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Health Benefits of Green Tea with Emphasis on Diabetes Mellitus

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Abstract Green tea (*Camellia sinensis*) is one of the most popular beverages in the world where about 3 Billon kg of tea are produced and consumed yearly. The chemical composition of green tea is very much complex and it contains higher amount of polyphenols (epicatechin, epicatechin gallate, eipgallocatechin and epigallocatechin gallate) as compared to black tea. The presence of this high amount of polyphenols in green tea makes it very important in the prevention of different diseases. So far green tea was shown to have many impacts in carbohydrate metabolism and it is considered as an alternative medicine for diabetes mellitus. Polyphenols in green tea reduce carbohydrate digestion and absorption in the intestine by inhibiting carbohydrate digesting enzymes and inhibiting glucose transporters across the intestine. They are also shown to increase secretion of insulin by pancreatic β cells and protect cytokine induced inflammatory damage of these cells. Increasing insulin activity and maintaining glucose homeostasis are other mechanisms by which green tea is involved in carbohydrate metabolism. In addition to its impact on carbohydrate metabolism green tea is known to have a preventive effect against cancer (of colon, esophagus, mouth, stomach, small intestine, kidney, pancreas, and mammary glands), bacterial, viral and fungal infections, cardiovascular diseases, lung injury, non-alcoholic fatty liver and neurodegenerative disorders. Even though the health benefit of green tea is high some dose dependant adverse effects may be observed. There is a need to conduct in depth human based studies to monitor pharmacological and clinical effects of green tea therefore people can be benefited from it as an alternative medicine.

Keywords: *catechins, camellia sinensis, green tea, diabetes mellitus, polyphenols*

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1. Introduction

Green tea is one of the most popular beverages in the world where about three billion kg of tea are produced and consumed yearly [1,2]. It is obtained from the tea plant *Camellia sinensis* which belongs to the family Theaceae and is cultivated in at least 30 countries around the world, commonly consumed in Japan, china, India and other Asian countries, some parts of North Africa, the United States, and Europe [3,4,5]. Green tea is a non-fermented tea that contains a large amount of non oxidized polyphenols, named catechins [6]. Green tea is produced by steaming fresh leaves at high temperature to inactivating the oxidizing enzymes. The minimal processing results in the preservation of highest proportion of polyphenols as compared oolong tea (partially fermented) or black tea (fully feremented) leaving the polyphenol content intact [7,8,9].

Green tea contains polyphenols, which may account for up to 30% of the dry weight, but the most common green tea polyphenols are flavanoids, commonly called catechins [5]. There are four major polyphenolic catechins in green tea: epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), of which EGCG is the most abundant and pharmacologically active of the catechins [10,11].

The presence of polyphenols in green tea has been found to be effective in preventing different diseases [2]. Both animal model studies and studies on humans have also indicated that green tea has different health benefits in preventing cancer, alleviating cardiovascular diseases, preventing infections caused by microorganisms, minimizing the development of non-alcoholic fatty liver (NAFLD) and maintaining glucose homeostasis [2,12,13]. For better benefits from green tea it is important to compile outputs researches conducted. Hence the aim of this review paper is to summarize results of different researches on the health benefit of green tea.

2. The Health Benefits of Green Tea

The history of the medical effects of green tea starts on the early eighth century with the Buddhist monks who recognized green tea for its medicinal powers; therefore nowadays there is also an increasing interest in the beneficial effects of green tea on disease prevention [14]. As reviewed by Ogale, green tea has been used as a stimulant and diuretic, to regulate body temperature and blood sugar, reduce excess fat, to prevent tooth decay, to treat conjunctivitis and corneal opacities in different countries including China, India, Mexico and Kenya since ancient times [8]. The most widely known health benefits of green tea related to the polyphenols as the principal active ingredients in protection against oxidative damage and in antibacterial, antiviral, anti-carcinogenic, and anti-mutagenic activities [3,15]. Increasing interest in its health benefits has led to the inclusion of green tea in the group of beverages with functional properties [3]. The health benefits of green tea are described in the following paragraphs.

2.1. The Impact of Green Tea on Diabetes Mellitus

Diabetes mellitus is now considered to be a worldwide epidemic and without primary prevention, the epidemic will continue increasing. The pathology of diabetes mellitus is caused by reactive oxygen species that activate the non-enzymatic glycation of proteins (leads to structural and functional changes), the aldose reductase pathway (causes sorbitol accumulation) and oxidative stress (results in protein, DNA and lipid damage). The complications of diabetes mellitus, like retinopathy, nephropathy and neuropathy, are results of such pathologic mechanisms. But these complications can significantly be prevented or their occurrence can be delayed by strict control blood glucose level [16,17]. The World Health Organization Expert Committee on diabetes recommended that traditional medicinal herbs considered being less toxic and relatively free from side effects. In general, herbal medicines are complex mixtures of different compounds that often act synergistically to exert their full beneficial effect on diabetes mellitus and other disease [5,18]. Green tea compounds may influence glucose metabolism by several mechanisms, such as inhibition of carbohydrate digestion and glucose absorption in the intestine, stimulation of insulin secretion from the pancreatic B cells, modulation of glucose release from liver, activation of insulin receptors (enhancing insulin binding) and glucose uptake in the insulin-sensitive tissues, and modulation of hepatic glucose output [19].

2.1.1. Influence of Green Tea on Carbohydrate Digestion and Glucose Absorption in the Intestine

Green tea catechins may reduce the amount of glucose that passes through the intestine and into the bloodstream which will benefit diabetics by preventing blood-sugar spikes when tea is taken with meals [20]. Polyphenols act through interference with digestion of complex sugars and absorption of glucose by inhibition of carbohydrate digestive enzymes may be of use to patients with T2DM as well as the growing pre-diabetic population around the world [19]. Animal model study conducted by Park, *et al*, on mice in Korea, has indicated different effects of green tea catechins on the concentration of blood glucose level. According to this study the Green catechins (GC) of green tea, such as EGCG and ECG, acutely reduces blood glucose levels mainly through its activities in the alimentary tract [21]. Another study has also reported by Haidari and his colleuges in Iraq, a similar result with a dose dependent decrement of serum glucose when the dose of green tea extract was increased from 100 mg/kg to 200 mg/kg among diabetic mice [22]. Oral glucose tolerance test on mice done by Tsuneki, *et al*, and humans also indicated that administration of green tea was successful in significantly lowering the blood glucose level as compared to the placebo group that took hot water [23]. The inhibitory effects of green tea polyphenols, against carbohydrate hydrolyzing enzymes contribute to the lowering of postprandial hyperglycemia in diabetic management as observed *in vivo* and *in vitro*. Green tea polyphenolic compounds in plants inhibit the activities of digestive enzymes because of their ability to bind with proteins [24,25]. The other effect of green tea on carbohydrate metabolism is through its effect on carbohydrate absorption. Orally administered green tea extract, which contains many monomeric flavonoids including EGCG and ECG, may inhibit glucose absorption from the lumen of the intestine [18,21]. A study conducted by Zhong *et al*, to see the impact of green tea in carbohydrate absorption using hydrogen breath test indicated that individuals who ingested green tea extract had increased breath hydrogen concentration as compared to their counter parts who took placebo. The increase in hydrogen breath concentration was due to malabsorption of carbohydrates, associated with tea extract ingestion, which was digested by colonic bacteria [26]. Intestinal absorption of glucose is mediated by active transport *via* the sodium-dependent glucose transporter (SGLT1) and by facilitated sodium-independent transport *via* the glucose transporter (GLUT2). EGCG was found to inhibit intestinal glucose uptake by the SGLT1 which is a mobile carrier protein molecules present in the apica cell membrane of intestine and absorbs glucose and galactose against their concentration gradient by coupling with Na^+-K^+ATPase, indicating its increase in controlling blood sugar level [5,27]. The effect of green tea on GLUT2 was also demonstrated by Kwon, *et al*. Accordingly *Xenopus laevis* oocysts were injected with human GLUT2 complement ribonucleic acid (cRNA) and glucose transportation was measured after 2 days. The result showed that glucose transportation was completely inhibited by the green tea at a concentration of 50 μM. A similar result was also observed in mammalian cells [28]. The green tea catechins that have an inhibitory effect on glucose absorption in the intestine may have a different effect in the circulation as demonstrated by Park, *et al*, in 2009. According to this study, when in the circulation green tea catechins elevate blood glucose level by blocking normal glucose uptake into the tissues, resulting in secondary hyperinsulinemia, whereas it decreases glucose entry into the circulation when they are inside the intestinal lumen [21].

2.1.2. Influence of Green Tea on Pancreatic β-Cell Function

During high blood glucose concentrations pancreatic β-cells respond to the increased demand of insulin by

various mechanisms including; increased insulin secretion, hypertrophy, proliferation of existing β-cells and formation of new ones from progenitor cells [19]. Chamler and his colleuges, in USA, examined whether catechins have an effect on pancreatic β-cells ability to secret insulin by challenging mouse insulinoma with glucose. Accordingly exposure of the cells to increased concentration of catechins and 25 mM of glucose was able to potentiate secretion of insulin from the cells [29]. Another study conducted by Nagao and his colleuges in Japan, on human also showed that T2DM patients who took catechins were able to produce high amount of biologically active insulin after the 12th week of follow up as compared to those who did not take catechins [30]. The increased insulin secretion in the presence of catechins may be due to their action on intracellular moieties which participate in insulin secretion, enhancing adenylate cyclase activity, inhibition of phosphate diesterases, changes in Ca^{2+} metabolism and protection of pancreatic β cells from inflammatory cytokine inducing disorders by inhibiting activation of nuclear factor κB [29,30]. Cytokine induced pancreatic β cell damage associated with the induction of inducible nitric oxide synthase (iNOS) which is one consequence for the development of insulin dependent diabetes mellitus (IDDM). This suggests that preventing cytokine mediated pancreatic damage as one way of preventing IDDM [31]. From this point of view when the role of green tea is evaluated, its effect on pancreatic β cells will not limited only to the stimulation of insulin production by these cells rather catechins, especially EGCG, prevented cytokine mediated damage of the β cells [31]. Han was able to demonstrate the effect of EGCG in preventing the death of pancreatic β cells when incubated with IL-1β and IFN-γ after treatment with EGCG. The prevention of cytokine induced pancreatic β cell damage was possible because EGCG was able to neutralize nitric oxide produced as a result of the cytokines [19,31]. Islets histomorphometry done by Ortsater and his colleagues in Sweden demonstrated that EGCG supplementation in diabetic mouse reduces the number of pathologically changed islets of Langehans, increases the number and the size of islets, and heightens pancreatic endocrine area [13]. Another histological study by Yenzeel Al-Hilfy, has also demonstrated that green tea extract reduced degeneration of histological structures of the pancreas [32].

2.1.3. Effect of Green Tea on Enhancing Insulin Activity

Elevated glucose concentration in blood promotes secretion of insulin from the β-cells of the islets of Langerhans in the pancreas, and insulin mediates the uptake of glucose in peripheral tissues including muscle, adipose tissue and kidney, promotes storage of glucose in liver as glycogen, and inhibits lipolysis in adipose tissue [19]. A study conducted by Wu and colleuges in Taiwan, to assess the impact of green tea supplementation on insulin sensitivity showed the beneficial effect of green tea in diabetes mellitus. According to this study insulin binding capacity among rats that took green tea supplementation was significantly higher than the control groups. The study has also confirmed that the increase in insulin induced glucose uptake among those rats with green tea supplementation by *in vitro* analysis of adipocytes tissue [33]. Another study by Yan, *et al*, also indicated that green tea catechins are able to ameliorate(improve) insulin resistance in adipose tissues by improving oxidative stress and this was demonstrated in their study by decreased serum reactive oxygen species and recovery of impaired insulin stimulated glucose up take in mice that took EGCG [34]. However a randomized controlled human trial indicated the absence of any significant difference in the insulin sensitivity, insulin secretion and glucose tolerance between those who took EGCG and the placebo group [35]. Insulin enhancing property of green tea was also determined using rat epididymal adipocytes. In this study both insulin dependent break down of glucose to carbon dioxide and incorporation of glucose in to lipids were enhance by green tea, indicating it ability to potentiate insulin activity [15].

2.1.4. Effect of Green Tea on Liver to Maintain Glucose Homeostasis

Liver plays a major role in the regulation of blood glucose level by storing glucose as glycogen (glycogensis) when glucose is excess and by producing glucose from glycogen (glycogenolysis) or from other metabolites such as pyruvate, lactate, glycerol, and amino acids (gluconeogensis) when blood glucose level is low [19]. The effect of green tea catechins on the liver glucose metabolism is demonstrated by different researchers. Collin and colleagues in 2007 demonstrated that EGCG was able to inhibit gluconeogensis in hepatocytes. According to their research, hepatocytes were activated by cyclic adonesine monophosphate (cAMP) in the presence and absence of increasing amount of EGCG followed by determination of glucose concentration. As expected cAMP was able to stimulate the synthesis of glucose but this was inhibited by EGCG in a concentration dependant manner. According to the results of this study EGCG inhibit gluconeogensis by hepatocytes through the activation of AMP-activated protein kinase (AMPK). This was known because EGCG cannot inhibit gluconeogenesis when AMPK was inactive. Ca^{2+}/calmodulin-dependent protein kinase (CaMPK) was mediator of AMPK activation by EGCG this indicates the role of CaMPK in glucose homeostasis [36]. A similar result from another study by Waltner-Law, *et al*, in 2002, on H4IIE rat hepatoma cells was also reported, but with a different mechanism of action of EGCG. According to this study EGCG was able to reduce expression of glucose 6 phosphatse (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) gene, an important gene that encode gluconeogenic enzymes [37].

2.2. Other Health Benefits of Green Tea

2.2.1. Anticancer Activity

Green tea polyphenols have been shown to have anti-mutagenic and anti-carcenogenic properties *in vitro* and *in vivo*. Green tea was found to activate intracellular antioxidants, inhibit precarcinogen formation and suppress angiogenesis and cancer cell proliferation in different tissues [8]. A study conducted in Japan indicated that EGCG was able to suppress cell adhesion, an important step in the development of disease in multi-cellular

organisms, through the inhibition of focal adhesion kinase (FAK) and insulin like growth factor I receptor (IGF-IR). The inhibition of FAK and IGF-IR was able to inhibit proliferation of pancreatic carcinoma cells [38]. Another study by Mantena, et al, also demonstrated that orally administered green tea polyphenols were able to prevent ultraviolet radiation induced skin cancer. According to this study the mechanisms involved were activation and recruitment of cytotoxic T-lymphocytes to the cancer microenvironment and inhibition of angiogenic factors like matrix metalloproteinase (MMP)-2 and MMP-9 which was also showed by another mouse model study conducted by Vayalil and collogues [39,40]. Other mechanism of green tea in cancer prevention include activation of mitogen activated protein kinase (MAPK) path way by inhibition of enzymes such as the cytocromes P450 which are involved in the bio-activation of carcinogens, it involve in phase II detoxification, inhibition of urokinase activity, induction of apoptosis in already induced carcinomas, inhibition of cellular proliferartion and tumor progression [14]. Through similar mechanisms green tea prevent many types of cancer associated with lung, colon, oseophagus, mouth, stomach, small intestine, kidney and mammary glands [5].

2.2.2. Antibacterial, Antiviral and Antifungal Effects

Catechin gallates such as ECG intercalate into phopsholipid bilayers and it is likely that they affect both virulence and antibiotic resistance by perturbing the function of key processes associated with the bacterial cytoplasmic membrane [41]. Antibacterial activity of green tea extracts against *Staphylococcus, Streptococcus, Pseudomonas, E.coli, Bacillus,* and *Proteus* reported that aqueous, ethanolic and methanolic extracts showed significant growth inhibition of these bacteria [42]. The effect of green tea catechins is extended to viruses. ECG and EGCG were able to inhibit plaque formation ability, replication and neuraminidase activity of influenza A and B viruses in Madin–Darby canine kidney (MDCK) cells [43]. A randomized control trial, conducted by Matsumotoin and his colleuges in Japan, among health care workers also showed that the incidence of clinically defined influenza infection and laboratory confirmed influenza among those who took green tea catechins was significantly low as compared to the placebo group [44]. The antifungal effect of green tea catechins was also demonstrated by its effect on *Candida albicans* and other types of fungi. When the PH is low the strains can grow. However the effect of EGCG on fungus was PH dependant with maximum inhibition at PH 7 with a concentration of 15.6-250 mg/l. As the PH is lowered the efficacy of EGCG required higher concentration. EGCG also improved the antifungal effect of amphotericin B [45,46]. Another study by Yassien in Baghdad also showed greater activity of green tea extracts on clinical isolates of *Trichophyton mentagrophytes, Trichophyton verrucosum, Trichophyton rubrum, Candida albicans* and *Cryptococcus neoformans.* Green tea extracts showed higher activities against dermatophytes due to the catechins attached the cell membrane and caused lysis of the conidia and hyphae [47].

2.2.3. Neurodegenerative Disorders

Parkinson's disease, Alzheimer's disease, and ischemic damage are among the neurodegenerative disorders and age related pathologies and green tea has been shown to have protective effects against these diseases [7]. Alzheimer’s disease is known to be caused by the abnormal deposition of β-amyloid (Aβ) peptide that activates glycogen syntase kinase 3β (GSK3β) and induce translocation of Ab1/Fe65 and that increase oxidative stress. A research conducted by Lin, *et al*, in Taiwan, indicated that green tea polyphenols were able to suppress Aβ-induced neurotoxicity by inhibiting c-Abl/FE65 nuclear translocation and GSK3β activation, thus prevent Alzheimer’s disease [48]. Long term administration of green tea catechins was also shown to prevent Aβ-induced cognitive impairment by increasing antioxidative effects [49]. A cross sectional study among Japanese people also indicated that the prevalence of cognitive impairment has decreased with increasing consumption of green tea [50].

Choi and colleuges demonstrated the protective effect of green tea catechins in Parkinson’s disease (PD), a disorder characterized by progressive degeneration of dopaminergic neurons in the substantia nigra (SN). According to this study administration of EGCG prevented loss of dopaminergic neurons induced by 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP). This was possible because EGCG was able to prevent the expression of neuronal nitric oxide synthase (nNOS) [51]. In contrary to the above finding a study conducted by Tan, et al in china, has reported the absence of any relation between green tea catechins and Parkinson’s disease risk [52]. A review by Douna, et al, also summarized the protective effects of green tea from PD and also the absence of any relation between taken green tea and the risk of Parkinson disease [53].

In addition to their known antioxidant properties, the catechins utilize many alternate neuroprotective mechanisms of action, including, iron chelation to protect the accumulation of iron in areas of the brain and free radical damage to brain cells are believed to be the major damaging factors responsible for many neurodegenerative disorders, modulation of pro-survival genes, the induction of protein kinase (PKC) signaling pathway, and elicit effects in both the primary neurodegenerative pathway, post ischemia and the subsequent neuroinflammatory cascade [54,55].

2.2.4. Cardiovascular Diseases

As reviewed by Wolfram, several intervention studies have demonstrated that green tea catechins containing 200–300 mg EGCG will exert beneficial effects on cardiovascular and metabolic health by decreasing oxidative stress which participates in the pathogenesis of cardiovascular disease [56]. A cohort study done by Kuriyama, *et al*, in Japan demonstrated that consumption of green tea was associated with reduced mortality due to cardiovascular risks [57]. Another study from the same country has also showed a reduced incidence of stroke among individuals who consumed green tea [58]. Mechanisms involved may include inhibition of angiotensin-converting enzyme activity by green tea polyphenols (when the enzyme is inhibited angiotensin I will not be converted to angitoensin II and this in turn lowers the blood pressure of individuals), increased nitric oxide production by endothelial cells, and improved

endothelium-derived nitric oxide bioactivity and suppress blood pressure [6].

2.2.5. Non-Alcoholic Fatty Liver Disease (NAFLD)

The development of NAFLD is attributed to obesity and insulin resistance that cause excess hepatic lipid accumulation and increase the vulnerability of the liver to hepatotoxic insults such as oxidative stress and inflammatory responses [59]. Green tea, likely through its catechins, is the best documented plants that have been used in the prevention of liver disease [59,60]. Mice model study has also demonstrated that green tea extract (GTE) intake was associated with hepatic steatosis and lower serum enzyme (alanine aminotransferase and aspartate aminotransferase) activities suggesting that GTE protects against fatty liver disease [61].

2.2.6. Lung Injury

Animal model studies on mice have indicated that GTE reduced carrageenan induced lung injury and infiltration by polymorphoneuclear cells [62]. Another study on cigarette smoke exposed mice also indicated that administration of GTE was able to abolish alveolar space enlargement and goblet cell hyperplasia. Moreover elevated activities of superoxide dismutase and catalase activities induced due to cigarette smoke were returned to the normal state after the administration of GTE [63].

3. Adverse Effects of Green Tea

Although green tea has several beneficial effects on health its effect is dose dependant. Higher doses may cause some unknown adverse effects and the effects of green tea catechins may not be similar in all individuals. The side effects of green tea overconsumption may be related to its caffeine content, presence of aluminum and its effect on iron absorption [5]. A study by Morita, *et al*, in Japan on the effect of oral green tea extracts (GTE) in cancer patients, showed that green tea in adult cancer patients has dose-limiting side effects on gastrointestinal complaints (abdominal bloating, dyspepsia (impaired digestion), flatulence, nausea, and vomiting) and central nervous system stimulation (agitation, dizziness, insomnia, tremors, and restlessness). According to this study the maximum-tolerated dose was 4.2 g/m^2 once daily or 1.0 g/m^2 three times daily [64]. Another study on rats showed that the adverse effect level for green tea catechins was 1200 mg/kg/day for males and for females. Female rats showed undesired weight loss at a dose of 400 mg/kg/day but there were no treatment related side effects of hematological, blood chemistry and urinalysis parameters [65]. Pregnant and breastfeeding women should drink no more than one or two cups per day, because caffeine can cause an increase in heart rhythm. In general the average cup of green tea contains from 10-50 mg of caffeine, and over-consumption may cause irritability, insomnia, nervousness, and tachycardia [9].

4. Conclusion

Different studies reviewed in this manuscript showed that green tea has effects in carbohydrate metabolism so thatit can be a good candidate in the alleviation of diabetes mellitus. Inhibition of carbohydrate digestion and glucose absorption, stimulation of pancreatic cells to produce insulin, increasing insulin activity and actions on the liver to maintain glucose homeostasis are the mechanisms of green tea polyphenols to prevent diabetes mellitus. Both human and animal model studies also showed that green tea has different health benefits such as anti-cancer activity, prevention of neurodegenerative diseases, prevention of cardiovascular disorders, amelioration of lung injury, antimicrobial and antiviral activity and prevention of NAFLD. Some of the mechanisms involved in the prevention of these diseases include antioxidant activity of polyphenols, their involvement in different signal transduction and their ability to inhibit cancer proliferation and metastasis. Together with its health benefits dose dependant adverse effects of green tea were observed in the gastrointestinal tract, liver and nervous system. But these side effects are absent or minimum if present. Such advantage of green tea is increasing interests to use it as an alternative medicine for different types of chronic diseases. Hence, further researches on determination of effective therapeutics dose, mechanism of action and any side effects must be conducted.

Statement of Competing Interest

The authors have no competing interests.

List of Abbreviations

AMPK: Adonesine Monophosphate -Activated Protein Kinase
Aβ: β Amyloid Peptide
cAMP: Cyclic Adonesine Monophosphate
EC: Epicatechin
ECG: Epicatechin Gallate
EGC: Epigallocatechin
EGCG: Epigallocatechin Gallate
FAK: Focal Adhesion Kinase
GC: Green Catechin
GLUT: Glucose Transporter
IDDM: Insulin Dependent Diabetes Mellitus
IGF-IR: Insulin Like Growth Factor I Receptor
MAPK: Mitogen Activated Protein Kinase
MMP: Matrix Metalloproteinase
MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
NAFLD: Non-alcoholic Fatty Liver Disease
PD: Parkinson's disease
PKC: Protein Kinase c
SGLUT: Sodium Dependant Glucose Transporter
T2DM: Type 2 Diabetes Mellitus

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