PROTECTIVE ROLE OF GREEN TEA ON DIABETIC NEPHROPATHY—A REVIEW

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Abstract: Nowadays, diabetes and diabetes-mediated dysfunctions are overwhelming at every nook and corner of the world which has been a sober concern to the current health care professionals. However, chronic hyperglycemic subjects often suffer from hypertension, atherosclerosis, insulin resistance, brain injury, and other dysfunctions due to high glucose level which lead to kidney failure. Altogether, diabetic nephritis, fibrosis, stenosis, iron overload, and hypertrophy may often escort towards diabetic nephropathy. Furthermore, hyperglycemia-generated free radical-mediated oxidative stress plays the central role to aggravate the condition. Oxidative stress also inhibits production of several natural antioxidant genes like Nrf2, Sirt1, PGC-1α, superoxide dismutase, and catalase. Similarly, production of pro-inflammatory cytokines such as IL, TNF-α, MIP, α-SMA, and NF-κβ has been observed high in the diabetic subjects. High glucose inside the body also activates mitogen-activated protein kinase family and facilitates diabetic nephropathy. On the other hand, green tea (GT) is a widely used drink which has several protective functions. This plant possesses multiple catechin, theoflavins, flavonoids, flavinol, caffeine, and other biological active components. Thus, this review will try to explain how GT-derived molecules prevent diabetic nephropathy, both by reducing free radical generation and improving insulin secretion. The molecular interactions between antioxidant genes and free radical-mediated oxidative stress will be explained.

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ABOUT THE AUTHORS

Our group endeavors to explore the role of oxidative stress in different diseases and the potential role of antioxidant derived from natural sources. In our current study, we tried to identify the role of green tea as a potential source of antioxidant against diabetic nephropathy. We focused on possible mechanism by means of which the molecules from green tea can suppress the oxidative damage as well as how it can restore the normal antioxidant level in the system. Our study was led by Sarif Mohiuddin, lecturer at Pioneer Dental College and Hospital. His area of specialization is Diabetology, Natural Antioxidant, and Angiotensin-II. He has completed his MBBS from Dhaka University and has been awarded FRSPH from The Royal Society for Public Health (RSPH) UK. He has also completed certified course on Diabetology, and extension of diabetic Care Course from BIRDEM Hospital, Dhaka, Bangladesh.

PUBLIC INTEREST STATEMENT

Diabetes is one of the most growing concerns of the world, and everyday more and more people are getting affected by diabetes. Thus, the risks of diabetes associated diseases are also on the rise. diabetic nephropathy is one of the most common diabetes-associated diseases, and just by developing a small habit people who are suffering from diabetes can avoid diabetic nephropathy. In this study, we tried to emphasize on how green tea is conducive to prevent diabetic nephropathy.
through activation of AMPK and mTOR. Finally, this study will try to correlate the possible therapy strategy and molecular mechanism of GT to reduce the pathogenesis of diabetic nephropathy.

**Subjects:** Bioscience; Health and Social Care; Medicine, Dentistry, Nursing & Allied Health

**Keywords:** diabetic nephropathy; free radicals; AMPK; Nrf2; Sirt1; green tea

1. Introduction

In this current era, it is often heeded that consumption of high fat diet and fructose-containing beverages, cigarette smoking, alcoholism, less or no physical exercise are rising in urban areas at an alarming rate which lead to several disorders like insulin resistance, obesity, hyperlipidemia, metabolic syndrome, and diabetes (Guh, Zhang, Bansback, Amarsi, Birmingham, & Anis, 2009). Diabetes, a heterogeneous disorder which is primarily characterized by impaired hormone secretion, in addition it is also caused by several impairments like protein, fat, and carbohydrate metabolism by either insufficient amount of insulin production or reduced sensitivity of tissue to insulin (Pistrosch et al., 2015). According to WHO report 2011, 9% of the total population above 18 years are suffering from Diabetes Mellitus (DM) (Alwan, 2011). If this scenario continues, the projected number of diabetic patients would be approximately 552 million in 2030 (Reno et al., 2015; Whiting, Guariguata, Weil, & Shaw, 2011). Evidences also documented that around one-third of diabetic subjects suffer from diabetic nephropathy (DN) resulting in the overall cost of the treatment beyond reach (Atkins & Zimmet, 2010).

DN is being considered as one of the major microvascular complications of DM and it has been claimed as a primary cause of end-stage renal diseases (Jin et al., 2012). Hyperglycemia-induced DN creates long-term complications which lead to high mortality and morbidity rate (Kim, Davis, Zhang, He, & Mathews, 2009). Several studies suggested that diabetes is also affiliated with other complications like retinopathy, cardio-myopathy, neuropathy, atherosclerosis, systemic hypertension, stroke, coronary ischemia, and most importantly diabetic kidney failure (Kupelian, Araujo, Wittert, & McKinlay, 2015; Rutter & Nesto, 2011). However, study also reported that renin-angiotensin system (RAS) plays a pivotal role in the pathogenesis of DN (Peti-Peterdi, Kang, & Toma, 2008). In the diabetic subjects, hyperglycemia often stimulates pro-inflammatory cytokines, neutrophil infiltration, and other pathogenic factors (Chow, Ozols, Nikolic-Paterson, Atkins, & Tesch, 2004) which generate reactive oxygen species that further exacerbates the situation (Ha, Yu, Choi, Kitamura, & Lee, 2002). On top of that, recent studies proved that diabetic subjects often lack antioxidant activities which may begin defenseless oxidative stress and progress diabetic complexity (Nourooz-Zadeh et al., 1997; Santini et al., 1997). Sometimes hypertension may develop DN by influencing inflammatory cytokines as well as generating free radicals (Lopes de Faria, Silva, & Lopes de Faria, 2011). In fact, DN kidney mostly lacks of AMPK/Sirt1 expression on experimented animal model (Chuang et al., 2011). Besides, diabetic kidneys also suffer from low level of TIMP3 and FoxO1; conversely, STAT1 level was noticed high (Fiorentino et al., 2013).

In recent years, green tea (GT) has become a very popular drink in several regions like South-East Asia (Wolfram, 2007). GT extracts possess several antioxidant group of molecules like flavonoids, flavonols, polyphenols, theaflavins, tannins and other important components (Lin, Juan, Chen, Liang, & Lin, 1996) which control several biological mechanisms (Polychronopoulos et al., 2008) like increased expression of antioxidant genes (Nomura et al., 2015), protect glomerulos (Peng et al., 2011), promote insulin sensitivity (Nomura et al., 2015), suppress pro-inflammatory cytokines (Kim, Murakami, Miyamoto, Tanaka, & Ohigashi, 2010), prevent RAS (Kurita, Maeda-Yamamoto, Tachibana, & Karnei, 2010), augment insulin production (Ortsätter, Granqvist, Wolfram, Kuehn, & Sjöholm, 2012), decrease α-amylase level (Gao, Xu, Wang, Wang, & Hochstetter, 2013), lower lipids levels (Ramadan, El-Beih, & Abd El-Ghffar, 2009), prevent free radical generation (Yokozawa, Noh, & Park, 2012), cyto-protective (Shin, Chung, Lee, & Kim, 2009), improve and protect podocyte production (Peixoto et al., 2015), enhance mitochondrial biogenesis (Rehman et al., 2013), stabilize cellular signaling (Kim, Quon, & Kim, 2014), protect genetic materials (Glei & Pool-Zobel, 2006), and inhibit cancer (Darvesh & Bishayee, 2013). In addition, experiment revealed...
that GT extract was able to reduce proteinuria on tacrolimus-induced nephrotoxic mice (Back et al., 2015). Reduced p-ERK1/2, MAPKp38, p-JNK, and p-AKT have been showed when EGCG 50 mg/kg/day was given to rats-induced crescentic glomerulonephritis (Ye et al., 2015). Similarly, another study described that long-term dietary antioxidant treatment lowers kidney inflammatory cytokines and oxidative stress markers on diabetic mice (Park, Park, & Lim, 2011). Restoration of antioxidant genes can be targeted as pharmacological approach for DN which can help in cell survival against diabetes-mediated dysfunctions (He et al., 2010). Therefore, this review will try to make a correlation among hyperglycemia, antioxidant genes, free radicals, and GT.

2. Pathology of diabetic nephropathy

Diabetes is often known as metabolic disorder which explains the inability of endocrine glands or hormonal secretion. Several approaches have been explained to develop diabetes inside a subject. Study described that diabetes is the outcome of either improper hormone secretion or insufficient and defective hormone production. However, it is also explained that improper Ca++ signaling or defective insulin mRNA are responsible for the development of diabetes (Kabir et al., 2015). Not only the clinical features of DN are 3P (Polyurea, Poly phasia, and Polydypsia) but also showed higher albumin elimination, abnormal glomerular filtration rate, and rapid decreasing renal functions which finally lead to end-stage renal failure. Besides, hyperglycemia may also induce oxidative stress by generating free radicals, advanced glycation end-products and activating protein kinase C to further aggravate diabetic kidney (Giacco & Brownlee, 2010). With the help of free radical, advanced glycation end-products (Lacmata et al., 2012) are formed that later interacts with its receptor RAGE and develop DN. It is suggested that blocking of RAGE or deletion of RAGE can be an effective approach in preventing diabetes-mediated complications at initial stage (Tan et al., 2010; Wendt et al., 2003). It has been evaluated that higher glucose in the body often stimulates diacylglycerol to increase the vascular permeability for inviting immune cell infiltration like neutrophil, monocyte, leukocytes, macrophage, and others. Taken together, protein kinase C also participates to activate local myofibroblastic cells which further secret collagen and extra cellular matrix that leads to kidney fibrosis. Furthermore, these pathways also regulate cell growth, cytokine and chemokine release, vasoconstrictions, apoptosis, and finally cell death (Noh & King, 2007). It was also noticed that RAS is highly responsible for DN by changing hemodynamic alteration and activating iNOS as well as endothelin (ET-1) in diabetic mellitus subjects (Har et al., 2013; Mohib et al., 2016; Ruggenenti, Cravedi, & Remuzzi, 2010). Likewise, hyperglycemia also found responsible for nephropathy by controlling blood flow and blocking small vessels (Elmarakby & Sullivan, 2012). Not only glucose or insulin is involved in the patho-physiology of DN, but family history and environmental factors are also responsible (Martini, Eichinger, Nair, & Kretzler, 2008). Patients who are suffering from DN found with excess accumulation of p62/SQSTM1 (Sequestosome 1) protein in proximal tubular cells from their kidney biopsy (Yamahara et al., 2013). Drug-induced kidney dysfunctions are on rise (Sagor, Mohib, Tabassum, Ahmed, & Reza, 2016) and these complications are making difficulties for diabetic patients to achieve an effective therapy.

3. Green tea history, traditional uses and its functional actives

The tea plant was first noticed in China and this plant was then cultivated by the Chinese traditional inhabitant from the ancient times (International Tea Committee, 2009). It has been reported that GT was first exported to Japan from India during seventieth century. Around 2.5 million tons of tea is produced currently and 20% of that leaves are being processed for GT which are generally consumed by USA, Europe, Asia, and some places of North Africa (Chacko, Thambi, Kuttan, & Nishigaki, 2010). Tea is the second most popular drink after water (Haidari, Shahi, Zarei, Rafiei, & Omidian, 2012). In last few decades, several beneficial properties on human health have been noticed from the consumption of GT (Cabrera, Artacho, & Giménez, 2006). Traditionally, tea is classified into GT and black tea. However, tea (Camellia sinensis) belongs to Theaceae family; oolong where GT is prepared from the young green leaves. On the other hand, black tea is made by steaming. The tree normally looks green and can grow around 30 feet high in wild environment, but for commercial cultivation it is pruned to 2–5 feet. In adult age, the leaves become dark green, seen oval shape, and appear singly or cluster. After collecting the tea leaves, black tea undergoes fermentation, in contrast GT is not
Collected young leaves undergo steaming process at higher temperatures which inactivates the oxidizing enzymes thereby polyphenols remain intact (Alschuler, 1998). Traditionally, GT has been used on several purposes to treat viral diseases (Weber, Ruzindana-Umunyana, Imbeault, & Sircar, 2003), antibacterial infections (Sudano Roccaro, Blanco, Giuliano, Rusciano, & Enea, 2004), inflammation (Dona et al., 2003), cardiovascular diseases (Sueoka et al., 2001), obesity, and lipid lowering (Roederstorff, Schlachter, Elste, & Weber, 2003), angiogenesis (Sartippour et al., 2002), cancer (Kavanagh et al., 2001), neuro-protective (Weinreb, Mandel, Amit, & Youdim, 2004), anti-arthritic (Haqqi et al., 1999), antioxidant (Osada et al., 2001), and other health-related disorders. GT possesses diverse types of bioactive molecules which have several protective mechanisms. So far, various types of flavonoids, polyphenols, and tannins have been isolated from GT leaves (Graham, 1992). Classically, four types of catechins have been studied from GT extract and those potent catechins are epigallocatechin-3-gallate (EECG), (+)-catechin (CE), epicatechin-3-gallate (ECG), and epigallocatechin (EGC) (Zaveri, 2006). All the catechins and other isolated molecules (Figure 2) from GT were found to be effective against diabetic-mediated kidney dysfunctions (Al-Attar & Zari, 2010).

4. Diabetes and free radical biology

Free radicals are parts of the body, sometimes they are called byproducts. They are normally generated either during ATP production or cellular degeneration or by any harmful stimuli (Sagor, Tabassum, Potal, & Alam, 2015). They often produce oxidative stress which further leads to organ dysfunctions by inducing pro-inflammatory cytokines, transcription factors for fibrosis (Figure 1(B)), hemeoxygenase (HO) for iron overload (Figure 1(C)), mast cell accumulation, and other detrimental factors (Reza, Sagor, & Alam, 2015; Reza et al., 2016). Interestingly, they are responsible for cell membrane damage by oxidizing membrane lipids through malondialdehyde (MDA) activity. Later, free radicals react with nucleus, DNA, alter genetic codes, and oxidized regulatory protein which results in the production of advanced oxidative protein products (AOPP) that further damage various components of cell (Abu Taher et al., 2016; Sagor, Chowdhury, et al., 2015). However, nitric oxide is potent vasodilator produced from nitric oxide synthetase (NOS) can be very harmful to a system once it is produced from induced nitric oxide synthetase (iNOS) (Gupta et al., 2005). iNOS, a potent oxidant, is generally processed by free radical which damages cytoplasm and has a powerful role to activate NF-κβ, which further stimulate several other pro-inflammatory cytokine (Alam, Chowdhury, Jain, Sagor, & Reza, 2015). Unfortunately, chronic hyperglycemia is often blamed for generation of free radical-mediated oxidative stress too (Tse, Anderson, Ganini, & Mason, 2015). Moreover, study also explored that oxidative stress has a significant role on production of advanced glycation end products (AGE) (Pazdro & Burgess, 2012). It is highly suggested that NAD(P)H-mediated oxidative stress helps in disease progression of DN (Jha et al., 2014). NAD(P)H oxidase has been also claimed for damaging cell membrane, cytoplasm, and mitochondria through oxidative-mediated stress as the expression of NOX-4 is always found high in DN (Eid et al., 2010; Sedeek et al., 2010). Another study recommended that suppression of NOX-4 reduced glomerulars damage and protected overall kidney functions on db/db BLKS mice by decreasing albuminuria production (Figure 3) (Sedeek et al., 2013).
5. Role of inflammation on diabetic nephropathy

Immunity is the ultimate hero of a biological system which fights against any foreign invaders. Most importantly, inflammation is considered as primary defensive mechanism and is generally induced by any noxious or harmful stimuli. Unfortunately, it is sometimes activated against its own host (Aldhabi & Hamdy, 2003). The relation between DN and inflammation is common and often inflammation plays a pivotal role to develop DN, although it is very difficult to show a single molecular mechanism to understand the pathophysiology of DN through inflammatory molecules and pro-inflammatory cytokines (Figure 1(A)) (Ruggenenti et al., 2010). It is extensively studied that diabetic status of a subject often attracts several inflammatory and pro-inflammatory cytokines like nuclear factor for (NF)-κβ, tumor necrosis factor (TNF)-α, interleukin (IL)-6, interleukin (IL)-1β, α-smooth muscle actin (SMA), macrophage inflammatory protein (MIP), T-lymphocyte, matrix metalloproteinase (MMP), cyclooxygenase-2 (Cox, Abu-Ghannam, & Gupta, 2010), mast cell, monocytes, macrophages,
myloperoxidase (Rojas, Ochoa, Ocampo, & Muñoz, 2006), PGE₂, interferon (INF)-ϒ, and others, some of them are associated with TLR4-MyDD88 interactions (Donate-Correa, Martín-Núñez, Muros-de-Fuentes, Moro-Fernández, & Navarro-González, 2015). Taken together, a study found out that hyperglycemia induces PKC which further activates pro-inflammatory cytokines. Likewise, high glucose also induces oxidative stress which plays a critical role inside kidney generating various harmful free radicals (Mora & Navarro, 2004). Most probably, inflammatory markers like IL-1 and TNF-α were first claimed for nephropathy in diabetic condition (Ienaga & Kondo, 1991). Another study explained that, mRNA expression of IL-6 found high in human renal sample on a diabetic study (Suzuki et al., 1995). A clinical study showed that, expression of IL-18 was found remarkably high in diabetic patients (Fantuzzi, Reed, & Dinarello, 1999) which further linked to mitogen-activated protein kinase (MAPK) (Miyauchi, Takiyama, Honjyo, Tateno, & Haneda, 2009). In addition, TNF-α was also claimed to generate free radicals in rat glomeruli via MAPK and protein kinase C (PKC) pathway (Koike, Takamura, & Kaneko, 2007). Reduction of antioxidant gene like Nrf-2 leads to chronic kidney diseases (CKD) through oxidative stress-mediated inflammation (Ruiz, Pergola, Zager, & Vaziri, 2013). It was also noticed that disruption in Nrf-2 gene signaling may also create lupus-like autoimmune nephritis and induce diabetic inflammation along with nephropathy (Yoh et al., 2001, 2008).
6. Role of green tea on diabetic nephropathy

In DN, cell membrane gets damaged due to diabetic inflammation which is a result of excess glucose concentration inside the organ (Giacco et al., 2014). High glucose concentration always hampers multiple cellular signaling like GLUT, MAPK, and PKC (Dronavalli, Duka, & Bakris, 2008). On top of that, it also increases AGEs, inflammatory cytokines, tumor necrosis factors, nuclear factor-κB, interleukin-1/β, and pro-inflammatory cytokines are often induced by methylglyoxal signaling (Wang, Meng, Gordon, Khandwala, & Wu, 2007). (+)-Catechins have been highly effective against DN and related other complications. One of the studies found that administration of (+)-catechin for 16 weeks was quite effective against DN by diminishing renal damage and methylglyoxal signaling on db/db mice. Similarly, catechin was found to be very effective against DN on human endothelium-derived cells (Zhu et al., 2014). Altogether, diabetic subjects possess free radicals generation, AGEs production, HbA1C level and free glucose concentration which always hamper kidney functions by preventing antioxidant genes like Nrf2, Sirt1, PGC-α, SOD, FOXO (Ding & Choi, 2015), and others which are mostly mediated through mTOR (Zoncu, Efeyan, & Sabatini, 2011) and AMPK pathway (Lee, Park, Takahashi, & Wang, 2010; Price et al., 2012). It is significantly observed that GT protects DN by either increasing antioxidant genes (Wang et al., 2015), or reducing free radical production (Khan et al., 2009) or suppressing pro-inflammatory mediators (Figure 4) (Sachdeva, Kuhad, Tiwari, Arora, & Chopra, 2010).

GT possesses several types of catechins and flavonoids which generally exert multiple mechanisms to protect from DN-related complexities (Funamoto et al., 2016). Nrf2, the most protective gene, known as the master regulator of a cell that fights against inflammation; fibrosis and free radicals mediated oxidative stress in chronic kidney diseases (Aminzadeh et al., 2014). Nuclear factor-erythroid-2-related factor 2 (Nrf2) plays the central role to regulate and coordinate in the induction of more than 250 gene which protect cell through several signaling. The genes which are expressed by the help of Nrf2 are generally known as antioxidant or protective gene and some of the potent components are SOD, heme oxygenase-1, glutamate cysteine ligase, catalase, NAD(P)H: quinone oxidoreductase-1 (NQO1), thioredoxin, glutathione S-transferase, and glutathione peroxidase which mainly work by either restoring antioxidant property or help in harmful substances metabolism like phase-II drug enzymes (Li et al., 2008; Wakabayashi, Slocum, Skoko, Shin, & Kensler, 2010). Activation and production of antioxidant genes like Nrf2, ARE, and SOD can protect a cell from any kind of stress which make them a target for drug molecules (Sriram, Kalayarasan, & Sudhendiran, 2009). It is often observed that nephropathy subjects always lack Nrf2 production in kidney (Aminzadeh, Nicholas, Norris, & Vaziri, 2013). Experiment showed that expression of Nrf2 also ameliorates oxidative stress, reduces inflammation, and kidney fibrosis in animal model via Nrf2-keap1 signaling (Soetikno et al., 2013). It is observed that Nrf2-mediated pathway reduces NF-κB-inflammatory signaling and thus initiates apoptosis (Li et al., 2008). GT flavonoids have been proposed for production of Nrf2 mRNA on DN subjects (Na & Surh, 2008; Yoon et al., 2014). One of the most potent catechins, epigallocatechin-3-gallate protects from Cisplatin-induced nephrotoxic rats through Nrf2/HO-1signaling pathway (Sahin et al., 2010). In addition, another study revealed that epigallocatechin-3-gallate stops lupus nephritis development by enhancing Nrf2 and inhibiting NLRP3 (Tsai et al., 2011). Several protective effects of GT molecules have been summarized in Tables 1 and 2.

Another important cell saving component is superoxide dismutase which protects cytoplasm, mitochondria, and nucleus of a cell (Wassmann, Wassmann, & Nickenig, 2004). Hyperglycemia generates several free radicals like superoxide anion which contributes in the development of DN progression (Ha & Kim, 1999) and damage kidney podocyte as well as glomerulas (United States Renal Data System, 2011). It has been also noticed that interaction of AT,R with Ang-II may generate superoxide anion which is a positive signal for pathogenesis of chronic kidney diseases through NAD(P)H oxidase (Kim, Sato, Rodriguez-Iturbe, & Vaziri, 2011; Vaziri, Dicus, Ho, Boroujerdi-Rad, & Sindhu, 2003). Diabetic kidney often suffers from various disturbances due to over production of
| Models                                      | Outcomes of the study                                                                 | References                                      |
|---------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------|
| Model: Albino mice of MF1 strain            | • Slight decreased serum triglycerides, cholesterol, total protein, creatinine, urea, and uric acid levels | Al-Attar and Zari (2010)                        |
| Wt of model: 26.4–32.2 gram                 |                                                                                       |                                                |
| Disease induced by: Streptozotocin          |                                                                                       |                                                |
| Dose of GT: 0.5 mL/day                      |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 30 days                           |                                                                                       |                                                |
| Model: db/db mice                           | • Reduced expression of DNA-damage inducible transcript 3 (Ddit3), DNA damage inducible protein 34 (Ppp1r15a) and cyclin dependent kinase inhibitor 1a (Cdkn1a) | Faria et al. (2012)                            |
| Age of model: 7 weeks                       | • The treatment also increased insulin sensitivity                                      |                                                |
| Disease induced by: N/A                     |                                                                                       |                                                |
| Dose of GT: 1% (w/w) of EECG                |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 10 weeks                          |                                                                                       |                                                |
| Model: Spontaneous Hypertensive Rats        | • Oral GT up regulated eNOS expression by reducing phospho-Thr495 eNOS and phospho-Ser1177 eNOS expression | Faria, Papadimitriou, Silva, Lopes de Faria, and Lopes de Faria (2012) |
| Age of model: 12 weeks                      | • It also enhanced eNOS uncoupling                                                     |                                                |
| Disease induced by: Streptozotocin          |                                                                                       |                                                |
| Dose of GT: 5 g GT/kg body weight/day       |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 12 weeks                          |                                                                                       |                                                |
| Model: Spontaneous Hypertensive Rats        | • Reduced oxidative stress by decreasing 8-hydroxy-2′-deoxyguanosine (8-OHdG) and NAD(P)H oxidase-dependent superoxide generation | Ribaldo et al. (2009)                          |
| Wt of model: 250 gram                       | • It also down regulated NAD(P)H oxidase (Nox)-4 and nitrotyrosine gene expression     |                                                |
| Disease induced by: N/A                     |                                                                                       |                                                |
| Dose of GT: 13.3 g/L with water             |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 12 weeks as                       |                                                                                       |                                                |
| Model: Male C57BL/Ks db/db mice             | • The numbers of Madin-Darby canine kidney epithelial Cells (MDCK Line) were increased | Kang et al. (2012)                             |
| Wt of model: N/A                            |                                                                                       |                                                |
| Disease induced by: N/A                     |                                                                                       |                                                |
| Dose of GT: 10% non-fermented GT extract    |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 24 weeks                          |                                                                                       |                                                |
| Model: Male Sprague–Dawley rats            | • Green tea caused reduction in serum glucose, glycosylated protein, as well as blood urea nitrogen excretion and glycogen-filled tubules found decreased | Renno, Abdeen, Alkhalaf, and Asfar (2008)     |
| Wt of model: 200–230 gram                  |                                                                                       |                                                |
| Disease induced by: Streptozotocin          |                                                                                       |                                                |
| Dose of GT: 16% (w/w) GT                   |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 12 weeks                          |                                                                                       |                                                |
| Model: Male Wistar albino rats              | • Oral GT extract decreased clotting time, serum glucose, total direct bilirubin ratio, urea and creatinine levels | Ramadan, El-Beih, and Abd El-Ghffar (2009)   |
| Wt of model: 120 gram                       |                                                                                       |                                                |
| Disease induced by: Alloxen                 |                                                                                       |                                                |
| Dose of GT: 50 or 100 mg/kg body weight GT extract daily |                                                                                       |                                                |
| Route: Oral                                 |                                                                                       |                                                |
| Duration: 4 weeks                           |                                                                                       |                                                |
| Models                  | Outcomes of the study                                                                                                           | References                                |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Model: Female Wister albino rats | • The level of glutathione, superoxide dismutase, and catalase (CAT) were increased and decreased thiobarbituric acid reactive substance (TBARS) levels in renal tissue | Abdel-Raheem, El-Sherbiny, and Taye (2010) |
| Wt of model: 150–200 gram |                                                                                                                               |                                            |
| Disease induced by: Gentamicin |                                                                                                                               |                                            |
| Dose of GT: 300 mg/kg/d GT extract |                                                                                                                               |                                            |
| Route: Oral            |                                                                                                                               |                                            |
| Duration: 7 days       |                                                                                                                               |                                            |
| Model: Male Wistar rats | • Increased phosphate (Pi) uptake in the presence of a Na-gradient in the uphill phase (30s),                               | Khan et al. (2009)                        |
| Wt of model: 150–180 gram | • It also enhanced activity of hexokinase (HK), malate dehydrogenase (MDH) in the renal cortex and medulla                  |                                            |
| Disease induced by: Cisplatin |                                                                                                                               |                                            |
| Dose of GT: GT extract (3%, w/v) with drinking water |                                                                                                                               |                                            |
| Route: Oral            |                                                                                                                               |                                            |
| Duration: 25 days      |                                                                                                                               |                                            |
| Model: Male Wistar rats | • The expression of Nrf2 and HO-1 were induced                                                                              | Sahin et al. (2010)                       |
| Wt of model: 200–215 gram | • Decreased NF-κB p65 and 4-Hydroxynonenal (HNE) expression                                                                 |                                            |
| Disease induced by: Cisplatin | • The contents of SOD, catalase (CAT), Gpx, and GSH in the kidney were also restored                                         |                                            |
| Dose of GT: 100 mg/kg/day EGCG |                                                                                                                               |                                            |
| Route: Orally          |                                                                                                                               |                                            |
| Duration: 12 days      |                                                                                                                               |                                            |
| Model: Mus musculus var albino mice | • Inhibited the thickening of the glomerular basement membrane, degeneration and necrosis of tubular epithelial cells slightly | Yapar, Çavuşoğlu, Oruç, and Yalçın (2009) |
| Wt of model: 25–30 gram | • It also increased                                                                                                           |                                            |
| Disease induced by: Cisplatin | • GSH level and reduced MDA level in the kidney                                                                             |                                            |
| Dose of GT: 100 mg/kg |                                                                                                                               |                                            |
| Route: Oral            |                                                                                                                               |                                            |
| Duration: 7 days       |                                                                                                                               |                                            |
| Model: Male sprague-dawley rats | • Increased mitochondrial DNA (mtDNA) numbers, ATP synthase-β (AS-β) and NADH dehydrogenase-3 (ND3),                           | Rehman et al. (2013)                      |
| Wt of model: 200–250 gram | • The treatment activated peroxisome proliferator-activated receptor-1α co-activator (PGC)-1α and renal mitochondrial transcription factor-α (TFAM) mRNA |                                            |
| Disease induced by: Cyclosporin A | • It also attenuated renal injury and improved renal function by enhancing brush border activity                             |                                            |
| Dose of GT: 80 mg/kg/day extract |                                                                                                                               |                                            |
| Route: Oral            |                                                                                                                               |                                            |
| Duration: 21 day       |                                                                                                                               |                                            |
| Model: Male 129/svJ mice | • Reduced proteinuria, lowered H2O2 level and                                                                                  | Peng et al. (2011)                        |
| Age of model: 8 weeks  | • In addition of EECG further reduced the p65/ nuclear factor (NF)-κB expression                                             |                                            |
| Disease induced by: Immune-mediated glomerulonephritis | • Also increased Peroxisome proliferator-activated receptor gamma (PPARγ) activity                                           |                                            |
| Dose of GT: 50 mg/kg/day EGC |                                                                                                                               |                                            |
| Route: Oral            |                                                                                                                               |                                            |
| Duration: 14 days      |                                                                                                                               |                                            |
| Models | Outcomes of the study | References |
|--------|-----------------------|------------|
| Model: Sprague–Dawley rats, Wt of model: 200–250 gram, Disease induced by: Cyclosporine, Dose of GT: 100 mg/kg GT extract, Route: S.C. injection, Duration: 21 days | • Normalized the proximal tubular necrosis and mild interstitial inflammation<br>• It also suppressed plasma renin activity (PRA) and serum aldosterone levels | Ryu et al. (2011) |
| Model: Male C57BLKS/J (db/db) mice, Age of model: 6 weeks, Disease induced by: Dose of GT: 15, 30, and 60 mg Catechin /kg, Route: Oral, Duration: 16 weeks | • Normalized glomerular cell loss (in a dose dependent way), plasma and renal methylglyoxal levels<br>• It also reduced glomerular hypertrophy<br>• Furthermore, it inhibited advanced glycation end products-receptor for advanced glycation end products (AGE–RAGE) mediated inflammatory pathway by attenuating nuclear factor kappa beta (NF-κβ) activation | Zhu et al. (2014) |
| Model: Wistar rats, Wt of model: 120–130 gram, Disease induced by: Nephrectomy along with streptozotocin, Dose of GT: 25, 50, and 100 mg/kg/day EECG, Route: Oral, Duration: 50 days | • Decreased albumin and AGE accumulation (in a dose-dependent way)<br>• It also down regulated cyclooxygenase (COX-2)<br>• Furthermore, the treatment decreased phosphorylated nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IkB-α), transforming growth factor beta (TGF-β) and fibranectin expressions | Yamabe, Yokozawa, Oya, and Kim (2006) |
| Model: ICR mice, Wt of model: 23.3 ± 1.2 gram, Disease induced by: Streptozotocin, Dose of GT: 50, 100, and 200 mg/kg EGCG, Route: S.C. injection, Duration: 1 week | • Decreased proteinuria level and expression of osteopontin (OPN)<br>• Renal histo-pathological observations of glomerular mesangial matrix found to be reduced | Yoon et al. (2014) |
| Model: Male C57BL/6 mice, Wt of model: 18–22 gram, Disease induced by: Unilateral Ureteral Obstruction-Induced Renal Interstitial fibrosis, Dose of GT: 5 mg/kg EECG, Route: IP, Duration: 14 days | • Decreased extracellular matrix, mRNA expression of MCP-1 and 3, TNF-α, IL-1β and phosphorylations of Smad 2 and 3 by reducing TGF-β1 | Wang et al. (2015) |
| Model: Male db/db mice, Age of model: 5 weeks, Disease induced by: Dose of GT: 2.5, 5, or 10 g/kg of diet EGCG supplement, Route: Oral, Duration: 5 weeks | • Improved oral glucose tolerance (in a dose-dependent manner)<br>• It also increased plasma concentrations of insulin and reduced expression of phosphoenol pyruvate carboxykinase (PEPCK) level | Wolfram et al. (2006) |

(Continued)
### Table 1. (Continued)

| Models | Outcomes of the study | References |
|--------|-----------------------|------------|
| Model: Male albino Wistar rats  
Wt of model: 160–180 gram  
Disease induced by: Fluoride intoxication  
Dose of GT: 40 mg/kg EECG  
Route: Oral  
Duration: 4 weeks | • Decreased the levels of tumor necrosis factor (TNF)-α, nitric oxide (NO), interleukin (IL)-6 and nuclear factor (NF)-κB p65, lipid hydroperoxide (LOOH) and protein carbonyl content (PCC)  
• It also increased vitamins C and E contents, β-cell lymphoma (Bcl-2) levels in kidneys  
• Restored expression of Nrf2, HO-1, and GST | Thangapandiyan and Miltonprabu (2014) |
| Model: Female CD:1 mice  
Age of model: 5 weeks  
Disease induced by: Streptozotocin  
Dose of GT: 0.01% of GT extract with drinking water  
Route: Oral  
Duration: 12 weeks | • Suppressed the insulin resistance  
• Improved the function of pancreatic β cell | Tang, Li, Liu, Huang, and Ho (2013) |
| Model: Female db/db-mice  
Wt of model: 30.1±0.5 gram  
Disease induced by: N/A  
Dose of GT: 1 g/kg GT extract  
Route: Oral  
Duration: 28 days | • Reduced plasma soluble cell adhesion molecules (sICAM) concentration | Wein et al. (2013) |
| Model: Female obese, diabetic KK-ay and C57BL/6 J mice  
Wt of model: N/A  
Disease induced by: Dextran sulfate sodium-induced colitis  
Dose of GT: 300 mg  
Catechins /kg/day  
Route: Oral  
Duration: 4 weeks | • Increased GLUT-4 content in plasma and insulin sensitivity by suppressing the c-Jun N-terminal kinase (JNK) pathway  
• It also suppressed the effect of Dexamethasone | Yan, Zhao, Suo, Liu, and Zhao (2012) |
| Model: Male ICR mice  
Wt of model: 17–19 gram  
Disease induced by: Dextran sulfate sodium-induced colitis  
Dose of GT: 1% (w/w) Polyphenols  
Route: Oral  
Duration: 6 days | • Normalized the heat shock protein (HSP) production in the kidney | Inoue et al. (2011) |
| Model: KK-Ay Diabetic Mice  
Age of model: 5 weeks  
Disease induced by: N/A  
Dose of GT: Fermented tea (0.4%)  
Route: Oral  
Duration: 90 days | • The level of glycate hemoglobin (HbA1c) and insulin resistance were reduced | Lee, Park, Nam, Yi, and Lim (2013) |
superoxide anion and hydroperoxide (Koya et al., 2003). SOD family exerts its protective function by residing inside membrane (EC-SO, mitochondria (Mn-SOD), and cytoplasm (Cu-Zn-SOD) (Bartz & Plantadosi, 2010; Rosenthal & Nocera, 2007). Production of mitochondrial SOD can also decrease hyperglycemia and related complications (Nishikawa et al., 2000).

Recently Sirt1 has achieved several protective functions like DNA repairing; neutralizing oxidants, maintaining glucose homeostasis, hormone secretion and others. Hence, it is now called silent information regulator (Weber et al., 2003) gene. It also regulates in the transcription of non-histone protein including FOXO1/3, p53, PPAR, and PGC-1α (Morris, 2013). Study also showed that expression of Sirt1 in the proximal tubules enhances glomerular function and defends against diabetes-induced renal damage (Hasegawa et al., 2013). A recent experiment explored that GT polyphenol (−)-epigallocatechin-3-gallate (EGCG, 50 mg/kg BW/day × 3 weeks) restored Sirt1 expression, resulting in the reduction of serum creatinine, proteinuria which ultimately protects kidney cell. The study also linked that supplementation of GT polyphenol reduced p-ERK1/2, p-Akt, p-JNK, and p-P38 signaling along with activating PPARγ activity (Ye et al., 2015). GT isoflavones have been investigated to induce Sirt1 and other protein content like TFAM for mitochondrial biogenesis when rat’s kidney were treated with cyclosporine A (Rehman et al., 2013).
AMPK, another master regulator, known as a nutrient sensor which is generally activated under energy-depleted conditions by phosphorylation of a preserved threonine residue (T172) (Alers, Wesselborg, & Stork, 2012). In type-1 and type-2 diabetic patients, AMPK phosphorylation and other activities were noticed lower inside both glomeruli and tubules (Kitada, Kume, Imaizumi, & Koya, 2011). GT treatment found to be protective against cyclosporine A-induced renal injury. Increased AMPK and PGC-1α help in the mitochondrial biogenesis and thus prevent drug-induced kidney dysfunctions (Rehman et al., 2013). Beside these, epigallocatechin-3-Gallate treatment also protected the kidney function by reducing MCP-1, MCP-3, and TGF-β content on fibrotic rat model (Wang et al., 2015). Another study showed that GT normalizes renal kidney injury by down regulating NOX-4 production on diabetic rats (Ribaldo et al., 2009). It was also found out that water extracts of GT lowered DN by controlling glomerular hypertrophy and interstitial inflammation on alloxan induced diabetic rats (Shokouhi et al., 2015). Recent study also revealed that GT polyphenol epigallocatechin-3-gallate up-regulated heme oxygenase-1through phosphatidylinositol 3-kinase/Akt and ERK and thereby prevent kidney damage (Wu et al., 2006). A proposed molecular mechanism has been explained in the (Figure 5) to show the possible interaction between GT and DN.

## 7. Problem with green tea treatment
A potent molecule must exert its action on biological system being stable, at the same time it should be safe and not interfere with other signaling pathways. Sometimes it is showed that high dose of a component often produces unwanted side effects, life-threatening ADR which may lead to necrosis-mediated cell death (Elsherbiny et al., 2012). Similarly, a study has also found that 1% GT polyphenols with food produced nephrotoxicity by down-regulating antioxidant protein expression and heat shock protein expression (Inoue et al., 2011). Likewise, another study explored that high dose of GT
Figure 5. Proposed mechanism explained that, Hyperglycemia induces ROS in numerous ways, such as by activating Mitochondria, or by increasing the accumulation of Transforming Growth Factor Beta (TGF-β), or by triggering protein kinase C (PKC), or it also enhances the accumulation of tumor necrosis factor alpha (TNF-α) and up regulates angiotensin-2 production. (1) Inside the mitochondria, hyperglycemia causes electron imbalance which converts oxygen molecule to a reactive one. (2) TGF-β generates ROS via PI3K-Smad2/3 pathway. (3) Activation of PKC by high level of glucose causes formation of ROS via different ways, PKC also possess interleukin 6, which regulates iNOS that is directly involved in the generation of ROS, PKC itself can help in the formation of iNOS directly; PKC causes activation of nuclear factor κB via IKK-IKB pathway. (4) In addition, hyperglycemia can cause accumulation of TNF-α adjacent the cell membrane, which binds TNF-α receptor that further activates NF-κB inside the DNA to produce iNOS gene that ultimately generates ROS. (5) Higher glucose level may facilitate the production of Angiotensin-II by Renin-Angiotensin-Aldosterone system, Ang-II binds with Ang-II Type 1 receptor (AT1R), which causes accumulation of ROS via MAPK p38-NIK (NF-κB inducing kinase) pathway which further activates NF-κB via IKK-IKB pathway. Green tea flavonoids and polyphenols block the activation/accumulation/generation of ROS by enhancing 5’ AMP-activated protein kinase (AMPK), nuclear factor-erythroid-2-related factor 2 (Nrf2) and Sirtuin-1 (Sirt1). (1) AMPK generally activates both Nrf2 and Sirt1, it further inhibits the expression of iNOS through Peroxisome proliferator-activated receptor gamma (PPAR-γ) in Eukaryotic elongation factor-2 kinase (EEF-2K) pathway, AMPK may also nullify the effect of TNF-α and PKC. (2) Green tea polyphenols and flavonoids induce Nrf2 which blocks both iNOS production and ROS accumulation by activating Keap1-ARE (antioxidant-responsive element) signaling. (3) Sirt1 up regulates Mn superoxide dismutase (MnSOD) production via Forkhead box O3 FOXO3-AKT (Protein kinase) pathway which prevents ROS generation, furthermore Sirt1 inhibits TNF-α and TGF-β by producing PGC-1α (Peroxisome proliferator-activated receptor gamma co-activator 1-alpha)–PPAR-γ (peroxisome proliferator-activated receptors-γ).
Table 2. Recent protective findings of green tea on diabetic patients through clinical trails

| Subjects                                                                 | Outcomes of the study                                                                 | References                                      |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------|
| 68 subjects, aging 20–65 years with type 2 diabetes                    | • Reduced in HOMA-IR index, and insulin level                                          | Hua et al. (2011)                               |
| 155 pre-diabetic individuals aging from 35 to 65 years                | • Reduced ALT level                                                                  | Toolsee et al. (2013)                           |
| 78 obese women aged between 16 and 60 years                           | • Reduced LDL-cholesterol and triglyceride                                            | (Hsu et al., 2008)                              |
| 54 subjects diagnosed of type 2 diabetes mellitus aging 65±6 years    | • Increased in the level of ghrelin                                                  | (Hsu et al., 2008)                              |
| 237 overweight and obese participants                                 | • Increased in HbA1c and it had no hypoglycemic effect                                | Mackenzie, Leary, and Brooks (2007)             |
| 56 obese, hypertensive subjects aging 30 to 60 years                  | • Reduced fasting serum glucose, insulin levels, and insulin resistance,              | Bogdanski et al. (2012)                         |
| 100 type 2 diabetes patients                                          | • Increased HDL-c and improve β-cell function,                                       | Mozaffari-Khosravi, Ahadi, and Tafti (2014)     |
| 42 diabetic subjects aging between 60–65 years                       | • Reduced albuminuria, serum DKK-1, and tumor necrosis factor -α                      | Borges et al. (2016)                            |
| 300 men and women aging 65–100 years                                 | • Limited podocyte apoptosis by activating Wnt pathway                                | Polychronopoulos et al. (2008)                  |
| 46 obese patients aging 30–60 years                                   | • Lowered Glucose, iron, total cholesterol, LDL, and triglyceride                     | Suliburska et al. (2012)                        |

*HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, ALT: Alanine Aminotransferase, eGFR: Estimated Glomerular Filtration Rate, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, DKK: Dickkopf-1, β-cell: Beta-cell, Wnt pathway, DKK-1: Dickkopf-1, C-reactive protein.*
(EECG) induced hepatic dysfunction by producing liver 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) (Lambert et al., 2010). In addition, similar kind of hepatic dysfunctions have been reported when people take daily GT supplements (Mazzanti et al., 2009). Furthermore, a cell culture study also investigated that EECG induced oxidative stress and also enhanced the production of pro-matrix metalloproteinase-7 (Kim, Murakami, & Ohigashi, 2007). Another report noticed that 1% GT polyphenol treatment induced carcinoma by increasing pro-inflammatory cytokines along with reducing antioxidants like SOD and catalase (Kim et al., 2010). A recent meta-analysis showed that intake of GT also increased the risk of endometrial cancer (Zhou et al., 2016). It has been also reported that GT component ECGE, has poor absorption via oral route due to metabolization by gut microbiota (Chan, Zhang, & Zuo, 2007) and also found very shorter half-life (maximum 30 min in cell culture and 30–60 min on animals) in both animal and human study (Lee et al., 2002). It is normally conjugated with glucuronidation and easily metabolized. Study showed that one-third of the ECGE gets eliminated from the body within first 24 h of its administration (Manach, Williamson, Morand, Scalbert, & Rémésy, 2005). Oxidation of ECGE may produce several free radicals like superoxide anion which later hampers multiple cellular signaling by binding on epidermal growth factor receptor (Hou et al., 2005; Smith, 2011; Wein, Schrader, Rimbach, & Wolffram, 2013). EGCE also blocks insulin secretion from β-cell by inhibiting glutamate dehydrogenase (GDH)-mediated signaling (Li et al., 2006). However, a cross talk has been shown from a clinical trial where 35 obese subjects were given GT (4 cups/a day), and after 8 weeks no significant alteration in serum biomarkers of inflammation including adiponectin, C-reactive protein (CRP), interleukin-(IL-6), interleukin-(IL-1/β), soluble vascular cell adhesion molecule-(sVCAM-1), leptin, or leptin: adiponectin ratio were observed, although the authors noticed reduced plasma serum amyloid alpha (Basu et al., 2011; Eid et al., 2010). Most of the studies were conducted with small number of subjects. Therefore, it is very difficult to conclude anything concrete against the obtained results. Clinical trial on a large population must be carried out to get a noble drug molecule from GT.

8. Conclusion and future directions
This study describes possible patho-physiology for kidney dysfunctions, especially in diabetic condition. As the complications of diabetes are increasing tremendously, a safe and alternative treatment must be approached. Beneficial roles of GT cathecons on diabetic-induced kidney dysfunctions have been well studied. Regular administration of GT supplements can be an effective treatment approach for the diabetic subjects. This study also provides strong evidences in favor of GT treatment in DN. The authors highly recommend for large clinical trial to establish the exact molecular mechanism of action of GT against DN.

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