Protective role of Pomegranate (punica granatam L.) juice in inhibition liver toxicity induced by amikacin in white Newzealad Rabbits

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Abstract

In present study, aminoglycosides as amikacin, was proved to induce alterations in the liver of experimental animals. The aim present study is to investigate the effect of amikacin on rabbit liver which is commonly used in infections resistant to other antibiotics and study treated and protective effect of Pomegranate juice(*Punica granatum* L.), which antibiotic inhibit & decrease liver toxic formed by amikacin in males and females white rabbits by measuring some of the criteria for biochemical variations, such as, blood serum cholesterol (Ch), triglyceride concentration (TG), blood serum high density lipoprotein-cholesterol (HDL-C),Low density lipoprotein-cholesterol (LDL-C) concentration. In those were given (amikacin80mg/kg) by injection in muscle for period of 15 days, caused a significant increase at the level ($p \leq 0.05$) in cholesterol(Ch), triglyceride(TG) concentration, Low density lipoprotein-cholesterol concentration(LDL-C) as compared with a control group, while decreased concentration of high density lipoprotein-cholesterol(HDL-C) significantly as compared with the control group. The rabbits treated with Pomegranate juice 100ml the concentration of 40% for a period of 15 days has recorded a significant decrease in the concentrations of cholesterol, triglyceride concentration and low density lipoprotein-cholesterol concentration as compared with a group Rabbits treated with amikacin only, and increased significantly in high density lipoprotein-cholesterol compared to the group treated with amikacin only.

Introduction:

Many human diseases have been recognized as being a consequence of free radicals damage(1). Interest in the role of antioxidants in human health has prompted research in the fields of food science to assess fruit and vegetable antioxidants (2,3). The majority of the antioxidant capacity of fruits or vegetables may be from compounds such as flavonoids, isoflavones, flavones, anthocyanins, catechins and isocatechins rather than from vitamins C, E or β-carotene (1,4,5).

These phytochemicals may help to protect cells against the oxidative damage caused by free radicals (6,7). The antioxidant activity of phenolics is mainly due to their redox properties, which allow them to act as reducing agents, hydrogen donors, singlet oxygen quenchers and metal chelators (4). Their antioxidant activity is generally based on the number and location of hydroxyl groups present as well as the presence of a 2-3 double bond and 4 oxofunction. The flavonoids, a large family of low molecular weight polyphenolic compounds, include the flavones, flavonols, flavonones, isoflavones, flavan-3-ols and anthocyanins (1,6). All of these aspects explain the increasing interest in fruit phenolics that has been manifested in the past few years. may initiate injury indirectly by inducing oxidative stress. Oxidative stress is caused by excessive production of reactive oxygen species and it may produce a major alteration of protein and nucleic acid structure, damage to DNA, induction of apoptosis, increase in intracellular free calcium, damage to membrane ion transport or destruction of the cells by lipid peroxidation.An imbalance between free radicals and defense mechanism leads to cell damage and several diseases. For this reason, the role of nutrition in human has captured the interest of researchers in antioxidants and their capacity to protect the body from damage induced by oxidative stress(4).

Many plants such as Pomegranate *(Punicagranatum*), *Citrus limon*possess antioxidant properties. Pomegranate, **Al-Ruemman**, that fruit mentioned in the holy **Quran** in more than two positions, and also descibed by other major religions and by folk medicine, has long been attracted a lot of attention for its medical importance (2,13,15,17,22). Pomegranate juice was indeed shown recently to possess impressive antioxidative properties due to its polyphenolics, tannins and anthocyanins. Also, in healthy humans, Pomegranate juice consumption was shown to possess potent antioxidative capabilities against lipoprotein oxidation, and increased serum *total* antioxidant status (14,16).

It was also shown to have significantly higher levels of antioxidants in comparison to commonly consumed fruit juices, such as grape fruit or orange juice(1,3,5). The principal antioxidant polyphenols in pomegranate juice include the ellagitannins and anthocyanins. Ellagitannins account for 92% of the antioxidant activity of pomegranate juice and are concentrated in the peel, membranes, and piths of the fruit. Punicalagins are the major ellagitannins in the whole fruit and can be hydrolyzed to ellagic acid (EA) and other smaller polyphenols in vivo. Commercial pomegranate juice obtained by pressing the whole pomegranate fruit and its peels contains significant amounts of the water-soluble punicalagins, and these levels are variable depending on the fruit cultivar, processing, and storage conditions (20, 21, 23).

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ(28,29). Other chemical agents, such as those used in laboratories and industries, natural chemicals

(e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins(27).

More than 900 drugs have been implicated in causing liver injury(32)and it is the most common reason for a drug to be withdrawn from the market. Hepatotoxicity and drug-induced liver injury also account for a substantial number of compound failures, highlighting the need for drug screening assays, such as stem cell-derived hepatocyte-like cells, that are capable of detecting toxicity early in the drug development process(31). Chemicals often cause subclinical injury to the liver, which manifests only as abnormal liver enzyme tests(34). Drug-induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures.

Drug metabolism is usually divided into two phases: phase 1 and phase *2*. Phase 1 reaction is thought to prepare a drug for phase 2. However many compounds can be metabolized by phase 2 directly. Phase 1 reaction involves oxidation, reduction, hydrolysis, hydration and many other chemical reactions(30,31). These processes tend to increase water solubility of the drug and can generate metabolites that are more chemically active and potentially toxic. Most of phase 2 reactions take place in cytosol and involve conjugation with endogenous compounds via transferase enzymes(33). Chemically active phase 1 products are rendered relatively inert and suitable for elimination by this step(7).

Aminoglycosides are potent bactericidal antibiotics; they act particularly against aerobic, gram-negative bacteria (27,28). Amikacin is one of the aminoglycoside , mostly used for treatment of severe, hospital-acquired infections with multidrug resistant Gram negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter,* and *Enterobacter*(7,8). Aminoglycoside induced nephro and oto-toxicity,which are the limiting factors for their clinical use ,in which the oxygen free radicals have been involved. aminoglycosides, exert their adverse renal effect by generation of reactive oxygen species. Additionally, it has been demonstrated that aminoglycoside form a complex with mitochondrial Fe^{+2} to catalyze the formation of free radicals(12).

Materials & Methods:

1.StudyAnimals:

In present study males and femaleswhite Newzealand rabbit. Their ages ranged between 8-10 months , their weight ranged between 900_1750 gm, which bought from local market. These rabbit kept in closed wooden boxes covered thin metal of AluminumIts distances 40*90*60cm.Floored by wood straws with complete cleaning and used antiseptic every two days. Light exposure12 hours Dark exposure 12 hours , temperature was exposure 25 ± 2c The animals kept for two weeks to adapt them to new medium and with no disease contacts. Feeding of the rabbits depend on mixture of(35% wheat,34% corn,20% Soya bean10% animal protein,1% dried milk). Added to it 50 conservative and antifungal, with regulate feeding and water continuously along the period from December 2012 to April 2013 .

The Chemicals: the chemicals study with their sources used in this study with there sources were as follow :

No.	Chemical material	Sources
1	HDL(KIT)	Biomerieux,france
2	Cholesterol(KIT)	Biolabo, france.

Instruments : The following table shows the main instrument used in this study and their sources, are :

No.	Instruments	Sources
1	Spectrophotometer	Cecil. England.7200 .
2	Spectrophotometer	Cecil. England. 1011.
3	Micro – pipette 20 -200 µl	Slamed , Germany.
4	Micro – pipette 100 -1000 µl	Slamed , Germany
5	Micro – pipette 50 µl	Slamed , Germany
6	Water bath	Memmert , Germeny
7	Centrifuge	Universal , Germany.
8	Light Microscope	Olympus , Japan.
9	Microscope slide	Sail Brand , China
10	Microscope Cover slip	Ataco , China
11	Plain tube	Afma – Dispo, Jordan.
12	Incubator	Fisher screntific , USA .

2-Preparation of Plant Extract:

Pomegranate (punica granatum L.). which belong to punicaceae family, its juice (250 ml) was obtained from cold pressed fruits (about 2kg fresh fruit weight) collected from local market during September, 2012 which was then concentrated by simple distillation.

The methodologies of **Harbone(1983)** and **Wagner *et al*., (1984)** (9, 13) were adopted to prepare the ethanolic extract of concentrated juice (1:1; v/v). The mixture was shaken for 12h on a shaker with reciprocal mechanism. After methanol evaporation and concentration of the remaining aqueous solution by freeze drying, the residue was weighed and further dried in desiccates.

3-Experimental Design: Twelve rabbits were used in present study, which are divided into three groups (each four rabbits) as following:

Group1- four rabbits male &femal were treated with I.P injection of normal saline for 14 days .This group served as control.

Group 2– four rabbits were treated with I.P injection of 80mg/Kg/day of amikacin by injection in muscle for 14 days .This group served as positive control for liver toxicityinduced by amikacin.

Group 3- four rabbits treated with oral dose of 100ml of 40% at several time daily from pomegranate juice concomitantly with amikacin (80mg/kg/ day) by injection in muscle for 14 days. This group utilized to investigate the possible protective effect of pomegranate juice against toxicity induced by amikacin. All animals were anesthetized by ether and dissected after 2 weeks of treatment.

Results :

The histology of the liver in control group show that the parenchyma of the liver was containing the polygonal liver cells arranged in the form of columns arranged in radial pattern extended form the periphery of the lobules to the central vein in the center of each lobule(fig1-a), between these cells there were blood sinusoid containing RBC .the portal area contained a branchem of hepatic artery ,portal vein and bile ducts ,these were surrounded by connective tissue and there was an infiltration of lymphocytes around it (fig -1-b).

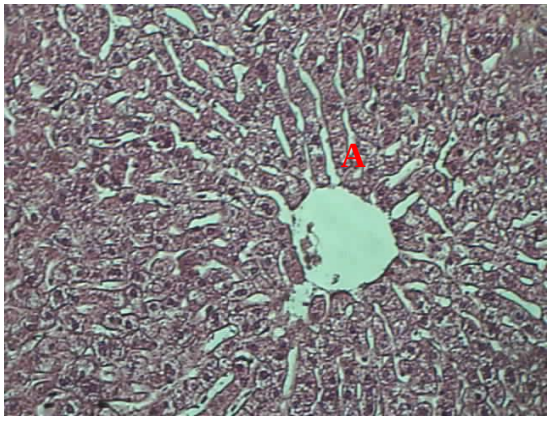

Fig 1-a Section in rabbit liver of control group show polygonl liver cells arranged radially around the central vein .(H2Ex20)

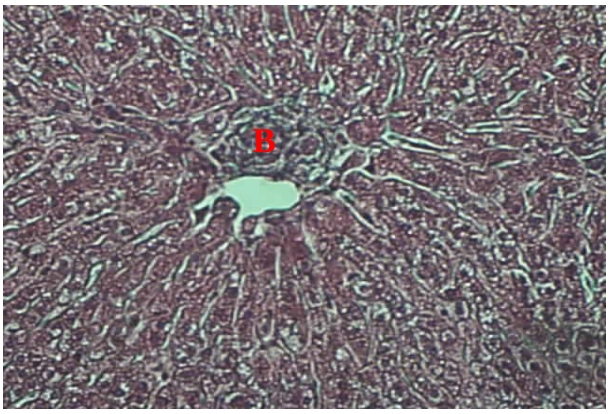

Fig- 1-b showing the portal area infilterated by lymphocytes(A).portal vein(B). (Heamatoxylin & eosin) (H2Ex20)

Effect of amikacin on the histology of the liver:

The parenchyma of the liver consist of normal size & shape of liver cell. However, in treated ones there were an hypertrophied cell and some of them were lost their nuclei, the blood were containing many lymphocyte cells (Fig-2). The portal veins were engorged with blood which present in the portal vein .

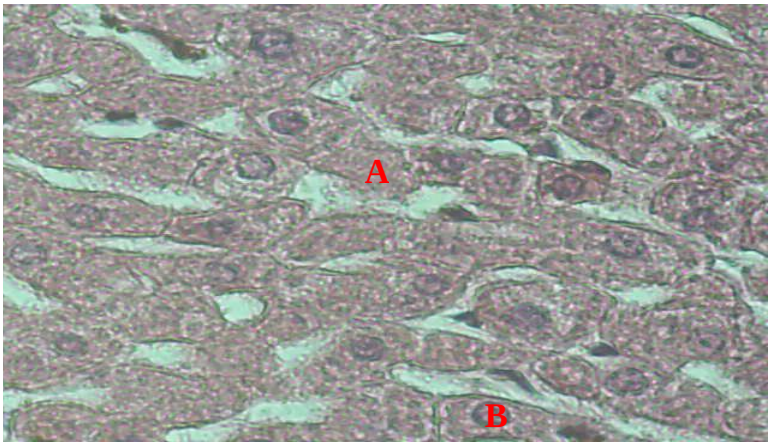

Fig -2- Section of the liver for the amikacin group showing normal size and appeovana of line cell(A)sinusoid(B).(H&Ex20)

The parenchyma of the liver was containing dilated blood sinusoid & some of them appeared, swollen ,spherical shape (Fig-3-a) and these sinusoids were containing bluffer cells abundantly (Fig-3-b).There was an aggregation of lymphocytes around central veins (Fig-3-c).However there was certain liver cells which appeared degeneration and others were normal in structure and shape.

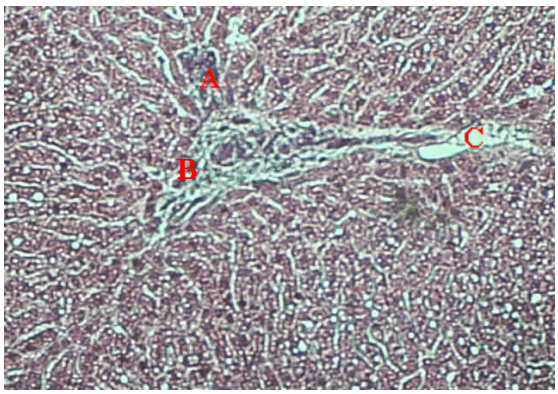

Fig-3-a- portal area (A)lymphocyte aggregation (B),portal vein (c)

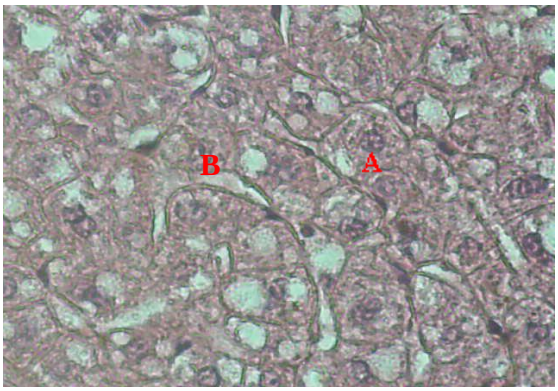

Fig -3-b-hypertrophy of liver cells (A) swallon sinusoid (B))(H2Ex10)

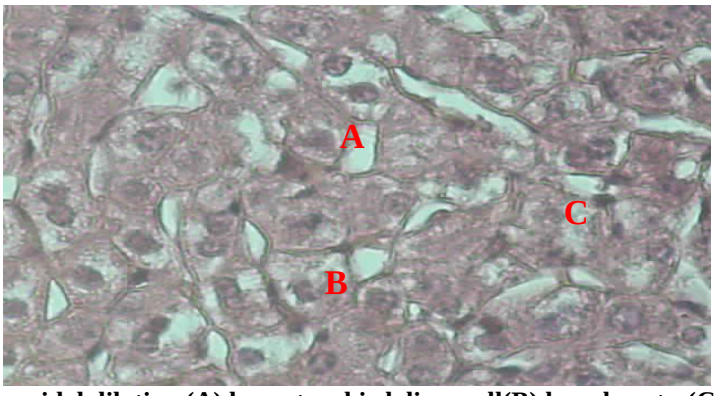

Fig -3-c-sinusoidal dilation (A),hypertrophied liver cell(B),lymphocytes(C) (H2Ex40)

Table: show the effect of amikacin & amikacin with P.J. on lipid profile of rabbits as follows:

GroupNo	Parameter	Ch mg/dL	TG mg/dL	LDL-c mg/dL	HDL-c mg/dL
Group 1 **X**±SD	**Control**	d 51.80±3-10	d 57.04±11.1	a 22.64±5.18	a 16.72±1.70
Group 2 **X**±SD	Amikacin	c 80.40±20.2	c 79.80±10.9	c 52.06±20.48	c 11.0±2.64*
Group 3 **X**±SD	Amikacin With pomegranate juice	d 70.40±1. 75	d 61.80±11.0	b 43.66±4.96	b 15.5±1.87*

-X= mean ,SD=standard deviation*=insignificant at ($p \leq 0.05$)
- 4 rabbits used for all *group*

Discussion:

Aminoglycoside antibiotics have long been used as antibacterial therapy. Despite their beneficial effects, aminoglycosides have considerable to and nephro-toxic and have a liver toxic side effects also (7). It has been reported that amikacin may induce free radical production which implicates a variety of pathological processes. (8,9) In the present study the marked deacrase of the levels of both blood serum high density lipoprotein-cholesterol concentration (HDL-C) and blood serum low density lipoprotein-cholesterol concentration (LDL-C)in group 2 compared with group 1 were observed. Since as reported in this study confirm an indication of functional damage of the liver and these results were in consistent with other studies.

Also it was found that aminoglycosides cause ATP depletion from either mitochondrial damage or direct inhibition of mitochondrial oxidative phosphorylation causing an oxidative injury.(10) Also liver cells undergo necrosis when their cellular ATP stores are severely depleted to a level incompatible with

maintenance of basal metabolism and activity of membrane transport pumps.(11)Results of this study also showed an improvement in the bloodserum cholesterol concentration, triglyceride, blood serum low density lipoprotein-cholesterol, levels of rabbit treated with combination of pomegranate juice with amikacin (group 3) as compared with group 2, and these levels are near the levels in group1; these results are in agreement with the results of other study which showed that combination of cimetidine (an inhibitor of cytochrome P450) with gentamicin showed decrease in serum levels of which(12,13). The antioxidant effects of Pomegranate juice was attributed to its constituents like antioxidant trace elements and flavonoids compounds; therefore; Pomegranate juice has been suggested to have an ability to decrease lipid peroxidation (14). Also the antioxidant activity of Pomegranate juice is due to phenolic compounds and enzymes (glucose oxidase, catalase and peroxidase) (30,16). Also its content of L-ascorbic acid has a significant impact on total antioxidant activity of Pomegranate juice (17). Results of this study are in agreement with results of(18), which found that natural Pomegranate juice has protective effect against the damage in liver and kidney cells from oxidative stress induced by toxic level of lead in rats (30,32.33). And other study which found that co- administration of vitamins C and E significantly prevented the aminoglycosides-induced liver toxicity demonstrated by preservation of GFR and GSH levels and prevention of the elevation of liver enzyme activities (31,34).

Pomegranate juice was used in present study as the antioxidant of choice, as it is very rich in polyphenol and demonstrates high capability to scavenge free radicals and to inhibit LDL oxidation in vitro and in vivo(20,21,22,23), have been shown to increase serum antioxidant capacity or decrease oxidative damage of biomolecules (24,25). Pomegranate juice has shown significant antiatherosclerotic, anti-hypertensive, antioxidant, and anti-inflammatory effects in human subjects and rabbits models, Pomegranate juice has also been shown to prevent oxidative destruction of nitric oxide and enhance its antioxidant and anti-inflammatory functions(26).

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الدور الوقائي لعصير الرمان في تثبيط سمية الكبد المستحدثة بواسطة عقار ايميكاسين في الأرانب

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الملخص

صممت الدراسة الحالية للكشف عن تأثير عقار ايميكاسين على كبد الأرانب النيوزلنديه وكذلك ملاحظة التأثير العلاجي والوقائي لعصير الرمان من خلال تقليل أو تثبيط سمية الكبد الناتجة عن استعمال عقار الايميكاسين في ذكور وإناث الأرانب البيضاء . تم استخدام اثنا عشرة أرنبا (12) لهذه التجربة وقسمت إلى ثلاثة مجاميع وهي مجموعة السيطرة والمجموعة الثانية تم حقنها ب80 ملغم / كغم من الايميكاسين في العضلة لمدة 15 يوم وتأثير ذلك على بعض الصفات الكيميوحيوية مثل (كولسترول الدم,HDL-C, LDL-C, TG) ومجموعة الثالثة تم أعطائها, عن طريق الفم, 100مل يوميا عصير الرمان وبتركيز 40% للأرانب المعاملة بعقار الايميكاسين وتأثير ذلك على الوظائف الكيميوحيوية كما في المجموعة الثانية. أظهرت النتائج زيادة معنوية في مستوى كولسترول الدم TG, HDL-C, عند مستوى احتمالية ($p\leq0.05$) للمجموعة المعاملة مع 80 ملغم / كغم من ايميكاسين لمدة 15 يوم مقارنة مع مجموعة السيطرة بينما سبب انخفاضا معنويا في تركيز HDL-C عند مستوى احتمالية($p\leq0.05$) مقارنة مع مجموعة السيطرة. وأظهرت الأرانب المعالجة ب 100 مل / يوم من عصير الرمان بتركيز 40% والمعاملة بعقار ايميكاسين انخفاضا معنويا في مستوى كولسترول الدم, LDL-C, TG مقارنة مع مجموعة الأرانب المجرعة بالايميكاسين. بينما سبب زيادة معنوية في تركيز HDL-C مقارنة مع المجموعة المعاملة بالايميكاسين لمدة 15 يوم.