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EXPLORATION OF ANTI-ATHEROSCLEROTIC ACTIVITY OF *ORIGANUM MAJORANA* L. IN EXPERIMENTAL ANIMALS WITH HIGH-FAT DIET-INDUCED ATHEROSCLEROSIS

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Keywords:

Atherosclerosis, *Origanum majorana L*, fibrinolytic, Thrombolytic and antiplatelet activity

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ABSTRACT: Atherosclerosis is a chronic inflammatory disease that is marked by atheroma and patchy intimal plaques in arteries that cause thickening and hardening of arteries. It is reported that "*Origanum majorana* L." possess antiulcerogenic, antiproliferative, antioxidant, and anticarcinogenic activities, and it is an important remedy against thromboembolic disease. The present study was designed for the evaluation of the anti-atherosclerotic activity of hydrodistilled volatile oil (OMO) of *Origanum majorana* L. in high-fat diet-induced atherosclerotic rats. The in vitro studies found that OMO possesses fibrinolytic, thrombolytic, and antiplatelet activity. These activities can play an effective role in the anti-atherosclerotic activity of OMO. Atherosclerosis was induced using a high-fat diet model in atherosclerotic activity of OMO. Atherosclerosis was induced using a high-fat diet model in histopathological examination of the aorta was determined at the end of the study. OMO significantly showed that the levels of total cholesterol (TC), triglyceride (TG), low-density lipid (LDL), and very low-density lipids (VLDL) levels were also decreased, there is a decrease in the level of liver function enzymes and significant changes in haematological parameters, the inflammatory biomarkers seem negative as compared to the normal group. The result suggested that OMO has fibrinolytic, thrombolytic, and antiplatelet activity; hence it contributed to antiatherosclerosis activity in high-fat diet-induced atherosclerotic rats.

INTRODUCTION: Atherosclerosis mainly involves the coronary and caratoid arteries, which remain the leading causes of morbidity and mortality in both men and women of all racial groups, with Coronary Heart Disease (CHD) the leading cause of death worldwide. The disease develops slowly over many years in the intima layer of large and medium-sized arteries [1].

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Atherosclerosis is marked by atheroma and patchy intimal plaques. The most common location is a lumen of medium-sized and large arteries. The plaque has cellular components, namely inflammatory cells, smooth muscle cells, a fibrous component of connective tissue and fat with a fatty streak, and an accumulation of lipid-laden Foam cells in the intimal layer of the artery.

Lipid retention is the first step in the pathogenesis of atherosclerosis which is followed by chronic inflammation at susceptible sites in the walls of the major arteries leading to fatty streaks, which then progress to fibroatheromas which are fibrous [2]. Atherosclerosis is a continuous progressive development. Fatty streak develops at 11-12 years

and fibrous plaques at 15-3 years, and they develop at the same anatomic sites as the fan streaks, making it more evident that fibrous plaques arise from fatty streaks. Pathologic intimal thickening leads to fatty streaks, fibrous cap atheromas, and plaques, finally leading to sudden cardiac death [3]. Prominent risk factors of consideration are Hypertension. Diabetes, dyslipidaemia, obesity, sedentary lifestyle, Family history, and smoking. Intraplaque rupture, bleeding, thrombosis, and stenosis cause symptoms. Diagnosis is a clinical and definitive diagnosis made through Imaging tests. The management plan includes behaviour modifications (physical activity with a low-caloric diet rich in fibre components). The main classes of drugs used in the treatment are antiplatelet and anti-atherogenic drugs.

Some medicinal plants have been reported to be weld in atherosclerosis worldwide and have been used as antiatherosclerosis and antiplatelet remedies. Despite the presence of known anti-atherosclerotic medicine in the pharmaceutical market, atherosclerosis and related complications continue to be major medical problems. Antiplatelet effects of these plants are attributed to their inhibition ability to platelet adhesion of activated platelet. So, many plant species having anti-atherosclerotic activity have been available in the literature; however, searching for new antiatherosclerosis drugs from natural plants is still attractive because they contain substances that demonstrate alternative and safe effects on atherosclerosis. Most plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, *etc*., that are frequently implicated as having anti-atherosclerotic effects.

The literature survey found that aerial parts of *Origanum majorana* L., *i.e.,* leaves and flowers, consist of 3% essential oil, having at least 40 different phenolic compounds. These phenolic compounds are responsible for various pharmacological activities. *Origanum majorana*. Significantly reduced the occurrence of ulcers, gastric secretion, and acid output. Moreover, the drug also restored the mucus of elastic walls, and non-protein sulfhydryl (NP- SH) in ethanol reduced ulcerations [4]. In the treatment of respiratory diseases, *Origanum majorana* is combined with *Plectranthus amboinicus*. For the management of diabetes, it is grouped with *Justica pectoralis* and *Ocimum tenuiflorum*. Another antidiabetic formulation uses *Stachytarpheta jamaicensis* and *Ocimum tenuiflorum* and *Origanum majorana* [5]. The attributed α- and B- glucosidase enzyme inhibition potential of *Origanum majorana* to a unique flavone having 6 hydroxy groups along with the 5, 7-dihydroxy substituents [6]. Methanol extract of *Origanum majorana* inhibited the formation of AGES, *i.e.,* advanced glycation end products in experimentally induced diabetes [7]. The PPAR-ϒ modulating potential of *Origanum majorana* and other herbs was revealed by various reports [8, 9]. Therefore the main objective of understanding this study is to evaluate the atherosclerotic activity of *Origanum majorana* L.

MATERIAL AND METHODS:

Animals: Experiments were performed on healthy male Wistar rats (200-250 gm) with the approval of the Institute's animal ethics committee. The animals were purchased from the National Institute of Biosciences. Pune, Maharashtra, India, and adapted in our own animal house for the experimental study. The animals were housed at 22 ± 10C, under a 12 h light/dark cycle, with free access to a commercial diet and water *ad libitum* throughout the study.

Drugs and Chemicals: Vitamin D3 (Gift sample) was obtained from Supreem Pharmaceuticals Mysore Pvt Ltd. Atorvastatin drugs were used as a standard. Urokinase 15,00000 IU was purchased from Cadila Pharmaceuticals.

Methods:

Pharmacognostic Evaluation:

Plant Collection & Authentication: *Origanum majorana* leaves were collected from Pune region markets and sent to BSI. Western Circle, Pune, for authentication. The authentication was done with voucher specimen no.: SWK-1 & ORK-1

Preparation of Extract:

Hydrodistilled Volatile Oil (OMO): Shade-dried *Origanum majorana* coarse powder was soaked in water for 15-20 min. and later distilled in a Clevenger apparatus (for low-density volatile oils).

Macroscopical, Microscopical and Phyto-chemical Analysis: The samples of leaves and fruit cuttings were observed with the unaided eye and

with the help of a 5 X lens on a simple microscope to determine their morphological characteristics. The anatomical features were observed under a compound microscope (Olympus) at X100 and X450 resolution. A motic microscope was used to record the histological details, micro-photographs and the images were studied with Image analyser software (Motic Image Plus II and Image). The detailed surface characterization of *Origanum majorana* leaves was recorded by scanning electron microscope (JEOL, JSM-6360).

The methods used for microscopy or histochemistry and the findings reported were as per the description in standards reference books like Iyengar, Kokate and Khandelwal [10].

Statistical Analysis: The result obtained was expressed as the mean + standard error means (SEM) and statistically analyzed by applying a one-way ANOVA, followed by Dunnett's method. Differences With $p< 0.01$ were considered statistically significant.

Preliminary Phytochemical Analysis Physico-chemical Analysis of Essential Oil: The essential oil extracted by hydrodistillation was analyzed for various physicochemical properties. The oil was pale yellow in colour with a characteristic aromatic odour and free flow. The yield was 1.76%; specific gravity and RI, when recorded at 20°C were found to be 0.903 and 1.464, respectively. Oil was freely soluble n ethanol and ethyl acetate, whereas insoluble in water.

Qualitative Phytochemical Analysis: Qualitative phytochemical analysis of three extracts of aerial parts of *Origanum majorana* showed the presence of active constituents such as phenolic compounds.

Determination of Fibrinolytic Activity:

Fig. 1 *In-vitro* Clot Dissolving Activity of OMO: The visual results were observed in **Fig. 1** for the blood clot-dissolving activity of both OMO and Urokinase. Both possessed fibrinolytic properties; the clot-dissolving effect of OMO and Urokinase is comparative.

RESULTS:

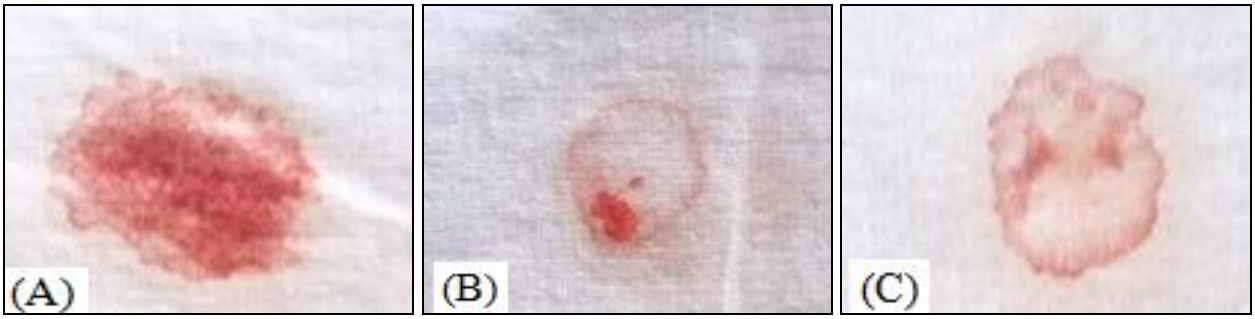

FIG. 1: *IN-VITRO* CLOT DISSOLVING ACTIVITY OF OMO A – BLOOD-STAINED CLOTH WASHED WITH WATER B – BLOOD-STAINED CLOTH WASHED WITH UROKINASE C- BLOOD-STAINED CLOTH WASHED WITH OMO

Fig. 2 Fibrinolytic Effect by Artificial Blood Clot Degradation Method: In **Fig. 2** the blood clot degradation was observed in the test tube containing the test drug (OMO) with the spread of red blood cells trapped by multiple fibrin nets as compared to normal. Fibrinolytic activity of OMO by degradation of the blood clot within 60 min.

FIG. 2: A- CONTROL, B- STANDARD (UROKINASE 5000U/ML), C- OMO

Determination of Thrombolytic Activity:

Thrombolytic Effect by UV-spectroscopic Bioassay Method: From the data presented in **Fig. 3,** estimation of the thrombin activity of OMO can be seen with a linear relationship between the concentration of OMO and the decrease in absorbance of the dispersed clot. This indicates the thrombolytic activity of OMO. Absorbance decreases due to the lysis of clots by OMO. The r^2 value is 0.9632 for OMO.

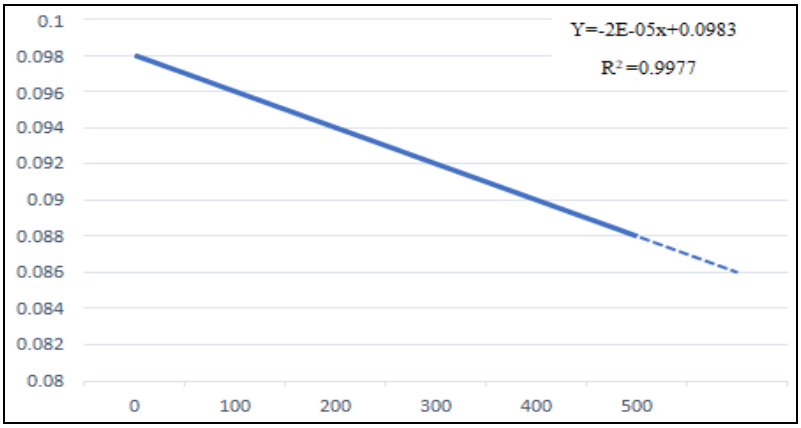

FIG. 3: CALIBRATION CURVE OF BIOASSAY OF OMO; CONCENTRATION VS ABSORBANCE

Thrombolytic Activity by Measuring Blood Clot Diameter: The thrombolytic activity of Oregano Oil was determined by using the modified method [11].

TABLE 1: THE RESULT OBTAINED FOR THROMBOLYTIC ACTIVITY EXPRESSED AS THE MEAN DIAMETER (CM) ± SD (N ¼ 3)

Groups	Control	Streptokinase	OMO
Clot lysis (Diameter in cm)	1.86 ± 0.013	0.36± 0.012	0.58 ±0.002 **

***In-vitro* Blood Clot Lysis (Measuring Weight) Activity:** The thrombolytic activity of Oregano oil was evaluated by measuring the clot weight;

(% of clot lysis = Weight of released clot / Clot weight × 100

Using UK as the positive control.

TABLE 2 THE BLOOD CLOT LYSIS ACTIVITY OF OMO AND UROKINASE IN PERCENT CLOT LYSIS

Groups	Control	Streptokinase	OMO
Clot lysis (Diameter in cm)	7.96± 0.2	2.54 ±0.98	65.92± 0.82

Table 2 shows the effect of Oregano oil on clot lysis activity; the percentage (%) clot lysis by Oregano oil was statistically significant (P<0.001) when compared with control.

Anti-Platelet Activity of OMO:

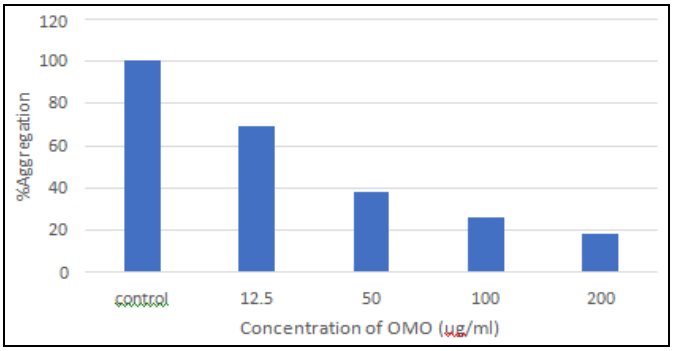

FIG. 4: % AGGREGATION OF VARIOUS CONCENTRATIONS OF OMO. Values are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. p<0.05, p<0.01. standard -AVT (10 mg/kg), OMO - (200 mg/kg).

Anti-Atherosclerotic Activity:

Fig. 5: Effect of Omo on Serum Lipid Level in a Model: From the data presented in **Fig. 5**, it could be noticed that Serum TC, LDL, and VLDL level were found to be increased, and HDL level was decreased in rats fed with the atherogenic diet for weeks. A significant reduction in serum TC, LDL.

VLDL, and TO levels, were observed in both OMO (200 mg/kg) treated group and standard Atorvastatin (10 mg/kg) when compared to the control group Atherogenic index ratio (Al ratio) was significantly decreased by OMO (200 mg/kg) Atorvastatin (10 mg/kg) treated group.

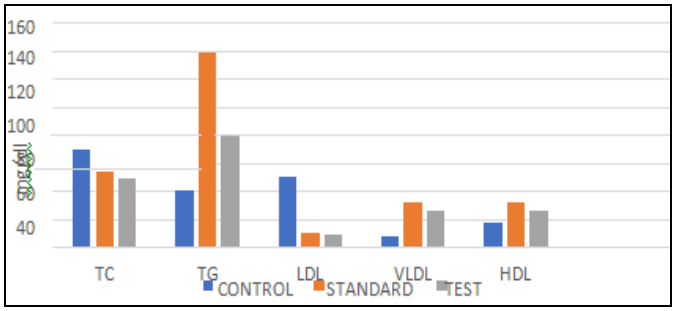

FIG. 5: TC-TOTAL CHOLESTEROL LEVEL-, TG- TRIGLYCERIDE, LDL-LOW DENSITY LIPID. VLDL-Very low-density lipid, HDL- High-density lipid. Values are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. $p<0.05$, $p<0.01$. standard -AVT (10 mg/kg), OMO - (200 mg/kg).

Effects of OMO on Body and Organ Weight and Food Intake in as Rats on 80th Day: Table 3 and **4** shows there was a significant increase in body weight with decreases in food intake of rats upon high-fat diet for 60 days. The standard and test groups had significantly increased food intake and lower body weight than the control group after 20 days of treatment.

TABLE 3: EFFECT OF OMO ON FOOD INTAKE ON THE 80TH DAY

Animal group	0 Day	60 Day	80 Day
Control	29.09± 0.6	15.26 ± 0.29	19.24 ± 0.32
Standard	28.21± 1.01	16.03 ± 0.29	24.3 ± 0.89
OMO	28.42 ± 0.60	17.03 ± 0.21	23.64 ± 0.26

TABLE 4: EFFECT OF OMO ON BODY WEIGHT IN AS RATS ON THE 80TH DAY

Animal group	0 Day	60 Day	80 Day
Control	240 ± 3.2	325 ± 3.4	397 ± 1.2
Standard	248 ± 3.2	321 ± 2.1	337 ± 3.5
OMO	245 ± 1.4	329 ± 0.21	385 ± 1.65

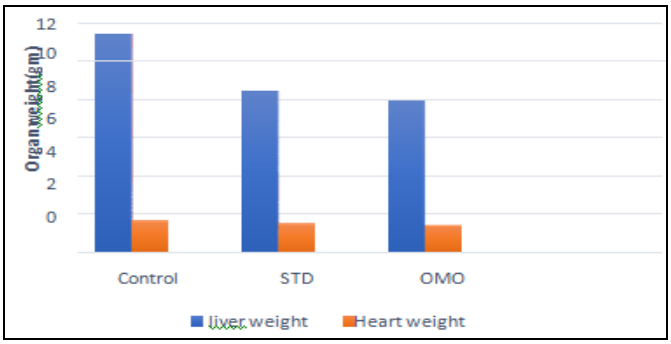

FIG. 6: EFFECTS OF OMO (200 MG/KG) ON LIVER AND HEART WEIGHT IN AS RAT MODELS ON 80 TH DA. Values are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. $p<0.05$, $p<0.01$. standard -AVT (10 mg/kg), OMO - (200 mg/kg).

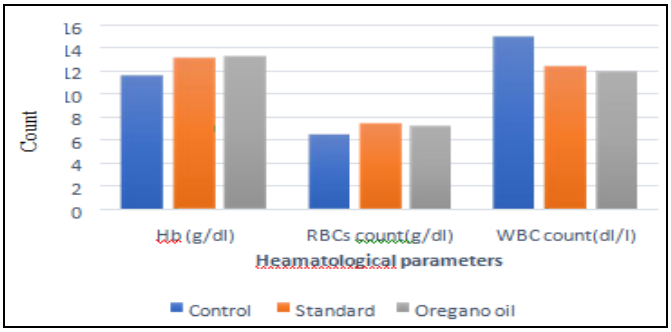

FIG. 7: EFFECTS OF OMO ON HAEMATOLOGICAL PARAMETERS IN A MODEL. Values are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. $p<0.05$, $p<0.01$. standard -AVT (10 mg/kg), OMO - (200 mg/kg)

From the data presented in **Fig. 7**, In Treatment with OMO (200 mg/kg) and Atorvastatin (10mg/kg) significantly decreased the total leukocytes and platelet count but not decrease total RBC and HB count significantly. From the data presented in **Fig. 8**, it could be noticed that OMO and Atorvastatin (10mg/kg) groups were shown a significant decrease in serum SGOT, SGPT, and ALP at p< 0.01 compared control group. **Fig. 9** shows the effects of oregano oil (200mg/kg) and AVT (10mg/kg) on CRP levels.

FIG. 8: EVALUATION OF TRANSAMINASE ENZYME LEVEL IN SERUM. Fig. 6.STD-AVT (10 mg/kg), OMO (200 mg/kg) alues are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. p<0.05, p<0.01. standard -AVT (10 mg/kg), OMO- (200 mg/kg).

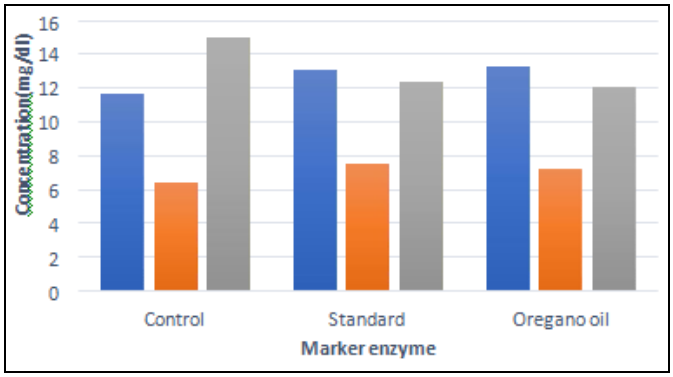

FIG. 9: DETERMINATION OF INFLAMMATORY MARKERS IN SERUM. Values are mean ± SEM (n=6). Statistical analysis by (one-way ANOVA followed by Dunnett's test: Control group compared with all treatment groups. p<0.05, p<0.01. standard -AVT (10 mg/kg), OMO- (200 mg/kg).

TABLE 5: ANTIOXIDANT ACTIVITY OF OMO

Experimental group	20 mg		40mg
Control (L-ascorbic acid)	30	67	91
OMO	19	60	75

Histopathology:

Effect of OMO on Atheromatous Aorta:

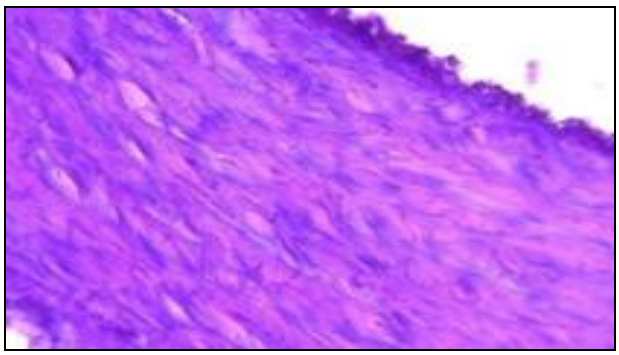

FIG. 10: NORMAL CONTROL

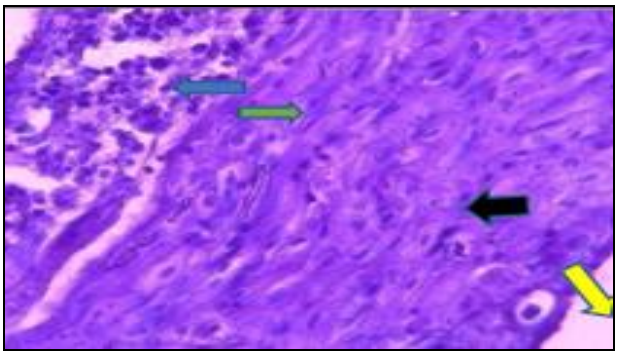

FIG. 11: DISEASED CONTROL

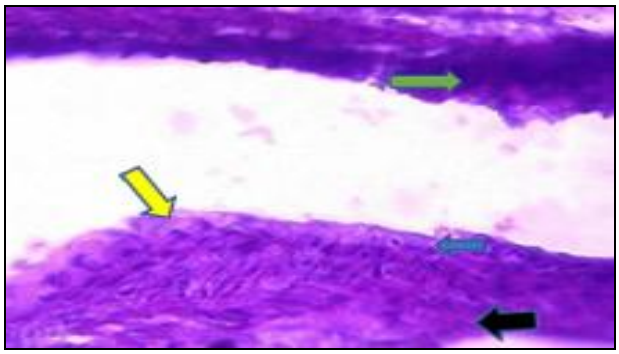

FIG. 12: STANDARD GROUP

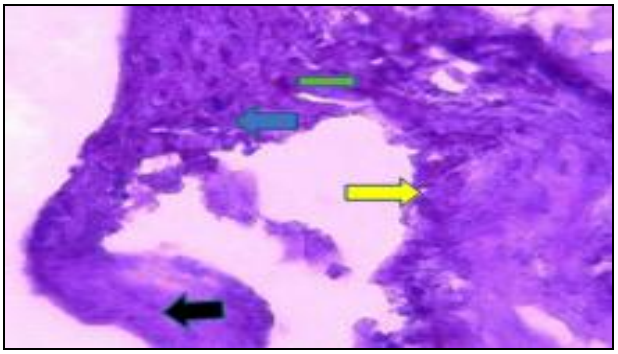

FIG. 13: TEST GROUP

Fig. 10, 11, 12, 13 photographs showing the aorta with variable thickness (black arrow), Cellular infiltration (blue arrow), Rough intimal structure (yellow arrow) and Necrosis of smooth muscles (green arrow).

Effect of OMO on Heart Muscle:

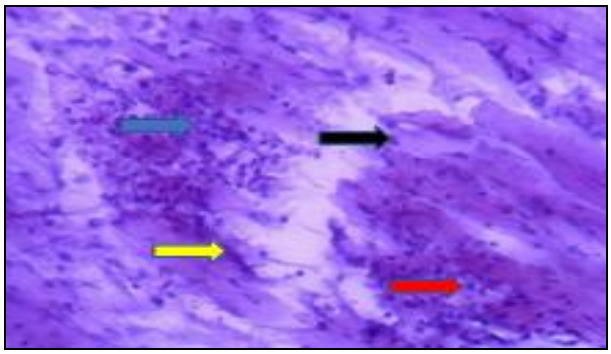

FIG. 14: DISEASED CONTROL GROUP

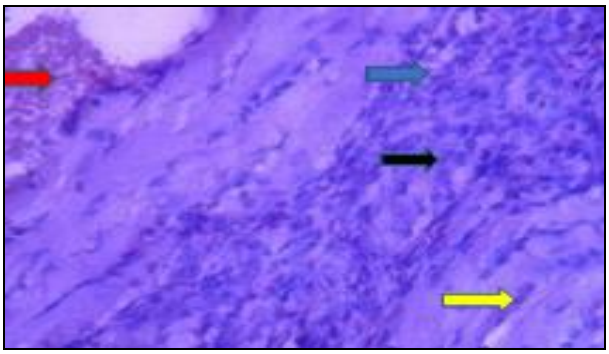

FIG. 15: TEST GROUP

Fig. 14, 15 photographs were showing Aorta Necrosis (black arrow), Cellular infiltration (blue arrow), Vascular changes (red arrow), fatty infiltration (yellow arrow) and connective tissue proliferation.

DISCUSSION: It is reported that *Origanum majorana* is an important remedy against thromboembolic diseases [12]. *Origanum majorana* contains 40 different phenolic compounds. Terpinen-4-yiol, cis and trans sabinene, and a-terpinol hydrate constituents. These constituents of *Origanum majorana* showed several physiological and pharmacological activities such as antidiabetic, inhibition of platelet adhesion, aggregation, and secretion [13]. The present study explored Origanum majorana for various pharmacological properties such as fibrinolytic, thrombolytic, antiplatelet, aggregation and antiatherosclerosis. Atherosclerosis is generally accepted as a chronic inflammatory disease [14]. It is known that local inflammation occurs in the formation of atherosclerotic lesions. Because of macrophages and other immune-competent cells. The most expressed cells are monocyte chemoattractant protein-1 (MCP-1), macrophage colony-stimulating factor (MCSF) and interferon-g (INF-g). MCP-1 activates leukocyte integrin, which results in firm initial monocyte attachment. MCSF promotes scavenger receptor protein synthesis and differentiation of monocytes. Once monocytes enter the subendothelial space they may mature into macrophages upon the uptake of LDL and cholesterol and then become foam cells.

INF-g promotes plaque development and foam cell Formation [14]. As lesion severity progresses into a fibroatheroma, macrophages, T- cells and mast cells infiltrate into the cap edges and stimulate the proliferation and migration of vascular smooth muscle cells (VSMCs) through the production of proinflammatory cytokines. Interleukin-1 (IL-1), IL-6, IL-18, and tumour necrosis factor-a (TNF-a) are common in forming foam cells and reduce plaque stability. Inflammation also plays an important role in weakening the fibrous cap of the

advanced plaque. After which disruption occurs, macrophage accumulation leads to thrombosis and complicated lesions, often accompanied by calcification in and around the central atheromatous core [15]. Platelet aggregation, low serum high-density lipoprotein cholesterol (HDLC), and high level of low-density lipoprotein cholesterol (LDLC) has been recognized as the most important risk factor in the development of atherosclerosis in humans and increase of the prevalence and consequences of atherothrombosis [16]. WBC, CRP and fibrinogen levels are significantly higher in patients with atherosclerosis [17].

In the present study, *Origanum majorana* oil was evaluated for its fibrinolytic properties as shown in **Table 2, 3** by the In-vitro blood clot dissolving method and shown to decrease the stained area of the blood-stained cloth as compared to the control. As per the **Fig. 2** in artificial blood clot degradation method, the colour intensity is higher in a test tube containing OMO compared to the control; hence, it can be stated that OMO has fibrinolytic activity.

The thrombolytic effect of OMO shown in **Fig. 3** was evaluated by UV spectroscopic bioassay method. A linear relationship was observed between the concentration of OMO and decrease in absorbance of a dispersed clot. *In vitro* blood clot lysis (measuring diameter) activity was evaluated using different concentrations of OMO-caused concentration-dependent clot lysis compared to the control group. In vitro blood clot lysis (measuring weight) method, the percentage (%) of clot lysis by OMO was statistically significant compared to control. The OMO showed moderate clot lysis activity in both models. This indicates the thrombolytic activity of OMO.

Platelets are directly involved in haemostatic and pathologic thrombotic processes through their platelet aggregation of proteins that will lead to the formation of platelet plugs and occlusion of the site of damage in the vessels. Platelet hypersensitivity and endothelial cell interactions contribute to the development and progression of many cardiovascular diseases like atherosclerosis and thrombosis. In our study, *Origanum majorana* showed inhibition of platelet aggregation. It decreased platelet aggregation as there was an increased concentration of OMO. As OMO showed fibrinolytic, thrombolytic, and inhibition of platelet aggregation, which are supportive for atherosclerotic treatment, further study was carried out by using high fat (lipid) diet-induced atherosclerosis model in rats. The continuous rise of lipids (LDL Cholesterol) in the blood leads to the accumulation of lipids in the endothelium of large vascular arteries. This accumulation makes endothelial injury release macrophage and proinflammatory reagents from plaque [18]. Inflammatory markers such as IL6, TNFα, monocytes, leukocytes, macrophages, small thrombus, fibrinogen and clotting factors are released after the bursting of plaque [19].

As shown in **Fig. 9**. The inflammatory biomarker *i.e.*, CRP level in experimental animals was found to be negative with OMO-treated animals whereas the control group was positive. The role of inflammatory proteins and cytokine profiles in atherosclerotic is an area of intense. The dysregulation of cytokines in these diseases represents a significant mechanism linking autoimmunity and atheroma formation [20].

The current study found that OMO and AVT-treated groups showed decreased LDL, VLDL, TG and TC levels and increased HDL levels compared with the control group. SGOT, SGPT. ALP was elevated in the control group, whereas OMO and standard treated group was found to reduce SGOT, SGPT, and ALP. On haematological parameters, OMO and NT-treated group significantly reduced WBC count and platelet count when compared to the control group.

The histopathology of the aorta showed destroyed endothelial cells, infiltration, and lipid deposition in control group animals, which are indistinct in OMO treated group. Thus, we can state that OMO has fibrinolytic, thrombolytic, and anti-platelet aggregation activity hence, antiatherosclerosis activity in the experimental animal. It showed antiatherosclerosis activity in experimental animals.

CONCLUSION: The study showed that *Origanum majorana* possesses anti-atherosclerotic activity when evaluated in high-fat diet-induced atherosclerosis. This is supported by the OMO showing the fibrinolytic, thrombolytic, and

antiplatelet aggregation activity. OMO significantly showed reduced TC, TG, LDL, and VLDL levels and increased HDL levels compared to the control group. It also affects the haematological parameters. There are significant changes in WBCs and Platelet counts compared to the normal groups OMO increases clotting time and decreases platelet count as compared to the normal group.

So, the study provides the scientific basis for using OMO for atherosclerosis and many cardiovascular diseases.

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CONFLICTS OF INTEREST: The author declares no conflict of Interest.

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