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## Section B: Pharmaceutical Analytical & Organic Chemistry, Medicinal & Biochemistry

### The Possible Effects of Green Coffee Bean Extract on Progression of Experimental Diabetes in Different Organs; A Review Article

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#### ABSTRACT

Green coffee bean water extract consumption has been stated to have a contrary association with type 2 diabetes and metabolic syndrome. Chlorogenic acid (CGA), an important biologically active dietary polyphenol, is produced by certain plant species and is a major component of coffee. Reduction in the risk of a variety of diseases following CGA consumption has been mentioned in recent basic and clinical research studies. This systematic review discusses in vivo animal and human studies of the physiological and biochemical effects of CGA on biomarkers of diabetic complication and the possible alterations produced by the administration of different doses of green coffee on biomarkers related to renal, testicular, and neurological antioxidant systems.

**Keywords:** Green coffee; Diabetes; Renal; Testicular; Brain.

#### INTRODUCTION

Diabetes mellitus (DM) is a chronic disease with a wide range of physiological complications and a high prevalence.<sup>1</sup> As a result, it is regarded as a major issue in the modern era<sup>2</sup>. According to the International Diabetes Federation, 382 million children and adults worldwide were diagnosed with diabetes in 2013, with that number expected to rise to over 592 million by 2025<sup>3</sup>.

Currently available diabetic therapy, which includes insulin and multiple oral hypoglycemic medicines, has had some success. Many of these drugs, however, have negative side effects<sup>4</sup>. As a result, a natural-based therapy that can help diabetic patients

reduce organ injury is required. Phytochemicals derived from plants can have anti-diabetic effects by interfering with glucose metabolism with minimal toxicity and side effects<sup>5</sup>.

The most important bioactive component in green coffee (*Coffea arabica*) is chlorogenic acid (CGA)<sup>6</sup>. Previous research on experimental animals and humans suggested that green coffee's therapeutic properties are linked to bioactive CGA's antioxidant and anti-inflammatory properties<sup>7</sup>.

We searched PubMed and Scopus using the following search terms: ("chlorogenic acid" OR "green coffee bean extract") AND (human OR animal) (last performed on April 1st, 2021) for relevant literature on the in vivo effects of CGA in animal and human

models, including clinical trials on testicular, renal, neurological functions. The biological properties of CGA in addition to its antioxidant and anti-inflammatory effects have recently been reported.

The wide range of potential health benefits of CGA, including its antidiabetic, anti-carcinogenic, anti-inflammatory, and anti-obesity impacts, may provide a non-pharmacological and noninvasive approach for treatment or prevention of some chronic diseases. In this review, the effects of CGA on different aspects of health by reviewing the related literature have been discussed.

## RESULTS AND DISCUSSION

### The effect of green coffee bean extract on renal dysfunction

AlAmri, Albeltagy et al. reported that an increase in kidney weight and kidney function parameters levels caused by diabetic model reversed by green coffee bean water extract (GCWE) administration. These results are confirmed with different studies which recorded a gradual decrease in kidney malfunction with increased coffee consumption<sup>8,9</sup>.

Kenza et al. (2017) stated the caffeic acid phenethyl ester as an effective agent against oxidative damage in rat tubular cells considers good renoprotection dependent treatment of GCWE significantly down-regulated level mostly in HFD/STZ-GCWE-100 group<sup>10</sup>. The possible mechanism behind this action is the ability of CGA in coffee to decrease the rate of intestinal absorption of glucose or to delay gastric emptying that prevents the state of hyperglycemia. Oxidants and antioxidants defense systems have been troubled in diabetic rats. Fernandes et al suggested that oxidative stress plays a central role in the incidence and expansion of diabetic nephropathy<sup>11</sup>.

Jia et al. showed a reduction in SOD, CAT, GPx, and GR activities (antioxidant capacity) and an increase of LPO, PCO, and NO levels (lipid peroxides) which may lead to renal injury<sup>12</sup>. Besides, the content of GSH was reduced. Amaral et al and Ahmed et al confirmed the raised LPO, decreased GSH content, and suppression of catalase activities<sup>13,14</sup>.

However, GCWE administration reserved prooxidant/antioxidant imbalance in renal tissue of diabetic rats. Priftis et al explained the mechanism that is through the Nrf2 (nuclear erythroid factor-related factor 2)/ARE (antioxidant response element) pathway that stimulated by coffee phenolic compounds<sup>15</sup>.

Moreover, positive influences on oxidative damage markers and antioxidant activity were observed in a dose-dependent manner in green coffee-treated groups. Butt et al reported that chlorogenic acid, caffeic acid, and hydroxyhydroquinone are antioxidants ingredients in green coffee<sup>16</sup>. The antioxidant capacity

of GCWE depends on the high antioxidant properties of chlorogenic acids<sup>17</sup>. Dziki et al confirmed the same result in vitro<sup>18</sup>. Zhou et al observed that The ability of coffee or its active ingredients to enhance CAT activity<sup>19</sup>.

Diabetic rats exhibited an increased level of proinflammatory cytokines in terms of TNF- $\alpha$  and IL-1 $\beta$  and this was confirmed by<sup>20</sup>. The mRNA of Nos2 is also overexpressed. Safavi et al observed IL-1 $\beta$  and TNF- $\alpha$  had an important role in enhancing inflammatory reactions. In diabetic nephropathy, pro-inflammatory cytokines can induce changes in the glomerular filtration rate and endothelial cell permeability and initiate the generation of ROS/free radicals<sup>21</sup>. However, inflammatory markers (TNF- $\alpha$ , IL-1 $\beta$ , and Nos2) were improved significantly when compared with HFD/STZ group and showed a great retain to their normal level specifically with HFD/STZ-GCWE-100 group.

Kempf et al. (2010) recorded a dose-response effect of coffee administration on serum levels of inflammation markers, and found increasing cups of coffee per day, for 12 weeks, improved the inflammatory response when compared with no coffee. This agrees with studies addressing the metabolic outcomes of T2DM risk<sup>22,23</sup>.

Clinical trials support an overall anti-inflammatory action of coffee consumption<sup>24</sup>. Two coffee components, trigonelline<sup>25</sup> and chlorogenic acid<sup>6</sup> were described to overturn the inflammatory response in cell-based and animal studies, and they are also the probable mediators in the anti-inflammatory properties of coffee.

Previous studies measured the concentrations of the pro-apoptotic proteins (Bax and caspase-3) and the anti-apoptotic protein (Bcl-2) and their relative gene expressions in the kidney tissue of diabetic rats. Consistently, the level of the pro-apoptotic proteins Bax and caspase-3 cleavage were increased markedly, whereas the level of the anti-apoptotic protein Bcl-2 was markedly decreased.

Green coffee and metformin treatments exert anti-apoptotic activity through upregulating Bcl-2 and down-regulating Bax and Casp3 as compared to the diabetic group. Interestingly, green coffee (100 mg kg<sup>-1</sup>) has a remarkable improvement in the levels of Bax, Casp3, and Bcl-2 compared to the control group. El-Deen et al. reported that treatment with green coffee diminished apoptosis and reduced the expression of caspase-3 in the renal tubules<sup>26</sup>.

### The effect of green coffee bean extract on testicular dysfunction

AL-Megrin et al founded that excessive oxidative stress and apoptosis in the tissues of the testes that dramatically give rise to testicular dysfunction leads to a significant weight loss of the testis

and the reduced levels of T, FSH, and LH detected in diabetic rats.

Importantly, was capable of attenuating testicular damage by diminishing the loss in weight of the testis and raising the concentrations of sex hormones suggesting a protective role of GCWE. Previously, Wedick et al found that coffee consumption significantly elevated total testosterone and declined both the total and free estradiol after 28 days which suggests that caffeine may act as an aromatase inhibitor<sup>27</sup>.

Wang et al reported that disturbance of antioxidant capability might be responsible for the stimulation of testicular oxidative injury<sup>28</sup>. Furthermore, Zhao et al. indicated that hyperglycemia causes excessive accumulation of ROS that accelerates cellular oxidative injury and endoplasmic reticulum stress<sup>29</sup>.

It was indicated that ROS causes harmful alterations in the male reproductive system<sup>30</sup>. Such alterations include testicular complications like abnormal spermatogenesis and oligospermia along with a decreased level of reproductive hormones<sup>31</sup>. Moreover, spermatozoa were found to be more susceptible to ROS production which could reduce sperm motility causing infertility<sup>32</sup>.

Some evidence reported an increased MDA level detected in the diabetic group<sup>28,33</sup>. The same studies demonstrated that a rise in free radical production causes overproduction of MDA that resulted in the imbalance of antioxidant integrity.

A previous study confirmed that the increased production of LPO and decreased content of GSH, SOD, GR, and GPx were obviously restored by the administration of GCWE, suggesting a clear antioxidant activity that was in line with those demonstrated in several studies<sup>34,35</sup>. Inflammation is widely accepted to be responsible for the pathogenesis of hyperglycemia and its complications<sup>5</sup>.

Fakhar zadeh et al stated that the levels of both TNF- $\alpha$  and IL-1 $\beta$  have a direct impact on the initiation and complications of diabetes<sup>36</sup>. Similarly, the TNF- $\alpha$  and IL-1 $\beta$  levels were significantly elevated in the testes of diabetic rats. Almeer et al explained that ROS resulted in the oxidation of protein and lipids in some cellular structures, which causes cell injury by triggering ER (endoplasmic reticulum) stress, debilitating normal mitochondrial function, and disrupting the DNA<sup>37</sup>.

These complications enhance NF- $\kappa$ B mediated inflammation in conjunction with the increased levels of proinflammatory mediators such as TNF- $\alpha$  and IL-1 $\beta$ . Santana et al founded that the levels of inflammatory cytokines decreased significantly after treatment with GCBWE, suggesting an anti-

inflammatory effect by decreasing the studies of the IL-1 $\beta$  and TNF- $\alpha$  level<sup>35,38</sup>.

Apoptosis is a genetically organized pathway for cell death under different pathophysiological conditions. Apoptotic pathways are associated with caspase-mediated degradation of DNA by DNases, giving it a ladder-like pattern<sup>39</sup>.

AL-Mergin et al stated that diabetic rats exhibited an increased expression of the proapoptotic Bax and caspase-3 along with the decreased level of antiapoptotic Bcl-2. proteins. This imbalance may induce the discharge of cytochrome c from the mitochondrial matrix to the cytosol resulting in the increased concentration of cleaved caspase-3 that promotes degradation of DNA by DNases<sup>40</sup>.

Sperm production from the germinal cell in the testes takes place by keeping a balance between cell proliferation and cell death<sup>41</sup>. Ghosh et al mentioned that apoptosis may be responsible for the testicular dysfunction as was mentioned by wang et al<sup>42</sup> and<sup>43</sup>. Oxidative stress may be considered a potent inducer of cell apoptosis<sup>44</sup>. However, GCWE treatment significantly inhibited STZ-induced apoptosis of testicular cells by decreasing the expression of the Bax and caspase-3 together with the increasing level of Bcl-2.

These observations suggested that suppressing the mitochondrial-dependent pathway of apoptosis might be an important pathway through which green coffee prevents abnormal spermatogenesis induced by HFD and STZ.

Some studies concluded that green coffee treatment attenuated testicular oxidative damage which modulates inflammatory reaction and apoptotic-related pathways. Green coffee exerts its effects by increasing the antioxidant activity and suppressing inflammatory response and the apoptotic pathway in the testes.

### **The effect of green coffee bean extract on brain dysfunction**

Diabetic neurodegeneration was reported as a result of oxidative stress, advanced glycation end products, and vascular distortion<sup>45</sup>. A study performed by Al-Barakati et al indicating the explanatory effect of oral supplementation with GCWE against HFD/STZ induced cortical the injury was explored in male rats in terms of alterations in neurotransmitters, inflammatory markers, antioxidants, and apoptotic factors.

Kaundal et al reported that diabetic rats showed a marked decline in neurotransmitters (DA, NE, and 5-HT) that have a pivotal role in learning and memory<sup>46</sup>. Monoamine oxidase (MAO) enzymes are involved in the metabolism of catecholamines and xenobiotics in the CNS and peripheral tissues<sup>47</sup>.

Diabetes disturbs the action of MAO which is located in mitochondria<sup>45</sup>. Therefore, the changes in the activity of brain MAO could result in significant alterations in the metabolism and levels of these amines in the brain tissue.

Shimomura et al reported that the significant decrease in the DA level in diabetic rats may be attributed to a reduction in DA synthesis and turnover in brain tissue<sup>48</sup>. In addition, decreased level of 5-HT in the brain may refer to the decreases in amino acids with a consequent decrease in 5-HT synthesis during diabetes<sup>49</sup>.

Owolabi et al confirmed that GCWE treatment improved the decline seen in the neurotransmitters alterations and this is in agreement with previous authors who found that caffeine administration augmented the release of serotonin and dopamine in the hippocampus region<sup>50</sup>.

Caffeine is a neuronal stimulant involved in the improvement of neural activities in the brain cortex. Administration of caffeine resulted in elevated levels of acetylcholine, 5-HT, DA, GABA, and glutamate which are considered as the primary brain transmitters as well as up-regulation of their receptors<sup>50</sup>.

Ito et al reported that GCA acts on the CNS via the blood-brain barrier (BBB) as in its intact form or as its metabolite especially m-coumaric acid<sup>51</sup>. Because of its high plasma level after coffee ingestion and its small molecular weight (MW 354), CGA is expected to permeate BBB<sup>52</sup>.

Furthermore, oral administration of CGA improved the disturbances in the adrenocorticotrophic hormone (ACTH) and catecholamine levels induced by ether stress in menopausal model rats. CGA significantly increased the levels of ACTH, adrenaline, noradrenaline, and dopamine decreased by ether stress in dose-dependent effects<sup>53</sup>.

Hence, the augmented neurotransmitters could be explained by the neuronal stimulant effect of caffeine and CGAs on the cortical activities in rats. Because of the beneficial roles of AMPK in brain diseases, it may be used to treat various neurological disorders, such as Alzheimer's disease and cognitive impairment.

Oxidative stress is considered a major pathway contributing to the progress of diabetic complications<sup>54</sup>. Xu et al illustrated the antioxidant potentials and DNA damage protective effects of chlorogenic acids<sup>55</sup>. Hoelzl et al. reported that the human consumption of coffee extracted from green and roasted coffee beans which contain high levels of chlorogenic acids protected against oxidative damage of cellular macromolecules such as proteins, DNA, and membrane lipids<sup>56</sup>.

Cavin et al explained the antioxidant properties of coffee by induction of Nrf2-mediated cellular defense in rodents<sup>57</sup>. In comparison with other drinks, Pellegrini et al declared that in vitro assessment of the

antioxidant power of coffee revealed that it possesses a greater antioxidant capacity (five-fold and threefold if compared to green tea and red wine, respectively)<sup>58</sup>. Moreover, the phenolic compounds in coffee are rich sources with antioxidants that exceed the contents of fruits and vegetables<sup>59</sup>.

Koga et al reported that mice administered caffeic acid for 30 days showed reduced levels of 4-hydroxynonena, a marker of lipid peroxidation induced by ROS and marked activation of the microglia in the hippocampus<sup>9</sup>. Caffeic acid reduced oxidative stress which may, in turn, illustrate its role to improve memory and cognitive functions. Then, the antioxidant potential of GCWE can be explained through redox homeostasis and the antioxidant capacity of its polyphenols.

Hyperglycemia has been shown to be associated with increased inflammatory mediators as IL-1 $\beta$  and TNF- $\alpha$  in the hippocampus, possibly affecting learning and memory<sup>60</sup>. The inflammatory response under hyperglycemic conditions may refer to an accumulation of ROS as a result of oxidative damage or mitochondrial dysfunction<sup>60</sup>.

Previous authors reported the activation of nuclear factor- $\kappa$ B (NF $\kappa$ B) and the expression of pro-inflammatory cytokines by hyperglycemia and its relationship with diabetic complications as diabetic neuropathy<sup>61</sup>.

Moreover, Muriach et al reported that activation of the NF $\kappa$ B pathway is involved in pathological brain inflammation via induction of cytotoxic products that exacerbate inflammation, oxidative stress, and cell dysfunction or cell death, respectively<sup>62, 63</sup>. This study revealed that the oral administration of GCWE relieved the neuroinflammation induced by diabetes in diabetic rats that can be explained by the anti-inflammatory effect of CGAs.

Dos Santos et al. stated that CGA strongly inhibited the production and synthesis of TNF- $\alpha$ , IL-6, and NO as well as other mediators such as IL-1 $\beta$ , interferon-gamma, monocyte chemotactic protein-1, macrophage inflammatory protein (MIP)-1 $\alpha$ . In addition, a CGA-rich fraction from the medicinal plant *Saussurea costus* strongly inhibits NO formation that is a crucial mediator involved in the inflammatory processes. Further, Dos et al also stated that CGA suppresses the release of NO from lipopolysaccharide/gamma interferon-stimulated C6 astrocyte cells<sup>64</sup>.

A previous study revealed a marked elevation in pro-apoptotic markers (Bax and caspase-3 levels) together with a decrease in antiapoptotic factor (Bcl2) as well as alterations in their mRNA gene expression in the cortical tissue of diabetic brains. These findings are in line with previous studies performed by Muriach et al.

who found that diabetic brains demonstrated a significant elevation in the apoptotic rate accompanied by an increase in oxidative stress markers in the cerebral cortex, hippocampus, and cerebellum indicating that diabetes augments oxidative damage-induced apoptosis in aforementioned brain regions<sup>63</sup>.

Additionally, daily treatment with GCWE for 28 days significantly decreased the cortical apoptotic markers as well as their gene expressions in the cortex of diabetic animals. Kim et al reported that CGA induced the expression of NADPH quinone oxidoreductase 1 (NQO1) in neuronal cells, explaining their role in the protection of neurons against apoptosis induced by hydrogen peroxide by up-regulation of this antioxidant enzyme<sup>65</sup>.

Also, CGAs employed their anti-apoptotic role via suppressing the release of cytochrome c from the mitochondria to the cytoplasm, the cleavages of casp-3 and casp-9, and lowering the intracellular calcium ions<sup>66</sup>.

Therefore, the antiapoptotic impact of GCWE can be explained by the underlying potentials of GCAs to mitigate neuronal cell apoptosis. Together with chlorogenic acid, other phytochemicals act synergistically to reveal the noticeable neuroprotective effects of GCBWE against diabetic neuronal injury in rats.

## CONCLUSION

We conclude that oral supplementation with green coffee treatment in diabetic patients attenuated renal, testicular and brain oxidative damage which modulates inflammatory reaction and apoptotic-related pathways. Green coffee exerts its effects by increasing the antioxidant activity and suppressing inflammatory response and the apoptotic pathway in these organs. Interestingly, metformin also has similar effects on green coffee on all the parameters investigated in those studies. This suggests that green coffee could be used to substantiate metformin in the treatment of diabetes-induced organs dysfunction.

## Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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