Clinical Experimental Evidence: Synergistic Effect of Gallic Acid and Tannic acid as Antidiabetic and Antioxidant Agents

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ABSTRACT

Gallic acid and tannic acids are a naturally abundant plant phenolic compound in the human diet and are known to have drug property for some diseases. In this study, the antidiabetic and antioxidant effect of the mentioned acids in an animal model of alloxan induced diabetes were investigated. Diabetes was induced in female local rabbits by injection of alloxan (150 mg/Kg body weight) . gallic and tannic acids and their mixture (1:1) were given as daily injection doses at the levels of 100 mg/kg rabbits for a period of three weeks. The results showed that blood glucose levels and serum malondialdehyde levels, marker of lipid peroxidation, of G group (treated with gallic) were slightly , non significant, decrease as compared with NC group (without treatment). Whereas the decrease in these parameters were significant in T group (treated with tannic) and GT group (treated with their mixture) in comparison with NC group. Serum total antioxidant capacity was significantly increased in T and GT groups in comparison with its value in NC group. While the increase in the same parameter was non significant in G group as compared with NC group. These experimental findings prove the synergistic effect of each acid to other. Consequently their mixture is more effective than each one of them as antidiabetic and antioxidant agents.

INTRODUCTION

Diabetes has became health problem of epidemic proportion in the wide world particularly in developed countries (1). It is well known that diabetes has two major types: the first depend on insulin called type I diabetes, while the second type is independent on insulin called type II diabetes. The latter represents about 90% of diabetic population (2). Furthermore approximately 7% of the world population suffer from this disease (1).. In general there are two disorders that lead to type II diabetes: weakened insulin secretion and insulin resistance (3). Therefore, the increase in insulin secretion as a compensatory mechanism for hyperglycemia, may not be useful to decrease blood glucose level (4). The risky of this disease comes from the complications accompanied it. These complications include the negative effects on: eye, kidney, and nervous system as well as the increase in free radical generation that leads to further complications (5). A recent pharmacological study illustrated that most present drugs used in diabetes treatment, have not activity to suppress the progress of this disease or prevent its complications (6). Therefore the researchers steered to the medicinal plants to manage diabetes. This due to its contents of active compounds that showed greater efficacy in most chronic diseases including diabetes mellitus (7). Tannic and gallic acids are a polyphenolic compounds. The latter are secondary metabolites of plants and are commonly distributed in plant-derived foods, such as cereals, legumes, nuts, vegetables, fruits, and in beverages such as green or black tea, wine, fruit juice, beer and so on(8–13). In general more than 8000 polyphenolic compounds have

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already been identified, and their natural function is correlated to protection of plants from diseases and ultraviolet light and prevention of damage to seeds until they grow (14). Natural polyphenols are grouped according to their structure as phenolic acids derivates, flavonoids, and tannins (14). Several studies have been pointed that polyphenols can be considered as a toxins, as some tannins have toxic effects such as reducing the absorption of proteins, binding to proteins, leading to some metabolic disorders.(15-20). Yet, polyphenols including tannins have been recognized as functionally active molecules, possessing antioxidant, anticancer, antimutagenic properties, hypoglycemic agents, as well as exerting protective effects against cardiovascular and other diseases (21-27). Additionally considerable studies recommended use of polyphenols in the diet because of their known beneficial properties, their metabolism, their interactions with nutrients, and their safety intake (28,29).

From such a serious situation view, in this study, we have examined the effects of a range of doses of tannic acid and gallic acid on blood glucose levels in rabbet with induced hyperglycemia , and investigate of the mentioned acids role in oxidant-antioxidant system.

Experimental Animals

Twenty five adult female rabbits weighing (1200-1800 g) of 18-24 weeks old were used for this study. All animals were maintained under standard laboratory conditions (12h light: 12h night cycle (LD) at 22 ± 2 C^o and relative humidity 45-55% . The animals were fed with normal laboratory diet and allowed to drink water *ad libitum* (30). All the experimental procedures conducted in the animal house of Biology Dept. College of Education, Thi-Qar University.

Induction of Diabetes

Diabetes was induced in overnight fasted rabbits by injection of alloxan monohydrate dissolved in normal saline (0.9% NaCl) at a dose of 150 mg/kg body weight. Whereas the animals of control group received normal saline only(31). Alloxan can induce fatal hypoglycemia as a result of massive pancreatic insulin release and to avoid this hypoglycemic effect, the animals were provided with 5% dextrose solution after 6 h of alloxan treatment for next 24 h. Induction of diabetes was tested after 72 h and the animals were allowed one week for the stabilization of blood glucose level. At seventh day, animals having a blood glucose level higher than 210 mg/dL were considered diabetic and used for the experiments (32).

Administration of Animals

The rabbits were divided into five groups of five each randomly: Group PC: positive control (normal) that were treated with normal saline (0.9%Nacl), group NC: negative control that were treated with alloxan (150mg/kg) B.W. only to induction of diabetes, then daily treated with normal saline (0.9%Nacl) for three weeks, group G: alloxan-induced diabetes rabbits that were daily treated with (100 mg/kg) B.W. of standard gallic acid for three weeks, group T: alloxan-induced diabetes rabbits that were daily treated with (100 mg/kg) B.W. of tannic acid for three weeks, and group GT: alloxan-induced diabetes rabbits that were daily treated with (gallic : tannic 50 : 50 mg/kg) B.W. for three weeks (33). On the ends of each week during the period of treatments , blood samples were collected at 10 a. m. . The serum was separated by centrifugation of blood at 3000 rpm for 10 minutes and the biochemical parameters were analyzed.

METHODS

Determination of Blood Glucose

Enzymatic colorimetric method was used for determination of blood glucose, which depend on Trinder-reaction in which glucose is oxidized by glucose oxidase to gluconic acid and hydrogen peroxide. The latter consequently reacts with phenol in presence of aminophenazone and peroxidase enzyme to form quinone that

has the best absorbance at 515 nm (34), (the kit provided by BIOLAB, France).

Determination of Serum Malondialdehyde (MDA):

Determination of serum malondialdehyde level that consider as a lipid peroxidation marker were performed according to the method of Fong *et a1.*1973(35).In this method MDA reacts with thiobarbituric acid (TBA) (Segma Co. Germany) in shaking water bath for 90 min at 60 C to developed a colored complex MDA $(TBA)_2$ which measured at 532 nm after cooling and centrifugation for 10 min at 600 g.

Determination of Total Serum Antioxidant

Total serum antioxidant activity was determined by the method of Koracevic *et al.* (36). The assay measures the capacity of the samples to inhibit the production of thiobarbituric acid reactive substances (TBARS) from sodium benzoate under the influence of the free oxygen radicals derived from Fenton's reaction. This reaction can be measured spectrophotometrically and the inhibition of the development of colour may be defined as the TAC. A solution of 1 mmol/L uric acid was used as standard

Statistical Analysis:

Statistical analysis was done using the software **SPSS** version 15.0; the results were expressed as mean ± standard deviations (mean ± SD). One way ANOVA-test was used to compare parameters in different studied groups. P-values ($P \leq 0.05$) were considered statistically significant.

RESULTS &DISCUSSION

Table (1) shows a significant increase in blood glucose levels in all studied groups compared to positive control (PC) group after one week of diabetes induction by alloxan injection. Alloxan is considered the perfect and traditional agent for diabetes induction in animals (37). These results are compatible with the results of Ramcumar et. al. (2004) (38). The mentioned table shows slightly , non significant, decrease in blood glucose levels after one, two, and three weeks of treatment with gallic acid whereas the levels of blood glucose were found to be significantly decreased after one and two weeks of treatment with tannic acid, T group, as well as mixture of gallic and tannic acids, GT group, as compared with their values before treatment. It is notable that the levels of blood glucose of GT group at the third week of treatment decreased to reach the normal value obtained from positive control group. Gallic acid (3,4,5-trihydroxybenzoic acid; GA (figure 1)) is a naturally abundant phenolic compound in wide range of vegetables and fruits. Several epidemiological evidence has demonstrated that phenolic compounds, included gallic acid, play a role in the prevention of several chronic diseases such as cancer, chronic vascular disease and diabetes (39,40). The results of the present study, showed in table (1), were compatible with the mentioned evidence. Where the treatment with gallic acid led to decreased levels of blood glucose. However these levels were not reach to the normal values even after three weeks of treatment. Generally the antidiabetic action of gallic acid may be due to the enhancement of insulin receptor sensitivity by this compound (41). Tannic acid (figure 1) is a specific commercial form of tannin which is either hydrolized (gallotannin) or condensed (ellagitannin). It generally consists of a glucose (or similar polyol) core which is esterified to up to five gallic acid groups. Gallic acid occurs as a free molecule or as part of a tannin molecule (42). The mentioned results of table (1) demonstrated that tannic acid may be useful for the treatment of diabetes. Where it could decrease the levels of blood glucose after three weeks of treatment. This effect was ideal when tannic acid was companied with gallic acid, where the levels of blood glucose approach to the normal values. Study of Xueqing Liu *et. al.* 2005 (43) had been showed that tannic

acid may have the potential to become the lead compound in the development of new types of antidiabetic pharmaceuticals that are able to reduce blood glucose levels without increasing adiposity. The study also suggested the mechanism by which tannic acid mediates this activity. The study demonstrated that tannic acid induces glucose transport through activation of the insulin-mediated signaling pathway in adipocytes antidiabetic in human diabetic patients (44). Table (2) shows a significant increase in serum malondialdehyde (MDA) levels in all studied groups compared to positive control (PC) group after diabetes induction by alloxan. After three weeks of gallic, tannic, and their mixture, the table shows, a significant decrease in serum MDA levels in G group as compared with its level before gallic acid treatment. Also the results show a significant decrease in serum MDA levels after three weeks of tannic acid as well as of gallic and tannic acids mixture intake in comparison with their values after one week of alloxan injection. Besides, table (2) shows that, after three weeks of treatment, the levels of serum MDA of GT group decreased to be near the normal value of PC group. Oxidative stress plays a major role in generation of free radicals in the pathogenesis of diabetes and its complications. In the pathogenesis of diabetic complication, peroxidation processes mediated by free radicals has essential role. In fact the autoxidation of glucose and non-enzymatic protein glycation occurs during continual hyperglycemia and this may cause disorder of cellular function and oxidative damage of cell membranes due to increased level of free radicals. The cell components such as lipid, protein, DNA and carbohydrates are affected by free radicals. In general the lipids are affected higher level than protein and carbohydrates (45). Therefore evaluation of lipid peroxidation reflects the oxidative stress in whole body. The famous marker of lipid peroxidation is malondialdehyde (MDA) compound. The latter is an organic compound that spontaneous breakdown end product of lipid peroxidation that can be produced from free radical activities on poly unsaturated fatty acids (46,47). The elevation in serum MDA after induction of diabetes which can be observed in table (2) reflects the increase in free radical generation during diabetes (48). This result is compatible with the result of Cole *et. al.* (2005) (49). Both gallic and tannic acids are considered as a free radical scavengers and consequently as a lipid peroxidation inhibitors. This activity is due to presence of multiple hydroxyl groups in each compound which are able to donate their protons to finally break the chain reaction of free radicals (50). Arshad *et. al*. (2006) (51) showed that the extract of green tea that contain both tannic and gallic acid have potent radical scavenging property. Also the reduction of serum MDA levels was reported by study of Egwaikhide *et. al.* (2008) (52) that proved the inhibitory effect of tannin components in grape seeds extract on lipid peroxidation process. The results of total antioxidant capacity are shown in table (3). This table shows a significant decrease in serum total antioxidant capacity (TAC) in all studied groups compared to positive control (PC) group after one week of diabetes induction by alloxan injection. Also the table shows after three weeks of treatment with gallic, tannic, and their mixture, , non significant increase in serum TAC in G group as compared with its value before gallic acid treatment. Yet the results show a significant increase in value of the mentioned parameter after three weeks of tannic acid as well as of gallic and tannic acids mixture intake in comparison with their values after one week of alloxan injection. Besides, table (3) shows that, after three weeks of treatment, the levels of serum TAC of GT group increased to approach from the normal value of PC group. It is well known that the bodies of humans and animals have effective antioxidant system. The latter consists of several types of complementary compounds called endogenous antioxidants such as ceruloplasmin, superoxide

dismutase, glutathione system, and vitamins E,A, and C. These compounds perform their routine work in scavenging of normally formed reactive species (53-56). However in cases of rapidly free radical generation in most diseases included diabetes, the endogenous antioxidants were decreased leading to disorder in oxidant antioxidant balance. Generally polyphenols are naturally occurring free radical scavengers called exogenous antioxidants (50). These compounds were found to be as effectively as endogenous vitamins E and A when tested *in vitro*(57). The antioxidant property of gallic acid and tannic acids have been reported (57,58) . In the present study, a significant elevation in serum MDA, marker of oxidative stress, levels were reported after diabetes induction (table 2). This elevation associated with decrease in serum total antioxidant capacity (table 3).The latter table also showed that gallic and tannic acids individually treatment for three weeks was able to elevate the value of total antioxidant capacity. Whereas treatment with their mixture was more effective than each one of them. In fact the suitable explanation of these results that gallic acid, low molecular compound, has a favorable redox potential and relative stability of the aryloxy radical that produced by donating the hydrogen of hydroxyl group to another high effective radical (50). Tannic acid in addition to it has this ability of gallic acid, it has also metal ions chelation property. This chelation can alter the redox potential of some metals such as iron and copper, or prevent their participation in redox reaction. Consequently tannic acid, by this property, can be inhibitor of metal driven oxidative reactions such as Fenton and Haber Weiss reactions (59).

CONCLUSION

Both gallic and tannic acids have hypoglycemic, antioxidant activities. Yet tannic acid is more effective than gallic acid in both the mentioned activities. While 1:1 mixture of tannic : gallic have the highest activity from each one of these acids as a hypoglycemic and antioxidant agents. These experimental findings prove the presence of synergistic effect of each acid to other to be perfect antidiabetic and consequently antioxidant agents. Also we can conclude, from this study, that the suitable period for treatment of hyperglycemia by both gallic and tannic acids is at least three weeks.

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Table (1): Effect of gallic acid , tannic acid, and their mixture(1:1) on blood glucose levels in rabbits with alloxan induced hyperglycemia

Blood Glucose Levels (mg/dL)					
Period	After one week diabetes induction (without treatment)		After one week treatment	After two weeks treatment	After three weeks treatment
Groups	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
PC	5	99.36 ±1.23 ^{a}	99.58 ±1.22 ^{a}	99.45 ±1.29 ^{a}	99.60 ±0.95 ^{a}
NC	5	213.78 ±4.89 ^{a*}	213.38 ±4.54 ^{a*}	210.92 ±5.69 ^{a*}	214.22 ±3.66 ^{a*}
G	5	210.06 ±5.15 ^{a*}	206.30 ±4.62 ^{b*}	193.52 ±3.17 ^{b*}	183.18 ±4.03 ^{b*}
T	5	212.18 ±5.74 ^{a*}	182.18 ±5.36 ^{b*}	122.94 ±3.35 ^{c*}	111.92 ±4.42 ^{d}
GT	5	214.64 ±3.74 ^{a*}	169.68 ±6.88 ^{b*}	113.96 ±3.21 ^{c*}	102.06 ±3.88 ^{d}

- a, b, c, d, differences are statistically significant among groups marked with different letters on the same line ($p \leq 0.05$) (horizontal comparison)
- * point to significant different compared to PC group ($p \leq 0.05$) (vertical comparison)

Table (2): Effect of gallic acid , tannic acid, and their mixture(1:1) on serum MDA levels in rabbits with alloxan induced hyperglycemia

Serum MDA Levels (nMol/mL)					
Period	After one week diabetes induction		After one week treatment	After two weeks treatment	After three weeks treatment
Groups	**n**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
PC	5	12.68 ± 0.93 ^{a}	11.86 ±1.96 ^{a}	12.04 ±2.38 ^{a}	11.22 ±1.64 ^{a}
NC	5	99.90 ±8.03 ^{a*}	101.18 ±7.38 ^{a*}	100.52 ±5.07 ^{a*}	99.18 ±2.06 ^{a*}
G	5	95.86 ±6.03 ^{a*}	101.50 ±8.30 ^{a*}	97.82 ±9.14 ^{a*}	81.94 ±9.92 ^{b*}
T	5	97.12 ±4.84 ^{a*}	86.00 ±5.08 ^{b*}	52.82 ±5.53 ^{c*}	21.52 ±5.04 ^{d*}
GT	5	99.50 ±6.74 ^{a*}	84.82 ±7.59 ^{b*}	38.70 ±5.32 ^{c*}	12.90 ±3.86 ^{d}

- Legend as in table (1)

Table (3): Effect of gallic acid , tannic acid, and their mixture(1:1) on serum total antioxidant capacity levels in rabbits with alloxan induced hyperglycemia

Serum TAC Levels (mmol/L)								
Period	After one week diabetes induction		After one week treatment		After two weeks treatment		After three weeks treatment	
Groups	**n**	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**		**Mean ± SD**
PC	5	0.71	± 0.03 **a**	0.71	± 0.02 **a**	0.73	± 0.04 **a**	0.71	± 0.01 **a**
NC	5	0.35	± 0.04 **a***	0.33	± 0.03 **a***	0.32	± 0.05 **a***	0.32	± 0.02 **a***
G	5	0.34	± 0.04 **a***	0.39	± 0.01 **a***	0.42	± 0.04 **b***	0.50	± 0.03 **c***
T	5	0.34	± 0.04 **a***	0.48	± 0.03 **b***	0.53	± 0.05 **c***	0.62	± 0.03 **d***
GT	5	0.36	± 0.03 **a***	0.45	± 0.02 **b***	0.60	± 0.05 **c***	0.69	± 0.03 **d**

- Legend as in table (1)

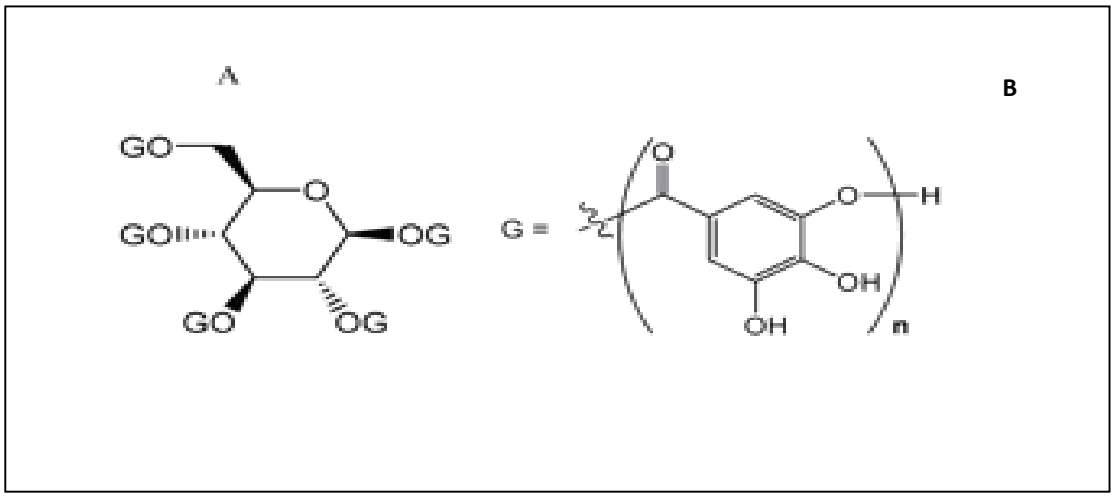

Fig.(1)A: Tannic Acid Structure

B: Gallic Acid Structure

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دلائل سريرية : تأثير تآزري لحامضي الكاليك والتانيك كمضادين للسكري وكمضادين للأكسدة

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الملخص

يعتبر حامضي الكاليك والتانيك من المركبات الفينولية المشهورة التي توجد بصورة طبيعية في النباتات المستخدمة كغذاء من قبل الإنسان والتي تستخدم أيضا كعلاج لبعض الأمراض. تم التحري في الدراسة الحالية على التأثير العلاجي للحامضين المذكورين كمضادين لارتفاع السكر في الدم وكمضادين للأكسدة في تجارب أجريت على الحيوانات المختبرية. إذ تم استحداث مرض السكري في ٢٥ من إناث أرانب محلية عن طريق الحقن بالالوكسان (150 mg/Kg من وزن الجسم) . تم حقن ثلاث مجاميع من الأرانب المصابة بالسكري بكل من حامض الكاليك (المجموعة G) وحامض التانيك (المجموعة T) ومزيجهما بنسبة (١:١) (المجموعة GT) يوميا وبكمية 100 mg/kg ولمدة ثلاثة أسابيع. بينت النتائج وجود انخفاض طفيف وغير معنوي في مستويي السكر في الدم والمالون داي ألديهايد(دليل الأكسدة الفوقية للدهون) في مصل الدم لدى المجموعة المعالجة بحامض الكاليك (G) عند المقارنة بمستوييهما في المجموعة (NC) (مجموعة السيطرة السالبة التي تشمل الحيوانات المصابة بالسكري وبدون أي علاج). بينما كان الانخفاض معنوياً في المجموعتين (T, GT) عند مقارنتهما مع المجموعة (NC) . وضحت النتائج أيضا وجود تناقص غير معنوي في مستوى مصل الدم من السعة الكلية لمضادات الأكسدة في المجموعة (G) مقارنة بمجموعة السيطرة (NC) . في حين إزدادت سعة مضادات الأكسدة في مصل الدم معنوياً في المجموعتين (T, GT) مقارنة بالمجموعة (NC) . أثبتت نتائج الدراسة الحالية الدور التآزري لكل من الحامضين أحدهما للآخر ليكون مزيجهما هو الأكثر فعالية من كل واحد منهما كمضاد للسكر وكمضاد للأكسدة.

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