The Egyptian Journal of Hospital Medicine (April 2012) Vol., 47: 279 – 290

Effect of Cynara Scolymus L. (Artichoke) Extraction on Hyperlipidemic Induced by Gamma Radiation in Male Rats

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Abstract:

Introduction

Excessive free radicals are caused by unnatural environmental influences such as air pollution, radiation, cigarette smoke, factories, pesticides, food contaminants and a myriad of other factor that are part of our modern life. Hypercholesterolaemia is directly associated with an increased risk of coronary heart disease (CHD).

Cynara scolymus L. (Artichoke) grows in Egypt and other countries. It is used as foods and has medicinal properties. Artichoke extracts have been shown to produce various pharmacological effects, such as the inhibition of cholesterol biosynthesis and low density lipoprotein (LDL) oxidation.

Aim

The present study aims to evaluate the antioxidative activities and radioprotector role of cynara scolymus L. (artichoke) against hyperlipidemic induced by gamma- irradiation in male rats.

Material and Method

Male Swiss albino rats were orally administrated by artichoke (head or leaves) (10% mg/rat/day) using suitable stomach tube (6weeks, 45 days) before exposure to a single dose (6.5 Gy) of whole body gamma radiation. Levels of lipids peroxides (MDA), reduced glutathione content (GSH), superoxide dismutase (SOD), total cholesterol (TC), triacylglycerol (TG), high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) were investigated in serum

Results

The results revealed that gamma radiation led to significant increase in MDA, TC, TG and LDL, Meanwhile, significant decrease in GSH and SOD, but groups administrated with Artichoke (head and leaf) before whole body gamma irradiation, artichoke exerted noticeable amelioration against the radiation induced changes in most of the biochemical tested parameters.

Keywords: Ionizing radiation, Cynara scolymus L. (artichoke), Atherosclerosis; Antioxidant, Lipid profile.

Introduction:

Free radicals are atoms, groups of atoms or particles having on their last orbital at least on unpaired electron. The most toxic radicals are oxygen radicals belonging to peroxidal anion radical, hydroxyl radical, peroxidal lipid radical and singlet oxygen **(Durackov et al., 1993).**

The ionizing radiation can produce free radicals which are oxygen atoms that contain unpaired electron. These unbalanced atoms then widely seek electrons from other atoms to replace their own, attacking normal cells and causing the chain reaction known as oxidation. Oxygen free radicals induce damage due to peroxidation to biomembranes and also to DNA, which lead to tissue damage, thus cause occurrence of a number of disease. Antioxidants neutralize the effect of

free radicals through different ways and may prevent the body from various diseases **(Manuchair, 2003).**

For evaluating the radiation hazards, it is recommended to study the variation in certain biological substances of the irradiated animals. The cell is equipped with a variety of defense mechanisms (e.g. glutathione, superoxide dismutase and catalase) to combat free radical damage to critical biomolecules however with increasing doses of radiation these system can be overwhelmed **(Ho et al., 1998)**.

Atherosclerosis is a complex multicellular process, resulting in an unstable atherosclerotic plaque that ultimately bursts, causing myocardial infraction. Botanical dietary supplements (herbs) can ameliorate this process and prevent cardiovascular disease at many steps in the process. Many herbs herbs have antioxidant activity and can reduce low density lipoprotein oxidation. Some phytosterols found in botanicals can inhibit cholesterol absorption **(Heber, 2001).**

Hypercholesterolaemia is directly associated with an increased risk of coronary heart disease (CHD) **(Holme, 1990)**.

The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and led to tremendous growth of phytopharmaceutical usage **(Bhattaram et al., 2002).**

Non of the pharmacological options is free of adverse events and some have been associated with potential carcinogenicity **(Expert Panel, 2002)**. A harmless yet effective treatment option would therefore be of considerable interest.

Antioxidants may be synthetic or nautral. Synthtic antioxidants have recently been reported to be dangerous for human health. Thus, the search for effective, non-toxic natural compounds with antioxidative activity has been intensified in recent years **(Vivek and Surendra, 2006).**

The present study includes a research on plant with antioxidant potential (artichoke).

Artichoke has been suggested as such an option. Effective non- pharmacological treatment consists largely of dietary interventions and increased physical activity and is considered the treatment of choice for primary and secondary prevention of CHD pharmacological **(Wegener, 2002** and **Bundy et al., 2008).**

Cynara scolymus L. (artichoke) is an important crop of ancient Greece, grows in Egypt, Mediterranean area and other countries. It has been known by the ancient Egyptians. Its green leaves and head are used as foods due to their high nutritive value. Artichoke is one of the world's oldest medicinal plants. It has medical properties. It is a good source of natural antioxidants such as vitamin C, hydroxycinnamic acids and flavones **(Jimenz et al., 2003** and **Wittemer, 2005)**.

Artichoke and its byproduct contain many compounds as caffeolquinic acid derivatives and flavonoid. Caffeic acid derivatives and flavonoids. Caffeic acid derivatives are the main phenolic compounds in artichoke head with a wide range of caffeolquinic acid derivatives. Apigenin-7-rutinoside and narirutin were found to be unique to artichoke heads **(Wang et al., 2003** and **Yang, 2005)**.

Kusku et al. (2010) indicate that artichoke leaf extract (ALE) may be useful for the prevention of hypercholesterolemia-induced pro-oxidant state in LDL+VLDL fraction and the reduction of increased serum cholesterol and triglyceride levels. **Cervellati et al. (2002)** and **Lupattelli et al. (2004)** found that cynarin are used to mobilize

fatty stores in the liver and detoxify it.

From the leaves of cynara scolymus the following substances where isolated: apigenin, lutealin, lutealin-4'-glucoside, cynaroside, scolimoside, cosmside, quercetin, rutin, chloro-genic acid, caffeic acid, isochlorogenic acid, luteolin-7-gentiobioside, along with the more uncommon scopoltin, hesperitin, hesperidoside, esculetin-6-O-beta-glucoside, maritimein, sesquiterpenes (cynaropicrin, sguerin B and grosheimin), sesquiterpene glycosides (cynara-scolosides A, B and C) **(Shimoda et al.,2003 and Schutz et al., 2006)**.

The anthocyanin of artichoke heads was cyanidin 3,5-diglucoside, cyanidin 3-glucoside, cyanidin 3,5-malonyldiglucoside, cyanidin 3-(3"-malonyl) glucoside and cyanidin 3-(6"-malonyl) glucoside which represent the major anthocyanin, two peonidin derivatives and one delphinidin derivatve. Total anthocyanin content ranged fromm 8.4 to 1,705.4 mg/kg dry mass **(Shimoda etal., 2003 and Schutz et la., 2006)**. Cynarine (1.5-di-caffeoyl-D-quinic acid) is of the principle active component of artichoke **(Yang, 2005).** The flavonoid luteolin has a role in the inhibition of cholesterol synthesis **(Kucukgergin, 2009)**.

Material and Methods:

Preparation of artichoke extract (head and leaves) (Wanger et al., 1984 and Wang et al., 2003):

A known weight of artichoke head was air dried at the room temperature and grinded using a blinder into fine powder. The powdered head was macerated in 70% methanol. Successive addition of aqueous methanol to powdered head was carried out till complete exhaustion of the head. The aqueous methanolic extract was concentrated under reduced pressure using rotatory evaporator till dryness and then weighed .The same was done on the leaves.

Radiation source:

Irradiation was performed by gamma cell 40 source (Cesium-137) belonging to the National Centre for Radiation Research and Tochnology (NCRRT), Egypt. This Cesium source offers a dose rate 1.3 rad/sec at the time of experiment.

Experimental design:

Seventy two male Swiss albino rats, weighing (140 10 g.) were housed individually in wire mesh cages. These rats were divided into six groups each contained 6 rats:

Group I : group (untreated) control.

Group II: group administrated with artichoke extract (head) (10% mg/rat/day) alone.

Group III:group administrated with artichoke extract (leaves) (10% mg/rat/day) alone.

Group IV:group exposed to single dose (6.5 Gy) whole body gamma irradiation.

Group V:group exposed to single dose of radiation after administrated with artichoke extract (head).

Group VI:group exposed to single dose of radiation after administrated with artichoke extract (leaves).

At the end of the experimental periods (7 and 15 post irradiation), rats were fasted over night before sacrificing, blood was collected, centrifuged and stored at -20℃ until analysis.

Analytical methods:

Malondialdehyde (MDA) level **(Yoshioka et al., 1979)**. Reduced glutathione content (GSH) **(Beulter et al., 1962),** superoxide activity (SOD) **(Minami and Yoshikawa, 1979)**, total cholesterol (TC) **(Allain et al., 1974),** triacylglycerol (TG) **(Bucolo and David, 1973),** high density lipoprotein (HDL) **(Lopes Virella et al., 1977)** and

low density lipoprotein (LDL) **(Levy, 1981)** contents were determined using suitable kits reagents.

Statistical analysis:

Data are sxpressed as Mean SE. Data were assessed by paired t-test **(Steel and Torrie, 1960** and **Avram, 1964).**

Results:

In the present study, the data revealed significant increase in lipid peroxide content, total cholesterol, triacylglycerol, low density lipoprotein, meanwhile, significant decrease in reduced glutathione content and superoxide dismutase due to irradiation effect.

The present data revealed significant depletion in both glutathione content and superoxide dismutase activity due to radiation exposure. These changes create a series of oxidative stress in the biological system leading to propagation of superoxide radicals, H_2O_2 and formation of hydroxyl radicals in the presence of metal ion catalysis **(Van-Klaverene et al., 1997).**

Discussion:

In the present study, the increased level of thiobarbituric acid reactive substance (TBARS) is an indication of increased lipid peroxidation (MDA). These results are in agreement with the results obtained by **Reiter et al. (1995)** who reported that free radicals attack any molecule they encounter, with destruction macromolecules.

Gatcko et al. (1990) reported that radiation exposure of rats caused changes in the antioxidant system, the status of which influenced the intensity of the lipid peroxidation. In addition, **Zheng et al. (1996)** demonstrated that the activities of bio-oxidase were significantly influenced by radiation damage which is the main cause of the increase in lipid peroxidation.

The present results reflected significant increase in the level of total cholesterol and triacylglycerol. These data are in harmony with those reported by **Sedlakova et al. (1998) and Abu-Gahdeer et al. (1996).** They reported that, the increase level of triacylglycerol in serum could be attributed to hormonal imbalance. **Yousri et al. (1991)** reported that the increased level of triacylglycerol in serum may be related to inactivation of lipoprotein lipase enzyme as a result of whole body irradiation.

Rabinowitz and Beideman (1976) and **Deng et al. (1997)**, they recorded that, after radiation exposure, an increase in 3-hydroxy-3-methyl glutaryl CoA (HMG-COA) reductase activity, which is the rate limiting enzyme in cholesterol synthesis, was accompanied by increased cholesterol content. **Fielding (1982)** attributed the hyper-cholesterolemia to the decrease in lecithine cholesterol acetyl transferase, leading to decrease in cholesterol esterification of rat serum.

Hypercholesterolemic effect could be attributed to destruction of cell membrane and enhanced released to cholesterol into the serum **(Dervson et al., 1981)** and/or disturbance in (HDL-H) receptors **(Kolomijteseva, 1986).**

Atherosclerosis is a complex multicellular process involving oxidation of cholesterol and the intracellular accumulation of oxidized cholesterol. This accumulation causes a cascade of inflammatory processes, resulting in an unstable atherosclerotic plaque that ultimately bursts, causing myocardial infraction. Botanical dietary supplements (herbs) can ameliorate this process and prevent cardiovascular disease at many steps on the process. Many herbs have antioxidant activity and can reduce low density lipoprotein oxidation. Some phytosterols found in botanicals can inhibit cholesterol absorption.

The results of this study shows that aqueous organic extract of artichoke (heads or leaves) can significantly reduce cholesterol, LDL-C and triacylglycerol concentration of hypercholesterolemic rats. The results are in agreement with **Pittler et al. (2002)** (leaves extract lowers cholesterol levels) and **Lupattelli et al. (2004)** (cholesterol and HDL-C) and **Englisch et al. (2000)** (Lowering cholesterol and LDL-C levels) using artichoke dry extract.

There are several possible mechanisms that's through it artichoke extract can cause a significant effect on hypercholesterolemia. Artichoke extracts have been shown to produce various pharmacological effects, such as the inhibition of cholesterol biosynthesis and of LDL oxidation. Artichoke dietary supplementation seems to positively modulate hypercholesterolemia. These therapeutic properties may be attributed to mono- and di-caffeoylquinic acids and cynarin (one of the caffeoylquinic acid family) content of artichoke **(Speroni et al., 2003** and **Wittemer, 2005)**.

Artichoke contain at least 22 major compounds, 11 caffeoylquinic acid and 8 flavonoids as apigenin 7-O-glucuronide which is considered as the major flavonoid, 1,5-di-O- caffeoylquinic acid, narirutin and cynarin **(Schutz et al., 2006).**

The oxygen functional groups at the 3- and 8-positions and exo-methylylene moiety in alpha-methylene-gamma-butyrolactone ring were found to be essential for the anti-hyperlipidemic activity of guaiane-type sesquiterpene. In addition, inhibition of gastric emptying was shown to be partly involved in anti-hyperlipidemic activity **(Shimoda et al., 2003).**

Aqueous organic artichoke leaf extract (ALF) increased the activity of the human endothelial nitric-oxide synthase (eNOS) promoter which produced nitric oxide that is considered as anti-oxide that is considered as anti-atherosclerotic principle in the vasculature thus could provide protection against cardiovascular diseases. Aqueous organic artichoke leaf extract increase the activity of eNOS mRNA expression and eNOS protein expression. The flavonoids Aqueous luteolin and cynaroside increased eNOS promoter activity and eNOS mRNA expression. The increase in eNOS gene transcription may also contribute to ALE beneficial cardiovascular profile. Artichoke flavonoids are likely to represent the active ingredients mediating eNOS up-regulation **(Li et al., 2004).** ALE also inhibited LDL oxidation **(Brown and Rice-Evans, 1998)** and reduced the production of intracellular reactive oxygen species by oxidized LDL in cultured endothelial cells and monocytes **(Zapolska-Downar *et al.*, 2002).**

Artichoke leaves extract (ALE) inhibits the incorporation of ^{14}C-labelled acetate into the non-saponifiable lipid fraction and thus reduces cholesterol biosynthesis at the level hydroxymethylglutaryl-CoA-reductase (HMG-CoA-reductase) through indirect modulation of HMG-CoA-reductase activity **(Gebhardt, 1995 and Gebhardt, 1998).** Furthermore, insulin stimulation of acetate incorporation was efficiently reduced by artichoke extracts. The reduction of HMGCoA-reductase activity by the artichoke extracts might be responsible for the selective effect on acetate incorporation. Other studies suggested indirect inhibitory effects exerted at the level of HMG-CoA-reductase, a key enzyme in cholesterol biosynthesis **(Fintlemann, 1996 a; Gebhardt, 1996 a; and Gebhardt, 1997).**

All of this might be due to some regulatory mechanism of HMGCoA-reductase, which is

influenced. This influence could possibly involve: 1) inhibition of activating mechanisms and/or 2) stimulation of inactivating mechanisms of the enzyme. Artichoke extracts effectively blocked insulin-dependent stimulation of HMGCoA-reductase without affecting insulin effects in general. Quantitative measurements show that artichoke extract inhibits cholesterol biosynthesis in a concentration dependent manner **(Artner-Dworzak, 2000, Gebhardt, 1996 b).** More recent findings indicate a role for the flavonoid luteolin in inhibiting effects of cholesterol synthesis **(Gebhardt, 1997).** Because artichoke extracts may also enhance biliary cholesterol excretion as a result of the choleretic influence **(Kirchhoff *et al.*, 1994** and **Saenz, 2002),** both mechanisms (physiologically through indirect mechanism and enhance biliary cholesterol excretion) may contribute to the clinically known reduction of blood cholesterol levels **(Gebhardt, 1996 b; and Gebhardt, 1998).** Our results are in agreement with **Bundy *et al.*, (2008).**

The present results allow us to emphasize that much remains to be studied in depth and much additional information is required and much present knowledge may have to be corrected about the potential and beneficial use of such flavonoids as radioprotectors against radiation damage. Hopefully, more clinical research on flavonoids will be forthcoming, as this in an area which is lacking. However, there is enough epidemiological, clinical and laboratory research on flavonoids and on antioxidant in general to make some conclusions about the clinical use of flavonoids and to warrant their use to the prevention and/or treatment of cardiovascular disease, cancer, inflammatory conditions, liver disease and muscular degeneration.

Table (1): Lipid peroxides as malondialdehyde (MDA) level, glutathione (GSH) and superoxide dismutase (SOD) in rats after whole body gamma irradiation and/or artichoke administration.

Groups	Time intervals	MDA (mol/l)	GSH (mg/dl)	SOD (g/ml)
Control G.	7	75.0±6.0 (100%)	45.0±3.2 (100%)	60.9±4.6 (100%)
	15	73.0±6.2 (100%)	47.4±3.0 (100%)	62.0±5.2 (100%)
Artichoke (head) G.	7	74.0±5.7 (98.6%)	46.3±4.2 (102.8%)	58.0±4.9 (95.2%)
	15	72.4±6.0 (99.1%)	48.2±3.5 (101.6%)	61.0±5.0 (98.3%)
Artichoke (leave) G.	7	76.0±5.9 (101.0%)	45.6±3.1 (101.3%)	60.0±4.7 (98.5%)
	15	75.0±6.2 (102.7%)	46.9±2.9 (97.0%)	60.9±5.4 (98.2%)
Irradiated G.	7	123.0±10.2*** (164.0%)	29.6±2.5*** (65.7%)	32.0±2.4*** (52.5%)
	15	137.0±11.6*** (187.6%)	26.4±2.0*** (55.6%)	30.4±2.6*** (49.0%)
Artichoke(head) + Irr. G.	7	90.0±7.4* (120.0%)	38.0±2.6 (84.4%)	52.8±3.8 (86.6%)
	15	84.6±6.9 (115.8%)	40.2±3.0 (84.8%)	55.6±4.3 (89.6%)
Artichoke(leave) + Irr. G.	7	94.0±8.2* (125.3%)	36.0±2.9* (80.0%)	50.1±3.9 (82.2%)
	15	91.0±7.8* (124.6%)	39.4±3.6 (83.1%)	52.0±4.0 (83.8%)

Each value represents the mean of 6 rats ± *SE.*

Significant different from the corresponding control at *P<0.01**, *P<0.01*** and *P<0.01****.

Table (2): Serum lipid profile in rats after whole body gamma irradiation and/or artichoke administration.

Groups	Time intervals	TC (mg/ml)	TG (mg/ml)	HDL (mg/ml)	LDL (mg/ml)
Control G.	7	90.5±7.3 (100%)	82.0±6.8 (100%)	30.6±2.2 (100%)	43.5±4.0 (100%)
	15	92.0±7.6 (100%)	86.0±7.2 (100%)	33.0±2.6 (100%)	41.8±3.4 (100%)
Artichoke (head) G.	7	88.0±6.6 (97.2%)	80.0±6.8 (97.5%)	31.0±2.4 (101.3%)	39.0±3.6 (89.6%)
	15	90.1±8.3 (97.9%)	84.3±7.0 (98.0%)	34.2±2.7 (103.6%)	39.0±3.5 (93.3%)
Artichoke (leave) G.	7	89.4±7.0 (98.7%)	81.2±6.5 (99.0%)	30.8±2.5 (105.8%)	42.4±4.0 (97.4%)
	15	91.2±7.8 (99.0%)	85.0±8.2 (98.8%)	32.4±3.0 (98.0%)	41.8±3.7 (100.0%)
Irradiated G.	7	*** 144.7±13.2 (159.8%)	*** 165.4±12.7 (201.7%)	** 21.4±1.9 (69.9%)	*** 90.2±9.8 (207.4%)
	15	*** 152.3±15.4 (165.5%)	*** 196.0±15.6 (227.9%)	** 24.6±2.1 (74.5%)	*** 88.5±10.4 (211.7%)
Artichoke (head) + Irr. G.	7	** 118.4±10.2 (130.8%)	** 122.0±9.4 (148.7%)	27.7±2.4 (90.5%)	*** 65.9±6.5 (151.4%)
	15	100.0±8.9 (108.6%)	104.0±8.0 (120.9%)	28.0±2.2 (84.8%)	* 51.2±4.7 (122.4%)
Artichoke (leave) + Irr. G.	7	** 120.0±11.3 (132.5%)	** 110.0±10.6 (134.0%)	26.4±1.9 (86.2%)	*** 61.6±7.2 (141.6%)
	15	110.0±10.9 (119.5%)	** 112.0±9.9 (130.2%)	* 25.7±2.3 (77.8%)	* 51.9±6.6 (124.0%)

Legands as in table (1).

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تأثير مستخلص الخرشوف على زيادة مستوى الليبيدات الذى يحدثها التعرض لأشعة جاما في ذكور الفئران

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الخلاصة:

تهدف هذة الدراسة لتقييم نشاطات مضادات الأكسدة و الدور الوقائى للإشعاع لنبات الخرشوف ضد زيادة نسبة الدهون التى تحدثها أشعة جاما.

تم إعطاء الفئران مستخلص نبات الخرشوف (الرأس أو الورق) عن طريق الفم بإستخدام أنبوبة المعدة المناسبة بجرعة (10%/ميلجرام/جرذ/يوم) لمدة ستة أسابيع قبل تعريض الفئران لجرعة واحدة (6،5 جراى) لأشعة جاما.

تم قياس محتوى الدهون المؤكسدة، مستوى الجلوتاثيون المختزل، سوبرأكسيد ديسميوتيز، الدهون الكلية، الدهون الثلاثية، الدهون عالية الكثافة و الدهون منخفضة الكثافة فى الدم.

النتائج:

أوضحت النتائج إن التعرض لأشعة جاما أدت إلى إرتفاع ملحوظ فى محتوى الدهون المؤكسدة، الدهون الكلية، الدهون الثلاثية و الدهون منخفضة الكثافة و كذلك إنخفاض ملحوظ فى مستوى الجلوتاثيون المختزل وسوبرأكسيد ديسميوتيز، لكن فى المجاميع التى أعطت لها نبات الخرشوف قبل التعرض لأشعة جاما، الخرشوف يحدث تحسن ملحوظ ضد التغيرات التى يحدثها الإشعاع فى معظم المعايير البيوكيميائية التى تمت دراستها.