applied sciences

MDPI

Article

Effect of Different Nuts Oil Consumption on Morphological Features and Some Biomarkers of Inflammation in Adjuvant-Induced Arthritis (AIA) Rat Model

Samiyah K. Al-Shammari, Doha M. Al-Nouri, Shaista Arzoo and Laila Naif Al-Harbi *

Department of Food Science and Nutrition, College of Food Science and Agriculture, King Saud University, Riyadh 11451, Saudi Arabia
* Correspondence: lalharbi1@ksu.edu.sa

Abstract: This study evaluated the protective effect of different dietary ω-6/ω-3 ratios in oils obtained from various nuts (walnut, peanut, cashew, and hazelnut) against morphological features and markers of inflammation on an adjuvant-induced arthritis rat model. Rheumatoid arthritis (RA) was induced via intradermal injection of heat-killed *Mycobacterium tuberculosis*. Five groups of rats with RA ($n = 5$) were randomly categorized as follows: control positive, walnut oil group, peanut oil group, cashew nut oil group, and hazelnut oil group. Another five healthy rats served as a normal non-arthritic (control) group. We assessed the therapeutic effects by measuring arthritis scores during the experiment and serum inflammatory markers at the end of the study. The serum levels of the rheumatoid factor, TNF-α, IL-6, IL-1β, and PGE2, were significantly ($p \leq 0.05$) reduced in all treatment groups. The daily consumption of nut oils ameliorates clinical and morphological abnormalities by inhibiting the inflammatory cells that produce inflammatory interleukins and eicosanoids.

Keywords: rheumatoid arthritis; inflammation; nuts; adjuvant-induced arthritis; cytokines

Citation: Al-Shammari, S.K.; Al-Nouri, D.M.; Arzoo, S.; Al-Harbi, L.N. Effect of Different Nuts Oil Consumption on Morphological Features and Some Biomarkers of Inflammation in Adjuvant-Induced Arthritis (AIA) Rat Model. *Appl. Sci.* **2023**, *13*, 3318. https://doi.org/10.3390/app13053318

Academic Editors: António José Madeira Nogueira and Andrea Luísa Fernandes Afonso

Received: 19 January 2023
Revised: 1 March 2023
Accepted: 3 March 2023
Published: 5 March 2023

1. Introduction

Rheumatoid arthritis (RA) is very common auto-inflammatory disease in middle-aged individuals [1]. The disease pathogenesis involves a complex interaction between different cell types including resident fibroblast, infiltrating macrophages, B-cells, and T-cells [2]. As a result of the overproduction of inflammatory cytokines and the suppression of anti-inflammatory markers, these cells exacerbate the inflammatory response which causes synoviocytes to hyperproliferate (hyperplasia), the synovial tissue to become inflamed (synovitis), as well as cartilage and bone destruction [3,4]. A lack of balance between inflammatory and anti-inflammatory cytokines is responsible for RA [1].

The clinical complications include the destruction of the synovial lining and tendon sheaths of diarthrodial joints of the hands and feet, which leads to joint and bone deformities [3,4]. It is currently largely accepted that RA is associated with increased levels of several inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β. RA is related to the suppression of numerous anti-inflammatory cytokines such as IL-10 [5]. The mechanisms by which these molecules affect RA are well-established [5–7]. However, recent reports suggest emerging roles of ω-3 and ω-6 fatty acids (FAs) in the pathogenesis and protection against RA. It is currently well established that ω-3PUFAs as well as monounsaturated fatty acids (MUFAs) can protect and prevent the development and progression of RA [8]. According to a recent systematic review, the ω-3 FAs may reduce pain and disease activity in patients with RA when consumed in higher amounts [9]. Clinical studies have shown that ω-3 FAs may reduce disease activity in RA [10,11]. Omega-3 fatty acids may also have an anti-inflammatory action and decrease disease activity in RA.

Indeed, ω-6 PUFAs exert a pro-inflammatory action mediated by reduced levels of ω-3 PUFA, thus generating an excess of inflammatory prostaglandins (PGs), thromboxanes (TX), and leukotrienes (LTs) through the metabolism of the arachidonic acid (ARA) [12–14].

In contrast, ω-3 PUFAs are anti-inflammatory agents that suppress the inflammatory cytokines production by obstructing T-cell proliferation and activating transcription factors and peroxisome proliferator-activated receptor α (PPARα) [13]. Likewise, the MUFAs' anti-inflammatory effect is largely attributed to a decreased activity and proliferation of the lymphocytes, the reduced expression of adhesion molecules on the blood mononuclear cells (BMNCs), and the suppression of IL-1 and LB4 [15]. Therefore, diets rich in ω-3 PUFAs and MUFAs are an important target in RA therapy.

Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs [16]. It is currently well established that nuts can exert potent anti-inflammatory and antioxidant effects due to their high content of many macro- and micro-nutrients, including ω-3 PUFAs, MUFAs, dietary fibers, minerals, and vitamins. Walnuts are very rich in ω-3 PUFAs, whereas the other nuts are very rich in MUFAs [17,18]. The nutritional characteristics of nuts can be beneficial to human health, notably when it comes to the management of diseases. Furthermore, the addition of these foods in the diet promotes the improvement of dietary quality since they contain MUFAs, PUFAs, proteins, fibers, vitamins, minerals, and bioactive compounds with antioxidant properties [19].

Previous reviews and clinical and epidemiological trials have suggested that the steady consumption of nuts has positive health effects, such as reducing mediators of chronic diseases such as inflammation and oxidative stress [20]. The addition of walnut paste in meat and meat products may reduce the soluble cell adhesion molecules (sVCAM-1 and sICAM-1, respectively) and proinflammatory leukotriene B4 [21]. In healthy young adults, walnut-enriched meals enhance postprandial adiponectin response and even decrease the expression of TNF-α and IL-6 afterward [22]. Cashew nuts reduce myeloperoxidase malondialdehyde and block pro-inflammatory cytokine response and nitrate/nitrite formation [23]. The oral intake of cashew nuts has been shown to counteract the intricate inflammatory and oxidative process in osteoarthritis [24].

Changes in the inflammatory state can be recognized via biomarkers of inflammation including TNF-α, IL-6, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion protein 1 (VCAM-1) [25]. Increased nut consumption was significantly associated with lower c-reactive Protein (CRP), IL-6, and tumor necrosis factor receptor 2 (TNFR2) [26]. The associations between nut intake and amounts of CRP and IL-6 were attenuated after adjusting for BMI [27]. Leukotrienes (LTs) and prostaglandins are biologically extremely active and are characterized by pro-inflammatory activity [28]. Somewhat surprisingly, the effectiveness of nut oils against RA is rarely investigated in human or animal models. Therefore, this study evaluated the effect of different nuts' oil (walnut, hazelnut, peanut, and cashew) on the morphological features and biomarkers (rheumatoid factor (RF), tumor necrosis factor (TNF-α), interleukins (IL-1β, IL-6), and prostaglandin E2 (PGE2)) of inflammation in an adjuvant-induced arthritis (AIA) rat model.

2. Materials and Methods

2.1. Chemicals and Oils

Complete Freund's adjuvants (CFAs) (Cat. No. 7024, 10 mg/mL) containing heat-killed *Mycobacterium tuberculosis*, were purchased from Chondrex, Woodinville, WA, USA. Walnut oil was purchased from The National Edible Oil Distributors Association (NEODA) (Catalogue Number, X001T3Y4VJ), China. Peanut oil was purchased from Dr. Adorable Inc. (Catalogue Number, 731086419133), Chicago, IL, USA. Cashew oil was purchased from Devi Traders, Virudhunagar, Tamil Nadu (Catalogue Number, ALGPN5477K1ZO33), India. Hazelnut oil was purchased from Basel Detox Natural Herbs and oils, Jordan. The compositions of the FAs in the walnuts, peanuts, cashew, and hazelnuts are shown in Table 1 as provided by the manufacturers.

Table 1. Fatty acids composition of different oils used in this study (g/100 g oil).

FAs	Walnut Oil	Peanut Oil	Hazelnut Oil	Cashew Oil
C(14:0)	2.7	0.0	-	0.70
C(16:0)	7.2	8.9	5.6	0.53
C(16:1)	0.2	0.1	0.2	0.05
C(17:0)	0.1	0.1	0.1	-
C(17:1)	0.0	0.1	0.1	-
C(18:0)	2.7	2.6	2.5	4.88
C(18:1), n-9	15.2	51.3	72.7	84.36
C(18:1), n-7	1.3	1.3	2.4	-
C(18:2), trans	0.3	0.2	0.1	-
C(18:2), n-6	57.1	23.5	12.9	8.68
C(18:3), trans	0.5	-	-	-
C(18:3), n-6	-	-	-	-
C(18:3), n-3	11.9	0.2	0.4	0.13
C(20:0)	0.1	1.2	0.2	0.36
C(20:1), n-9	0.2	1.5	0.2	-
C(20:2), n-6	-	-	-	-
C(22:0)	0.1	2.5	0.0	0.14
C(22:1), n-9	-	0.1	-	-
C(24:0)	-	1.4	-	0.52
SFA	12.9	16.7	8.4	7.13
MUFA	16.9	54.4	75.6	84.41
PUFA	69.8	23.9	13.4	8.81
PUFA n-3	11.9	0.2	0.4	0.13
PUFA n-6	57.1	23.5	12.9	8.68
n6/n3 ratio	4.8	117.5	32.25	66.77
trans-FA	0.8	0.2	0.1	-
Total FA	99.6	95	97.4	100.35

2.2. Animals

Thirty adult male Wistar Albino rats (*Rattus norvegicus*) (9 weeks old, weighing 230 ± 10 g) were obtained from the Experimental Surgery and Animal Laboratory, College of Medicine, King Saud University (KSU), Riyadh, Saudi Arabia (KSA). This experiment was conducted at the Experimental Surgery and Animal Laboratory of the College of Medicine at KSU. This study was conducted in compliance with the ethical principle of the Declaration of Helsinki. This study was approved by King Saud University (Reference #: KSU-SE-19-37), and the study is in accordance with the Policy of the Research Centre. All rats were always housed under controlled conditions (temperature = 22 ± 1 °C, humidity = 59%, and 12/12 h light/dark cycle) in polypropylene cages. Standard diet (4RF21 certificate) obtained from (Mucedola, s.r.l, Settimo Milanese, Milano, Italy) and tap water were offered ad libitum during the experimental period. Animals were acclimatized to the laboratory environment for 7 days before the experiment began.

2.3. Adjuvant-Induced Arthritis (AIA) Rat Model

The adjuvant-induced arthritis (AIA) model is one of the most commonly used standard arthritis models to induce RA in rats [29]. The manifestations induced by this protocol in rats are very similar to the clinical manifestations of RA [29]. The Sprague Dawley and Wistar rats are higher-responding strains than mice, other strains of rats, and other rodents. Control rats were injected with normal saline. The adjuvant was first emulsified with an equal volume of saline with a homogenizer (30 s and then cooled in ice) to produce a final concentration of 10 mg/mL. Each rat was injected with emulsified CFA (subcutaneously inject 0.1 mL of CFA containing 10 mg/mL of heat- killed *Mycobacterium tuberculosis* (MT) at the base of the tail as per the method established by Ablin et al. [29]. Using this protocol, severe arthritis usually develops in one or all paws between days 12 and 14 and often reaches the maximum between days 20 and 25, as recommended. Figure 1 illustrates the method used to induce RA and the clinical findings during this procedure.

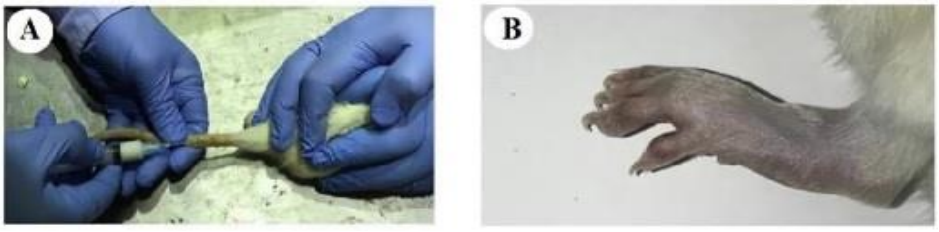

Figure 1. Induction of adjuvant-induced arthritis (AIA) and the progression of RA in the model rats. (**A**) Injection of the complete Freund's adjuvants (CFAs) containing heat-killed *M. tuberculosis* emulsification reagent at 1.5–2 cm from the base of the tail. (**B**) the progression of arthritis (swelling, redness, and joint deformities) on the first day of consuming the diet.

2.4. Experimental Diet

A fat-free diet was purchased from Dyets (AIN-93M, Bethlehem, PA, USA). The American Institute of Nutrition Rodent Diets has been used extensively around the world. Young animals from age 3–7 weeks need about twice of what is needed for adult maintenance in terms of energy requirements. The AIN-93M formula is used for adult maintenance while AIN-93G is used for growth, pregnancy, and lactation. Due to a better balance of essential nutrients, AIN-93 diets may be a better choice than others for long-term and short-term studies with laboratory rodents [30]. Each oil was separately and mixed with the diet (5% fat by adding 50 g/kg nut oils) [31] using a machine designated for mixing. Five percent fat is the minimum requirement for all stages of life [32,33]. The mixing machine was cleaned after contact with each of the nut oils. For the control groups, the same diet was mixed with 5% fat and 50 g/kg soybean oil instead of the nut oils. This process was repeated every week to produce the diets used in the experimental procedure. The composition of each diet is shown in Table 2.

Table 2. Formulation of the AIN-93M * diet for maintenance of adult rats.

Ingredient	Control	Walnut	Peanut (g/kg)	Cashew	Hazelnut
Corn starch	465.692	465.692	465.692	465.692	465.692
Casein	140	140	140	140	140
Maltodextrin	145	145	145	145	145
Sucrose	100	100	100	100	100
Soybean	50	-	-	-	-
Walnut oil	-	50	-	-	-
Peanut oil	-	-	50	-	-
Cashew oil	-	-	-	50	-
Hazelnut oil	-	-	-	-	50

Table 2. *Cont.*

Ingredient	Control	Walnut	Peanut (g/kg)	Cashew	Hazelnut
Cellulose	50	50	50	50	50
Minerals mix1	35	35	35	35	35
Vitamin mix2	10	10	10	10	10
L-Cystine	1.8	1.8	1.8	1.8	1.8
Choline Bitartrate	2.5	2.5	2.5	2.5	2.5
TBHQ **, antioxidant	0.008	0.008	0.008	0.008	0.008

* AIN-93M: American Institute of Nutrition; ** TBHQ: tert-Butylhydroquinone.

2.5. Experimental Groups

All animals consumed a normal diet during the first seven days of acclimatization, and they were then injected with CFAs and left for 15 days (consuming a normal diet), which is the period required to induce AIA. On day 16, the rats began to consume the experimental diet and continued for 30 days. The total duration of the study was 45 days starting from the day of injection until the last day of feeding. The rats were divided into six groups (each with five rats) as follows:

1. Control group: normal rats + normal diet;
2. AIA-RA model group: RA rats + normal diet;
3. AIA + walnut oil: RA rats + diet with walnut oil;
4. AIA + peanut oil: RA rats + diet with peanut oil;
5. AIA + cashew oil: RA rats + diet with cashew oil;
6. AIA + hazelnut oil: RA rats + diet with hazelnut oil.

Food cups were refilled every day, and the provided and remaining food was weighed to calculate daily food consumption (DFC) and total food consumption (TFC). Initial and final body weight was recorded in the non-fed state to calculate weight gain (WG). The food efficiency (FE) was also calculated.

DFC (g) = Food provided (g) − Food remaining (g)
TFC (g) = Σ DFC
WG (g) = Final wt. (g) − Initial wt. (g)
FE = WG ÷ TFC

2.6. Evaluation of Body Weights and Arthritis

RA severity in all rats was assessed by body weight changes and by recording the arthritis score of four paws every three days for 30 days from the first day of the experiment when they started consuming the experimental diet until its completion. The evaluation described by Cuzzocrea et al. [34] for classifying the severity of the AIA on a scale of 0–4/paw (an overall 16 for the four paws) was followed to measure the arthritis score. A score of 0.0 indicates no swelling or redness; a score of 1 indicates redness or swelling in one paw or digit (one joint); a score of 2 indicates redness and swelling in two digits or joints; a score of 3 shows swelling and redness in more than two digits or joints; and a score of 4 indicates swelling and redness in all joints or digits or the entire paw.

2.7. Blood Collection

By the end of the experiment, all rats fasted for 12 h and were anesthetized with pentobarbital sodium (50 mg/kg, v/v, intraperitoneal) which is a short-acting barbiturate sedative–hypnotic and it shuts down their heart and brain functions usually within one or two minutes and leads to the rapid onset of coma and perception of a peaceful death. A 2-person technique (one holder and one injector) has been used in this study as it leads to reduction in the misinjection rate [35]. Due to the possibility that the euthanasia protocol may affect physiological variables and genes' expression, sodium pentobarbital overdose should be avoided during euthanasia in order to prevent interference with

biochemical, molecular, and histological measurements [36]. Blood samples (2 mL) were directly collected from the heart by cardiac puncture into plain tubes. After the blood was drawn, it was left for 15 min at room temperature until clotting formed after which it was put in a centrifuge at 1912× *g* for 10 min at room temperature to collect the serum. This serum was stored at −20 °C and used later for the biochemical analysis to determine the levels of RF, TNF-α, IL-6, IL-1β, and PGE2.

2.8. Measurement of the Inflammatory Indicators in the Blood

2.8.1. Rheumatoid Factor (RF) Level

Serum levels of RF were measured by a sandwich ELISA kit (My Biosource Company, San Diego, CA, USA, Catalogue Number, MBS702417) as instructed by the kit manufacturer. This assay has no cross-reaction with other factors and its sensitivity was typically less than 3.9 mIU/mL.

2.8.2. Measurement of Tumor Necrosis Factor-α

The levels of TNF-α were measured by sandwich ELISA kit (My Biosource Company, USA, Catalogue Number, MBS267737) as per the manufacturer's instructions. This assay has no cross-reaction with other factors and its sensitivity was up to 5 pg/mL.

2.8.3. Measurement of Interleukin-6

The level of IL-6 was measured by a sandwich ELISA kit (My Biosource Company, USA, Catalogue Number, MBS269892) as per the manufacturer's instruction. The sensitivity of this assay was up to 5 pg/mL and it has no cross-reaction with other factors.

2.8.4. Measurement of Interleukin-1β

The level of IL-1β was measured by sandwich ELISA kit (My Biosource Company, USA Catalogue Number, MBS 264984) as per the manufacturer's instructions. This assay has no cross-reaction with other factors and its sensitivity was up to 5 pg/mL.

2.8.5. Measurement of Prostaglandin E2

The level of PGE2 was measured using an ELISA detection kit (My Biosource Company, USA, Catalogue Number, MBS262150) as per the manufacturer's instructions and allocated in duplicate of the pre-coated plate. This assay has no cross-reaction with other factors and its sensitivity was up to 5 pg/mL.

2.9. Statistical Analysis

The results are described as means ± SD. Normality was verified by using the Shapiro–Wilk test using SPSS software. Statistical data were examined using a one-way analysis of variance (ANOVA) with a statistical significance assumed at $p \leq 0.05$. If the *p*-value was statistically significant, then the study groups were further compared using Tukey's HSD post hoc test. All statistical data were analyzed using Statistical Package for the Social Sciences software (SPSS version 22. Inc., Chicago, IL, USA).

3. Results

3.1. Effect of Different Nuts' Oil on Food Consumption and Growth Indicators in Adjuvant-Induced Arthritis (AIA) Rat Model

Figure 2A–E presents changes in TFC, food efficiency, initial and final body weight, as well as weight gain in all groups of rats. The animal model was validated by changes in the final body weights of rats during the induction of AIA as well as one month later. The difference in TFC was insignificant ($p = 0.714$) between the groups. The TFC (Figure 2A) in the control group, AIA group, AIA + walnut oil, AIA + and peanut oil, AIA + cashew nut oil, and hazelnut oil groups was 129.6 ± 10.407 g, 131.2 ± 11.077 g, 131.2 ± 17.513 g, 127.6 ± 10.237 g, 120.8 ± 5.119 g, and 126.4 ± 11.393 g, respectively. In addition to an increase in the FE (Figure 3B) of the oil groups, the increase in the AIA group (1.758 ± 0.218%)

was reported versus the control group (0.843 ± 0.154 g). The highest oil groups in terms of nutritional efficiency were the cashew nut oil group (1.598 ± 0.178%) followed by the AIA + hazelnut oil (1.407 ± 0.273%), AIA +walnut oil (1.195 ± 0.115%), and AIA + peanut oil (1.083 ± 0.073%) groups.

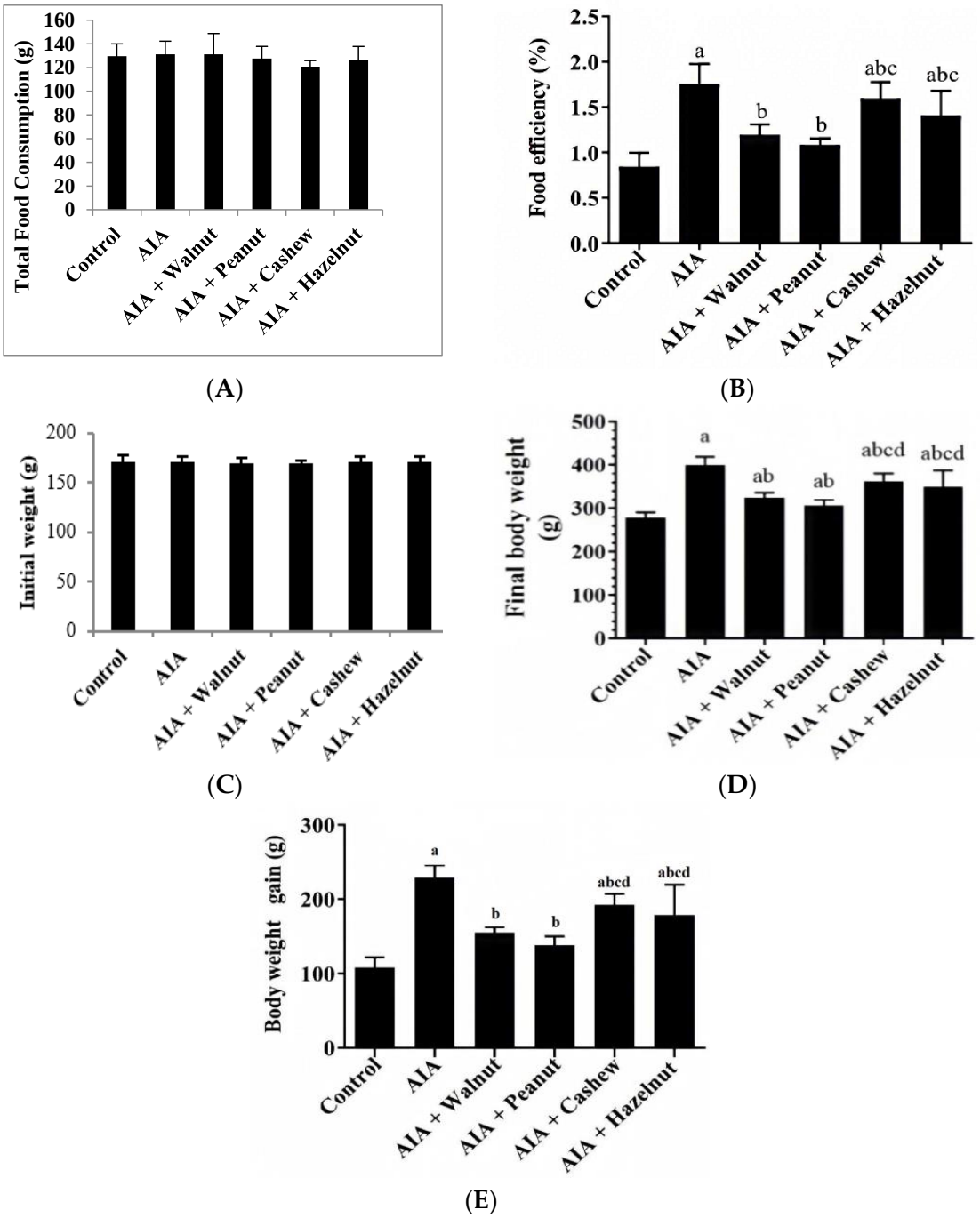

Figure 2. Changes in total food consumption (**A**), food efficiency (**B**), initial body weight (**C**), final body weight (**D**), and weight gain (**E**) in all groups of rats. Model: One-way analysis of variance (ANOVA) with a statistical significance assumed at $p \leq 0.05$ followed by Tukey's HSD post hoc test for statistically significant *p*-value. Data are presented as mean ± SD for $n = 5$ rats/groups. a: Significantly different from the control rats. b: Significantly different from the adjuvant-induced arthritis model rats (AIA). c: Significantly different from AIA + walnut oil. d: Significantly different from AIA + peanut oil.

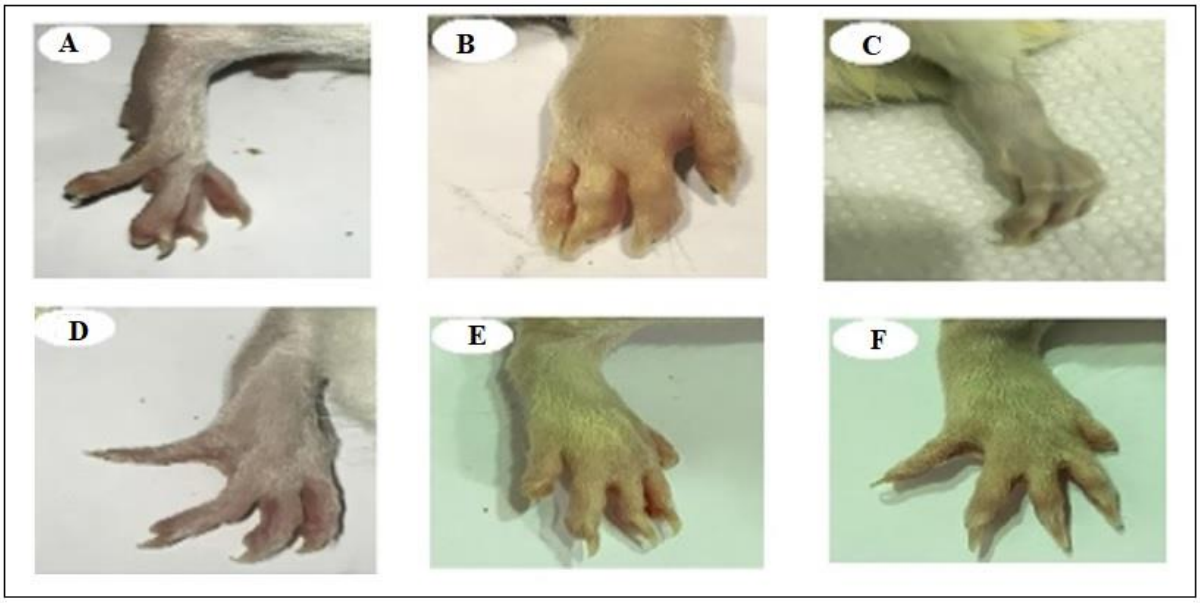

Figure 3. Effect of different nuts' oil on the morphological appearance of the back paw from all groups of rats. (**A**) (Control rats): shows normal appearance of the digits, and joint with no redness or swelling. (**B**) (AIA rats): shows severe swelling in the whole paw including the digits with deformities in all-paw digits. (**C**) (AIA + Walnut) and (**D**) (AIA + peanut): shows almost normal appearance of the back paws with reduced swelling and deformities in most of all digits. (**E**) (AIA + Cashew) and (**F**) (AIA + Hazelnut): shows improvement in the deformities of the digits but with the presence of some swelling.

Most of the growth indicators in the AIA group significantly changed versus those in the control group, although the rate of diet consumption was very similar among all groups. Although insignificant (p = 0.977), differences have been observed in terms of initial weight (Figure 2C) between all groups, but the AIA rats exhibited a significant (p = 0.00) increase in their final body weight versus the control group and rats in the nut oil groups (Figure 2D). All diet oils, including walnut, peanut, hazelnut, and cashew, significantly reduced the final body weights relative to the AIA model rats (400 ± 18.775 g). The maximum improvement in weight loss was seen among rats fed peanut and walnut oil. A significant (p = 0.00) increase in the weight gain of rats (Figure 3E) was observed in the AIA group (229 ± 16.897 g), while the increase in weight was only 108.2 ± 13.719 g in the control group. However, the body weight gain of rats in the AIA + peanut oil group (138 ± 12.247 g) and in the AIA + walnut oil group (155.2 ± 7.362 g) was significantly (p = 0.00) lesser than those in the AIA group. Similarly, the body weight gain in the AIA + hazelnut oil group (178.6 ± 40.906 g) and in the AIA + cashew nut oil group (192.4 ± 15.093) was also significantly (p = 0.094, p = 0.009, respectively) lesser than those in the AIA group.

3.2. Effect of Different Nuts' Oil on the Morphological Appearance in Adjuvant-Induced Arthritis (AIA) Rat Model

Figure 3A–F shows the morphological appearance of the back paw in all groups of rats. Swelling, redness, and stiffness in digits, as well as joint deformities, were observed in AIA-induced rats (Figure 3B) fed a normal diet versus control rats (Figure 3A) fed a normal diet. Feeding the rats a diet rich in walnut, peanut, cashew, and hazelnut oils significantly reduced the degree of redness, swelling, joint deformities, and paw pain in all AIA-induced rats (C–F) versus AIA-induced rats fed on a normal diet containing soybeans as a fat source (B).

3.3. Effect of Different Nuts' Oil on Arthritis Score and Rheumatoid Factors (RFs) in Adjuvant-Induced Arthritis (AIA) Rat Model

Figure 4A illustrates the changes in arthritis scores in AIA rats. AIA rats displayed a significant (p = 0.00) increase in their arthritis score versus the control group and rats in the nut oil groups. Although a reduction in the arthritis score has been observed in the AIA + walnut oil group (1.67 ± 0.650) and the AIA + peanut oil group (1.87 ± 0.361), the difference in arthritis score between these two groups was insignificant (p = 0.996) The arthritis scores in the AIA + cashew oil (5.97 ± 0.680), and the AIA + hazelnut oil (6.82 ± 0.527) groups were also significantly (p = 0.00) lesser than in the AIA rats.

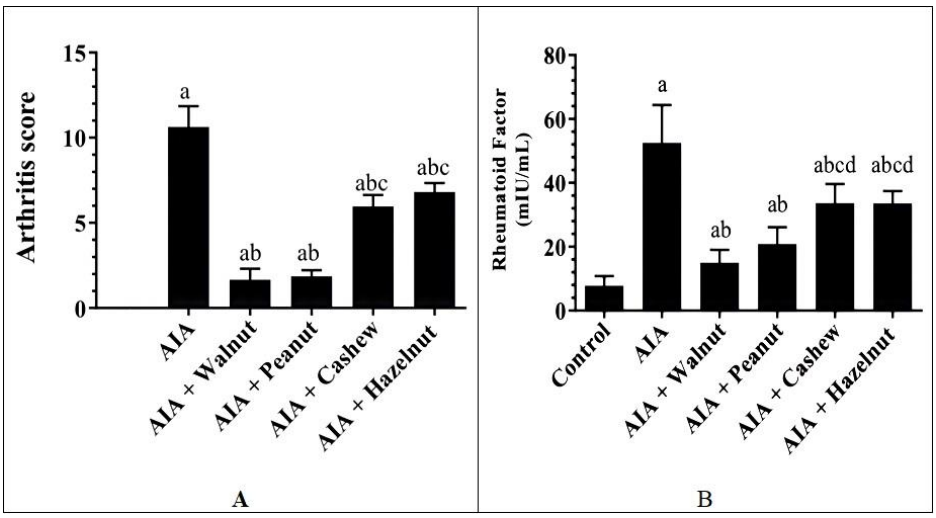

Figure 4. Effect of different nuts' oil on arthritis score (**A**) and serum levels of rheumatoid factors (**B**) in adjuvant-induced arthritis (AIA) rats. The arthritis score was calculated on a scale of 0–4/paw (an overall of 16 for the four paws). Accordingly, score 0.0: swelling or redness; score 1: redness or swelling in one paw or digit (one joint); score 2: redness and swelling in 2 digits or joints; score 3: swelling and redness in more than two digits or joints; and score 4: swelling and redness in all joints or digits or the entire paw. Model: One-way analysis of variance (ANOVA) with a statistical significance assumed at $p \leq 0.05$ followed by Tukey's HSD post hoc test for statistically significant p-value. Data are presented as mean ± SD for n = 5 rats/groups. a: Different from the control rats. b: Significantly different from the adjuvant-induced arthritis model rats (AIA). c: Significantly different from AIA + walnut oil. d: Significantly different from AIA + peanut oil.

Figure 4B shows the effects of all treatments on the RF in all experimental groups. Serum levels of RF were significantly (p = 0.00) increased in the AIA model rats versus the controls. However, the RF levels were significantly ($p \leq 0.05$) decreased in the rat groups that received walnut, peanut, cashew, and hazelnut oils versus the AIA group (52.478 ± 11.859 mIU/mL). The maximum decrease in the levels of RF was seen in the AIA + walnut oil (14.965 ± 4.080 mIU/mL) and AIA + peanut oil (20.845 ± 5.283 mIU/mL) groups with no significant (p = 0.862) difference between the two groups. The results were nearly the same for the two groups of AIA + cashew oil (33.612 ± 6.024 mIU/mL) and AIA + hazelnut oil (33.539 ± 3.925 mIU/mL); there was insignificant (p = 1.00) difference between them.

3.4. Effect of Different Nuts' Oil on Serum Levels of Pro-Inflammatory Cytokines in Adjuvant-Induced Arthritis (AIA) Rat Model

Figure 5A–C lists the effects of different nut oils on pro-inflammatory cytokines. As confirmed by the CFA-induced arthritis model, the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β significantly increased ($p \leq 0.05$) in the AIA group versus the control group. The levels of all these markers reduced in the nut oil groups, which received the walnut, peanut, cashew, and hazelnut oils versus the AIA model rats. Parallel with the

previous observations in terms of RF results, the maximum decrease in the levels of TNF-α was observed in the rats that received AIA + walnut oil (111.482 ± 23.284 pg/mL) and AIA + peanut oil (122.485 ± 9.813 pg/mL) with no significant (p = 0.974) difference in any of these parameters between the two groups. The TNF-α also decreased in AIA + hazelnut oil (143.085 ± 14.842 pg/mL) and the AIA + cashew nut oil (183.721 ± 27.419 pg/mL). The maximum decrease in the levels of IL-6 was observed in the groups of rats that received AIA + walnut oil (138.60 ± 35.748 pg/mL) followed by the AIA + peanut oil (164.16 ± 48.261 pg/mL) versus AIA group (344.72 ± 58.827 pg/mL). The IL-1β level decreased in all treatment groups, but the lowest level was observed in the AIA + peanut oil (121.58 ± 37.45 pg/mL) and AIA + walnut oil (122.69 ± 34.07 pg/mL) groups, although the difference was insignificant (p = 1.000) among them. A significant ($p \leq 0.05$) decrease in the AIA + cashew nut oil (210.36 ± 31.69 pg/mL) and the AIA + hazelnut oil (235.69 ± 37 ± 59 pg/mL) groups versus the AIA group (263.41 ± 52.29 pg/mL) has also been observed, but the difference was insignificant (p = 0.890).

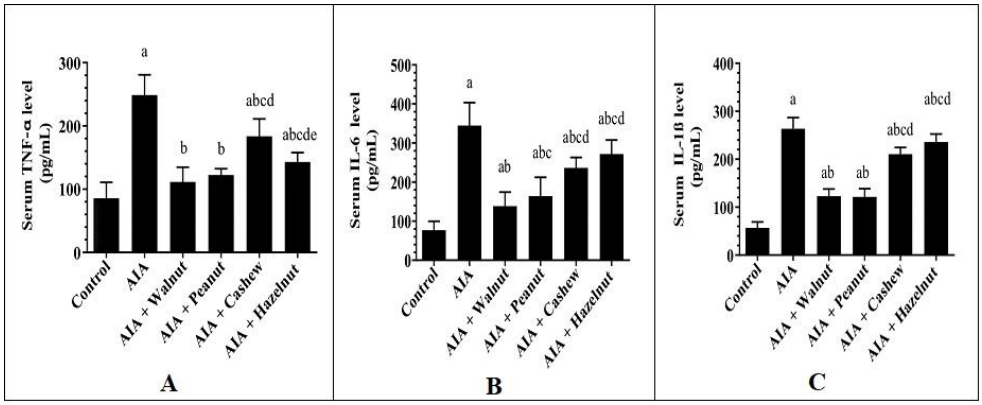

Figure 5. Effect of different nuts' oil on serum levels of pro-inflammatory cytokines TNF-α (**A**), IL-6 (**B**), and IL-1β (**C**) adjuvant-induced arthritis (AIA) rats. Model: One-way analysis of variance (ANOVA) with a statistical significance assumed at $p \leq 0.05$ followed by Tukey's HSD post hoc test for statistically significant p-value. Data are presented as mean ± SD for n = 5 rats/groups. a: Different from the control rats. b: Significantly different from the adjuvant-induced arthritis (AIA) model rats. c: Significantly different from AIA + walnut oil. d: Significantly different from AIA + peanut oil. e: significantly different from AIA + cashew nut oil.

3.5. Effect of Different Nuts' Oil on Serum Levels of Prostaglandin E2 in Adjuvant-Induced Arthritis (AIA) Rat Model

Figure 6 summarizes the effect of different oils on PGE2. The serum levels of PGE2 were significantly (p =0.00) increased in AIA model rats versus control rats. The levels of PGE2 were significantly ($p \leq 0.05$) decreased in the AIA-treated rats, which received the walnut, peanut, cashew, and hazelnut oils. The maximum decrease in the levels of PGE2 was shown in AIA + walnut oil (59.78 ± 12.66 pg/mL) and AIA + peanut oil (72.88 ± 13.58 pg/mL)-treated rats versus AIA-induced rats (168.57 ± 31.49 pg/mL). However, no significant (p = 0.838) variation in the levels of PGE2 was noticed in the AIA + walnut and AIA + peanut-treated rats, and their levels were higher than in the control group. Similarly, no significant (p = 1.00) differences in the level of PGE2 were noticed between AIA + cashew oil (96.26 ± 8.75 pg/mL) and AIA + hazelnut-treated rats (99.32 ± 13.55 pg/mL).

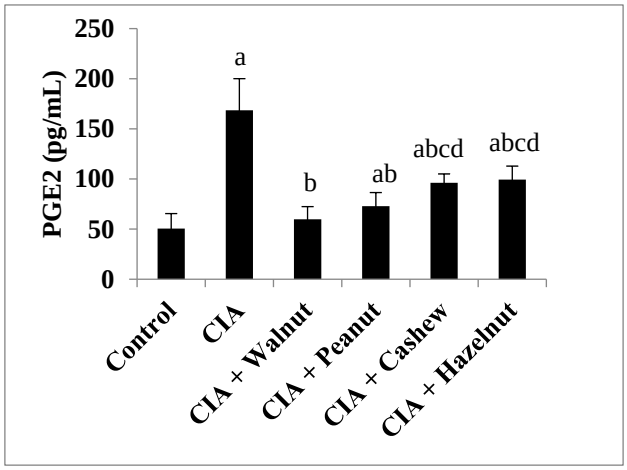

Figure 6. Effect of different nuts' oil on serum levels of prostaglandin-E2 (PGE2) in adjuvant-induced arthritis (AIA) rat. Model: One-way analysis of variance (ANOVA) with a statistical significance assumed at $p \leq 0.05$ followed by Tukey's HSD post hoc test for statistically significant p-value. Data are presented as mean $\pm$ SD for $n = 6$ rats/groups. a: Significantly different from the control rats. b: Significantly different from the adjuvant-induced arthritis (AIA) model rats. c: Significantly different from AIA + walnut oil. d: Significantly different from AIA + peanut oil.

4. Discussion

RA is a chronic, systemic, and autoimmune disorder characterized by symmetric, erosive synovitis and, in some cases, extra-articular involvement [37]. There is a tendency for patients to experience a chronic fluctuating course of disease that may lead to progressive deformity and disability as a result of progressive joint destruction despite standard treatment [38,39]. The pathogenesis and pathological manifestations of the adjuvant arthritis rat model are similar to those of human RA [34]. This study is the first to examine the therapeutic effect of nut oils with a high content of PUFAs as an anti-inflammatory effect on RA.

Females are at higher risk to develop RA [40,41] [but Tuncle et al. [42] [have shown no variations between male and female rats in the development and progression of CIA. Moreover, there were no significant differences between RA males and females in response to anti-inflammatory drugs such as dexamethasone [43] However, age is an important factor that plays a key role in the early development of experimentally induced CIA in rodents. Indeed, younger rats demonstrated an earlier onset but similar progression and severity as compared to older rats [42] [The study results revealed a significant increase in the final body weights and arthritis index of the rats in the AIA group. Nevertheless, since the food intake was not changed in all groups of rats, our data indicated that the weight gain in the AIA rats was caused by inflammation and swelling. Shamlan et al. [44] also reported increased body weight in the control arthritic group as compared to the normal group in his study on the antiarthritic, anti-inflammatory activity of Moringa peregrina seed oil and leaves in Freund's complete adjuvant-induced arthritis in rats. In this study, we particularly used young male rats to induce RA and to monitor the therapeutic effect of nut oils. Nut fats are enclosed within cell membranes, which are not readily available to digestive enzymes. Therefore, the properties of nut cell walls and their fiber-rich skins may be responsible for the rate and extent of lipid release. Therefore, the proposed mechanism of lesser weight gain with peanut includes a reduced level of lipid bio accessibility due to it [45].

Dietary-induced changes in tissue levels of PUFAs modify inflammatory reactions through changes in the synthesis of lipid and peptide mediators of inflammation [8]. A positive correlation has been reported previously between BMI and inflammation where each can affect the other [46,47]. Any increase in BMI is considered to be a strong indication of inflammatory biomarkers, and weight loss occurs after resolving inflammation with a

decrease in inflammatory markers [26,47]. Since food intake was nearly similar between the AIA and AIA-treated rats that received the four nut oil diets, we suggest that the reduction in weight in all these treated rats was due to the suppression of inflammation. The accumulation of abnormal or extra fat leads to obesity, which can affect the maintenance of an optimal state of health, and a reduction in weight can decrease adipose tissue and restore normal secretion patterns [48]. The extra macronutrients in adipose tissues stimulate them to release inflammatory mediators and reduce the production of adiponectin, thus predisposing this tissue to a pro-inflammatory state and oxidative stress. Obesity is associated with chronic inflammation in obese subjects [49], and in obesity, the overexpressed pro-inflammatory cytokines are considered in light of the association between obesity and inflammation [50].

Warnberg et al. [51] studied the association between BMI and low-grade inflammation in Spanish adolescents and found that the levels of IL-6 and TNF-α were elevated with increased BMI in both males and females. A study on obese mice showed less inflammation and adipocyte hypertrophy with macadamia nut oil supplementation [52]. Being overweight is a positive indicator of inflammation, and Yu et al. [26] showed that nut consumption is allied with a reduction in BMI and weight gain. Nuts may also reduce the BMI of rats by affecting lipid metabolism and deposition of fats in the adipose tissue [53,54]. Redness, swelling, and paw digit deformities are major clinical morphological symptoms used for the rapid diagnosis of RA. In a study investigating the effect of high doses of ω-3 on RA pain and swelling, there was a significant decrease in pain associated with RA, redness, and swelling [55]. Accordingly, this study observed severe swelling, redness, and digit deformities (Figure 3) in all paws of the induced arthritis (AIA) rats one week after the induction. All types of nut oils, including walnut, peanut, cashew, and hazelnut, decreased the severity of RA in AIA-treated rats as evidenced by the decrease in redness, swelling, and digit deformities in the front and hind paws of all treated rats. These data suggest that these nut oils can protect against the progression and reverse AIA in rats by reducing joint inflammation. Indeed, several studies have suggested the anti-inflammatory effects of several types of nuts that contain large amounts of PUFAs, MUFAs, vitamins, and essential minerals [18,55].

Here, as compared to the control group, the RF levels were greater in the AIA group, which is consistent with a previous study [56]. However, this effect was lessened with the consumption of walnut, peanut, cashew, and hazelnut oil groups. During the development of RA, B-cell accumulation in the inflamed synovium increases significantly [57]. The accumulation of B-cells in the inflamed synovial plays a crucial role in the development of articular and other systemic complications in affected individuals and animals. Indeed, the activation of B-cells was shown to activate numerous pathways including the production of autoantibodies, T-cell activation, cytokine production, and immune regulation [57]. These data suggest that all four nut oils significantly ameliorate the AIA in the treated rats by regulating the production and function of B-cells. This could be mediated by restoring the normal tolerance barriers of these cells, which reduces their accumulation in the synovium and reduces the observed inflammatory cytokine levels. Therefore, the anti-inflammatory effect of walnut, peanut, cashew, and hazelnut oils is moderated—at least by suppressing the activity of B-cells. The major inflammatory cytokines released in the synovial tissue during RA include TNF-α, IL-6, IL-1α, IL-1β, IL-33, and IL-36, whereas the released anti-inflammatory cytokines include IL-4 IL-5, IL-10, IL-37, and IL-38. The increased release of inflammatory markers in the synovial tissues and in the RA patients' serum and animal models is the most recognizable hallmark of RA and increased TNF-α, IL-6, IL-1β, and IL-10 levels were seen in the synovial tissue, in RA individuals' serum, and AIA animal models [6,7]. These results support our findings according to which TNF-α, induced from macrophages, can progress RA by several mechanisms including the release of other inflammatory cytokines and growth factors (i.e., IL-6, IL-1, and GM-CSF from neutrophils, fibroblast, and endothelial cells [58]). On the other hand, IL-1α and IL-1β induced synovial hyperplasia and synovitis by stimulating the proliferation of fibroblasts and endothelial

cells [59]. This study showed the significant inhibition of all inflammatory cytokines in the serum of AIA rats that received walnut, peanut, cashew, and hazelnut oil. The biggest effect was seen with the walnut and peanuts oil diets.

Nuts exert a potent anti-inflammatory effect due to the high content in many macro- and micro-nutrients including ω-3 PUFAs, oleic acid, dietary fibers, magnesium, L-arginine, vitamins, and polyphenols (phytosterols and phenolic compounds) [17]. Therefore, it seems reasonable to say that the protective effect of all these nuts oils on the AIA group is due to their anti-inflammatory potential. In cohort studies, the regular daily serving and consumption of different types of nuts are allied with reduced coronary heart disease (CHD), diabetes, cardio-metabolic risk, the majority of cancers, and mortality rates possibly due to their antioxidant and anti-inflammatory properties [60–62]. Similarly, a cross-sectional study by Jiang et al. [27] investigating the connotation between nuts and systemic inflammation in a multiethnic population demonstrated that regular nut intake was inversely proportional to blood levels of CRP, IL-6, and fibrinogen. The maximum improvement in RA severity was noticed with walnut, which could be related to its effect on inflammatory mediators. The effects of EPA and DHA on inflammation and immunity were consistent with the existing mechanisms of fatty acid action. The highly unsaturated nature of EPA and DHA have discernible effects on membrane order in immune cells [63]. DHA and EPA are incorporated into inflammatory and immune cells at the expense of ARA acid [64], reducing the substrate quantity available to produce inflammatory and immunoregulatory eicosanoid [65,66]. ω-3 fatty acids can modify the production of eicosanoids and cytokines and the expression of key cell surface proteins [67]. The ω-3 PUFAs compete with ω-6 ARA, thus reducing the production of lipid-derived pro-inflammatory compounds. In addition, the anti-inflammatory action exerted by EPA and DHA is mediated by a decrease in the expression of adhesion molecules both on immune cells and on endothelium [12]. Dietary fat composition affects the fatty acid composition of inflammation and immune cells. These cells contain different compositions of PUFAs that can readily change, providing a link between inflammation and immunity and dietary PUFAs intake [68]. Fish oil supplementation leads to a partial replacement of ARA in cell membranes by EPA. This in turn decreases the production of ARA-derived mediators [68]. Our data are consistent with a previous study [69] that revealed that the levels of pro-inflammatory cytokines decreased with increasing dietary components from ω-3. The observed significant differences were the reductions in CRP, IL-6, and TNF-α. The study findings also agreed with Caughey et al. [70], who stated that a high dose of α-linolenic acid decreased IL-1 and TNF-α production by monocytes cells. Adding linseed oil with a high content of ALA to a low-fat diet caused a significant reduction in lymphocyte proliferation, but circulating antibody levels were unaffected [71].

The majority of nuts contain MUFAs as the dominant FAs. However, walnuts are very rich in ω-3 PUFAs (13–18 g/1 oz or 6.9–17.6%) [72,73]. Such high levels of ω-3 PUFAs could explain the inhibitory effect of walnut oil on the levels of RF and all of the measured inflammatory cytokines in AIA-treated rats in this study. Supporting this, the inhibitory effect of ω-3 PUFAs against RA is well-reported in the literature. Indeed, several experimental, clinical, and cross-sectional studies have illustrated the ability of ω-3 PUFAs to suppress the severity of RA and prevent cartilage and bone destruction mainly via their potent anti-inflammatory effects that suppress the synthesis of inflammatory cytokines by nuclear factor kappa B (NF-κB); inhibit matrix metalloproteinases (MMPs), LTs, and PGE2; and reduce macrophage infiltration and osteoclasts activation [74,75]. Osteoclasts are terminally differentiated cells of the monocyte/macrophage lineage that resorb bone matrix. The abnormal activation of osteoclasts is mostly responsible for bone destruction in RA [76]. The inhibition of osteoclast formation and function was noticed in serum acquired four hours following the almond meal consumption. Gene expression data in cultured human osteoclast precursors provide evidence for a positive effect of almonds on bone health [77]. Papoutsi et al. [78] showed that the walnut extract has a high anti-atherogenic potential and impressive osteoblastic activity for cardio protection and bone health.

Walnuts are an excellent source of dietary fibers and magnesium that suppress inflammation. ALA is the major precursor of both EPA and DHA and is the major ω-3 PUFA; it is abundant in walnut oil [75]. The precise molecular mechanism behind the anti-inflammatory potential of ω-3 PUFAs, including ALA, EPA, and DHA, is attributed to the suppression of iNOS (nitric oxide), COX-2 (PGE2), NF- κB, and inflammatory cytokines (IL-1β, IL-6, and TNF-α [75,79,80]). In addition, the decrease in the severity of RA and the concomitant reduction in the circulatory levels of IL-6, TNF-α, and IL-1β in AIA + walnut oil is mediated by the direct inflammatory effect of the ALA and its metabolites, EPA and DHA, on the expression of NF-κB. In addition to their high content of ω-3 PUFAs, walnuts can protect against numerous inflammatory conditions via their high content of several antioxidants and bioactive anti-inflammatory components, including gamma-tocopherol (vitamin E), folate, selenium, and flavonoids such as ellagic acid [75,81]. Of the 1113 different food items tested for their antioxidant potentials, walnuts ranked second place [82].

Peanuts are one of the most common nuts in the world with good nutritional value and low cost. Peanuts have the highest lipid (oil) and protein contents (50% and 25%, respectively) [83]. A higher peanut intake was connected with lower serum levels of IL-6 and CRP among healthy individuals, thus suggesting a potent inflammatory effect [26]. The protective effect of oleic acid was attributed to decreased lymphocyte activities; inhibited macrophage infiltration; suppressed production of LB4, IL-1, and TNF-α; and decreased expression of several adhesive molecules and MMP activity.

Cashew nuts are also an excellent source of lipids (47.8 g/100)—most are MUFAs in the form of oleic acid (84%) [84]. Cashew nuts are very rich in flavonoids such as tannin and anacardic acids as well as anthocyanins, fibers, folate, and tocopherols, which are known for their hypolipidemic, antioxidant, and anti-inflammatory effects [84,85]. Cashew nuts suppressed the levels of TNF-α, IL-6, ICAM-1, and P-selectin; they also inhibited NF-κB [85]. Our data showed that cashew nuts could suppress the AIA in rats by suppressing the synthesis and release of inflammatory markers. Therefore, we suggest that the anti-arthritic and anti-inflammatory effect of cashew nuts observed here is due to their high content of oleic acid and other ingredients such as flavonoids, anthocyanins, tannins, fiber, folate, and tocopherols [23].

Hazelnuts are very rich in FAs (>60% of dry weights) and are an excellent source of MUFAs and oleic acid (80%); they are comparable to olive oil. Other fatty acids found in hazelnuts include linoleic, palmitic, and stearic acid. Hazelnuts are also an excellent source of vitamin B (i.e., B1, B2, B6), α-tocopherol niacin, thiamin, phytosterols (mainly α-sitosterol and gallic acid, caffeic acid, sinapic acid, and quercetin), and many other essential minerals [86,87]. In one study, the consumption of hazelnuts reduced inflammation and increased the expression of several antioxidant enzymes without weight gain [86]. Hazelnuts augment cellular antioxidant properties and reduce levels of several inflammatory cytokines and oxidation of LDL in healthy subjects [87]. Hazelnuts can also suppress inflammation and reduce the circulatory levels of inflammatory cytokines [88]. RA is an inflammatory disorder characterized by the overproduction of inflammatory cytokines and PGs—especially type E (i.e., PGE2) [89]. PGs, including prostacyclin (PGI_2), PGE_2, prostaglandin F2α ($PGF_{2\alpha}$), PGD, and TXA2 (a vasoconstrictor), are lipid products produced from the metabolism of the membrane ARA by the action of COX-2 [90]. The levels of all PGs are significantly amplified in the RA patients' synovial tissue and AIA animal model [89,91]. All PGs are involved in different aspects of RA, and PGE2 is synthesized by the chondrocytes and synovial fibroblasts in response to inflammatory cytokines.

PGE2 is among the most effective PGs in the pathogenesis of RA and amplifies the disease. The damaging effect of PGE2 is via numerous mechanisms, including the death of the hyperplasia of the synovium, limiting protection of T-cells from apoptosis, erosion of cartilage, vasodilatation, fluid extravasation, and pain [89]. However, the inhibition of COX-2 activity by non-steroidal anti-inflammatory drugs (NSAIDs) and the suppression of PGE2 signaling by blocking or deleting their receptors ameliorates the severity of RA and prevents

its progression [89,91–93]. The ratio of ω-6/ω-3 is a key index for the balanced synthesis of eicosanoids in the body [94]. The ω-3 fatty acids can reduce the production of eicosanoids from ARA [95]. EPA is a substrate for the COX and LOX enzymes leading to the synthesis of alternative eicosanoids that are typically less potent than those produced from ARA [95]. In this study, all nut oils reduced PGE2 (Figure 6), suggesting two possibilities. The first suggestion is that walnut, peanut, cashew, and hazelnut oils reduce the inflammatory levels of TNF-α and IL-1β. The other possibility is that these oils suppress the activity of COX-2, thus suppressing the generation of PGE2. In addition to their high content of ω-3 PUFAs, nuts are a good source of several antioxidants and bioactive anti-inflammatory components.

Walnuts contain significant amounts of antioxidants, i.e., more than 20 mmol/100 g, followed by peanuts (2.0 mmol/100 g), hazelnuts, and cashew nuts (0.3–0.7 mmol/100 g) [96]. Similarly, another study has reported the highest content of phytosterol (which is supposed to have anti-inflammatory effects) in walnut (307 mg/100 g), followed by peanut (284 mg/100 g), cashew nut (199 mg/100 g), and hazelnut (165 mg/100 g) [97]. Therefore, other than the fatty acid profile, the synergetic interaction between antioxidants and many bioactive constituents of walnut and peanuts can be the possible cause of higher inflammation-decreasing properties in walnut and peanut oil than in other groups such as hazel nut and cashew nut.

5. Conclusions

The cause of RA remains unknown, but dietary interventions are becoming more popular due to an increased understanding of the beneficial effects of nutrients on inflammation and immunity. The improved understanding of the pathogenesis of the disease will open the way to innovative dietary therapies from nature such as nut oils that target the cytokines directly involved in its pathogenesis. Overall, our findings reveal very compelling anti-arthritic effects of different nut oils on AIA in rats. The data recommend including walnuts, hazelnuts, peanuts, and cashew nuts in our regular daily diets for both healthy individuals and patients with RA—particularly walnuts with a high content in PUFAs such as ω-3. PUFAs greatly reduce redness, deformities, and pain and they have a significant effect on inflammatory indicators. Apart from the regular DMARDs and anti-TNFs consumption, the patients should also change their eating habits as dietary interventions can potentially delay the early signs of RA. Dietary manipulations may not show immediate benefits, but their long-term effects are already evident. In summary, by incorporating these foods into daily diets, it is possible to reduce RA disease activity, delay disease progression, and prevent joint damage, which in turn will cut the number and amount of drugs administered for treatment.

The present study assessed the anti–arthritic potential of walnut, peanut, cashew nut, and hazelnut oil. All these oils effectively improved the morphological appearance and decreased the anti-arthritic biomarker, which shows that the use of plant-based natural therapeutics is economic, safer than prescription medication with a reduced amount of harmful effects, and effective in preventing and managing RA. Short-term experiments, along with lack of blood collection over time, more nutritional and biochemical analyses, and a dose-dependent design were the main limitations of the present study. Although our data provide explicit substantiation of the prospective of nut oils for their use in the prevention and management of RA, further studies are required to explicate their mechanisms of action.

Author Contributions: Conceptualization, D.M.A.-N. and L.N.A.-H.; methodology, S.K.A.-S.; software, S.K.A.-S. and S.A.; validation, D.M.A.-N., S.A. and L.N.A.-H.; formal analysis, S.K.A.-S.; investigation, S.K.A.-S.; resources, D.M.A.-N. and L.N.A.-H.; data curation, S.K.A.-S. and D.M.A.-N.; writing—original draft preparation, S.K.A.-S.; writing—review and editing, S.A. and L.N.A.-H.; visualization, S.K.A.-S. and D.M.A.-N.; supervision, D.M.A.-N.; project administration, D.M.A.-N. and L.N.A.-H.; funding acquisition, L.N.A.-H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Researchers Supporting Project, King Saud University, Riyadh, Saudi Arabia, grant number RSPD2023R460.

Institutional Review Board Statement: This study was conducted in compliance with the ethical principle of the Declaration of Helsinki. The study was approved by King Saud University (Reference #: KSU-SE-19-37), and this study is in accordance with the Policy of the Research Centre. All rats were always housed under controlled conditions.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author.

Acknowledgments: The authors extend thanks to the Researchers Supporting Project number (RSPD2023R460), King Saud University, Riyadh, Saudi Arabia.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

DFC	daily food consumption
TFC	total food consumption
WG	weight gain
FE	food efficiency
PBS	phosphate-buffered saline
TBS	tris-buffered saline
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
ALA	alpha-linolenic acid
ARA	arachidonic acid
MMPs	matrix metalloproteinases
LTs	leukotrienes
TNF-α	tumor necrosis factor-α
IL-6	interleukin-6
IL-1β	interleukin-1β
ICAM-1	intercellular adhesion molecule 1
TXA2	thromboxane A2
COX	cyclooxygenase
LOX	lipoxygenase
LB4	leukotriene B4
TMB	3,3′,5,5′-Tetramethylbenzidine
iNOS	inducible nitric oxide
HRP	horseradish peroxidase
ELISA	enzyme-linked immunosorbent assay
PGE2	prostaglandin E2
SABC	strept avidin biotin–peroxidase complex
CFA	complete Freund's adjuvants
CRP	C-reactive protein
TNFR2	tumor necrosis factor receptor 2
BMI	body mass index
DMARDs	disease-modifying antirheumatic drugs
NF-κB	nuclear factor kappa B
MMPs	matrix metalloproteinases

References

1. Trouw, L.A.; Huizinga, T.W.J.; Toes, R.E.M. Autoimmunity in rheumatoid arthritis: Different antigens—Common principles. *Ann. Rheum. Dis.* **2013**, *72* (Suppl. 2), ii132–ii136. [CrossRef]
2. Guo, Q.; Wang, Y.; Xu, D.; Nossent, J.; Pavlos, N.J.; Xu, J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. *Bone Res.* **2018**, *6*, 15. [CrossRef] [PubMed]
3. Tak, P.P.; Kalden, J.R. Advances in rheumatology: New-targeted therapeutics. *Arthritis. Res. Ther.* **2011**, *13*, S5. [CrossRef]

4. Klarenbeek, N.B.; Güler-Yüksel, M.; van der Heijde, D.M.F.M.; Hulsmans, H.M.J.; Kerstens, P.J.S.M.; Molenaar, T.H.E.; de Sonnaville, P.B.J.; Huizinga, T.W.J.; Dijkmans, B.A.C.; Allaart, C.F. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. *Ann. Rheum. Dis.* **2010**, *69*, 2107–2113. [CrossRef]
5. Mauri, C.; Menon, M. Human regulatory B cells in health and disease: Therapeutic potential. *J. Clin. Investig.* **2017**, *127*, 772–779. [CrossRef]
6. Park, M.J.; Lee, S.H.; Kim, E.K.; Lee, E.J.; Baek, J.A.; Park, S.H.; Kwok, S.K.; Cho, M.L. Interleukin-10 produced by myeloid-derived suppressor cells is critical for the induction of Tregs and attenuation of rheumatoid inflammation in mice. *Sci. Rep.* **2018**, *8*, 3753. [CrossRef] [PubMed]
7. Farrugia, M.; Baron, B. The role of TNF-α in rheumatoid arthritis: A focus on regulatory T cells. *J. Clin. Transl. Res.* **2016**, *2*, 84–90. [CrossRef] [PubMed]
8. Volker, D.H.; FitzGerald, P.E.B.; Garg, M.L. The eicosapentaenoic to docosahexaenoic acid ratio of diets affects the pathogenesis of arthritis in Lew/SSN rats. *J. Nutr.* **2000**, *130*, 559–565. [CrossRef]
9. Tański, W.; Świątoniowska-Lonc, N.; Tabin, M.; Jankowska-Polańska, B. The relationship between fatty acids and the development, course and treatment of rheumatoid arthritis. *Nutrients* **2022**, *14*, 1030. [CrossRef] [PubMed]
10. Kostoglou-Athanassiou, I.; Athanassiou, L.; Athanassiou, P. The Effect of Omega-3 Fatty Acids on Rheumatoid Arthritis. *Mediterr. J. Rheumatol.* **2020**, *31*, 190–194. [CrossRef] [PubMed]
11. Gioxari, A.; Kaliora, A.C.; Marantidou, F.; Panagiotakos, D.P. Intake of omega-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Nutrition* **2018**, *45*, 114–124.e114. [CrossRef]
12. Navarini, L.; Afeltra, A.; Gallo Afflitto, G.G.; Margiotta, D.P.E. Polyunsaturated fatty acids: Any role in rheumatoid arthritis? *Lipids Health Dis.* **2017**, *16*, 197. [CrossRef] [PubMed]
13. Patterson, E.; Wall, R.; Fitzgerald, G.F.; Ross, R.P.; Stanton, C. Health implications of high dietary ω-6 polyunsaturated Fatty acids. *J. Nutr. Metab.* **2012**, *2012*, 539426. [CrossRef] [PubMed]
14. Simopoulos, A.P. Evolutionary aspects of diet, the ω-6/ω-3 ratio and genetic variation: Nutritional implications for chronic diseases. *Biomed. Pharmacother.* **2006**, *60*, 502–507. [CrossRef] [PubMed]
15. Yaqoob, P. Monounsaturated fats and immune function. *Braz. J. Med. Biol. Res.* **1998**, *31*, 453–465. [CrossRef]
16. Donahue, K.E.; Jonas, D.E.; Hansen, R.A.; Roubey, R.; Jonas, B.; Lux, L.J.; Gartlehner, G.; Harden, E.; Wilkins, T.; Peravali, V.; et al. *Drug Therapy for Rheumatoid Arthritis in Adults: An Update*; Comparative Effectiveness Review No. 55; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2012.
17. Ros, E. Health benefits of nut consumption. *Nutrients* **2010**, *2*, 652–682. [CrossRef]
18. Salas-Salvadó, J.; Casas-Agustench, P.; Murphy, M.; López-Uriarte, P.; Bulló, M. The effect of nuts on inflammation. *Asia Pac. J. Clin. Nutr.* **2008**, *17*, 333–336.
19. De Souza, R.; Schincaglia, R.M.; Pimentel, G.D.; Mota, J.F. Nuts and human health outcomes: A systematic review. *Nutrients* **2017**, *9*, 1311. [CrossRef]
20. Blanco Mejia, S.; Kendall, C.W.C.; Viguiliouk, E.; Augustin, L.S.; Ha, V.; Cozma, A.I.; Mirrahimi, A.; Maroleanu, A.; Chiavaroli, L.; Leiter, L.A.; et al. Effect of tree nuts on metabolic syndrome criteria: A systematic review and meta-analysis of randomized controlled trials. *BMJ Open* **2014**, *4*, e004660. [CrossRef]
21. Canales, A.; Sánchez-Muniz, F.J.; Bastida, S.; Librelotto, J.; Nus, M.; Corella, D.; Guillen, M.; Benedi, J. Effect of walnut-enriched meat on the relationship between VCAM, ICAM, and LTB4 Levels and PON-1 activity in ApoA4 360 and PON-1 allele carriers at increased cardiovascular risk. *Eur. J. Clin. Nutr.* **2011**, *65*, 703–710. [CrossRef]
22. Lozano, A.; Perez-Martinez, P.; Marin, C.; Tinahones, F.J.; Delgado-Lista, J.; Cruz-Teno, C.; Gomez-Luna, P.; Rodriguez-Cantalejo, F.; Perez-Jimenez, F.; Lopez-Miranda, J. An acute intake of a walnut-enriched meal improves postprandial adiponectin response in healthy young adults. *Nutr. Res.* **2013**, *33*, 1012–1018. [CrossRef]
23. Cordaro, M.; Siracusa, R.; Fusco, R.; D'Amico, R.; Peritore, A.F.; Gugliandolo, E.; Genovese, T.; Scuto, M.; Crupi, R.; Mandalari, G.; et al. Cashew (*Anacardium occidentale* L.) nuts counteract oxidative stress and inflammation in an acute experimental model of carrageenan-induced paw edema. *Antioxidants* **2020**, *9*, 660. [CrossRef] [PubMed]
24. Fusco, R.; Siracusa, R.; Peritore, A.F.; Gugliandolo, E.; Genovese, T.; D'Amico, R.; Cordaro, M.; Crupi, R.; Mandalari, G.; Impellizzeri, D.; et al. The Role of Cashew (*Anacardium occidentale* L.) Nuts on an experimental model of painful degenerative joint disease. *Antioxidants* **2020**, *9*, 511. [CrossRef] [PubMed]
25. Stoner, L.; Lucero, A.A.; Palmer, B.R.; Jones, L.M.; Young, J.M.; Faulkner, J. Inflammatory biomarkers for predicting cardiovascular disease. *Clin. Biochem.* **2013**, *46*, 1353–1371. [CrossRef] [PubMed]
26. Yu, Z.; Malik, V.S.; Keum, N.; Hu, F.B.; Giovannucci, E.L.; Stampfer, M.J.; Willett, W.C.; Fuchs, C.S.; Bao, Y. Associations between nut consumption and inflammatory biomarkers. *Am. J. Clin. Nutr.* **2016**, *104*, 722–728. [CrossRef] [PubMed]
27. Jiang, R.; Jacobs, D.R., Jr.; Mayer-Davis, E.; Szklo, M.; Herrington, D.; Jenny, N.S.; Kronmal, R.; Barr, R.G. Nut and seed consumption and inflammatory markers in the multi-ethnic study of atherosclerosis. *Am. J. Epidemiol.* **2006**, *163*, 222–231. [CrossRef]
28. Sokoła-Wysoczańska, E.; Wysoczański, T.; Wagner, J.; Czyż, K.; Bodkowski, R.; Lochyński, S.; Patkowska-Sokoła, B. Polyunsaturated fatty acids and their potential therapeutic role in cardiovascular system disorders—A review. *Nutrients* **2018**, *10*, 1561. [CrossRef]

29. Ablin, J.N.; Entin-Meer, M.; Aloush, V.; Oren, S.; Elkayam, O.; George, J.; Barshack, I. Protective effect of eotaxin-2 inhibition in adjuvant-induced arthritis. *Clin. Exp. Immunol.* **2010**, *161*, 276–283. [CrossRef]
30. Reeves, P.G.; Nielsen, F.H.; Fahey, G.C., Jr. AIN-93 purified diets for laboratory rodents: Final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. *J. Nutr.* **1993**, *123*, 939–951. [CrossRef]
31. Reeves, P.G. Components of the AIN-93 diets as improvements in the AIN-76A diet. *J. Nutr.* **1997**, *127*, 838S–841S. [CrossRef]
32. Lucke, V. *Laboratory Animal Medicine*; Fox, J.G., Cohen, B.J., Loew, F.M., Eds.; Academic Press Inc.: San Diego, CA, USA, 1984; ISBN 0-12-263620-1.
33. National Research Council (US) Subcommittee on Laboratory Animal Nutrition. *Nutrient Requirements of Laboratory Animals*, 4th ed.; National Academies Press (US): Washington, DC, USA, 1995.
34. Cuzzocrea, S.; Mazzon, E.; Paola, R.D.; Genovese, T.; Muià, C.; Caputi, A.P.; Salvemini, D. Effects of combination M40403 and dexamethasone therapy on joint disease in a rat model of collagen-induced arthritis. *Arthritis Rheum.* **2005**, *52*, 1929–1940. [CrossRef]
35. Laferriere, C.A.; Pang, D.S. Review of intraperitoneal injection of sodium pentobarbital as a method of euthanasia in laboratory rodents. *J. Am. Assoc. Lab. Anim. Sci.* **2020**, *59*, 254–263. [CrossRef] [PubMed]
36. Mohamed, A.S.; Hosney, M.; Bassiony, H.; Hassanein, A.S.; Soliman, A.M.; Fahmy, S.R.; Gaafar, K. Sodium pentobarbital dosages for exsanguination affect biochemical, molecular and histological measurements in rats. *Sci. Rep.* **2020**, *10*, 378. [CrossRef] [PubMed]
37. Harris, E.D., Jr. Rheumatoid arthritis: Pathophysiology and implications for therapy. *N. Engl. J. Med.* **1990**, *322*, 1277–1289. [PubMed]
38. Hochberg, M.C. Adult and juvenile rheumatoid arthritis: Current epidemiologic concepts. *Epidemiol. Rev.* **1981**, *3*, 27–44. [CrossRef]
39. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum.* **2002**, *46*, 328–346. [CrossRef] [PubMed]
40. Kvien, T.K.; Uhlig, T.; Ødegård, S.; Heiberg, M.S. Epidemiological aspects of rheumatoid arthritis: The sex ratio. *Ann. N. Y. Acad. Sci.* **2006**, *1069*, 212–222. [CrossRef]
41. Chancay, M.G.; Guendsechadze, S.N.; Blanco, I. Types of pain and their psychosocial impact in women with rheumatoid arthritis. *Womens Midlife Health* **2019**, *5*, 3. [CrossRef]
42. Tuncel, J.; Haag, S.; Hoffmann, M.H.; Yau, A.C.; Hultqvist, M.; Olofsson, P.; Bäcklund, J.; Nandakumar, K.S.; Weidner, D.; Fischer, A.; et al. Animal Models of Rheumatoid Arthritis (I): Pristane-Induced Arthritis in the Rat. *PLoS ONE* **2016**, *11*, e0155936. [CrossRef]
43. Song, D.; DuBois, D.C.; Almon, R.R.; Jusko, W.J. Modeling Sex Differences in Anti-inflammatory Effects of Dexamethasone in Arthritic Rats. *Pharm. Res.* **2018**, *35*, 203. [CrossRef]
44. Shamlan, G.; Al-Nouri, D.M.; Alathbah, A.A.; Arzoo, S.; Habibullah, M.M. Antiarthritic, anti-inflammatory activity of *Moringa peregrina* seed oil and leaves in Freund's complete adjuvant-induced arthritis in rats. *J. King Saud Univ. Sci.* **2021**, *33*, 101350. [CrossRef]
45. Ellis, P.R.; Kendall, C.W.; Ren, Y.; Parker, C.; Pacy, J.F.; Waldron, K.W.; Jenkins, D.J. Role of cell walls in the bioaccessibility of lipids in almond seeds. *Am. J. Clin. Nutr.* **2004**, *80*, 604–613. [CrossRef]
46. Ellulu, M.S.; Patimah, I.; Khaza'ai, H.; Rahmat, A.; Abed, Y. Obesity and inflammation: The linking mechanism and the complications. *Arch. Med. Sci.* **2017**, *13*, 851–863. [CrossRef] [PubMed]
47. Ziccardi, P.; Nappo, F.; Giugliano, G.; Esposito, K.; Marfella, R.; Cioffi, M.; D'Andrea, F.; Molinari, A.M.; Giugliano, D. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* **2002**, *105*, 804–809. [CrossRef] [PubMed]
48. Hauner, H. Secretory factors from human adipose tissue and their functional role. *Proc. Nutr. Soc.* **2005**, *64*, 163–169. [CrossRef]
49. Stępień, M.; Stępień, A.; Wlazeł, R.N.; Paradowski, M.; Banach, M.; Rysz, J. Obesity indices and inflammatory markers in obese non-diabetic normo and hypertensive patients: A comparative pilot study. *Lipids Health Dis.* **2014**, *13*, 29. [CrossRef]
50. Hotamisligil, G.S. Inflammation and metabolic disorders. *Nature* **2006**, *444*, 860–867. [CrossRef]
51. Warnberg, J.; Moreno, L.A.; Mesana, M.I.; Marcos, A.; The AVENA Group. Inflammatory mediators in overweight and obese Spanish adolescents. The AVENA Study. *Int. J. Obes.* **2004**, *28*, S59–S63. [CrossRef] [PubMed]
52. Lima, E.A.; Silveira, L.S.; Masi, L.N.; Crisma, A.R.; Davanso, M.R.; Souza, G.I.; Santamarina, A.B.; Moreira, R.G.; Martins, A.R.; de Sousa, L.G.; et al. Macadamia oil supplementation attenuates inflammation and adipocyte hypertrophy in obese mice. *Mediat. Inflamm.* **2014**, *2014*, 870634. [CrossRef]
53. Terzo, S.; Caldara, G.F.; Ferrantelli, V.; Puleio, R.; Cassata, G.; Mulè, F.; Amato, A. Pistachio consumption prevents and improves lipid dysmetabolism by reducing the lipid metabolizing gene expression in diet-induced obese mice. *Nutrients* **2018**, *10*, 1857. [CrossRef]
54. Tindall, A.M.; Petersen, K.S.; Lamendella, R.; Shearer, G.C.; Murray-Kolb, L.E.; Proctor, D.N.; Kris-Etherton, P.M. Tree nut consumption and adipose tissue mass: Mechanisms of action. *Curr. Dev. Nutr.* **2018**, *2*, nzy069. [CrossRef]
55. Abdulrazaq, M.; Innes, J.K.; Calder, P.C. Effect of ω-3 polyunsaturated fatty acids on arthritic pain: A systematic review. *Nutrition* **2017**, *39*, 57–66. [CrossRef]

56. Yau, A.C.Y.; Holmdahl, R. Rheumatoid arthritis: Identifying and characterizing polymorphisms using rat models. *Dis. Model. Mech.* **2016**, *9*, 1111–1123. [CrossRef]
57. Bugatti, S.; Vitolo, B.; Caporali, R.; Montecucco, C.; Manzo, A. β cells in rheumatoid arthritis: From pathogenic players to disease biomarkers. *BioMed Res. Int.* **2014**, *2014*, 681678. [CrossRef] [PubMed]
58. Kalliolias, G.D.; Ivashkiv, L.B. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat. Rev. Rheumatol.* **2016**, *12*, 49–62. [CrossRef]
59. Dinarello, C.A. Historical insights into cytokines. *Eur. J. Immunol.* **2007**, *37* (Suppl. 1), S34–S45. [CrossRef]
60. Aune, D.; Keum, N.; Giovannucci, E.; Fadnes, L.T.; Boffetta, P.; Greenwood, D.C.; Tonstad, S.; Vatten, L.J.; Riboli, E.; Norat, T. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Med.* **2016**, *14*, 207. [CrossRef] [PubMed]
61. Mayhew, A.J.; de Souza, R.J.; Meyre, D.; Anand, S.S.; Mente, A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *Br. J. Nutr.* **2016**, *115*, 212–225. [CrossRef] [PubMed]
62. Afshin, A.; Micha, R.; Khatibzadeh, S.; Mozaffarian, D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: A systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2014**, *100*, 278–288. [CrossRef] [PubMed]
63. Calder, P.C.; Yaqoob, P.; Harvey, D.J.; Watts, A.; Newsholme, E.A. Incorporation of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty acid composition and membrane fluidity. *Biochem. J.* **1994**, *300*, 509–518. [CrossRef]
64. Rees, D.; Miles, E.A.; Banerjee, T.; Wells, S.J.; Roynette, C.E.; Wahle, K.W.; Calder, P.C. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: A comparison of young and older men. *Am. J. Clin. Nutr.* **2006**, *83*, 331–342. [CrossRef] [PubMed]
65. Meydani, S.N.; Endres, S.; Woods, M.M.; Goldin, B.R.; Soo, C.; Morrill-Labrode, A.; Dinarello, C.A.; Gorbach, S.L. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: Comparison between young and older women. *J. Nutr.* **1991**, *121*, 547–555. [CrossRef]
66. Von Schacky, C.; Kiefl, R.; Jendraschak, E.; Kaminski, W.E. N-3 fatty acids and cysteinyl-leukotriene formation in humans in vitro, ex vivo, and in vivo. *J. Lab. Clin. Med.* **1993**, *121*, 302–309.
67. Calder, P.C. N-3 fatty acids, inflammation and immunity: New mechanisms to explain old actions. *Proc. Nutr. Soc.* **2013**, *72*, 326–336. [CrossRef] [PubMed]
68. Calder, P.C.; Grimble, R.F. Polyunsaturated fatty acids, inflammation and immunity. *Eur. J. Clin. Nutr.* **2002**, *56*, S14–S19. [CrossRef] [PubMed]
69. Sundrarjun, T.; Komindr, S.; Archararit, N.; Dahlan, W.; Puchaiwatananon, O.; Angthararak, S.; Chuncharunee, S. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor-α and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *J. Int. Med. Res.* **2004**, *32*, 443–454. [CrossRef]
70. Caughey, G.E.; Mantzioris, E.; Gibson, R.A.; Cleland, L.G.; James, M.J. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am. J. Clin. Nutr.* **1996**, *63*, 116–122. [CrossRef]
71. Kelley, D.S.; Branch, L.B.; Love, J.E.; Taylor, P.C.; Rivera, Y.M.; Iacono, J.M. Dietary α-linolenic acid and immunocompetence in humans. *Am. J. Clin. Nutr.* **1991**, *53*, 40–46. [CrossRef]
72. Poggetti, L.; Ferfuia, C.; Chiabà, C.; Testolin, R.; Baldini, M. Kernel oil content and oil composition in walnut (*Juglans regia* L.) accessions from north-eastern Italy. *J. Sci. Food Agric.* **2018**, *98*, 955–962. [CrossRef]
73. Gharibzahedi, S.M.T.; Mousavi, S.M.; Hamedi, M.; Khodaiyan, F. Determination and characterization of kernel biochemical composition and functional compounds of Persian walnut oil. *J. Food Sci. Technol.* **2014**, *51*, 34–42. [CrossRef]
74. Miles, E.A.; Calder, P.C. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. *Br. J. Nutr.* **2012**, *107* (Suppl. 2), S171–S184. [CrossRef] [PubMed]
75. Ros, E.; Izquierdo-Pulido, M.; Sala-Vila, A. Beneficial effects of walnut consumption on human health: Role of micronutrients. *Curr. Opin. Clin. Nutr. Metab. Care* **2018**, *21*, 498–504. [CrossRef]
76. Sato, K.; Takayanagi, H. Osteoclasts, rheumatoid arthritis, and osteoimmunology. *Curr. Opin. Rheumatol.* **2006**, *18*, 419–426. [CrossRef] [PubMed]
77. Platt, I.D.; Josse, A.R.; Kendall, C.W.; Jenkins, D.J.; El-Sohemy, A. Postprandial effects of almond consumption on human osteoclast precursors-an ex vivo study. *Metabolism* **2011**, *60*, 923–929. [CrossRef]
78. Papoutsi, Z.; Kassi, E.; Chinou, I.; Halabalaki, M.; Skaltsounis, L.A.; Moutsatsou, P. Walnut extract (*Juglans regia* L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483. *Br. J. Nutr.* **2008**, *99*, 715–722. [CrossRef]
79. Erdinest, N.; Shmueli, O.; Grossman, Y.; Ovadia, H.; Solomon, A. Anti-inflammatory effects of alpha linolenic acid on human corneal epithelial cells. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 4396–4406. [CrossRef]
80. Ren, J.; Chung, S.H. Anti-inflammatory effect of alpha-linolenic acid and its mode of action through the inhibition of nitric oxide production and inducible nitric oxide synthase gene expression via NF-kappaB and mitogen-activated protein kinase pathways. *J. Agric. Food Chem.* **2007**, *55*, 5073–5080. [CrossRef]
81. Fukuda, T.; Ito, H.; Yoshida, T. Antioxidative polyphenols from walnuts (*Juglans regia* L.). *Phytochemistry* **2003**, *63*, 795–801. [CrossRef]

82. Chauhan, A.; Chauhan, V. Beneficial Effects of Walnuts on Cognition and Brain Health. *Nutrients* **2020**, *12*, 550. [CrossRef] [PubMed]
83. Bonku, R.; Yu, J. Health aspects of peanuts as an outcome of its chemical composition. *Food Sci. Hum. Wellness* **2020**, *9*, 21–30. [CrossRef]
84. Dias, C.; Madruga, M.S.; Pintado, M.; Almeida, G.; Alves, A.; Dantas, F.A.; Bezerra, J.; de Melo, M.; Viera, V.B.; Soares, J. Cashew nuts (*Anacardium occidentale* L.) decrease visceral fat, yet augment glucose in dyslipidemic rats. *PLoS ONE* **2019**, *14*, e0225736. [CrossRef] [PubMed]
85. Siracusa, R.; Fusco, R.; Peritore, A.F.; Cordaro, M.; D'Amico, R.; Genovese, T.; Gugliandolo, E.; Crupi, R.; Smeriglio, A.; Mandalari, G.; et al. The Antioxidant and Anti-Inflammatory Properties of *Anacardium occidentale* L. Cashew Nuts in a Mouse Model of Colitis. *Nutrients* **2020**, *12*, 834. [CrossRef]
86. Di Renzo, L.; Cioccoloni, G.; Bernardini, S.; Abenavoli, L.; Aiello, V.; Marchetti, M.; Cammarano, A.; Alipourfard, I.; Ceravolo, I.; Gratteri, S. A hazelnut-enriched diet modulates oxidative stress and inflammation gene expression without weight gain. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 4683723. [CrossRef]
87. Di Renzo, L.; Merra, G.; Botta, R.; Gualtieri, P.; Manzo, A.; Perrone, M.A.; Mazza, M.; Cascapera, S.; de Lorenzo, A. Post-prandial effects of hazelnut-enriched high fat meal on LDL oxidative status, oxidative and inflammatory gene expression of healthy subjects: A randomized trial. *Eur. Rev. Med. Pharmacol. Sci.* **2017**, *21*, 1610–1626.
88. Tey, S.L.; Brown, R.C.; Chisholm, A.W.; Delahunty, C.M.; Gray, A.R.; Williams, S.M. Effects of different forms of hazelnuts on blood lipids and α-tocopherol concentrations in mildly hypercholesterolemic individuals. *Eur. J. Clin. Nutr.* **2011**, *65*, 117–124. [CrossRef] [PubMed]
89. Fattahi, M.J.; Mirshafiey, A. Prostaglandins and Rheumatoid Arthritis. *Arthritis* **2012**, *2012*, 239310. [CrossRef]
90. Shimizu, T. Lipid mediators in health and disease: Enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 123–150. [CrossRef]
91. McCoy, J.M.; Wicks, J.R.; Audoly, L.P. The role of prostaglandin E2 receptors in the pathogenesis of rheumatoid arthritis. *J. Clin. Investig.* **2002**, *110*, 651–658. [CrossRef] [PubMed]
92. Hata, A.N.; Breyer, R.M. Pharmacology and signaling of prostaglandin receptors: Multiple roles in inflammation and immune modulation. *Pharmacol. Ther.* **2004**, *103*, 147–166. [CrossRef]
93. Bombardier, C.; Laine, L.; Reicin, A.; Shapiro, D.; Burgos-Vargas, R.; Davis, B.; Day, R.; Ferraz, M.B.; Hawkey, C.J.; Hochberg, M.C.; et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N. Engl. J. Med* **2000**, *343*, 1520–1528. [CrossRef]
94. Abedi, E.; Sahari, M.A. Long chain polyunsaturated fatty acid sources and evaluation of their nutritional and functional properties. *Food Sci. Nutr.* **2014**, *2*, 443–463. [CrossRef] [PubMed]
95. Calder, P.C. Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases. *Mol. Nutr. Food Res.* **2008**, *52*, 885–897. [CrossRef] [PubMed]
96. Blomhoff, R.; Carlsen, M.H.; Andersen, L.F.; Jacobs, D.R., Jr. Health benefits of nuts: Potential role of antioxidants. *Br. J. Nutr.* **2006**, *96* (Suppl. 2), S52–S60. [CrossRef] [PubMed]
97. Alasalvar, C.; Bolling, B.W. Review of nut phytochemicals, fat-soluble bioactives, antioxidant components and health effects. *Br. J. Nutr.* **2015**, *113* (Suppl. 2), S68–S78. [CrossRef]