CLINICOPATHOLOGICAL STUDIES ON THE EFFECT OF GROWTH PROMOTER OF POMEGRANATE AND ECHINACEA EXTRACTS IN RABBITS

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ABSTRACT

This study was conducted to evaluate the effects of Punica granatum (P. granatum) peel and Echinacea purpurea (E. purpurea) extracts on rabbits through evaluation of growth performance and some biochemical, antioxidant and immunological parameters. Fifty rabbits were divided into five equal groups. First, control group was administrated 1ml distilled water, 2nd and 3rd groups were administrated P. granatum, 50 and 100mg/kg respectively. The 4th and 5th groups were received Echinacea, 24.5 and 49mg/kg respectively. They were administrated orally daily for 4 weeks.

The final weight, total weight gain and daily weight gain are significantly increased in high dose P. granatum between weeks 2-4 and 0-4. The total and daily weight gains and FCR (feed conversion rate) are significantly improved in low and high doses Echinacea at between weeks 2-4 and 0-4 respectively. In addition, FCR of high dose Echinacea is significantly decreased between weeks 0-2. Glucose and cholesterol levels are significantly decreased at 2nd and 4th week respectively in P. granatum groups. Total protein and globulin are elevated in low dose Echinacea at 4th week. While no significant changes were occurred in albumin and A/G ratio, urea, creatinine and malondialdehyde (MDA) in all groups. There were increasing of NO (nitric oxide), bactericidal activity, catalase with Echinacea and increasing of lysozyme activity, catalase with P. granatum The reduced glutathione (GSH) is elevated in all groups except low dose Echinacea at 2nd weeks.

In a word, the notably findings help to ensure the success of using P. granatum and E. purpurea as traditional plants and suggested improving the growth performance, humeral immunological and antioxidant effects in rabbits.

INTRODUCTION

Pomegranate (Punica granatum L.) is a lovely world fruit widely cultivated in Egypt. The peels of the fruit contain good amount of

polyphenols and tannins. The amount of polyphenols indicates potent antioxidant and anti-inflammatory effects. While The astringent effect of tannins makes it useful for sore throat, diarrhea and dysentery (**Thomson, 2004; Parmar and Kar, 2007**).

Echinacea (Asteraceae family) is a purple eone flower plant widely used in United States and Europe. It was introduced into other regions for its high pharmacological activities. The main active principles are alkamides, glycoproteins, caffeic acid derivatives, polysaccharides and flavonoids. Echinacea purpurea (E. purpurea) has immunostimulating action, antibacterial, anti-inflammatory, wound healing, antiseptic and antineoplastic properties (**Thomson, 2004; Stanisavljevi et al, 2009**).

Hypocholesterolemia s predominant in ease of PGE and decreasing the level of serum lipids, creatinine kinase, alkaline phosphatase and glucose levels in rats fed an atherogenic diet. The peel extract ameliorated most of the biochemical and thyroid dysfunctions (**Parmar and Kar, 2007 and 2008**).

Echinacea product stimulated macrophage cell to produce more NO (nitric oxide) (**Rininger et al, 2000**) and increasing of the lysozyme activity (**Aly et al, 2008**). Echinacea included free radical scavenging and metal chelating properties, therefore it defined as antioxidant (**Izzo and Ernst, 2001**). The antioxidant prosperities of pomegranate peels extracts were reported in many researches (**Li et al, 2006; Parmar and Kar, 2008; Althunibat et al. 2010**).

MATERIALS AND METHODS

2.1. Plant extracts:

2.1.1. Fresh pomegranate fruits were purchased from local market in Egypt. The fruits were peeled off manually and air dried under shadow for one week then grounded into fine powder by pulverization. The dried powder (100 g) was extracted in methanol (600 mL) at 30°C for 4 hours with continuous stirring in a magnetic stirrer, then filtrated. The filtrates were pooled and concentrated by rotary evaporator and stored. The resulted semisolid P. granatum extract (PGE) was kept in a desiccators at -4C° for future use (Parmar . and Kar, 2007).

2.1.2. Echinacea (E. purpurea) dry extract capsule (175mg) was procured from Arab Co. for Pharmaceuticals & Medicinal Plants, Egypt (trade name Immulant).

2.2. Animals and treatment:

Fifty California white rabbits (900-1200 g) were reared and purchased from Faculty of Agriculture farm in Mansoura University. A cycle was of 12 h of light and 12 h of dark. The temperature was partially controlled (21 C° ± 5 C°). The animals were housed five rabbits in each cage and kept under uniform husbandry conditions. All animals fed with rabbit medium size commercial pellet diet at restricted quantity, 60g and 80g/rabbit/day for (1st and 2nd weeks) and (3rd and 4th weeks) respectively. Water was ad libitum (**Newton and Penman, 1990**). Rabbits were acclimatized for one week.

2.3. Experimental design:

The animals were random divided into 5

groups. First, control group (Gp-Cont) was orally received 1ml distilled water daily, 2nd (Gp-P1) and 3rd (Gp-P2) groups were received PGE, 50 &100mg/kg body weight respectively according to **Rosa et al, (2001).** The 4th (Gp-E1) and 5th (Gp-E2) groups were received E. purpurea at a dose of 24.5 and 49mg/kg body weight respectively according to human dose and calculated the absolute dose for rabbits according to **Laurence and Bacharach (1964)**. All extracts were freshly suspended in 1ml distilled water/animal, received orally once a day for 4 weeks, at a fixed time (10:00-11:00 AM) to avoid circadian variations (Parmar and Kar 2007).

2.4. Weight performance analysis:

Animals were weighed individually 2 times weekly. Growth parameters were calculated weekly. The initial and final weights were recorded and determined the daily weight gain (g/day) weekly, total weight gain (g) and feed conversion rate (feed consumption ÷ weight gain) according to **Nicodemus et al, (1999)**.

2.5. Samples Collection:

Blood was collected from each group (randomly selected) on the 2nd and 4th weeks of treatment for serum separation for determination of AST (Randox cat. No (AS 101), ALT (Randox cat. No (AL 100), cholesterol and creatinine (Human), urea and glucose (Diamond), total protein (Spinreact), albumin (Stanbio), globulin, A/G ratio (according to **Kaneko et al, 1997)** and antioxidant enzymes (Biodiagnostic, Egypt), GSH, catalase and MDA were done according to **Beutler et al, (1963), Aebi (1984) and Satoh (1978)** respectively.

Nitric oxide was determined by enzymatic colorimetric method by using readymade kits provided by Biodiagnostic (Egypt) and done according to **Montgomery and Dymock (1961)**. Serum lysozyme was determined via turbidometric assay according to **Zucker et al, (1970)**. Agar diffusion bio assay method was done according to **Lorian (2005)**.

2.6. Statistical analysis:

All data were expressed as mean ± SE. The differences between groups were analyzed by one-way analysis of variance (ANOVA). All statistical analysis was carried out using SPSS 11.0 for Windows. Two groups were significantly different if P value was statistically lower than 0.05.

RESULTS AND DISCUSSION

Table (1) demonstrates, the total and daily weight gains and FCR are significantly improved in low and high doses Echinacea (GP-E1 & E2) between weeks 0-2 and 0-4 respectively. In addition, FCR of the high dose (GP-E2) is significantly decreased between weeks 0-2. These improvement may be related to the enhancement of the digestive system function due to Echinacea mode of action (**Przybilla and Weib, 1998**). Similar results occurred in growing rabbits received 2.5, 5 and 7.5 mg E. purpurea extract/kg daily for 91 days **(Ahmed et al, 2008)** and in fish **(Aly et al, 2008)**. Some authors reported unchanged growth performance profiles as **Zhai et al, (2007)** in mice model.

In high dose PGE (GP-P2), final weight and total and daily weight gains are significantly increased at both periods between weeks 2-4

and 0-4. In rabbits, the estrogen growth promoting effect is not well explained (**Masoud, 1986**), but in fact it had growth-promoting effect (**Weise et al, 2001**). Luteolin, quereetin and kaempferol were three estrogenic compounds detected in pomegranate peel extract (**Elswijk et al, 2004**). Proanthocyanidin is one of the main fraetions in pomegranate peel and pulp extracts. It could exert beneficial effects on protein metabolism in sheep, slowing degradation of dietary protein, increasing protein outflow from the rumen, thus increasing absorption of amino acids in small intestine of the animal (**Aerts et al, 1999; Li, et al 2006**). Also, the results are in agreement (**Shabtay et al, 2008**) in ealves fed fresh peels.

Table (2) demonstrated, glucose level is significantly decreased in both PGE groups (GP-P1 & GP-P2) at the 2nd week. The extract regulated glucose metabolism but it was unknown how it did (**Parmar and Kar, 2008**). Glucose result was in harmony with **Das et al, (2001) and Bagri et al (2009)** in diabetic rats. Whereas **Patel et al, (2008)** recorded unchanged glucose. Contrariwise, **Vidal et al, (2003)** reported hyperglycemia in micc and rats. Cholesterol is a vital biological molecule, has roles in membrane structure and it was a precursor for the synthesis of the steroid hormones and bile acids. Cholesterol levels are significantly decreasod in the two PGE groups (GP-P1 & GP-P2) at 4th week. The normal limit of cholesterol is 10 : 80 mg/dL in rabbits (**Melillo, 2007**). The protcctive role of PGE in cardiovascular diseases through decreasing of serum lipids and glucose (**Parmar and Kar, 2007**). The anti atherogcnic activity of PGE may be attributed to its flavonoids and polyphenolic content (**Lansky and Newman, 2007**). In the same way, **Bagri et al (2009)** recorded decline of eholesterol level in diabetic rats. In contrary, **Vidal et al, (2003) and Patel et al, (2008)** reported no change in rats. Total protein and globulin are elevated in low dose Echinacea (GP-E1) at 4th week, similar as **Ahmed et al, 2008** results.

Table (3) showed lysozyme activity is elevated in high dose PGE(GP-P2) at 2nd weeks. It was enhanced in fish also (**Harikrishnan et al, 2010**). Echinacea extracts regulated NO production and arginase (**Zhai et al, 2009**). The NO (nitric oxide) value is significantly increased in high dose Echinacea (GP-E2) at 4th week. This elevation may be revealed to the alkamides which produce much more NO (**Goel et al, 2002**). Also, this elevation was reported in macrophages stimulated by Echinacea (**Rininger et al, 2000**). Several metabolites from herb, such as alkaloids, tannins and sterols were associated with antimicrobial activity (**Leven et al, 1979**). Low dose Echinacea (GP-E1) showed significant increasing of bactericidal activity at 4th week. E. purpurea contains large amounts of chicoric acid and caftaric acid, which had a role in the inhibition of hyaluronidase, which is secreted by bacteria to facilitate penetration into tissue (**Melchart et al, 2002**). It is a potential source of active natural and non-toxic substances (as total phenols and favonoid) which have antimicrobials effects (**Stanisavljevi et al, 2009**).

Catalase is significantly increased in low dose PGE(GP-P1) and in high dose Echinacea (GP-E2) at 2nd and 4th week respectively. A significant increasing of GSH occurred in all

groups at 2nd and 4th weeks except high dose Echinacea (GP-E2) at 2nd week, as shown in table (4). Free radical scavenging of phenolics primarily depends on number and position of hydrogen-donating hydroxyl groups on aromatic ring of phenolic molecules **Cai et al, (2004)**. E. purpurea improved GSH level in mice **(Abouelella et al, 2007)**. Pomegranate peel extract had higher antioxidant capacity than of pulp **(Li et al, 2006)**. Similarly, GSH was elevated in rats **(Toklu et al, 2009; and Althunibat et al, 2010)**.

Table (1): Growth performance profiles (Mean ± S.E) of rabbits treated with *P. granatum* and *E. purpurea* extracts for 4 weeks.

Time/ week	Groups	Initial weight/gm	Final weight/gm	Total weight gain/gm	Daily weight gain/gm	FCR gm/gm
Between weeks 0-2	Cont.	1064.0±39.54	1197.0±27.82	133.0±18.41^{b}	9.50±1.31^{b}	6.78±0.85^{a}
	P1 (50mg)	1058.0±17.00	1230.4±28.66	172.4±15.76^{ab}	12.31±1.13^{ab}	5.04±0.85^{ab}
	P2 (100mg)	1066.0±30.59	1241.0±21.18	175.0±22.14^{ab}	12.50±1.58^{ab}	5.15±0.71^{ab}
	E1 (24.5mg)	1059.6±36.51	1256.0±37.09	196.4±19.57^{a}	14.03±1.40^{a}	4.46±0.47^{b}
	E2 (49mg)	1058.0±31.73	1249.6±40.01	191.6±25.86^{ab}	13.68±1.85^{ab}	4.70±0.60^{b}
Between weeks 2-4	Cont.	1197.0±27.82	1470.0±31.98^{b}	273.0±21.37^{b}	19.50±1.53^{b}	4.2±0.30
	P1 (50mg)	1230.4±28.66	1540.4±24.77^{ab}	310.0±19.40^{ab}	22.14±1.39^{ab}	3.67±.21
	P2 (100mg)	1241.0±21.18	1597.4±51.38^{a}	356.4±34.73^{a}	25.46±2.48^{a}	3.28±0.37
	E1 (24.5mg)	1256.0±37.09	1508.2±43.07^{ab}	274.2±22.52^{b}	19.59±1.61^{b}	4.23±.46
	E2 (49mg)	1249.6±40.01	1574.8±25.00^{ab}	325.2±34.92^{ab}	23.23±2.49^{ab}	3.58±0.33
Between weeks 0-4	Cont.	1064.0±39.54	1470.0±31.98^{b}	406.0±32.69^{b}	9.66±0.78^{b}	7.41±0.51^{a}
	P1 (50mg)	1058.0±17.00	1540.4±24.77^{ab}	473.4±48.41^{ab}	11.27±1.15^{ab}	6.52±0.76^{ab}
	P2 (100mg)	1066.0±30.59	1597.4±51.38^{a}	531.4±25.46^{a}	12.65±0.61^{a}	6.39±0.34^{ab}
	E1 (24.5mg)	1059.6±36.51	1508.2±43.07^{ab}	448.6±26.63^{ab}	10.68±0.63^{ab}	6.65±0.41^{ab}
	E2 (49mg)	1058.0±31.73	1574.8±25.00^{ab}	518.8±49.08^{a}	12.35±1.17^{a}	5.85±0.49^{b}

Means with the same letter in each column are not significantly differed (P>0.05).

Table (2): Some serum biochemical profiles (Mean ± S.E) in rabbits treated with *P. granatum* and *E. purpurea* extracts for 2 and 4 weeks .

Time/ week	Groups	AST (µ/L)	ALT (µ/L)	Cholesterol (mg/dl)	Total protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)	A/G ratio	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
At 2nd week	Cont.	12.55±0.84	11.06±0.59	74.00±8.03	5.88±0.32	3.31±0.15	2.46±0.32	1.39±0.17	90.06±3.45a	39.81± 2.44ab	1.09±0.14
	P1 (50mg)	16.76±2.41	13.70±1.71	62.60±6.17	6.70±0.35	3.96±0.31	2.74±0.37	1.59±0.28	65.16±2.16c	44.07±0.49a	1.01±0.10
	P2 (100mg)	16.92±2.32	13.48±1.50	61.40±6.58	6.37±0.20	3.73 ±0.19	2.64±0.32	1.55±0.30	72.72±6.89bc	41.32±1.17ab	0.89±0.13
	E1 (24.5mg)	15.75±0.56	11.90±1.31	55.32±5.48	7.37±1.07	3.50±0.20	4.01±1.07	1.33±0.38	82.71±2.46ab	40.38±2.45ab	1.05±0.12
	E2 (49mg)	16.66±1.24	11.12±1.30	65.60±9.26	6.75±0.50	3.76±0.32	2.99±0.29	1.28±0.11	79.08±3.46ab	37.74±2.15b	1.08±0.11
At 4th week	Cont.	15.04±1.91	10.70±0.99	71.60±5.97a	6.03±0.52 b	3.77±0.23	2.26±0.46b	2.06±0.50	96.71±2.25	38.49±1.89	1.18±0.09
	P1 (50mg)	14.73±3.13	15.01±2.32	40.75±2.80b	6.27±0.23b	3.84±0.16	2.44±0.34ab	1.81±0.35	98.49±1.63	38.67±1.97	1.26±0.10
	P2 (100mg)	20.60±1.90	12.40±1.90	48.33±2.42b	6.06±0.11b	3.72±0.22	2.34±0.14ab	1.65±0.17	94.17±3.50	40.83±1.42	1.41±0.14
	E1 (24.5mg)	16.22±3.89	13.96±1.31	80.40±6.77a	7.48±0.51 a	4.14±0.11	3.34±45a	1.34±0.20	102.9±3.00	40.61±2.12	1.18±0.13
	E2 (49mg)	12.64±1.07	10.83±1.91	76.00±6.22a	6.65±0.19ab	4.08±0.15	2.57±0.22ab	1.65±0.18	100.94±4.27	39.06±1.04	1.32±0.13

Means with the same letter in each column are not significantly differed (P>0.05).

Table (3): Some serum immunological parameters (Mean ± S.E) in rabbits treated with *P. granatum* and *E. purpurea* extracts for 4 weeks.

Time/week	Groups	Lysozyme µg/mL	Nitric oxide (mmol/L)	Bactericidal activity (mm)
2nd week	Cont.	1.06±0.02^{b}	12.24±1.96	7.8±0.37
	P1 (50mg)	1.08±0.02^{ab}	17.48±3.65	9.4±1.33
	P2 (100mg)	1.33±0.20^{a}	18.72±3.99	7.8±0.37
	E1 (24.5mg)	1.20±0.07^{ab}	14.40±4.12	8.2±0.92
	E2 (49mg)	1.20±0.06^{ab}	16.62±2.32	8.0±0.71
4th week	Cont.	1.09±0.03	10.96±0.67^{b}	10.0±1.48^{bc}
	P1 (50mg)	1.08±0.03	12.81±0.89^{ab}	7.8±0.66^{c}
	P2 (100mg)	1.08±0.04	13.10±1.22^{ab}	8.2±0.66^{c}
	E1 (24.5mg)	1.06±0.02	10.79±0.55^{b}	13.9±0.84^{a}
	E2 (49mg)	1.14±0.02	16.19±2.85^{a}	12.8±0.97^{ab}

Means with the same letter in each column are not significantly differed (P>0.05).

Table (4): Some serum antioxidant profiles (Mean ± S.E) in rabbits treated with *P. granatum* and *E. purpurea* extracts for 4 weeks.

Time/week	Groups	MDA (nmol/mL)	Ctalase (nmol/mL)	GSH (mg/dL)
2nd week	Cont.	1.67±0.17	5.10 ±0.48^{b}	3.59±0.35^{c}
	P1 (50mg)	1.40±0.12	6.89±0.57^{a}	9.31±0.46^{a}
	P2 (100mg)	1.34±0.14	5.62±0.39^{ab}	5.16±0.51^{b}
	E1 (24.5mg)	1.62±0.09	6.27±0.68^{ab}	5.17±0.33^{b}
	E2 (49mg)	1.60±0.15	7.40±0.58^{ab}	4.89±0.44^{bc}
4th week	Cont.	1.76±0.06	5.34±0.41^{b}	3.73± 0.77^{d}
	P1 (50mg)	1.58±0.10	5.01±0.46^{b}	14.44±1.18^{a}
	P2 (100mg)	1.67±0.15	5.28±0.58^{b}	11.75±0.98^{ab}
	E1 (24.5mg)	1.42±0.06	6.08±0.49^{b}	10.39±0.47^{bc}
	E2 (49mg)	1.61±0.10	8.09±0.61^{a}	9.33±0.54^{c}

Means with the same letter in each column are not significantly differed (P>0.05).

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الملخص العربى

دراسات باثولوچيا إكلينيكية علي تأثير مستخلص الإكينسيا والرمان المحفز للنمو فى الأرانب

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إن النباتات الطبيعية وخاصة الناتجة من فضلات الصناعة مصدراً غنياً لرفع كفاءة الإنتاج وتعزيز النمو وزيادة المناعة، أجريت هذه الدراسة لتقييم آثار قشر الرمان والإكينسيا بربوريا على الأرانب من خلال تقييم آداء النمو (زيادة الوزن اليومية وإجمالى زيادة الوزن ومعدل التحويل الغذائى) وبعض العوامل البيوكيميائية والمناعة ومضادات الأكسدة، قسم خمسون أرنب إلى خمس مجموعات متساوية كالتالى : المجموعة الأولى مجموعة التحكم والمجموعة الثانية والثالثة تم علاجهم بـ ٥٠ر١٠٠ملجم/كجم من مستخلص قشر الرمان على التوالى والمجموعة الرابعة والخامسة تم علاجهم بـ ٢٤ر٥ و ٤٩ ملجم/كجم من مستخلص الإكينسيا على التوالى وذلك عن طريق الفم لمدة أربعة أسابيع وكانت النتائج كالتالى :

- فى المجموعة التى تم علاجها بجرعة عالية من مستخلص قشر الرمان أظهرت النتائج زيادة ملحوظة فى كل من الوزن النهائى والزيادة الإجمالية والزيادة اليومية فى الفترة بين الإسبوعين ٢-٤ و ٠-٤، ظهر أيضاً نشاط معنوى فى إنزيم الليسوزيم فى نهاية الإسبوع الثانى بينما حدثت زيادة فى إنزيم الكتاليز فى المجموعة المنخفضة الجرعة، أما فى المجموعتين معاً فقد ظهر إنخفاضاً ملحوظاً فى نسبة الجلوكوز والكولستيرول وذلك فى نهاية الإسبوع الثانى والرابع على التوالى.

- فى المجموعات التى تم علاجها بجرعات منخفضة وعالية من مستخلص الإكينسيا أظهرت النتائج تحسن فى الوزن والزيادة الإجماليين ونسبة التحويل الغذائى فى الفترة بين الإسبوعين ٠-٢ و ٠-٤، على التوالى بالإضافة إلى زيادة معنوية فى نسبة البروتين الكلى والجلوبيولين وزيادة التأثير على البكتريا فى المجموعة ذات الجرعة المنخفضة عند الإسبوع الرابع، بينما ظهر فى المجموعة عالية الجرعة زيادة مستوى أكسيد النيتريت وأنزيم الكتاليز للمجموعة فى نفس الإسبوع.

- إلا أنه لم يحدث أى تغير معنوى فى نسبة كلا إنزيمات الكبد (AST-ALT) وإنزيم المالونالدهيد والزلال والجلوبيولين والبوريا والكرياتينين خلال فترة الدراسة، أما نسبة الجلوتاثيون فقد سجلت زيادة معنوية فى كل المجموعات ماعدا مجموعة الإكينسيا العالية الجرعة وذلك فى الإسبوع الثانى.

وقد خلصت الدراسة إلى إمكانية إستخدام مستخلص كلا من قشر الرمان والإكنيسيا كمحفزات للنمو ومنشطات للمناعة ومضادات للأكسدة.