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Flavonoids green tea against oxidant stress and inflammation with related human diseases

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SUMMARY

The liver is the most important organ and may be regarded as the metabolic entry point of the body. It contributes the metabolism of nutrients, endobiotics and drug/xenobiotics with absolute efficacy. It performs anabolic enrichment of the larger-molecule to generate more calorific storage-materials. At the same time, catabolic end-products of hundreds of molecules are either recycled or efficiently excreted by this organ. The strongest drug-metabolizing enzymatic machinery helps this organ to fight thousands of molecules. Chronic/acute-toxicity, metabolic-syndrome, oxidative-stress, inflammatory-responses and mutagenesis carcinogenesis severely challenge this organ and make the situation life-threatening. At a severe condition during hepatitis, fatty-liver syndrome, cirrhosis, fibrotic-liver damage end-stage situation arise. Present report suggests that green tea and its constituents offer the strongest herbal remedy/therapy in liver anomalies. A large number of polyphenols with the effective galloyl group, several instaurations, hydroxyl groups and other structural specialty attribute to its antioxidant, anti-inflammatory, anti-proliferative, anti-mutagenic/anti-carcinogenic potentials. Green tea has been shown to offer its protections at cellular, biochemical and

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molecular levels influencing a large number of metabolic pathways.

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1. Introduction

Tea is manufactured in three basic forms. Green tea is prepared in a way to enrich leaf polyphenols. During the production of black-tea oxidation is promoted so that most of these substances are oxidized. Fresh tea leaf is highly rich in the flavonol group of polyphenols known as catechins. Other polyphenols include flavanols and their glycosides, and despite such as chlorogenic acid, coumarylquinic acid, and one unique component of tea, theogallin (3-galloylquinic acid) [1,2]. Tea leaf contains an active polyphenol oxidase, which catalyzes the aerobic oxidation of the catechins during black tea production [1,2]. This increases number of compounds, including bisflavanols, theaflavins, epitheaflavic acids, and thearubigens [2]. Other components include three kinds of flavonoids, known as kaempferol, quercetin, and myricetin [1,2]. A remarkably higher content of myricetin is detected in tea and its extracts which are related to some bioactivity of the green tea extract [1,2].

1.1. Scientific classification of green tea

Kingdom: Plantae(unranked): Angiosperms(unranked): Eudicots(unranked): AsteridsOrder: EricalesFamily: TheaceaeGenus: CamelliaSpecies: *Camellia sinensis*.

1.2. Binomial name: C. sinensis

Flavonoids are natural products widely distributed in the plant kingdom and currently consumed in large amounts in the daily diet like tea, apple, berries, broccoli, strawberries, citrus fruit, grapes, lettuce etc. [3]. Flavonoids are capable of modulating the activity of enzymes and affect the behavior of many cell systems and exerting beneficial effects on the body (Fig. 1). These are categorized according to their molecular structures into flavonols, flavones, flavanones, isoflavone, catechin, anthocyanidin and chalcones [3]. More than 4000 varieties of flavonoids have been identified. The biological properties of

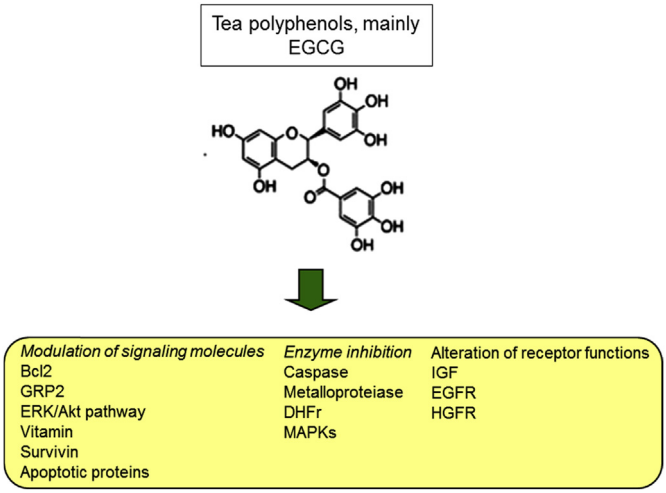

Fig. 1. Flavonoids modulate signaling molecules, causes enzyme inhibition, and regulates ateration of receptor functions.

citrus flavonoids and the effectiveness of polyphenolics in tea regarding cancer prevention and induction of apoptosis have been widely studied [4].

2. Therapeutic and preventive role of green tea: epidemiological and human study

Several reports suggest that GT may have some adverse health effect. Some of the investigation and follow up studies have been reported from human studies. It is demonstrated that daily consumption of green tea does moderately impair liver function and alter cardiovascular disease risk factors in healthy men. This has been reported after studying some haematologic parameters and important biomarker levels [5]. Increased consumption of green tea, especially more than 10 cups a day, was related to decreased concentrations of hepatological markers in serum, aspartate aminotransferase, alanine transferase, and ferritin [6]. Influence of green tea catechins was studied on oxidative stress metabolites at rest and during exercise in healthy humans. The results of the study indicate that single-dose consumption of GTC influences oxidative stress biomarkers when compared between the GTC-NEX and GTC-EX groups, which could be beneficial for oxidative metabolism at rest and during exercise, possibly through the catechol-O-methyltransferase mechanism [6]. The acute effects of green tea and carbohydrate co-ingestion were studied on systemic inflammation and oxidative stress during sprint cycling. While acute green tea ingestion prevents the post-exercise decrease in testosterone and lymphocytes, it does not appear to benefit cycling sprint performance or reduce markers of oxidation and inflammation when compared with carbohydrate alone [7]. This suggests that energy metabolism is performed better by potential nutrients. But Malnutrition associated stress may be well managed by the green tea extracts. The effect of green tea extracts supplementation was evaluated on exercise-induced oxidative stress parameters in male sprinters. GTE caused an increase in total polyphenols and TAC at rest, and a decrease in MDA and SOD after RST [8]. Influence of green tea catechins was observed on oxidative stress metabolites at rest and during exercise in healthy humans. The results of the study indicate that single-dose consumption of GTC influences oxidative stress biomarkers when compared between the GTC-NEX and GTC-EX groups, which could be beneficial for oxidative metabolism at rest and during exercise [6]. Green Tea Extract (GTE) is shown to improve differentiation in human osteoblasts during oxidative stress. Stimulation of primary human osteoblasts with low doses of GTE during oxidative stress over 21 days improved mineralization. Furthermore, GTE supplementation in combination with H_2O_2 leads to a higher gene expression of osteocalcin and collagen1α1 during osteoblasts differentiation [9]. The effect of green tea extract supplementation was screened on exercise-induced oxidative stress parameters in male

sprinters. Repeated cycle sprint test performed after PL induced an increase in MDA, TAC, and SOD [8]. Moreover, an increase in UA, AL, and CK were observed after RST irrespective of experimental conditions (PL, GTE). Supplementation with GTE caused an increase in total polyphenols and TAC at rest, and a decrease in MDA and SOD after RST [8]. No significant changes in sprint performance were noted after GTE, as compared to PL. Supplementation with GTE prevents oxidative stress induced by RST in sprinters. Furthermore, GTE supplementation does not seem to hinder training adaptation in antioxidant enzyme system [8].

3. Therapeutic role of green tea and its different constituents

3.1. Green tea protects from oxidative threat

A large body of evidences strongly suggests the hepato-protective and therapeutic role of green tea. Green tea consumption reduces the risk of a number of liver diseases. Green tea extract has been shown to improve the oxidative state of the liver and brain tissues in rats with an experimental arthritis model [10]. Environmental pollution and industrial hazard are the main sources of contamination of the atmosphere. Pollution results in metabolic disorder and health anomalies in human and other animals. Heavy metal toxicity is of great importance where the liver has been demonstrated as the prime affected organ. This contamination via drinking water initially affects the gastro-intestinal (GI) tract and the intestinal epithelial cells. The green tea has been suggested to perform as therapeutic agents against this toxicity [11]. Most abundantly used hepatic toxicity model is the CCL4 treated rat model. This experimental model has shown that green tea can reverse the CCL4-induced liver injury (Fig. 3) [12]. Several of the works demonstrated as macro-molecular structure to be the major affected substances in any types of toxicity. Proteins and DNA are those types of molecules. Report reveals that arsenic-induced rat DNA breakage is protected by green tea. This protection is attributed at the level of protein (SOD) and DNA structural stability. Moreover, not only protection of DNA structure but green tea also increases the annealing and recovers the partially-broken DNA [13].

Oxidative stress has been regarded as one of the most important influencing factors to initiate liver injury. Liver is the metabolic entry point of any endogenous or exogenous substances. The complex-IV of the electron transport chain is a major source of superoxide and other oxygen radicals. The cytochrome oxidase (complex-IV) serves as a facultative superoxide dismutase enzymatic role against erroneously generated O_2-. A large number of free radicals are produced from these sources during oxidatively stressful conditions [14]. H_2O_2 is also produced with significant amount. Similarly, metabolism and oxygen transport in RBC, uric acid metabolic pathways are the important sources of free radical formation [15].

The H_2O_2 is a potent oxidizing agent which participates in some physiological signaling and pathological processes [16]. Now, transition metals like Fe and Cu are the most abundant in the body. Eventually, H_2O_2 augments the generation of superoxide anion (O_2-), peroxyl radical (HOO·), hydroxyl radical (· OH) and different lipid-peroxides after reacting with these transition metals. Moreover, the interaction of O_2- and H_2O_2 can also lead further to the formation of highly reactive and damaging ROS as follows; $O_2- + H_2O_2 \rightarrow O_2 + OH- + OH\cdot$ [17]. Amongst iron and copper the Cu2+ induces faster generation of OH· [18]. In critical analysis, H_2O_2 is a powerful oxidant with a high E0 value (1.78 v). So, it promptly oxidizes Cu + to Cu2+ and Fe2+ to Fe3+ and itself reduced to H_2O. In addition, the Cu+/Cu2+ reaction system will run faster as a net change in E0 value being highest 1.62 v than 1.01 v for Fe2+/Fe3+ [19]. The generation of cuprous (1+) and ferrous (2+) salt is also an important factor when cupric (2+) or ferric (3+) salt reacts with H_2O_2. The better stability in electronic orbital is attributed by d10 (Cu+) and d5 (Fe3+) distribution in these case [19]. Green tea has been decisively shown to protect the hepatic tissue from transition metal associated oxidative reaction cascade.

3.2. Protective role of flavonoid constitutes in experimental liver injury

A report reveals that the antioxidant effect of catechin, a green–tea component ameliorates oxidant stress-induced experimental liver injury. Stress associated necrotic tissue injury is fibrotic in nature.

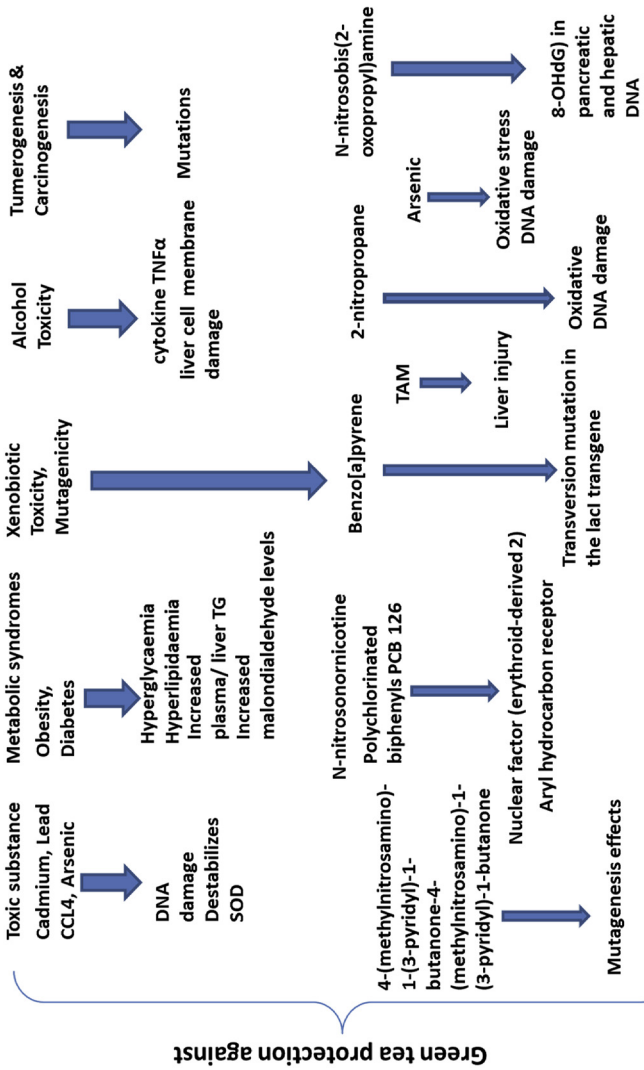

Fig. 2. Protective effect of Green tea.

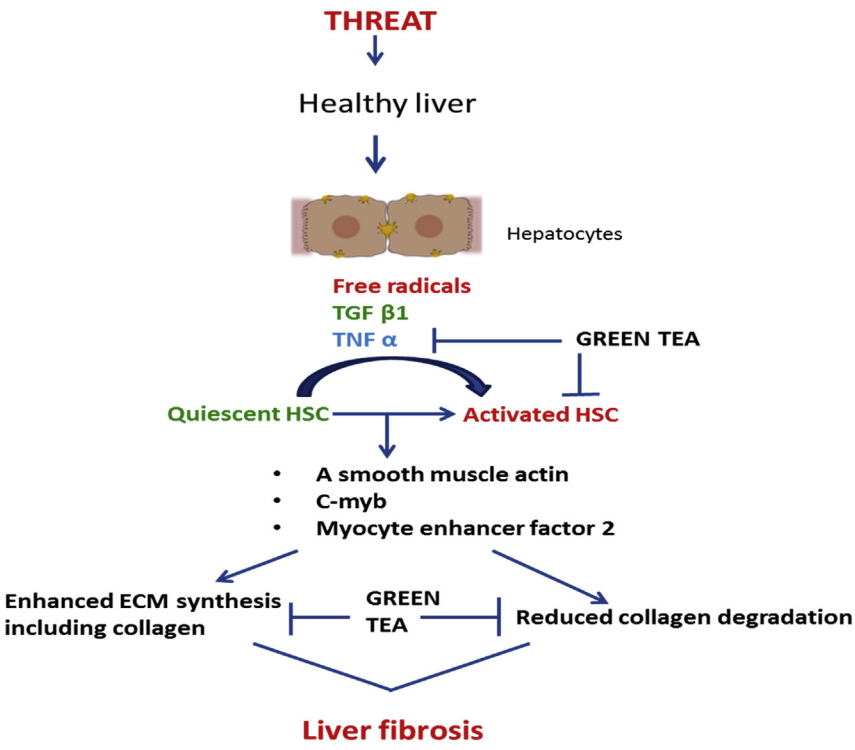

Fig. 3. Green Tea protects liver from fibrosis.

Like several other necrotic lesions, generation of the oxidative stress and antioxidant depletion are shown to augment hepatic fibrosis. Anti fibrotic effects of green tea on different animal experimental models of liver-fibrosis are evident (Fig. 3) [20]. A report suggests that the drinking of green tea with high catechin content may help to prevent and/or attenuate the development of fibrosis in hepatitis [21]. The abilities of EGCG to suppress matrix metalloproteinase MMP-2 activation and hepatic stellate cells (HSC) invasiveness suggest that EGCG can be used hepatic fibrosis [22]. One report demonstrated that EGCG inhibited collagen production regardless of enhanced collagen transcription and suppressed collagenase activity (Fig. 3). It emphasizes the therapeutic potential of EGCG in liver fibrosis [23]. EGCG also strongly inhibited lysophoaphatidic acid (an activator of Rho) and induced phosphorylation of mitogen-activated protein kinases (Erk1/2, c-jun kinase, and p38) (Fig. 1). These findings demonstrate that EGCG has therapeutic potential in the setting of liver fibrosis [19,24]. Evidence suggests that ROS can activate the important transcription factor NF-κ-β [25] and several mitogen-activated protein kinases (MAPKs) which are counteracted by the tea flavonoids in the metal toxicity–related oxidant stress [26]. Green tea protects from oxidative and inflammatory threats via signaling pathway. A large number of reports suggest that GT flavonoids are effective against a wide variety of experimental, synthetic and natural materials to protect liver associated injuries. D-galactosamine is known to promote acute liver injuries. Glycosidic flavonoid-compounds from green tea is shown to suppress the D-galactosamine-induced increase of plasma alanine aminotransferase and asparatate aminotransferase activities in rats [27]. The whole green tea extract has also been shown to reduce the D-galactosamine-induced acute liver injury. While searching the mechanistic approach, it is found that GT augment the inhibition of apoptotic and proinflammatory signaling [28]. Proinflammatory markers include TNF-α and several other cytokines (Fig. 3). In addition to the necrotic events inflammation makes more severe condition during hepatic damage. Intercellular communications, the matrix build-up are of importance for the maintenance of the cellular integrity which is impaired during necrotic lesions. In this regard,

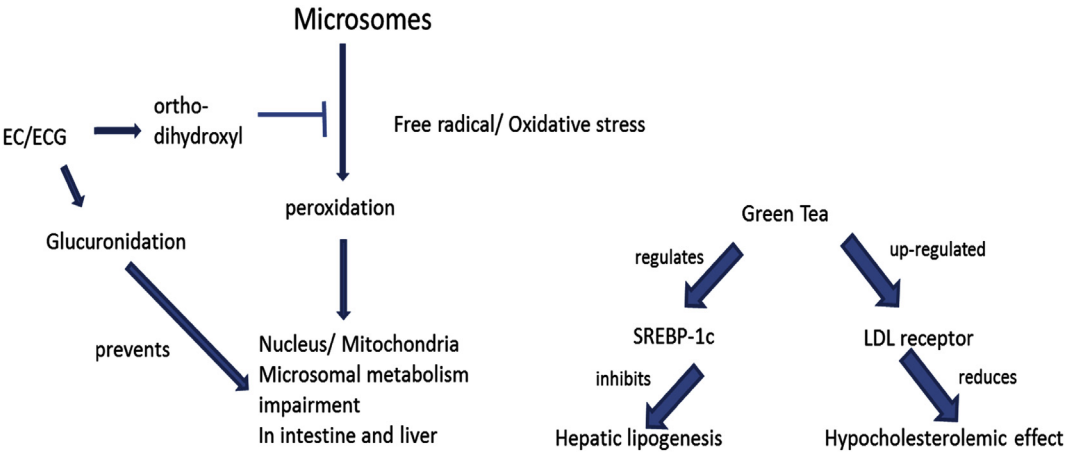

Fig. 4. Green Tea protects microsomes from oxidative threat and Hepatic lipogenesis.

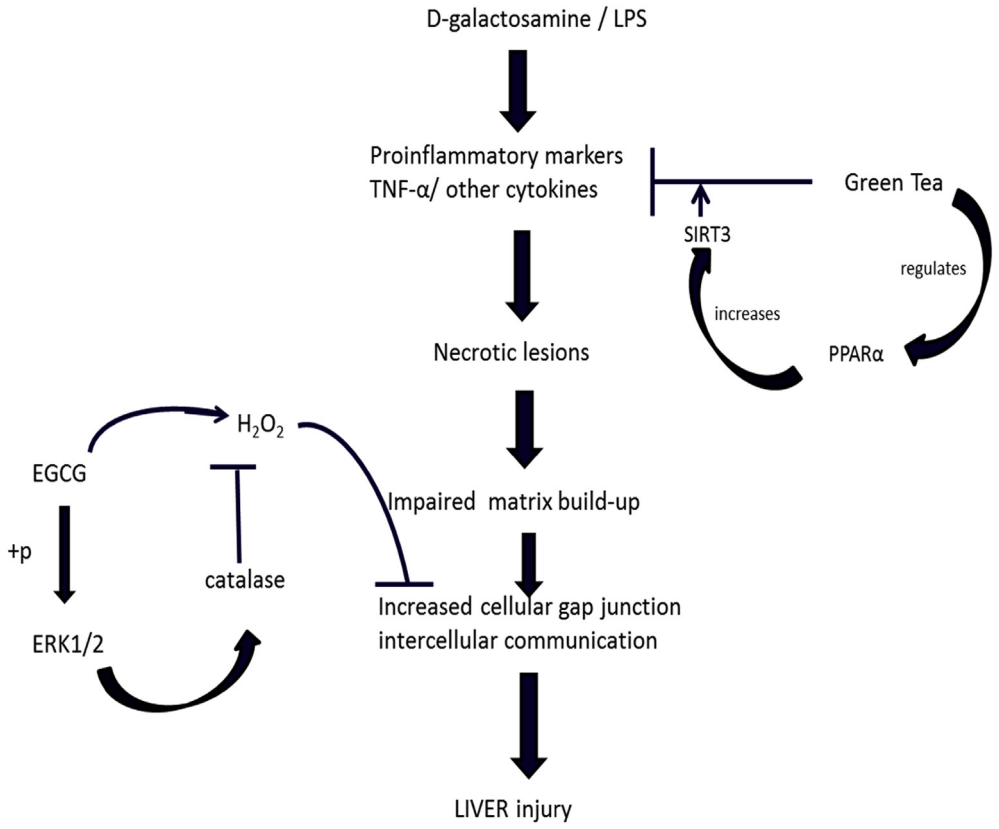

Fig. 5. Green Tea protects against D-galactosamine/LPS induced liver injury. EGCG.

cellular gap junction plays a crucial role [29]. The (−)-epigallocatechin gallate is shown to inhibit gap junctional intercellular communication in normal rat liver epithelial cells. This is an important finding that with a certain dose schedule EGCG inhibited gap junctional intercellular communication mainly due to its pro-oxidant activity [29]. The production of high amounts of H_2O_2 is associated with this phenomenon (Fig. 5). Though, sufficient amount of catalase promoted an inhibition to this via secondary effect by influencing phosphorylation of certain biomolecule including ERK1/2 (Fig. 1 and Fig. 5) [29].

3.3. *Flavonoids also protect non-hepatic organs*

Liver is not only the affected organ during free radical associated damages. Damages to different other organs including brains, by systemic stress and are also noticed. Lipid peroxidation products are increased several fold in these situations. Protective effect of green tea against lipid peroxidation products is noticed in rat liver, blood serum and in the brain. In the central nervous tissue the activity of superoxide dismutase and glutathione peroxidase decreased while the activity of glutathione reductase and catalase increased after drinking green tea [30,31]. Microglial Cells are noticed to be more threatened by oxidative stress initiated during hypoxia/reperfusion events. That initiates autophagy-activated apoptosis and cell death. Green tea catechin is shown to be the most effective against systemic damages by oxidative stress. It strongly protects microglial cell-death. Mechanistically it can be explained that the catechin component up-regulates the Akt and mTOR phosphorylation and inhibits the hypoxia/reperfusion-induced autophagy in microglia [32]. Memory deficits and oxidative stress in

cerebral ischemia-reperfusion is evident. The neuroprotective role of physical exercise and green tea supplementation is reported against this oxidative stress is noticed. Eight weeks of physical exercise and/or green tea supplementation before the ischemia-reperfusion event showed a neuroprotective effect; both treatments in separate or together reduced the cognitive deficits and were able to maintain the functional levels of antioxidant enzymes and glutathione [33].

Green tea protects from high calorie consumption, obesity and other metabolic syndromes. A number of metabolic syndromes are the outcome of high calorie consumption which leads to the obesity. A brief report suggests that high-fat diet-induced obesity in mice and its associated liver metabolomic profiles are protected by the application of green tea [34]. The EGCG is reported to suppress metabolic syndrome, obesity and fatty liver disease in high fat-fed mice. Moreover, short term use of EGCG demonstrated to reverse pre-existing high-fat-induced metabolic pathologies in obese mice by decreasing lipid absorption and inflammation [35]. High-fat diet-induced obesity may also result in serum high cholesterol and triglyceride level. An in vitro study indicates that 200 μM, EGCG increases (HepG2) cellular cholesterol efflux. The EGCG has been shown here as an active constituent and provides mechanisms by which green tea modulates cholesterol metabolism and indicates that EGCG might be its active constituent [36]. Furthermore, in HepG2 cells, green tea upregulates the low-density lipoprotein receptor via sterol-regulated element binding proteins. It decreased the cellular cholesterol concentration by approximately 30%. The green tea extract also increased the conversion of the sterol-regulated element binding protein (SREBP-1). The mRNA expression of the rate-limiting enzyme in cholesterol synthesis was also increased by green tea. In conclusion, green tea up-regulated the LDL receptor in HepG2 cells. The LDL receptor is known to serve as cholesterol transportation. Accordingly, the LDL receptor plays a role in the hypocholesterolemic effect which was effectively restrained by green tea in vivo [37] (Fig. 4). Dietary green tea is demonstrated to lower plasma and hepatic triglycerides in fructose-fed, ovariectomized rats. It decreases the expression of sterol regulatory element-binding protein-1c mRNA and its responsive genes. The results suggest that the lipid-lowering effect of GT is mediated partly by its inhibition of hepatic lipogenesis involving SREBP-1c and its responsive genes without affecting lipoprotein assembly [38]. Green tea polyphenols (GTP) attenuate high fat diet induced renal oxidative stress through SIRT3-dependent deacetylation. GTP treatment positively regulated SIRT3 and PPARα expressions. It increased the PPARα mRNA level, reduced the MnSOD acetylation level. It also decreased the MDA production in high fat-fed rats. The reduced oxidative stress detected in kidney tissues after GTP treatment was partly due to the higher SIRT3 expression, which was likely mediated by PPARα [39]. Not only necrotic lesions, but also inflammation has been shown to be restricted by green tea. Report reveals that the GTP significantly attenuated LPS-induced hepatic damage either by its antioxidant activity or by inhibiting LPS induced cytokine production in rats [40]. That ultimately restricted inflammatory events and their markers. Green tea with high catechin content suppresses inflammatory cytokine expression in the galactosamine-injured rat liver. Oral administration of green tea rich in catechins restored these biomarkers in the galacotsamine-treated rats. By this way this quality of tea prevents and/or attenuates the development of a certain type of hepatitis [41]. Other than nuclear and mitochondrial components microsomal metabolism may also be impaired by different oxidative stresses. Specially intestinal and hepatic microsomal environment is very much concerned with different drug metabolism processes and xenobiotic modifications. Antioxidant effects of green tea polyphenols have demonstrated against free radical initiated peroxidation of rat liver microsomes. A large number of efficient polyphenolic compounds are available in whole tea extract, which has varied redox potential, lots of electron instauration and diverse electron acceptability of different types of free radicals. This may offer a greater compatibility and reciprocity in whole tea extract as most efficient electron-scavengers compared to vitamin C (scavenger of superoxide radical) [42], vitamin E (scavenger of peroxyl radical) [43] DMSO (scavenger of hydroxyl radical) [44] or even their combination as demonstrated in our previous study [13]. Especially EC and ECG which bear ortho-dihydroxyl, functionality are good antioxidants for microsomal peroxidation (Fig. 4). The antioxidative potency of tea polyphenols is synergistically strong when it works with alpha-tocopherol (vitamin E) [45]. Glucuronidation are shown to one important metabolic pathway of the green tea catechins, (−)-epigallocatechin-3-gallate and (−)-epicatechin-3-gallate. This process is predominant in the rat hepatic and intestinal microsomes [46]. Although the rates were lower than quercetin, intestinal microsomes exhibited higher

activity on the galloyl group of ECg and EGCg compared to the flavonoid ring, whereas hepatic glucuronidation was higher on the flavonoid ring of EGCg and ECg compared to the galloyl groups [47].

3.4. Protective/therapeutic role of green tea in mutagenesis, tumerogenesis and carcinogenesis

An impressive and long-term follow up study may establish the efficient role of GT in disease therapy. Over nine years of follow-up, among more than three hundred thousand people in Japan suggest that green tea consumption was inversely associated with the incidence of liver cancer [48]. Moreover, GT showed its efficacy as a potential activator of other anticancer drug also. Green tea catechin augments the anti-tumor activity of doxorubicin induced mouse model for chemo-resistant liver cancer [49]. The report suggests that urinary excretions of EGC/EC can be regarded as reliable biomarkers for green tea consumption in human populations. This is evaluated from a phase II chemoprevention trial of green tea polyphenols in high-risk individuals of liver cancer. Green tea polyphenols augment the urinary excretion of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage (Fig. 2) [50]. The other important deleterious damage is the abstraction of hydrogen atom at any one or both position from C3 or C5 of ribose sugar in the DNA, which may result in hydrolytic phosphoester cleavage and complete separation of phosphate as phosphoric acid, ribose, and a nitrogen base. It may be induced irreversible DNA degradation by $Cu{-}H_2O_2$ reaction system (Fig. 4). The formation of peroxyl radicals on pyrimidine rings may also contribute DNA strand breaks [13]. The DNA protective function of green tea but also specific nuclear-destabilization and mitochondrial ROS production by green tea component EGCG play a role in the inhibition of oral cancer [51]. Here, it is shown that the anti-carcinogenic activity of green tea may be related to its effect on the tumor promotion stage of the cancer process [52]. Inhibition of green tea catechins against the growth of cancerous human colon and hepatic epithelial cells are also reported [53]. N-Nitrosobis (2-oxopropyl) amine are demonstrated to increase the oxidative DNA damage of hamster pancreas and liver and production of 8-oxodG. And this was suppressed by the green tea supplementation [54]. Induction of mutagenesis in rodents by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosonornicotine is demonstrated in liver tissues of rodents. But, green tea significantly reduced mutagenesis in liver, lung, pooled oral tissue and esophagus in this study [47]. Another finding suggests that green tea might act as an anti-promoter against pentachlorophenol PCP-induced mouse hepatocarcinogenesis via its ability to prevent down-regulation of gap junctional intercellular communication (Fig. 2) [55]. Report suggests that GTE is a possible chemopreventive agent for nitrosamine-initiated hepatocarcinogenesis, but not with a choline deficient diet. This suggests that essential nutrient and micronutrient exert its obvious involvement in the metabolic processes [56]. So, suggestion can be made that GTE with some other combination substance might have been more effective in this situation. This has been described in some other place in this write up. Drug metabolizing enzymes have a great role in the modification of endobiotics and xenobiotics. And the gene for this enzyme protein may be induced these drug molecules. As for example, selective induction of rat hepatic CYP1 and CYP4 proteins and of peroxisomal proliferation is observed with the application of green tea. This report suggest that anticarcinogenic and antimutagenic properties of green tea dependant its modification by the microsomal enzyme system. And in this situation green tea can influence the promutagenic role of N-nitrosopyrrolidine [57]. In this regard it can be said that green tea polyphenols and epicatechin derivatives can be interacted with hepatic cytochrome P-450. Green tea also significantly inhibited NADPH-cytochrome c reductase activity. An examination of the structure activity relationship of epicatechin derivatives suggests that the inhibitory effect on the microsomal enzyme system may be due to the galloyl groups or hydroxyl groups on the molecule [58]. Report suggests that flavonoids may undergo at least three types of intracellular metabolism: (1) Oxidative metabolism, (2) P450-related metabolism and (3) conjugation with thiols, particularly GSH. Flavonoids may undergo at least three types of intracellular metabolism: (1) Oxidative metabolism, (2) P450-related metabolism and (3) conjugation with thiols, particularly GSH. Although there has been intense interest in the ability of flavonoids to modulate

kinases, thus far there is no indication that they may affect signalling pathways via a modulation of phosphatase activity.

4. Prominent mechanistic action of flavonoids

4.1. Flavonoid interaction with membrane receptor and channels

Flavonoids like quercetin was found to affect the function of plasma membrane transport by inhibiting Na+, K+, mitochondrial ATPase and Ca2+ ATPase, hog gastric H+, K + ATPase [59,60]. A study exceptionally found that quercetin caused conformational changes in myosin structure along with an increase in ATPase activity, but again at higher concentration ATPase activity was inhibited. Quercetin suppressed thyroxine stimulation of the human red blood cells (HRBC) Ca2+ ATPase in vitro and interfered with hormone binding to HRBC membrane. Whereas low concentration of quercetin stimulated Ca2+ ATPase in the absence of hormone and the high concentration inhibited Ca2+ ATPase [61]. Thus, it may be interpreted that thyroxin like structure of quercetin which may bind to the hormone binding site may further interferes with hormone activity. Quercetin inhibited mouse neuroblastoma cell growth. Valinomycin (1 nM) the k + ionophore, antagonized the antiproliferative effects of quercetin by 80%. Directing towards K+ channel blockade mediated growth inhibitory actions [62].

4.2. The effect of flavonoids on cytosolic signaling proteins and enzymes

Protein kinase C (PKC) has been shown to be inhibited in vitro by certain flavonoids like fisetin, quercetin, and luteolin [63,64]. Mitogen activated protein (MAP) kinase in human epidermal carcinoma cells was strongly inhibited by quercetin (30 mM) [65]. Fisetin (and luteolin) competitively blocked the ATP binding site on the catalytic unit of PKC. Several other ATP-utilizing enzymes inhibited by flavonoids were affected by competitive binding of the flavonoid to the ATP binding site (vide infra). Rat liver cyclic AMP-dependent protein kinase catalytic subunit could be inhibited by a variety of flavonoids [66]. Again, C2–C3 instauration and polyhydroxylation of two or more flavonoid rings favored the development of inhibitory activity. Methoxylated and glycosylated agents were much less active. Several flavonoids inactive against MLCK were good inhibitors of cyclic AMP-dependent protein kinase catalytic subunit. Once entered into the cell flavonoid may come in the vicinity of several cytoplasmic proteins and interestingly flavonoids have been shown to have modulatory, inhibitory and stimulatory effects on various cellular functions like cell proliferation, division, differentiation, immunological responses and also showing some carcinogenic, anticarcinogenic effects by inhibiting kinase pathways. Antioxidant properties of flavonoids Quercetin and several other flavonoids were quite effective inhibitors of O_2.- produced by the cells [67]. A study recently reported a similar inhibitory effect of different flavonoids on ROS production by activated human neutrophils. Essential determinants for inhibition of O_2.-release appeared to be the OH groups located in the B ring of the flavonoid molecule. The formation of O_2.- is dependent on the activation of NADPH oxidase localized in the plasma membrane, which is also subject to flavonoid inhibition [68]. Tumor promoter (TPA)-induced formation of H2O2 was inhibited by genistein in a concentration-dependent manner (1–150 mM) in human polymorphonuclear leukocytes and HL-60 cells [69]. The inhibition of neutrophil Myeloperoxidase (MPO) activity by flavonoids could result in the impairment of ROS production [70]. Phosphorylation of a specific neutrophil protein (mol. wt. 67,000) was reported to be particularly sensitive to quercetin at concentrations that also diminished neutrophil degranulation and O_2.- production, suggesting that its phosphorylation may be an important intracellular event associated with neutrophil activation [71]. Quercetin was found to have an ability to directly scavenge HOCl, a highly reactive chlorinated species generated by the MPO–H_2O_2–Cl system [70]. O_2 itself does not appear to be capable of initiating lipid peroxidation, HO_2.- (the protonated form of O_2.-) appears to do so in isolated polyunsaturated fatty acids [72]. Both isoflavonoid glycoside and wogonin inhibited lipid peroxidation in rat liver, but only wogonin inhibited the Fe2+ by NADPH-dependent cytochrome P450 reductase and not the isoflavonoid glycoside. Suggesting that isoflavonoid glycoside had no role in terminating the end chain reaction of the enzymatic lipid peroxidation system rather it can scavenge the free radical involved in

the initiation of lipid peroxidation [73]. Comparatively it was seen that presence of OH group in the B ring and C2–C3 double bond determines the antioxidative strength of the flavonoid. Kaempferol is a very good scavenger having only one hydroxyl group on the B ring and C2–C3 double bond and 4-oxo group on ring C. Catechin, which has the catechol group on ring B and the 3-OH group on ring C is a weak scavenger because it lacks the C2–C3 double bond and the 4-oxo group on ring C. Flavonoids can function as 1) metal chelators and reducing agents, 2) scavengers of ROS, 3) chain-breaking antioxidants, 4) quenchers of the formation of singlet oxygen, and 5) protectors of ascorbic acid; conversely, ascorbic acid can protect flavonoids against oxidative degradation.

5. Conclusions

It can be hypothesized that green tea extract is chemically very much enriched. Structural diversification of its different constituents and physico-chemical properties of all those components are so varied that any one of its constituents find compatibility, analogy of any one of the large number of biomolecules. And this is the main feature for its ability to more or less influence all types of metabolic pathways. This is the main reason that why these extract becomes anti-oxidant, anti-inflammatory, anti-proliferative, anti-mutagenic and anticarcinogenic. Different reactive groups in several of its components become highly interactive with different biomolecules. Green tea extract or specific of its any constitutes alone or in combination with other molecules like micronutrients/vitamins or else may be of good therapeutic potentials. Further studies are awaited for conclusive remark.

Conflict of interest

There is no conflict of interests in any form regarding this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yclnex.2018.12.004.

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