Effects of Dietary Flaxseed and Atorvastatin on Blood Hematology and Renal Health Metrics in Rats Fed High-Fat Diet

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Abstract- Flaxseed is rich in omega-3 fatty acids and dietary fiber, both of which contribute to reduced inflammation and oxidative stress in the kidneys. Moreover, atorvastatin appears to enhance the activity of important antioxidant enzymes, potentially reducing the risk of chronic kidney disease and hematological disorders. Eighty male Wistar rats were divided randomly into ten groups: 1) ND (normal diet) 2) HFD (high-fat diet), 3) HFD+ ATO 10, 4) HFD+ ATO 20, 5) HFD+ FO (flaxseed oil), 6) HFD+ F (flaxseed), 7) HFD + ATO 10 + FO, 8) HFD + ATO 20 + FO, 9) HFD + ATO 10 + F, and 10) HFD + ATO 10 + F. Atorvastatin 10 and 20 mg/kg, FO 40 mg/kg, and flaxseed 40 g/kg were administrated for 8 weeks. After 23 weeks, serum level of kidney markers and CBC parameters were evaluated. ATO 20 led to reduce WBC, RBC, and HCT. Furthermore, ATO 20 + FO decreased WBC and ATO 20 + F reduced PLT, RBC and HCT. Administration of ATO 10 cause to increase creatinine (Cr) levels but other interventions had better effect on Cr, however these effects weren't notable. There weren't significant differences in Hb, MCV, MCH, MCHC, and urea between groups. F/FO therapies with ATO seems to have synergistic effects to improved dyslipidemia-associated kidney injuries and hematological indices. Although high dose of ATO can be more efficient than low dose.

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Introduction

Non-alcoholic fatty liver disease (NAFLD), a prevalent condition characterized by excessive fat accumulation in the liver, has emerged as a significant public health concern globally due to its rising prevalence and association with obesity, insulin resistance, type 2 diabetes, and cardiovascular diseases (1,2). It affects about 25% of the global population and can progress to more severe conditions (3). The dysregulation of lipid metabolism, inflammation, oxidative stress, and insulin signaling are critical factors contributing to the development and progression of NAFLD (4). Several signaling pathways have been implicated in the pathogenesis of NAFLD. These include AMP-activated protein kinase (AMPK) pathway involved in regulating energy balance and lipid metabolism; peroxisome proliferator-activated receptor alpha (PPARα) pathway responsible for fatty acid oxidation; nuclear factor kappa B (NF-κB) pathway associated with inflammation; SREBP (Sterol Regulatory Element-Binding Protein) pathway involved in lipid accumulation in the liver; c-Jun N-terminal kinase (JNK) pathway linked to insulin resistance; and transforming growth factor-beta (TGF-β) pathway contributing to fibrosis development (5). Current treatment options primarily focus on lifestyle modifications including diet and exercise, as well as certain pharmacological interventions targeting metabolic pathways; however, their efficacy remains limited (6). With the limited treatment options available, there is a pressing need to explore alternative therapies that can effectively manage this condition. Flaxseed,

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particularly due to its omega-3 fatty acids, lignans, and other bioactive compounds, has been shown to affect several signaling pathways that may be involved in its beneficial effects on NAFLD (7). Additionally, flaxseed oil has emerged as a promising candidate with potential benefits for liver health, particularly in addressing NAFLD by reducing liver inflammation, improving liver function, and lowering liver fat content (8). This might potentially normalize any elevations in WBC counts that are associated with inflammatory conditions like NAFLD. Studies suggest omega-3 fatty acids may improve lipid profiles (9,10). By improving lipid metabolism and reducing liver fat, flaxseed may also help maintain kidney function and possibly lower levels of urea and creatinine (Cr) (11). The mechanisms underlying flaxseed oil's effects on liver are multifaceted and may involve modulation of lipid metabolism through activation of PPARs (12), anti-inflammatory actions via inhibition of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), or antioxidant activities attributed to its rich content of omega-3 fatty acids. These mechanisms intersect with signaling pathways implicated in NAFLD pathogenesis, suggesting that flaxseed oil exerts its beneficial effects through targeted regulation of key molecular pathways driving disease progression. (13). On the other hand, atorvastatin, a commonly prescribed statin drug for lowering cholesterol levels, has shown promising effects in improving NAFLD through its impact on signaling pathways (14). For instance, studies have demonstrated that atorvastatin can activate AMPK leading to increased fatty acid oxidation and improved hepatic steatosis (15,16). Additionally, it can inhibit NF-κB activation thereby reducing inflammatory responses within the liver tissue (17). By targeting multiple pathways simultaneously, atorvastatin exhibits pleiotropic effects that go beyond its lipid-lowering properties. Atorvastatin exerts its therapeutic effects by inhibiting the activity of the HMG-CoA reductase enzyme, which is essential for cholesterol biosynthesis in the liver. By reducing cholesterol production, atorvastatin decreases intracellular cholesterol levels leading to upregulation of LDL receptors on hepatocytes for increased uptake of circulating LDL cholesterol from the blood. This mechanism not only lowers serum cholesterol but also influences lipid metabolism within the liver cells (18). Although statins can improve metabolic parameters associated with NAFLD, they can provide some degree of protection against kidney dysfunction (19). Some studies suggest that atorvastatin might lead to a reduction in urea and Cr levels by improving liver function and lipid profiles, thereby indirectly supporting renal function (20,21). Otherwise, in some cases, they can lead to mild increases in creatinine, especially in patients with pre-existing renal conditions (19). Atorvastatin primarily targets lipid levels rather than directly affecting CBC parameters. There is some evidence that statins may have anti-inflammatory effects that could lead to a reduction in white blood cell count (WBC), especially in conditions marked by inflammation (22). However, significant changes in WBC are not commonly reported. Studying these two agents in the context of NAFLD is rational due to their potential impact on lipid metabolism and inflammation pathways implicated in the pathogenesis of the disease. There's limited specific data on the combined effects of flaxseed and atorvastatin on complete blood count (CBC) parameters, urea and creatinine levels in NAFLD patients. So, more focused research would be required to draw definitive conclusions regarding their specific impacts on CBC outcomes in this population.

Materials and Methods

Animals and diet

Eighty male Wistar rats were purchased from Shahid Mirghani Research Institute (200-250 g) and they were randomized into ten groups (eight rats per group): 1) ND (normal diet) 2) HFD (high-fat diet), 3) HFD + ATO 10, 4) HFD + ATO 20, 5) HFD+ FO, 6) HFD + F, 7) HFD + ATO 10 + FO, 8) HFD + ATO 20 + FO, 9) HFD + ATO 10 + F, and 10) HFD + ATO 10 + F.

The animals in ND groups fed a chow diet (4.30 kcal per gram with 3.87% fat (soy oil), 17.46% casein protein, 68.7% carbohydrates, 8.97% minerals, and 1% vitamins) (23,24) and HFD groups fed chow and HFD (55% fructose solution and 0.1 ml/kg CCl4 (1:4 V/V dissolved in olive oil). Furthermore, atorvastatin administration was done at two different dosages (gavage, 10 and 20 mg/kg) diluted in 6% dimethyl sulfoxide (DMSO). Additionally, flaxseed and flaxseed oil were orally administrated 40 g/kg and 40 mg/kg, respectively. Flaxseed and flaxseed oil were purchased from Abkar Golestan Agro-industry Company (*VERJEN*).

They had ad libitum access to feed and water and were kept in a 12: 12 h light/dark cycle at 20-24° C. HFD-induced NAFLD was fed for 15 weeks (25) and the interventions were administrated once daily for 8 weeks. At the end of 23th week, after 12 hours of fasting, the animals were anesthetized by injection of 50 mg/kg ketamine and 5 mg/kg xylazine (Merck, Germany) (26) and then sacrificed.

All animals received humane care according to the Principles of Laboratory Animal Care, formulated by the

National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals designed by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised in 1985). The research was approved by the local ethics committee (IR.GOUMS.REC.1397.274).

Biochemical analysis

The concentrations of urea and Cr were measured by specific enzymatic kits following the manufacturer's instructions (Pars Azmoon., IRAN) (Autoanalyzer BT 3500, Med system, USA).

Blood cell parameters

CBC parameters (RBC, WBC, Hemoglobin: Hb, Hematocrit: Hct, mean corpuscular hemoglobin: MCH, mean corpuscular hemoglobin concentration: MCHC, mean corpuscular volume: MCV, Platelet count: Plt) were assessed by the automated hematology analyzer Sysmex-KX-21N (Japan).

Statistical analysis

The sample size was determined using G*Power software. We consider significance level (α) at 0.05 and power (1-β) at % 80 to determine sample size. Data are expressed as the mean±sd. The statistical analysis was carried using the Statistical Package for Social Science (SPSS) software program. Significant differences among the groups were determined by a one-way ANOVA. A probability value of 0.05 was determined to be statistically significant.

Results

Hematologic parameters

CBC analysis showed that administration of ATO 20 (P=0.015) led to decrease but co-administration of ATO 20 and FO (P=0.017) cause to increase in WBC compared to HFD. Also, WBC was lower in HFD+ATO 20 compare to HFD+ATO 10 (P=0.002). On other hand, administration of ATO 20 alone (P=0.020) or with F (P=0.026) led to decrease in RBC compared to HFD. In this regard, HFD+ATO 20 (P=0.000), HFD+FO (P=0.005), HFD+ATO 20+F (P=0.000), and HFD+ATO 20+FO (P=0.043) had lower HCT compared to the HFD (Figure 2). The results revealed that there weren't significant differences in Hb, MCV, MCH, and MCHC in intervention groups compared to HFD. Additionally, PLT had the lowest level in HFD+ATO 20+F compared to other HFD groups (Figure 3 and 4).

Renal indices

To assessment the renal indices, serum level of Cr was significantly higher in HFD+ATO 10 compared to the HFD (P=0.007). In intervention groups Cr were significantly lower in HFD+ATO 20 (P=0.001), HFD+F (P=0.004), HFD+FO (P=0.004), HFD+ATO 10+F (P=0.015), HFD+ATO 10+FO (P=0.007), and HFD+ATO 20+F (P=0.029) compared to HFD+ATO 10. Additionally, Cr level was lower in HFD+ATO 20 compared to HFD+FO+ATO 20 (P=0.017). Otherwise, there weren't significant differences in urea levels between all groups (Figure 1).

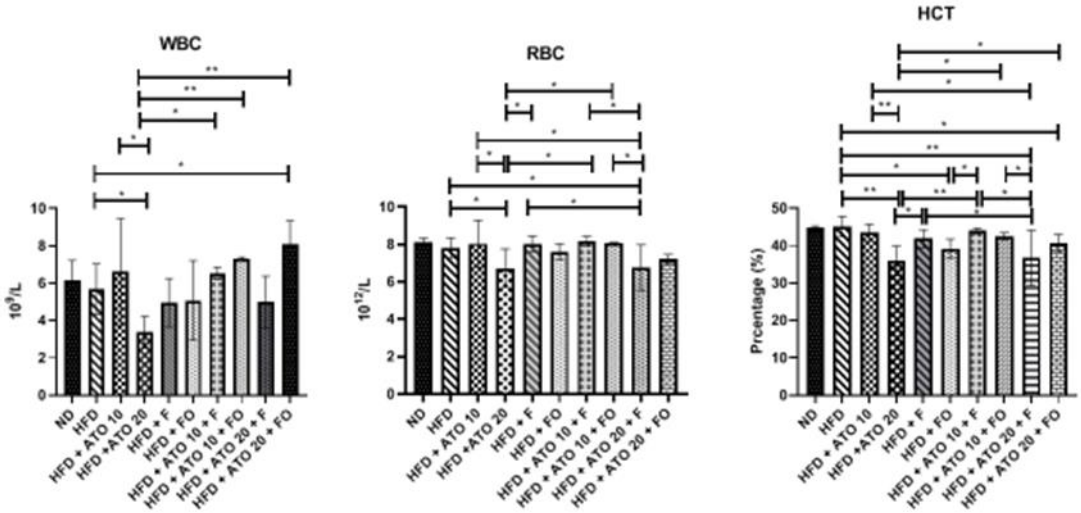

Figure 1. CBC indices (WBC, RBC, and HCT) in the study groups. The results are expressed as mean±SD for each group. Individual data points within the columns are indicated with dots. *P<0.05 compared to HFD, **P<0.001 compared to HFD. The lines connecting the columns indicate that groups differ from each other

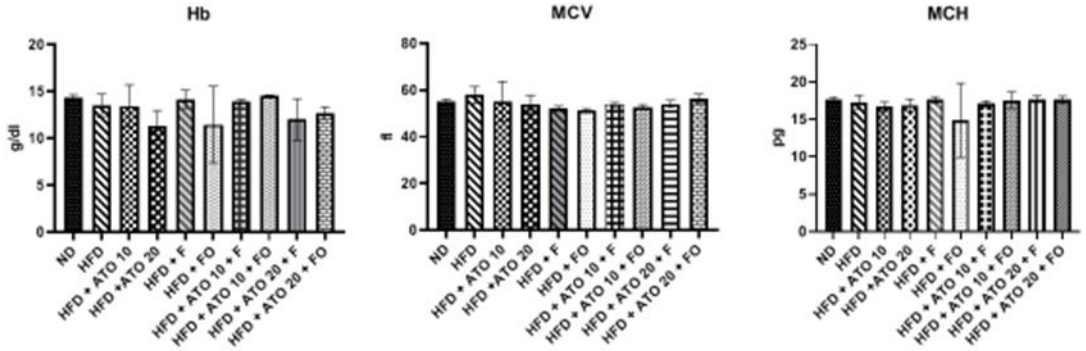

Figure 2. CBC indices (Hb, MCV, and MCH) in the study groups. The results are expressed as mean ± SD for each group. Individual data points within the columns are indicated with dots. **P*<0.05 compared to HFD, ***P*<0.001 compared to HFD. The lines connecting the columns indicate that groups differ from each other

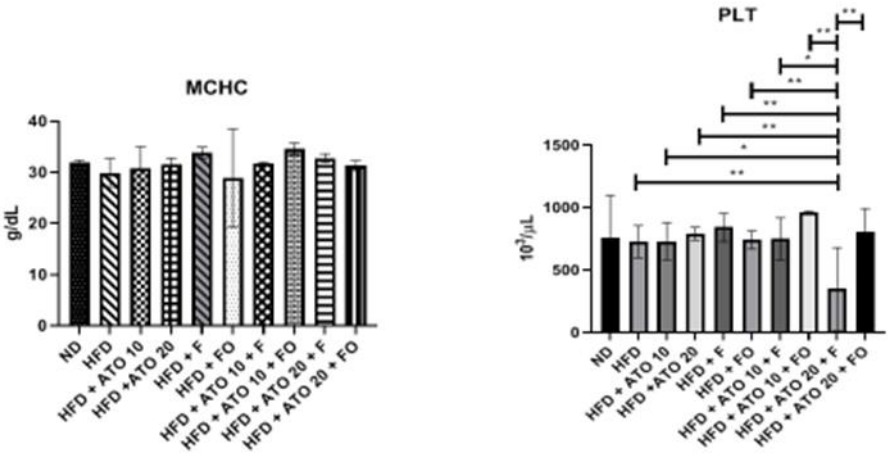

Figure 3. CBC indices (MCHC and PLT) in the study groups. The results are expressed as mean ± SD for each group. Individual data points within the columns are indicated with dots. **P*<0.05 compared to HFD, ***P*<0.001 compared to HFD. The lines connecting the columns indicate that groups differ from each other

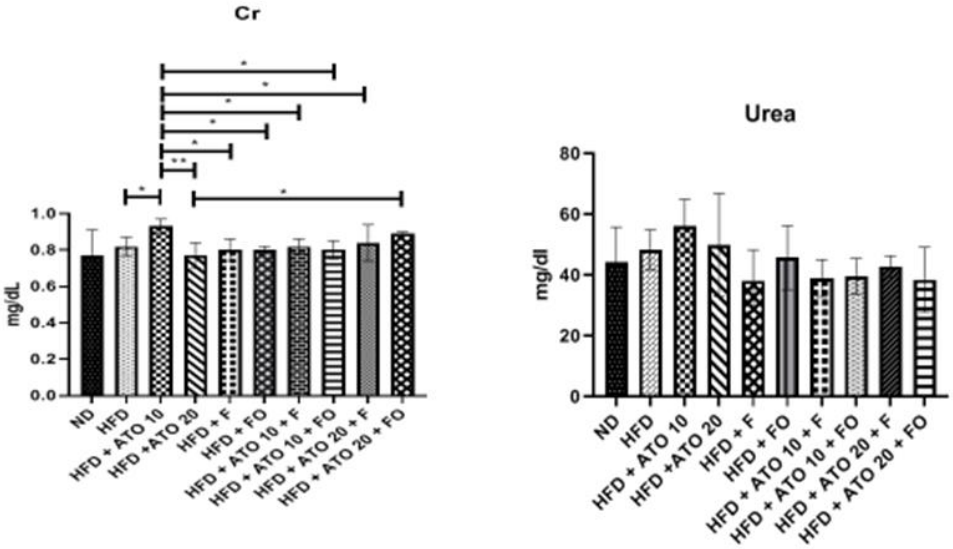

Figure 4. Renal indices in the study groups. The results are expressed as mean ± SD for each group. Individual data points within the columns are indicated with dots. **P*<0.05 compared to HFD, ***P*<0.001 compared to HFD. The lines connecting the columns indicate that groups differ from each other

Discussion

The management of NAFLD has gained significant attention due to its increasing prevalence and association with metabolic syndrome. Both flaxseed/flaxseed oil and atorvastatin have been investigated for their potential benefits in improving various metabolic parameters, including urea, Cr, and CBC metrics.

Emerging evidence suggests that atorvastatin may also exert protective effects on kidney function, potentially through mechanisms like reducing oxidative stress and inflammation in the kidneys. Improved renal function can lead to a decrease in creatinine levels (27). By improving lipid metabolism and reducing liver fat content, atorvastatin can enhance insulin sensitivity, leading to better kidney function and lower levels of urea and Cr (20). Our results showed that administration of ATO 10 mg/kg in rats fed HFD led to increase Cr and higher dose of it (ATO 20 mg/kg) cause to reduce Cr level, however this effect wasn't significant. At clinically relevant and moderate doses, atorvastatin exerts vascular and renal protective actions through improved endothelial function (increased NO bioavailability), anti-inflammatory signaling (reduced NF-κB activity and cytokine release), and decreased oxidative stress. These effects can increase renal perfusion and glomerular filtration and thereby lower circulating creatinine or prevent its rise (28,29). Higher statin doses may produce dose-dependent adverse effects that offset pleiotropic benefits. Mechanistically, high doses of atorvastatin can cause mitochondrial dysfunction in skeletal muscle and, in susceptible animals, subclinical myotoxicity (30).

Also, coadministration of ATO 10 mg/kg with F/FO was more efficient compared to administration alone. Although, this effect is reversed for ATO 20 mg/kg. Moreover, urea levels didn't show significant differences between groups. Along with our results, Stuglin, C. and K. Prasad determined that 32.7 g flaxseed for 4 weeks decreased Cr but didn't change urea levels in healthy men (31). These alternations can relate to antioxidant activity (scavenging ROS), anti-inflammatory signaling (↓NF-κB, ↓proinflammatory cytokines), improved endothelial function, and mitigation of oxidative injury in muscle and kidney. These actions can preserve mitochondrial function, reduce muscle catabolism, and improve renal perfusion/GFR, thereby lowering serum creatinine or preventing its rise (13). At moderate ATO exposure, the atorvastatin's anti-inflammatory and endothelial benefits complement flaxseed's antioxidant and anti-inflammatory actions, producing additive or synergistic improvement in renal perfusion and tubular function. This combined effect likely underlies the greater reduction in creatinine observed with coadministration at the 10 mg/kg ATO dose. Higher doses of atorvastatin have been associated with greater potential for statin-induced mitochondrial stress and/or subclinical myotoxicity. This can (a) cause rise in creatinine through a greater turnover of muscle mass, or altered creatine metabolism and/or (b) deteriorate renal tubular energetics, despite the protective signaling of flaxseed, negating the benefit that flaxseed affords. Pharmacokinetic interactions are also plausible whereby high levels either of atorvastatin alter the metabolism of flaxseed bioactive in the liver, or their tissue distribution, decreasing their effective tissue concentrations (32,33). Serum urea primarily reflects hepatic urea cycle activity and whole-body protein catabolism rather than short-term changes in renal perfusion alone. In this protocol neither ATO nor F/FO plausibly produced large changes in whole-body protein breakdown or hepatic urea production; therefore, blood urea remained stable across groups despite modest creatinine fluctuations.

Flaxseed consumption may influence the activity and function of various subtypes of WBCs, including T cells, monocytes, and neutrophils (22). Flaxseed may influence the production of pro-inflammatory cytokines, thereby reducing the signaling that leads to WBC proliferation and activation. This can result in a more controlled immune response and potentially lower WBC counts (13). Atorvastatin may exert anti-inflammatory effects that can influence WBC activity. By reducing inflammation, it can help modulate the immune response and potentially decrease the recruitment of WBCs to sites of inflammation (34,35). Studies have shown that atorvastatin can affect the function of various WBC populations, including monocytes and T cells, enhancing the regulatory functions of immune cells (22,36). This may lead to a more balanced immune response. Atorvastatin has been associated with decreases in total WBC counts (38). This could be beneficial in preventing excessive inflammation associated with high WBC counts, which is often linked to conditions like cardiovascular disease. Along with evidence, our results demonstrated that ATO 20 mg/kg caused to reduce WBC but coadministration of ATO with F led to increase. However, low dose of ATO (10 mg/kg) had higher level of WBC compared to high dose (20 mg/kg). Statins exert dose-dependent immunomodulatory and anti-inflammatory effects through inhibition of HMG-CoA reductase and downstream isoprenoid

synthesis, which reduces prenylation of small GTPases and suppresses proinflammatory signaling and cytokine production (e.g., ↓TNF-α, ↓IL-6). At higher doses these effects are stronger and can result in net reductions in circulating inflammatory leukocytes or in leukocyte production/mobilization, which can present as reduced WBC counts in animal models or patients receiving high statin exposure (22). Conversely, lower statin doses may produce weaker anti-inflammatory signaling while still allowing baseline or compensatory immune activation; this can explain why ATO 10 mg/kg produced higher WBC than ATO 20 mg/kg in our model (10 mg/kg insufficient to fully suppress leukocyte mobilization/production whereas 20 mg/kg produced greater immunosuppressive/anti-inflammatory effect). Co-administration with flaxseed attenuated statin-induced leukocyte suppression (by antioxidant and pro-survival effects on immune cells or their progenitors), producing the observed increase in WBC when ATO was combined with F.

Chronic inflammation can lead to erythropoiesis as a compensatory mechanism, which can raise RBC and HCT levels (38). The omega-3 fatty acids found in flaxseed can improve the fluidity and stability of RBC membranes, which is crucial for their functionality and resilience under various physiological stresses (39). Because of anti-inflammatory effect of Omega-3 fatty acids in flaxseed and atorvastatin, they may affect RBC production and, consequently, lower hematocrit levels. In this direction, in our study ATO 20 mg/kg and ATO 20 mg/kg + F had lower RBC and HCT. Additionally, FO or in combination with ATO 20 mg/kg had impact on lowering HCT. It means that combination of F/FO and ATO may provide synergistic effects. High-dose atorvastatin (ATO 20 mg/kg) likely reduced RBC and Hct via stronger anti-inflammatory signaling and dose-related effects on hematopoietic progenitor mitochondrial function and erythrocyte membrane lipid composition (31,40). On the other hand, F/FO alters erythrocyte membrane fatty acid composition, improves deformability and reduces blood viscosity and inflammation (22,41), and when combined with high-dose ATO these effects are additive or synergistic, resulting in further lowering of RBC and Hct. The interplay of flaxseed's nutrients with atorvastatin's mechanisms presents a multifaceted approach toward improving the integrity and functionality of RBCs, signaling a potential for enhanced therapeutic strategies.

Omega-3 fatty acids, including alpha-linolenic acid (ALA), have been shown to exhibit antiplatelet properties through incorporating into cell membranes which can lead to changes in platelet receptor activity (42). On the other hand, Omega-3 fatty acids compete with omega-6 fatty acids (like arachidonic acid) for enzymes that produce eicosanoids, which are signaling molecules that promote inflammation and platelet aggregation (43). By increasing omega-3 levels, flaxseed promotes the production of less inflammatory eicosanoids, thereby reducing platelet activation. Flaxseed has been associated with improved endothelial function. The endothelium plays a critical role in regulating platelet activity. Improved endothelial health can lead to the release of substances that inhibit platelet aggregation (44). According to our results, coadministration of F and ATO 20 mg/kg cause to decrease PLT compared to HFD (P=0.001). Also HFD + F + ATO 20 mg/kg significantly had the lowest level of PLT in comparison with other HFD groups. Flaxseed's anti-inflammatory properties may also contribute to improved platelet function. Chronic inflammation can lead to increased platelet activation (45), and by reducing inflammation, flaxseed may help to normalize platelet behavior. Indeed, high-dose atorvastatin (ATO 20 mg/kg) likely reduced PLT through stronger anti-inflammatory and isoprenoid-dependent inhibition of platelet activation and, at marrow level, by dose-dependent effects on progenitor energetics and F/FO further reduced PLT via ALA-mediated shifts in eicosanoid signaling, antioxidant effects and decreased thrombopoietic stimuli. So, combined ATO 20+ F/FO produces additive suppression of platelet activation and production, accounting for the lowest PLT observed in the HFD+F+ATO20 group

Some studies have indicated that supplementation with flaxseed or flaxseed oil can lead to reductions in markers of platelet activation (44,46), although the effects can vary depending on the dosage and form of flaxseed used. In this regard, Mocanu, V *et al.,* showed that 15 g flaxseed/100 g food significantly reduced platelet adhesion in ovariectomized female rats (47). Moreover, secoisolariciresinol diglucoside (SDG) in flaxseed, inhibits lipid peroxidation, which could reduce oxidative changes of plasma lipoproteins and platelet adhesion to oxidized LDLs (48,49). Besides, Statins like atorvastatin improve endothelial function by enhancing the production of nitric oxide (NO), a potent vasodilator. Nitric oxide helps to inhibit platelet activation and aggregation (50). Improved endothelial health can promote a balance between pro-aggregatory and anti-aggregatory factors (51). Some studies have suggested that atorvastatin can directly affect platelet function, leading to reduced aggregation. This may be due to changes in the expression of receptors involved in platelet

activation (52,53).

Atorvastatin's ability to target multiple signaling pathways implicated in metabolic disorders highlights its potential as a therapeutic agent beyond just lowering cholesterol levels. The potential effects of flaxseed and atorvastatin on urea, Cr, and CBC parameters in metabolic disorders highlight a multifaceted approach to managing this complex disease. Both interventions show promise in improving kidney function and modulating inflammatory responses, which may lead to better overall health outcomes. However, further research with larger sample sizes and controlled studies is essential to elucidate the specific mechanisms and clinical relevance of these findings.

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