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## **Oxidative Stress Diminishing Perspectives of Green and Black Tea Polyphenols: A Mechanistic Approach**

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Ali Imran, Muhammad Umair Arshad,  
Sana Mehmood, Rabia Shabir Ahmed,  
Masood Sadiq Butt, Aftab Ahmed,  
Muhammad Imran, Muhammad Sajid Arshad,  
Neelam Faiza, Ihtisham Haq,  
Shahzad Ali Shahid Chatha, Muhammad Shahbaz,  
Qasim Ali and Muhammad Waseem

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### **Abstract**

Polyphenols have credentials to tackle the oxidative stress. Oxidative stress is the imbalance between free radicals production and antioxidant enzymes ability to tackle these radicals resulting the onset various metabolic related disorders. Polyphenols based foods have credential as a shield against these glitches mainly owing to their antioxidant potential. In this context, tea polyphenols have gained paramount attention of scientific community as therapeutic agents for the prevention and treatment of various oxidative stress induce maladies owing to their structural diversity, strong antioxidant ability and capacity to modulate various expression involved in the pathogenesis of these maladies. The notable polyphenols are catechins which are mainly present in green tea and further subdivided into various compounds like ECG, EGC, EGCG which has their unique therapeutic potential. The catechins undergo various structural changes and transformed into theaflavins and thearubigins in the process of black tea formation. These are high molecular weight polyphenols and promising candidates in obesity, diabetes and cancer treatment. Mechanistically, these polyphenols ameliorate oxidative stress by trapping the noxious radicals like superoxide and peroxy, promote the activity of glutathione, suppressing the malondialdehyde (MDA) activity. The current chapter is an attempt to highlight the therapeutic potential of tea polyphenols.

**Keywords:** polyphenols, diabetes, oxidative stress, cardiovascular complications, catechins

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## 1. Introduction

A fundamental relationship between nutrition, health and disease is diverting the attention of consumers from a medicine towards plant based natural products. Science is progressing with leaps and bounces and the modern era of food technology makes it easy to produce plant based natural products to combat life threatening diseases. In diet based regimen, functional and nutraceutical foods are getting popular especially among scientific community because of their therapeutic potential [1]. Likewise, tea polyphenols have gained paramount importance in modern era of dietary regimen and proved to have potential against several chronic malady. In addition, tea either green or black acts as functional food and is easily available, cheap and safe to use [2]. Tea; a wonderful beverage that has strong historical background and it is being consumed in various part of the world from last 5000 years [3]. Tea has three basic types: black tea, green tea, and oolong that vary due in biological, chemical profile, and in processing methods. However, processing of green and black tea is quite different from each other. Firstly, fresh harvested leaves gone through steaming process in order to avoid fermentation, as a result stable dry final product is obtained. Enzymes which are responsible for the catalysis of color pigments in the leaves is eventually destroyed by steaming [4]. Consequently, with the help of this process green color and natural polyphenols remain stable and provide health promoting properties to tea. Secondly, green tea is fermented to Oolong, and then subsequently, into the black tea. Leaves of black tea are crushed and subjected towards enzymatic oxidation process called fermentation. Green tea and black tea both have different biological properties because the polyphenols of green tea dimerized into several the aflavins as well as higher molecular weight polymers i.e., thearubigins. In other words, these two compounds impart specific flavor and color to black tea [4].

Globally, tea is the most famous beverage but now recent evidences show that it is more than a beverage because it has characteristics of functional food. In addition, it contains unique aroma, desirable taste, caffeine and potential therapeutic property. Tea is produced from plant named "*Camellia sinensis*" family "Theaceae", which is consumed worldwide as green or black tea because of its nutraceutical properties [4]. According to an estimate, tea leaves production in the world is about 3.6 million tons annually, whilst consumption as 120 mL/capita/day [5]. China, India, Sri Lanka, Vietnam and Indonesia are the major producers of tea but among them China is the dominant in production line. Green tea contributes about 20% of total tea production, and famous beverage among East and South-East Asia. On other hand, black tea covers up about 78% of the world share and primarily, consumed in North America, Europe and North Africa.

### 1.1. Bioactive components of tea

Green tea has complicated chemical composition: proteins including some amino acids like theanine or 5-N-ethylglutamine, glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine, arginine, and lysine; carbohydrates including pectins, glucose and fructose; minerals including calcium, magnesium, chromium, manganese, iron, copper, zinc, molybdenum, selenium, sodium, phosphorus, cobalt, strontium, nickel,

potassium, fluorine, and aluminum; trace amount of lipids, sterols, vitamins, pigments, caffeine and volatile compounds [6]. Epigallocatechin gallate is the major component of green tea, make green tea extract more stable due to the presence of some antioxidant as compared to pure form of epigallocatechin gallate [7]. In contrast, major portion of black tea leaves consist of polyphenols. Whereas, along with some macronutrients also contains 6.5% lignin, 5% ash, 1.5% organic acid, 6–9% flavonols, 10–12% phenolic acids, 8–12% methylxanthines, 0.5% chlorophyll, 0.1% carotenoids, and 0.1% volatile substances. Naturally, tea contains phenolic acid, theophylline and linalool as flavoring agents. Furthermore, leaves of black tea have alkaloids including caffeine and theobromine [6]. Like other plant based food products, tea also contains a wide variety of bioactive components, which provide therapeutic potential, including antioxidant, anti-inflammatory, anti-hypertensive, anti-cancerous and immune-modulatory effects [8]. Especially, polyphenols in tea help to prevent from cardiovascular diseases, hyperlipidemia, cancer, diabetes and scavenge free radical species [9]. For instance, kaempferol has potential against metabolic disorders; myricetin modify white blood cell ability to scavenge free radical; quercetin act as antioxidant: so, prevent from cancer; theaflavin work against oxidative stress and cell toxicity thus prevent from DNA cleavage [8, 10, 11] (Table 1).

## 1.2. Classification of polyphenols and its properties

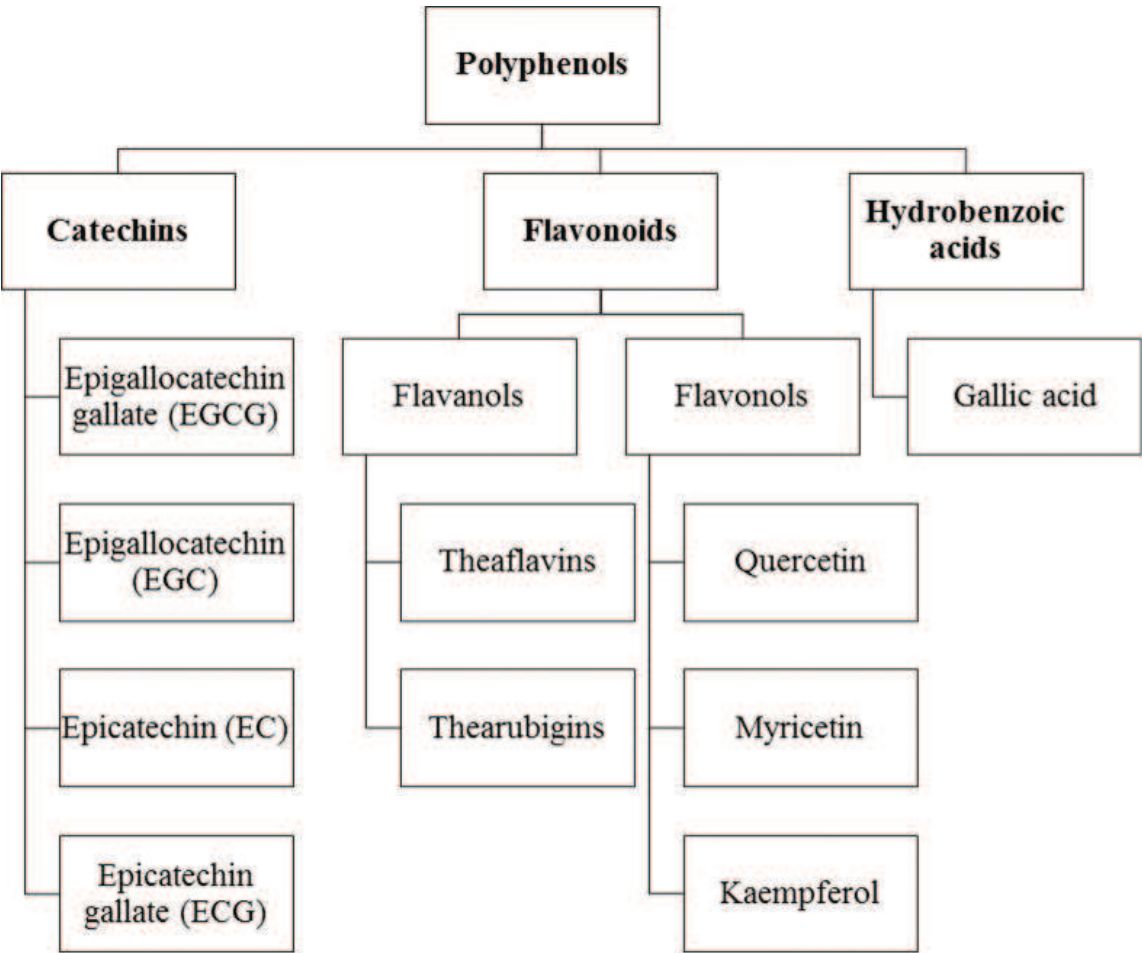
Tea polyphenols has a complex acidic structure which consists of 2-phenylbenzpyran skeleton with several hydroxy groups and aromatic ring. So, electron density of their structure is decrease which leads to weak O—H bond strength and promote proton loss [14]. Presence of asymmetric carbons at the 2 and 3 positions of the pyran ring of the 2-phenylbenzopyran nucleus give it therapeutic and functional potential. Therefore, activation of numerous enzyme systems indicates structural and functional alteration of tea polyphenols [15]. Eventually, black tea holds array of polyphenols approximately 36%; which is in form of oxidized and un-oxidized polyphenols. About 5% are in un-oxidized form like catechins and remaining is in oxidized form including theaflavin and thearubigins which is also produced from catechins

Nutrients	Concentration (%)	
	Black tea	Green tea
Carbohydrates	10–15	5–7
Proteins	12–14	15–20
Lipids	2	Trace amount
Minerals	5	55
Vitamins	Trace amount	Trace amount
Fibers	15–20	Trace amount
Alkaloids	2–5	3–4

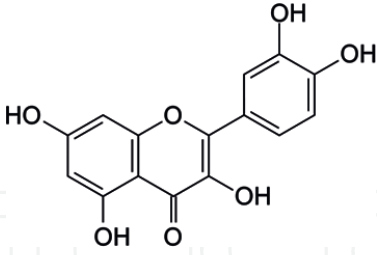
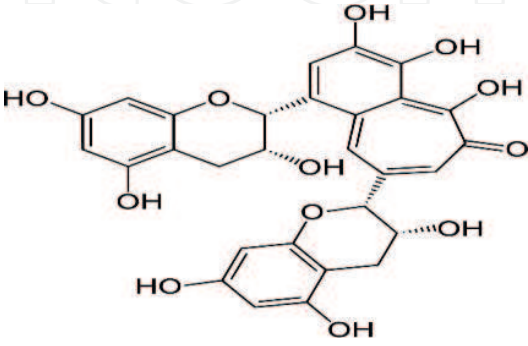
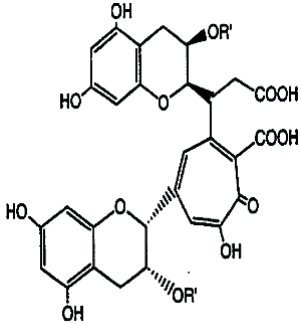
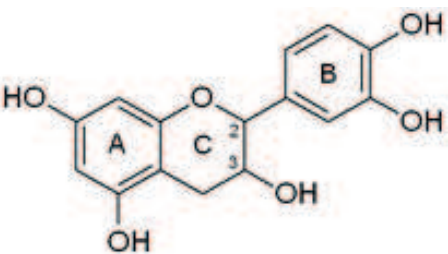
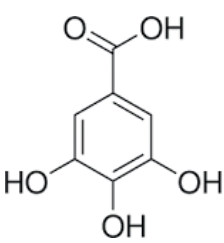
Source: [6, 12, 13].

**Table 1.** Percentages of nutrients in black and green tea.

oxidation. Enzyme mediated fermentation: a step in black tea processing converts 3–6% of catechins into its oxidized form [16]. Simultaneously, 12–19% thearubigins are produce when catechins is further oxidized. Significantly, only 5–10% catechins are able to maintain their structure in form of epigallocatechin gallate and provide anti-oxidative potential [12]. Catechins are present in various form like epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC) and gallocatechin, epigallocatechin digallate, 3-methylepicatechin gallate, catechin gallate, gallocatechin gallate in smaller amount [17]. Certainly, catechins content: present more in black tea as compare to green tea and amount depends upon the age of leaves. During tea production, approximately 75% of tea catechins undergone oxidation and partial polymerization with the help of enzyme called tea leaf polyphenols oxidase. However, black tea composition depends upon technological process, so there is no definitive composition [18]. In addition, it also has a wide range of flavonoids especially flavanols and flavonols. The promising candidates of aforementioned categories of tea flavonoids and other polyphenols of both types of tea are illustrated in **Figure 1** [19]. Major class of polyphenols in tea is flavonoids which is synthesized when carbohydrates act as precursor and adopt metabolic pathways including shikimic and *p*-coumaric acid. Phenylalanine ammonia lyase triggered flavonoids biosynthesis: a photosensitive mechanism [21].



**Figure 1.** Classification of polyphenols in tea. *Source:* [19, 20].

Polyphenol	Structure	Functions	References
Catechins		Act as antioxidant. So, inhibit LDL oxidation. Consequently, prevent heart disease, diabetes and obesity	[12, 16]
Theaflavins		Help to reduce glucose level in the body. However, effective against cancer and neurological disorders	[3, 9]
Thearubigins		Assist in excretion of toxins, especially, in inflammatory diseases. Moreover, reduce oxidative stress and risk of cardiovascular diseases	[23]
Flavonols		Has property to scavenge free radicals and metal chelation. Hence, act as antioxidant, anti-oncogenic, anti-inflammatory and helps in reduction of foam cell formation	[10, 11]
Gallic acid		Protect against oxidative damage	[10]

**Table 2.** Structure and functions of polyphenols.



Alternatively, Green tea also contains 30% polyphenols: flavanols, flavandiols, flavonoids and phenolic acids. Among them flavonols is most common which is also known as catechins; green tea hold catechins in greater proportion as compared to the black or oolong tea [22]. In green tea, four different kinds of catechins are present: epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin gallate. Whereas, proportion of polyphenols especially catechins vary both qualitatively and quantitatively, depends upon the preparation methods [20] (**Table 2**).

## 2. Tea polyphenols and its health claims

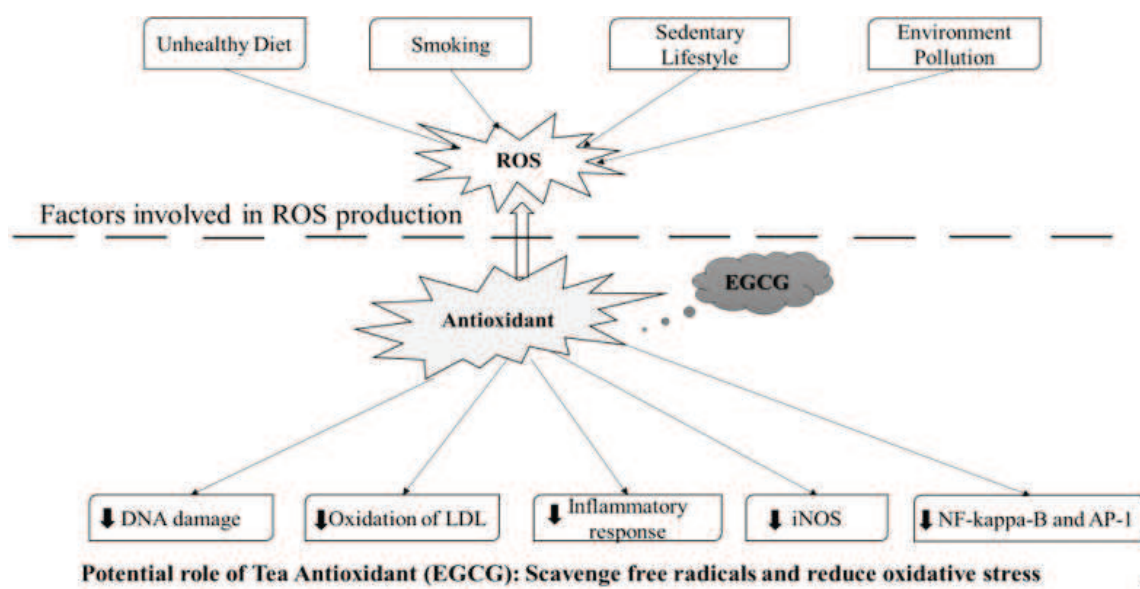
### 2.1. Free radical scavenging activity and its anti-oxidative potential

Reactive oxygen species (ROS) are formed due to mitochondrial oxidative metabolism and some cellular response against xenobiotics, cytokines, and bacterial invasion. Although, excessive ROS leads to imbalance in oxidative stress, they may also cause damage at macromolecular level including lipids, proteins, carbohydrates, DNA; and results in various diseases: atherosclerosis, diabetes, aging, cancer, neurological damage and so forth [24, 25]. Moreover, some other outcomes of oxidative stress are DNA damage, production of mutated tumor suppressor genes and may induce cell death [26, 27].

Antioxidants provide protection against free radicals: by neutralizing and donating electron to free radicals [28]. Improvement in antioxidant defense system helps to reduce free radicals production. Admittedly, glutathione is natural anti-oxidant of the body that maintains intracellular redox status and it acts as co-factor in metabolic reactions. All polyphenols in tea has property of antioxidant, which lessen oxidative stress in the body [29]. Ref. [30] demonstrated antioxidant activities of water extracts of different tea including reducing power, the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging potential and the inhibition of hemolysis caused by 2,2'-azo-bis(2-amidinopropane) dihydrochloride (AAPH)-induced lipid oxidation in erythrocyte membranes and they supported the use of green tea as significant antioxidant. To illustrates, green tea polyphenols: an antioxidant against iodophenol-derived phenoxyl radicals, superoxide anion radicals and lipid peroxidation was observed in rat liver microsomes [31, 32]. Furthermore, several factors are involved in the production of reactive oxygen species; which disrupt the overall intrinsic environment of the body. However, tea polyphenols prevent from DNA damage, reduce oxidation of low density lipoprotein and some other factors shown in **Figure 2**. Thereby, prevent from various life-threatening diseases like cancer, heart disease, inflammatory disorders [29].

### 2.2. Immunomodulatory and anti-inflammatory effect of polyphenols

Immunity is defined as an ability to fight against infection, any abnormal function within the body and prevent from diseases [35]. Certain organs are involved to build up defense mechanism in body including thymus gland, spleen, lymph nodes and bone marrow [36]. Generally, humoral and cell-mediated immunity is enhanced by green tea consumption and reduce the risk of cancers and cardiovascular disease [37]. For instance, tea polyphenols act as antioxidant



**Figure 2.** Free radical scavenging activity of tea antioxidants. *Source:* [29, 33, 34].

and anti-inflammatory agent [38, 39]. Although, inflammation is fundamental to immune system but in some complicated disease, it become causative agent [40]. Dona et al. [41] demonstrated molecular and cellular insight properties of green tea and found that epigallocatechin-3-gallate (EGCG) assist to reduce inflammation. It was observed that mice injected with lipopolysaccharide (LPS), fed them with green tea polyphenols showed a significant reduction in production of tumor necrosis factor- (TNF) and prevented from death even after administration of lethal dose of LPS [42]. Moreover, some studies showed a reduction in joint diseases like arthritis due to consumption of tea polyphenols [43, 44].

Many chemicals are used in order to induce inflammatory response like topical application of phorbol esters: TPA, to check the effect of anti-inflammatory agents. Several studies proved a beneficial effect of green tea polyphenols, by inducing tea polyphenols in mice skin that inhibits TPA-mediated induction of epidermal ornithine decarboxylase (ODC) activity in a dose-dependent manner [45]. Polyphenols prevents TPA-induced oxygen radical-induced cytotoxicity, inhibits intercellular communication in normal human epidermal keratinocytes and also inhibits TPA-induced protein kinase-C activity [46, 47]. Further, tea polyphenols inhibits 12-0-tetradecanoylphorbol-13-acetate and other skin tumor -promoter-caused induction of protein and mRNA expression of the pro-inflammatory cytokines interleukin (1L)-1  $\alpha$  and TNF- $\alpha$ . Skin applications of green tea polyphenols inhibits UV-radiation-induced local and systemic suppression of contact hypersensitivity and edema responses in C3H/HeN mice. In various *in-vitro* studies, green tea polyphenols/crude extracts of green tea have shown preventive effects in system considered essential in inflammatory processes [48]. Flavonoids in tea i.e., epigallocatechin-3gallate inhibits the activation of NF-kappa-B; helps in modulation of MyD88- and TRIF-dependent signaling pathways of TLRs and subsequent inflammatory target gene expression [49]. Nuclear factor-kappa-B is a transcriptional factor in oxidative stress that regulates numerous gene expression crucial in cellular responses, including inflammation, innate immunity, and growth. In a similar study [50] researchers illustrated that EGCG



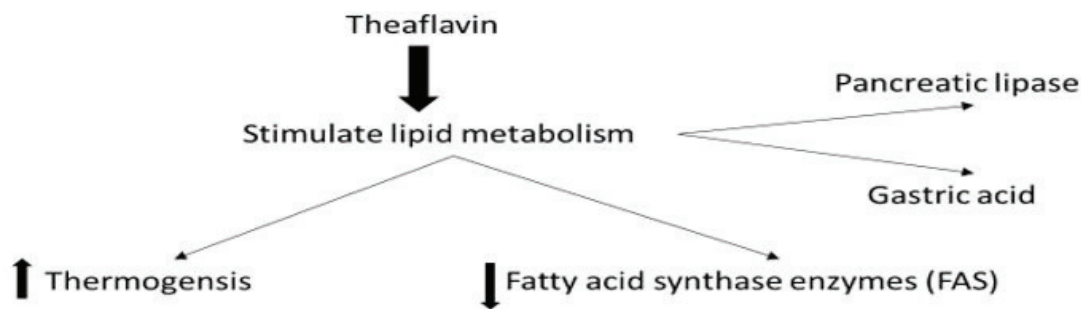
inhibits LPS-induced inducible nitric-oxide synthase gene expression in mouse peritoneal macrophages by subsequently, lowering NF- $\kappa$ B. To put all aforementioned mechanism in nutshell, tea has certain elements like polyphenols that proved to have anti-inflammatory response.

### 3. Regulation of several physiological process and disease prevention by tea polyphenols

#### 3.1. Therapeutic properties of polyphenols in hyperlipidemia and hypercholesteremia

Hyperlipidemia is characterized as high lipid level in the body which may leads to certain metabolic dysfunctions: cardiovascular diseases, high blood pressure and stroke. Black tea is proved to be beneficial against hypercholesterolemia and platelet aggregation because it contains oxidized and un-oxidized catechins. In addition, black tea contains antioxidants which can combat with oxidative stress, endothelium dysfunction and arterial complications [51, 52]. Tea polyphenols: prevent LDL oxidation; balance HDL level and limits intestinal cholesterol absorption [53]. A scientist [54] mentioned in their study that polyphenols administration about 7 g/L for a course of 35 days attenuating lipid profile and hepatic oxidative abnormality in both normal and hypercholesterolemic male Wistar rats. It was observed that, black and green tea increases fecal excretion of fatty acids and sterols, thus provides protection against serum and hepatic abnormalities in hypercholesterolemic phase [55]. Moreover, Black tea polyphenols in amount: 500 and 1000 mg/kg body weight provision to male Wistar rats for 8 weeks caused a significant reduction in total cholesterol, increase LDL and triglycerides along with better HDL profile [56].

Theaflavin is helpful against lipid related abnormalities because it stimulates cellular energy expenditure at mitochondrial level. However, it also suppresses FAS expression by down regulating EGF-receptor/PI3K/Akt/Sp-1 signal transduction pathway, hence, inhibits the cellular lipogenesis and tissue growth. Furthermore, theaflavin especially TF-3, ultimately suppresses biosynthesis of cholesterol, triglycerides and fatty acids by inhibiting growth factor EGF; binding to receptor EGFR, restricts PI3K/Akt signal pathway activation and decreases DNA-binding capacity of nuclear transcription factor Sp-1; consequently, down regulates FAS gene and modulates LDL receptors that facilitate in cholesterol and triglycerides reduction [57, 58]. Likewise, theaflavin a potent antioxidant, stimulates lipid metabolism by regulating pancreatic and gastric secretion; thereby, cause reduction in lipid level and fatty acid synthase enzyme shown in **Figure 3**. Another possible route, cholesterol micelle solubilization interferes with lipid lowering [60]. Theaflavin causes change in structure of micelles and leads to reduction in cholesterol re-synthesis and eventually, alters its metabolism [57, 61]. Development of atherosclerosis takes place due to LDL oxidation: abnormal changes in macrophages and join with macrophage scavenger receptor; results in foam cell formation that deposit in the walls of arteries. Tea polyphenols has an ability to scavenge free radicals and inhibit foam cell formation and deposition [56, 62]. Tea polyphenols also scavenge  $H_2O_2$ , so, a natural antioxidant including glutathione, glutathione peroxidase and glutathione reductase activity is increased. Moreover, it enhances LDL particle size and improve the adiponectin metabolism



**Figure 3.** Role of theaflavin in regulating lipid mechanism. *Source:* [14, 56, 59].

[63, 64]. It is observed that there is a direct relationship between high fat diet or high sucrose diet and triglycerides production which triggers lipogenesis [32]. Whereas, tea polyphenols possess potential to normalize lipid abnormalities: inhibit intestinal lipid absorption, increasing fecal excretion of fat through bile acid, suppressing the activity of fat synthesis enzymes and thereby, prevent lipogenesis [65]. Furthermore, high sucrose diet cause hypertriglyceridemia because production of acetyl CoA elevated which in turn raise triglycerides. Polyphenols activate activation of LKB1-AMPK pathway; AMPK (protein) involve in glucose homeostasis that consequently, involve in the synthesis of glucose-6-phosphate and cause fatty acid metabolism. Hence, in short tea provide a helping hand towards lipid metabolism; reduce lipid oxidation and lipid absorption; thus reducing risk of hyperlipidemia [58].

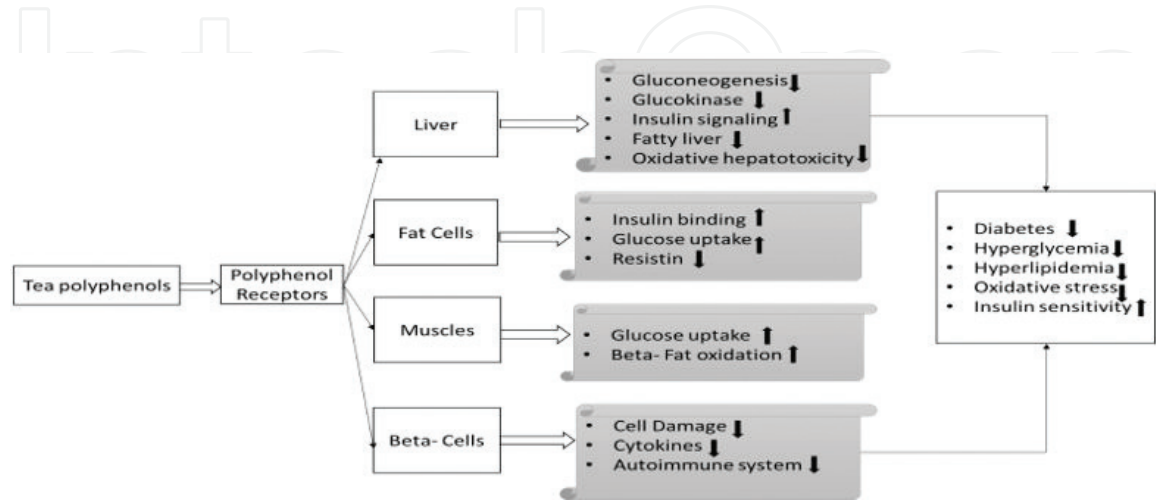
### 3.2. Effect on carbohydrates metabolism-diabetes mellitus

Diabetes has been increasing at an alarming rate, due to poor dietary habits and sedentary lifestyle. According to an estimate, 300 million people will be affected by diabetes until 2025. In general, type 2 diabetes is defined as malfunctioning of pancreatic  $\beta$ -cell but dietary intervention and healthy life style is the best way to manage diabetes. Moreover, evidence showed that tea act as anti-diabetic agent: attenuate hyperglycemic state; thus, modify glucose metabolism and insulin secretion [66]. Tea polyphenols improve glycogen syntheses system by re-activating the glycogen synthesis and lower liver glucose-6-phosphatase activity [67]. Similarly, in one study, 16 subjects were provided 75 g of glucose and water per day with simultaneous provision of 3 g instant black tea. It was found that tea polyphenols help to stimulate the pancreatic enzymes that enhance  $\beta$ -cell ability towards insulin [68]. Mechanistically, tea: a hypoglycemic agent, modulate glucose transporter (GLUTs) that helps to maintain glucose homeostasis and requires  $IR\beta$  and AMPKR proteins for their translocations. However, in hypercholesterolemia, diet high in fats leads to reduce GLUT4 and other associated proteins. Subsequently, there is a disturbance in glucose incorporation into the cells, thus, cause progression of diabetes and insulin resistance [69, 70]. Surprisingly, tea polyphenols inhibit  $\alpha$ -glucosidase and  $\alpha$ -amylase activity which leads to reduction in intestinal glucose absorption and insulinomimetic action [71]. Further, diet rich in fructose and sucrose trigger abnormal glucose production, and effect hormones in plasma including adiponectin and intestine GLUT1 [72]. Studies proved that tea has an ability to improve insulin resistance in both hypercholesterolemic and hyperglycemic models [65]. It has been estimated that about 15-fold increase in insulin activity due to black tea extract consumption was observed in *in-vitro* study.

The identified bioactive constituents theaflavin, thearubigins, EGCG and catechins in tea enhanced activity of GIP and GLP-1 factors in order to improve the insulin secretion. Besides, theaflavin, its derivatives and thearubigins regulate insulin signaling process including growth factors insulin/IGF-1 in FOXO1a, PEPCK of mammalian cells thus, improved dysregulation of hepatic gluconeogenesis [73]. Glycemic response can be managed through tea polyphenols intake, that in turn lower risk of diabetes and increase insulin sensitivity; a mechanism described in **Figure 4**. Thereby, tea polyphenols proved to reduce the risk of diabetes and diabetic complications by improving glucose uptake in adipocytes and decreasing leptin production [71, 74].

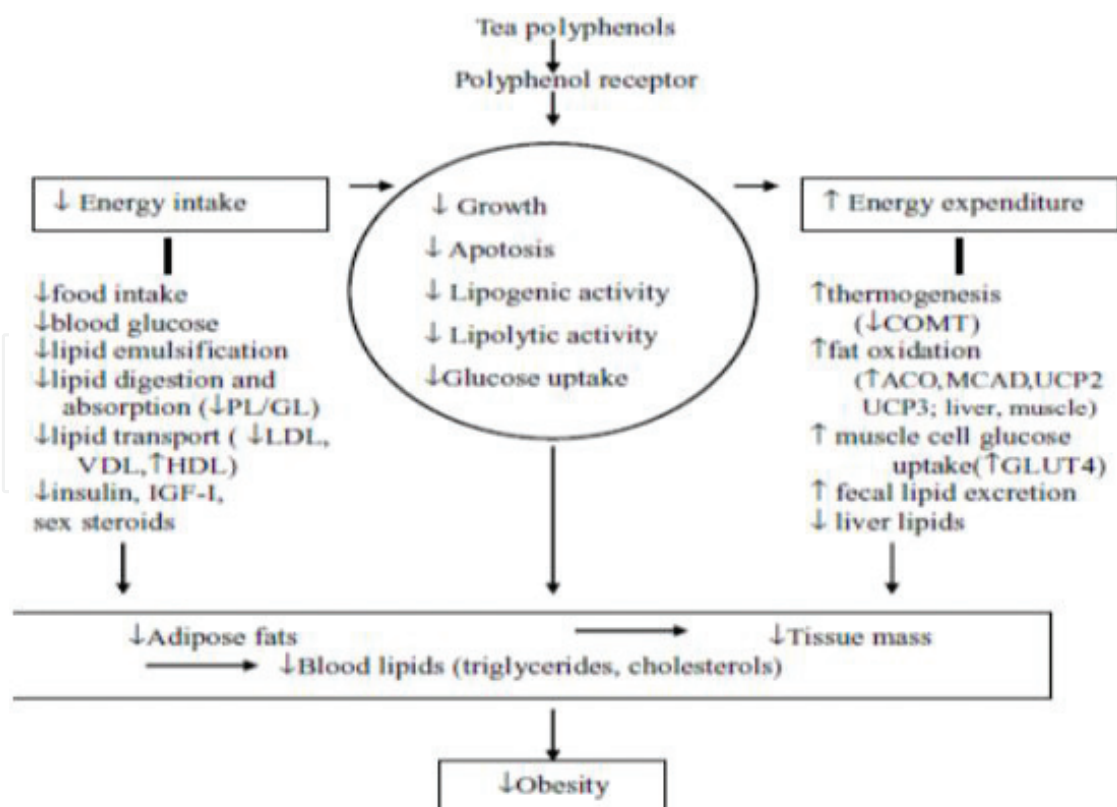
### 3.3. Effect on obesity

Obesity and the existence of other diseases associated with obesity persist a global health problem. Current estimates in the USA demanded a fear full situation that almost one-third of the adult peoples obese. Obesity defined as body mass index  $\geq 30\text{kg/m}^2$  is a universal lifestyle-related illness increasing at an upsetting rate. Among related factors, dietary habits are measured one of reasons for its postponement [47]. During the last limited years, enlarged consumption of carbohydrate and animal fat has backed to obesity thereby increased occurrence of hyperlipidemia and diabetes mellitus. For the cause, functional ingredients are getting devotion to improve lipid metabolism and resistor obesity. In this background, black tea is a promising tool to improve thermogenesis and fat oxidation. Provision of black tea remove (0.2%) rich in polyphenols caused significant decline in the markers related with obesity (body weight) of obese CF-1 mice [39]. Black tea antioxidants like theaflavin and thearubigins have probable to prevent fat oxidation and decrease the fascination of nutrients in gastrointestinal track. Furthermore, they manage the energy feeding thus prevent LDL testimony and obesity. In an animal trial model, rats were fed on high fat diet with immediate drink delivery containing 5% black tea polyphenols cutting (BTPE) and seen 44.2% decrease in weight [16]. Mechanically, the aflavin constrains the pancreatic lipase activity together with intestinal lipid absorption thus lessens the gain in weight. Previous research inquiries have painted that the



**Figure 4.** Glycemic response management: mechanistic illustration of black tea polyphenols. *Source:* [74].

compounds containing galloyl moiety blocked the post prandial hypertriacylglycerolemia by decelerating down the triacylglycerol absorption through the hang-up of pancreatic lipase [9]. The aflavin comprises two digallate groups thereby have more probable for weight managing than thearubigins. On molecular level, dissimilar enzymes played a key part to regulate lipid metabolism yet, fatty acid synthase (FAS) is a thoughtful factor. Its Imbalance activates the cascade of certain sicknesses like obesity, cardiovascular problems and cancer uprising [28]. The FAS inhibitors may assistance in weight management and in this background, black tea theaflavin is a gifted ingredient. It blocks FAS over the deactivation of PI-3 K/AKT/Sp-1 trail owing to galloyl moiety. Unlike scientific opinions are explained that the black tea gallate polyphenols (theaflavin) achieve the body weight by moderating the cholesterol metabolism, constrain the reabsorption of bile acid and delay the synthesis of fatty acid enzymes via impersonating the AMP-activated protein kinase trail in HepG2 cells [22]. Among the other likely anti-obesity ways are modulating the action of superoxide dismutase and catalase that hunk the start of oxidative stress, by up regulating the GLUT1 and GLUT4 genes appearance, different genes expression and defend the hepatic tissue through black tea polyphenols therefore helpful in the weight management package [25]. Many observational studies have interweaved the ingesting of black and green tea with reduced low-density lipoprotein oxidation and improved insulin action in animals and humans. In a community based test, tea polyphenols administration resulted helpful impact on the aging diabetic subjects by controlling insulin and glucose metabolism [13] (Figure 5).



**Figure 5.** Mechanism of tea polyphenols on obesity reduction. Source: [64].



High cholesterol diet i.e., 1.5% of cholesterol beside with high sucrose diet 40% was assumed to the normal rats to persuade hypercholesterolemia as well as obesity. Periodic examination of rats was approved out to assess the orientation of obesity. The functional drinks were providing to the rats alongside to harmonize their effect on the own group [17]. Obesity is related with systemic oxidative stress, adipokine inequity and condensed antioxidant defenses, top to dyslipidemia, vascular disease and hepatic steatosis. Gastrointestinal lipase inhibitors delay fat digestion and fascination. Phenolic lipase inhibitors such as epigallocatechin-3-gallate, grape seed, kaempferol, quercetin, ellagitannin, tannins and proanthocyanidins are existing in green and black tea, berries (lingonberry, bearberry, arctic bramble, cloudberry, strawberry, raspberry and blueberry); garden pea (*Pisum sativum*), Norway spruce (*Picea abies*), large-leaved lime (*Tilia platyphyllos*) [23].

Obesity is related with bigger health-care costs, compact quality of life, and rise risk for premature death, Cholesterol is one of the vibrant compounds, lipophilic in nature that does numerous metabolic functions in the body. It is essential four lipoproteins; chylomicron (CM), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) for its carriage. In hypercholesterolemic state, numerous metabolic dysfunctions like coronary complications, high blood pressure and stroke are the allied syndromes [66]. Black tea polyphenols deliver protection in contradiction of hypercholesterolemia and platelet combination owing to the occurrence of oxidized and un-oxidized catechins. Moreover, black tea antioxidants have possible to challenge oxidative stress, endothelium dysfunction and arterial complications [2].

### 3.4. Cardiovascular diseases and hypertension

Cardiovascular diseases are leading reason of morbidity and mortality all over the world. High cholesterol and oxidation of LDL activate the cascade of events leading to start of atherosclerosis. Defective immune system results in onset of numerous health disparities branded as autoimmune disorders and immune dysfunction [7]. In the light of some previous epidemiological studies it was assumed that the higher flavonoids consumption through natural commodities measured allied with decrease risk for cardiovascular disease by improving endothelial role. Inhibit low-density lipoprotein and recover dyslipidemia. In the routine of diet based therapy, polyphenols reached core care as a coronary cover agent [14]. Among the polyphenols, tea bioactive moieties catechins, theaflavin and thearubigins are in attention for curtailing the menace. Many scientific explorations exposed an opposite suggestion between tea intake and lipid abnormalities as it opposites LDL oxidation and rises HDL level in obese and diabetic models. The slogan “good cholesterol” is credited to HDL due to its skill to reverse the cholesterol transport (RCT), eliminates the extra cholesterol from the tissues and arteries back to liver. It chiefly acts on sub-endothelial planetary in medium caliber artery that is the place where actual cholesterol testimony in the form of atheroma happens [26]. In contrary, LDL called as bad cholesterol because it transports the cholesterol from liver to the body. Now, great attention is being paid to the decrease of LDL by different therapeutic devices but, various epidemiological studies also specified the role of HDL for the administration of cardiovascular health [43].



Decreasing the atherogenic index and reverse the oxidation of fat are the possible mechanisms by which theaflavin may improve the plasma HDL level. Atherogenic index is the proportion between LDL and HDL and theaflavin significantly modifies the cholesterol metabolism, over-turns the activity of lipid synthesis enzymes and protects the LDL in contradiction of oxidation thus improve the HDL. Cholesterol testimony in arterial wall needs a receptor called as prostacyclin [38]. Frequent studies floodlit that the high HDL may stop this process. In fresh lipid talking therapies, HDL enhancement advances importance and in this context prostacyclin inhibitors are in attention. Black tea polyphenols have skill to act as prostacyclin inhibitors thus progresses HDL that finally protect cardiovascular health [51].

Flavonoids contain of a large group of 6000 familiar phytochemicals originate in vegetables and fruits. Fresh scientific exploration point outs upon their antioxidant and anti-inflammatory actions. Such flavonoids typically don't deliver any nutrition, because they display very important useful act in the cardiovascular, gastrointestinal, cancer, and neurodegenerative like life risking maladies prevention. Metabolic syndrome is a disorder of at least three of the cardiovascular risk factors: obesity, unnecessary visceral fat storage, dyslipidemia, hypertension and hyperglycemia or Type 2 diabetes. It is a state of insulin fight, oxidative stress and chronic inflammation. Cardiovascular disease is the uppermost cause of death globally. Convinced dietary components and over 800 plants help stop or moderate metabolic syndrome by secondary the body homeostasis mechanisms [1].

Hypertension, also known as high blood pressure, is extra condition related to metabolic syndrome. Tea polyphenols has been shown to decrease blood pressure and recover endothelial function in animal studies. Endothelial dysfunction is a change of endothelial cells, resultant from oxidative stress and reduced vasodilator reply. Both hypertension and disturbed homeostasis of the ratio of HDL-cholesterol and low-density lipoprotein-associated (LDL)-cholesterol are danger factors for cardiovascular disease. The effect of green tea cutting on arterial hypertension in Sprague-Dawley rats was inspected [73]. The animals were preserved with angiotensin (Ang) II to encourage to the progress of hypertension. At the end of 13 days experiment, Ang II treated rats had amplified blood pressure and left ventricle mass. Co-treatment with 0.6% green tea quotation as the sole basis of drinking fluid rounded these rises. Green tea treatment also condensed Ang II-induced rises in plasma hydroperoxides and aortic endothelial appearance of hemeoxygenase I and SOD, representative a decrease in vascular oxidative stress. A second study by the similar group originate that 0.6% green tea quotation as the sole source of drinking fluid abridged final systolic and diastolic blood pressure by 20 and 24%, correspondingly in Ang II treated rats after 14 days. Gene expression trainings in the hearts of treated rats displayed that green tea extract treatment abridged Ang II persuaded expression of NAD(P)H oxidase appearance and activity linked to Ang II-treated controls [19]. This protein plays a key role in the initiation of endothelial oxidative stress by Ang II. Alike decreases in the appearance of Akt and extracellular responsive kinase (Erk) 1/2 were observed. Both enzymes are downstream effectors of NAD(P)H oxidase. He examined the effect of EGCG on spontaneously hypertensive rats (SHR), a sketch of hypertension, insulin resistance and obesity. The absence of effect on blood pressure may be due to change in this model from the SHR model, alterations in dose, or some other factor [36]. Treatment of a type 2 diabetes rat model, the Otsuka Long-Evans Tokushima Fatty rat, with 30 mg/kg/day tea

catechins for 12 weeks was revealed to advance endothelial function. Systolic blood pressure was abridged by 10% associated to saline-treated regulator rats. Catechin-treated rats also showed increased vasodilation in answer to sodium nitroprusside treatment. These effects look to associate with decreased NADH oxidase appearance and activity. Green tea provisions have been exposed to encourage vasodilation *in vitro*. Using rat aortic rings, have exposed that EGCG can facilitate dose-dependent vasodilation. Green tea and green tea polyphenols have been revealed to modulate plasma and tissue levels of both HDL- and LDL-cholesterol. Many investigators have reported that tea polyphenols can stop the oxidation of LDL cholesterol *in vitro*. For example, 1–10 µg/mL green tea extract was shown to dose powerlessly reduce LDL oxidation persuaded by umbilical vascular endothelial cells. A 61% decrease in LDL oxidation was experiential following treatment with 10 µg/mL green tea excerpt [74].

### 3.5. Hepatic disorder and oxidative stress

Liver has a pivotal role in modification of numerous physiological processes in the body such as metabolism, secretion and storage. It has great size to detoxicate toxic matters and synthesize useful principles. Therefore, harm on the liver imposed by hepatotoxic agents is of grave significances [35]. Indications developed over the last years have optional that numerous forms of liver damages may be caused by free radical creation and subsequent oxidative stress. It is supposed that reactive oxygen species (ROS), such as hydroxyl radical, superoxide radical anion and nitric oxide may hurt cell membranes done lipid peroxidation [40]. Deceptively ROS adjust or damage biomolecules, i.e., proteins, lipids, carbohydrates and DNA [7].

### 3.6. Prevention of obesity-related fatty liver disease by green tea polyphenols

Hepatic steatosis (fatty liver) is a disorder that is defined by fat addition within hepatocytes that surpasses 5% of the liver by weight [39]. Firstly, it was supposed that this condition was mostly attributable to additional alcohol ingesting, but studies in the last numerous decades have also related obesity and diabetes to the attendance of fatty liver [60]. Characteristically, fatty liver syndrome related to etiological factors other than alcohol is mentioned to as non-alcoholic fatty liver illness (NAFLD). Now, non-alcoholic fatty liver disease (NAFLD) is the most mutual form of liver disease [8]. It is now extensively putative that NAFLD is the hepatic constituent of the metabolic syndrome; risk factors for the disease comprise obesity, insulin confrontation, and hypertriglyceridemia [30]. Dysfunction in lipoprotein metabolism may also play a part in the growth of hepatic steatosis. Treatments with tea in animal models have exposed to modulate numerous of these conditions. More studies essential to be lead on the specific mechanisms of green tea that arbitrate its benefits on liver function, and the fundamental mechanisms of action. For example, EGCG and other catechins decrease fatty acid synthase in cells and cell-free studies but effects by exact tea catechins need to be proved *in vivo* [49].

### 3.7. Oxidative stress and safety concerns

Oxidative stress is an inequity between the reactive oxygen species and endogenous antioxidants that disturbs normal detoxification of free radicals, made in a biological system. This situation troubled the body redox potential and compensations the cell mechanisms including

protein and lipid thereby changes the cellular motioning [44]. Reactive oxygen species (ROS) are produced continuously within the body though; some factors like unhealthy diet, smoking, deskbound lifestyle, environmental pollutant etc. may improve their production. Improvement in the antioxidant defense system is of primary anxiety to mitigate free radicals manufacture. In this milieu, intake of polyphenols rich diet is inevitable to maintain the body antioxidant potential [14, 68].

### 3.8. Renal complication

Kidney does numerous life supporting functions counting body homeostatic, directive of electrolyte stability, blood pressure and exclusion of poisons in the form of urine. Throughout the recent era, in the emerging countries there is a fast rise in the chronic kidney disease (CKD) due to chemical contact, environmental toxins and poor dietary ways. In CKD, nephrons lost their physical and functional integrity that clues to reduce glomerulus filtration, rise blood urea and creatinine [3]. Chronic kidney disease (CKD) is a quiet killer branded by the liberal loss in renal function at a gentler pace. It comprises blood vessel disorders foremost to nephrons dysfunction that eventually reduces the glomerulus filtration. Renal dysfunctionality is more predominant in patients with high blood pressure, diabetes and cardiovascular problems [10]. Raised creatinine and blood urea levels were seen in the chronic renal letdown due to damage in glomerular filtration rate thus reduce urinary excretion. Recent studies supported the competence of black tea polyphenols to trigger antioxidant enzymes thus recover kidney detoxifying ability. Similarly, plasma creatinine and blood urea nitrogen levels were weakened in the diabetic rats after tea polyphenols treatment [47]. Black polyphenols decrease creatinine level by their anti-platelet exploit and allow kidneys to recover their normal function. It has been experiential that black tea polyphenols exhibit diuretic result thereby enhance the general kidney functioning like renal blood flow, capillary expansion and glomerular filtration. The *in vivo* renal functioning parameters like blood urea nitrogen and creatinine were augmented during the oxygen lacking state. However, black tea abridged urea and creatinine by 11.74 and 14.62%, respectively. The oxidative stress persuaded some morphological abnormalities in glomerulus, capillaries and tubules structures [59]. Furthermore, inflammation, sore lesion and distortion in tubules were also experimental. Provision of black tea elevates the renal functioning by mitigating the abnormal signs of kidney and inflammation. In a study, improvement in urea and creatinine stages in rats fed on high arginine diet was experiential due to the manufacture of uremic acid toxins and conquest of certain key hormones. However, black tea polyphenols supplementation caused discount in these abnormal indicators. The effective role of tea polyphenols in the arachidonic acid metabolism pathway may be one of the likely route by which they regularize the kidney malfunctioning. Numerous scientific evidences are in errand that tea polyphenols abridged kidney inflammation by overpowering the prostaglandin (PG), thromboxane A<sub>2</sub> and cyclooxygenase words of arachidonic acid in microsomes and glomeruli. Impaired glomerulus filtration that is a first sign of CKD and black tea is lime lighted for handling the irregularities of glomerulus filtration by dipping toxic impact of sensitive oxygen species and refining the overall antioxidant status. Black tea polyphenols resulted noticeable decline in the creatinine level by their act on platelets thus allows kidneys to recover their normal functioning [46]. Furthermore, the diuretic effect of black tea improves renal blood flow, capillary expansion and glomerular filtration. The black tea

decreases the formation of toxins, quenches free radicals and counteracts reactive oxygen species together with diuretic effect. Furthermore, improvement in inflammation, sore lesion and deformation in tubules are the foremost routes for renal modulating action. In an initial attempt, renal dysfunctionality was persuaded in Sprague Dawley rats by sub chronic administration of 3-methyl-2-quinoxalin benzenevinylketo-1,4-dioxide (QCT). The rats were providing black tea polyphenols blood urea, creatinine and urinary 8-OHdG levels were the board outcomes. The QCT persuaded higher urea, creatinine and 8-OHdG that were weakened significantly by black tea polyphenols [64].

## **4. Dosage and adverse effect of excessive use of black tea**

### **4.1. Black tea side effects**

#### *4.1.1. Diarrhea*

As caffeine boost up digestive secretions so if you drink black tea in large quantities, then it might have an adverse effect on your health. As a basic ingredient of black tea, it also results frequent and watery stool.

#### *4.1.2. Constipation*

As minor agent's black tea contains lot of tannins which might cause constipation and also makes the stool hard to pass out due to more water absorption capacity of tannins.

#### *4.1.3. Disturbed stomach*

Your stomach may feel irritation and discomfort due to excessive caffeine in black tea. The major side effect associated with heavy black tea consumption is increased gastric abnormalities.

#### *4.1.4. Heart diseases*

For patients recovering from heart attacks or acute cardiovascular disorders black tea is highly limited due to its unfavorable effects on heart muscles.

#### *4.1.5. Other health hazards*

Women of reproductive age should not consume more than 2 cups a day of black tea due to increased chances of miscarriage. The high caffeine content is also associated with a negative effect on people eyes health, high blood pressure and anxiety related disorders [33].

### **4.2. The side effects of green tea**

#### *4.2.1. Stomach maladies*

Caffeine could be the most widely recognized offender. Although it has a lower measure of caffeine than different sorts of tea, still it can cause issues. This is because caffeine expands the



measure of corrosive engaged with the stomach related process. This can cause torment or sickness [26]. Likewise, however green tea has been touted to anticipate growth, particularly gastric tumor, contemplates say that there is deficient data in such manner.

#### *4.2.2. Iron deficiency and anemia*

Green tea contains tannins that square the assimilation of iron from sustenance and nourishment supplements. Certain sources say that adding lemon to green tea or savoring it between suppers can counter this issue. Additionally, expending tea can diminish the assimilation of iron from plant-based sources (as much as by 64%). For alleviating the impact, one can drink tea no less than 1 h earlier or after dinners; and furthermore, incorporate more sustenance rich in vitamin C (as vitamin C helps in press assimilation). This happens when the polyphenols tie to the iron in the intestinal cells and keep it from entering the circulation system. This polyphenol-press complex is in the long run discharged from the body [65].

#### *4.2.3. Irregular heartbeat*

Once more, due to the caffeine, green tea may make mellow extreme cerebral pains. What's more, cerebral pains can likewise be caused by press insufficiency, which, as we have seen as of now, could happen through an over the top admission of green tea. Aside from migraines, green tea can likewise cause discombobulation. What's more, according to contemplates, the most extreme endured dosage of green tea in people is 9.9 g for every day—which is generally comparable to some the refreshment in a day. One vital point to note is that however the green tea extricate is recorded in more than 100 over-the-counter natural supplements and arrangements, its utilization as a treatment for any sickness isn't entirely managed by the FDA. Likewise, the security of the long-haul utilization of green tea separates is not unmistakably characterized. Green tea can make one feel unsteady and temperamental, which may not be the situation with decaffeinated green tea items [69].

#### *4.2.4. Vomiting and diarrhea*

According to one Indian investigation, green tea polyphenols can, truth be told, cause oxidative pressure. What's more, exorbitant admission of caffeine, including that from green tea, can trigger sickness and regurgitating. Direct measures of caffeine are noted to be 300–400 mg for each day. In the event that the sum surpasses, it can bring about certain symptoms, including retching. Loose bowels could happen on the off chance that you are new to green tea. Free stools could be one of the gentle symptoms (because of the caffeine content), which can in the long run die down as you get used to the drink. The runs can likewise occur with over the top admission of green tea. One approach to stop this is to decrease the utilization [55].

#### *4.2.5. Muscle tremors and contractions*

Over the top caffeine utilization has likewise been connected to muscle fits and jerking. Also, people with a strange sinus musicality must utmost caffeine admission. Caffeine has likewise been connected to anxious leg disorder. In the event that you are a person with mellow to direct seriousness of this condition, it is better you check your green tea (or caffeine)



consumption. One basic normal for fretful leg disorder is the indications happening when the individual is dormant. This could occur in the night while going to bed, or an irritated agony at night, or jerking of the legs in the evening time [53]. Caffeine could irritate any of these side effects, including muscle fits. 240 ml of green tea contains around 25 mg of caffeine, and as indicated by one report, this caffeine can likewise cause tremors.

#### 4.2.6. *Heartburn*

Green tea is acidic, and thus can aggravate the esophageal coating, causing indigestion or indigestion. The condition could deteriorate if an individual is now experiencing indigestion (or heartburn). Despite the fact that ordinary prepared green tea could not be so intense, the packaged green tea that you so frequently find in the business sectors could be the genuine risk. This is on account of the greater part of the green teas that come in bottles are strengthened with an acidic additive like ascorbic corrosive. This additive can relax the lower esophageal sphincter, which generally shields the stomach corrosive from ascending the throat [52].

#### 4.2.7. *Hepatic disorders*

These days, green tea removes are enthusiastically showcased as weight reduction supplements. In spite of the fact that there is little proof supporting the adequacy of green tea in this viewpoint, certain genuine reactions, including intense liver disappointment, are being accounted for further research. The catechins in green tea convey tremendous advantages like brought down cholesterol and lessened danger of tumor and cardiovascular infection. In any case, if taken in high measurements, particularly like the dose in weight reduction supplements, these catechins cause liver poisonous quality. Green tea supplements contain tremendous measures of polyphenols, the most surely understood of them being EGCG (likewise called epigallocatechin gallate). According to certain case reports, utilization of 700–2000 mg of EGCG every day prompted genuine liver issues [18]. Consequently, on the off chance that you are at a danger of building up a liver infection, confine your green tea admission.

#### 4.2.8. *Osteoporosis*

Caffeine has been found to restrain calcium ingestion. It can likewise build the rate of calcium discharge in the body. According to one investigation by the University of Connecticut, utilization of green tea extricates brought about lower femur length. It likewise prompted bring down volume, mineral substance, cortical volume and thickness of the bone. This recommends utilization of substantial amounts of green tea can prompt a lessened rate of bone collection amid the developmental years of a person.

#### 4.2.9. *Kidney issues*

An audit of studies has demonstrated that the very polyphenols that are credited with averting tumor and coronary illness can likewise cause kidney harm if taken in over the top amounts. According to specialists, individuals devouring green tea supplements must exercise alert, specifically.

## 5. Safe dose level of green and black tea

A perfect measurement of green tea is 3–5 glasses for every day, which could be equivalent to 1200 ml (or 250 mg of catechins). Never take green tea on an unfilled stomach as it may cause liver poisonous quality. It is recommended to take 2 or less than 4 cups of black tea per day for a normal adult to be active due to high concentration of caffeine in black tea and its associated side effects prevention [61].

## 6. Summary

Tea is an important commodity with significant health benefits. The tea polyphenols are of sufficient capabilities to ameliorate numerous lifestyle related maladies. A wide range of functional ingredients from tea phytoceutics provide a great tool to be utilized as a dietary remedy to avoid health issues like diabetes, cardiovascular disorders, hepatic and renal stress. Alongside, antioxidant potential of black and green tea is promising to prevent oxidative stress induced metabolic malfunctions in the body. Tea polyphenols also exhibit anti-obesity and anti-inflammatory effects. These further assuage lipid metabolism and show positive effects on lipid profile of an individual. Despite various health promoting perspectives, overconsumption of black and green tea may give rise to certain uncomfortable side effects. However, these side effects can be managed by utilizing recommended amounts of tea. In a nutshell, tea polyphenols are promising dietary components with significant disease preventing perspectives and easy to be utilized hence, providing a low cost strategy in prophylaxis of oxidative stress mediated malfunctions.

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## Acronyms and abbreviations

EC	Epicatechins
ECG	Epicatechin gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
PPO	Polyphenol oxidase
ROS	Reactive oxygen species
DPPH	1,1-diphenyl-2-picrylhydrazyl

AAPH	2,2'-azo-bis(2-amidinopropane) dihydrochloride
LPS	Lipopolysaccharide
TNF	Tumor necrosis factor
TPA	Tropical phorbol esters
ODC	Ornithine decarboxylase
1L-1 $\alpha$	cytokines interleukin
TC	Total cholesterol
TFs	Theaflavins
TG	Triglycerides
TRBs	Thearubigins
NF-kappa-B	Nuclear factor-kappa-B
TRIF	TIR-domain-containing adapter-inducing interferon- $\beta$
TLRs	Toll-like receptors
FAS	Fatty acid synthase enzyme
EGFR	The epidermal growth factor receptor
SP1	Specificity protein 1
H <sub>2</sub> O <sub>2</sub>	Hydrogen peroxide
AMPK	Activation of activated protein kinase
CoA	Co-enzyme A
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
GLTU	Glucose transporters
PEPCK	Phosphoenolpyruvate carboxykinase
RCT	Reverse the cholesterol transport
PG	Prostaglandin
SHR	Spontaneously hypertensive rats
NAFLD	Non-alcoholic fatty liver disease
OHdG	8-hydroxy-2'-deoxyguanosine
CKD	Chronic kidney disease
QCT	3-methyl-2-quinoxalin benzenevinylketo-1,4-dioxide

## Author details

Ali Imran<sup>1\*</sup>, Muhammad Umair Arshad<sup>1</sup>, Sana Mehmood<sup>1</sup>, Rabia Shabir Ahmed<sup>1</sup>, Masood Sadiq Butt<sup>2</sup>, Aftab Ahmed<sup>1</sup>, Muhammad Imran<sup>3</sup>, Muhammad Sajid Arshad<sup>1</sup>, Neelam Faiza<sup>1</sup>, Iahtisham Haq<sup>4</sup>, Shahzad Ali Shahid Chatha<sup>5</sup>, Muhammad Shahbaz<sup>6</sup>, Qasim Ali<sup>7</sup> and Muhammad Waseem<sup>8</sup>

\*Address all correspondence to: [aliimran.ft@gmail.com](mailto:aliimran.ft@gmail.com)

1 Institute of Home and Food Sciences, Government College University, Faisalabad, Pakistan

2 National Institute of Food Science and Technology, University of Agriculture Faisalabad, Pakistan

3 Department of Nutrition and Dietetics, University of Lahore, Pakistan

4 Department of Diet and Nutritional Sciences, Faculty of Health and Allied Sciences, Imperial College of Business Studies, Lahore, Pakistan

5 Department of Applied Chemistry, Government College University, Faisalabad, Pakistan

6 Department of Food Science and Technology, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan

7 Department of Botany, Government College University, Faisalabad, Pakistan

8 Department of Microbiology, Government College University, Faisalabad, Pakistan

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