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Full Length Research Paper

The effects of *Ginkgo biloba* L. and *Camellia sinensis* L. extracts on oxidative stress in patients with type 2 diabetes

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In the case of diabetes, hyperglycemia appears to be a significant contributor to oxidative stress which is also linked to diabetes related complications. In this study, we evaluated the effects of *Ginkgo biloba* L. and *Camellia sinensis* L. leaves extracts on oxidative damage in type 2 diabetic patients with surrounding diabetic complications. We found no significant effects of Green tea and *Gingko biloba* extracts on antioxidative enzymes (superoxide dismutase, catalase and glutathione peroxidase) and Total antioxidant status. However, *G. biloba* extract significantly reduced the amount of malondialdehyde and 4-hydroxy-2-nonenal ($p < 0.05$) while the Green tea extract and mix of both extracts did not have significant effects. Overall, the present findings are not beneficial in diabetic patients with more acute diabetic complications and further study in different circumstance needs to be done.

Key words: *Gingko biloba* extract, *Camellia sinensis* extract, antioxidant, oxidative stress.

INTRODUCTION

Oxidative stress represents an imbalance between the production of reactive oxygen species (ROS) and a biological systems ability to readily detoxify the reactive intermediates or easily repair the resulting damage. Excessive amounts of ROS can have deleterious effects on many molecules including protein, lipid, RNA and DNA since they are very small and highly reactive (Lu et al., 2010). However, during times of environmental stress and cell dysfunction, ROS level can increase dramatically and causes significant cellular damage in the body. There is no doubt that oxidative damage significantly contributes to the pathogenesis of type 2 diabetes mellitus and its complications (Pitocco et al., 2010; Giacco and Brownlee, 2010; Rahman, 2007).

In order to prevent or reduce the ROS-induced oxidative damage, the human organism has developed an antioxidant defense system that includes enzymatic (enzymes-superoxide dismutases (SOD), catalases (CAT), glutathione peroxidases (GPx) and others), metal-chelating, and free radical-scavenging activities to neutralize these radicals after they are formed. Polyphenol antioxidants assist in preventing ROS damage by directly scavenging free radicals or by enhancing the activities and expressions of antioxidant enzymes such as SOD, CAT and GPx (Lu et al., 2010; Lambert and Elias, 2010). In addition, intake of natural antioxidants such as

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Abbreviations: ABTS, 2,3-Azino-di-(3-ethylbenzthiazoline sulphonate); **BMI,** body mass index; **CAT,** catalase; **DM,** diabetes mellitus; **ECs,** standardized green tea (*Camellia sinensis* L.) leaves extract; **EGb,** standardized (*Ginkgo biloba* L.) leaves dry extract; **GCP,** grinvitals cereloba plus capsules; **GPx,** glutathione peroxidase; **HbA1c,** glycated hemoglobin; **HNE,** 4-hydroxy-2-nonenal; **MDA,** malondialdehyde; **ROS,** reactive oxygen species; **SD,** standard deviation; **SOD,** superoxide dismutase; **TAS,** total antioxidant status.

G. biloba and Green tea, may help to maintain an adequate antioxidant status in the body.

G. biloba L. has been reported to have strong antioxidant activities due to flavone glycosides that scavenge free radicals (Kudolo et al., 2005; Lu et al., 2010; Yeh et al., 2009). Flavonoids such as catechin and epicatechin in Green tea extract could be responsible for its potent antioxidant activities (Chacko et al., 2010; Lambert and Elias, 2010; Kanwar et al., 2012). These antioxidants may help to protect cellular damages from oxidative stress and also lower the risk of chronic diseases (Lu et al., 2010). There is some evidence from recent studies that Green tea and *G. biloba* extracts have beneficial effects on oxidative stress. Moderate consumption of Green tea increases the total antioxidant activity in healthy patients (Leenen et al., 2000; Erba et al., 2005) and decreases serum level of malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) (Freese et al., 1999; Coimbra et al., 2006).

There are convincing evidences from later study *in vitro* that epigallocatechin-3-gallate, the main component of Green tea, increases activity of antioxidant enzymes and total antioxidant status (TAS) in aged rats (Kumaran et al., 2008). Whereas, other study regarding Green tea effects on oxidative stress in diabetic rats show converse results of antioxidative enzymes (Babu et al., 2006). Though the interest in Green tea beneficial effects increased in recent decade and there are a lot of studies regarding its antioxidant effects but the results are contradictory and dependent on circumstance whereas the results of the researches on antioxidant properties of *G. biloba* extract are incontrovertible and confirm its influence on reducing oxidative stress (Ulbricht and Basch, 2005). The mechanism of action is not clarified. *G. biloba* extract reduces level of MDA (Kudolo et al., 2005), increases activities of CAT and SOD (Bridi et al., 2001) and increases serum level of TAS (Thanoon et al., 2012).

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by uncontrolled concentrations of glucose in the blood, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of DM include long-term damage, dysfunction and failure of various organs (Fowler, 2008). The prevalence of DM has been accelerating at an alarming rate in the last decade. More than 366 million people live with diabetes worldwide and this number is expected to rise to 552 million by the year 2030, if no urgent action is taken (International Diabetes Federation, 2011). Although the abnormally high glucose concentration play an important role in development of diabetic complications, the increased evidence from clinical research show that oxidative stress is associated with the pathogenesis of DM too (Akash et al., 2011; Bashan et al., 2009; Jay et al., 2006). Oxidative stress influence the pathogenesis of insulin resistance and beta-cell dysfunction that is, two most relevant mechanism in the pathophysiology of type 2 diabetes (Pitocco et al., 2010) and lead to vascular damage (Giacco and Brownlee, 2010). The data of recent decade research on role of oxidative stress in development of DM complications stimulate the search for antioxidants, to reduce the hyperglycemia–induced oxidative stress.

The aim of this study was to estimate the effects of *G. biloba* L. and *C. sinensis* L. leaves extract on plasma oxidative stress parameters in patients with type 2 diabetes. In order to assess the effects of these extracts on oxidative stress, we evaluated the quantity and activity of antioxidative enzymes (SOD, CAT, GPx), lipid peroxidation markers (MDA + HNE) and total antioxidant status. This study is a part of international “Eureka“ project No.E! 3695 "Creation of the methodology for effects of natural antioxidants on the development of the Diabetes mellitus complications“.

MATERIALS AND METHODS

Study design and participants

The randomized double blind placebo-controlled study was conducted in Endocrinology Clinic, Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Lithuania. The experimental protocol used in this study was approved by the Lithuanian Bioethics Committee, State Data Protection Inspectorate. Written, informed and voluntary consent was obtained from all subjects. All subjects were outpatients of the Endocrinology Clinic, Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Lithuania. Subjects diagnosed with type 2 diabetes mellitus (treated with Insulinum, Metforminum or combination of both) aged from 35 to 80 years old and followed up for diabetic retinopathy, nefropathy or neuropathy, were enrolled into the study. The exclusion criteria include HbA1c > 13%, BMI > 45 kg/m^2, history of uncontrolled hypertension, other significant medical problems (major cardiovascular, hepatic, and other endocrine diseases), hypersensitivity to the test drug, and not being able to comply with the study protocol. The subjects were not deprived of taking their regular prescribed medications, but were advised to abstain from other dietary supplements rich in antioxidants.

The status of type 2 diabetes and its complications, oxidative stress parameters and biochemical measurements were evaluated at the baseline. The baseline measurements were repeated after 9 and 18 months of receiving preparations. First nine months patients received capsules twice a day, second nine months, three times a day.

Study preparations

All patients were randomly allocated to receive standardized *G. biloba* dry extract, Green tea extract, compound of both extract or placebo capsules. Placebo capsules were made from microcrystalline cellulose, a material indifferent to disease (Joint-stock company “Sanitas”, Veiveriu street, 134B, LT-46352 Kaunas, Lithuania). EGb capsule contains 80 mg of standardized dry extract of *G. biloba* leaves, adjusted to 19.2 mg ginkgo flavone glycosides and 4.8 mg terpene lactones (ginkgolides, bilobalide) (Joint-stock company “Aconitum”, Inovaciju street, 4, LT-54469 Kaunas District,

Table 1. Mean age and duration of DM.

Group	N	Mean age	Mean duration of DM
EGb	22	61.22±10.55	10.45±7.49
ECs	13	63.70±8.34	9.45±5.18
GCP	11	62.27±6.46	10.45±4.16
Placebo	20	61.78±11.71	11.50±7.97

The age and duration of DM were similar in all groups. All the patients were older age with long duration of diabetes and more progressive diabetic complications.

Lithuania). ECs capsule contains 200 mg standardized extract of *C. sinensis* leaves, adjusted to 70% polyphenols (Joint-stock company "Sanitas", Veiverių street, 134B, LT-46352 Kaunas, Lietuva). Grinvitals Cereloba plus capsules contains 37.5 mg EGb, 37.5 mg ECs and 100 mg garlic (*Allium sativum* L.*)* extract (Joint-stock company "Grindeks", 53 Krustpils street, Riga, LV 1057, Latvia).

Biochemical measurements

All measurements of plasma oxidative stress parameters were performed in Laboratory of Biochemistry, Riga Stradins University, Latvia. Total antioxidant status, superoxide dismutase and glutathione peroxidase in blood were performed on an automatic chemical analyzer RX Daytona based on spectrophotometer methods according to instructions provided by Randox Limited and using its own kits (Randox Laboratories Limited, 55 Diamond Road, Crumlin, UK) (Miller et al., 1993; Paglia and Valentine, 1967; Suttle, 1986). Erythrocyte catalase activity was measured by the method of Aebi (1984) with Varian Cary spectrometer (Varian Cary® 50 UV-Vis Spectrophotometer, Varian, Australia Pty Limited). The degree of lipid peroxidation was evaluated by quantitative determination of MDA + HNE by using a commercial kit (LPO Microplate Based Assay Kit, Cat. No FR22) according to manufacturer instructions (Oxford Biomedical Research, USA) on microplate absorbance reader (SunriseTM, TECAN, Switzerland) (Esterbauer and Cheesman, 1990; Janero, 1990).

Statistical analysis

Data were analysed using the computer software package SPSS for Windows, Version 20.0 and STATISTICA 6. Data are expressed as mean ± SD. There were used nonparametric tests because of small number of variables. The comparisons between the groups were made by Kruskal-Wallis test (between all groups) and by Mann-Whitney U Test (between each antioxidant group and placebo) at each time point. The comparison between three different measurements (at baseline, after 9 and 18 months) were made using Friedman Test and Wilcoxon Signed Ranks Test. The results were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The study was performed to evaluate whether natural antioxidants present in the *G. biloba* L. and *C. sinensis* L. leaves extract are capable of protecting or reducing oxidative damage in diabetic patients with surrounding diabetic complications. There are a lot of previous studies and evidence on Green tea and *G. biloba* antioxidative properties and benefits to healthy patients, but we decided to evaluate its effect on diabetic patients with more advanced complications. Because there are no doubt that Green tea and *G. biloba* leaves extract have strong antioxidant activities (Chacko et al., 2010; Coimbra et al., 2006; Ulbricht and Basch, 2005), we expected to get significant evidence in reducing amount of lipid peroxidation markers and increasing activity of antioxidant enzymes.

There were total of 91 patients involved in the project. Currently, the results are from 66 patients who have finished the study. Mean age and duration of DM in all groups are shown in Table 1. Male preponderance in all groups was observed. Mean body weight and BMI at baseline and after 9 and 18 months were similar in all groups. Mean level of HbA1c was 7.65 ± 1.41% and there were no significant changes of HbA1c during all the study in all groups.

All investigated parameters of all groups and at different time point of the study are shown in Table 2. All parameters were within established reference ranges, except the amount of MDA + HNE was slightly increased in the beginning of the study. That confirms the hypothesis that ROS generation and lipid peroxidation processes are accelerated in diabetic patients.

We found no statistically significant effects of Green tea and *G. biloba* extracts (except the GCP group) on antioxidative enzymes (SOD, CAT and GPx) in patients with type 2 diabetes either after 9 month or after 18 months of follow up. There were statistically significant differences of SOD between GCP and placebo groups at the beginning of the study and this amount increased in GCP group after 18 months ($p = 0.051$) as compared with placebo group. When data was analyzed separately for each group, the significant changes were observed after 9 months in all groups, respectively in EGb group ($p = 0.007$), ECs group ($p = 0.003$), GCP group ($p = 0.003$) and placebo group ($p = 0.002$). The quantities of SOD slightly decreased in all groups (except the GCP group) after next nine months.

In the GCP group was observed significant increment ($p = 0.008$) after 18 months, as compared with baseline. The significant increment of SOD in GCP group may be due to the common effect of both extracts or content of the garlic extract, because separately these extracts did not induced significant changes. Though there were no significant differences of CAT and GPx between all groups, but there were observed, some changes within the groups. The amount of CAT after 9 months decreased in EGb and ECs groups and increased in placebo group, while after next 9 months, these amounts contrarily changed, decreased in placebo group ($p = 0.049$) and increased in EGb ($p = 0.039$) and ECs groups as compared with measurements after 9 months but the amount of CAT were similar and without significant

Table 2. Comparison of the oxidative stress parameters between groups at baseline, after 9 and 18 months.

Parameter	Group	Baseline	9 months	18 months
SOD (U/g Hb)	EGb	1386.27±129,72	1486.14±119.23	1464.76±170.55
	ECs	1340.00±151.97	1496.15±156.24	1426.38±136.54
	GCP	1278.09±110.06	1502.00±169.40	1551.33±144.72
	Placebo	1382.20±128.19	1495.70±130.84	1440.22±148.41
		p = 0.18	p = 0.97	p = 0.19
CAT (k/g Hb)	EGb	226.18±72.61	199.64±50.10	217.94±49.57
	ECs	230.15±83.11	205.00±58.53	208.00±60.59
	GCP	188.00±72.46	212.60±67.73	224.22±73.72
	Placebo	208.65±60.79	242.65±75.54	196.33±74.92
		p = 0.35	p = 0.22	p = 0.29
GPx (U/L)	EGb	6393.55±2034.25	6834.55±1779.31	6137.61±1642.81
	ECs	6881.08±2090.74	7741.38±3213.90	6195.27±1401.17
	GCP	6517.73±1868.06	6423.91±1730.89	6301.10±2173.81
	Placebo	6230.45±1641.16	7384.89±2067.51	6765.89±1772.71
		p = 0.76	p = 0.66	p = 0.66
MDA+HNE (µM)	EGb	6.84±2.77	5.58±2.38	4.68±2.25
	ECs	5.31±3.56	6.58±3.32	5.67±2.04
	GCP	7.66±3.28	6.68±3.36	6.49±3.36
	Placebo	8.90±4.98	7.49±2.81	6.63±2.90
		p = 0.09	p = 0.16	p = 0.18
TAS (mmol/L)	EGb	1.59±0.18	1.65±0.17	1.67±0.22
	ECs	1.62±0.11	1.66±0.19	1.64±0.13
	GCP	1.62±0.15	1.64±0.09	1.64±0.09
	Placebo	1.55±0.17	1.68±0.19	1.57±0.14
		p = 0.35	p = 0.96	p = 0.46

differences after 18 months in comparison with baseline measurements while the amount of CAT in GCP group increased during all study and there was significant difference after 18 months (p = 0.038) as compared with baseline.

The amount of GPx in GCP group slightly decreased during all the study while in the others groups, the amount of GPx increased after 9 months and decreased after next 9 months but neither of these changes reached statistical significance. Overall, the effects of EGb and ECs on the amount of antioxidative enzymes were similar, contrarily to the effect of GCP. This may be related to the content of the garlic extract. According to the data, the concentration of Green tea and *G. biloba* extracts was not of great importance, thought there were some changes, albeit insignificant and numerically small.

Evaluation of the lipid peroxidation markers (MDA + HNE) show significant differences between the ECs and placebo groups in the beginning of the study (p = 0.034) while increment after 9 and decrement after 18 months was not of great significance. The reduction in the next 9 months may be related to the largest concentration of Green tea extract, or to the longer usage. In any case, these data were not consistent with previous findings (Coimbra et al., 2006). These differences may be due to the total organism damage by long duration diabetes and more progressive diabetic complications. The strongest effect on the amount of lipid peroxidation markers was observed by *G. biloba* exctract. There was a trend for a reduction in the amount of MDA + HNE in EGb group after 9 (p = 0.019) and 18 (p = 0.041) months compared with placebo group. Evaluation within EGb group showed statistically significant changes too. Amount of MDA + HNE significantly decreased after 9 months (p = 0.046) and after 18 months (p = 0.037) compared with baseline.

In agreement with others studies (Kudolo et al., 2005)

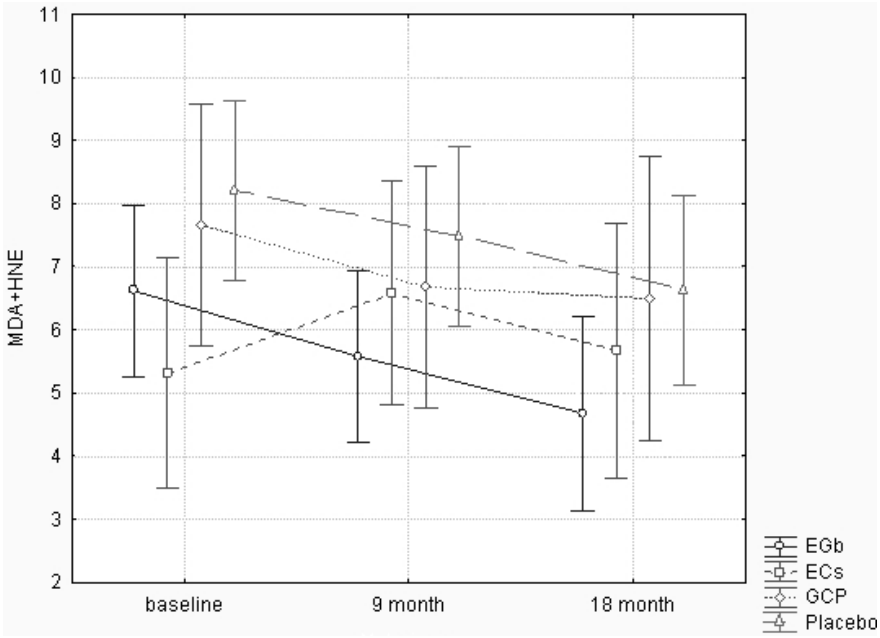

Figure 1. Amount of MDA + HNE at baseline after 9 and 18 months in all groups.

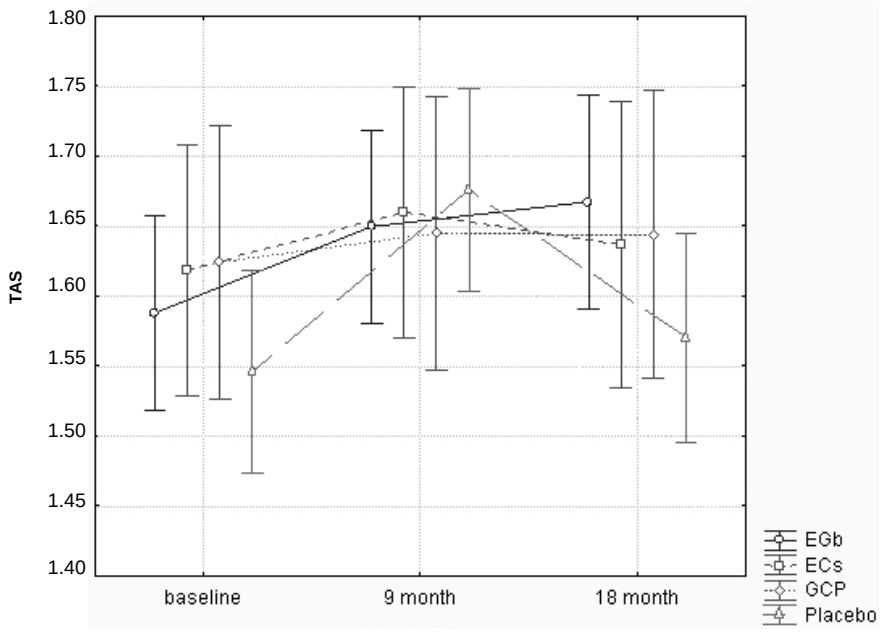

Figure 2. Mean of the TAS at baseline, after 9 and 18 months in all groups.

these data showed beneficial effect of *G. biloba* extract on oxidative damage by reducing amount of MDA + HNE. No significant changes were observed in GCP group, though the amount of MDA + HNE in this group, as in placebo group, decreased during all the study (Figure 1).

We did not observe statistically significant differences of TAS neither between groups nor between three different measurements in each group but there were some changes, albeit insignificant, within placebo group. Whereas the values of TAS did not fluctuate in ECs and GCP groups, and fractionally increased in EGb group (Figure 2). Evaluation of TAS did not show significant

effect of *G. biloba* and Green tea extracts. These results were unexpected and should be reviewed, taking into account all available evidence in the context of the benefits of Green tea and *G. biloba* extracts. Supposedly, it was influenced by the older age of patients, already existing significant diabetic complications and duration of the study but further exploration needs to be done to evaluate effects of Green tea and *G. biloba* extracts, maybe in patients with early diabetic complications.

Conclusion

This study confirms the beneficial influence of *G. biloba* extract on reducing amount of MDA and HNE in diabetic patients while the Green tea extract and mix of both extracts with less concentrations did not have significant effects. Overall, the present findings are not beneficial in diabetic patients with more acute diabetic complications and the further study in different circumstance needs to be done.

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