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Exploring antioxidant potential of green tea catechins (camellia sinensis) against type 2 diabetes mellitus

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Green Tea (Camellia Sinensis) powder is called as mtacha. The richest source of polyphenols that provide some additional health benefits beyond the basic needs. Green tea is rich in catechin, thioflavin, flavonoids, and other bioactive components. Moreover, green tea catechins are involved in many biological activities such as anti-oxidation and modulation of various cellular lipid and proteins. In addition, it has been associated with the positive effects in the treatment as well as management of diabetes. Previous studies reported that daily consumption of tea catechins may help in controlling type-2 diabetes. The purpose of current review is to elaborate the role of green tea catechins extracted from the Camellia sinensis plant in the management of type 2 diabetes. Green Tea derived molecule has antioxidant properties which scavenges the free radicals and regulate the insulin secretion.

Keywords: Green tea, camellia sinensis, diabetes, polyphenols, Catechins.

INTRODUCTION

In this modern era, intake of saturated fat, processed foods and refined carbohydrates is very common. This situation is increasing at an alarming rate and contributes in metabolic disorders such as obesity, diabetes, insulin resistance as well as CVDs. Diabetes mellitus is a heterogenous disorder that occur due to the impaired secretion of hormones as well as dysfunction in the metabolism of carbohydrates and lipids (Alam et al. 2015). According to the world health organization 20% of the population above 18 years old is suffering from diabetes mellitus. Moreover, if this situation continues at the same rate 553 million will be in 2030. Hyperglycemia and associated complication contribute in high morbidity and mortality rate. Previous researches documented as camellia sinensis (green tea) extract has different biological activities due to the presence of polyphenols (Al-Attar & Zari, 2010).

1.0.1 Role of green tea (camellia sinensis) in diabetes:

Diabetes mellitus (DM) is a metabolic disorders which is discovered by elevated levels of glucose in blood.The prevalence of the disease is increasing daily worldwide. According to International Diabetes Federation (IDF) DM prevalence is estimated to increase from 8.4% to 9.9% in 2045 (Cho et al. 2018). It elevates the risk of other chronic diseases such as depression, kidney disease, cancers, heart diseases and high lipid levels (Thibaut, 2018; Zheng, et al. 2018).

Due to the increasing rates of DM it has a great impact on public health and lead to a social and financial load all over the world (Pietzke, 2019; Larsson et al. 2018). Therefore prevention, management, and treatment are required for DM to help to reduce hazard of DM and improve public health. Other than water the most consumable drink on the second number is tea. In comparison to black tea and oolong tea, green tea has more benefits (Huang et al. 2018; Choghakhor et al. 2017).

1.0.2 Chemical composition of green tea:

Camellia sinensis (green tea) incorporates 4000 active components and one-third of them are by polyphenols. Other components are alkaloids such as caffeine, theophylline and theobromine. Amino acids, carbohydrates, proteins, chlorophyll, volatile organic compounds, fluoride, aluminium, minerals and trace elements are also present. Major Polyphenols are flavonoids including catechins (Chawla et al. 2017).

Catechins are considered as family polyphenolic antioxidants. Polyphe- nols are mainly divided into categories of phenolic acids, flavonoids and lignans due to their carbon structure.Flavonoids are the most rich polyphenols in the diet. Flavonoids are separated into flavones, flavonols, isoflavones, anthocyanins, flavanols, the proanthocyanidins and flavanones.Soy in isoflavones, citrus fruits in flavanols citrus, fruits and vegetables in flavonols, are considered as their major food sources. Catechins are considered mainly as flavones. Catechin types include: catechin, gallocat- echin, catechin-3-gallate, Gallocatechin 3- gallate, epicatechin, epigallo catechin, epicatechin 3-gallate, epigallo catechin-3-gallate. Ctechins are presant in abundant amount in green tea. EGCG is the most abundant and strongest catechins in the green tea and consist of 65% of the total content (Alipour et al. 2017).

The catechins found in Green Tea have numerous medical advantages in body weight control and diabetes prevention. Experimental studies have demonstrated that green tea concentrate can expand insulin affectability and lower blood glucose levels in diabetic mice, while in people, epidemiological examinations propose thatutilization of GT might decrease the frequency of diabetes. Various randomized controlled preliminaries have revealed that every day utilization of GT may upgrade oral glucose resistance in individuals just as diminishing fasting plasma glucose and glycosylated hemoglobin (HbA1c) levels in individuals in danger of diabetes (Yu et al. 2017).

Research was done to see the effect of green tea on the wristar rats in which herbal green tea extract from white mangrove leaves with concentration of 100, 200 and 300 mg/200g BW/day, and positive control, i.e. glybenclamid (0.09 mg/200 g BW/day) was given to diabetic rats injected with Streptozotocin (STZ) and Nicotinamide (NA). The rats were observed on day 0, 5, 10 and 15. Positive results were seen by the herbal green tea extract from white mangrove leaves which decreased the blood glucose level of diabetic rats. The effective extract dose that decreased the blood glucose level of diabetic rats was 300 mg/200 g BW, which is comparable to the effect produced by glybenclamid (antidiabetic medicine) (Hardoko et al. 2019).

Another study was done to check the efficacy of Epigallocatechin 3-gallate (EGCG) from green tea may decrease plasma glucose and reduce the complications of diabetes. Dietary EGCG was tested in C57BL/6 mice that were placed on a high-fat diet with or without ECGC for 17 weeks and compared to a control group placed on low-fat diet for the same period. Weight gain and fasting blood glucose were taken. Supplementation of high fat diet with dietary EGCG significantly reduced weight gain, plasma glucose, insulin level, liver and kidney weight. This study demonstrated that EGCG has the potential to help control hyperglycemia, reduce weight, and alleviate diabetes complications (Sampath et al., 2017; Dower et al.2015)

The purpose of current review is to explore the role of green tea catechins extracted from the Camellia sinensis plant in the management of type 2 diabetes and associated consequences. Green tea is widely used beverage in the worldwide. Due to the presence of bioactive components, it has antioxidant, anticancer, and anti-inflammatory properties. Antioxidants scavenge the free radicals and help in the management of metabolic disorders as well as associated complication.

2.0 LITERATURE REVIEW

2.1 Comprehensive overview of Epigallocatechin-3-Gallate (EGCG) reaction on diabetes

Green tea extract (GTE) has many naturally occurring biological components of which polyphenolic epicatechins (ECs) are

predominantly active (Fukino et al. 2005). These include (–)-epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin-3-gallate (ECG), and (–)-EC (Mackenzie et al. 2007). Daily consumption of green tea by patients with diabetes for several months is ineffective for ameliorating diabetes-related parameters, including blood glucose levels, HbA1C levels, insulin resistance, and inflammation markers (Nagao et al. 2009). However, some retrospective cohort studies in Japan and Taiwan suggest that green tea is effective against type 2 diabetes (Iso et al. 2006) (Wu et al. 2003).

Previous studies revealed that EGCG, the most abundant form of catechin in green tea, inhibits adipocyte proliferation and differentiation, increases cellular defense against oxidative stress, and blocks sodium-dependent glucose transporter 1 (SGLT1) and lipid micelle formation in the intestine (Hung et al. 2009) (Wang et al. 2009) (Wu et al. 2005). Though, the concentration of EGCG required to decrease the number of pre-adipocytes and adipocytes may too high to be consumed by humans without considerable side effects (Sung et al. 2010). Moreover, green tea catechins have the molecular structure to scavenge oxygen-free radicals, their effectiveness in biological systems has not been clarified. Some reports demonstrate that EGCG is a pro-oxidant and harmful for beta-cell survival in streptozotocin-induced diabetic rats (Yun et al. 2006). Blockage of SGLT1 and lipid micelle formation is the most important and strongest mechanisms for gallate catechinsto exert their effects against diabetes. Although, there is a limitation to use gallate catechins as a remedy for this metabolic disease. A lower concentration of gallate catechins than those that block SGLT1 blocks sodium-independent glucose transporters (GLUTs) in various tissues. Although dietary glucose absorption into the circulation is mainly performed by intestinal SGLT1 as well as by some GLUTs, cellular glucose uptake as an energy source in most cells is performed by insulin-dependent (GLUT4) and insulin-independent GLUTs. Maximum blood EGCG concentrations are achieved 90 minutes after green tea ingestion and considerable concentrations of EGCG are present in circulation for hours. This means that the effects of EGCG in the alimentary tract remain only for 1 hour, but the effects in circulation remain for several hours. Blocking cellular glucose uptake during the postprandial period resembles insulin resistance, eventually leading to failure of beta cells to secrete more insulin (Park et al. 2009).

The discrepancy among human epidemiological data for the anti-diabetogenic effects of green tea catechins can be attributed to several reasons. As shown in Table 1, one cup of green tea contains approximately 100 mg EGCG in 1 g GTE. This quantity easily makes blood concentrations of EGCG about 100nM in a fasting state, and a concentration that can inhibit various GLUTs. In addition, there are significant inter individual variations in blood concentrations of EGCG after green tea ingestion, suggesting that there are difficulties in controlling EGCG concentration in experiments involving humans, as the meals make absorption of the GTE slower (Nakagawa et al. 1997). By contrast, animal experiments are more controllable and show that rats have the lowest oral bioavailability of EGCG compared with mice and humans (Table 1); in fact, the oral bioavailability of EGCG is lower in mice than that in humans (Lee et al. 2002). Therefore, during animal experiments, oral ingestion of GTE or EGCG only shows the intestinal effects but not the effect in circulation. Thus, the results may be more interpreted as positive results against diabetes than those obtained from humans (Chen et al. 1997). Therefore, to extend the intestinal effects of EGCG and to decrease the circulatory effect of EGCG, entry of EGCG into circulation should be blocked, at least for using EGCG to treat type-2 diabetes (Lambert and Yang, 2003).

Table 1: Species variation in the amount of EGCG to be absorbed into circulation after IG ingestion of EGCG*

	IG ingestion of EGCG	Blood concentrations	Refs
Rat	75 mg/kg	35nM	21
Mouse	75 mg/kg	280nM	22
Human	2 mg/kg	170nM	20
	525 mg in GTE/man	4.4 μM	19

*A cup of green tea contains approximately 100 mg EGCG in 1 g GTE. EGCG, (–)-epigallocatechin-3-gallate; GTE, green tea extract; IG, intragastric.

2.2 EGCG EFFECT IN METABOLIC TISSUES

2.2.1 Impact of green tea consumption on the intestinal effect of EGCG

Kobayashi et al. (2000), indicated that the 50% of rabbit intestinal glucose uptake which was 390μM block by the 50% inhibitory concentration

(Ki) of ECG (Kobayashi et al. 2000). Park et al. (2013), found that the EGCG in the human colon adenocarcinoma CACO-2 cells affected by 50% inhibition of glucose uptake was around 100μM, instead of inhibitory effect was observed at 10μM (Park et al. 2013). Moreover, concentration of EGCG >100 are compulsory to obstruct lipid micelle formation (Raederstroff et al, 2003). In addition, Raederstroff et al. (2003), also concluded that for the inhibition of 50% cholesterol absorption among rats 500-mg EGCG/kg body weight is compulsory. Park et al, (2013), revealed that if EGCG is applied as a constituent of an intact GTE then the EGCG effect can be enhanced, whereas the constituents of GTE also protect EGCG from degradation and ECG also gives the same effect as EGCG (Park et al, 2013). Utilization of GTE not EGCG means that the reduction of the amount of EGCG used (Park et al. 2009). Bae et al, (2013), observed that GTE consist of at least 100mg EGCG which might be compulsory to exert an effect on lipid micelle formation as well as on SGLT1 in the gastrointestinal tract (Bae et al. 2013). Opportunely, this extent would not block polypeptide and amino acid transporters in the intestine (Kobayashi et al, 2000). Thus, it would be ample to have one cup of green tea just before the meal. Though, as shown in Table 1 and 2, with normal daily consumption of green tea, plasma concentration of EGCG could easily reach 100nM. By the level of this concentration might be cause a shortage of glucose in cells due to inhibition of numerous GLUTs among tissues (Park et al. 2014). This situation originates a load on beta cells and glucose-deficient cells to reduce the blood glucose level during the postprandial period.

2.2.2 Effect of EGCG on oxidative stress

Cell viability is impaired significantly when preadipocytes are treated with 50 μM EGCG, but recover by treatment with the antioxidant vitamin E (Sung et al. 2010). This means that this concentration of EGCG may act as a pro-oxidant (Yun et al. 2006). Low cell viability was not observed until the concentration of EGCG is 10 μM. These phenomena are also true for mature adipocytes; when 50 μM but not 10 μM EGCG was applied for 4 days during the early3T3-L1 adipocyte differentiation (Days 0–3) or during the maturation period (Days 4–7), cell viability and cellular triglyceride accumulation decreased, and intracellular reactive oxygen species (ROS) accumulation increased. This ROS accumulation caused by EGCG may be linked to the gallate moiety in the EGCG molecule, as catechin does not possess the gallate moiety and has no effect on intracellular ROS concentrations (Arita et al. 1999). The aspect of peroxisome proliferator-activated receptor γ is downregulated in mature adipocytes, correspondingly downregulated adiponectin; it happens when EGCG increases intracellular ROS concentrations (Matsuzawa et al. 2004). Besides this, the expression of retinol binding protein-4 (RBP-4) may be upregulated. The expression of RBP-4 is partially elevated by 50 μMEGCG but not totally cured by co-treatment with EGCG as well as vitamin E. In addition, it was observed that increased ROS generation could be constituent for EGCG-induced RBP-4 upregulation (Hung et al. 2005). Furthermore, increased expression of RBP-4 was also recovered by co-treatment of methyl pyruvate with the combination of vitamin E, which is a cellular energy source by passing GLUT and glycolysis (Wu et al. 2005). Lin et al. (2005), revealed that impaired glucose uptake by EGCG may also a contributory mechanism for RBP-4upregulation. In human adipocytes, secretion of RBP-4 may be consistently increased due to 10 μMEGCG; in addition 50 μMEGCG may be needed to induce intracellular ROS accumulation (Lin et al. 2005). Moon et al., (2007), analyzed that elevated level of RBP-4 expression and secretion is also happened due to ROS-independent mechanism which blocks glucose uptake. Thus, RBP-4 signaling could be increased by the long-term application of lower EGCG concentrations (Moon et al. 2007). Park et al. (2014) indicated that, the EGCG concentration dependency of intra-cellular ROS accumulation in adipocytes was consistent as compare to the previous studies. Yin et al. (2009), revealed that EGCG-induced ROS generation does not show tissue specificity at the higher EGCG concentration level (Yin et al., 2009). Moreover, it would be useful for the treatment of obesity or may be for the recovery of certain localized cancer if it targets only specific tissue (Li et al. 2009). Besides this, in human plasma higher concentrations of EGCG could not be achievable without the adverse effects (Chow et al., 2001). That's why the pro-oxidative nature of higher concentrations of EGCG is not a defensible mechanism for the cure of obesity as well as cancer (Sakurai et al. 2009). Salah et al. (1995) describes reports related to the EGCG concentration dependencies in the EGCG-

oxidative stress relationship such as nano-molar concentrations of EGCG have an antioxidant action whereas micro molar concentrations of EGCG have a pro-oxidant action (Salah et al. 1995). Although, the pro-oxidative activity of EGCG can take place at concentrations <50 μM, withal at about 1μM concentrations previously damaged by streptozotocin18 or hippocampal neuronal cells among beta cells (Yin et al. 2009). Mukai et al. (2005), suggested that EGCG always prompt ROS stress in cells which cannot be happen if the cell's scavenging system is intact. Thus, EGCG action against oxygen-free radicals may be modified by the kinds of radicals' stimulants included cellular conditions and also the exposed time to EGCG (Oikawa et al. 2003). Green tea catechins can deploy their impact as both antioxidants and pro-oxidants. The existence of the catechol (C) ring, the gallate(G) ring, the pyrogallol (P) ring, or the sorcinol (R) ring is vital for the antioxidants activities of catechins (Fig.1) (Hirasawa and Takada, 2004). Furthermore, the P ring is also play an important role for the antifungal action of catechins (Nicoli et al. 2000). Moreover, the pro-oxidative activity of catechins is attributed to their potency from auto-oxidation and peroxidase-catalyzed oxidation(Nicoli et al. 2000).

2.2.3 Effect of EGCG on cellular glucose uptake

Nomura et al. (2008), observed that to increase RBP-4 secretory signaling from the mature adipocytes is the effect of EGCG to reduce cellular glucose uptake (Nomura et al. 2008). Previous studies revealed that cellular glucose uptake in various tissues is impaired in the insulin-resistance state, making beta cells secrete more insulin and causing early beta-cell exhaustion throughout life (Nomura et al., 2008). Nomura et al. (2008), stated that Impaired glucose uptake by EGCG can be observed at EGCG concentrations < 10 μM (Nomura et al. 2008). Park et al. (2009, also analyzed that EGCG inhibits cellular glucose uptake at 100nM in myocytes, adipocytes, and beta cells, and 1 μM in hepatocytes, which is easily achievable in human plasma by oral intake of two to three cups of greentea24(Table 1) (Park et al. 2009). These findings are consistent with the results obtained in other tissues by previous observations, suggesting that most tissues possessing either of various GLUT scan be hindered with glucose use in the presence of EGCG (Naftalin et al. 2003) (Strobel et al. 2005) (Johnston et al. 2005). Moreover, the adipokine RBP-4 is secreted from mature adipocytes when adipocytes detect deficient glucose uptake (Yang et al. 2005). In addition, in the fasting state, secretion of RBP-4 stimulates hepatic glucose output and inhibits muscular glucose uptake, probably to spare blood glucose levels (Graham and Khan, 2005). Therefore, abnormally increased expression and secretion of RBP-4 may elicit insulin resistance. Morikawa et al. (2007). resulted that; it would be difficult to normalize blood glucose levels by insulin during the postprandial period if plasma EGCG hinders most tissues to uptake glucose (Morikawa et al. 2007). Slavic et al. (2009), reported that the action of EGCG on GLUTs maybe related to its gallate moiety, because ECG and genistein also have a blocking effect toward GLUTs, and ECG is the more potent (Slavic et al. 2009).The mechanism of EGCG to inhibit cellular glucose uptake may be either blockade of insulin signaling or direct competition with glucose for GLUTs (Srobel et al. 2005). Park et al. (2009), analyzed that insulin-induced Ser473 phosphorylation of protein kinase B remained unchanged in the presence of EGCG in hepatocytes, adipocytes, myocytes, and beta cells (Park et al. 2009). The impact of this EGCG action on cellular glucose uptake can be observed in vivo and it may observed that EGCG at about 1 μM in blood acutely elevates blood glucose and insulin levels during the oral glucose tolerance test (OGTT) in humans (Park et al. 2009). Park et al. (2009), also confirms that daily intake of green tea is clinically relevant (Park et al. 2009).

2.2.4 Unmediated KATP channel modulation of EGCG

The plasmalemmal KATP channel is an octamer that includes four inwardly rectifying potassium (Kir) 6.2 and four sulfonylurea receptors (SURs). EGCG inhibits the activity ofKir6.2/SUR1 (beta-cell type) in Xenopus oocytes expressing KATP channels, with an inhibitory concentration 50 (IC50) of about 140 μM, which is also observed in Kir6.2/SUR2A (cardiac type) and Kir6.2/SUR2B (vascular type). The inhibitory potency ofEGCG was similar to the IC50of EGCG for voltage-dependent potassium (Kv) 1.5 channels (101 μM) (Choi et al. 2001). Kajiya et al. (2001), indicated that ECG is three times more effective for this inhibition than EGCG, and nongallate catechins did not have any effect.

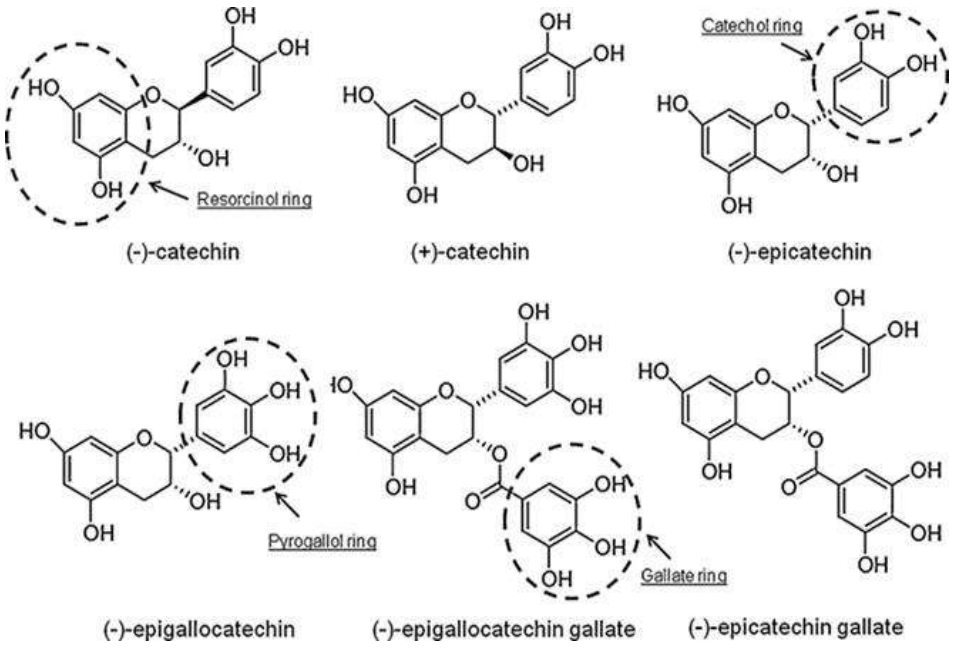

Figure1: Naturally occurring catechins extracted from green tea.

Table 2: Dose-dependent effects of EGCG

Functions	Concentrations, μM	Refs	Catechins
SGLT1 block	>1	23 13	<ECG 13 (only GC)
GLUTs block	<1	24 39 16 40	<ECG (only GC)
Micelle formation block	>100	14	≈ECG (probably)
Alcohol absorption block	>100	23	≈ECG (only GC)
In KATP channels			
PIPs sensitivity block	<1	48	only EGCG
ATP sensitivity block	>1	48	only EGCG
Direct channel block	>10	46	>EGC, <ECG
In adipocytes			
Increased RBP-4 secretion	>1	15	>ECG
Increased ROS generation	>10	15	>ECG
Decreased adipocyte survival	>10	15	>ECG
Decreased PPAR- _ expression	>10	15	>ECG
Decreased adiponectin expression	>10	15	>ECG

*ATP, adenosine triphosphate; ECG, (–)-epicatechin-3-gallate; EGC, (–)-epigallocatechin; EGCG, (–)-epigallocatechin-3-gallate; GC, gallatecate- chin; GLUTs, glucose transporters; KATP, ATP-sensitive K+; PIPs, phosphatidylinositol polyphosphates; PPAR- _, peroxisome proliferator-activated receptor- _; RBP-4, retinol binding protein-4; ROS, reactive oxygen species; SGLT1, sodium-dependent glucose transporter 1.

Moreover, the IC50of EGCG for channel inhibition was about 20 μM with Kir6.2 μC36 channels, which are the channel pore forming subunits. Besides this the absence of the SUR subunits suggests that the regulatory subunit SUR may hinder the inhibitory action of EGCG on Kir6.2.

The principal mechanism for Kir6.2 blockade of gallate catechins may be due to the interaction between EGCG and ECG with lipid bilayers

embedded in the KATP channels, because the interaction of catechins with lipids is stronger when the catechol ring and gallate ring are both present as in ECG (Kajiya et al. 2001). Baek et al. (2005), documented that a small contribution of the pyrogallol ring is also detected45because EGC can inhibit KATP channels, but only slightly (Baek et al. 2005).

2.2.5 Change in KATP channel sensitivity to Phosphatidylinositol Polyphosphates and ATP by EGCG

The KATP channel activity is inhibited by ATP through theKir6.2 subunit and activated by Mg ADP through the SURsubunit (Ashcroft, 2005). Phosphatidylinositol polyphosphates (PIPs) such asPIP2 and PIP3 activate the channel through the Kir6.2. The KATP channels play crucial roles in glucose-stimulated insulin secretion in beta cells and protect cardiac myocytes from metabolic inhibition. Although direct KATP channel inhibition was accomplished by gallate catechins such as EGCG and ECG, the reducing effect of the GTE on KATP channel ATP and PIP sensitivity only occurred in EGCG, which additionally has the hydroxyl group (–OH) on the pyrogallol moiety (Jin et al. 2007). The ATP sensitivity of the KATP channel in the presence of 10 μM EGCG was 10 times less than that in the absence of EGCG (13.4 μM vs. 120 μM). EGCG did not eliminate the bound ATP molecules from the channels but inhibited channel binding of ATP. The adenosine monophosphate (AMP) and adenosine diphosphate blocks for KATP channels were not hindered by EGCG. The γ phosphate tail of ATP is bound to R50 in the N terminal of Kir6.2, and ATP binding to Kir6.2 is facilitated by incorporating SUR1. Our results show that EGCG may inhibit the facilitating function of SUR1 (Park et al. 2009). Moreover, the decrease in the channel PIP sensitivity caused by EGCG appears even at 1 μMEGCG. This may have occurred due to direct hindrance of the PIP interactions with their binding sites on Kir6.2 by EGCG. The mechanism may be due to the negative charges of EGCG and the positive charges on the PIPs binding sites of the channels against the negative charges of PIPs. It would require a serious involvement of EGCG in KATP channel gating kinetics if the two major modulators ATP and PIPs have a limitation to play their actions (Park et al. 2009).

CONCLUSION

Impact of green tea as an anti-oxidative can be a substitute for other well-known antioxidants. Blockage of adipocyte differentiation and proliferation by EGCG is not practicable in humans because intolerable plasma concentrations of EGCG are required. Green tea intake to exert beneficial intestinal effects sufficiently elevates blood EGCG levels to inhibit cellular glucose uptake. Numerous past experimental data showed that the downstream phenomena for the effect of EGCG on inhibiting cellular glucose uptake, such as elevated AMP-activated protein kinase activity. Furthermore, EGCG may be beneficial for cancer recovery due to its inhibitory action on cancer-cell glucose utilization. Blocking the absorption of green tea gallate catechins, which block cellular glucose uptake in the circulation, may be a clue for green tea use against diabetes. Thus, it shows that the prolongation of their effects in the intestine. Polyethylene glycol-3350 or poly- -glutamate dramatically and selectively block entry of gallate catechins into circulation, prolonging their intestinal effects. Human clinical trials should proceed to develop a safer treatment tool against type 2 diabetes and related obesity.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

S.B. and F.I. conceived of the presented idea. F.I. developed the theory and performed the computations. F.I. and A.I. verified the analytical methods. F.I. encouraged A.I. to investigate the role of green tea catechins extracted from the Camellia sinensis plant in the management of type 2 diabetes and supervised the findings of this

work. All authors discussed the results and contributed to the final manuscript.

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