of Bio-diagnostic Egypt- Spinreact, Girona, Spain-BIOMED Diagnostics, Oberschleißheim, Germany- Diamond Diagnostics, Germany-SPECTRUM, Egypt. The chemicals and reagents employed were sourced from standard commercial suppliers and met the requirements for analytical grade.

Plant Material and Authentication

During December 2022, *A. monosperma* and *M. piperita* were harvested from the northern Sinai desert in Arish, Egypt. Dr. Nashwa A. M. Mostafa, a taxonomist, confirmed the plants' identity, and voucher specimens were kept in the Herbarium of the Faculty of Science, Arish University, North Sinai, Egypt. Accession numbers A3448 and L4532 were allocated to the specimens.

Aqueous Extracts Preparation

The aerial parts of *A. monosperma* were dried in the shade, then finely ground using an electric blender. A hot water extract was created using the process outlined by **Abdel-Salam *et al.* (2009)**. This involved adding 50 g of Artemisia powder to a flask containing 1000 ml of distilled water, boiling for 15 minutes, and filtering the mixture twice with Whatman No.2 filter paper. The final concentration of the extract was 5% total solid and it was stored in a sterile dark bottle in a cool place (4°C) until needed.

M. piperita leaves were washed, dried, and had their roots removed before being placed in tap water. The extract was made using a concentration of 100 mg/ml, which is equivalent to the daily intake of an adult man (**Barbalho *et al.*, 2013**). The resulting water extract was filtered into a dark bottle and stored at -80C. Prior research has demonstrated that a dosage of 290 mg/kg b.wt. over 14 days is safe for all organs (**Johari *et al.*, 2015**). When ready for use, the extract was thawed and left at room temperature for two hours.

Combining the Extracts

The preparation of the polyherbal formulation proceeded following the determination of the optimal dosages through previous studies. Under aseptic conditions, precisely measured volumes of each extract, corresponding to the chosen doses, were combined within a sterilized container. Gentle agitation ensured homogeneous mixing to achieve a uniform blend. The final formulation is stored in a dark, airtight container in a cool environment (4°C).

Ethical Considerations

The Animal Care and Ethics Committee (ACEC) of Arish University in North Sinai, Egypt, gave us ethical clearance for our work (No. ARU/SF.07#). We took great care to lessen the pain and suffering of the

research animals in accordance with ACEC recommendations.

Animals

We bought adult male albino rats from Cairo-based Egyptian vaccination producer VACERA. The experiments started after they had a week to become used to their new environment. The rats were kept in an animal facility that had good ventilation, a 12-hour light and dark cycle, and a temperature control of 22–24°C. The rats were given *adlib tum* and fed pellets of rat chow. The investigation was carried out at Arish University's Faculty of Science's Animal House Lab. All animal studies were conducted in accordance with the rules set forth by the Institutional Animals Ethics Committee of the Faculty of Science, Arish University, El-Arish, Egypt, and the **National Institutes of Health's (NIH Publication, 1985)** guidelines for the care and use of laboratory animals.

Experimental Design

Consisting of male albino rats that were in good health, aged between 2-3 months, and weighing between 260-275 grams. After that, the rats were split up into eight groups, each with five rats. Group 1 (control) got distilled water whereas Groups 2, 3, and 4 (AL, AM, and AH) received an aqueous extract of *A. monosperma* at doses of 1000, 3000, and 5000 mg/kg, respectively, Group 5: was given 290 mg/kg of *M. piperita* aqueous extract. The extract of the polyherbal formulation of *A. monosperma* and *M. piperita*, given at the identical dosages of the two plants previously mentioned, was given to the remaining three groups (6), (7), and 8 (ALM, AMM, and AHM). For fourteen days, each treatment was given orally once a day. The *A. monosperma* doses were selected based on the findings of **El Sayed *et al.* (2017)**, a study that reported the LD50 of the species to be as high as 6.1g/kg b.wt. The animals were observed during the treatment period for any abnormalities, and at the end of the trial, their body weights were noted.

Blood Sample and Organs Collection

At the end of treatment, the animals were fasted overnight but had access to water. The rats were given isoflurane anesthesia and killed with a sterilized surgical blade to ensure that the procedure was humane. For morphological and hematological examination, we took blood samples using a tube containing the anticoagulant ethylene diamine tetra acetic acid (EDTA), and for clotting, we used a different set of plain sample vials. To extract serum, the clotted blood samples were centrifuged for 20 minutes at 3,000 rpm. Before they were ready for analysis, the serum samples were stored in a freezer at -80 °C.

Determination of Body and Relative Organs Weight

During the 14-day experiment, the gain of body weight (BWG) was determined by recording the initial and final body weight of each group, using the formula provided by **Chapman *et al.* (1959)**.

BWG%= (Final body weight – Initial body weight)/ Initial body weight×100

The selected organs liver, kidneys, heart, brain, stomach, and spleen were removed immediately after animal dissection. The organs have been cleaned in saline of any accessory tissues. The absolute organs weight was divided by the final body weight (×100) to calculate the relative organs weight.

Hematological Parameters Determination

Freshly EDTA blood samples were performed on an ABX Pentra (Horiba, Montpellier, France) following the manufacturer's instructions. The following analyses were carried out: total RBCs, hemoglobin (HB) concentration, mean cell hemoglobin (MCH), haematocrit (Hct), mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), red blood cell

distribution width (RDW-CV), total white blood cells (WBCs), LYM, and platelet (PLT) were analyzed.

Morphological Examination

For morphological examination, EDTA blood samples were collected for Scanning electron microscope (SEM) and Light microscope (LM) analysis.

Light microscope (LM) analysis

EDTA blood samples were smeared on slides and allowed air dry. The blood smear specimens were fixed with absolute methanol for 10 minutes. Once air-dried, the specimens were stained using Giemsa stain solution (Sigma Aldrich Company, USA) for 20 minutes, as per the manufacturer's recommendations. The cells were then observed under an optical microscope (100x, Olympus) and photos were taken using an Olympus E 420 camera. The RBCs were classified as normocytes, target cells, echinocytes, Rouleaux, and acanthocytes (**Jones, 2009**).

Scanning electron microscope (SEM) analysis blood sample preparation for SEM

Upon arrival at the laboratory, EDTA blood samples were promptly processed at room temperature for microscopic investigation. The blood sample was obtained, and after 10 minutes of centrifugation at 2,000 rpm, the leukocyte layer was separated and placed in a 1.5 ml Eppendorf tube. To fix the leukocytes till additional examination, glutaraldehyde from Adwic-El Nasr Pharmaceutical Co. (Cairo, Egypt) was applied. The sample was then centrifuged one more for one minute at 6,000 rpm, and only the precipitate was extracted by decanting the mixture. The precipitate was combined with 1X phosphate buffered saline solution (pH = 7.4) obtained from Adwic-El Nasr Pharmaceutical Co. (Cairo, Egypt), left for five minutes, and then stirred again. This process was iterated three times. Subsequently, 60% alcohol was introduced, and the resulting precipitate was allowed to settle for 10 minutes. Afterward, the sample underwent centrifugation at 6,000 rpm for 1 minute. This sequence was replicated using alcohol concentrations of 70%, 80%, 90%, 96%, and finally 100%. Following this, 100% pure acetone was applied and fixed within a dark-bottomed aluminum cylinder, ready for coating with gold particles using the Desk II Denton vacuum equipment in Lawrence, Kansas. The sample was then examined utilizing a Zeiss Ultra plus Field Emission Gun Scanning Electron Microscope (SEM) from Carl Zeiss Microscopy, Europe, Germany, as described by **Fischer *et al.* (2012)**, to capture micrographs of the erythrocytes.

Biochemistry Parameters Analysis

Liver functions determination

Serum was analyzed for the determination of levels of glucose using Kits from Bio-diagnostic Egypt (Catalogue #: GL 13 20). Additionally, commercial kits from Spinreact in Girona, Spain were used to assess the activities of serum aminotransferase alanine (ALT) and aspartate (AST) (**Kodikonda and Naik, 2017**). The content of total protein was determined by commercial kit (REF: TP116150; BIOMED Diagnostics, Oberschleißheim, Germany) (**Weichselbaum, 1946**). Direct and total bilirubin levels were assessed with a kit from Diamond Diagnostics, Germany (REF: BIL099100) (**Doumas *et al.*, 1973**). The level of albumin was assessed by the colorimetric modified bromocresol green method by using commercial kit (ALB210002, SPECTRUM, Egypt) (**Peters *et al.*, 1982**).

Kidney functions determination

For determining the levels of urea and creatinine, commercially available testing kits were employed (URE118200, CRE106240; BIOMED Diagnostics, Oberschleißheim, Germany) (**Kodikonda and Naik, 2017**). Meanwhile, the uric acid testing kit used was from SPECTRUM, Egypt (REF: 323001) (**Fossati and Prencipe, 1982**).

Determination of lipid profile

Commercial kits (TC; CAT. No.: CH 1220, TG; CAT. No.: TR 2030, HDL-C; CAT. No.: CH 1230, respectively; Biodiagnostic, Dikka, Egypt) were utilized to measure the levels of triglyceride (TG), Total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C), as outlined in the study by **Kodikonda and Naik (2017)**, for the evaluation of the lipid profile.

Determination of minerals

The levels of calcium (**Farrell and Calcium, 1984**), potassium (**Berry, 1989**), and sodium (**Henry, 1974**) in the serum were assessed using commercial kits provided by SPINREACT, Obour city industrial area.

All parameters were determined by using suitable kits and according to the manufacturer's instructions.

Statistics of Analysis

Statistical analysis were conducted using Graphpad Prism 8.0.1 software (San Diego, CA, USA). Results are expressed as mean ± SEM of n = 5. One-way analysis of variance (ANOVA) was performed, followed by Tukey's multiple comparisons tests, to compare the means of all groups to each other. Statistical significance was considered at $p \leq 0.05$. Symbols *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001 were used to denote statistical differences compared to the control group, while #P < 0.05, ##P < 0.01, ###P < 0.001, and ####P < 0.0001 were used for statistical differences compared to the mint group.

RESULTS

Effect of PF Administration on Body Weight Gain and Relative Organ Weight in Rats at 14 Days of treatment

The impact of administering polyherbal formulation (PF) on body weight gain and relative organ weight in rats was recorded in Tables 1 and 2. The rats showed no toxic reactions to the herbs, whether used alone or together. After comparison to the control group, no significant differences were found ($p \leq 0.05$) in the weight gain or organ weight of in all treated rats.

Effect of PF Administration on Red Blood Cell Morphology in Rats at 14 Days of Treatment

To assess the impact of a polyherbal extract on the shape of RBCs, LM and SEM microscopy were used (Fig. 1A and 1B; Fig. 2). The LM analysis revealed that the RBCs of the control group rats were round, biconcave discs with a central pallor, which is a typical RBC shape known as a discocyte in SEM analysis or a normocyte in LM analysis. When stained with Geimsa's solution, RBCs appear pink because the hemoglobin content of the RBC picks up eosin, the acidophilic component of the dye. In contrast, the groups that were treated with *A. monosperma* extracts showed significant morphological changes such as echinocytes, acanthocyte, target cell, and Rouleaux. Moreover, the SEM results of ultrastructural analysis revealed abnormal morphology, including acanthocyte and echinocytes.

Effect of PF Administration on Hematological Parameters in Rats at 14 Days of Treatment

During a 14-day study, the oral administration of aqueous extract of *A. monosperma* or *M. piperita* or polyherbal extract at different doses did not result in any significant alterations in hematological parameters, except for platelet count which was found to be significantly increased at 3000 mg/kg of *A. monosperma* ($p<0.05$). In contrast, the animals treated with polyherbal extract at all doses did not exhibit any change in platelet count when compared to the control and mint groups.

Table1. Effect of PF administration on body weight gain in rats at 14 days of treatment

Parameter	Group							
	Control	AL	AM	AH	M	ALM	AMM	AHM
Initial body weight (g)	266±11.2	272±17.1	259±15.42	276±22.8	275±12.2	273±13.2	268±22.6	270±13.8
Final body weight (g)	277±15.4	265±17.7	296±25.1	316±65.1	300±33.1	292±21.2	285±55.2	271±24.1
Body weight gain. BWG (%)	6.17 ± 0.54	4.06±0.54	8.84±1.28	7.12±1.05	8.58±0.70	10.19±0.47	8.93±0.75	8.28±1.27

The values were expressed as mean ± SEM. Distinguishing symbols on the bars (*, #) indicate significant differences at $p < 0.05$ (* versus control group, # versus mint group), determined by a one-way ANOVA test followed by Tukey's test.

Table 2. Effect of PF administration on relative organ weight in rats at 14 days of treatment

Parameter	Group							
	Control	AL	AM	AH	M	ALM	AMM	AHM
Relative liver weight (%)	2.58± 0.11	2.49± 0.06	2.44± 0.15	2.39± 0.04	2.12± 0.06	2.33± 0.05	2.68± 0. 38	2.52± 0.21
Relative Heart weight (%)	0.35±0.02	0.42±0.01	0.32±0.04	0.35±0.15	0.35±0.03	0.33±0.02	0.46±0.07	0.35±0.02
Relative L. Kidney weight (%)	0.33±0.02	0.36±0.02	0.32±0.02	0.57±0.17	0.3±0.009	0.33±0.02	0.35±0.04	0.3±0.01
Relative R. Kidney weight (%)	0.34±0.02	0.37±0.02	0.29±0.03	0.36±0.01	0.3±0.01	0.32±0.01	0.33±0.06	0.34±0.01
Relative Lung weight (%)	0.93±0.12	0.62±0.03	0.56±0.05	0.71±0.13	0.58±0.03	0.56±0.03	0.59±0.07	0.63±0.08
Relative Spleen weight (%)	0.28±0.02	0.24±0.02	0.24±0.01	0.26±0.01	0.26±0.006	0.23±0.01	0.29±0.02	0.26±0.03
Relative Brain weight (%)	0.55±0.03	0.53±0.04	0.56±0.05	0.67±0.08	0.56±0.01	0.57±0.03	0.54±0.03	0.62±0.05
Relative Stomach weight (%)	0.54±0.04	0.58±0.06	0.5±0.03	0.53±0.05	0.52±0.02	0.58±0.05	0.54±0.04	0.55±0.03

The values were expressed as mean ± SEM. Distinguishing symbols on the bars (*, #) indicate significant differences at $p < 0.05$ (* versus control group, # versus mint group), determined by a one-way ANOVA test followed by Tukey's test.

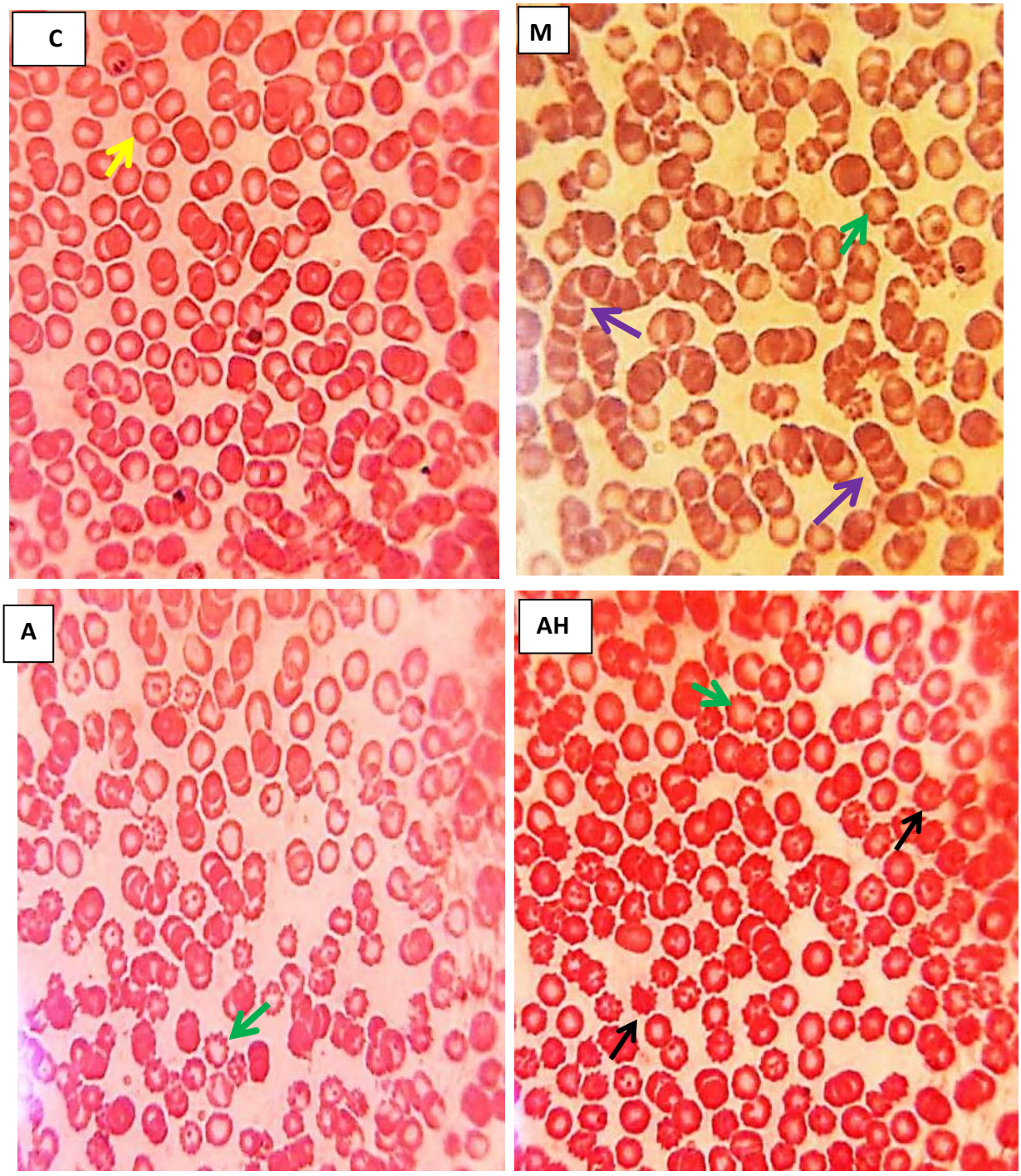

Fig. 1A. Light microscopy smears and optical micrographs at 100 × of rats, showing the normal (yellow arrow) and abnormal forms of RBCs. Echinocytes (green arrow), Acanthocytes (black arrows), target cells (blue arrows) and Rouleaux (purple arrow)

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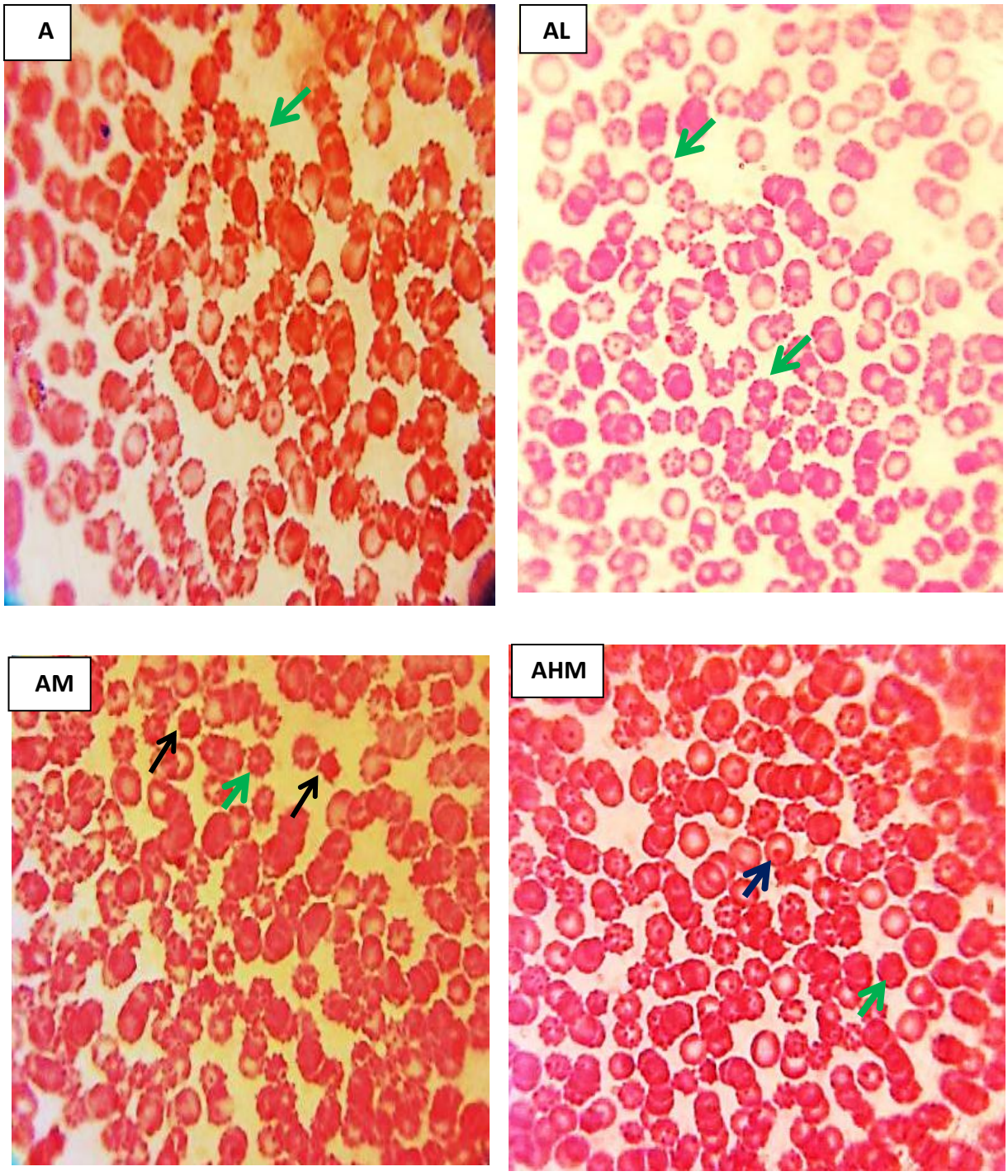

Fig. 1B. Light microscopy smears and optical micrographs at 100 × of rats, showing abnormal forms of RBCs. Echinocytes (green arrow), Acanthocytes (black arrows), target cells (blue arrows) and Rouleaux (purple arrow)

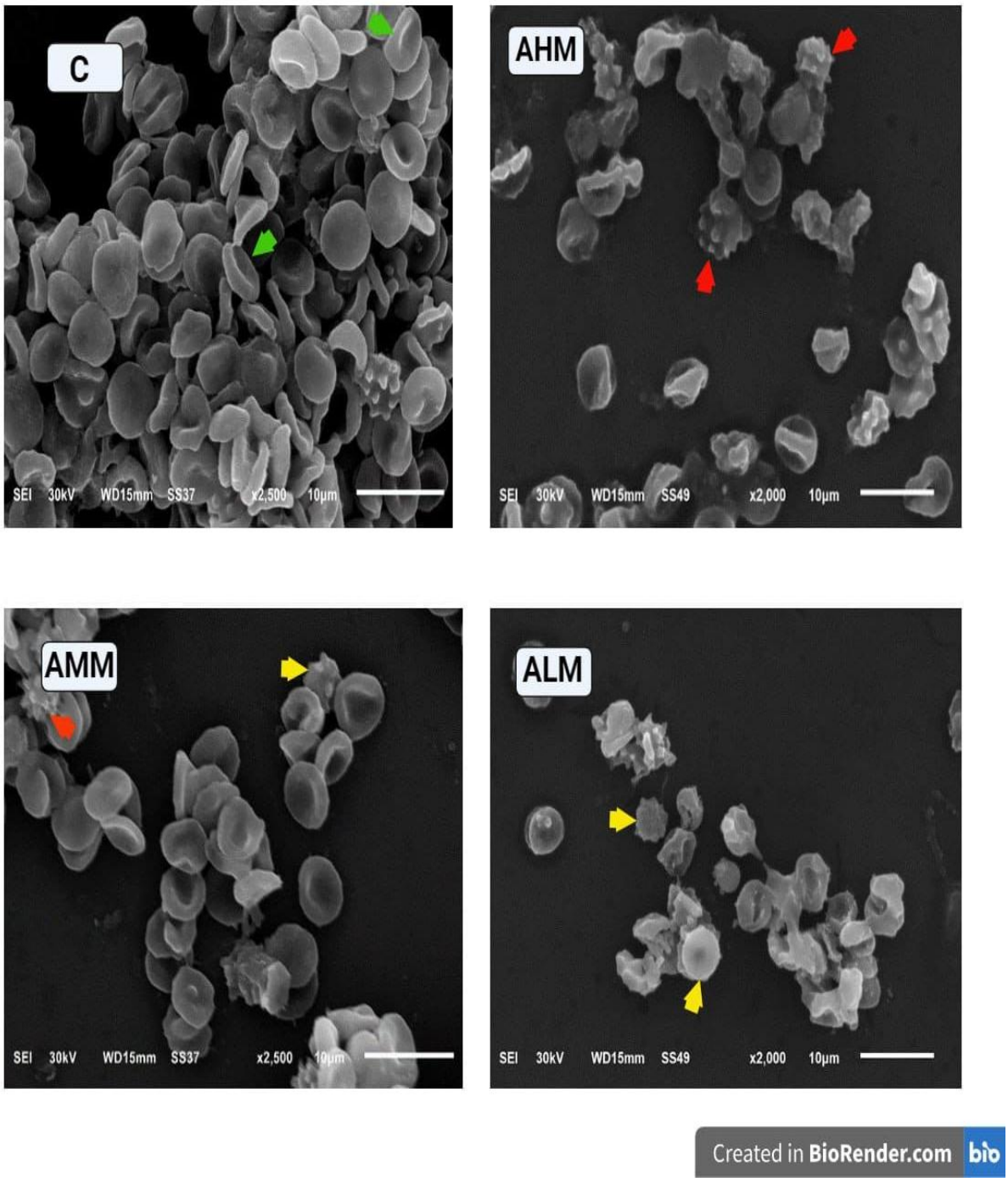

Fig. 2. SEM images of normal and abnormal RBCs in rats: (c) Normal erythrocyte morphology (green arrowhead), echinocytes (yellow arrowhead), and acanthocytes (red arrowhead arrow)

Table 3. Effect of PF administration on hematological parameters in rats at 14 days of treatment

Parameter	Group							
	Control	AL	AM	AH	M	ALM	AMM	AHM
RBCs ($\times 10^6$ /mm^3)	8.08 ± 0.16	7.44 ± 0.2	7.50 ± 0.19	8.04 ± 0.16	8.11 ± 0.15	8.18 ± 0.2	7.94 ± 0.14	7.55 ± 0.21
HB g/dL	13.67 ± 0.31	12.73 ± 0.33	13.08 ± 0.12	13.22 ± 0.26	13.3 ± 0.23	13.95 ± 0.33	13.33 ± 0.21	12.67 ± 0.31
HCT %	42.9 ± 0.85	40.65 ± 1.22	40.92 ± 0.74	42.9 ± 0.85	43.72 ± 0.58	45.72 ± 1.37	43.28 ± 0.64	40.55 ± 1.1
MCV fL	53.27 ± 2.26	54.97 ± 0.96	54.68 ± 0.49	53.38 ± 0.55	53.96 ± 0.85	55.9 ± 0.81	54.55 ± 1.09	53.75 ± 0.34
MCH pg	16.83 ± 0.35	17.13 ± 0.4	17.47 ± 0.28	16.45 ± 0.27	16.42 ± 0.4	17.08 ± 0.28	16.8 ± 0.42	16.82 ± 0.13
MCHC g/dL	30.7 ± 0.1	31.38 ± 0.37	31.93 ± 0.27	30.83 ± 0.27	30.42 ± 0.25	30.57 ± 0.27	30.8 ± 0.19	31.23 ± 0.28
WBCs ($\times 10^3$/mm^3)	8.13 ± 0.57	7.68 ± 1.17	9.0 ± 0.63	8.22 ± 0.86	7.52 ± 0.83	10.3 ± 1.54	9.17 ± 1.41	8.68 ± 1.12
LYM (%)	5.95 ± 0.33	5.5 ± 0.77	6.32 ± 0.48	5.78 ± 0.52	5.78 ± 0.89	7.55 ± 1.62	6.88 ± 1.2	7.1 ± 1.14
PLT (x10^3/mm^3)	1084 ± 18.68	1111 ± 53	1375 ± 41.0*	1121 ± 100.45	1012 ± 24.1	1066 ± 20.33	1074.67±72.55	1166 ± 43.66

The values were expressed as mean ± SEM. Distinguishing symbols on the bars (*, #) indicate significant differences at $p < 0.05$ (* versus control group, # versus mint group), determined by a one-way ANOVA test followed by Tukey's test.

Effect of PF Administration on Biochemical Parameters in Rats at 14 Days of Treatment

The results indicated that rats supplemented with *A. monosperma* or *M. piperita* administered either alone or in combination had lower serum glucose concentrations. Meanwhile, the data presented in Table 4 indicate that neither the administration of *A. monosperma* nor *M. piperita*, either alone or in combination, resulted in significant changes in hepatic transaminases AST and ALT activities, as well as T. BIL and CRA levels. However, the administration of the polyherbal extract at a high dose led to a substantial increase in ALB levels ($p < 0.001$) and T. protein levels ($p < 0.0001$) compared to the control and mint groups. Moreover, the level of D.BIL was elevated in the AH and ALM groups ($p < 0.0001$). Additionally, a significant change in urea levels ($p < 0.0001$) and uric acid levels ($p < 0.05$) in a dose-related manner were observed in the treated groups compared to the control.

Effect of PF Administration on Serum Lipid Profile and Electrolytes Levels in Rats after 14 Days of Treatment

The results of the serum lipid profile, which includes TC, TG, and HDL-CH, as well as serum electrolytes, are presented in figure 3. The rats that were supplemented with either M. piperita or *A. monosperma*, either alone or in mixture, had lower levels of TG and TC, while higher levels of HDL-CH and K concentration were noticed when compared to the control rats. Additionally, the data demonstrated a slight fluctuation in the levels of Ca and Na.

DISCUSSION

In Ayurveda, herbs are used either singly or in combination (polyherbal) for treatment. The concept of polyherbalism was introduced in the 'Ayurvedic Literature Sarangdhar Samhita' to increase the effectiveness of treatments (**Ramdas, 2020**). The active ingredients of a single plant are not enough to produce the desired therapeutic outcomes.

Table 4. Effect of PF administration on biochemical parameters in rats at 14 days of treatment

Parameter	Group							
	Control	AL	AM	AH	M	ALM	AMM	AHM
Glucose (mg/dl)	68±2.51	47.2±5.54*	48.4±1.44*	45.8±2.29**	48±1.05*	44.2±1.83**	45.8±3.18**	36.2±7.57***
ALB (g/dl)	3.25 ± 0.19	3.88 ± 0.29	3.67 ± 0.24	4.31 ± 0.34*	3.48 ± 0.17	3.7 ± 0.4	3.42 ± 0.21	4.54 ± 0.39$^{**\#}$
T.Protein(g/dl)	6.66 ± 0.29	7.66 ± 0.18	6.86 ± 0.17	6.46 ± 0.1	6.54 ± 0.43	6.56 ± 0.18	6.62 ± 0.29	8.84 ± 0.35$^{****\#\#\#\#}$
T.BIL (mg/dl)	0.31 ± 0.09	0.45 ± 0.24	0.33 ± 0.07	0.18 ± 0.0 7	0.34 ± 0.03	0.26 ± 0.05	0.21 ± 0.01	0.21 ± 0.00
D.BIL (mg/dl)	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.15 ± 0.03****	0.02 ± 0.01	0.09 ± 0.02$^{***\#\#\#}$	0.05 ± 0.01	0.05 ± 0.01
ALT (IU/l)	23.87 ± 2.33	18.27 ± 0.5	27.94 ± 5.61	21.83 ± 0.88	19.76 ± 4.9	29.73 ± 6.14	20.42 ± 2.53	24.1 ± 2.04
AST (IU/l)	129.53±10.25	116.5 ± 1.5	159.93 ± 7.33	120.8 ± 0.00	142.9 ±4.43	154.6 ± 12.56	122.53 ± 7.09	127.03 ± 8.72
CRA (mg/dl)	0.37 ± 0.1	0.44 ± 0.05	0.27 ± 0.1	0.4 ± 0.15	0.37 ± 0.02	0.28 ± 0.07	0.39 ± 0.04	0.42 ± 0.1
UREA (mg/dl)	20.77 ± 1.2	35.3 ± 11.8	47.6 ± 3.51***	52.36 ± 2.04****	25.19 ± 4.11	20.9 ± 7.53	22.55 ± 2.00	55.3 ± 0.69$^{****\#\#\#\#}$
URIC ACID (mg/dl)	3.93 ± 0.98	2.8 ± 0.26	2.18 ± 0.52*	2.85 ± 0.25	3.6 ± 0.58	2.7 ± 0.29	3.03 ± 0.18	2.3 ± 0.06*

The values were expressed as mean ± SEM. Distinguishing symbols on the bars (*, #) indicate significant differences at $p < 0.05$ (* versus control group, # versus mint group), determined by a one-way ANOVA test followed bv Tukev's test.

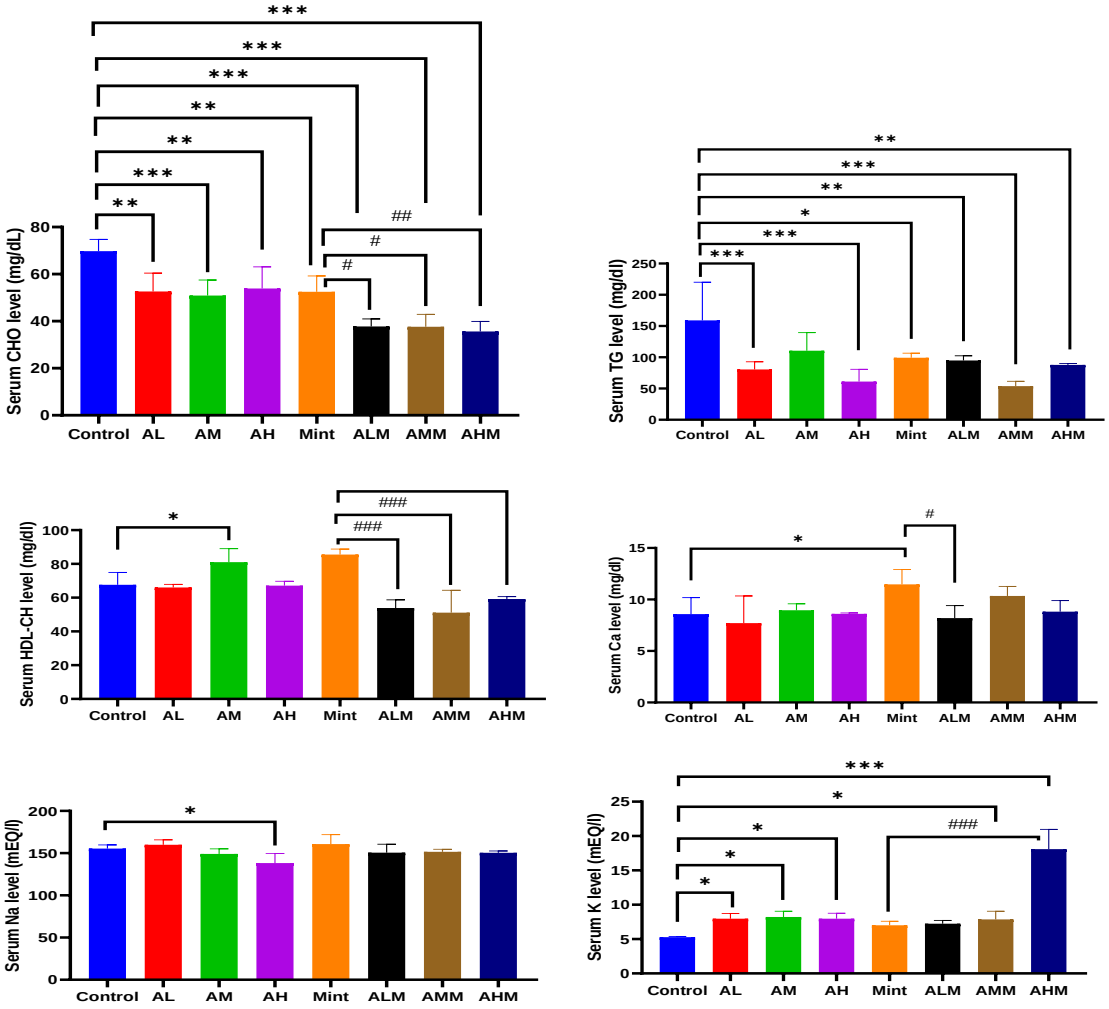

Fig. 3. Effect of PF administration on serum lipid profile and electrolytes levels in rats after 14 days of treatment

The values were expressed as mean ± SEM. Distinguishing symbols on the bars (*,#) indicate significant differences at $p<0.05$ (* versus control group, # versus mint group), determined by a one-way ANOVA test followed by Tukey's test.

However, when several herbs are mixed in a specific ratio, the therapeutic effects are intensified while maintaining safety. We have formulated an herbal remedy by blending two famous Egyptian medicinal plants *A. monosperma* and *M. piperita*. To ensure the safety of this blend, we conducted tests to evaluate appropriate parameters.

Numerous Artemisia species possess potent, bitter tastes that deter herbivory from consuming them, owing to the presence of terpenoids, lactones and sesquiterpene (**Bora and Sharma, 2011**). Our investigation confirmed this, the rats were unpalatable with the taste of *A. monosperma*, particularly at higher doses, often spitting it out. However, when combined with mint, the disagreeable taste was effectively masked, evidenced by rats in the ALM, AMM, and AHM groups not rejecting it. In traditional medicine, Artemisia species are commonly utilized in tea preparations, often alongside peppermint. The aromatic and flavorful properties of Mentha genus plants have historically been employed to disguise the unpalatable taste of medicinal plants well before the era of modern pharmaceuticals (**Silva, 2020; Patrignani *et al.*, 2021**). Peppermint leaves are characterized by their sweet, potent aroma and warm, pungent taste, with a refreshing cooling sensation afterward (**Kokkini *et al.*, 2003**).

The administration of *A. monosperma* at three doses was chosen according to the study of **El-Sayed *et al.* (2017)** which documented LD50 of *A. monosperma* which was up to 6.1g/kg b.wt. To ensure the safety and effectiveness of *A. monosperma* or M. *piperita* for clinical use, it is necessary to analyze their in vivo hemocompatibility and interaction with cellular blood elements such as red blood cells (RBCs), platelets, and leukocytes. Measuring hematological indices is essential in determining the severity of damage caused by foreign substances, such as plant extracts, on the blood components of animals. Several researchers, including **Ashafa *et al.* (2009), Muriithi *et al.* (2015), Jorum *et al.* (2016) and Beack *et al.* (2020)**, have studied this extensively. In our study, the administration of *M. piperita* or *A. monosperma* alone or in combination did not result in significant changes in the levels of RBCs, Hb, PCV, MCH, and MCHC, suggesting that the tested plants do not cause haematotoxicity, making it a safe option for future use. This is in parallel with the study of **Adam *et al.* (2000)** which indicated that adding *A. abyssinica* at 2% of the normal diet is not toxic on hematological parameters. On the other hand, the administration of *A. monosperma* alone or in combination with *M. piperita* increased the platelet total number.

Hematological components provide information for evaluating the biotoxicity of certain compounds (**Celik and Suzek, 2008**). Among the various constituents of blood, RBCs have been found to be particularly susceptible to damage caused by foreign compounds affecting their plasma membranes (**Li *et al.*, 1999**) as well as plant extracts (**Tripathi and Srivastav, 2010; Kengkoom and Ampawong, 2016**). Normally, mammalian RBCs are flexible, biconcave disks in shape. Studies have shown that RBCs can change their shape in response to various treatments from different agents (**Przybylska *et al.*, 1998**).

The current results show that oral administration of *A. monosperma* for 14 days caused echinocytosis in rat erythrocytes, which agree with the findings **of Suwalsky *et al.* (2008)**. In their study, an incubation of aqueous extract of *Aristotelia chilensis* polyphenols with human RBCs resulted in an alteration in morphology from the normal discoid shape to an echinocytic form. According to **Suwalsky *et al.* (2008)**, the polyphenols found in Aristotelia chilensis may have an impact on the lipid bilayers of cell membranes. **Koren *et al.* (2010)** suggested that RBCs could be consistently coated by

polyphenols such as resveratrol, morin, curcumin and tannic acid from supplemented nutrients. These polyphenols act as antioxidant depots and can protect the erythrocytes from the harmful effects of oxidative stress. Various studies have found that polyphenols, such as those found in apples, chokeberries, and strawberries, along with anthocyanins like callistephin chloride and ideain chloride, and amphiphilic compounds, interact with erythrocytes and embed themselves into the external monolayer of the RBCs membrane. This leads to the formation of additional echinocytes. These compounds not only go through the outer part of the external lipid layer of liposomes but also interact with proteins in the RBCs membrane, such as olive oil polyphenol, altering their packing order. These findings suggest that the capacity to shield RBCs from hemolysis is associated not only with radical scavenging activity but also with the capability of polyphenols to directly engage with cell membranes, leading to alterations in the protein profile. Curiously, another study showed that guava extract had an influence on the plasma membrane (**Abreu *et al.*, 2006**). The interaction between amphiphatic drugs and human red blood cells is explicated by the bilayer couple theory (**Sheetz and Singer, 1974**).

Artemisia, a genus of plants, has been found to have hypoglycemic properties in several species according to research by **Ribnicky *et al.* (2006) and Nofal *et al.* (2009)**. **Ahmad *et al.* (2013)** discovered that administering a hydro-methanolic crude extract of *A. indica* as well as a chloroform fraction at 200 mg/kg b.w, resulted in a significant reduction in blood glucose concentration. Our study found that rats given Artemisia at various doses also had lower glucose levels. This aligns with previous research of **Al-Shamaony *et al.* (1994)**, and **Marrif *et al.* (1995)**, who observed hypoglycemic effects of *A. herba alba* in both hyperglycemic and normal rabbits. Additionally, **Iriadam *et al.*, (2006)** reported that administration of an *A. herba-alba* aqueous extract had a hypoglycemic effect in both normal and streptozotocin treated rabbits. Our findings align with those of **Subramoniam *et al.* (1996)**, who showed that fasting normal rats experienced a moderate decrease in blood glucose levels when given a higher dose (1000 mg/kg) of *A. pallens* Wall extract. Additionally, groups of alloxan-induced diabetic mice that received methanolic or aqueous extracts of *A. afra* showed significant reductions in blood glucose levels. The aqueous extract proved more effective at a lower dose because of the existence of phytochemicals like flavonoids, polyphenols, and tannins, which have antioxidant characteristics (**Issa and Bule, 2015**). More recently, **Azzane *et al.* (2023)** demonstrated that administering A. *arborescens* orally to diabetic rats led to a marked antihyperglycemic effect by improving the lipid profile and glycogen content. These results indicate that Artemisia species might exhibit hypoglycemic effects through the stimulation of pancreatic β cells, prompting the release of more insulin into the bloodstream (**Wadood *et al.*, 1992**). This action could result in enhanced glycogen deposition in the liver, contributing to decreased glucose levels, or by upregulating the number of insulin receptors (**Kouzi *et al.*, 1994**). Based on our findings, it appears that utilizing *A. monosperma* could prove advantageous in thwarting hyperglycemia by mimicking the effects of insulin. Additionally, it was observed that this approach resulted in noteworthy reductions in blood sugar levels in animals with normal glycemic levels.

In the meantime, rats that were given *M. piperita* experienced a decline in their serum glucose content, similar to the findings of **Mesbahzadeh *et al.* (2015)**. Heat-stressed broiler chicks also saw a reduction in their serum glucose levels with the use of peppermint and chromium picolinate, according to **Akbari and Torki (2014).** The hypoglycemic effects of peppermint tea may be attributed to the

antioxidant properties found in it (**Buyukbalci and El SN, 2008**). The polyherbal extract at all doses of *A. monosperma* exhibited a highly reduction ($p< 0.001$ & $p< 0.0001$) on glucose level. These results suggest that the combination of *A. monosperma* and *M. piperita* is the promising candidate for hypoglycemic activity.

Indicators of toxicity resulting from drug exposure can be detected using liver and kidney biochemical enzymes, according to **Farag *et al.* (2006)**. Liver dysfunction is signaled by heightened liver enzymes (AST, ALT, and ALP) and proteins (**Naseem *et al.*, 2016**). The kidney plays a pivotal role in removing xenobiotics, including drugs, from the body, alongside regulating electrolyte and water levels. Waste products of protein metabolism, such as urea and creatinine, are eliminated through the kidney, with their levels rising in case of kidney damage. However, **Ene-ojo *et al.* (2013)** highlight that factors like dehydration, medication, and dietary habits can also contribute to elevated urea concentrations. No changes were observed in the serum creatinine, total bilirubin (T. BIL) content, ALT and AST activities of rats fed with *A. monosperma* or *M. piperita* alone or in mixture as compared to the normal rats. A study by **Romeilah *et al.* (2021)** suggested that the beneficial outcomes observed could be linked to the antioxidant capabilities of *A. monosperma*. Similarly, research conducted by **El-Toumy *et al.* (2011)** provided further evidence, indicating that extracts from *A. monosperma* contain active ingredients like flavonoids and polyphenolic compounds known for their hepatoprotective effects. **Iriadam *et al.* (2006)** discovered that the water extract of *A. herba-alba* aerial parts resulted in a reduction of ALT and AST. However, **Adam *et al.* (2000)** found that rats who consumed a diet with 10% *A. abyssinica* leaves extract had higher content of ALT and AST than the control rats, indicating damage to the liver. Another study revealed that serum ALT activities did not change significantly, but the AST value increased after a single dose (100 and 1000 mg/kg) of *A. afra* water extract was orally administered for three months. This implies that AST levels elevated with time, but continuous treatment with a high dose of water extract eliminated this increase. It is possible that the extract has a hepatoprotective effect (**Mukinda and Syce, 2007**). **Al-Soqeer (2011)** found that the administration of *A. monosperma* extract resulted in a significant decline of AST activity in rats. This effect was likely due to the antioxidant properties of the extract. Other studies have demonstrated that *A. capillaris* (**Lim *et al.*, 2013**) and *A. annua* (**Choi *et al.*, 2021**) can also protect the liver by reducing hepatic lipid content, as well as ALT and AST levels in serum, thereby preventing weight gain and improving dyslipidemia in vivo. Meanwhile, the study illustrated by **Iriadam *et al.* (2006)** revealed that the treatment with *A. herba alba* did not show any effect on creatinine levels in both normal and STZ-induced diabetic rabbits. On the contrary, the latest information contradicts the research conducted by **Noori *et al.* (2014 and 2016)**. Their study revealed that administering *A. deserti* extract to animals resulted in a notable variation in creatinine levels at a 200 mg/kg dose, compared to other groups. Additionally, the extract led to alterations in kidney tissue, such as shrinking of the glomerulus, inflammation cell build-up, and degeneration of renal tubules. These anomalies were linked to oxidative stress in certain groups.

It is worth noting that the treatment with *M. piperita* extract alone did not have a significant change in the values of all serum liver and kidney markers at 300mg/kg body weight as compared to control group. This partially agrees with the previous studies of **Mesbahzadeh *et al.* (2015)**.

According to recent findings, the use of extracts from *A. monosperma* or *M. piperita*

led to a reduction in cholesterol and triglycerides in rats' serum. This outcome aligns with previous research that indicated a significant decrease in triglycerides levels through the use of *A. vulgaris*. The root extracts of *A. vulgaris* contain flavonoids, saponins, tannins, triterpenoids, steroids, and polyphenolics. Flavonoids have been found to increase HDL and decrease LDL and VLDL content in rats with hypercholesteremia. Various studies have shown that steroids and saponins derived from plants having antihyperlipidemic and hypolipidemic activities (**Wang and Ng, 1999**). According to **Khan (2015)**, the aqueous extract from the root of *A. vulgaris* has a similar ability to reduce lipids as rosuvastatin. Recently, **Xu *et al.* (2019)** found that a combination of linolenic acid (9), acetylene (E)-2 (2), and chamazulene (1) from *A. integrifolia* had an antihyperlipidemic action in rats with Triton WR-1339-induced hyperlipidemia. These compounds inhibited the increase of TG, LDL-C and TC levels. **Ahmad *et al.* (2014)** discovered that *A. indica* can help regulate blood sugar, reduce lipids, and improve liver and kidney function in diabetic rats, confirming its traditional use. In the meantime, recent information indicates that using *M. piperita* extract alone can lower cholesterol and triglyceride levels in the blood, which aligns with findings from a study done by **Mesbahzadeh *et al.* (2015)**. Prior research has also shown that *M. piperita* juice and tea can have a similar effect on the lipid levels in Wistar rats by decreasing food intake and weight gain, as noted by **Barbalho *et al.* (2009) and Abdel-Rahman (2017)**.

Research has shown that peppermint may have anti-lipidemic benefits. In a human study, university students who consumed peppermint had lower levels of serum cholesterol, LDL, and triglycerides (**Barbalho *et al.*, 2013**). The decrease in these lipids may have been due to the antioxidant and cholesterol protection mechanisms of peppermint's components (**Luadicina and Marnett, 1990**). Lipid and glucose metabolic disorders often lead to cardiovascular dysfunction, but Artemisia may help by reducing serum triglycerides, cholesterol, and glucose levels and restoring insulin function (**Watcho *et al.*, 2010 and 2011; Weinohrl, 2010**). These effects of Artemisia may improve vascular resistance and blood circulation.

The primary function of HDLs is to transport excess and unused cholesterol from the body's tissues back to the liver, thus preventing the build-up of atherosclerotic plaque and promoting good health (**Gordon *et al.*, 1977**). The observed increase in HDL-C levels in the AM-treated group is consistent with findings from studies involving *A. annua* treatment (**Gordon *et al.*, 1977**). **Kim *et al.* (2012)** demonstrated that administering *A. vulgaris* L. leaves powder to broilers led to a significant elevation in HDL levels and a notable reduction in LDL levels, attributed to the powder's high antioxidant and flavonoid content. Additionally, **Jafari *et al.* (2010)** found that LDL levels decreased in rabbits treated with *A. aucheri*, while HDL levels increased compared to those on a high-cholesterol diet.

The results indicated that the use of polyherbal aqueous extract may have a combined and beneficial effect on reducing lipids in the ALM, AMM, and AMH groups. This aligns with **Tao *et al.* (2020)** findings, which demonstrated that the combination of *A. annua* and a lipid-lowering ursolic acid drug was more efficacious in lowering levels of CHO, TG, and LDL-C, while increasing HDL-C, than *A. annua* water extract alone.

The hypo-lipidemic effects obtained with polyherbal formulation were similar to those found in previous studies by **Ghorbani *et al.* (2013) and Uddin *et al.* (2016)**. Another study by **Naseem *et al.* (2016)** showed that a combination of lemon juice, ginger juice, and apple cider vinegar

had hypo-lipidemic effects. Other studies have linked ginger, garlic, and lemon to hypo-cholesterolemic effects in experimental animals, with no side effects reported (**Naseem *et al.*, 2021**). **D´eciga-Campos *et al.* (2021)** also found that *Syzygium aromaticum* and *Rosmarinus officinalis* interacted synergistically to produce anti-inflammatory effects.

Sachdeva *et al.* (2013) found that a 1000 mg/kg dose of polyherbal formulation is considered safe for the long-term treatment of hepatic diseases. Additionally, research has shown a strong link between glucose levels in the blood and lipid levels. Evidence suggests that extracts from plants like Artemisia and peppermint may affect insulin-sensitive cell receptors or binding activity, which can lower the levels of triglycerides and glucose in the blood. **Xie *et al.* (2011)** confirmed this idea by showing that cinnamaldehyde, found in cinnamon essential oil, can increase insulin release.

The amount of potassium in *A. monosperma* increased when given in different doses, either alone or in combination. This is similar to the high potassium content found in other Artemisia plants like *A. annua* and *A. herba alba*, which have very small amounts of sodium. The antimalarial plant is rich in potassium, which is why there was an increase in platelet count in this study. *A. monosperma* contains significant amounts of Ca, K, and Phosphorus, as well as micro-minerals like Cu and Mn. Peppermint contains various vitamins and minerals, such as vitamins C and A, iron, potassium, copper, magnesium, silicon, iodine, sulfur, niacin, and inositol. Because of their traditional medicinal uses, peppermint and *A. monosperma* may be promising candidates for developing innovative nutra-pharmaceuticals.

Conclusion

The outcomes of the current investigation demonstrate that administering Polyherbal Formulation (PF) of *A. monosperma* and *M. piperita* orally, at a dose of up to 5000 mg/kg for a period of 14 days, did not result in any fatalities, changes in behavior, or any signs of toxicity. Moreover, treatment with PF did not have any impact on the gain of body weight, relative organ weight, hematological parameters, as well as liver and kidney function in rats. The noticeable reduction in glucose and lipid levels implies that PF could be an effective remedy for diabetes, and the study indicates that the newly developed Polyherbal formulation is harmless and non-toxic. Nevertheless, further investigation into long-term uses and clinical trials may be necessary to validate these findings.

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الملخص العربي

تقييم سلامة تركيبة عشبية من الشيح والنعناع على ذكورالجرذان البيضاء

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لا يزال عدد الدراسات العلمية حول فعالية وسلامة العديد من التركيبات العشبية محدودا للغاية على الرغم من استخدامها التقليدي. لذلك تهدف الدراسة إلى استكشاف التأثيرات التآزرية المحتملة وسلامة التركيبة العشبية التي تحتوي على نبات الشيح ونبات النعناع على بعض المعايير الهيماتولوجية والبيوكيميائية داخل الجسم. تم تقسيم الحيوانات إلى ثماني مجموعات تكونت كل منها من 5 حيوانات. المجموعة1: عوملت كمجموعة ضابطة؛ المجموعات 2 و 3 و 4 (AL ، AM و AH) تلقت الحيوانات مستخلص نبات الشيح بجرعات 1000 و 3000 و 5000 مجم/كج من الجسم على التوالى؛ المجموعة 5: عولجت الحيوانات بجرعة 290 مجم/كج من مستخلص نبات النعناع. بينما تلقت المجموعات الثلاث الأخيرة 6 و 7 و8 (ALM، AMM وAHM) مستخلص التركيبة العشبية من نبات الشيح والنعناع بنفس الجرعات المذكورة، وذلك مرة واحدة يومياً لمدة 14 يوماً. أظهرت النتائج عدم وجود وفيات من الحيوانات المعالجة أو ظهور أى من علامات السمية. علاوة على ذلك، لم يلاحظ تغيرات معنوية في وزن الجسم ووُجدت القيم الدموية ضمن الحدود الفسيولوجية الطبيعية مقارنة بالمجموعة الضابطة، وفى الوقت ذاته لم تتأثر وظائف الكبد والكلى مثل AST ، ALT، *T. bilirubin* والكرياتينين بالتركيبة العشبية. يُستنتج أن التركيبة العشبية المكونة من نبات الشيح والنعناع آمنة وغير سامة حتى بجرعة تصل إلى 5000 ملجم/كجم، ويمكن أن تكون مرشح جيد لعلاج مرض السكري.

الكلمات الاسترشادية: نبات الشيح، نبات النعناع، التركيبات العشبية، دلالات الدم والكيمياء الحيوي، الميكرسكوب الإلكتروني الماسح.

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