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The possible anti-inflammatory effect of extra virgin olive oil with colchicine in treatment of resistant cases of familial Mediterranean fever in a cohort of pediatric Egyptian patients

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Abstract

Background People of Mediterranean descent are primarily affected by the autoinflammatory genetic condition known as familial Mediterranean fever (FMF). The disease is resistant to colchicine therapy in 10–20% of patients. Numerous recent animal studies showed promising results of extra virgin olive oil (EVOO) to control inflammation. The objective of this study was to assess the effectiveness of combining EVOO with colchicine in the treatment of colchicine-resistant familial Mediterranean fever (CRFMF) patients.

Results Both the frequency of episodes and inflammatory indicators significantly decreased after a three-month course of daily EVOO treatment with colchicine. The average erythrocyte sedimentation rate (ESR) of patients was 78.6 mm/h before the EVOO administration, and it dropped to 27.8 mm/h, after that. Additionally, after taking EVOO, the mean serum amyloid A (SAA) decreased from 123.82 mg/dl to 59.78 mg/L. Also, the average C-reactive protein (CRP) decreased from 34.22 to 7.84 mg/dl following its administration; the mean nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) level decreased from 134.92 to 64.23 pg/ml. The mean caspase-1 level decreased from 7.8 to 4.98 ng/ml; and the mean levels of cytokines, interleukin 6 (IL-6), interleukin 1 beta (IL-1 β), and tumor necrosis factor-alpha (TNF-α) decreased from 9.8, 18.14, and 52.7 pg/ml, respectively, to 5.95, 12.51, and 29.39 pg/ml. Finally following the administration of EVOO, there was a notable overall improvement in the quality of life of (CRFMF) patients.

Conclusion EVOO demonstrated a significant positive impact when paired with the tolerated dosage of colchicine in the management of CRFMF. Improvements were observed in both clinical and laboratory settings, including a reduction in the attack frequency and serum levels of inflammatory markers, such as NLRP3, caspase-1, ESR, CRP, IL-1β, IL-6, and TNF-α without any negative side effects.

Keywords Colchicine, Extra virgin olive oil, Colchicine resistant Familial Mediterranean Fever, Inflammasome

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Background

The autoinflammatory condition known as familial Mediterranean fever (FMF) is represented by repeated episodes of fever, polyserositis, arthritis, and skin manifestations as well as a strong acute-phase response lasting 12–72 h [1, 2]. It is the most prevalent autoinflammatory illness globally [3, 4]. In 1945, the illness was initially referred to as "benign paroxysmal peritonitis." People in the Mediterranean region, such as Arabs, Greeks, Italians, and Turks, are primarily affected by the disease, but, throughout the twentieth century, migration and travel have increased its incidence [5, 6]. Prodromal signs of FMF include pain in the area where the flare is expected to occur one or two days before symptoms manifest. FMF fever is usually recurring and of a high degree (> 38 °C). It usually rises quickly for one to three days, reaching a plateau then falls off [7].

Severe abdominal pain and stiffness are brought on by peritoneal inflammation (aseptic peritonitis), which starts locally and spreads throughout the body. It is possible to develop pericarditis or pleuritis, in the form of unilateral chest pain [8]. When FMF attacks occur in children, arthritis is frequently the accompanying symptom. It is usually monoarticular and commonly affects the big joints in the lower limbs such as ankles and knees. These arthritis symptoms can arise during FMF attacks and may also occur intermittently between episodes [9]. The dermatological manifestation of FMF is the skin lesions that resemble warm, painful erysipelas on the lower limb. Renal amyloidosis is the main FMF consequence that leads to end-stage renal failure [10, 11].

FMF arises from a mutation in the MEFV gene found on chromosome 16's short arm (p). This specific gene is responsible for producing pyrin protein, comprising 781 amino acids [12].

Over the past few years, evidence linking inflammation to FMF has grown. Pyrin is a member of the cytosolic pattern recognition receptors (PRRs) group expressed in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts. It is responsible for regulating innate immune responses upon detecting specific signals from pathogens or host-derived danger molecules, known as pathogen/danger-associated molecular patterns. When activated, pyrin, along with other receptors, forms inflammasomes, which are multiprotein signaling complexes. These inflammasomes recruit and activate caspase-1, an enzyme involved in promoting inflammation. Active caspase-1 facilitates the proteolytic maturation and secretion of cytokines, such as interleukin (IL)-1β that triggers a form of cell death characterized as pyroptosis, which is necrotic in nature [13, 14]. Mutation of MEFV genes disrupts pyrin protein and its function leads to unrestricted pyrin activity, causing excessive production of the NLRP3 inflammasome which in turn triggers the complete inflammatory cascade. This uncontrolled inflammation is responsible for the characteristic febrile inflammatory episodes seen in FMF [15]. Therefore, addressing these inflammatory pathways can stop attacks from happening, return inflammation to normal in between episodes, and stop amyloidosis from developing [16].

The clinical presentation of FMF varies greatly, depending on the specific sequence variations found in the MEFV gene [17]. According to the European Alliance of Associations for Rheumatology (EULAR) recommendations, the objective of treating FMF is to achieve control over acute episodes, reduce chronic and subclinical inflammation, and prevent consequences, primarily renal amyloidosis that leads to renal failure [18].

Since 1972, colchicine has remained the primary treatment for FMF. This alkaloid compound inhibits a variety of cellular processes, including cell adhesion, microtubule assembly, and inflammasome activation. Administration of colchicine ultimately helps prevent FMF flare-ups in patients receiving this treatment [19]. However, approximately 10–20% of FMF patients exhibit resistance to colchicine. Colchicine resistance is typically described as experiencing one or more attacks per month even though receiving the maximum tolerated dose for six months, while others may only partially respond or be intolerant to high doses of colchicine. This poses a challenge for rheumatologists in managing such cases [20].

On the other hand, macrophages are crucial components of the immune system, playing a central role in the regulation of infections and inflammatory processes through their involvement in both innate and adaptive immune responses [21]. Regrettably, FMF patients with MEVF mutations experience an overabundance of macrophage activation. When macrophages are stimulated, they release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [22].

Extra virgin olive oil (EVOO) is commonly used as a dietary supplement or an over-the-counter remedy for various health benefits. EVOO comprises over 200 distinct chemical compounds, encompassing fatty acids, sterols, terpenoids, carotenoids, tocopherols, flavonoids, and olive polyphenols such as tyrosyl, hydroxytyrosol, oleuropein, oleacein, olive ligstroside, and oleocanthal (OC) [23]. Among these polyphenols, OC has garnered significant scientific attention due to its intriguing biological activities, despite representing only 10% of the olive's polyphenol content (100–300 mg/kg olive oil). This variability is influenced by various factors, including the type of olive cultivars, the environmental conditions in which the olives are grown, agricultural practices employed, the maturity of the olives, the methods used for processing

the olives into oil, as well as the storage and heating conditions [24].

Research has revealed that OC exhibits potent anti-inflammatory properties [25]. Given that the development of numerous chronic diseases involves both inflammatory and oxidative components. OC was shown to be able to block catabolic genes like Matrix metalloproteinase-13 and ADAM Metallopeptidase with Thrombospondin Type 1 Motif (ADAMTS-5) as well as inflammatory genes like IL-6, IL-8, cyclo-oxygenase-2, nitric oxide synthase-2, macrophage inflammatory protein-1 alpha, TNF-α, and lipocalin-2 in osteoarthritis chondrocytes and macrophages studies. These findings demonstrated the compound's significance in the management of rheumatic and inflammatory disorders by controlling the NF-kB and mitogen-activated protein kinases pathways [26]. Additional recent data demonstrated that when EVOO polyphenolic extract OC and oleoresin were added to human synovial SW982 cell line, a substantial decrease in IL-1β-induced TNF-α and IL-6 production was observed [27].

Oleocanthal shows promise as a potential agent for preventing such conditions. It is worth noting that oleocanthal may work with other bioactive compounds present in EVOO to maximize its therapeutic potential. Additionally, several studies have suggested that combining colchicine with biological therapy targeting FMF inflammatory markers can be valuable for patients who do not respond adequately [28, 29]. However, the high cost associated with lifelong treatment using biological therapy and concerns about safety, [30] including an increased risk of cancer and infection, have prompted the need for alternative approaches [31]. Therefore, our study aims to investigate the effect of using extra virgin olive oil, which is rich in polyphenols, in combination with colchicine to achieve better control of attacks in FMF patients who have not responded to colchicine treatment alone clinically and laboratory, furthermore to determine the molecular mechanisms by which EVOO exerts its effect if found.

Patients and methods

This study was a single-center prospective single-arm study design. A total of 50 patients were assessed for eligibility in this single-arm study, 20 patients were excluded (17 patients did not meet the inclusion criteria, and three patients refused to consume olive oil due to taste preferences). Then, 30 FMF patients continued the study. Among the participants, there were 14 males and 16 females who were being monitored at the Pediatric Rheumatology Outpatient Clinic of Children's Hospital (Pediatrics Specialized Hospital) at Cairo University. The study has lasted three months, starting in October and concluding at the end of December. The patients included in the study were children ≤16 years old, diagnosed with FMF based on the Yalcinkaya new FMF criteria [32] and showing +ve MEFV gene mutation who had at least one attack per month despite adhering to the maximum tolerated dose of colchicine treatment (up to 2 mg/day). The researchers assessed the participants' compliance by asking them and their relatives, and by counting the number of the remaining medication in the strip inside the package with the patient at each visit. It was observed that despite the patients taking their medications correctly, their response to colchicine was still limited, and hence, they were classified as colchicine resistance FMF patients [33].

Patients over 16 years old or those with conditions that could impact compliance with the treatment protocol were excluded from the study. Patients receiving concurrent medications with biological or disease-modifying antirheumatic drug (DMARD), systemic steroids, or those with various autoimmune and other autoinflammatory diseases that could affect FMF activity, such as systemic lupus or juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, diabetes mellitus, gastrointestinal diseases, active ischemic cardiovascular disease, congestive heart failure, renal amyloidosis, or chronic renal failure, were also excluded.

Following the protocol's (N.320.2023) approval by Clinical Research Ethics Committee and the acquisition of informed consent from each patient's parents. A thorough history was obtained of each patient, including the age at which symptoms first appeared, the age of diagnosis, the length of the illness, the characteristics of attacks (frequency, duration, and clinical signs), and the dosage of colchicine the patient had taken. Quality of life (QOL), baseline data, and a physician checkup were completed during the first visit and evaluated again at the end of the study. The patient data confirmed the MEFV gene alterations.

Intervention and assessment

Over three months, the patients in the study received the maximum tolerated dose of colchicine (COLCHICINE OPO CALCIUM, France) along with a daily oral dose of (15–30 ml) of EVOO [34]. The specific EVOO used was chosen by an expert based on its high content of polyphenolic compounds, which are recognized by their characteristic smell and strong taste on the back of the tongue. The selected EVOO was obtained from ELSALHYA company at the Ministry of Agriculture outlet in Dokki, Cairo. To preserve the phenolic compounds, EVOO was stored in dark glass containers to protect it from light.

The patients were given instructions to maintain diaries, recording any concomitant medications used, and

FMF attacks experienced, including their duration and affected sites, the need for analgesics, hospital visits during attacks, and the number of school days missed due to pain or FMF-related attacks. Additionally, one of the investigators was responsible for contacting the patients to ensure treatment compliance and to assist in interpreting symptoms as true attacks or not.

To evaluate QOL, the patients' pre- and post-treatment assessments were conducted using the Arabic-translated version of the PedsQL 4.0 Generic Core Scales (Mapi Research Trust, Lyon, France) [35]. This self-report scale covered physical functioning (eight items), emotional functioning (five items), social functioning (five items), and school functioning (five items). The scale items were scored on a 5-point Likert response scale ranging from "never a problem" to "almost always a problem." The scores were reverse scored and linearly transformed to a 0–100 scale, where higher scores indicated a better quality of life.

Blood samples were collected from the patients at the beginning and the end of three months. ESR was measured, and then, samples were allowed to clot before being centrifuged at 10,000 rpm for 20 min. The separated serum was frozen and stored at -80°C until further analysis. The laboratory tests conducted on the serum samples included CRP screening using the latex agglutination test [36] and confirmation via nephelometry analysis, serum amyloid A (SAA) analysis using ELISA kits catalog no. CSB-E08589h supplied by (Cusabio, USA) according to the manufacturer's instruction [37]. IL-1β levels catalog no. MBS012415, IL-6 levels catalog no. MBS355306, TNF-α levels catalog no. MBS2502004, NLRP3 levels by NACHT, LRR, and PYD domains-containing protein 3 (NLRP3/C1orf7/CIAS1/NALP3/PYPAF1) catalog no. MBS917009, Caspase-1 catalog no. MBS264676. All kits of IL-1β, IL-6, TNF-α, NLRP3, and Caspase-1 were ELISA kits supplied by (MyBioSource, S, USA) according to manufacturer instructions.

Statistical analysis

Sample size calculation

To obtain a two-sided 95% confidence interval, a total of 30 patients were required based on a previous study [38]. Initially, thirty-three FMF patients were included but three patients discontinued their participation, resulting in a dropout rate of 1%. The sample size estimation was conducted using the Epi info7 statistical package, with a power of 95% and a type I error of 0.05. The data collected at the end of the study were coded and entered into the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Quantitative data were summarized using measures such as mean, standard deviation, median, minimum, and maximum, while categorical data were summarized using frequency (count) and relative frequency (percentage). For comparing serial measurements within each patient (before and after), a paired t test was used for normally distributed quantitative variables, whereas the nonparametric Wilcoxon signed-rank test was employed for non-normally distributed quantitative variables [39]. *P* values less than 0.05 were considered statistically significant.

Results

Participant characteristics

All participants in this study showed genetic mutation as the following: The allelic frequency of MEFV mutations was M694V (36.6%), M694I (30%), E148Q (20%), and M680I (13.3%).

As illustrated in Fig. 1 ($n=30$), patients were included in this study, 16 females (53.3%) and 14 males (46.7%) with a mean age of 6.25 ± 3.07 years at diagnosis, and a mean disease duration of 5.54 ± 3.19 years.

Clinical presentation data

The main symptoms of the studied group during periods of active disease were abdominal pain (100%), arthralgia (80%), fever (53.3%), and pleurisy (46.7%) Fig. 2.

Numbers of attacks before and after receiving EVOO

All participants were taking the maximum tolerated dose of colchicine that was not enough to control the attacks and they were in need for frequent intake of analgesics. However, they exhibited resistance to these treatments, experiencing frequent attacks at varying intervals. These ranged from two attacks every two weeks (four attacks per month) for 6.7% of participants, to two attacks every four weeks (two attacks per month) for 23.3% of participants. Most participants experienced one attack every two weeks (33.3%) or one attack every three weeks

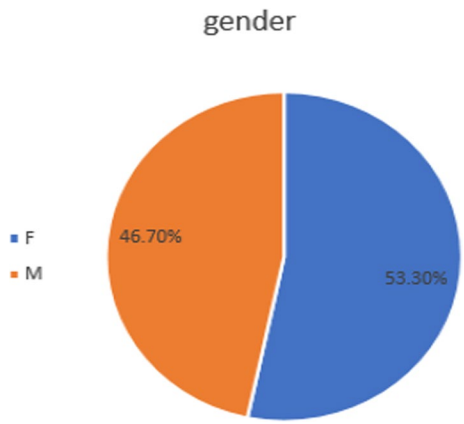

Fig. 1 The percentage of male and female participants

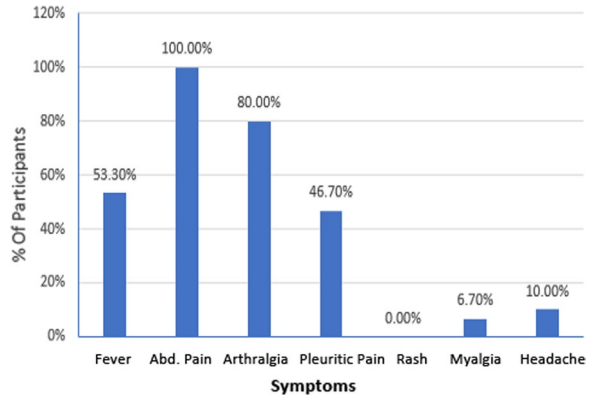

Fig. 2 The percentage of the main symptoms observed within the studied group

(33.3%) before starting a daily regimen of extra virgin olive oil (EVOO), as shown in Fig. 3A**.** After three months of daily EVOO consumption, a reduction in the number of attacks was observed. Specifically, 40% of participants had one attack every four weeks, while 36.7% experienced one attack every six weeks, as depicted in Fig. 3B.

Inflammatory markers

Analysis of acute-phase reactants and cytokine levels, which indicate the presence of inflammation, before and after the administration of extra virgin olive oil (EVOO), demonstrated a significant reduction in all inflammatory markers. Before receiving EVOO, the mean ESR was 78.6 mm/h, which decreased to 27.8 mm/h. after treatment with a *P* value less than 0.001. The mean SAA level decreased from 123.82 to 59.78 mg/L after EVOO administration, also with a *P* value less than 0.001. The mean CRP level decreased from 34.22 to 7.84 mg/dl after EVOO treatment, with a *P* value of 0.007. Furthermore, the mean concentrations of NLRP3 dropped from 134.92 to 64.23 pg/ml with a *P* value less than 0.001 (Fig. 4A–D).

Additionally, the mean caspase-1 level decreased from 7.8 to 4.98 ng/ml with a *P* value less than 0.001. The mean levels of IL-6, IL-1β, and TNF-α were also reduced from 9.8, 18.14, and 52.7 pg/ml, respectively, to 5.95, 12.51, and 29.39 pg/ml, respectively, with a *P* value less than 0.001. These findings indicate a significant difference after the administration of extra virgin olive oil (EVOO), (Fig. 5A–D).

Quality of life (QOL)

The subjects were assessed using the Arabic version of the PedsQL 4.0 Generic Core Scales before and after receiving olive oil. The administration of EVOO led to a significant enhancement in the overall quality of life, as evidenced by significantly higher mean scores in school, emotional, social, and physical domains (p value: < 0.001) (Table 1).

Discussion

Colchicine resistance is characterized by a higher frequency or increased severity of attacks or elevated levels of acute-phase proteins such as CRP and/or SAA (greater than 1.5 times the upper limit between attacks) [33]. Clinically, colchicine resistance is defined as at least one attack per month for six months at the maximal tolerable dose of colchicine in totally compliant individuals [40, 41].

In the present study, FMF patient-reported manifestations were considered attack only if they met the specific criteria identifying an attack and were confirmed by a study team member. In summary, an attack was defined

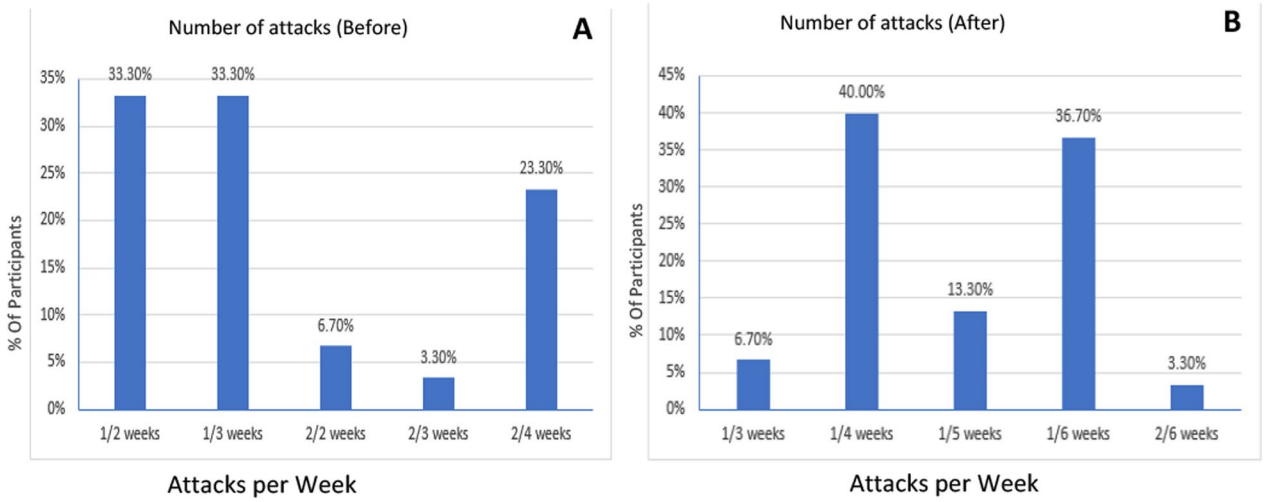

Fig. 3 **A** and **B** Comparison between numbers of attacks before and after EVOO administration

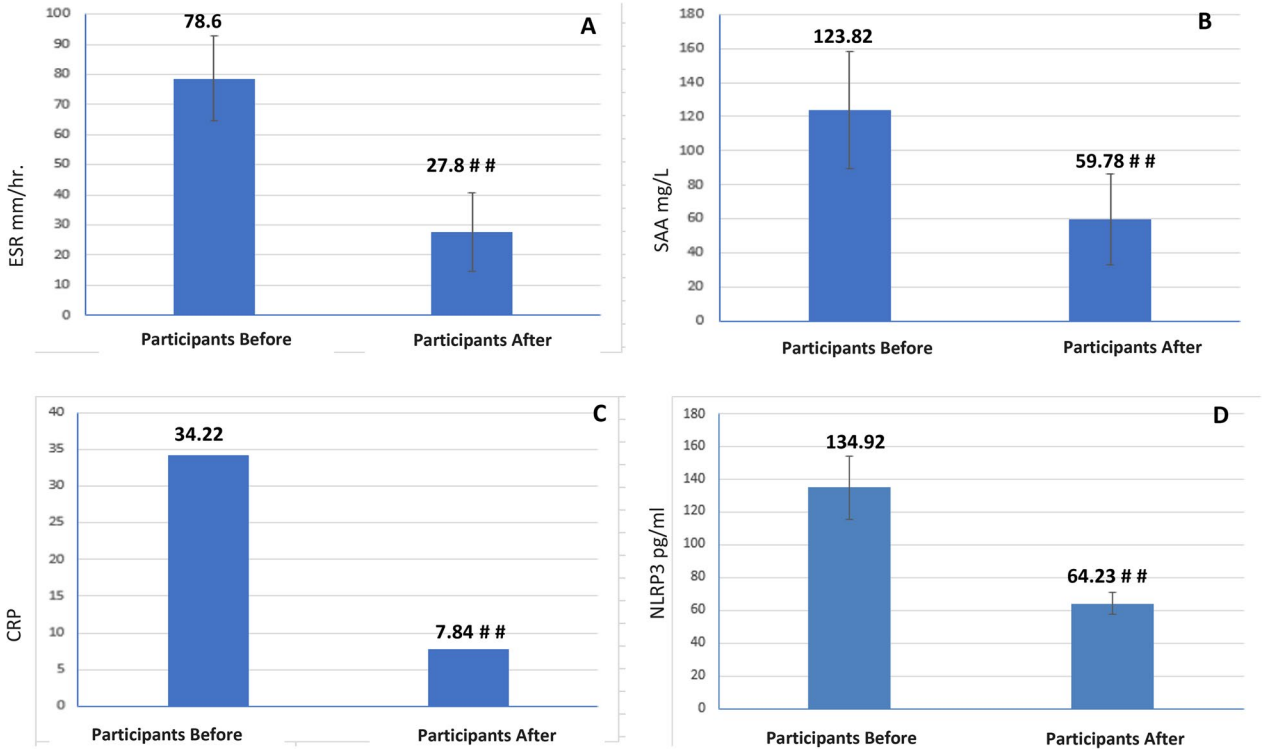

Fig. 4 **A**–**D** Comparison between levels of acute-phase reactants (A: ESR; B: SAA; C: CRP and D: NLRP3 before and after EVOO administration in the study group. ESR: Erythrocyte sedimentation rate; SAA: serum amyloid A; CRP: C-reactive protein; NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (n = 30). # # (*p* value: < 0.001) Significantly different as compared to the patient in the group before EVOO administration, using a paired t test for normally distributed quantitative variables, whereas using Wilcoxon signed-rank test for the nonparametric data

as having the following characteristics: a fever equal to or greater than 38 °C, lasting from 6 h up to 7 days, and along with painful symptoms in the abdomen with signs consistent with peritonitis, chest symptoms consistent with pleuritis, joints symptoms consistent with monoarthritic involvement of large lower extremity joints, or skin symptoms.

For evaluation of improvement in those patients, we used a modified FMF50 score. According to this scoring system, the fulfillment of five out of six criteria was considered an improvement [42]. This score required improvement by ≥ 50 in the following: attack frequency, attack duration, global patient assessment, global physician assessment, frequency of attacks with arthritis, and levels of acute-phase reactants or the normalization of these markers. In our study, quality-of-life values (substituting patient global assessment in the original score). The measurements taken at the beginning of the study were compared to those obtained at the end to assess changes according to these criteria.

There is abundant evidence encouraging the significant role of EVOO in safeguarding against amyloidosis, a condition that can result in renal failure among patients with FMF. This protective effect is attributed to EVOO's capability to reduce the levels of SAA. Marina Aparicio et al. conducted a study demonstrating that a diet abundant in extra virgin olive oil can alleviate kidney injury in a pristane-induced model of systemic lupus erythematosus model [43]. Our own results align with these previous findings, as we observed a significant drop in SAA levels after three months of EVOO treatment.

Research has demonstrated that the underlying cause of FMF, an autoinflammatory illness, is mutations in the genes that produce pyrin [12]. This autoinflammation is mediated by IL-1β. Many studies have revealed that pyrin forms an inflammasome, which is a complex formed by the oligomerization of a nucleotide-binding domain-like receptor (NLR) in response to various pathogenic or sterile danger signals. This inflammasome facilitates the maturation of IL-1β by activating caspase-1 and triggers the pro-inflammatory cytokines release, including IL-1β [13, 44]. Another study carried out by Omenetti et al. also showed that those with FMF have increased NLRP3-dependent IL-1β release [45, 46]. It was discovered that OC inhibits both canonical and non-canonical inflammasome signaling pathways.

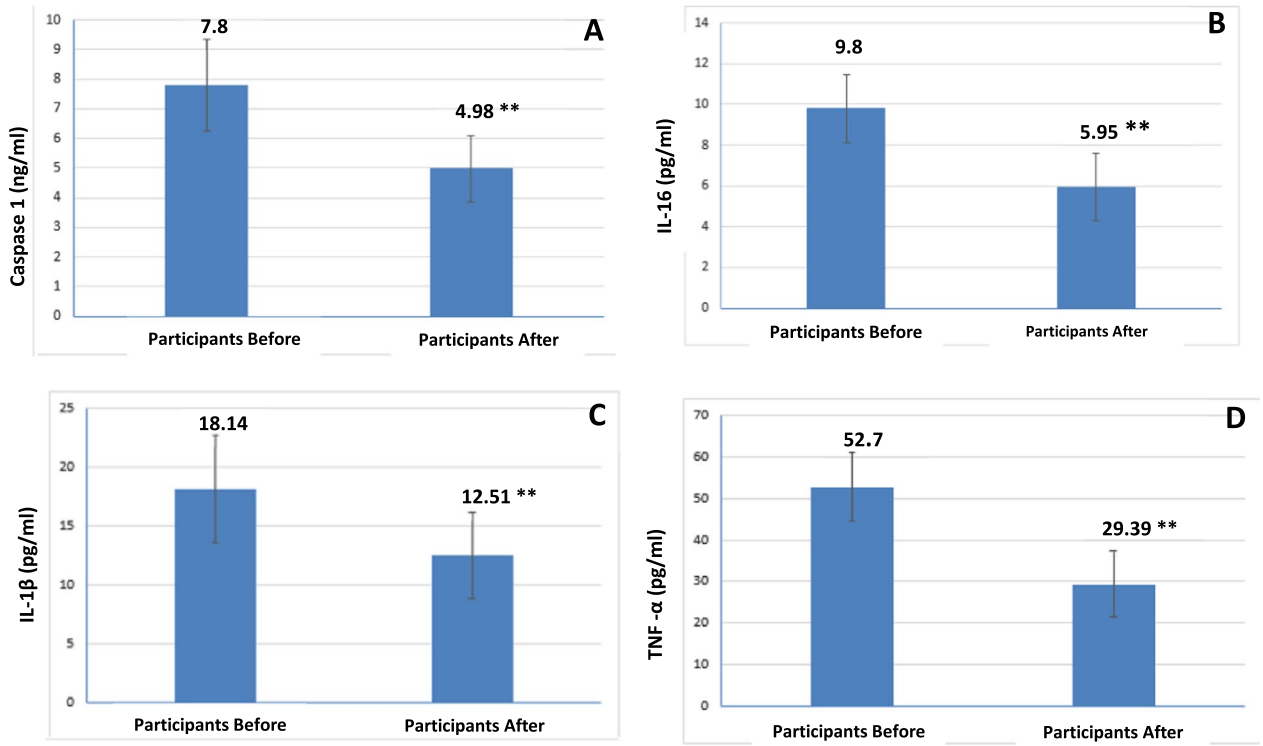

Fig. 5 **A–D** Comparison between inflammatory markers (**A**: Caspase-1; **B**: IL-6; **C**: IL-1β; & **D**: TNF-α) before and after EVOO receiving by the study group. IL-6: Interleukin-6; IL-1 ß: Interleukin-1 beta; TNF-α: Tumor Necrosis Factor Alpha. (n = 30). ** (*p* value: < 0.001) Significantly different as compared to the patient in the group before EVOO administration, using a paired t test for normally distributed quantitative variables, whereas using Wilcoxon signed-rank test for the nonparametric data

Table 1 Comparison between PedsQL domains of functioning before and after receiving EVOO

Score Item	Before	After
School	8.33 ± 5.45	89.79 ± 6.83 **
Emotional	10.00 ± 4.89	83.12 ± 13.97 **
Social	7.08 ± 5.50	84.17 ± 9.74 **
Physical	7.16 ± 3.96	96.48 ± 10.80 **

Data are expressed as mean ± SD (n = 30)

** Significantly different as compared to mean value in the group before EVOO administration using a paired t test was used for normally distributed quantitative variables, whereas the nonparametric Wilcoxon signed-rank test was employed for non-normally distributed quantitative variables (*p* value: < 0.001)

Therefore, EVOO with oleocanthal properties may be a viable natural remedy for immune-inflammatory disorders in the future [47, 48]. In the current study, after three months of daily EVOO consumption, a significant reduction in the number of FMF attacks was observed. The levels of NLRP3 showed a significant reduction. Additionally, the mean caspase-1, IL-6, IL-1β, and TNF-α levels also showed marked reduction and according to much scientific evidence this improvement may be due to the oleocanthal content of EVOO.

Several studies, both clinical and experimental, revealed novel, relevant pharmacological properties of OC in a range of inflammatory disorders. Mice fed an oleocanthal-rich diet in an animal model of collagen-induced arthritis demonstrated significantly lower levels of matrix metalloproteinase-3, IL-17, TNF-α, IL-1β, IFN-γ, and IL-6 than mice fed on diet lacking in oleocanthal [49]. The observation by Rosillo et al. [50] of a significant reduction in IL-1β-induced TNF-α and IL-6 release in human synovial SW982 cells after exposure to a polyphenolic extract primarily composed of oleocanthal and oleacein from EVOO lends credence to these results. These findings have been confirmed also by Scotece et al., who found that OC has an inhibitory effect on particular cellular pathways engaged during inflammation in human osteoarthritis. As a result, genes linked to inflammation, such as COX-2, MIP-1α, TNF-α, IL-6, IL-8, and lipocalin-2, were expressed less frequently. The study also showed that OC could stop the action of an inflammatory protein called macrophage inflammatory protein-1 alpha [48].

These results were consistent with earlier studies [51] that showed OC can suppress the upregulation of pro-inflammatory signaling molecules mediated by lipopolysaccharides, such as IL-6, IL-1β, TNF-α, macrophage inflammatory protein-1α, and granulocyte macrophage-colony stimulating factor (GM-CSF).

Furthermore, previous study suggested that phenolic components in EVOO have an anti-inflammatory and immunomodulatory role in systemic lupus erythematosus patients and may therefore be taken into consideration as a dietary component in the management of systemic lupus erythematosus [52]. Another study found that EVOO experienced synergistic analgesic, antipyretic, and anti-inflammatory properties when combined with ibuprofen in various albino mouse experimental models [53].

The current study findings indicate a significant improvement in the symptoms of abdominal aseptic peritonitis, which could be attributed to the capacity of oleocanthal present in EVOO to modulate peritoneal macrophages activation. This finding was supported by Montoya et al., who noticed that OC was able to attenuate macrophage activation induced by lipopolysaccharide via regulation of inflammasome: nuclear factor erythroid 2-related factor 2, and mitogen-activated protein-kinase signaling pathways.[51].

Furthermore, our findings also indicate a significant improvement in the school performance of the patients under study after three months of EVOO administration. This aligns with the research undertaken by Al Rihani et al., who demonstrated that EVOO rich in oleocanthal can restore the function of the blood–brain barrier and reduce Alzheimer's-associated pathology by inhibiting NLRP3 inflammasome, thereby reducing neuroinflammation [54].

The benefits of EVOO and its phenolic components are currently well understood. These benefits include their biological characteristics and antioxidant potential in thwarting immune-mediated inflammatory reactions. These include inflammatory bowel disease, cancer, diabetes, obesity, rheumatoid arthritis, atherosclerosis, and neurodegenerative disorders. The growing body of research conducted on this subject provides strong evidence, suggesting that olive polyphenols have the potential to be effective in addressing chronic inflammatory conditions. Furthermore, their potential clinical applications make them promising candidates in the fight against such inflammatory states.

Conclusion

Our study revealed that combining extra virgin olive oil, which is abundant in polyphenols, with the maximum tolerated dose of colchicine effectively reduced both the intensity and frequency of FMF attacks. Additionally, this treatment approach showed promising results in improving the overall quality of life for the patient. These findings provide hope for individuals with FMF, as it offers the potential for a better quality of life with reduced complications from the disease itself and the use of various biological therapies typically employed in FMF cases resistant to conventional treatments.

Limitations

It is a relatively short duration study, and it did not involve random assignment of participants to different groups (as it was pre- and post-study design). Furthermore, because all patients were recruited from a single hospital's Pediatric Rheumatology Outpatient Clinic, the findings of our investigation require confirmation in large multicenter prospective randomized future trials lasting considerably longer.

Abbreviations

FMF	Familial Mediterranean fever
EVOO	Extra virgin olive oil
CRFMF	Colchicine-resistant familial Mediterranean fever.
ESR	Erythrocyte sedimentation rate
SAA	Serum amyloid A
CRP	C-reactive protein
NLRP3	Nucleotide-binding domain, Leucine-Rich-containing family, Pyrin domain-containing-3
IL-6	Interleukin-6
IL-1 ß	Interleukin-1 beta
TNF-α	Tumor Necrosis Factor Alpha
MEFV	Familial Mediterranean fever gene
PRRs	Cytosolic pattern recognition receptors
IL-18	Interleukin-18
EULAR	European Alliance of Associations for Rheumatology
OC	Oleocanthal
ADAMTS-5	ADAM Metallopeptidase with Thrombospondin Type 1 Motif
NF-kB	Nuclear Factor Kappa Beta
DMARDS	Disease Modifying Antirheumatic Drug
QOL	Evaluation of quality of life
GM-CSF	Granulocyte–macrophage–colony-stimulating factor
Nrf-2	Nuclear factor erythroid 2-related factor 2
MAPKs	Mitogen-activated protein kinase

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Author contributions

WO designed the work. WO, HT, HA, and HD all contributed to data gathering and analysis. WO, HA, DL, HT, HD, MA, and OS wrote the original draft; supervision, material procurement, and facility support were supplied by all authors, as was the final text.

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Availability of data and materials

The corresponding author can provide data supporting the study's conclusions upon reasonable request.

Declarations

Ethics approval and consent to participate

The study has been approved by the Clinical Research Ethics Committee (N.320.2023) of Cairo University. All participants provided informed written permission after explaining the study aims and before the blood sample. The confidentiality of patient data was assured.

Consent for publication

Not applicable.

Competing interests

No competing interest to disclose.

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