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Cannabidiol oil's effects on blood measurements in rats with experimentally generated leukemia

Nabil A. Soliman[1], Samih I. El Dahmy [2], Sara Mohamed Alashqar[1], Samia Hussein[3,4].
[1] Department of Zoology, Faculty of Science, Zagazig University, Sharkia, Egypt
[2] Department of Pharmacognosy, Faculty of Pharmacy, Zagazig University, Sharkia, Egypt
[3]Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Zagazig University, Sharkia, Egypt
[4]Department of Basic Medical Sciences, Ibn Sina University for Medical Sciences, Amman, Jordan.

ABSTRACT: Background: Background: Within a few weeks of application, the chemical carcinogen 7,12-Dimethyl benzaanthracene (DMBA) causes the development of carcinomas. For pharmaceutical purposes, natural medicines (Cannabinoid), (CBD) made from plant extracts have continued to be produced. Production of all-natural, less dangerous mutagenic compounds that have the potential to lessen the challenges given by neoplastic diseases like leukemic cancer. Aim of the study:- Examination of the antioxidant activity of CBD in male albino rats that were injected with DMBA. Method:- This experiment was conducted on 30 male rats sectioned into 6 groups with 5 each, Group1 (control), Group2 (olive oil), Group3 (cannabinoid), Group 4 (leukemic), Group5 (prophylactic), Group 6 (Treated). Result Compared to the leukemic rat group, both the prophylactic and the CBD-treated groups. CBD was successful in returning normal levels of total white blood cells (WBC), lymphocytes, red blood cells (RBCs), haemoglobin (Hb), platelets, granulocytes, and spleen tissue. Conclusion:- Our findings demonstrate how CBD can repair the harm done to the body by DMBA's toxicity.

Keywords:- leukemia 7,12- Dimethyl benzaanthracene (DMBA), Cannabinoid (CBD), and blood picture.

Abbreviations

(DMBA) 7,12-Dimethyl benzaanthracene, (CBD) cannabinoids, (WBCs) white blood cells, (RBCs) red blood cells, Haemoglobin (Hb).

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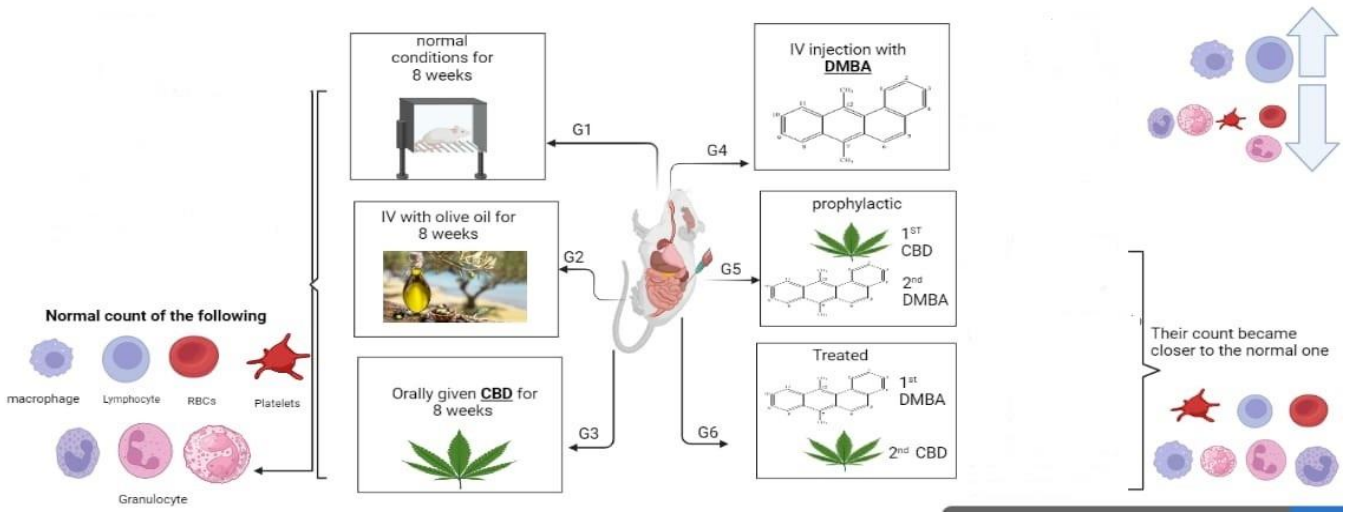
Graphical Abstract



1. INTRODUCTION

A malignant condition of the blood-forming tissues known as laeukemia causes an excessive synthesis of immature blood cells to enter the blood stream.(**Azher & Shiggaon, 2013).** Leukemia is described as the uncontrolled growth of abnormal white blood cells, often known as blasts or leukemia cells, in the bone marrow. It affects both children and adults and is quite common**. (Burhan 2016)** Chemotherapy is one of the treatments for cancer, however it comes with serious side effects and dose-limiting toxicity. **(Schulmeisteret al., 2000).** In the past, various traditional and modern medical systems used medicinal herbs to treat or prevent disease. Approximately 60 000 years ago, according to historical records, plants have been utilized as medications.(**Dinda et al., 2022 & Maran et al., 2022).** Contrary to chemotherapy and radiotherapy, many patients prefer safe medicinal plants. **(Fathifar, Zahra, et al 2023).** People have exploited medical herbs to treat illnesses from the beginning of time, and they have also looked to nature for remedies.(**Naghizadeh et al., 2020**).) Furthermore, herbal medicine typically include a variety of pharmacologically active chemicals; occasionally, it is unclear which components are crucial for the therapeutic action.(**Schulz et al., 2001)**. Natural compound cannabinoid (CBD) is well-known for its pleiotropic antioxidant and anti-inflammatory properties. It also has analgesic, antiepileptic, and anxiolytic properties and is devoid of the psychotropic effects and dependence typical of tetrahydrocannabinol. (**Brunetti et al., 2020).** Due to its anti-inflammation and anti-oxidation actions, it has demonstrated excellent pharmacological values in neuropsychiatric illnesses**. (Campos et al., 2016 Melas et al., 2021, Scarante et al., 2021**) .Numerous cancer types have been studied in relation to cannabinoids, in preclinical studies, they exhibit anticancer action against ovarian cancer, lung cancer, glioma, neuroblastoma, leukemia, melanoma, pancreatic cancer, and colorectal cancer. **(Mangal et al.,2021).** Cannabinoids are used by cancer patients to treat symptoms brought on by the disease, such as anxiety, discomfort, and appetite loss. Cancer patients also utilize cannabinoids to lessen side effects of their treatments, such as nausea and vomiting. For instance, the FDA has approved the cannabinoid-based medicines Dronabinol and Nabilone to treat nausea and vomiting brought on by cancer chemotherapy**.(Abbott, et al., 2020)**. Numerous cannabinoids, either alone or in conjunction with traditional antiseptics, are useful for treating nausea and vomiting brought on by chemotherapy. Despite more often occurring side effects, patients seem to prefer marijuana to traditional antiseptics. **(Schussel et al., 2018)**.Depending on CBD's anticancer competence, we used it to inspect its anti-leukemic effects in a leukemic rat model induced with 7,12 dimethylbenz(a)anthracene,(DMBA). 7,12-Dimethylbenz[a] anthracene.(DMBA) is an immune suppressant and potent lab carcinogen that targets particular organs. (**Miyata et al., 2001)**.(DMBA) a substance that falls within the category of polycyclic aromatic hydrocarbons, has both mutagenic and carcinogenic properties. It is extensively used in animal models for scientific investigation. DMBA has been shown in animal studies to be effective in the growth and proliferation of cancer cells. **(Uyar et al., 2020 and Alexander et al., 2011).**Also as previously shown that exposure to DMBA causes pathological changes in the liver and kidneys, including the development of parenchyma hepatocellular damages that increase the risk of cancer and hepatic lesions. **(Paliwal et al., 2011).**

2-MATERIALS AND METHODS

CBD was obtained from Zova Co from San Diego Pharmacy, California USA, both 20 gm of CBD and 20gm of Acacia gum were added to 100 ml warm distilled water after mixing with 1000 ml of distilled water, each ml of the solution contains 10 mg of the previously mentioned components.

Experimental design:-

Thirty male adult albino rats aged between 6 and 8 weeks and weighing between 80 and 150 mg were obtained from the Faculty of Veterinary Medicine, Zagazig University, Egypt, and were housed in plastic cages under controlled temperature in the animal house in the Zoology Department, Faculty of Veterinary Medicine, Zagazig University, animals are sectioned into 6 groups of 5 each for this experiment as:- Group (1) (Normal Control): rats were food and water for 8 weeks. Group (2) (Olive Oil group) rats were orally given Olive Oil 1ml/100gm for 8weeks **(Farahat *et al*., 2019)**. Group (3) (CBD group): rats were orally given 0.5ml/rat CBD for 2 weeks. **(Hussein et al., 2014).** Group (4) :- (Leukemic group) rats were intravenously injected with 40 mg/kg(DMBA) biweekly for 6 weeks **(Kabeel *et al*., 2018)**.Group (5): (Prophylactic Leukemia) rats were orally given 0.5ml/rat CBD as immunization daily for two weeks **(Hussein et al., 2014),** then IV injected with DMBA biweekly for 6 weeks**(Kabeel *et al*., 2018)**. Group (6)(Treated group) rats were intravenously injected biweekly with 40 mg/Kg DMBA for 6 weeks **Kabeel *et al*., 2018)**.then rats were given 0.5ml/rat CBD orally for two weeks. **(Hussein et al., 2014).**

Leukemia induction and assessment:

Through a series of intravenous injections of 7, 12-dimethyl benza[a]anthracene (DMBA) that obtained from Sigma Egypt, leukemia was experimentally generated in rats, a 20 mg/ml emulsion was prepared in olive oil and injected to rats. **(Kabeel *et al*., 2018)**.

ETHICS APPROVAL STATEMENT

An Institutional Animal Care and Use Committee approval (ZU-IACUC/1/F/193/2023) was granted for the study procedure.

Statistical analysis

All data were collected, tabulated and statistically analyzed using statistical product and service solutions (SPSS) software version 19. Data were expressed as the mean ± standard deviation (SD). The difference was assessed by a one-way analysis of variance (ANOVA) test. P-value < 0.05 was considered statistically significant, P-value < 0.001 was considered highly statistically significant, and p-value ≥ 0.05 was considered statistically insignificant. (**Aho. et al., 2019**)

3-RESULTS

Control group

The level of percent of White blood cells (WBCs) in this group was (12.07±0.88), Lymphocytes (74.48 ± 2.02), Haemoglobin (13.75±0.63), Red blood cells (RBCs) (7.72±0.43), Granulocytes (15.90±2.19) and platelets (508.80±20.03).

Olive oil group.

As olive oil is the medium where DMBA is dissolved to be transmitted to rats, to demonstrate that it hasn't any effect on rats, the olive oil group was compared with the normal control group for different hematological parameters (A,B,C,D,E&F) in figure (1) and table (1), where A represents WBCs , B represents percentage of Lymphocytes, C represents RBCs count D represents the percentage of Granulocytes, E represents Hemoglobin and F represents the platelets count . It showed no significant difference in all studied parameters, total lymphocyte P > 0.05, total WBCs, total RBCs, total Granulocytes and Hemoglobin, except in platelet count where there was a significant difference between olive oil group and each of normal control group and cannabinoid group (P <0.05, for each)

CBD group

To clarify the effect of CBD on rats, CBD was given orally to this group daily for 2 weeks and compared with the normal control group, the results shows no significant difference (P > 0.05) in total lymphocyte, total WBCs, total RBCs, total Granulocytes ,Hemoglobin and platelets count.

Leukemic group

To examine the efficacy of DMBA in leukemia induction, the leukemic rat group was compared with the control group, CBD group and the olive oil group. Results show a significant increase P < 0.05 in WBCs, percentage of Lymphocytes, and there is a significant reduction (P < 0.05) in RBCs count, Hemoglobin, and in platelets count.

Prophylactic group

To prove the immunizing role of CBD, this group were orally given CBD daily for 2 weeks, then was compared with the leukemic group that received DMBA, the results shows a significant reduction P < 0.05 in WBCs, Lymphocytes, while there was a significant increase in Granulocytes, Platelets count, while there wasn't a significant difference P > 0.05 in either RBCs count or Hemoglobin.

Treated group

As previously mentioned that CBD exhibits anticancer action against leukemia cancer, **(Mangal et al.,2021),** the results of this group approved on this as, when compared with the leukemic group , there was a significant reduction P < 0.05 in WBCs count, Lymphocytes count, a significant increase P < 0.05 in RBCs count, Platelets count , Granulocytes and Hemoglobin.

4-DISCUSSION

This study was initiated to start exploring the mechanism of leukemia induction by 7,12-Dimethyl benz(a)anthracene (DMBA), and how CBD, a potent herbal remedy, can heal it. Information provided in this study demonstrate that (DMBA) has successfully caused leukemia in rats. Myelogenous laeukaemia, lymphoblastic laeukemia, diffuse hepatic laeukemia of erythroblasts stem cells, and thymus lymphoma are all known to be caused by DMBA. **(Huggins & Sugiyama, 1966)** The toxic, cancer-causing, mutagenic, and immunosuppressive properties of DMBA are well documented (**Buters et al., 2003**). In the spleen, thymus, and bone marrow, DMBA causes toxins to the immune system. It has been demonstrated to inhibit spleen and cultured splenocytes' humorous and cell-mediated immune responses**.(Thurmond et al., 1987& 1988), (Dean et al., 1986) & (Ward et al., 1984).** In fact, when treated with DMBA, a variety of haematological and haematochemical parameters changed, proving that DMBA caused hepatocellular malignancies. In accordance with to recent studies, DMBA causes ovarian, mammary, cutaneous, and oral malignant. **(Suzuki et al., 2003).** As a result of exposure to DMBA, there is a significant increase in WBCs count as reported in **(Al-Asady et al., 2020) and (Kabeel *et al*., 2018),** which suggests that leukaemia has been induced. CBD was the natural remedy utilised in this study's therapeutic procedure, Given the reported benefits of cannabis, especially CBD, such as

pain relief, anti-inflammatory properties, antioxidant, diabetes prevention, anticancer, anxiolytic, anticonvulsive, and antiepileptic properties, as well as the lack of psychoactive effects brought on by THC, there is growing interest in the use of cannabis for medical purposes.(**Mechoulam et al., 2002), (Suryavanshi et al., 2020).** New research indicates success when utilising CBD as a cancer treatment**.** Its interactions with the endocannabinoid system (ECS), which lead to the reduction of pain and the encouragement of immune cell modulation, are one of the main mechanisms of CBD's anticancer effects.**(Śledziński et al., 2018).** Cell cycle arrest, activation of apoptosis, suppression of movement of cells, cancer cell movement, adhesion, angiogenesis, invasion, and metastasis are just a few of the effects of cannabinoids. **(Seltzer et al., 2020), (Alexander rt al., 2009), (Carracedo et al., 2006), (Ramer et al., 2017), (Shrivastava et al., 2011).**The fact that CBD is not intoxicating is significant since it facilitates higher patient acceptance of the substance as a cancer treatment. In recent years, the usage of non-intoxicating cannabinoids, such as CBD, which are typically linked to less severe, non-intoxicating adverse effects, has increased in the treatment of cancer. (**Ligresti et al., 2006).** CBD typically has a good safety profile and is well tolerated. **(Massi et al., 2004).** CBD has been shown to have anti-tumor properties, relieve cancer-related pain, and lessen the side effects of chemotherapy like nausea and vomiting. **(Grimison et al., 2020).**Our results show that application of CBD was successfully restored the normal count of WBC, Lymphocytes, RBC, Granulocytes and platelets in leukemic rat group compared to the normal control group. These results are in agreement with previous studies demonstrating the anticancer effect of CBD as in (**Anti-leukemic activity of a four-plant mixture in a leukemic rat model**) **(Kabeel *et al*., 2018),** Kabeel's study doesn't rely on CBD in the treatment process, but it depends on another herbal medicine that is much similar to CBD in its action pathway, as mentioned before that CBD has anticancer effect, Low doses of CBD (up to 3 M) dramatically reduced intercellular adhesion molecule-1 (ICAM-1)-dependent cell invasion in a study employing lung cancer cell lines, including A549, H358, and H460 NSCLC, through cannabinoid receptors, TRPV1, and p42/44 mitogen-activated protein kinase (MAPK), **(Ramer et al., 2011).** CBD (3 M) increased the vulnerability of lung cancer cells to lymphokine-activated killer (LAK) cell-mediated tumor-cell killing in an ICAM-1-dependent manner in A549, H460 NSCLC cells, and metastatic cells taken from a lung cancer patient.**(Haustein et al., 2004).** CBD has proven its effectiveness as an anticancer agent not only in lung cancer treatment but also in breast cancer as reported by **Harpe et al**. CBD (20 M) specifically targeted ROS-induced endoplasmic reticulum stress and unfolded protein response (UPR) activation in MCF7, an estrogen receptor-positive cell line, but not in MDA-MB-231, in a study employing these two cell lines. . Ca2+ influx via the TRPV1 receptor caused the MCF7 cells to produce more intracellular ROS. CBD (20 M) did not generate oxidative stress-induced endoplasmic reticulum stress or activate the UPR, but it did reduce the proliferation of MDA-MB-231 cells. This might have resulted from the TRPV1 receptor's varied location in these two cell lines.**(Harpe et al., 2021).** Although many preclinical studies and some human clinical trials have shown CBD to have good effects on cancer management, mechanistic research on the effectiveness of CBD's anticancer activities is still scarce. New research reveals that CBD and other cannabis therapies may improve chemotherapy side effects and reduce cancer pain. But more investigation into CBD's underlying mechanisms of action as a cancer therapy, particularly in significant clinical studies, is necessary.

1- Conclusion

The current study has a number of advantages that increase the importance and applicability of our results, as it demonstrates CBD's capacity to repair the tissue damage brought on by DMBA's toxic effects in the blood .

DECLARATION OF COMPETING

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Nabil A. Soliman , data collection:- Samih I. El Dahmy; analysis and interpretation of results: Sara Mohamed Alashqar; draft manuscript preparation: Samia Hussein.. All authors reviewed the results and approved the final version of the manuscript.

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Table (1):- Displayed the impact of CBD oil on some blood parameters in control and all other groups of rats that had been given DMBA to cause leukemia.

Groups	WBCs	Lymphocytes	Haemoglobin	RBCs	Granulocytes	Platelets
Control	12.70 ± 0.88	74.48 ± 2.02	13.75±0.63	7.72±0.43	15.90±2.19	508.80±20.03
Olive Oil	12.66 ± 0.66	74.80±1.67	14.20±0.41	7.78±0.57	13.90±3.13	526.20±11.25
Cannabinoid	12.73 ± 0.85	74.17±1.27	13.43±0.84	7.44±0.46	16.08±1.99	561.60±26.52
Leukemic	27.94 ± 3.21	90.56±2.88	10.36±1.37	5.47±0.68	8.90±1.47	399.20±17.28
Prophylactic	16.59 ± 1.36	79.69±1.65	10.63±0.68	5.98±0.26	12.88±1.52	503.20±11.36
Treated	14.56 ± 0.81	76.38±3.43	11.35±0.77	6.64±0.39	16.44±2.39	508.80±20.17

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