

Biochemical Effect of Some Antioxidant on Metabolic Changes in Experimentally induced Tumor in Female Mice

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Abstract

Biochemical effect of tannic acid and curcumin on female mice experimentally induced Ehrlich Ascitis Carcinoma (EAC) was investigated. This study was carried out on 220, 12-14 weeks old female mice and weighted 25-30 g. Mice were classified into two main large experiments. Experiment 1: Non-tumor bearing mice (NTB) Included 100 of animals and divided into four groups each one comprised 25 mice. Group 1: NTB- control saline treated .Group 2:NTB-treated with curcumin orally (350 mg/kg/day) for 6 weeks. Group 3:NTB-treated with tannic acid orally (160 mg/kg/day) for 6 weeks. Group 4:NTB-treated with curcumin and tannic acid orally at ratio (50% : 50%) for 6 weeks. Experiment 2: Tumor bearing (TB) mice. Included 120 of animals and divided into four groups each one comprised 30 mice. Group 1:TBM-control saline treated. Group 2: TBM-treated with curcumin orally (350 mg/kg/day) for 6 weeks. Group 3:TBM-treated with tannic acid orally (160 mg/kg/day) for 6 weeks. Group 4:TBM-treated with curcumin and tannic acid orally at ratio (50%: 50%) for 6 weeks. Blood samples were collected from all animals groups after 2, 4 and 6 weeks from treatment. Serum were separated and processed directly for glucose, insulin, total cholesterol, triacylglycerol, total protein determination. The obtained results revealed that, a highly significant decrease in serum glucose, total cholesterol, total protein concentration. Mean while, a highly significant increase in serum triacylglycerol concentration. But a non significant decrease in serum insulin levels were observed in tumor bearing mice when compared with control. The results of this study indicated that curcumin, tannic acid and their combination treatment have potential benefits in cancer treatment.

Kew words: Curcumin, tannic acid, triacylglycerols, tumor and anticancer.

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1. Introduction

Ehrlich ascites carcinoma (EAC) is one of the experimental breast tumor derived from spontaneous mouse adenocarcinoma. Similar to other tumors developing in body cavities, EAC cells fill the peritoneal cavity by rapid division. During this rapid increase,

besides the tumor cells, accumulation of a fluid named ascetic fluid is also observed With the growth of the tumor, the amount of the fluid increases and as a consequence, due to the pressure induced by both tumor cells and the ascetic fluid and also the tumor's damage to the organism, animal dies following 17-18 days of EAC transplanted [1] Curcumin, a

polyphenolic compound extracted from rhizomes of Curcuma species, has in fact been shown to possess interesting anti-inflammatory and antitumor properties [2].

Tannic acid (TA), a glucoside of gallic acid polymer which is found, along with other condensed tannins, in several beverages including red wine, beer, coffee, black tea, green tea, and many foodstuffs. It has been shown to possess anti-bacterial, anti-enzymatic and antitumor properties [3]. Curcumin exhibits anti-cancer activities both in vitro and in vivo through a variety of mechanisms. It inhibits proliferation and induces apoptosis in a wide array of cancer cell types in vitro, including cells from cancers of the bladder, breast, lung, pancreas, prostate, cervix, head and neck, ovary, kidney, brain, bone marrow, skin, chemotherapeutic agents and of c-radiation[4]. Administration of tannic acid in drinking water caused inhibition of Ehrlich ascites carcinoma (EAC) bearing mice [5].

Although our knowledge of cancer biology has advanced a great deal, neither the incidence of cancer nor the rate of death due to cancer has changed in the last 50 years ago. Most drugs currently available for the treatment of cancer have limited potential because they are very toxic, highly inefficient in treating cancer, or highly expensive and thus beyond the reach of the majority that treatments without these disadvantages are needed. Accordingly, the purpose of this experiment to investigate the possible protective effect of treatment curcumin and tannic acid in experimentally induced tumor in female mice.

2. Material and Methods

A total number of 220 Australian females' albino mice of 12-14 weeks old age and weighting 25-30 gm were used in the experimental investigation of this study. Mice were obtained from the Research Institutes of Ophthalmology, Giza, Egypt. Animals were housed in separate metal cages, fresh and clean drinking water was supplied ad-libitum through specific nipple. Mice were kept at a constant environmental and nutritional condition throughout the period of the experiment.

Tumor induction: The experimental induction of tumor in female mice was carried out at the National Cancer Institute Egypt. Every 1 ml of Ehrlich ascites adenocarcinoma was diluted with 4 ml of normal saline. Each mouse was injected subcutaneously (S/C) in the medial aspect of the right thigh with 0.2 ml of Ehrlich ascites adenocarcinoma (2.5×10^6 tumor cells with single cell suspension) [6]. The tumor developed

and become palpable in all injected animals at 5-7 days post tumor inoculation

Experimental design: The experimental work was classified into two main large experiments as follow:

Experiment A: Non-tumor bearing mice. "NTB- mice" Included 100 of female mice divided into four groups, each one consisting of 25 animals placed in separate metal cages and classified as follows:

Group 1: Non tumor bearing control (NTB-C) administered with 0.2 ml of normal saline.

Group 2: Non tumor bearing (NTB-cur) treated with curcumin orally administered daily at adose level of (350 mg/kg/day) for 6 weeks.

Group 3: Non tumor bearing (NTB-tan) treated with tannic acid orally administered daily at adose level of (160 mg/kg/day) for 6 weeks.

Group 4: Non tumor bearing (NTB-cur+tan) treated with curcumin and tannic acid orally and daily at ratio of (50%: 50%) for 6 weeks.

Experiment B: Tumor bearing mice."TB- mice"

A total number of 120 female TB-mice were divided into four groups, each one included 30 mice placed in a separate metal cage and classified as follows:

Group 1: Tumor bearing control (TB-C) administered with 0.2 ml of normal saline.

Group 2: Tumor bearing (TB-cur) treated with curcumin orally administered daily at adose level of (350 mg/kg/day) for 6 weeks.

Group 3: Tumor bearing (TB-tan) treated with tannic acid orally administered daily at adose level of (160 mg/kg/day) for 6 weeks.

Group 4: Tumor bearing (TB-cur+tan) treated with curcumin and tannic acid orally and daily at ratio of (50% : 50%) for 6 weeks.

Sampling: Blood samples were collected in the morning after overnight fasting from all mice by decapitation every 2, 4, 6 weeks from the onset of treatment, then obtained in dry and clean tubes and serum was separated by centrifugation at 3000 RPM for 15 minutes. The clear serum were aspirated by Pasteur pipette and received in dry sterile sample tube, processed directly for enzymes determination, then kept in a deep freeze at -20°C until used for subsequent biochemical analysis.

Biochemical analysis: Serum glucose, insulin, total cholesterol, triacylglycerols and total protein were

analyzed calorimetrically according to the methods described by [7, 8, 9, 10, 11] respectively.

Statistical analysis: Statistical analysis of the results was carried out using T-test and student's F-test according to [12].

3. Results and Discussion

The presented data in tables (1) revealed that, tumor bearing female mice demonstrated a highly significant decrease of serum glucose, total cholesterol and total protein concentration. Mean while, a non significant decrease in serum insulin level. In contrary, highly significant increases of serum triacylglycerols concentration in tumor-bearing female mice were observed all over the experimental period of tumor induction as compared to control.

A highly significant decrease of serum glucose concentration was confirmed by the finding of [13,14,15] who observed that, the value of plasma glucose level showed a significant decrease of experimentally induced tumor in female mice. This decrease was not due to an over production of insulin level. But due to general changes in energy metabolism associated with tumor growth. A non significant decrease in serum insulin level observed in tumor bearing mice was confirmed by [13,16] who reported that, tumor growth cause reduction in plasma insulin level in women having breast cancer and this may be contributed to the catabolic effect of progressive tumor growth. Our results demonstrated a highly significant decrease in serum total cholesterol concentration in tumor bearing mice were Similar results reported by [17,18] who showed that, the level of total cholesterol concentration tended to decrease during the later stages of tumor growth, where there was a statistically significant reduction on day 5 and 10. The observed a highly significant decrease of serum total protein concentration in tumor bearing mice was confirmed by the finding of [13] who observed that, there was a highly significant decrease in plasma total protein and albumin concentrations in tumor-bearing female mice. The author attributed such decrease in plasma total protein concentration in TB-mice either due to the distant catabolic effect of tumor on host tissue protein which incorporate nitrogen of the expense of skeletal muscle protein or to the broken down of tissue proteins to provide gluconeogenic precursors [19].

Our results demonstrated a highly significant increase in serum triacylglycerols concentration in tumor bearing mice were Similar results reported by

[20,21] who reported that, a significant increase of plasma triacylglycerol, free fatty acids and ketone bodies were observed in tumor bearing mice. The presented data in table (2) revealed that, Administration of (cur) to TBM showed a significant decrease observed all over the experimental period in serum glucose concentration as compared to control (S) and (tan) treated groups. Furthermore, a significant decrease after 4 weeks while a significant increase after 6 weeks as compared to (cur+tan) treated group. Similar results were reported by [22] showed that, treatment with curcumin to tumor bearing mice caused a significant decrease in glucose level. Also, [23] showed that curcumin reduced hepatic glucose production. They demonstrated that curcumin inhibits both hepatic gluconeogenesis and glycogenolysis by suppressing both glucose-6-phosphatase (G6Pase) activity and phosphoenolpyruvate carboxykinase (PEPCK) activity. As curcumin had no suppressive effect on DNA synthesis in isolated hepatocytes. Our results in TBM (tan) group showed a significant decrease after 4 weeks, which became a significant increase after 6 weeks as compared to control (S) group was observed. Moreover, a significant increase observed all over the experimented period as compared to (cur) treated group. Furthermore, a significant increase after 2 and 6 weeks as compared to (cur+tan) treated group. Similar results were reported by [24] showed that, the ingestion of TA at the concentrations of 0.5,1.0 and 1.5 g delayed the uptake and transport of glucose from the intestinal lumen and reduced the total concentration of plasma glucose by 54, 69 and 67%, respectively. Increasing in plasma glucose concentration in TA administrated TBM was agree with the results reported by [25] reported that, an increase in glucose level after oral administration of tannic acid due to increased utilization of glucose by the liver. A significant decrease in serum glucose concentration was observed all over the experimental period in TBM (cur+tan) group as compared to control (S) group, while a significant increase after 4 weeks and a significant decrease after 6 weeks as compared to (cur) treated group. Moreover, a significant decreases after 2 and 6 weeks as compared to (tan) treated group.

These results similar to curcumin results because in the mixture, Tannic acid absorbs substances in the stomach and intestines. Taking tannic acid along with medications taken by mouth can decrease how much medicine your body absorbs, and decrease the effectiveness of your medication [26].

Table (1): Mean values of serum glucose (mg/dl), insulin levels (μ IU/ml), T.cholesterol (mg/dl), triacylglycerol (mg/dl) and total protein concentrations (g/dl) of experimentally induced tumor in female mice and their control.

Parameters	2 weeks		4 weeks		6 weeks	
	NTB	TBM	NTB	TBM	NTB	TBM
S.glucose concentration (mg/dl)	159.80 \pm 1.35	150.00 ^{**} \pm 0.70	136.20 \pm 1.24	132.80 \pm 1.28	140.60 \pm 1.07	89.00 ^{***} \pm 1.22
S.insulin levels (μ IU/ml)	9.16 \pm 0.53	5.53 \pm 0.29	7.50 \pm 0.52	6.20 \pm 0.61	9.73 \pm 0.68	7.80 \pm 0.83
S. T.cholesterol concentration (mg/dl)	130.66 \pm 0.84	93.66 ^{***} \pm 0.62	127.99 \pm 1.13	40.33 ^{***} \pm 0.62	88.33 \pm 1.39	31.99 ^{***} \pm 0.97
S. triacylglycerol concentration (mg/dl)	156.50 \pm 1.27	167.00 ^{**} \pm 1.45	152.00 \pm 2.00	203.50 ^{***} \pm 2.31	149.50 \pm 1.27	226.00 ^{***} \pm 2.03
S.total protein concentration (g/dl)	5.04 \pm 0.12	5.92 \pm 0.088	6.02 \pm 0.088	4.86 ^{***} \pm 0.088	6.96 \pm 0.10	3.88 ^{***} \pm 0.21

Data are presented as (mean \pm S.E) & S.E. = standard error.

* = a significant after $p < 0.05$

** = a highly significant after $p < 0.01$

*** = a very highly significant after $p < 0.001$

A significant increase in serum insulin levels after 4 weeks in TBM (cur) group as compared to control (S) group was observed. Furthermore, a significant increase after 4 weeks as compared to (tan) treated group. Moreover, a significant decrease after 4 weeks as compared to (cur+tan) treated group. Similar results were reported by [23,27] who reported that, oral administration of curcumin to tumor bearing mice was found to induce heme oxygenase-1 expression, which has been reported to have cytoprotective effects in mouse pancreatic beta-cells that increase insulin level. Administration of (tan) to TBM showed a significant decrease in serum insulin levels after 4 weeks as compared to (cur) and (cur+tan) treated groups. Similarly, [28] who found that, oral administration of tannic acid to TBM had a significant decrease in serum insulin concentration. Our results in TBM (cur) group showed a significant decrease in serum total cholesterol concentration was observed all over the experimental period as compared to control (S) and (tan) treated groups. Moreover, a significant decrease after 2 weeks as compared to (cur+tan) treated group. These results are in agreement with [29,30] who showed that, curcumin reduced cholesterol and increased HDL-c, indicating that curcumin may be mobilizing cholesterol from extrahepatic tissues to the liver where it is catabolised.

A significant increase in serum total cholesterol concentration all over the experimental period in TBM (tan) group as compared to control (S) and (cur) treated groups was observed. Moreover, a significant decrease after 2 weeks followed by a significant

increase after 4 and 6 weeks as compared to (cur+tan) treated group.

These results are in agreement with [31] who reported that, the hypercholesterolemia effects have been described both in human subjects and in animals fed diets containing grape tannins and tannic acid due to endogenous oxidative stress induced by tannic acid produced a clear decrease in microsomal and mitochondrial cholesterol concentration.

TBM (cur) group showed a significant decrease in serum triacylglycerols concentration was observed all over the experimental period as compared to other groups. Similar results were reported by [29,32] who reported that, the reduction in serum and hepatic triglycerols and cholesterol in human received turmeric extract as curcumin is the result of a direct effect on liver or an indirect effect through thyroid hormones, since thyroid hormones affect reactions in almost all the pathways of lipid metabolism.

Our results in TBM (tan) group showed a significant decrease in serum triacylglycerols concentration after 6 weeks as compared to control (S) group. Mean while, a significant increase observed all over the experimental period with comparison to (cur) and (cur+tan) treated groups. Similar results were reported by [28] who observed a decrease in triglycerides level after ingestion of tannic acid, which might be due to the lower ingestion of diet. Because tannin rich feed reduces the feed intake and exhibit deleterious effect on growth, food consumption and food utilization as well as on haematological variables due to the phenolic constituents present in the feed materials.

Table (2): Effect of curcumin, tannic acid alone or in combination on serum glucose (mg/dl), insulin levels (μ IU/ml), T.cholesterol (mg/dl), triacylglycerol (mg/dl) and total protein concentrations (g/dl) in NTB and TBM.

Parameters		TBM C(s)	TBM (DMSO)	TBM(cur)	TBM (tan)	TBM (cur+tan)
S.glucoseconcentration (mg/dl)	2	150.00 ^{a,b} ±0.7	152.00 ^a ±1.18	140.60 ^c	148.20 ^b ±1.35	143.40 ^c ± 1.07
	4	132.80 ^b ± 1.28	139.60 ^a ±0.81	118.60 ^d ±1.0	128.00 ^c ±1.58	126.00 ^c ±1.73
	6	89.00 ^b ±1.22	100.00 ^a ±1.51	81.60 ^c ±1.96	101.40 ^a ±1.32	77.00 ^d ± 1.41
S.insulin levels (μ IU/ml)	2	5.23 ^a ±1.18	5.53 ^a ±0.29	5.40 ^a ±0.41	6.06 ^a ±0.44	5.86 ^a ± 0.66
	4	6.20 ^c ± 0.61	4.23 ^d ±0.64	8.30 ^b ±0.28	5.60 ^{cd} ±0.81	10.53 ^a ± 0.50
	6	7.80 ^a ±0.83	6.6 ^a ±0.73	8.80 ^a ±0.75	7.33 ^a ±0.60	9.70 ^a ± 0.70
S. T.cholesterol concentration (mg/dl)	2	93.66 ^c ±0.62	87.98 ^d ±1.33	54.53 ^e ±0.90	98.66 ^b ±1.10	104.59 ^a ± 1.91
	4	40.33 ^b ± 0.62	41.51 ^b ±0.99	34.33 ^c ±1.13	49.99 ^a ±1.48	31.66 ^c ± 0.74
	6	31.99 ^b ±0.97	33.33 ^b ±0.97	26.33 ^c ±0.62	40.66 ^a ±1.45	23.99 ^c ± 0.85
S. triacylglycerol concentration (mg/dl)	2	167.00 ^a ±1.45	158.50 ^b ±1.27	138.00 ^c ±1.45	165.50 ^a ±0.93	156.00 ^b ±1.27
	4	203.50 ^{a,b} ±2.3	198.50 ^b ±1.27	123.00 ^d ±1.4	207.50	176.00 ^c ± 2.03
	6	226.00 ^a ±2.03	221.50 ^{a,b} ±1.27	104.00 ^d ±2.3	217.00	180.00 ^c ± 1.76
S.total protein concentration (g/dl)	2	5.92 ^a ±0.08	5.89 ^a ±0.23	5.04 ^a ±0.12	4.72 ^a ±0.15	4.96 ^a ± 0.15
	4	4.86 ^b ±0.08	4.03 ^b ±0.08	6.00 ^a ±0.16	3.88 ^b ±0.23	5.85 ^a ±0.10
	6	3.88 ^b ±0.21	3.21 ^b ±0.28	6.36 ^a ±0.24	2.90 ^b ±0.29	6.24 ^a ± 0.24

Mean values with different super script letters in the same rows are significantly different at ($p < 0.05$).

A significant increase in serum total protein concentration after 4 and 6 weeks in TBM (cur) group as compared to control (S) group was observed. Furthermore, a significant increase after 4 and 6 weeks as compared to (tan) treated group. Similar results were reported by [33,34] who found that, administration of curcumin to tumor bearing mice significantly increase the concentration of serum total protein mainly due to an increase in serum globulin content which related to stimulation of immunity.

Our results in TBM (tan) group showed a significant decrease in serum total protein concentration after 4 and 6 weeks as compared to (cur) treated group. Moreover, a significant decrease after 4 and 6 weeks as compared to (cur+tan) treated group. Similar results were reported by [35] who demonstrated that, the oral administration of tannic acid to TBM may decrease total protein concentration due to nephrotoxicity and renal tubular damage.

4. Conclusion

Curcumin has potent chemopreventative activity against a wide variety of tumors and has great potential in the prevention and treatment of cancer, also prevent LDL oxidation. In addition, tannic acid exerts chemopreventative activity against cancer by its poly phenols, which has antioxidant and free radicals

scavenging activity and trapping of activated metabolites of carcinogene. So we recommended by using curcumin in our food as prophylactic and preventive for many diseases. Also, drinking tannic acid after food by times to take it is benefit and alone.

Conflict of Interest: None

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Cite this article as:

Omayma A. R. Abou Zaid, Mohammed R. R. Hassanein, Yakout A. EL-Senosi and Mohammed F. EL-Shiekha, 2013. Biochemical Effect of Some Antioxidant on Metabolic Changes in Experimentally induced Tumor in Female Mice, *Inn. Pharmacotherapy*, Vol 1. (1), 16-22.