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Original Research Article

Comparison of Saffron (*crocus sativus* l.) and Atorvastatin for Anti-dyslipidaemic and Anti-Oxidant Effects in Dyslipidaemia Male Rat Models

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ABSTRACT

Dyslipidaemia is characterized by abnormal blood lipid profiles and is commonly treated with atorvastatin. However, its effectiveness may be reduced due to statin intolerance (SI). Saffron has gained interest as an alternative due to its potential lipid-modulating and antioxidant properties. This study aimed to compare the anti-dyslipidaemic and antioxidant effects of saffron extract and atorvastatin in male Wistar rats with dyslipidaemia. Thirty male Wistar rats (90 days old, 150–200 g) were divided into five groups. Group P1 received a standard diet, while groups P2–P5 were fed a high-fat diet (HFD) for 15 days to induce dyslipidaemia. Groups P3 and P4 received saffron extract at doses of 16 mg/200 g BW and 32 mg/200 g BW, respectively, while group P5 received atorvastatin at 0.2 mg/200 g BW. Lipid profiles (total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG)) were assessed on days 16 and 37. Serum malondialdehyde (MDA), an oxidative stress marker, was measured on day 37. Results showed that saffron extract at 32 mg/200 g BW/day significantly reduced TC, LDL, and TG levels, and increased HDL compared to the 16 mg/200 g BW/day dose. However, atorvastatin showed greater improvements in the lipid profile. Saffron at 32 mg/200 g BW/day also led to a greater reduction in serum MDA levels than doses of 16 mg/200 g BW/day and atorvastatin. Saffron demonstrated superior antioxidant activity, while its lipid-lowering effect was inferior to atorvastatin. Further research involving inflammatory biomarkers is needed to better elucidate its therapeutic potential.

Keywords: Antioxidant, Dyslipidaemia, Lipid Profile, Malondialdehyde, Saffron

Introduction

Dyslipidaemia is a disorder in lipoprotein metabolism that results in elevated levels of total cholesterol (TC; >200 mg/dL), low-density lipoprotein (LDL; >130 mg/dL), triglycerides (TG; >150 mg/dL), and a decrease in high-density lipoprotein (HDL; <50 mg/dL).[1,2] This condition has been identified as a major risk factor for various cardiovascular diseases (CVDs), including coronary artery disease, stroke, and peripheral artery disease.[3,4] According to the 2023 World Health Organization (WHO) report,[5] 39% of the global adult population suffers from dyslipidaemia, with a higher prevalence observed in women (40%) compared to men (37%). The increasing prevalence of dyslipidaemia is estimated to contribute to 2.6 million deaths (4.5% of the total) and 29.7 million Disability-Adjusted Life Years (DALYs), accounting for 2% of the total DALYs.[5,6] The prevalence of dyslipidaemia continues to rise across all age groups, including adults, adolescents, and children. Individuals with dyslipidaemia have a twofold higher risk of CVDs and diabetes mellitus compared to those with normal lipid levels.

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Dyslipidemia is a complex condition with multiple underlying mechanisms, frequently resulting from intrinsic factors, extrinsic factors, or a combination of genetic predisposition and environmental influences. This disorder is driven by increased delivery of free fatty acids to the liver due to higher total and visceral adiposity, insulin resistance, and a pro-inflammatory state induced by macrophage infiltration into adipose tissue. A high-fat diet promotes lipid absorption in the intestine, where lipids are transported to the liver via chylomicrons to synthesize triglycerides (TG) and endogenous cholesterol. The liver subsequently releases TG and very low-density lipoprotein (VLDL) into the bloodstream, which is hydrolysed into intermediate-density lipoprotein (IDL) and later converted to low-density lipoprotein (LDL). In dyslipidaemia, circulating adiponectin levels are diminished. Adipokines, including adiponectin and resistin, are essential in regulating lipid metabolism. Lower adiponectin levels are linked to increased serum triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels. Elevated circulating cholesterol levels can also induce oxidative stress and mitochondrial dysfunction, which leads to increased production of reactive oxygen species (ROS) and pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and interleukin-12 (IL-12), during lipid metabolism. Activation of the inflammatory response also decreases HDL-C, impairing reverse cholesterol transport and causing concurrent alterations in apolipoproteins, enzymes, and antioxidant defence. This reduction in HDL-C and phospholipids triggers compensatory responses, ultimately leading to hypertriglyceridemia. Additionally, increased ROS production enhances lipid peroxidation, as elevated serum malondialdehyde (MDA) levels indicate. If this process continues, it accumulates cholesterol within cells, damaging cell membranes and contributing to organ dysfunction in the heart, liver, and kidneys.
Atorvastatin is a statin-class drug used in the management of

dyslipidaemia. It works by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby preventing HMG-CoA conversion to mevalonate.[20,21] Statins are among the most widely prescribed medications due to their ability to prevent cardiovascular disease.[22,23] However, recent reports indicate that statin intolerance occurs in some patients and requires careful consideration. Statin intolerance occurs when a patient cannot continue using a statin due to side effects or because blood tests show that specific liver or muscle function markers are sufficiently abnormal.[24,25] Moreover, recent reports also mention that many statin users have developed resistance as they fail to achieve adequate cholesterol reduction targets.[26,27] Therefore, alternative therapies with less risk of side effects need to be studied, including phytochemicals that have also shown therapeutic effects.

Saffron (*Crocus sativus L.*) is a widely used Mediterranean herbal plant that has gained significant attention for its beneficial properties and mechanisms. Animal and human studies have reported the therapeutic effects of saffron and its biologically active compounds (crocin, crocetin, picrocrocin, and safranal) as anti-dyslipidaemic and antioxidant agents. The antioxidant activity of saffron can scavenge free radicals and inhibit lipid peroxidation. Its hypolipidemic activity occurs through the inhibition of lipase enzymes and cholesteryl ester transfer protein (CETP). Previous studies have extensively discussed the hypolipidemia effects of saffron, but there has been limited discussion on the combined hypolipidemic and antioxidant effects of saffron. However, whether oral saffron extract possesses drug-like properties comparable to statins remains to be investigated. Therefore, this study aims to investigate the anti-dyslipidaemic and antioxidant effects of saffron extract and atorvastatin in male Wistar rats with dyslipidaemia.

Materials and Methods

Drugs and Chemicals

Materials used in this research include saffron extract (Piping Rock Saffron Extract®) made in the United States by Piping Rock Health Products, LLC; Atorvastatin 10 mg (OGB Dexa Medica®) made in Indonesia by PT. Ferron Par Pharmaceutical; and an MDA ELISA kit made in China by Bioassay Technology Laboratory (BT Lab) with catalog number E0156Ra.

Animal preparation

Systematic random sampling was used in this experimental study. A total of 30 healthy male Wistar rats (90 days old and weighing 150-200 g) were acclimatized prior to the study. The research was conducted in Surabaya, Indonesia, from April to June 2024. Animals were fed a standard rat diet (Pokphand CP 593, PT Charoen Pokphand, Indonesia) and provided with aquadest for drinking water. The rats were housed under standard conditions at a temperature of 21-24°C, with controlled lighting of 60-80 g W/cm (lights on at 07:00 hours) and a 12:12 hour light-dark cycle. This experiment was conducted in accordance with the Ethical Guidelines of WHO 2011 and CIOMS (Council for International Organizations of Medical Sciences) 2016.[32, 33] The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Airlangga, under certificate number 40/EC/KEPK/FKUA/2024.

Induction of Dyslipidemia with High Fat Diet (HFD)

After a week, animals in high-fat diet cages were fed a high-fat diet that contained 4 g cow brain, 5 g duck egg yolk, 46 g starch, 10g corn oil, with lard oil 10ml/kg body weight/day), for 15 days.[34,35] The proportions were carefully measured using a digital scale (SF-400, Panasonic, Jakarta).[34]

Animal Experimental Design

The animals were acclimatized for seven days prior to the experiment (n = 30). All animals were randomly divided into five groups (P1, P2, P3, P4, and P5), with each group consisting of six rats. The P1 group received a standard diet and normal saline treatment. Meanwhile, the other groups (P2, P3, P4, and P5) received a HFD for 15 days. The P2 group continued to receive the HFD for the next 21 days. The P3 and P4 groups were gavaged with saffron extract at a daily dose of 16 mg/200 g BW and 32 mg/200 g BW, respectively, for 21 days. The P5 group were gavaged with atorvastatin at a daily dose of 0.2 mg/200 g BW for 21 days. The saffron extract dose was based on a previous study by Hoshyar et al., while the dose of Atorvastatin was calculated using the animal equivalent dose (AED) according to body surface area.

Measurement of body weight

The body weight of each individual rat (g) was measured three times: at the beginning of the experiment (day 1), after HFD induction (day 16), and after the administration of saffron and Atorvastatin (day 37), using an Ohaus Triple Beam balance (Shimadzu, Japan).[38]

Measurement of Lipid Profile

Lipid profile measurements (total cholesterol, HDL, LDL, and triglycerides) were taken after HFD induction on day 16 (L1) and after treatment on day 37 (L2). The first blood sample was collected from the lateral tail vein, while the second sample was obtained via cardiac puncture.[11,39] Using an Automatic Clinical Chemistry Analyzer, total cholesterol (TC) was measured using the CHOD PAP method (Cholesterol Oxidase Para Aminophenazon), LDL and HDL levels were measured using the direct enzymatic method, while Triglyceride (TG) levels were measured using the enzymatic glycerol method.[40,41]

Measurement of Malondialdehyde (MDA)

At the end of the study, Blood samples were collected via cardiac puncture in sterile vials without anticoagulant for serum separation. The serum MDA level was measured using an immunoassay method using MDA ELISA kit made in China by Bioassay Technology Laboratory (BT Lab) with catalog number E0156Ra.[42,43] Normal levels of Free MDA in rat blood serum are 89-195 nmol/mL.[44]

Statistical analysis

The data on body weight, lipid profile, and MDA levels were tabulated and analyzed. We conducted the Shapiro-Wilk test and Levene's test to assess the homogeneity and normality of the data. If normally distributed, and homogeneous variance was assumed, data were expressed as the mean ± standard deviation (X±S). One-way analysis of variance (ANOVA) and Post-hoc Bonferroni were used for two-group comparisons. Nonnormally distributed data were expressed as median (M) and interquartile range (25th and 75th percentiles) and analyzed using the Kruskal–Wallis and Post hoc Mann-Whitney for two-group comparisons. $p < 0.05$ was considered statistically significant.[45,46] SPSS 24.0 was used for statistical analyses.[47]

Results and Discussion

Saffron Improves Lipid Profile

The first lipid profile measurement (TC, LDL, TG, and HDL levels) was conducted after HFD induction on day 16 (L1). The second measurement was taken after the administration of saffron extract and atorvastatin on day 37 (L2). The results indicated that the administration of saffron extract at doses of 16 mg/200 g BW/day or 32 mg/200 g BW/day for 21 days resulted in a significant decrease in TC, LDL, and TG levels, along with an increase in HDL levels, compared to the control group with a standard diet (SD) ($p < 0.01$). Notably, the 32 mg/200 g BW/day dose led to greater improvements the lipid profiles than the 16 mg/200 g BW/day dose. Both groups receiving saffron extract (HFD + saffron at 16 mg/200 g BW/day and HFD + saffron at 32 mg/200 g BW/day) and the group receiving atorvastatin (HFD + atorvastatin) exhibited significantly lower TC, LDL, and TG levels, and higher HDL levels compared to the HFD group ($p < 0.01$). Comparative data for all groups are presented in Table 1.

Lipid profile levels were measured after HFD administration on days 16 and 37. Animals induced with an HFD exhibited increased levels of TC, LDL, and TG, along with decreased HDL levels, compared to the group on a standard diet. Previous studies have demonstrated that 15 days of HFD induction in a dyslipidemia rat model can significantly elevate plasma cholesterol levels, as observed in our research model. A high-fat diet increases lipid absorption in the intestine, where lipids are transported to the liver via chylomicrons for TG and endogenous cholesterol synthesis. The liver releases TG and very low-density lipoprotein (VLDL) into circulation, hydrolysed into intermediate-density lipoprotein (IDL) and then converted into LDL.

Table 1: Effects of Saffron Extracts on lipid profile in Rats

No	Groups	TC (Mean±SD)		LDL (Mean±SD)		HDL (Mean±SD)		TG (Mean±SD)	
		L1	L2	L1	L2	L1	L2	L1	L2
1	**P1**	31.2 ±2.167	30.8 ±0.836[a]	15.6 ±1.140	16.8 ±1.923[a]	37.6 ±3.049	38.4 ±3.507[a]	88 ±3.674	89.2 ±3.271[a]
2	**P2**	60.1 ±3.763	68.6 ±3.614[b]	30 ±1.414	30.0 ±2.607[b]	31.5 ±2.880	27.6 ±1.516[c]	126.5 ±4.037	131.5 ±3.016[c]
3	**P3**	63 ±5.966	39.3 ±2.065[c]	31.1 ±2.136	24.1 ±1.471[c]	29.5 ±3.016	47.5 ±5.244[b]	133.5 ±4.929	117 ±2.966[d]
4	**P4**	63.3 ±6.055	34.3 ±3.141[a]	32.1 ±2.786	20.0 ±2.000[a]	29.5 ±1.870	49.8 ±7.277[b]	130.6 ±6,186	107.6 ±7.763[b]
5	**P5**	62.6 ±6.024	32.6 ±2.880[a]	30.8 ±2.774	18.2 ±1.303[a]	27.8 ±1.923	52.3 ±1.923[d]	135.2 ±5.069	99.8 ±6.942[b]
	p-value	0.000*	0.000*	0.000*	0.000	0.000*	0.000*	0.000*	0.000*

*Significance with $p<0.05$ (ANOVA); L1 = Measurement on day 16 after the induction of a high-fat diet (HFD); L2 = Measurement on day 37 after treatment; **K-** (Standard diet); **K+** (high-fat diet (HFD)); **P1** (HFD + *saffron extract* 16 mg/200 g BW/day); **P2** (HFD + *saffron extract* 32 mg/200 g BW/day); **P3** (HFD + Atorvastatin 0.2 mg/200 g BW/day).

Elevated circulating cholesterol levels can trigger oxidative stress and mitochondrial dysfunction, resulting in increased production of reactive oxygen species (ROS) and proinflammatory cytokines such as TNF-α, Interleukin-6 (IL-6), Interleukin-1β (IL-1β), and Interleukin-12 (IL-12) during fat metabolism. Activating the inflammatory cascade decreases HDL cholesterol (HDL-C), impairing reverse cholesterol transport and causing parallel alterations in apolipoproteins, enzymes, antioxidant capacity, and ATP-binding cassette A1 (ABCA1)-dependent efflux. This reduction in HDL-C and phospholipids stimulates compensatory changes, resulting in hypertriglyceridemia. If this process persists, it increases cholesterol accumulation in cells, causing organ dysfunction in the heart, liver, and kidneys.

Significant reductions in LDL, TG, and TC levels, along with increased HDL levels, were observed in the experimental animals treated with saffron extract compared to the HFD group. The findings from previous studies indicated that saffron extract has a hypolipidemic effect through several mechanisms. Crocin, the active ingredient in saffron, is a competitive inhibitor of the pancreatic lipase enzyme, which plays a role in emulsifying lipids into fatty acids and glycerol, resulting in malabsorption of fat and cholesterol in the digestive tract.[58,59] These results are consistent with a previous study by Zhang et al.[60] which reported decreased lipase enzyme activity in rats treated with saffron. Crocin also lowers lipid profile levels by inhibiting cholesterol absorption in the intestine.[61,62] Additionally, another active ingredient in saffron, crocetin, can also reduce LDL, TG, and TC levels by inhibiting cholesterol ester transfer protein (CETP). [63,64] CETP is a plasma glycoprotein that lowers HDL concentration by transferring HDL cholesterol esters to lipoproteins containing apo B for TG formation.[63] Two other studies further support the use of saffron extract in reducing serum TG, TC, and LDL while increasing HDL levels.[65,66]

This study also demonstrated that administering saffron extract at a dose of 32 mg/200 g BW/day to greater improvements in the lipid profile compared to a 16 mg/200 g BW/day dose. These results are consistent with previous studies, which found that administering saffron extract at 32 mg/200 g BW/day for 20 days improved the lipid profile in blood serum more effectively than a 20 mg/200 g BW/day dose.[67] Similarly, a study by Rahim et al.[63] reported that saffron extract at 32 mg/200 g BW/day significantly reduced TC, LDL, and TG levels, comparable to the effects of standard therapy.[36,63]

In our study, although the administration of saffron extract improved the lipid profile, the improvement was more pronounced in the HFD + Atorvastatin group. Our results demonstrate that administering the standard drug Atorvastatin significantly reduces TC, LDL, and TG levels while increasing HDL levels compared to the HFD group (P = 0.000). Research conducted by Kahn et al.[68] reported that Atorvastatin administration significantly reduces TC, LDL, and TG levels in HFD-induced mice. Similarly, a study by Ji, et al.[69] demonstrated that Atorvastatin effectively improved dyslipidemia in mice by reducing serum TC and LDL levels. The anti-hypolipidemic effect of Atorvastatin is achieved through the competitive inhibition of HMG-CoA reductase. This enzyme catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis.[68,70] The inhibition of the conversion of mevalonate to cholesterol by statins reduces the intracellular content of isoprenoids such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), thereby lowering cholesterol synthesis in the bloodstream.[20,71]

Saffron exerts an MDA-lowering effect

MDA levels were measured after the administration of saffron and atorvastatin on day 37. The results indicated that administering saffron extract at doses of 16 mg/200 g BW/day or 32 mg/200 g BW/day significantly reduced serum MDA levels compared to the control group on a standard diet ($p < 0.001$). The reduction in serum MDA levels was more pronounced in the group receiving the 32 mg/200 g BW/day dose compared to the group receiving the 16 mg/200 g BW/day dose. Additionally, the administration of saffron extract at 32 mg/200 g BW/day demonstrated greater efficacy in reducing serum MDA levels than standard atorvastatin therapy. Comparative data for all groups are presented in Figure 1.

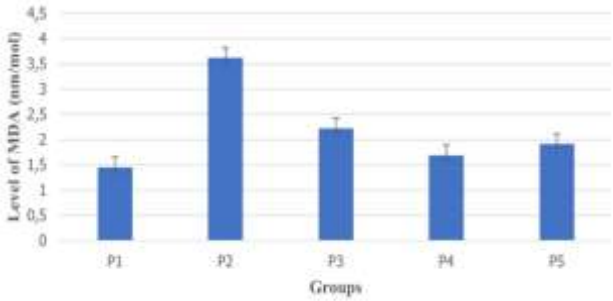

Figure 1: Effects of Saffron Extracts on MDA serum in Rats. **P1** (Standard diet); **P2** (high-fat diet (HFD); **P3** (HFD + *saffron extract* 16 mg/200 g BW/day); **P4** (HFD + *saffron extract* 32 mg/200 g BW/day); **P5** (HFD + Atorvastatin 0.2 mg/200 g BW/day)

HFD administration is known to induce oxidative stress and stimulate the production of various pro-inflammatory cytokines, such as TNF-α, interleukin-6 (IL-6), interleukin-1β (IL-1β), and interleukin-12 (IL-12), during fat metabolism.[54,72] Lipids, especially unsaturated fatty acids, are among highly susceptible to oxidative stress. Oxidants extract hydrogen atoms, forming unstable lipid radicals (L-). Subsequent addition of an oxygen molecule produces lipid peroxyl radicals (LOO-), which extract hydrogen from other sources. This chain reaction leads to lipid peroxidation, forming more stable compounds such as lipid hydroperoxides (LOOH). By-products, including malondialdehyde (MDA), are produced during this process.[73,74] MDA is a lipid peroxidation product generated in vivo by decomposing arachidonic acid (AA) and more prominent polyunsaturated fatty acids (PUFAs).[75,76] It has been widely used as a biomarker to measure oxidative stress in various biological samples, including blood serum.[74,77]

The use of saffron in reducing MDA levels in our study aligns with previous research, which reported that saffron extract and its secondary metabolites exhibit antioxidant effects. Saffron extract demonstrates hydroxyl radical scavenging activity and inhibits lipid peroxidation, resulting in decreased MDA levels. The antioxidant and anti-inflammatory activities of saffron extract are attributed to its components, including carotenoids, flavonoids, and anthocyanins. Water-soluble carotenoids in saffron, known as crocin, exhibit a more potent antioxidant effect than α-tocopherol. Crocin and safranal possess double the free radical scavenging activity at a concentration of 500 ppm. Crocin captures free radicals, while crocetin removes free radicals and inhibits lipid peroxidation. Additionally, saffron can induce endogenous antioxidants, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD).

The results of this study are consistent with a previous study conducted by Vakili, et al.[67] which demonstrated that saffron effectively reduced serum MDA levels in mice treated with an HFD and saffron extract at 100 mg/kg BW/day for 20 days. Their results showed lower MDA levels in the treatment group compared to the control group. Another study by Altinoz, et al.[83] also reported significant reductions in MDA levels in the treatment group compared to the HFD group ($p < 0.05$). Furthermore, Hoshyar, et al[36] demonstrated that MDA levels in the treatment group receiving saffron extract at a dose of 80 mg/kg BW/day for 14 days were 1.94 ± 0.1 nm/mol, compared to 4.92 ± 0.3 nm/mol in the HFD-only group.[67,83] In our study, the administration of Atorvastatin reduced MDA levels to 1.92 ± 0.122 nm/mol. However, the decrease in MDA levels was more significant in the saffron group receiving a dose of 32 mg/200 g BW/day. These results demonstrate that at this dose, saffron's antioxidant capacity is more significant than Atorvastatin's. The primary mechanism of action of Atorvastatin is known to improve the lipid profile. However, numerous studies have shown that statins also exert pleiotropic effects, acting as anti-inflammatory and antioxidant agents. These pleiotropic effects are typically observed at the onset of treatment. As an antioxidant, Atorvastatin reduces oxidative stress in cells by increasing glutathione reductase activity and inducing the heme-oxygenase 1 system. Additionally, Atorvastatin inhibits prooxidant enzymes, such as nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase, and increases antioxidant enzymes, such as catalase (CAT). Although the anti-dyslipidemic effect of saffron extract was lower than that of Atorvastatin, we have successfully demonstrated that the antioxidant effect of saffron at specific doses is superior to Atorvastatin's. Further studies focusing on the specific phytochemical content of saffron are needed to identify the effects of each compound on improving lipid profiles and reducing MDA levels. Further research on other inflammatory biomarkers is also essential to provide more comprehensive evidence of saffron's antioxidant capabilities.

Conclusion

Saffron extract has been shown to improve the lipid profile by reducing TC, LDL, and TG levels, while increasing HD levels. However, its efficacy in Improving lipid profile remains significantly lower than that of atorvastatin. In contrast, when it comes to reducing MDA levels, saffron extract demonstrates superior efficacy compared to atorvastatin. Further research is warranted to explore the mechanisms underlying saffron's antioxidative properties and its potential synergistic effects when combined with standard lipid-lowering therapies.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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