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ARTICLE

Barrel Medic Bloom Extract: A Natural Aid against Breast Cancer

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ABSTRACT

Breast cancer continues to be the foremost cause of cancer-related deaths among women globally. *Medicago truncatula* (Barrel medic) is acknowledged as a herbaceous plant possessing significant therapeutic and anticancer properties. The investigation examined the cytotoxic and inhibitory effects of aqueous and ethanolic extracts prepared by heating extraction, tested on human breast cancer cells (MCF-7, MDA-MB-231, T47D) and a normal breast epithelial line (MCF-10A), along with Jurkat lymphocytes, and evaluated in white mice, both in vitro and in vivo. Gas chromatography was used to find bioactive compounds in the extracts. Cytotoxicity was evaluated using MTT and ELISA assays, while the in vivo effectiveness was assessed in white mice implanted with breast tumors. Findings indicated that the aqueous extracts comprised biologically active molecules such as resveratrol and glucosidase, and exerted significant inhibitory effects on breast cancer and normal cells in a dose-dependent fashion ($p \leq 0.01$ and $p \leq 0.05$), without causing notable inhibition in lymphocytes (NS). In vivo, the extracted substances facilitated tumour shrinkage and improved liver and kidney function in treated mice. The results suggest that Barrel medic concentrates may serve as an alternative anticancer agent for breast cancer treatment, exhibiting selective cytotoxicity alongside no effects on immune cells.

Keywords: Therapeutic; Cytotoxicity; *Medicago truncatula*; Breast Tumors

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1. Introduction

Breast cancer is the most prevalent disease in women globally, while lung cancer is the main cause of cancer-related mortality in women [1]. Breast cancer of the adenocarcinoma variety begins in the milk ducts or lobules of the breast [2]. Although the precise causes of breast cancer are unknown, socioeconomic and lifestyle factors are thought to contribute to the disease [3]. Breast cancer is the outcome of the abnormal development of a malignant cell [4]. It begins in the epithelial cells that line the glandular tissue of the breast's ducts (85%) or lobules (15%) [5]. The malignant growth first stays inside the duct or lobule, where it typically shows no symptoms and has a low chance of spreading to other areas. However, the illness varies in histology grade, immunohistochemistry, and clinical presentation, making it exceedingly diverse [6]. These include menopausal symptoms, sexual dysfunction, and impairment of fertility. Whatever the case, cancer has the potential to spread to other parts of the body if untreated [7]; in Iraq, twenty-three percent of all cancer cases [8] were breast cancer cases, the most frequent disease affecting women. Additionally, there are currently 31.5 incidences of breast cancer per 100,000 people, up from 26.6 occurrences in 2000 [9]. Although the exact causes of breast cancer are still unknown [10], some factors, including age, gender, family history of the disease, certain gene abnormalities, early menstruation or late menopause, radiation or chemical exposure, and obesity [11]. Even though the same histological subtypes present differently in different age groups and are characterized by different fertility-related factors, they may also have an impact on the progression and management of the disease or may increase the risk of developing the condition [12]. The Fabaceae family plant Barrel medic is used to treat diabetes and renal problems. As a natural diuretic, it is also used to treat kidney stones and urinary tract infections (UTIs) [13].

A lower risk of cancer has been linked to high flavonoid intake. Due to their high nutritional content, Barrel medic leaves have been extensively employed in traditional medicine and are today used as dietary supplements [14]. The capacity of refined Medicago sativa polysaccharides to inhibit the activities of HIV reverse transcriptase and protease was examined in earlier research on the cytotoxic effect of Barrel medic leaf extracts against a variety of susceptible and drug-resistant cell lines [15]. HIV reverse transcriptase and protease have been shown to be inhibited by refined polysaccharide components of *M. truncatula* [16]. Polysaccharides isolated from *M. truncatula* L. were evaluated for their immunological potentiating action. In an in vitro study, mouse lymphocytes absorbed more [3H] thymidine from polysaccharides isolated from *M. truncatula*, suggesting that these compounds may have immunological potentiating potential [17].

Plants have been genetically modified to generate a variety of pharmacological and anti-cancer properties; the general public might potentially get chemoprevention techniques [18]. It has been demonstrated that the substance resveratrol (3,5,4'-trihydroxystilbene) possesses anti-cancer properties, making it a prime candidate for this use [19]. Using genetically altered Barrel medic that expresses resveratrol-synthase as a paradigm, biotechnological techniques for cancer prevention were implemented [20]. The potential health advantages of transgenic crops can be investigated. Exogenous glucosidase enzyme, which has been introduced to food preparations such as transgenic Barrel medic, has been demonstrated by Kineman et al. to appear to protect against AOM formation of ACF in the distal colon of Crypt Foci-1 mice [20].

According to Gatouillat and others [21], these results demonstrate that medicarpin and millepurpan influence P-gp-mediated drug efflux to enhance the cytotoxicity of chemotherapy drugs in multidrug resistant P388 leukemia cells and to induce death. These flavonoids can be used as chemopreventive agents or sensitizers to boost the cytotoxicity of chemotherapeutic drugs in cancer cells that are resistant to various therapies. Also, Barrel medic leaf extracts were prepared, and their cytotoxic effects on a number of susceptible and drug-resistant tumor cell lines were evaluated. The activation of caspase-3, which causes PARP cleavage, enabled the execution of planned cell death. Three terpene derivatives and five flavonoids were found when toluene extract (To-1), the most active extract made from crude extract, was fractionated. Among these, P388 and P388/DOX cells were sensitive to (−)-medicarpin, (−)-melilotocarpan E, millepurpan, tricin, and chrysoeriol. These findings show that Barrel medic leaf extract may have intriguing potential in the treatment and prevention of

cancer [22].

Medicago sativa, also known as Barrel medic, has been used to treat a number of diseases. However, only a small number of studies have shown its breast anticancer effects. Therefore, the purpose of this study is to demonstrate the potential benefits of Barrel medic leaf extract for the treatment and prevention of cancer.

2. Materials and Methods

2.1. *M. truncatula* Extraction

M. truncatula was purchased from a local market in Baghdad, Iraq. The plant material was cleaned, washed, and dried with the help of paper. The flowers, thus obtained, were kept in a paper bag in a dark place with proper ventilation at a temperature of 25 °C for a period of 30 days. The dried flower material was pulverized into a coarse powder and then sieved through a BSS 0.4 mm sieve. The shade-dried flower powder (500 g) was subjected to extraction with 99% ethanol or water at 60 °C with continuous stirring for 20 min. A vacuum filtration assembly was performed for the collection of extracts, followed by drying in a rotary evaporator. The obtained mass of powder was weighed and then stored in a closed vial at 4°C. Extraction was carried out using the heating maceration technique, which depended on the procedure following standard phytochemical extraction protocols [23].

2.2. Active Compounds Extracts

The biologically active compounds in the extracts of Barrel medic were detected using Gas chromatography equipped with an MS detector at 25° [24]. The analysis conditions were optimized to detect volatile bioactive compounds present in aqueous extracts [25]. In the present work, various bioactive compounds were identified from the aqueous extracts of dried flowers of *M. truncatula*.

These phytochemicals were in SD format from the ZINC15 compound database and uploaded into the MVD workspace to question the possible mechanisms of action of bioactive compounds. The ligands were prepared for docking using the MVD molecule preparation tool. The 2D structures were derived from the ZINC15 database, while the 3D ligand structures were drawn using UCSF Chimera's Structure Build module. The prepared 3D structures of each compound were then optimized for docking using UCSF Chimera tools.

2.3. In Vitro Study

The aqueous extracts of dried *M. truncatula* flowers were tested for their in vitro and in vivo cytotoxic activity on human cell lines, including breast cancer cells, normal cells, and blood lymphocytes. The herb was extracted with cold water, and the extract was tested using the MTT assay and ELISA to determine its effect on breast cancer cells, normal cells, and lymphocytes isolated from blood outside the body. Cancer cells isolated from the breast affected by cancer were treated with the extract in six dilutions, while normal cells not affected by cancer were also treated with the same extract under the same conditions. Another fraction of normal human blood lymphocytes was treated the same way as described above. All assays were performed under controlled laboratory conditions.

2.4. In Vivo Study

It was further carried out outside the living body on laboratory animals (white mice), wherein three groups of mice were taken; each group was treated according to the experimental design. One of them was treated with the above self-same treatments concerning concentration. Mice were dosed with the therapeutic concentration for 60 days, and then liver and kidney samples were collected, and tissue sections were prepared. All procedures were conducted following standard laboratory [26].

2.5. Cytotoxicity Assay

Standard cytotoxicity evaluation methods were applied in the MTT cell proliferation and cytotoxicity assay. MTT, which is used to form formazan purple, is also used to determine the viability of the cells. Trypan blue was used to stain the tissue-cultured cells infected by a virus for its replication that is finally examined by a cytometer. It is reduced by the cells in culture in metabolically active cells to give a purple solution. Cells were harvested at the exponential point from tissue culture. The data were read at 520 nm using a spectrophotometer after 24, 48, and 72

h of incubation, for both spectral absorbance of the lysates and ELISA reader microplate determination data. Cytotoxicity data were standardized by determining the absorbance reading at 520 nm and relating this to aqueous extracts at appropriate concentrations of dried *M. truncatula* flowers. The resulting data was utilized to plot a dose-response curve in which the amount of extract desired to kill 50% of the cell number (IC50) was revealed. Cell viability (%) = Mean OD/control OD × 100. The assays allowed determination of cell viability and inhibitory concentration [27].

3. Results

Table 1 presents a comparison of white blood cell (WBC) count, lymphocyte count, and percentage of lymphocytes between untreated and treated groups. The data is presented as mean ± standard error (SE). The untreated group had a mean WBC count of 2.35 ± 1.21, a mean lymphocyte count of 1.69 ± 0.72, and a mean percentage of lymphocytes of 68.05 ± 0.65. In contrast, the treated group had a mean WBC count of 6.53 ± 1.24, a mean lymphocyte count of 4.84 ± 1.09, and a mean percentage of lymphocytes of 77.46 ± 15.31.

A U-test was conducted to compare the means between the two groups for each variable. The U-test values for WBC count, lymphocyte count, and percentage of lymphocytes were 2.5, 2.5, and 6.5, respectively. However, these values were statistically significant, as indicated by the *p*-values of 0.031, 0.041, for WBC count, and lymphocyte count, respectively, and the *p*-value for percentage of lymphocytes 0.222, which wasn't statistically significant.

In conclusion, there were differences in the mean values for WBC count and lymphocyte count compared to the untreated group; while the percentage of lymphocytes showed no statistically significant difference.

Table 2 presents the effect of treatment concentration on cell inhibition in cancer cells, normal cells, and lymphocytes. The data is presented as mean ± standard error (SE) for each group, along with the least significant difference (LSD) value.

Table 1. Comparison between untreated and treated groups in WBC, Lymphocyte and % Lymphocyte.

Group	Mean ± SE		
	WBC	Lymphocyte	Lymphocyte (%)
Untreated	2.35 ± 1.21	1.69 ± 0.72	68.05 ± 0.65
Treated	6.53 ± 1.24	4.84 ± 1.09	77.46 ± 15.31
U-test	2.5*	2.5*	6.5
p-value	0.031*	0.041*	0.222

Note: *: Significant.

Table 2. Effect of concentration and methods on cell inhibition.

Concentration (mg)	Mean ± SE			LSD Value
	Cancer	Normal	Lymph	
0: Untreated	0.59 ± 0.00 a	0.906 ± 0.00 a	1125.00 ± 0.00	---
12.4	0.2235 ± 0.026 b	0.506 ± 0.086 b	1192.00 ± 90.00	482.37 **
6.2	0.1985 ± 0.021 b	0.592 ± 0.051 b	1176.50 ± 47.50	507.61 **
3.1	0.0735 ± 0.022 cd	0.524 ± 0.159 b	586.94 ± 586.06	469.20 **
1.55	0.067 ± 0.020 cd	0.494 ± 0.052 b	1137.50 ± 108.50	477.09 **
0.775	0.0345 ± 0.002 d	0.483 ± 0.068 b	504.96 ± 504.03	319.57 **
0.3875	0.0995 ± 0.008 c	0.407 ± 0.121 b	570.93 ± 570.06	307.53 **
0.19375	-	0.348 ± 0.056 b	830.49 ± 829.51	593.04 **
0.059688	-	-	620.93 ± 620.06	-
0.029844	-	-	1190.00 ± 111.00	-
0.014922	-	-	576.44 ± 575.56	-
0.007461	-	-	531.98 ± 531.02	-
LSD value	0.0641 **	0.282 *	1525.00 NS	---

Note: The LSD values indicate the statistical significance of the differences between the means. Means marked with different letters in the same column differed significantly. * ($p \leq 0.05$); ** ($p \leq 0.01$): A LSD value with an asterisk (*) denotes significance at the 0.05 level, while an LSD value with two asterisks (**) denotes significance at the 0.01 level. For instance, the LSD value for cancer cell inhibition at a concentration of 12.4 mg is 482.37 **, indicating that the difference between the mean cancer cell inhibition at this concentration and that of the untreated group is statistically significant at the 0.01 level.

The first column displays the treatment concentration in mg. The second, third, and fourth columns show the mean and SE for cancer cells, normal cells, and lymphocytes, respectively. The fifth column displays the LSD value.

The untreated group (0 mg concentration) exhibited a mean cancer cell inhibition of 0.59 ± 0.00, a mean normal cell inhibition of 0.906 ± 0.00, and a mean lymphocyte inhibition of 1125.00 ± 0.00. As the treatment concentration increased, the mean cancer cell inhibition decreased, reaching a minimum value of 0.0345 ± 0.002 at a concentration of 0.775 mg. The mean normal cell inhibition also decreased with increasing concentration, reaching a minimum value of 0.348 ± 0.056 at a concentration of 0.19375 mg.

In conclusion, **Table 2** demonstrates that increasing treatment concentration resulted in enhanced inhibition of cancer cells and normal cells, as reflected by the decreasing mean values.

Tissue sections were prepared, fixed, and stained for histological examination. The figures of the liver revealed a normal appearance of the central vein with marked disarrangement of hepatic cords (**Figure 1**).

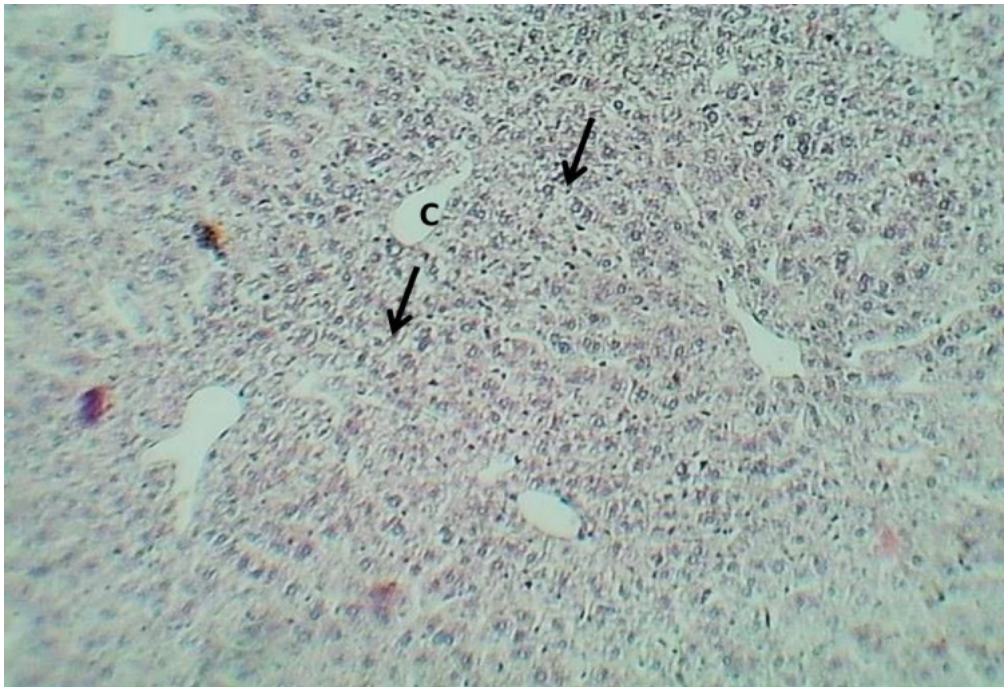

Figure 1. Hematoxylin and eosin (H&E)-stained histological section of liver tissue, magnified by 100 times.

Note: The central vein (C), which is situated in the middle of the hepatic lobule, appears normal in the image; however, there is a noticeable disarray of the hepatic cords (black arrows). The lobular architecture has changed, as evidenced by the disruption of the hepatic cords, which are typically organised in neat radiating rows of hepatocytes from the central vein.

Figure 1 shows the normal appearance of the central vein in the liver, but with marked disarrangement of hepatic cords. The central vein is a blood vessel found in the center of a liver lobule, which is a small functional unit of the liver. The hepatic cords are rows of liver cells (hepatocytes) that radiate out from the central vein. Normally, these cords are arranged in an orderly fashion, but in **Figure 1**, they appear to be disarranged. This could indicate some form of liver damage or disease. However, without more information and context, it is difficult to determine the exact cause or significance of this finding. A lot of studies have looked into how ALE affects the liver's function and structure. One study found that ALE affected the amounts of genes in the liver that are responsible for generating and transporting cholesterol. These genes are HMG-CoA reductase, LDL receptor, and ABCA13. Another study showed that ALE alleviated the oxidative stress and inflammation induced by nicotine in the rat liver, evidenced by the decreased levels of malondialdehyde (MDA), liver enzymes ALT, AST, ALP, GGT, and LDH, as well as proinflammatory cytokines TNF-α, IL-1β, and IL-6. Furthermore, ALE mitigated the histological alterations in the liver caused by nicotine exposure, including the disarray of hepatic cords, vacuolation of hepatocytes, congestion of

central veins, and infiltration of inflammatory cells. ALE may potentially have certain adverse consequences since it interacts with various hormones or drugs. When used with anticoagulants or antiplatelet drugs, ALE may increase the risk of bleeding. ALE may make oral contraceptives or hormone replacement therapy less effective since it possesses phytoestrogenic effects. By making the immune system work harder, ALE may potentially make autoimmune diseases like lupus or rheumatoid arthritis worse. Therefore, it is advisable to consult with a physician before taking ALE or any other herbal supplement. The hepatic cords showed mild cellular swelling with vascular degeneration and necrosis of hepatocytes (**Figure 2**). On the other hand, the figures of the renal cortex and medulla revealed normal appearance of the renal glomeruli and normal renal tubules (**Figures 3–5**). The kidney is composed of two main regions: the renal cortex and the renal medulla. The renal cortex contains the renal corpuscles, which consist of glomeruli and Bowman's capsules, and most of the proximal and distal convoluted tubules. The renal medulla contains the loops of Henle and the collecting ducts. The nephrons, which are the functional units of the kidney, span both regions and are responsible for filtering the blood, reabsorbing water and electrolytes, secreting waste products, and maintaining acid-base balance. Numerous substances may impact the ways the kidneys perform and appear through affecting the way that they filter, reabsorb, secrete, or excrete. Certain herbal remedies could help the kidneys by functioning as diuretics, anti-inflammatories, or antioxidants. Various naturally occurring diuretics raise the amount of urine produced and lower blood pressure by changing how the kidneys reabsorb salt and water. Certain herbal anti-inflammatories can mitigate kidney inflammation by suppressing the synthesis of proinflammatory cytokines inside renal tissue. Certain botanical antioxidants may save the kidney from oxidative stress by neutralizing the radicals within renal cells. But these effects aren't only from Barrel medic leaf extract (ALE), which is a nutritional supplement made from the leaves of Medicago sativa. Saponins, phytoestrogens, and coumarins are among the bioactive chemicals found in ALE. People have said that ALE offers several health advantages, such as decreasing blood cholesterol levels, increasing glucose metabolism, reducing inflammation, and protecting the liver from oxidative damage. Nonetheless, research on the impact of ALE on the renal cortex and medulla is insufficient. Additionally, ALE could have certain adverse interactions since it interacts with various medicines or hormones. When used with anticoagulants or antiplatelet medications, ALE may raise the risk of bleeding. Because it has phytoestrogenic effects, ALE may potentially make oral contraceptives or hormone replacement treatment less beneficial. ALE may also exacerbate autoimmune diseases, such as lupus or rheumatoid arthritis, by stimulating the immune system.

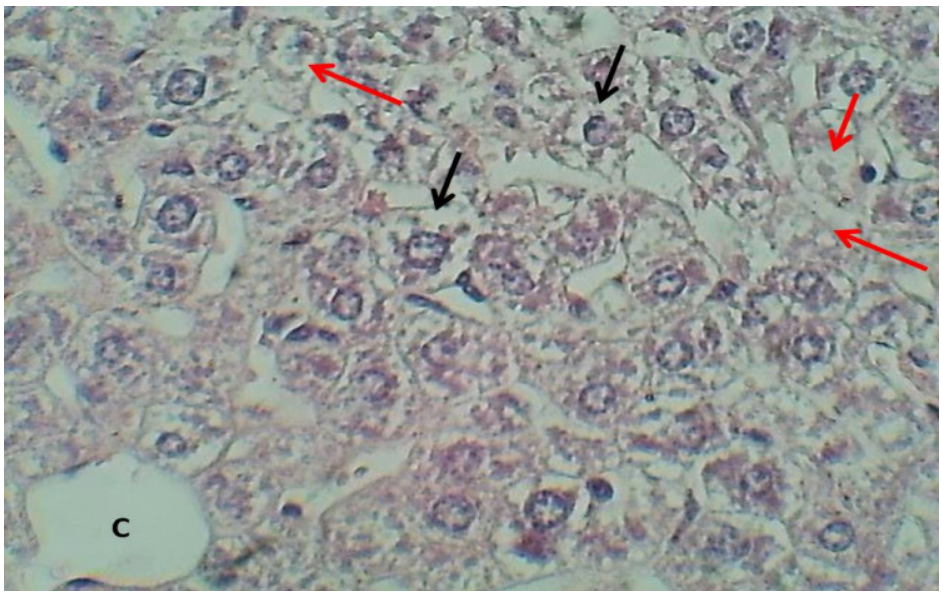

Figure 2. Hematoxylin and eosin (H&E)-stained histological section of liver tissue, magnified by 400 times.

Note: A central vein (C) with preserved morphology is visible in this section. Hepatocytes in the vicinity exhibit clear pathological alterations, such as necrosis (red arrows) and cellular swelling (black arrows). Vascular degeneration and a disturbed appearance of the hepatic cords suggest a change in the typical lobular architecture and the advancement of tissue damage.

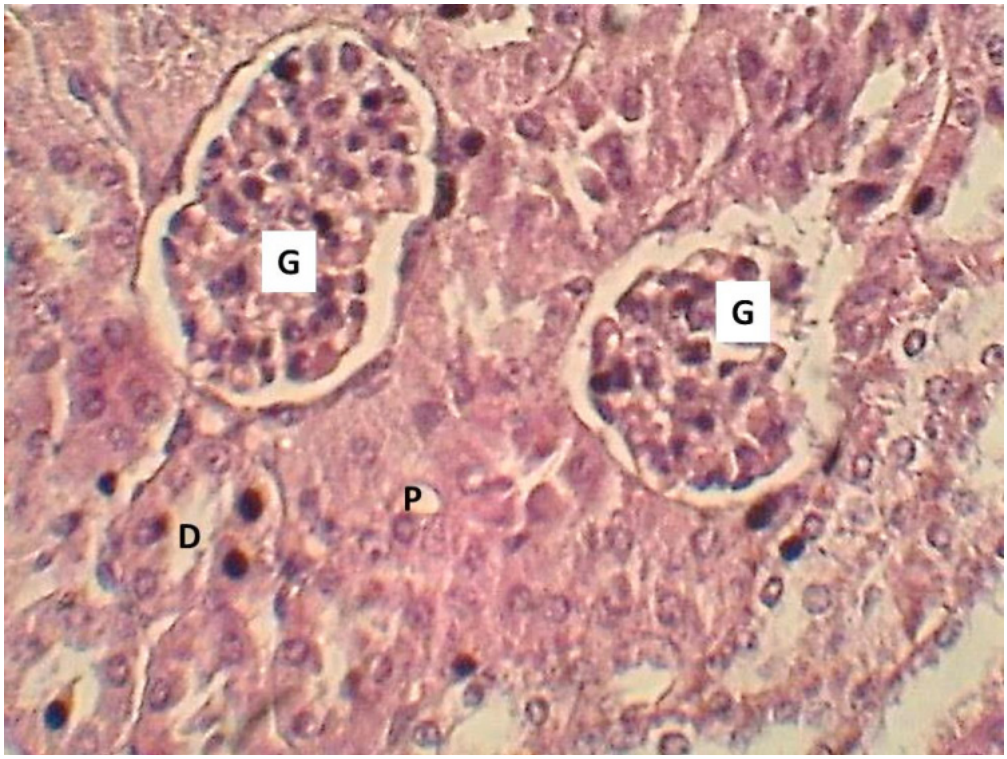

Figure 3. A histological section of the renal cortex stained with H&E (×100) demonstrates the typical appearance of a renal corpuscle (G) encircled by Bowman's capsule, as well as proximal (P) and distal (D) convoluted tubules that represent the renal tubular system.

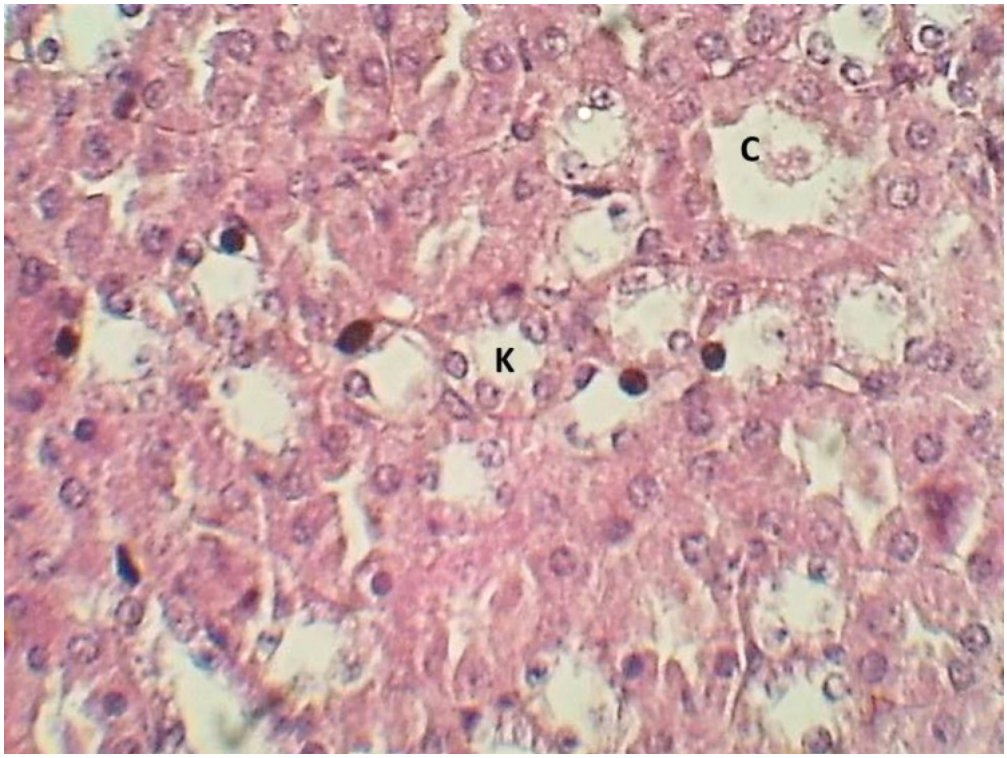

Figure 4. Liver histology section stained with H&E (×400).

Note: The figure displays the Kupffer cells (K) and central vein (C) among the hepatic cords.

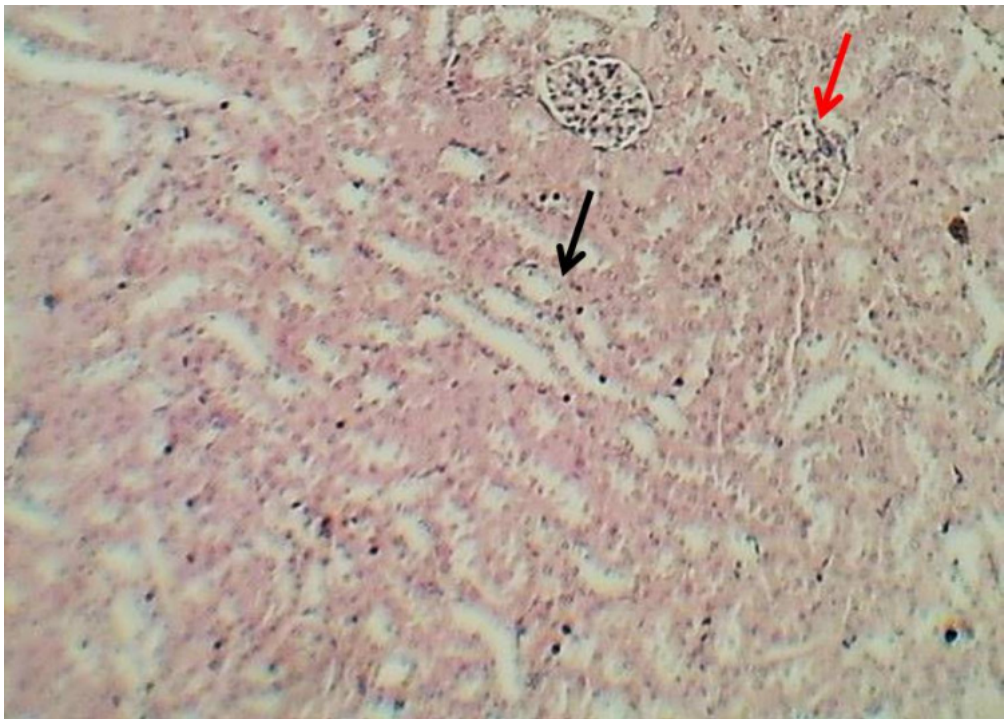

Figure 5. Liver tissue histological section stained with H&E (×400).

Note: The central vein (C), encircled by hepatocyte cords, is situated at the centre of the hepatic lobule in the figure. Additionally visible are Kupffer cells (K), which are specialised macrophages found in the sinusoidal lining. These features demonstrate the liver's typical structure as well as the function of Kupffer cells in immune protection and cell debris removal.

4. Discussion

The present study illustrates that Medicago sativa leaf extract (ALE) possesses immunomodulatory, selective cytotoxic, and histoprotective characteristics relevant to breast cancer therapy. The administration of ALE significantly increased white blood cell and lymphocyte counts, signifying substantial immunological activation. This finding aligns with the study by Jiménez-Medina et al. [28], which demonstrated that Calendula officinalis extract enhances lymphocyte activity and exhibits antitumor properties [29], as well as with the research by Shen et al. [30], which emphasized the immunoregulatory role of plant saponins in cytokine production and immune cell activity. ALE exhibits dose-dependent cytotoxicity by impeding the growth of breast cancer cells while preserving normal cells and lymphocytes. Cytotoxicity corresponds with the findings of Nguyen et al. [31], who reported the activation of apoptosis in breast cancer cells by Hibiscus flower extract, and with Uğur et al. [32], who identified similar selective effects among diverse medicinal plant extracts. The effects observed may be partially elucidated by the antioxidant and anticancer properties of phytochemicals, including resveratrol and its derivatives, as investigated by Szczepańska et al. [33]. The preservation of normal cells contrasts with prior studies [34] that demonstrated certain plant extracts, including betel nut and tobacco leaf, elicited nonspecific cytotoxicity, underscoring the necessity for chemical specificity and enhanced extraction methodologies. The cautionary note from Yasueda et al. [34] regarding the unregulated use of antioxidants underscores the necessity for stringent pharmacological assessment and controlled dosing. Histopathological analysis exhibited moderate hepatic alterations, suggesting a transient oxidative stress response rather than definitive hepatotoxicity marked by vesicular degeneration and localized hepatocyte necrosis [32]. Renal tissue remained intact, displaying normal glomerular and tubular architecture, thereby confirming ALE's renal safety, consistent with the protective effects of antioxidants as outlined by Ostróżka-Cieślik [35]. In the future, plant metabolic engineering to boost the production and purity of bioactive compounds such as resveratrol could enhance the therapeutic use of ALE and facilitate standardization. These advancements may expedite the formulation of ef-

fective and dependable treatments for adjunctive cancer therapy. This study shows that ALE boosts the immune system, mostly goes after cancer cells, and doesn't hurt the body very much. These findings highlight the necessity for additional translational research to evaluate ALE's clinical efficacy and its integration into breast cancer treatment protocols.

5. Conclusions

Medicago sativa leaf extract (ALE) has significant immunomodulatory, selective cytotoxic, and histoprotective effects in the context of breast cancer. ALE effectively augmented the population of immune cells, selectively inhibiting the proliferation of tumor cells while sparing normal cells, and induced no alterations in the liver or kidneys, indicating its safety. These findings indicate that ALE might serve as a beneficial adjunct to breast cancer therapy, integrating traditional herbal medicine with contemporary oncological treatment approaches. Future studies should focus on molecular mechanisms, dose optimization, and clinical validation to thoroughly assess its therapeutic potential and integration into existing treatment protocols.

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Institutional Review Board Statement

All procedures involving human and animal subjects were conducted in accordance with the ethical standards of Al-Nahrain University, as approved under protocol number 524, dated 10 September 2025.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data are available from: 1. Medicinal herbs production to discourage and eliminate germs that contaminate burns: In silico study | Journal of Biotechnology Research Center (JOBRC); 2. https://www.researchgate.net/profile/Raghad-Mouhamad/publication/366445418_THE_PRODUCTION_OF_NANO_BASED_MEDICINAL_HERBAL_MIXTURE_AND_ITS_APPLICATION_IN_AN_INHIBITION_AND_ELIMINATION_OF_BURN-CONTAMINATING_GERMS/links/63c45017e922c50e9999ef9a/THE-PRODUCTION-

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Conflicts of Interest

The author declares no conflict of interest regarding the publication of this work.

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