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THE POSSIBLE PROTECTIVE AND CURATIVE ROLES OF MELATONIN IN NORMAL AND ARTERIOSCLEROTIC ADULT MALE RATS.

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ABSTRACT

Arteriosclerosis is a strictly age-dependent disease. In the present work, we studied the possible protective and curative roles of melatonin (Mlt) against the development of arteriosclerosis. The protective role was studied by giving Mlt at 2 dose levels (3 mg/kg and 30 mg/kg) for 6 weeks in normal adult male rats followed by induction of arteriosclerosis along with Mlt administration. It is found that Mlt decreased serum levels of calcium (Ca^{2+}), triglycerides (TG) and increases high density lipoprotein-cholesterol (HDL-C) without significant effect on serum total cholesterol (TC) or low density lipoprotein-cholesterol (LDL-C) at 3 mg/kg dose level. However, at 30 mg/kg dose level a significant decrease in serum TG and increase in serum HDL-C was noticed without significant effect on serum TC, LDL-C or Ca^{2+} levels. Histo-pathological examination of blood vessel revealed no changes in the walls of blood vessels. The possible curative role of Mlt on arteriosclerosis was studied by treating arteriosclerotic rats with Mlt (3 mg/kg and 30 mg/kg) or with bezafibrate (Bzf) in order to compare the activity of Mlt against a common hypolipidemic drug in use. We found that both drugs lowered TC, TG, LDL-C, Ca^{2+} and increased HDL-C levels. Only Mlt at 30 mg/kg level was able to cause complete regression of the arteriosclerotic lesions. We concluded that Mlt has both protective and curative roles against arteriosclerosis and that it suppresses lipid levels and enhances Ca^{2+} level in normal rats. The high dose level of Mlt (30 mg/kg) is the most potent in treatment of experimental arteriosclerosis.

INTRODUCTION

Arteriosclerosis is a disease of arterial intima especially large arteries that leads to fatty lesions which is called atheromatous plaques [1]. The key step in atheriosclerosis is the formation of lipid-laden macrophages or foam cells [2].

Cholesterol is generally taken up by LDL-receptors. Macrophages have only few, if any LDL-receptors. The uptake of cholesterol by macrophages can be explained by the observation that LDL is oxidized and modified as it enters the intima [3]. The oxidation is initiated by the attack of free radicals on fatty acid double bond. This will result in an oxidative chain reaction leading to accumulation of a number of very reactive and toxic compounds e.g. H_2O_2, OH, lipid hydroxy peroxides, malondialdehyde and oxysterols [4]. Lipid peroxides are generated *in vivo* either due to generation of superoxide radicals that participate in further LDL oxidation or endothelial release of lipoxygenase to initiate peroxidation [5]. Oxidized LDL is taken up by scavenger receptors on the macrophages [6] with subsequent formation of foam cells [7]. In the later stage, fibroblasts infiltrate the degenerated area and cause progressive sclerosis (fibrosis) of arteries [8,9]. Later, Ca^{2+} often precipitates with lipids to develop calcified plaques [10]. The disease is then called arteriosclerosis. In the current study we have investigated the possible role of Mlt (a familiar anti-aging drug) in arteriosclerosis prevention and treatment.

MATERIALS AND METHODS

Adult male rats (obtained from the National Research Center, Cairo, Egypt) were used in the present study. They were housed under optimal care conditions and classified into 3 main groups:

Group (1), Normal group: which is divided into 4 other sub-groups.

Subgroup (1-a): Pretreated with Mlt (3 mg/kg) for 6 weeks then vitamin D2 (7.5 mg/kg orally dissolved in olive oil) for 10 days then cholesterol 1.5% for 6 weeks (for induction of arteriosclerosis) and concurrently given Mlt in the same dose level [11,12].

Subgroup (1-b): Pretreated with Mlt (3 mg/kg) for 6 weeks then olive oil for 10 days (2 ml/kg), then corn oil for 6 weeks concurrently given Mlt (3 mg/kg).

Subgroup (1-c): Similar to group (a) but Mlt was administered in 30 mg/kg dose level.

Subgroup (1-d): Similar to group (b) but Mlt was administered in 30 mg/kg dose level.

Group (2) Arteriosclerotic group: Rats in this group, arteriosclerosis was induced by administration of vitamin D2 for 10 days (7.5 mg/kg in olive oil) then cholesterol 1.5% orally for 6 weeks [11,12]. At the end of the induction period, the group is further divided in 4 subgroups.

Subgroup (2-a): Treated with Mlt, 3 mg/kg for 6 weeks, as a single dose in the morning.

Subgroup (2-b): Treated with Mlt, 30 mg/kg for 6 weeks, as a single dose in the morning.

Subgroup (2-c): Treated with Bzf, 50 mg/kg for 6 weeks, as a single dose in the morning.

Subgroup (2-d): Arteriosclerotic control received solvent only.

Group (3): Normal control received solvent only.

Drugs and chemicals:

Melatonin was supplied by Amoun Company (El Salam City, Egypt). Vitamin D2 was obtained from Misr Co., Cairo, Egypt). Bezafibrate was obtained from Boehringer Mannheim Germany. Cholesterol was supplied from Adwic Co., Egypt. Mlt and Bzf were suspended in Tween 80, 1% and administered orally. Vitamin D2 was dissolved in olive oil and orally administered also. Cholesterol was dissolved in corn oil and administered orally.

Sample Collection

After the period of administration, blood was obtained from orbital sinus plexus and serum was separated by centrifugation. Serum TC, TG, HDL-C and Ca^{2+} were determined in the serum using Stanbio (USA) kits,a colorimetric method. LDL-C was calculated using Friedwald equation. At the proper times, animals were sacrificed and samples of blood vessels were separated and kept in formalin (10%) for histo-pathological examination.

Statistical Analysis:

All data are expressed as percent change from control values and presented as mean ± standard error of mean (SEM). Differences between groups were analyzed for statistical significance by one-way analysis of variance (ANOVA) or Students' t-test procedures when appropriate [13]. Differences regarded significant at $p<0.05$ level of significance.

All statistical procedures are analyzed by a computer-assisted program (PC- Stat, version IA, The University of Georgia, Athens, Georgia, USA 1985).

RESULTS

1-Effect of Melatonin on the development of arteriosclerosis in Melatonin-pretreated rats:

Oral administration of Mlt as a single dose (3 mg/kg) at each morning for three months to normal rats induced reduction in serum TC (62.6 ± 6.8 %) when compared to control values.

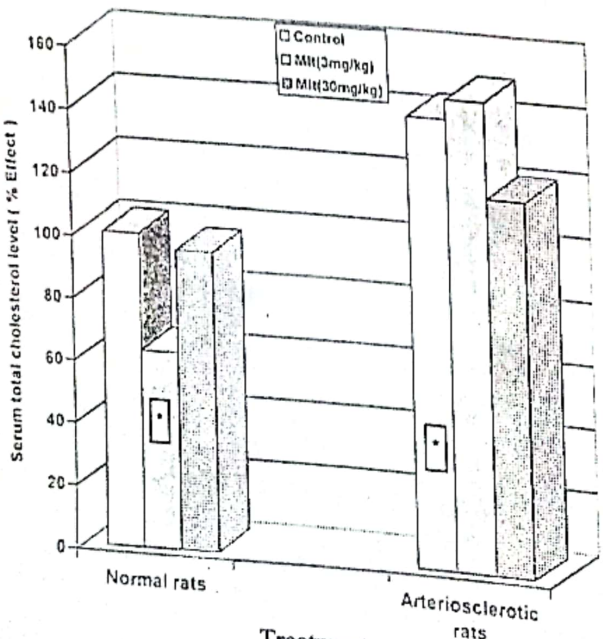

Fig. (1-a): effect of oral co-administration of melatonin (3mg/kg and 30 mg/kg), cholestrol (1.5%) and vitamin D2 (7.5 mg/kg) on total cholesterol serum level in melatonin pretreated adult male rats.

*Significantly different from normal control value ($p< 0.05$).

Arteriosclerotic rats showed significant elevation in serum TC (149.2 ± 10.6 %) which was not responsive to either low (3mg/kg) or high (30mg/kg) Mlt, (Fig.1-a).

However, Mlt in both dose levels reduced serum TG in normal and arterioscerotic rats. In case of atherioscrotic rats, serum TG was elevated to 199.6 ± 0.3 % and was reduced to 125.7 ± 14.2 % and 101.67 ± 17.9 % in response to low and high Mlt dose levels, (Fig.1-b).

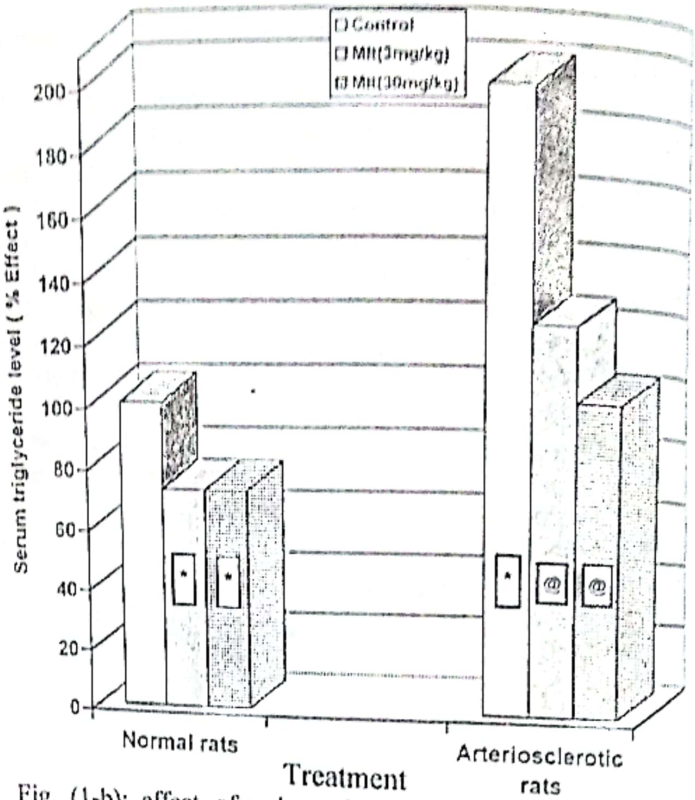

Fig. (1-b): effect of oral co-administration of melatonin 93 mg/kg and 30 mg/kg), cholesterol (1.5%) and vitamin D2 (7.5 mg/kg) on serum triglycide level in melatonin pretreated adult male rats.

*Significantly different from normal control value ($p<0.05$).

@ Significantly different from arteriosclerotic control value ($p<0.05$).

Serum HDL-C level was significantly elevated (171.5 ± 11 %) in normal rats only in response to 30 mg/kg. While, in arteriosclerotic rats both dose levels induced comparable elevation in serum HDL-C levels, 126.33 ± 7.3 % and 136.2 ± 11.6 % consequently, (Fig.1-c). Moreover, oral administration of Mlt produced similar elevation in serum Ca^{2+} level at both dose levels. In arterioscelrotic group, the elevated Ca^{2+} level (139.7 ± 10.7 %) was significantly reduced (117.8 ± 4.9 %) in response to only 3 mg/kg Mlt, (Fig.1-e).

Histo-pathological examination of blood vessels showed that Mlt induced protection against the development of arteriosclerosis.

2-Effect of Melatonint and Bezafibrate on serum lipids and calcium levels in arteriosclerotic adult male rats:

Administration of Mlt (3mg/kg and 30 mg/kg) or Bzf (50mg/kg) for 6 weeks in arteriosclerotic rats reduced the elevated serum TC (142.9 ± 4.89 %) to comparable normal level, (Fig.2-a). Serum TG was also reduced with the same treatments. Maximum reduction was achieved with 3mg/kg Mlt (69.6 ±5.3 %), which was significantly different from all treated groups (Fig.2-b).

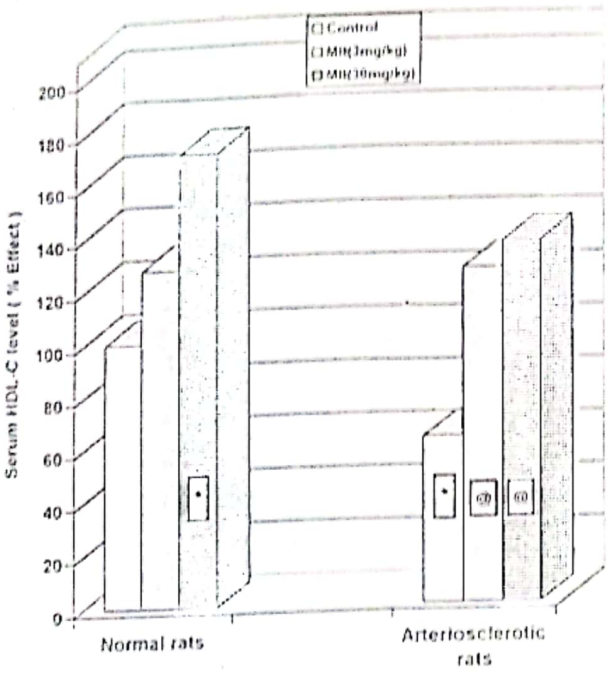

Fig. (1-c) effect of oral co-administration (3 mg/kg and 30 mg/kg), cholesterol (1.5%) and vitamin D2 (7.5 mg/kg) on serum high density lipoprotein – cholesterol (HDL-C) level in melatonin pretreated adult male rats.

*Significantly different from normal control value ($p< 0.05$).

@Significantly different from arteriosclerotic control value ($p< 0.05$).

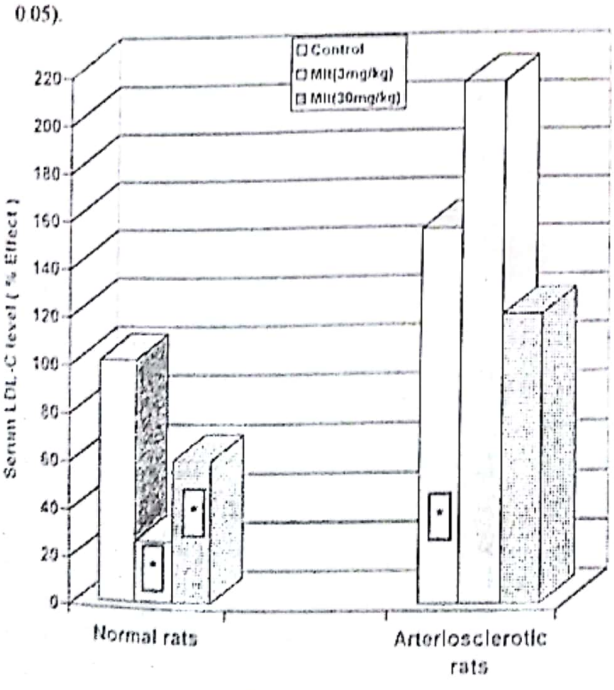

Fig. (1-d): effect of oral co-administration of melatonin (3 mg/kg and 30 mg/kg), cholesterol (1.5%) and vitamin D2 (7.5 mg/kg) on serum low density lipoprotein – cholesterol (LDL-C) level in melatonin pretreated adult male rats.

*Significantly different from normal control value ($p<0.05$).

Control arteriosclerotic rats demonstrated reduction in serum HDL-C when compared to normal rats (62.79 ± 0.61 %). Treatment with Mlt at both low and high levels or Bzf produced elevation in serum HDL-C (111.14 ± 17 %, 116.3 ± 16.8 %, and 95.222 ± 3 % consequently) when compared to normal rats, (Fig.2-c). Induction of arteriosclerosis significantly elevated serum LDL-C level (152.96 ± 11.8 %) above normal level.

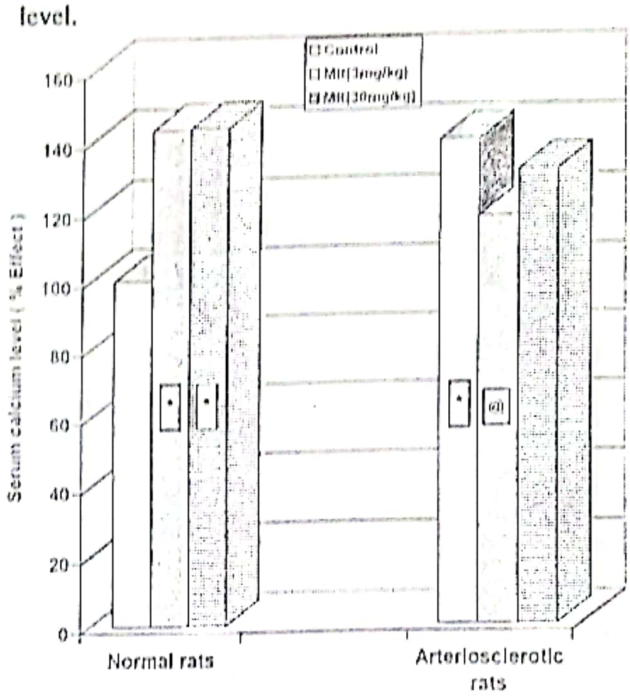

Fig (1-e): effect of oral co-administration of melatonin (3 mg/kg and 30 mg/kg), cholesterol (1.5%) and vitamin D2(7.5 mg/kg) on serum calcium level in melatonin pretreated adult male rats.

*Significantly different from normal control value ($p<0.05$).

@ Significantly different from adult arteriosclerotic control value ($p<0.05$).

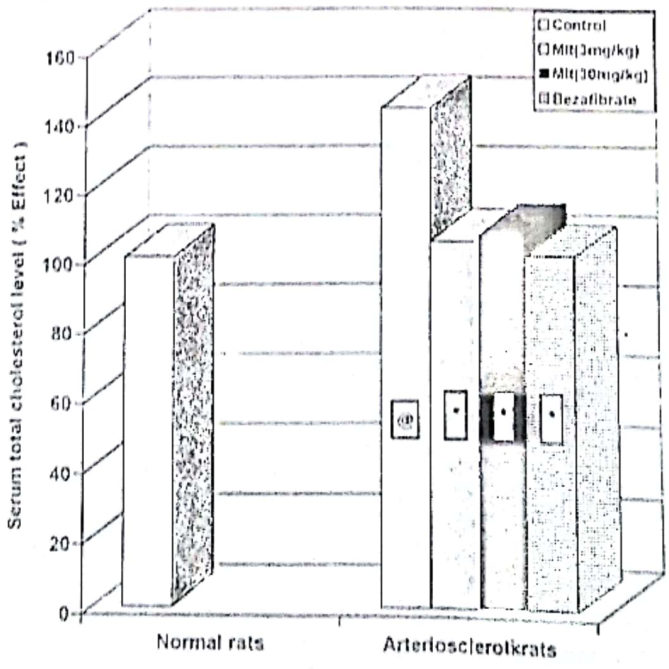

Fig (2-a): effect of oral administration of melatonin (3 mg/kg and 30 mg/kg) and bezafibrate (50 mg/kg) on serum total cholesterol level in aeteriosclerotic adult male rats.

@ Significantly different from normal control value ($p< 0.05$)

* Significantly different from arteriosclerotic control value ($p<0.05$).

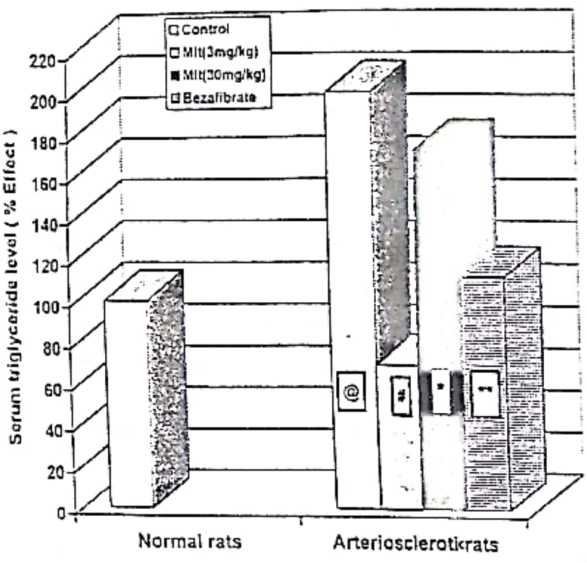

Fig (2-b): effect of oral administration of melatonin (3 mg/kg) and bezafibrate (50 mg/kg on serum triglyceride level in arteriosclerotic adult male rats.

*Significantly different from normal control value ($p<0.05$).

@Significantly different from arteriosclerotic control value ($p<0.05$)

**Significantly different from arteriosclerotic control and meltatonin (30 mg/kg) ($p<0.05$).

Significantly different from all treatments and control value ($p<0.05$).

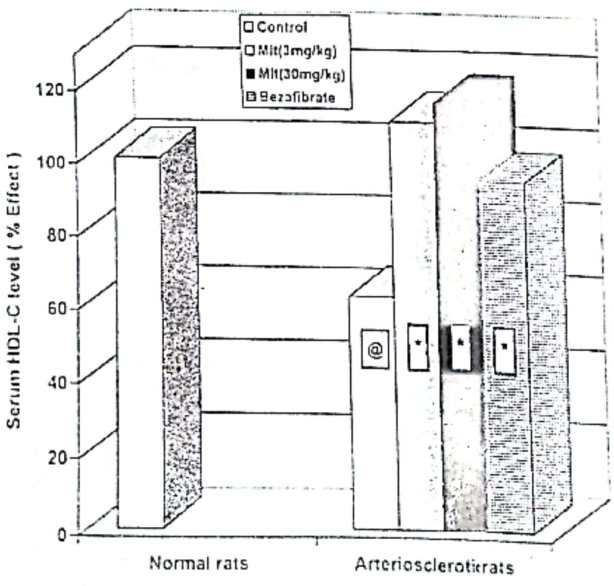

Fig. (2-c): effect of oral administration of melatonin (3 mg/kg and 30 mg/kg) and bezafibrate (50 mg/kg) on serum high density lipoprotein- cholesterol (HDL-C) level in arteriosclerotic adult male rats.

*Significantly different from normal control value ($p<0.05$).

@ Significantly different from arteriosclerotic control value ($p<0.05$).

Treatment with Mlt at low and high dose levels or with Bzf reduced serum LDL-C levels to 95.25 ± 12.4 %, 55.49 ± 9.6 % and 96.7 ± 15.6 %, (Fig.2-d). Serum Ca^{2+} level was reduced after treatment with Mlt, 30mg/kg to 98.6 ± 16.6 % or with Bzf to 73.7 ± 5 %, where control arteriosclerotic level was elevated to 141.6 ± 10.55 % when compared to normal rats, (Fig.2-e).

Histo-pathological examination of blood vessels showed partial regression in arteriosclerotic lesions in response to Mlt (3 mg/kg) and Bzf (50 mg/kg). On the other hand, Mlt (30 mg/kg) produced complete regression of arteriosclerotic lesions as shown in Fig.3(a-f).

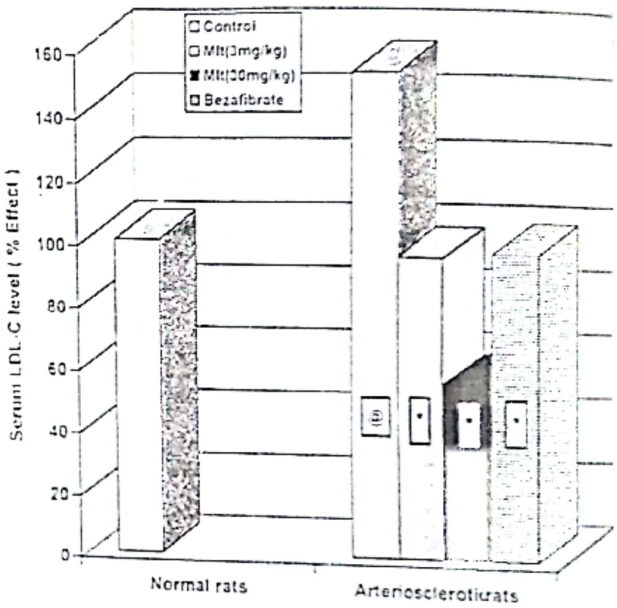

Fig. (2-d): effect of oral administration of melatonin (3 mg/kg and 30 mg/kg) and bezafribate (50 mg/kg) on serum low density lipoprotein – cholesterol (LDL-C) level in arteriosclerotic adult male rats.

* Significantly different from normal control value ($p<0.05$).

@ Significantly different from arteriosclerotic control value ($p<0.05$).

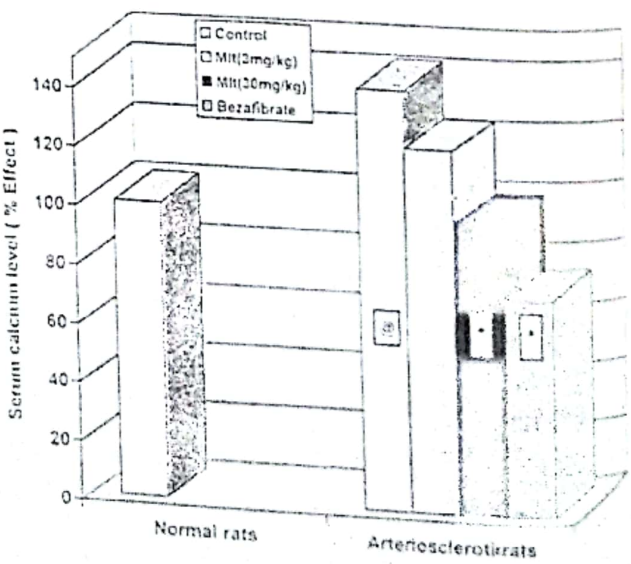

Fig.(2-e): effect of oral administration of melatonin (3 mg/kg) and bezafibrate (50 mg/kg) on serum calcium level in arteriosclerotic adult male rats.

* Significantly different from normal control value ($p<0.05$)

@ Significantly different from arteriosclerotic control value ($p<0.05$).

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DISCUSSION

In the present study, oral administration of Mlt at low and high dose levels (3 mg/kg and 30 mg/kg) for 6 weeks in arteriosclerotic rats produced significant decreases in serum TC, TG and LDL-C levels and produced significant increase in HDL-C level. Our results are in agreement with the results of Aoyama and his coworkers who found that Mlt exerted antihypercholesterolemic action [14]. In addition, our results are supported by the finding that pinealectomy in rats and rabbits was associated with elevation of blood cholesterol level [15,16].

Mlt lowers serum cholesterol, which may be due to increase cholesterol metabolism into bile acids [17]. In addition the hypocholesterolemic action of Mlt may be due to inhibition of cholesterol biosynthesis. As Muller and his coworkers found that Mlt inhibits cholesterol synthesis by inhibiting conversion of lanosterol to cholesterol [18]. Moreover, the hypocholesterolemic effect of Mlt may be due to an increase in cholesterol consumption in the synthesis of steroid hormones, as Mlt induced a significant increase in cortisol level in rats [19].

As supported with other studies [17,20], Mlt administration at both dose levels (3 mg/kg and 30 mg/kg) in arteriosclerotic rats induced a significant reduction in LDL-C level.

The current results showed that Mlt lowered serum TG both in normal and artherosclerotic animals. This effect may be explained via reduction in VLDL synthesis in liver or via increase in catabolism of TG by Mlt. This explanation is supported by the observation of John et al who found that Mlt increases free fatty acid level [21].

The protective action of Mlt against arteriosclerosis may be due to an antioxidant effect of Mlt as it protects LDL-C against oxidation by free radicals [22,23]. It protects polyunsaturated fatty acids LDL-C against peroxidation and decreases the rate of diene formation. Mlt also inhibits 5-lipoxygenase enzyme activity that initiates lipid peroxidation [24]. It scavenges peroxy radicals, which propagate lipid peroxidation [25]. It increases the efficiency of known antioxidant such as vitamin E [26]. In addition to the antioxidant effect of Mlt, it possesses a blood pressure lowering effect [27] and exerts a good protective action against arteriosclerosis.

Moreover, in the present study, Bzf induced a significant increase in serum HDL-C and significant decrease in serum TC, TG, LDL-C and Ca^{2+} levels when given to arteriosclerotic rats. These results agree with the finding of other investigators that series of fibric acid derivatives were effective in reducing TG and cholesterol levels [28,29]. The hypocholesterolemic effects of Bzf may be due to interference with cholesterol synthesis [30-32] and also increase the secretion of cholesterol in the bile [32-35]. The decrease in TG levels may be due to the increase in lipoprotein lipase activity caused by Bzf which in turn accelerates the catabolism of TG-rich lipoprotein, VLDL and LDL [36,37] or due to the interference with VLDL synthesis or TG synthesis [38-41].

Fig. (3-a): Artery of a normal rat showing normal vascular wall (HandE stain).

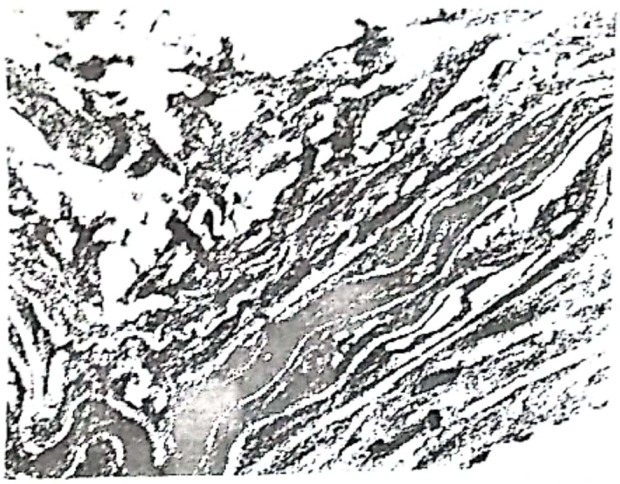

Fig. (3-b) Artery of an arterioscletoric rat showing calcium deposition represented by blue granules (Hand E stain).

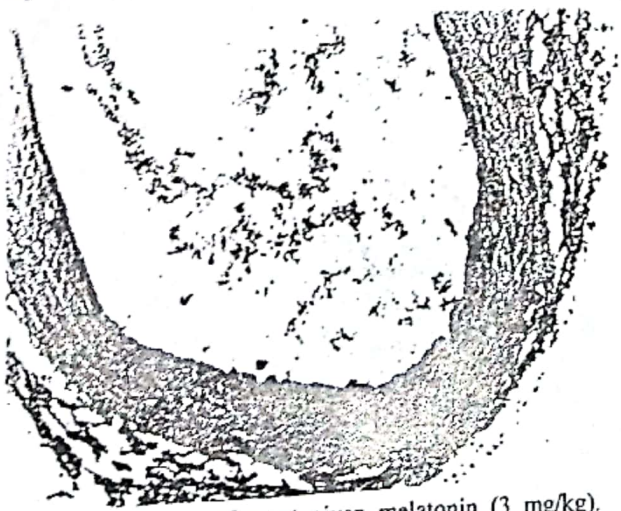

Fig. (3-c): Artery of a rat given melatonin (3 mg/kg). Vitamin D2 (7.5 mg/kg) and cholesterol for 6 weeks and pretreated with meltaonin showing unremarkable pathological changes (Hand E stain)

In hypercholesterolemic patients, fibrate was also able to lower LDL level [42], an effect that is similar to that obtained by Bzf in arteriosclerotic rats. This effect may be mediated by decreasing cholesterol biosynthesis, which in turn increases the number of LDL receptors, thus increases the clearance of LDL [36]. In the same study by Trundy and Vega, they also demonstrated a

similar increase in HDL-C. This effect of fibrate may be attributed to activation of lipoprotein lipase which in turn converts HDL2b (rich in TG) to HDL2a (rich in cholesterol). The net effect is an increase in HDL-C [36].

In the current study, Bzf showed only partial regression of the arteriosclerotic lesion, while Mlt at high dose (30 mg/kg) was more potent and caused complete regression of arteriosclerotic lesions.

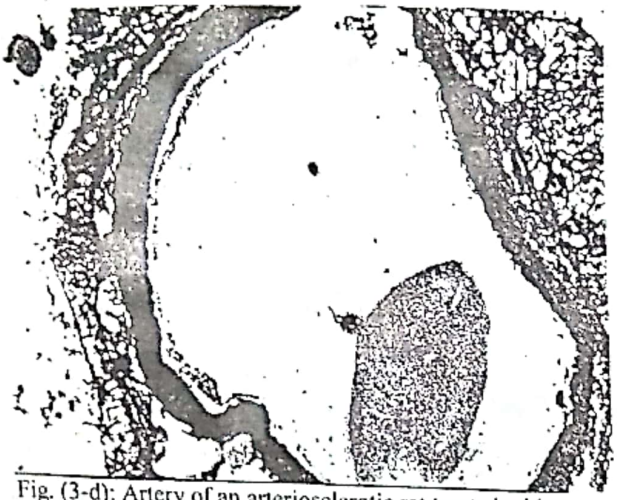

Fig. (3-d): Artery of an arteriosclerotic rat treated with melatonin (30 mg/kg) for 6 weeks appears more or less normal (Hand E stain).

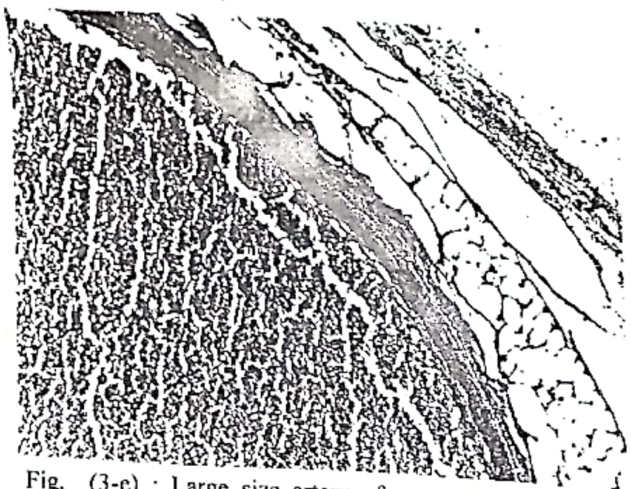

Fig. (3-e) : Large size artery of an arteriosclerotic rate treated with 3 mg/kg melatonin for 6 weeks showing aggregations of calcium grandus and cholesterol of clefts in the tunica intima and media accompanied by destruction of arterial wall (Hand E stain).

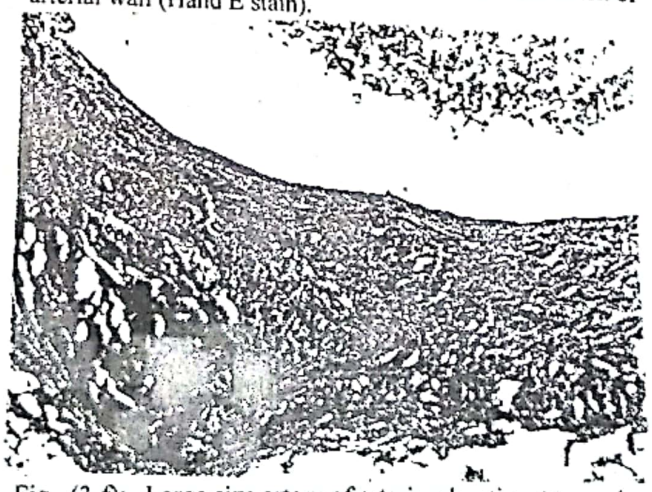

Fig. (3-f): Large size artery of arteriosclerotic rat treated with bezafibrate for 6 weeks showing focal deposition of calcium and cholesterol (Hand E stain).

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دراسة الدور الوقائي والعلاجي للميلاتونين في ذكور الفئران البالغة الطبيعية والمصابة بمرض تصلب الشرايين

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يعتبر مرض تصلب الشرايين من أمراض الشيخوخة ولقد درسنا في هذا العمل الدور المحتمل لمادة الميلاتونين في الوقاية من وعلاج مرض تصلب الشرايين . وقد تم دراسة الدور الوقائي عن طريق إعطاء الميلاتونين بجرعتين أحدهما ٣ مجم/كجم والأخرى ٣٠ مجم/كجم لمدة ٦ أسابيع تلاها إحداث مرض تصلب الشرايين مع استمرار استعمال الميلاتونين بجرعتيه . و قد تم الحصول على النتائج التالية عند استعمال الميلاتونين بجرعة قدرها ٣مجم/كجم أحدث الميلاتونين انخفاضا معنويا في مستوي كل من التراي جليسريدات والكاليسوم في مصل الدم بمقارنته بمصل الفئران المصابة بتصلب الشرايين ولم تتلقى أي علاج. كذلك أحدث الميلاتونين ارتفاعا معنويا في مستوي كل من الكوليسترول الكلي واللبيوبروتين كوليسترول منخفض الكثافة في مصل الدم.

وعند استعمال الميلاتونين بجرعة قدرها ٣٠مجم/كجم احدث انخفاضا معنويا في مستوي التراي جليسريدات في مصل الدم بينما أحدث أيضا ارتفاعا معنويا في مستوي الليبوبروتين كوليسترول عالى الكثافة. على النقيض من ذلك لم يحدث أي تغيير معنوي في كل من الكوليسترول الكلي ، و الليبوبروتين كوليسترول منخفض الكثافة وكذلك الكالسيوم في مصل الدم عند المقارنة بالفئران المصابة بمرض تصلب الشرايين ولم تتلقى أي علاج (المجموعة الضابطة المصابة) . ومن خلال فحص شرايين الفئران تبين أن الميلاتونين بجرعتيه قد منع حدوث تصلب الشرايين .

ولدراسة الدور المحتمل الذي قد يلعبه الميلاتونين في علاج مرض تصلب الشرايين ، فقد تم علاج الفئران المستحدث بها مرض تصلب الشرايين بالميلاتونين بجرعتيه بالمقارنة بعقار البيزافيبيرات (٥٠مجم/كجم) و المعروف بتأثيره على خفض نسبة الدهون في الدم . وقد تسبب استعمال العقارين إلى انخفاض معنوي في مستوي الكوليسترول الكلي والتراي جليسريدات والليبوبروتين كوليسترول منخفض الكثافة والكاليسوم مع زيادة معنوية في نسبة الكوليسترول عالى الكثافة . وبفحص الأوعية الدموية لتأكيد المؤشرات البيوكيميائية وجد أن الميلاتونين في جرعة ٣٠مجم/كجم قد تسبب في انحسار كلي للمرض .

من خلال ما سبق يتبين أن للميلاتونين دور في الوقاية من وعلاج مرض تصلب الشرايين ، ويقتصر الدور العلاجي على الجرعة العالية (٣٠مجم/كجم) لعلاج مرض تصلب الشرايين المستحدث تجريبيا .