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# ANTI-HYPERLIPIDEMIC ACTIVITIES OF ETHYL ACETATE PARTITIONED EXTRACT OF *Daucus carota* L. SEED IN TRITON X-100 INDUCED HYPERLIPIDEMIC MICE

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## ABSTRACT

This study evaluated the anti-hyperlipidemic properties of aqueous (AQF) and ethyl acetate (EAF) partitioned fractions of *Daucus carota* seed in triton X-100 induced hyperlipidemia in mice. Hyperlipidemia was induced by single intraperitoneal injection of freshly prepared triton X-100 (100 mg/kg body weight) in forty (40) mice, which were randomly distributed into 8 groups of 5 mice each (group B - I) and treated with 0.2 mL distilled water, simvastatin, AQF and EAF. Group A served as non-induced untreated mice, which received 0.2 ml distilled water. AQF and EAF did not significantly ($p$>0.05) improve the liver-body weight ratio except in EAF at 2 mg/kg body weight. Treatment with AQF and EAF significantly decrease ($p$<0.05) total cholesterol, triglyceride, low-density lipoproteins, atherogenic, coronary artery, and cardiac indices when compared with hyperlipidemic untreated mice. Furthermore, treatment with the partitioned extracts significantly ($p$<0.05) improved high-density lipoprotein levels in AQF at dose of 6 mg/kg body weight and EAF at dose of 5 mg/kg body weight when compared with hyperlipidemic untreated mice. The results indicated that AQF and EAF partitioned fractions of *D. carota* seed possesses significant anti-hyperlipidemic activities in triton X-100 induced hyperlipidemic mice and could be beneficial in preventing cardiovascular diseases associated with hyperlipidemia.

**Keywords**: *Daucus carrota*, Seed, Anti-hyperlipidemia, Lipid profile, Cardiovascular index

## INTRODUCTION

Hyperlipidemia is a disorder that is characterized by an abnormal rise in lipid levels in the blood. Hyperlipidemia has been ranked a risk factor, which contribute to the prevalence and severity of coronary heart diseases (Grundy, 1986). It is characterized by elevated levels of cholesterol (CHOL), triacylglycerides (TRIG), very low-density lipoprotein cholesterol (VLDL-chol) and low-density lipoprotein cholesterol (LDL-chol) with corresponding low level of high density cholesterol (HDL-chol). Cholesterols are essential constituents of biological membranes, and they play other roles such as precursor in the biosynthesis of bile acids, steroid hormones and vitamins (Repa and Mangelsdorf, 2000). However, the resulting disorders from hyperlipidemia can lead to atherosclerosis, coronary heart disease and stroke, which are among the primary cause of death (Smith, 1993). The class of drugs used in lowering of plasma cholesterol are the statins. Simvastatin is a member of the statins that is widely used, and act by the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity (Collins *et al*., 2002). Statins are prescribed in the treatment of hypercholesterolemia, and have been linked to the reduced morbidity and mortality from hypercholesterolemia in high-risk adults (Belay *et al.,* 2006). Furthermore, statins are

well tolerated, but there are reports of adverse effects (Mahley and Bersot, 2001; Bellosta *et al.,* 2004; Mills *et al.,* 2011). Hence, the search for alternative therapy in the management of hyperlipidemia has been extended to natural products due to their efficacy, availability and little or no side effects.

*Daucus carota* L. (Carrot) is a popular vegetable, from the angiosperm, which is grown throughout the world. Its economical usage includes the production of juice (Schieber *et al*., 2001) among others. *D. carota* seed are cardio-protective (Muralidharan *et al*., 2008), hypolipidemic (Singh *et al*., 2010), anti-inflammatory, analgesic (Vasudevan *et al*., 2010), hepatoprotective (Singh *et al*., 2012) and have demonstrated potent antioxidant activities (Tijjani *et al*., 2020a; 2020b; 2020c; Tijjani and Imam, 2021). In addition, *D. carota* seed has been used traditionally in the treatment of diabetes mellitus (Khaki, 2011) which is associated with dyslipidemia. However, there is punity in the knowledge of the anti-hyperlipidemic activity of *D. carota* seed, as to the role it can play in ameliorating the dyslipidemia and its related complications. Thus, this study evaluated the anti-hyperlipidemic activities of aqueous and ethyl acetate partitioned extracts of *D. carota* seed in triton X-100 induced hyperlipidemic mice.

## MATERIALS AND METHODS

### Plant Material

*Daucus carota* L. seed was purchased from Alheri Manoma, Musty Agroallied Nigeria, LTD and identified by Mr. Azila Joseph, a curator with the Federal College of Forestry, Jos, Plateau state.

### Chemicals and Reagents

Triton X-100 used in this study was purchased from Technicho Laboratory Chemicals, Coimbatore. Simvastatin (SIMCARD) was a product of SwissPharma, Gujarat, India. Total Cholesterol, Triacylglyceride and High Density Lipoproteins Cholesterol kits were products of Randox Laboratories, Ardmore, Co. Antrim, UK. All other chemicals were of analytical grades.

### Preparation of Seed Extract

*Daucus carota* L. seed was pulverized into powder and 167 g of the powder was macerated in 250 mL of distilled water for 24 h as earlier reported (Tijjani *et al*., 2020b). The extract was filtered, and concentrated using a rotary evaporator at 40$^{o}$C. The filtrate (20 g) was re-dissolved in distilled water and partitioned in water-ethyl acetate (2/1 v/v) in a separation funnel. The partitioned extracts were collected and concentrated using a rotary evaporator at 40$^{o}$C to give the aqueous partitioned fraction (AQF, 11.56g , 6.92% yield) and ethyl acetate partitioned fraction (EAF, 4.87g, 2.92% yield). The extracts were kept in a tight stopper glass container until required for use. The percentage yields were used in the calculation of the respective doses for AQF and EAF treatments.

### Experimental Animals

Four-five (45) Wister albino mice with average weight of 21±2 g were obtained from the animal house unit, University of Jos, Plateau state, Nigeria. The mice were acclimatized for two weeks to the laboratory conditions of 12 h light–dark cycles, at 25±2°C in standard plastic cages. They were also allowed free access to mice feeds and water *ad libitum*.

### Induction of Hyperlipidemia

Hyperlipidemia was induced in forty (40) experimental mice by a single intraperitoneal injection of a freshly prepared 100 mg/kg body weight solution of triton X-100 in physiological saline (0.9% NaCl solution)

after an overnight fasting for 12 h (Thanga *et al*., 2013).

**Animal Grouping and Treatments**

The method reported by Tijjani *et al*. (2020b) was used in the animal grouping and treatments. Briefly, group A consisting of 5 mice, which served as control and received 0.2 ml of distilled water. The hyperlipidemic mice were distributed into 8 (B-I) groups of five (5) mice each, and treated with distilled water, simvastatin (10 mg/kg body weight), AQF (6, 11, and 22 mg/kg body weight) and EAF (2, 5 and 9 mg/kg body weight) of *D.carota*L. seed respectively as shown below:

- Group A: Control mice received distilled water (0.2 ml *p.o.*) 30 min before saline (2.5 ml/kg body weight, *i.p.*).
- Group B: Hyperlipidemic mice untreated received distilled water (0.2 ml *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group C: Hyperlipidemic mice treated with simvastatin received simvastatin (10 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group D: Hyperlipidemic mice treated with AQF received AQF at 6 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group E: Hyperlipidemic mice treated with AQF received AQF at 11 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group F: Hyperlipidemic mice treated with AQF received AQF at 22 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group G: Hyperlipidemic mice treated with EAF received EAF at 2 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group H: Hyperlipidemic mice treated with EAF received EAF at 5 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).
- Group I: Hyperlipidemic mice treated with EAF received EAF at 9 mg/kg body weight, *p.o.*) 30 min before triton X-100 (100 mg/kg body weight, *i.p.*).

All animals remained in a fasted state for the duration of the experiment (36 h) (Rocha *et al*., 2009) and were sacrificed 24 h after triton X-100 treatment and blood and liver were collected for analysis. After the last 24 h, feacal materials were also collected.

**Preparation of Samples**

The mice were sacrificed under diethyl ether anesthesia and blood samples was collected through the incision of their jugular vein into ethylene diaminetetraacetic acid (EDTA) anti-coagulant bottles, and plasma was separated by centrifugation (2400 × g) for 15 min. The liver was excised, blotted with tissue paper, weighed and homogenized in ice-cold 0.25M sucrose solution (1:5 w/v). The homogenates were centrifuged (3000 × g) for 15 min to obtain supernatants, which were kept in plain specimen bottles and maintain frozen until required for analysis. Feacal matters collected within the last 24$^{th}$ h were dried at 40°C until a constant weight was achieved and they were ground to a fine powder using a pestle and mortar. They were then diluted using phosphate buffer saline (pH 7.1) solution (1:5 w/v). The solutions were centrifuged (1000 × g) for 5 min to obtain supernatants, which were kept in plain specimen bottles for analysis. The feacal cholesterol and triglyceride content were measured using the procedure outlined in commercial kits (Randox Laboratories Ltd., Antrim, UK).

**Lipid Profile**

Plasma total cholesterol (CHOL), triacylglycerides (TRIG), high density lipoprotein cholesterol (HDL-chol), and total protein were estimated using the procedure

outlined in commercial kits (Randox Laboratories Ltd., Antrim, UK). The following formula was used to calculate low-density lipoprotein cholesterol (LDL-chol); LDL-chol = TC– (TG/5) − HDL-chol (mmol/L) (Friedwald *et al*., 1972), Coronary artery index (CAI), CAI = LDL-chol/HDL-chol, Cardiac index (CI), CI = TC/HDL-chol, and Atherogenic index (AI), AI = (total cholesterol - HDL-chol) / HDL-chol (Kayamori and Igarashi, 1994; Kang *et al*., 2004).

### Statistical Analysis

Data are presented as mean ± SEM. Data were subjected to one way analysis of variance (ANOVA) followed by Duncan multiple range tests using SPSS version 20, SPSS Inc., Chicago. IL, USA. Significant levels were taken at $p<0.05$.

## RESULTS

### Organ Body Weight Ratio

Induction of hyperlipidemia reduces liver-body weight ratios of experimental mice (Table 1). Treatments with simvastatin, AQF and EAF did not significantly ($p>0.05$) improve the ratio except in EAF at 2 mg/kg body weight.

**Table 1:** Percentage liver-body weight ratio of hyperlipidemic mice treated with AQF and EAF extracts of *Daucus carota* seed

| Groups (mg/kg body weight) | Liver-body weight ratio |
|---|---|
| Control | 6.53±0.69[a] |
| Hyperlipidemic | 4.28±0.36[b] |
| Hyperlipidemic + SIM 10 | 4.49±0.11[b] |
| Hyperlipidemic + AQF 6 | 3.55±0.21[b] |
| Hyperlipidemic + AQF 11 | 5.16±0.43[b] |
| Hyperlipidemic + AQF 22 | 3.33±0.64[b] |
| Hyperlipidemic + EAF 2 | 4.97±0.91[a] |
| Hyperlipidemic + EAF 5 | 4.65±0.19[b] |
| Hyperlipidemic + EAF 9 | 3.92±0.52[b] |

Values are Mean ± SEM, n=5, Values in each column with different superscripts are significantly different from control at $p<0.05$. **AQF** – Aqueous fraction**, EAF** – Ethyl acetate Fraction, **SIM** –Simvastatin.

### Lipid Profile

Treatment with AQF and EAF significantly decrease ($p<0.05$) total cholesterol, triglyceride and low density lipoproteins cholesterol when compared with hyperlipidemic untreated mice (Table 2). Furthermore, treatment with the partitioned extracts significantly ($p<0.05$) improved high density lipoprotein cholesterol levels in AQF at 6 mg/kg body weight and EAF at 5 mg/kg body weight when compared with hyperlipidemic untreated mice.

**Table 2:** Lipid profile of hyperlipidemic mice treated with AQF and EAF extracts of *Daucus carota* seed

| Groups (mg/kg body weight) | CHOL (mmol/L) | TRIG (mmol/L) | LDL-CHOL (mmol/L) | HDL-CHOL (mmol/L) |
|---|---|---|---|---|
| Control | 37.88±8.34$^{a}$ | 5.99±0.88$^{a}$ | 18.72±1.53$^{a}$ | 43.36±8.37$^{a}$ |
| Hyperlipidemic | 96.35±19.92$^{b}$ | 10.14±1.55$^{b}$ | 45.54±3.89$^{b}$ | 25.20±3.35$^{b}$ |
| Hyperlipidemic + SIM 10 | 41.89±2.83$^{a}$ | 5.54±1.12$^{a}$ | 9.66±4.69$^{c}$ | 32.43±3.38$^{a}$ |
| Hyperlipidemic + AQF 6 | 39.69±1.60$^{a}$ | 2.30±0.20$^{c}$ | 4.27±1.40$^{c}$ | 34.37±1.24$^{a}$ |
| Hyperlipidemic + AQF 11 | 39.49±9.42$^{a}$ | 2.43±0.09$^{c}$ | 13.88±4.55$^{c}$ | 24.50±1.18$^{b}$ |
| Hyperlipidemic + AQF 22 | 38.68±2.46$^{a}$ | 2.89±0.09$^{c}$ | 7.93±1.46$^{c}$ | 29.43±1.44$^{b}$ |
| Hyperlipidemic + EAF 2 | 36.68±3.35$^{a}$ | 2.70±0.28$^{c}$ | 6.02±3.38$^{c}$ | 29.43±2.93$^{b}$ |
| Hyperlipidemic + EAF 5 | 37.68±4.40$^{a}$ | 2.94±0.22$^{c}$ | 4.09±2.62$^{c}$ | 32.25±2.12$^{a}$ |
| Hyperlipidemic + EAF 9 | 45.10±3.09$^{a}$ | 2.49±0.06$^{c}$ | 15.24±4.79$^{ac}$ | 28.73±1.99$^{b}$ |

Values are Mean ± SEM, n=5, Values in each column with different superscripts are significantly different from control at $p<0.05$. **AQF** – Aqueous fraction**, EAF** – Ethyl acetate fraction, **CHOL** - Total Cholesterol, **TRIG** – Triglyceride, **LDL-CHOL** – Low Density Lipoprotein, **HDL-CHOL** – High Density Lipoprotein, **SIM** – Simvastatin.

Results from hepatic cholesterol, hepatic triglyceride and hepatic protein is presented in Table 3. Significant decrease ($p<0.05$) was observed in hepatic cholesterol with simvastatin, AQF at 22 mg/kg body weight and EAF at 2, 5 and 9 mg/kg body weight treatments. Similarly, significant decrease ($p<0.05$) were observed in treatment with AQF (6, 11 and 22 mg/kg body weight) and EAF at 2 mg/kg body when compared with hyperlipidemic untreated mice. Simvastatin, AQF and EAF significantly ($p<0.05$) decrease atherogenic, coronary artery, and cardiac indices when compared with hyperlipidemic untreated mice (Table 4). The last 24$^{th}$ h feacal matter indicated a significant increase ($p<0.05$) in feacal cholesterol at all doses in AQF and EAF, but significantly, decreased feacal triglyceride at all doses except in EAF at 5 mg/kg body weight when compared with hyperlipidemic untreated mice (Table 5). Treatment with extracts increase feacal protein at all doses compared with hyperlipidemic untreated.

**Table 3:** Hepatic cholesterol, triglyceride and protein concentrations of hyperlipidemic mice treated with AQF and EAF extracts of *Daucus carota* seed

| Groups (mg/kg body weight) | Hepatic Cholesterol (mmol/L) | Hepatic Triglyceride (mmol/L) | Hepatic Protein (mg/ml) |
|---|---|---|---|
| Control | 3.02±0.83$^{a}$ | 4.13±1.59$^{a}$ | 12.20±8.04$^{a}$ |
| Hyperlipidemic | 15.71±1.33$^{b}$ | 19.84±1.43$^{b}$ | 19.92±1.62$^{a}$ |
| Hyperlipidemic + SIM 10 | 9.44±3.67$^{c}$ | 10.52±2.58$^{c}$ | 50.99±4.46$^{b}$ |
| Hyperlipidemic + AQF 6 | 13.64±2.48$^{b}$ | 9.76±0.49$^{c}$ | 19.48±2.00$^{a}$ |
| Hyperlipidemic + AQF 11 | 17.28±4.50$^{b}$ | 9.58±2.75$^{c}$ | 39.50±8.03$^{b}$ |
| Hyperlipidemic + AQF 22 | 9.23±1.61$^{c}$ | 11.85±1.72$^{c}$ | 17.65±5.36$^{a}$ |
| Hyperlipidemic + EAF 2 | 8.10±1.80$^{c}$ | 10.28±4.17$^{c}$ | 28.08±4.92$^{a}$ |
| Hyperlipidemic + EAF 5 | 9.13±1.38$^{c}$ | 15.88±4.07$^{bc}$ | 22.25±5.02$^{a}$ |
| Hyperlipidemic + EAF 9 | 10.45±1.99$^{c}$ | 22.30±1.22$^{b}$ | 19.50±3.53$^{a}$ |

Values are Mean ± SEM, n=5, Values in each column with different superscripts are significantly different from control at $p<0.05$. **AQF** – Aqueous fraction**, EAF** – Ethyl acetate fraction, **SIM** – Simvastatin.

**Table 4:** Coronary artery, atherogenic and cardiac indices of hyperlipidemic mice treated with AQF and EAF extracts of *Daucus carota* seed

| Groups (mg/kg body weight) | Atherogenic index | Coronary artery index | Cardiac index |
|---|---|---|---|
| Control | 0.46±0.17[a] | 0.46±0.08[a] | 1.00±0.36[a] |
| Hyperlipidemic | 3.63±0.87[b] | 3.45±0.87[b] | 4.63±0.87[b] |
| Hyperlipidemic + SIM 10 | 0.44±0.16[a] | 0.33±0.19[a] | 1.34±0.22[a] |
| Hyperlipidemic + AQF 6 | 0.15±0.12[a] | 0.12±0.02[a] | 1.15±0.20[a] |
| Hyperlipidemic + AQF 11 | 0.61±0.39[a] | 0.57±0.39[a] | 1.61±0.39[a] |
| Hyperlipidemic + AQF 22 | 0.31±0.05[a] | 0.27±0.05[a] | 1.31±0.05[a] |
| Hyperlipidemic + EAF 2 | 0.25±0.12[a] | 0.21±0.12[a] | 1.25±0.12[a] |
| Hyperlipidemic + EAF 5 | 0.18±0.10[a] | 0.14±0.10[a] | 1.18±0.10[a] |
| Hyperlipidemic + EAF 9 | 0.60±0.20[a] | 0.56±0.19[a] | 1.60±0.20[a] |

Values are Mean ± SEM, n=5, Values in each column with different superscripts are significantly different from control at $p<0.05$. **AQF** – Aqueous fraction**, EAF** – Ethyl acetate fraction, **SIM** – Simvastatin.

**Table 5:** Feacal cholesterol, triglycerides and protein for the last 24 h of hyperlipidemic mice treated with AQF and EAF extracts of *Daucus carota* seed

| Groups (mg/kg body weight) | Feacal cholesterol (mmol/L) | Feacal triglycerides (mmol/L) | Feacal protein (mg/ml) |
|---|---|---|---|
| Control | 8.63±1.53[a] | 2.89±0.46[a] | 2.83±0.33[a] |
| Hyperlipidemic | 5.03±0.65[b] | 3.49±0.82[b] | 4.15±1.03[b] |
| Hyperlipidemic + SIM 10 | 4.25±0.38[b] | 1.76±0.44[c] | 2.29±0.54[a] |
| Hyperlipidemic + AQF 6 | 7.58±1.03[a] | 2.83±0.32[a] | 3.73±0.73[b] |
| Hyperlipidemic + AQF 11 | 8.89±1.82[a] | 2.89±0.43[a] | 5.36±0.45[c] |
| Hyperlipidemic + AQF 22 | 14.44±2.81[c] | 2.53±0.44[a] | 9.81±1.66[d] |
| Hyperlipidemic + EAF 2 | 6.47±1.22[ab] | 2.51±0.71[a] | 5.72±1.42[b] |
| Hyperlipidemic + EAF 5 | 9.48±2.86[a] | 3.00±0.57[ab] | 6.02±1.11[b] |
| Hyperlipidemic + EAF 9 | 9.41±2.12[a] | 2.12±0.81[a] | 5.42±1.07[b] |

Values are Mean ± SEM, n=5, Values in each column with different superscripts are significantly different from control at $p<0.05$. **AQF** – Aqueous fraction**, EAF** – Ethyl acetate fraction, **SIM** – Simvastatin.

## DISCUSSION

*Daucus carota* has been used in the management of diabetes mellitus (Khaki, 2011), which is associated with oxidative stress and hyperlipidemia. The search for safer and effective anti-hyperlipidemia agents are important in correcting the dyslipidemia and subsequently prevent the complications that is associated with dyslipidemia. Therefore, experimental models such as the use of triton X-100 have been employed in inducing hyperlipidemia (Thanga *et al*., 2013; Gundamaraju *et al*., 2014; Adigun *et al*., 2016; Tijjani *et al*., 2020a), which is characterized by an increase in total cholesterol, triglyceride, VLDL-chol and decrease HDL-chol. Treatment with AQF and EAF fractions of *D. carota* did not significantly ($p<0.05$) improve the liver-body weight ratio of experimental mice after 24 h of treatment (Table 1), and this may be due to excessive reduction of the hepatocyte.

The mechanism by which triton X-100 induces hyperlipidemia is by the preventing

the clearance of triglyceride rich lipoprotein (Kellner *et al*., 1951). AQF and EAF reverse the high levels of total cholesterol, triglyceride, LDL-chol and improved the circulating HDL-chol in triton X-100 induced hyperlipidemic mice (Table 2). Lipids are important biomolecule in the human body where they play vital roles including their inclusion in membrane, precursors of steroid hormones and in the protection of organs of the body. However, excess lipids in the body predispose human to several diseases such as atherosclerosis and cardiovascular disease (Sharma *et al*., 2004). Results suggest that AQF and EAF fractions can prevent the development of atherosclerosis, which can result from dyslipidemia. The significant increase in the HDL-chol may slow down atherosclerosis process (Demarin *et al*., 2010; Rafieian-Kopaei *et al*., 2014). Coronary artery, atherogenic and cardiac indices are important indicators of cardiovascular disease (Kayamori and Igarashi, 1994; Panagiatakos *et al*., 2003; Kang *et al*., 2004). AQF and EAF treatment at all doses in hyperlipidemic mice improved these indices in a similar manner with simvastatin, when compared with hyperlipidemic untreated mice (Table 4). Suggesting that treatment with the extracts did not predispose the experimental animals to cardiovascular disease; rather it ameliorates this effect in triton X-100 treatment.

Triton X-100 treatment in experimental mice increases hepatic cholesterol and hepatic triglyceride (Table 3). This observation is in agreement with the reports of Adigun *et al*. (2016). Similarly, hepatic protein was significantly increased in triton X-100 induced hyperlipidemic mice. AQF at 22 mg/kg body weight and EAF at all doses, decrease hepatic cholesterol levels and hepatic triglyceride levels at all doses with AQF treatment. The major source of lipids in the body aside from their biosynthesis by the liver is from dietary sources. Treatment with AQF and EAF partitioned extracts of *D. carota* seed improved feacal cholesterol and feacal triglyceride excretion, except in AQF feacal cholesterol at the highest dose of 22 mg/kg body weight (Table 5), which suggests that treatment with the extract may not enhance the accumulation of lipids from dietary sources.

## CONCLUSION

The results indicated that AQF and EAF partitioned extract of *Daucus carota* L. seed possesses significant anti-hyperlipidemic activities, and may play an ameliorating role against dyslipidemia and related complications.

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