International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 347-353 www.ijprajournal.com ISSN: 2249-7781

Olive Oil Constituents' Health Benefits in the Treatment of Leukemia

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Date Of Submission: 05-05-2021 Date Of Acceptance: 22-05-2021

ABSTRACT: Leukaemia is a kind of cancer that affects the haemopoietin tissues, which include bone marrow. Radiation therapy, drug therapy, and surgery are all options for treating leukaemia. However, a naturally accessible substance, such as olive oil, can eliminate these tumours, slowing their progress and curing the disease at its source. The goal is to determine the function of olive oil in the treatment of leukaemia. The powerful elements of olive oil, such as hydroxytyrosol, Oleuropein, Oleocanthal, and Oleic acid, cause tumour cells to die by several processes such as apoptosis, inactivation, and lysosomal membrane permeabilization. These constituents work in such a way that they do not have any effect on the normal cells but only on the cancerous cells. In a study, trials were done on the patients who were suffering from leukaemia by diagnosing with methods like Flow cytometry, Phase contrast microscopy, test for abnormalities in the chromosomes, complete blood test to diagnose the presence of abnormal cells.

The findings of many studies were astounding, demonstrating that using olive oil significantly inhibited the development and spread of HL60 and K562 cells (these are the leukemic cell lines). The concentration of olive oil affected. Anti-inflammatory, anti-proliferative, and anti-angiogenesis are the three primary ways through which olive oil acts. These activities increase the synthesis of caspases 3 and 7, as well as an increase in the production of tumour suppressor cells p53 and the activation of pro-apoptotic genes Bak and Bax, which leads to tumour cell apoptosis.

The present review discusses leukaemia, its genesis, olive oil extraction, and its effects on various disorders, with an emphasis on leukaemia. The article also discusses the effects of olive oil on malignancies in the human body, as well as how it was employed in a few studies and trials conducted in various nations, demonstrating its promise in treating leukaemia patients.

KEYWORDS: Olive oil, HL60 cells, K562 cells, Hydroxytyrosol, Oleic acid, Oleocanthal, Flow cytometry, Apoptosis, Lysosomal membrane permeabilization

I. INTRODUCTION

Leukaemia is a cancer of the blood cells. There are broad categories of blood cells, including red blood cells, white blood cells, and platelets. Generally, leukaemia refers to cancers of the WBCs. WBCs play a vital role in our immune system. They protect our body from the attack of bacteria, viruses, and fungi, also the atypical cells and other foreign substances. In leukaemia, the WBCs do not function properly. They divide too quickly and eventually crowd out normal cells (1). A person may be genetically predisposed to develop leukaemia, but lifestyle risk factors, such as cigarette smoking, are more likely to develop leukaemia. Other environmental factors, such as exposure to certain chemicals and radiation, are responsible for the DNA abnormalities that can cause leukaemia (2). There are approximately 3,76,508 people in the US who are either living with or alleviating from leukaemia. The highest leukaemia prevalence for both men and women were estimated in Australia and New Zealand, ASR per 100 000 11·3 in males and 7·2 in females, in Northern America it was 10·5 in males and 7·2 in females. In Western Europe, it was 9·6 in males and 6·0 in females, and the lowest was found to be in western Africa where it was, 1·4 in males and 1·2 in females. Rates were generally higher in males than females with an overall male to female ratio of 4:1. (3). Treatments like Chemotherapy, Targeted drug therapy as well as Radiation therapy are more probably used. Surgery is done in chronic stages. Common drugs used are Bendamustine (Bendeka), Fludarabine (Fludara), more commonly for patients who are younger and do not have a deletion in chromosome 17, Pentostatin (Nipent), Cladribine (Leustatin), Chlorambucil (Leukeran), Cyclophosphamide (Cytoxan). The side effects of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 347-353 www.ijprajournal.com ISSN: 2249-7781

chemotherapy depend on the individual and the dose used, but they can include fatigue, risk of infection, nausea and vomiting, alopecia, anorexia, and diarrhea. Targeted drug therapy includes MAB like Rituximab (Rituxan), Ofatumumab (Auzerra), and Kinase inhibitors like Ibrutinib (Imbrevica), Idelalisib (zydelig) its side effects depends upon the drug used. Radiation therapy involves the use of high-energy radiations like X-rays, or other cancer cells destroying particles. Its adverse effects include fatigue, mild skin reactions, upset stomach, and loose bowel movements (4). Several countries have performed trials on Olive oil for the treatment of leukaemia. Olive oil is selected for trials for the treatment of leukaemia as it does not show any adverse effects and cost-effective and also easily available. Olive oil is the oil that has been exacted from the olives. Olives can simply be pressed to extract their oil but there several modern methods that involve crushing the olives and separating the pulp by centrifugation, chromatography (HPLC), etc. Each tablespoon of olive oil that is 13.5 grams consists of saturated fat 14% monounsaturated fats 73% which is mostly oleic acid, Vitamin E 13%, and vitamin K 7%. It also has antioxidants to reduce oxidative damage. The antioxidants like oleocanthal and oleuropein are used in reducing inflammation and preventing oxidation of LDL respectively (5-11). Olive oil especially the extra virgin has small amounts of hydroxytyrosol, tyrosol rendering it Anti Cancerous. (12-13) Olive oil has been proven to be useful in many diseased conditions like prevention of strokes, prevention against heart diseases, obesity, Alzheimer's disease, diabetes, and most importantly cancer. Oleic acid can act by interfering in the myelocytic cell's genome, it also reduces inflammation. Oleocanthal destroys the cancer cell and does not cause any harm to the non-cancerous cells. Fig 1 depicts the mechanism action of Olive oil. The oleocanthal causes the death of the cancerous cells through lysosomal membrane permeabilization (LMP). (14-19).

Olive oil's cytotoxic activities

The extra Virgin olive oil phenol extract induced inhibition of proliferation of HL 60 cells in a time and concentration-dependent manner. The growth of cells was completely inhibited at a concentration of 13.5mg/L, which can be identified by fluorescence microscopy and flow cytometry(20-21). The effect of olive oil can be determined in the damaged DNA obtained from the peripheral blood mononuclear cells and the promyelocytic cells by using “single cell gel electrophoresis”. The olive oil and its constituents have also proved to reduce the cancer cells-induced DNA damage at concentrations as low as 1 micromole/L. At 10 micromoles/L a 93% protection was provided against the HL60 cells. At 50 to 100 micromole/L, hydroxytyrosol caused apoptosis in the HL60 cells after incubation for 24 hours (5-6). The DNA cell cycle which was quantified by flow cytometry proved that the HL60 cells were arrested in the G○/G1 phase with a decrease in the cellular percentage in the S and G2/M phase at a concentration of 50-100 micromol/L (21-23).

It was found that the oncotic cells were getting destroyed rapidly by the oleocanthal activity. The time taken by these cells ranged between 30 minutes to an hour. The oleocanthal and oleic acid work by disrupting the recycle centres. The organelles known as the “lysosomes” are bigger in the oncotic cells when compared to the normal cells. Once these are disrupted, the cells become weaker. These compounds do not cause any harm to the normal cells but just put them in the quiescent stage making them inactive. (23-24).

In the world's first human study on the oleocanthal effects on cancer, the first batch of 10 patients with chronic lymphocytic leukaemia were given 40g of olive oil, dividing the dose between morning and evening for three months. Also then, a batch of 5 patients was given high phenolic olive oil but it did not have oleocanthal. The results revealed that oleocanthal showed a high decrease in the oncotic white cells and it also caused an increase in apoptosis of the cancerous white cells in 9 out of 10 patients. (24-25)

Some patients with chronic lymphocytic leukemia who were at a stage of the disease where it was important to start the chemotherapy were tested. These patients were given no particular diet plans for an exception to stop the use of other oils except olive oil 40 ml a day. The results were astonishing, which showed a drastic increase in the cancerous white blood cells apoptosis and there was also a significant reduction in the cancer markers (24-26). The Lysosomal membrane permeabilization (LMP), which is also the mechanism of oleocanthal in disruption of HL60 cells has proven to be of high therapeutic interest in treating Leukemia (26-27). Olive oil may render antioxidant, antimicrobial, antiviral, anti-inflammatory, hypoglycemic, neuroprotective, and most importantly anti-cancerous properties (28-37,47).

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Olive oil not only inhibits HL60 cells but also the strong cells having resistance to chemotherapy, the K562 cells (36, 44, 46) It was also found that apoptosis also causes differentiation of myeloid precursors. (37,38).

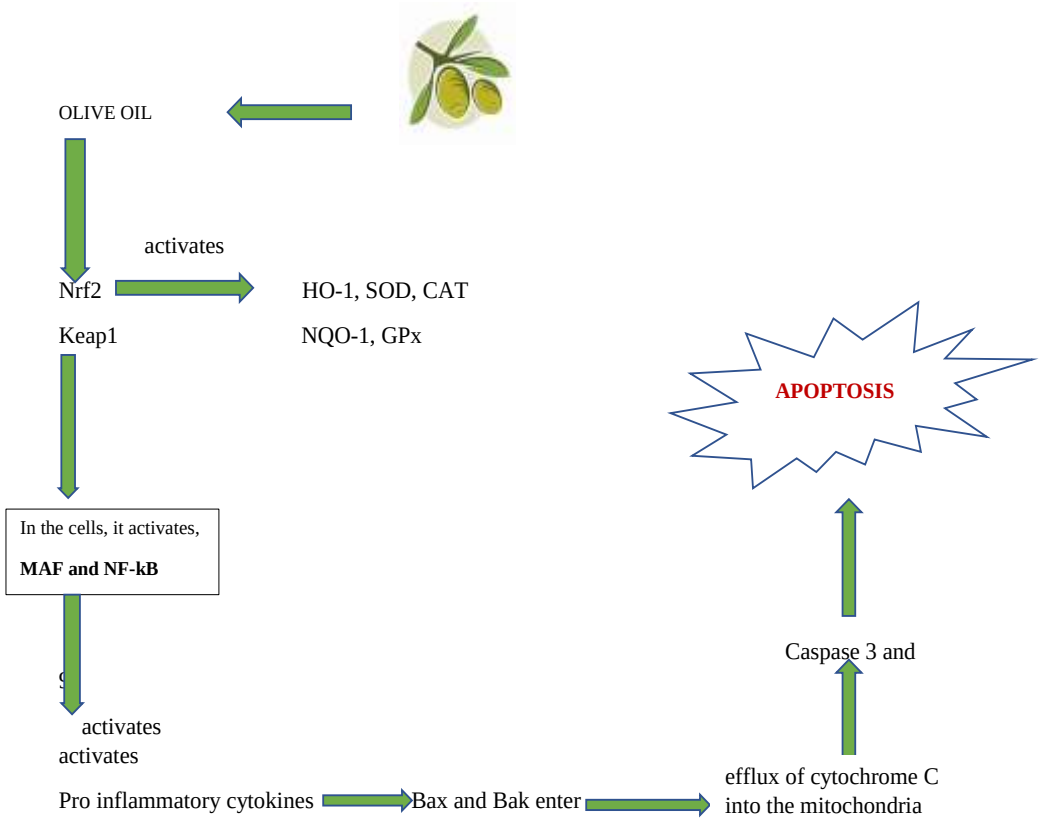

Fig 1. Mechanism action of Olive oil

Methods used to detect to function of olive oil

I. Cell proliferation assay

The investigation for the cellular proliferation was done by MTT (3-(4,5-dimethylazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.

1. The K562 cell were incubated for 24 hours in the 95 well plates
2. Olive extract medium diluted was added to it at some final concentrations of 50, 75, 100, 125, and 150 microgram/ml.
3. The sample cells were then treated by ethanol at a concentration of 0.3 %.
4. MTT was added preparation after incubation for 24 hours, 48 hours, 72 hours.
5. Then the MTT was mixed and the resulting formazans was dissolved in 100ml of 10% sodium dodecyl sulfate for 24 hours.

II. Cell differentiation assay

In a study this assay performed or detected by flow cytometry measuring the CD11b and CD14 with expressions on the k562 cell surfaces.

1. The cells were incubated for 24 hours in a 6 well played at 2×10^4 cells/ml.
2. The Olive extract was added at the concentrations of 5101 50 mg/ ml.
3. Then the sample cells were again added 0.3 % ethanol.
4. After the completion of the incubation period the cells were collected and was with cold PBS for two times and adjust to the same number
5. The cells were then tag with anti CD14, CD11b anti glycophorin-A which are phycoerythrin conjugated for 30 minutes.
6. The coloured cells were cleaned with cold PBS for two times again and left in 500 microliters PBS for recording.

III. Annexin assay

The K562 cells were seeded in 6 well plates and 50, 100, 150 µg/mL of Olive oil were added. After incubation for the desired time, the cells are collected and stained with annexin and incubated for 20 mins in dark.

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Cell viability and morphology tests can be done by flow cytometry and phase contrast microscopy respectively.

These resultant graphs from a study, (Fig 1) shows the decreased proliferation and viability of leukemic cells, respectively.

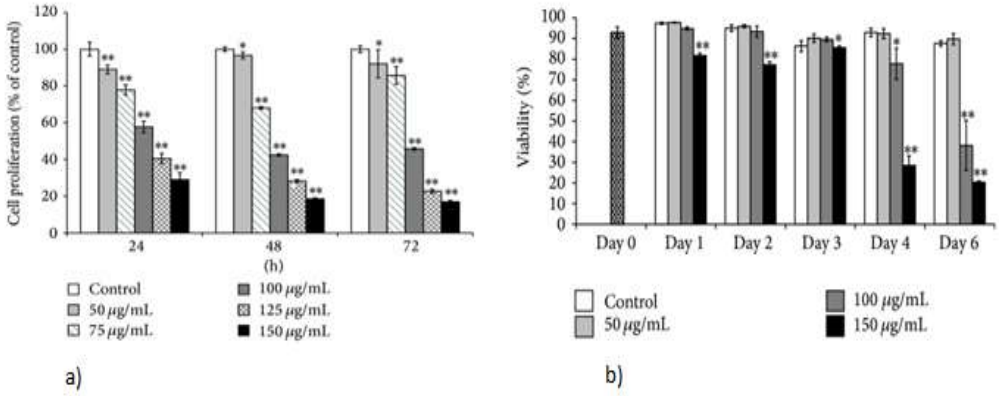

Fig 2. Shows the decreased a) cell proliferation, b) viability of leukemic cells

The results determined, showed that 150 ug/mL of Olive oil caused increase in the K562 cell size and decrease in their viability leading to a slower growth rate. The K562 cells treated with 150 ug/mL, on the 1st and 2nd day were arrested in the G○/G1 and showed drastic reduction in the 3rd and 4thdays. The genes expressed in the Olive oil treated cells showed presence of MAP3K2, MAP3K5 and MAP3K7 while MAP2K5 and MAPK14 were downregulated. The activated MAPKs activate the JNKbut the MAP3K2 activates it (39,40,41).MAP3K7 activates the NFKBwhich is theactivator of apoptosis and also plays a vital role in survival and development of T cells, and causes its upregulation. The JNK and NFKB both activities are balanced which decide the fate of the cancer cells.(42, 43, 44)

II. CONCLUSION

The findings reveal that components of olive oil, such as hydroxytyrosol, oleeuropein, oleic acid, and oleocanthal, have the capacity to kill and inhibit the proliferation of leukemic cells (HL 60 and K562 cells) by preventing their passage through many cell cycle phases. TNF-alpha, arachidonic acid, IL-6, NF-KB, PEG-2, anti-inflammatory, anti-proliferative (cytotoxicity, clonogenic survival, tumour development, cell proliferation), anti-angiogenesis (migration, metastasis, VEGF). These three processes cause an increase in caspase 3 and 7, an increase in the tumour suppressor cell p53, an increase in the pro-apoptotic genes Bak and Bax, and a decrease in cell viability, as well as apoptosis and cell death by perforating the vesicles (47-55).

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