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EVALUATION OF GREEN TEA EXTRACT AS A HYPOGLYCEMIC AGENT IN EXPERIMENTALLY DIABETIC RATS

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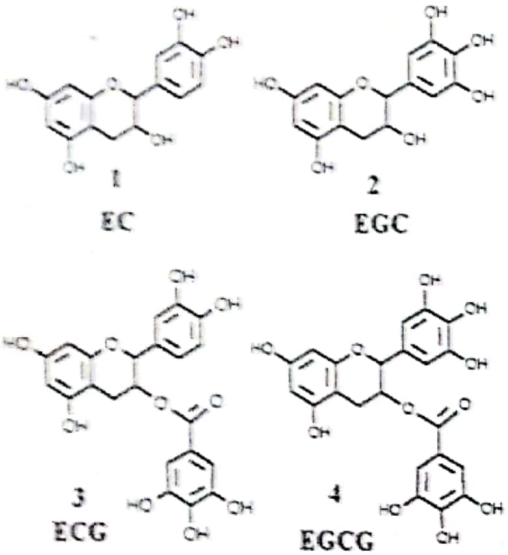
ABSTRACT:

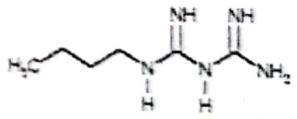
Recently great attention has been forwarded to natural products especially those owing medicinal properties e.g. Korean ginseng roots, *Nigella sativa*, *Curcuma longa* and green tea. In our study we select the last product as drinking tea is a traditional dietary habit in Egypt. Green tea, catechin is its active constituent, has received a great attention as a protective agent against cancer and cardiovascular diseases. Data reported regarding the effect of catechin on carbohydrate metabolism are scarce, few of them referred to its hypoglycemic effect, but without a definite explanation for the exact mechanism of action. The present work aimed mainly to study some of the metabolic actions of catechin. Metformin (Biguanide) which is a well known hypoglycemic drug has been included for comparison. Administration of both catechin and metformin individually for four and ten weeks respectively to normal and alloxan diabetic rats was done. Parameters studied were blood glucose, lactate, pyrurvate, liver glycogen, insulin, total cholesterol (Tc), triacylglycerol (TG), non esterified fatty acids (NEFA) and lipid peroxidation product (MDA).

INTRODUCTION

Green tea is nontoxic so it is readily available to the general population[1].

Catechins, the main constituents of green tea leaves are a group of polyphenolic flavonoids, the major sources of them are green tea(61%), onions (13%) and apple(10%)[2]. Tea catechins are composed mainly of (-) epicatechin (Ec), (-) epigallo catechin (EGC), (-) epicatechin gallate (ECG) and (-) epigallocatechin gallate (EGCG)[3]. (Fig. 1)

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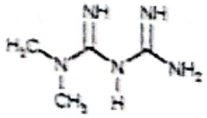
Metformin

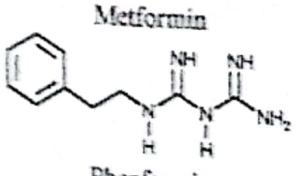
Phenformin

Fig. 2: Structural formulae of the biguanide drugs[4].

Catechins have been shown to exert diverse pharmacological actions including antihypertensive, antimutagenic and antioxidative effects[5,6].

Animal studies revealed the protective effect of green tea against cardiovascular diseases. However there is no clear evidence for such effects concerning humans[7,8].

Metformin (dimethyl biguanide), is used for the purpose of comparison, it is a potent hypoglycemic derivative of guanidine (Fig. 2).
It increases insulin sensitivity and used for treating type2 diabetes[9].

MATERIALS AND METHODS ANIMALS

Male albino rats of average (120-150 G) body weight were used, they were fed standardized diet formula, allowed free access to water and kept under constant environmental conditions during the study.

Induction of experimental diabetes:

Animals were fasted for 18 hrs. then injected I.P with freshly prepared aqueous alloxan solution (Mesoxyalylurea), 200mg/kg body weight[10]. Blood glucose level was assayed eight days later, animals with blood glucose over 200mg/dl, were selected for the present study[11].

Drugs:

1- Metformin (ADWIC Pharmaceutial Co., Egypt).
2- Catechin (Sigma – Aldrich Chem. Germany)

Experimental design:

Rats were divided into two main groups (A and B), each one was further subdivided into 4 subgroups:
Group (A): Treated for 4 weeks

Subgroup I: Normal, non diabetic rats received saline only and served as normal control.

Subgroup II: Alloxan diabetic rats received saline only and served as diabetic control.

Subgroup III: Diabetic rats received metformin 100mg/kg body weight orally, daily for 4 weeks[12].

Subgroup IV: Diabetic rats received catechin, 10 mg/kg body weight, orally, daily for 4 weeks[13].

Group (B): The same classification and doses as for group (A) but the treatment was continued for 10 weeks.

Blood sampling:

Blood samples were collected from the sinus orbitus vein of 12 hours fasted rats. Blood was received in EDTA coated glass tubes [14].

Blood was centrifuged at 1000 xg for 20 minutes at 4°c, plasma was separated and used for the determination of blood glucose, lactate, pyruvate, insulin, total cholesterol (TC), triglycerides (TG), non esterified fatty acids (NEFA) and lipid peroxides (MDA).

Tissue sampling:

At the end of treatment period, rats were decapitated, dissected and representative liver samples were isolated and directed instantly for the determination of liver glycogen contents.

Methods

The methods followed were as follows:

Raabo and Terkildsen[15] for blood glucose, Noll[16] for the determination of lactate, Czok and lamprect[17] for pyruvate, kemp and Adrienne[18] for liver glycogen contents.

Insulin was measured following (RIA) technique according to the method of Rasmussen et al.[19].

Total cholesterol was measured following the method of McNamara and Schaefer[20] that of Bucolo and David[21] was applied for triaylglycerol. The method of Matsubara et al.[22] was adopted for the measurement of nonesterified fatty acids.

Lipid peroxides value was determined as described by Jain[23] as modified by Janero[24].

RESULTS

Table (1) illustrates the effect of the single I.P injection of alloxan on five of the chosen parameters, where a significant increase in the level of plasma glucose, lactate and pyruvate was observed.

Liver glycogen contents showed a significant decrease. Serum insulin showed a non significant change.

Table (1): Effect of alloxan administration (200 mg/kg body weight) on plasma glucose, lactate, pyruvate, liver glycogen contents and serum insulin in experimental rats. Values are expressed as means ± S. D (n =8)

Parameter \ Group	Normal group	Alloxan Diabetic group
Glucose (mg/dl)	70.1 ±8.5	214.5 ±15.7 **
Lactate (mg/dl)	21.2 ±1.43	136.7 ±27.5 **
Pyruvate (mg/dl)	0.42 ±0.8	1.75 ±0.35 **
Liver glycogen (mg/g liver)	62.6 ±5.5	20.0 ±2.7 **
Insulin (µ lu/ml)	6.8 ±1.7	8.9 ±1.28

** Significantly different from normal control at P < 0.01.

Table (2): Effect of alloxan administration (200 mg/kg body weight) on total cholesterol, triacylglycerol, non esterified fatty acids and lipid peroxides in experimental rats. Values are expressed as means ±S.D (n = 8)

Parameter \ Group	Normal group	Alloxan Diabetic group
Cholesterol (mg/dl)	99.9 ±5.0	248.8 ± 9.0 **
Triacyglycerol (mg/dl)	48.3 ±12.6	249.8 ±10.8 **
NEFA (m mol/L)	0.46 ±0.2	1.5 ±0.09 **
Lipids peroxidation (n mol/L)	54.0 ±4.5	157.0 ±10.6 **

** Significantly different from normal control at p < 0.01.

Table (3): Effects of catechin (10 mg / kg) and Metformin (100 mg/kg body weight) daily on plasma glucose levels (mg/dl) in alloxan diabetic rats for 4 and 10 weeks. Values were expressed as means ± S.D (n = 8)

4 Weeks			10 Weeks		
Alloxan diabetic group (control)	Catechin	Metformin	Alloxan diabetic group (control)	Catechin	Metformin
214.5 ±15.7	117.9 ±10.9**	111.2 ±17.3**	214.5 ±34.5	87.9 ±7.3**	99.4 ±13**

** Significantly different from alloxan diabetic group (control) at P < 0.01.

Total cholesterol, triacylglycerol, non esterified fatty acids and lipid peroxides registered a significant increase (Table 2).

Table (3), refers to the effects exerted by both of catechin and metformin on blood glucose level in alloxan diabetic rats, where it was reduced by (45%,

48%) and (59%, 53%) after 4 and 10 weeks respectively.

Table (4), showed that lactate and pyruvate were reduced by (84%, 30%) and (72%, 38%) respectively. While liver glycogen contents increased by (184%, 91%) after 10 weeks. Insulin on the other hand showed a non significant change.

Table (4): Effects of catechin (10 mg/kg) and metformin (100 mg/kg) body weight daily on plasma lactate level (mg/dl), pyruvate (mg/dl),liver glycogen contents (mg/g) and plasma insulin level (μ lu/ml) in alloxan diabetic rats after 10 weeks. Values are expressed as means ±S D (n = 8).

10 Weeks			
Treatment / Parameter	Alloxan diabetic group (control)	Catechin	Metformin
Lactate (mg/dl)	136.7 ±27.5	21.1 ±1.9**	95.8 ±19.6 **
Pyruvate (mg/dl)	1.75 ±0.35	0.48 ±0.1**	1.08 ±0.56 **
Glycogen (mg/g)	20.0 ±2.7	56.9 ±2.7**	38.2 ±3.9 **
Insulin (μ lu/ml)	8.9 ±1.28	8.3 ±3	9.5 ±3.4

** Significantly different from alloxan diabetic group (control) at P < 0.01.

Table (5), illustrated the actions induced by both of catechin and metformin on the level of both total cholesterol and triacylglycerol in alloxan diabetic rats. Where total cholesterol was reduced by (74%, 69%), (77%, 69%), while triacylglycerol was lowered by (72%, 80%) and (74%, 76%) after 4 and 10 weeks respectively.

Lastly nonesterified fatty acids and lipid peroxides were decreased by (76%, 76%) and (66%, 35%) respectively after 10 weeks (Table 6).

Table (5): effects of catechin (10mg/kg) and metformin (100mg/kg body weight) daily on plasma total cholesterol levels (mg/dl) triacylglycerol levels (mg/dl) in alloxan diabetic rats for 4 and 10 weeks. Values were expressed as means ± S. D (n = 8).

	4 Weeks			10 Weeks		
Treatment / Parameter	Alloxan diabetic group (control)	Cate-chin	Met-formin	Alloxan diabetic group (control)	Cate-chin	Metfor min
Total cholesterol (mg/dl)	248 ±9	64.2 ±11.0**	76.8 ±19.3**	254.8 ±7.1	57.9 ±0.2**	77.3 ±13.8**
Triacylgly-cerol (mg/dl)	249.9 ±0.8	68.6 ±3.5**	49.9 ±10.9**	247.9 ±11.8	63.3 ±17.2**	57.6 ±8.4**

** Significantly different from alloxan diabetic group (control) P<0.01.

Table (6): Effects of catechin (10mg/kg) and metformin (100mg/kg body weight) daily on plasma NEFA levels (n mol/L) and lipid peroxides levels (n mol/L) in alloxan diabetic rats for 10 weeks.

Values were expressed as means ± S.D (n = 8).

Treatment / Parameter	Alloxan Diabetic group (control)	Catchin	Alloxan Diabetic group (control)	Catchin
Plasma NEFA (n mol/L)	1.5 ±0.09	0.35 ±0.1**	1.5 ±0.09	0.35 ±0.15**
Lipid peroxides (n mol/L)	157 ±10.6	51.9 ±7.5**	157 ±10.6	102 ±30.8**

** Significantly different from alloxan diabetic group (control) at P<0.01.

DISCUSSION

The present work has been designed to study the metabolic effects of green tea in alloxan diabetic rats.

Table (1) showed a significant hyperglycemia induced by alloxan administration. The same was reported[25], and was attributed to B cells destruction either by H_2O_2 liberated by alloxan[26] or to the activation of immune cells including macrophages which are in turn cytotoxic to B – cells[27].

Lactate and pyruvate showed a significant increase, while liver glycogen contents showed the reverse, this may be secondary to hyperglycemia and insulin deficiency.

Plasma insulin showed a nonsignificant change, this was in agreement with the work of Milagro et al.[28].

Total cholesterol and triacylglycerol illustrated also a significant increase, Table (2) Hypertriglyceridemia observed here may be a consequence of very low density lipoproteins either overproduction of VLDL by the liver or defective removal of triglyceride rich lipoproteins from circulation or both, the latter possibility can be explained through lipoprotein lipase, an insulin dependant enzyme involved in triglyceride removal[29,30]

Table (2) illustrated also a significant increase in lipid peroxidation products this was in agreement with the work of wolff[31].

Sunduram et al.[32], added that, plasma MDA showed 80% increase in the early stages of diabetes which are progressively increased later.

This was attributed to H_2O_2 formation under the influence of superoxide dismutase, followed by the production of other hydroxyl radicals [33].

Oxygen free radicals formed may lead to oxidative breakdown of different types of lipids resulting in MDA accumulation [34].

Oxygen free radicals and lipid peroxides may be the main cause of the complication that usually

accompany chronic diabetes mellitus leading through certain sequences to tissue damage[35].

Results of metformin:

Table (3) showed the hypoyglycemic effect of metformin in experimentally diabetic rats administered the drug for 4 and 10 weeks respectively. The same was seen by Robinson et al.[36] and was explained as due to inhibition of glucose flux[12]. Mayer, and Davidson[4] attributed the hypoglycemic properties of metformin to:

- Decrease or delay of glucose absorption from the gastro intestinal tract or increased glucose conversion to lactate by intestinal cells.
- Metformin may inhibit gluconeogenesis, secondary to inhibition of hepatic lactate uptake, decreasing in turn glucose out put from the liver.
- It may potentiate insulin activity through increasing insulin receptors. However the precise mechanisms are still obscure till now.

Table (4) referred to a significant decrease in the plasma level of both lactate and pyruvate in experimentally diabetic rats administered metformin for 10 weeks.

This may be explained as due to stimulation of pyruvate kinase accompanied by a decrease in cellular ATP level inducing inhibition of gluconeogensis and stimulation of lactate and pyruvate flux[12].

In Table (4) a significant increase in liver glycogen contents was seen. Our result was supported by the study of both Huupponen et al., and Fery et al.,[38] but the exact mechanism was ignore.

A non significant increase in plasma insulin level was registered after 10 weeks of treatment Table (4). This may be attributed either to potentiation of insulin sensitivity (Bell – and Hadden)[9] or to the increase in insulin receptors (Mayer, and Davidson)[4].

The significant decrease in plasma cholesterol, triacylglycerol after 4 and 10 weeks and non esterified fatty acids after 10 weeks following administration of metformin (Table 5, 6) was in accordance with the work of Robison et al.[36]; Niazi and Muzaffar[39].

Certain studies referred to Beta - 3 - adrenergic receptors stimulation which mediate lipogenesis and transcriptional activity of the nuclear receptor peroxisome[40].

Metformin is more effective in increasing mitochondrial and peroxisomal fatty acids β-oxidation and basal lipolysis as reported by Lenhard et al.[41].

Table (6) showed a significant decrease in plasma lipid peroxides in experimentally diabetic rats after 10 weeks of treatment. This may be secondary to the improvement in the glycemic and lipogram pattern following metformin administration[36].

Beisswenger et al.[42] added that, the protective action exerted by metformin against diabetic complication may be via mechanisms independent of its hypoglycemic properties.

Results of green tea (catechin):

The effect of varying concentrations of catechin on blood glucose levels was studied in male rats, the results revealed that it exerted maximum hypoglycemic actions at a dose level 10mg/kg body wt./day[13].

Treatment of alloxan diabetic rats with catechin induced a significant decrease in plasma glucose level after 4 and 10 weeks respectively table (3). Our results agreed with that of Elsewefy et al.[43] and was attributed to the ability of catechin to block dietary glucose uptake in intestinal epithelium[44, 45].

Honda et al.[46] added that, catechin can supress pancreatic α - amylase activity in the intestine leading to a reduction in blood glucose level.

Table (4) represents the effect of catechin on plasma level of both pyruvate and lactate where a significant reduction was observed in the level of each of them after 10 weeks of treatment.

Catechins appeared to be more effective than metformin in this respect. This may be attributed to the insulin like properties of catechin or to the potention of insulin activity or it may be secondary to the hypoglycemic action exerted by catechin.

Concerning liver glycogen contents Table (4) illustrated a significant increase in it after 10 weeks administration of green tea. This may be attributed to the increased activity of glycogen synthase and the inhibition of glycogen phosphorylase[13].

Table (2) showed a non significant alteration in plasma insulin level.

A similar finding was reported by Honda et al.[46] who reported that, it is unclear whether catechin may affect insulin resistance, sensitivity and secretion. Rizvi - et al.[47] revealed that catechin mimic insulin in actions but through another different mechanisms.

Concerning the plasma level of total cholesterol, triacylglycerol and non esterified fatty acids, Tables (5, 6) illustrates a significant reduction in the level of all of them following catechin treatment. Our results were confirmed by the studies of others[43,48].

Kono - et al.[49] added that, green tea consumption was inversely associated with serum level of total cholesterol and low density lipoprotein cholesterol.

The mechanism of action was unclear but it may be regulated through intestinal absorption or through inhibition of acyl cholesterol acyl transferase activity[50].

Valsa et al.[51] demonstrated the binding of catechin with dietary cholesterol in the intestinal lumen. In turn the availability of cholesterol for absorption is reduced Chan et al.[52] added that, the hypolipemic effect of catechin is most likely mediated through decreased absorption of dietary fat and cholesterol.

The conversion of cholesterol to bile acids may be one of the mechanisms of lowering total cholesterol[51].

Table (6): demonstrated a significant decrease in plasma level of lipid peroxides, catechins were more effective than metformin in this respect.

The same was registered by Elsewefy et al.[63] where they revealed the antioxidant properties of lyophilized green tea extract in diabetic hamsters.

The antioxidant properties of green tea may be attributed to a significant decrease of phospholipase (A2) activity and lipid peroxide formation[83].

Complete inhibition of lipid peroxidation of pure erthrocytes membrane by black tea extract is reported before [54].

Again it can delay the consumption of endogenous lipid soluble antioxidants, inhibiting in turn lipid oxidation[88].

Halder and Bahaduri,[84] indicated that, catechin seemed to be a better protecting agent against various types of oxidative stress.

Quantitative analysis suggests that one or more major catechins from the tea polyphenols preparations behave as iron – binding agents, this may account for the antioxidant properties of them[84].

So tea flavonoids are scavengers of free radicles, such as superoxide anions and lipid peroxy radicals and can interrupt radical chain reactions[87].

Moreover, it can inhibit oxidative modification of LDL by macrophages in vitro[89].

Hasegawa et al.[89] added that, green tea can effectively block oxidative DNA damage and diminish the hepatotoxic effects of other toxic agents in experimental animals.

SUMMARY AND CONCLUSION

Uncontrolled diabetes especially chronic cases demonstrate hypercholesterolemia, hyperlipidemia and increase in their oxidation derived products.

Additionally they may have higher level of plasma lactate and pyruvate.

Catechin a constituent of green tea may play a favourable role in our daily life especially in persons suffering from chronic diseases associated with certain complications like higher lipid peroxidation products and free radicals accumulation. The hypoglycemic effect of catechin observed in the present study may indicate benefical effects of green tea.

Present work demonstrated a hypoglycemic effects of catechin (major polyphenol constituent of green tea extract). Certain reported data indicated similarity, between it and insulin regarding biological and pharmacological actions but through mechanisms which are obscure till now.

Its significant effect dealing with lactate and pyruvate levels in addition to its high antioxidant property may indicate its superiority than metformin.

Clinical evaluation of catechin is certainly required before the recommendation of its use as hypoglycemic agent.

However results of the present experimental work may encourage such hypothesis.

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تقييم مستخلص الشاى الأخضر كمادة خافضة لسكر الدم فى فئران التجارب المستحدث فيها مرض البول السكرى

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تعد هذه الدراسة محاولة لإلقاء الضوء على ما يلى:

دراسة تأثير الكاتيكين (مستخلص الشاى الأخضر) على حيوانات التجارب المستحدث فيها مرض البول السكرى التجريبى ومقارنة ذلك بتأثير الميتفورمين كعقار شائع الاستعمال وعلى نطاق واسع لمرضى البول السكرى.

وقد استحدث مرض السكر عن طريق الحقن بمادة الألوكزان (٢٠٠ مجم/كجم) من وزن الجسم وتم تقسيم الفئران إلى مجموعات تناولت الأدوية المشار إليها لمدة أربعة أسابيع متتالية واستكملت إلى عشرة أسابيع.

هذا وقد تم تقدير كل من المعدلات التالية:

الجلكوز ، اللاكتات ، البيروفات ، تحديد كمية الجليكوجين الموجودة بالكبد وكذا معدل الأنسولين بالبلازما. تم أيضا تقدير معدل الكوليسترول الكلى والتراى جليسيريدات والأحماض الدهنية الغير مشبعة والليبيدات فوق المؤكسدة.

وكانت النتائج كالتالى:

١- الكاتيكين (مستخلص الشاى الأخضر) (١٠ مجم/كجم/يومياً):

أدى تعاطى هذا المستخلص الطبيعى إلى انخفاض معنوى فى نسبة السكر واللاكتات والبيروفات.

بينما زاد محتوى الكبد من الجليكوجين ولم يكن له تأثير واضح على الأنسولين. أدى أيضا إلى انخفاض معنوى فى نسبة الكوليستيرول الكلى والتراى جليسيريدات وكذا الأحماض الدهنية الحرة الغير مؤسترة والليبيدات فوق المؤكسدة.

٢- الميتفورمين (كمادة مشيدة كيميائياً) (١٠٠ مجم/كجم/يومياً):

أدى تعاطى هذا المستحضر الكيميائى إلى انخفاض معنوى أيضا فى نسبة السكر واللاكتات والبيروفات بينما زاد محتوى الكبد من الجليكوجين ولم يكن له تأثير واضح على نسبة الأنسولين .

وبالنسبة للدهون لوحظ انخفاض معنوى فى معدل الكوليسترول الكلى والتراى جليسيريدات والأحماض الدهنية الحرة (الغير مؤسترة وكذلك الليبيدات فوق المؤكسدة فى البلازما)

الخلاصة

مما سبق يمكن استخلاص الآتى:

١- مرضى البول السكرى خاصة اللذين لا يخضعون لبرنامج علاجى متكامل ومستمر غالباً يتعرضون لزيادة نسبة الليبيدات فوق المؤكسدة وكذلك نسبة اللاكتات والبيروفات وغيره من المضاعفات.

٢- فاعلية الكاتيكين واضحة فى خفض معدلات السكر ونسبة الدهون فى الدم وبالتالى فإنه من المحتمل أن يلعب دوراً مهماً فى إعادة الاتزان للخلل الناجم لدى هؤلاء المرضى.

٣- هذه الدراسة أثبتت أن الكاتيكين (مستخلص الشاى الأخضر) أكثر فاعلية من الميتفورمين بالنسبة لتأثيرهم على اللاكتات والبيروفات.

٤- أظهر الكاتيكين تأثيراً مضاداً للأكسدة أقوى من الميتفورمين.

٥- أثبتت الدراسة أن الكاتيكين والميتفورمين ليس لهم علاقة بإفراز الأنسولين.

٦- أوضحت الدراسة التأثير المتشابه فى كل من الكاتيكين والميتفورمين على مستوى الأحماض الدهنية الحرة (الغير مؤسترة) مما يرجح عدم حدوث تحلل للدهون فى الأنسجة الدهنية.

أظهرت الدراسة التجريبية الحالية نتائج مشجعة ولكن التقييم الإكلينكى لهذا المستحضر مطلوب بالتأكيد قبل التوصية باستعماله كخافض لسكر الدم.