

ROLE OF GREEN TEA AND ITS CONSTITUENT EPIGALLOCATECHIN-3-GALLATE IN THE HEALTH MANAGEMENT

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ABSTRACT

Green tea and its constituents is natural beverage used worldwide especially in Asian countries and also used as natural medicine for thousands of years. The current approaches for diseases treatment based on allopathic drugs offer restricted options, adverse effect and also show alterations in biochemical and genetic pathways. Considerable achievement on green tea and its constituents has been made based on experimental studies to confirm its mechanism of action in disease modulation but the exact mechanism still under investigation. It is thought that, green tea is rich in antioxidant and shows a pivotal role in the scavenging of free radical generation and prevention of disease pathogenesis. However, further studies are needed to confirm the safe dose and the exact mechanism of action in relation to health management. In the present review, an attempt has been made to explore the role of green tea in diseases prevention and its approach on modulation of various biochemical and physiological process.

Keywords: Green tea, Health management, Antioxidant and anti-tumour.

INTRODUCTION

Alternative medicines are a primary health care in different part of the world due to safe and affordable properties to poor people especially in the developing world. Experimental based studies have confirmed that natural products or herbs show a significant and effective role in the disease management via modulation of biological activities without any changes in biochemical and physiological processes. The importance of herbs or products from natural sources has been discussed in religious books and traditional medicines such as Chinese, Ayurveda and Unani. In this vista, Islamic literature also has description of the natural remedy in the health benefit and our Prophet Mohammad (SAW) recommended various plants/fruits in the cure of several types of diseases [1].

Nowadays various researches based on *in vivo* and *in vitro* studies are in progress to check the safety, dose level and mechanism of action of various herbs in diseases protection. However, tea such as green, black and white is an important dietary constituent and among all tea, green tea shows a pivotal role in the diseases protection due to the rich source of antioxidant. The main flavanols found in green tea, are (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC). EGCG is a chief polyphenol of green tea and shows therapeutic implications in the diseases protection through regulation of biochemical, physiological and molecular process.

An important finding has shown that, the risk of developing hypertension decreased by 46% for those who drank green tea 120 to 599 mL/d and those consuming more than 600 mL/d was further reduced by 65% as compared to subjects consuming less than 120 ml per day [2]. A study based on rat model showed that, supplementation of green tea extract (GTE) attenuates cyclosporine A-induced oxidative stress [3]. Additionally, another study has shown that green tea polyphenols GTP was also found to significantly reduce serum glucose level in alloxan diabetic rats at a dose level of 100 mg/kg b. wt and furthermore, daily administration of the extract 50, 100 mg/kg b. wt for 15 days produced 29 and 44% reduction in the elevated serum glucose level [4]. In this review, we focused on the therapeutic implications of green tea and its constituents in the health management through modulation of various biological activities such as antioxidant, anti-inflammatory and anti-tumour.

Biological activities of green tea in the health management described as followings

Antioxidant activity

There are many evidences have gathered from the earlier studies based on experimentation on plants and its extract shows pivotal role in the inhibition of pathogenesis of various diseases due to rich source of antioxidant. Natural or plants products enhance the body antioxidant capacity, inactivate the free radical species and finally prevent the disease's progress. Previous reports have proved that, medicinal plants shows role in diseases control via antioxidant activity [5-6]. In this vista, tea is one of the good sources of antioxidants and commonly used tea are green tea, oolong tea, and black tea. All types of tea contain various constituents such as Chatechins, Cartenoids, Phenolics and tannins, that play a vital role in diseases control due to antioxidant activity. Green tea constitutes has better antioxidant potential or capacity than other types of teas such as oolong and black teas [7-11]. A report confirmed that, non-polymeric phenolic (NP) constituents are major contributors to the antioxidant and antibacterial properties of *C. sinensis tea* [12].

A study was performed on 40 male smokers in China and 27 men and women (smokers and non smokers) in the United States, where oxidative DNA damage, lipid peroxidation, and free radical generation were reduced after consuming ~ 6 cups/day of green tea for seven days [13]. Earlier finding investigated the antioxidant effect of green tea based on *in vivo* and results revealed that, total antioxidant capacity of plasma increased significantly 7.0% and 6.2% after 60 min and 120 min; respectively after consuming 300 ml of green tea [14]. Finding also showed significant increase of total antioxidant capacity to 12.0% and 12.7% after 60 min and 120 min after taking green tea in amount of 450 ml [14] and beneficial effect of green tea including antioxidant activity was reported by earlier study [15]. The tea contains large amounts of polyphenolic compounds with antioxidant properties, which may prevent oxidative damage of DNA [16-17].

Anti-tumour activity

Various medicinal plants show a role in inhibition of cancer development and progression via modulation of genes involves in the cancer initiation, promotion and progression. Earlier studies based on *in vivo* and *in vitro* has confirmed that green tea and its constituents EGCG inhibit the cancer through the up regulation or down regulation of various genes involves in the cancer formation.

An important experiment was performed to examine whether FKHL1/FOXO3a modulates antitumor activity of (-)-epigallocatechin-3-gallate (EGCG) in pancreatic cancer model and results confirmed that EGCG showed significant inhibition of tumor growth that was associated with reduced phosphorylation of ERK, PI3K, AKT, and FKHL1/FOXO3a [18]. The effects of EGCG and other catechins on the cell cycle progression were studied and the results showed that 30 microM of EGCG, a chief constituents of green tea blocked cell cycle progression at G1 phase in asynchronous MCF-7 cells [19].

The oral administration of green tea enhanced 2.5-fold the inhibitory effects of doxorubicin on tumor growth [20] and other investigation reported that epigallocatechin-3-gallate (EGCG), sensitizes TRAIL-resistant LNCaP cells to TRAIL-mediated apoptosis via modulation of intrinsic and extrinsic apoptosis pathways [21].

Other supportive results showed that, ECG and EGCG, the chief polyphenolic of green tea, potently enhanced the susceptibility to doxorubicin DOX cytotoxicity in the resistant HCC cell line and significantly inhibited BEL-7404/DOX tumor growth in nude mice [22].

Another investigation was carried out on human prostate carcinoma DU-145 cells to determine the effect of (-)-epigallocatechin-3-gallate (EGCG) on the synthesis and activation of tumor invasion-specific MMP-2 and MMP-9 and it showed that treatment of EGCG resulted in dose-dependent inhibition of FCM-induced pro and active forms of MMP-2 and MMP-9 concomitant with noticeable inhibition of phosphorylation of ERK1/2 and p38 [23].

A mice model results has shown that, oral dose of EGCG, chief green tea catechin at 50 to 100 mg/kg/day significantly slows a growth curve of breast cancer in C57BL/6 female mice as compared to the control group and that was noticed via 65% and 68% reduction in the tumor cross section area and tumor weight, respectively [24]. Other interesting finding determined the effects of human oral cancer cell line OC2 cells exposed to EGCG and results revealed that EGCG exhibited a dose-dependent inhibitory effect on the invasion and migration of OC2 cells in the absence of cytotoxicity [25].

Anti-inflammatory activity

Numerous medicinal plants and its constituents play an important role in the management of inflammatory process [26]. In this vista, green tea and its constituents play a vital role in the regulation of an inflammatory process via modulation of genetic pathways such inhibition of cyclooxygenase, lipoxygenase and other transcription factors [fig.1].

Earlier researchers have reported the anti-inflammatory activity of both green tea and black tea [27-30], another study concluded that both green and black tea leaves possessed a anti-inflammatory effect against the denaturation of protein, *in vitro* [31] and tea play an important role or effect in the various molecular targets such as TNF- α [32], interleukin2 (IL-2) [33].

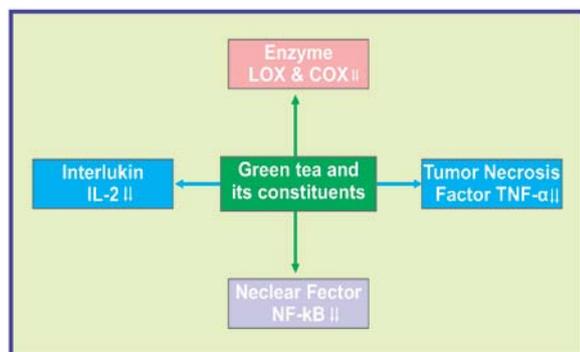


Fig. 1: Green tea and its constituents show role as anti-inflammatory through the regulation of genetic pathways

Important studies suggest that drinking adequate amounts of green tea may show important role in the prevention of inflammatory-related diseases [34]. Tea play role in the modulation of Ttp mRNA

levels in animals and suggest that a post-transcriptional mechanism through TTP that could partially account for tea's anti-inflammatory properties [35].

Anti-microbial activity

Numerous medicinal plants and its constituents show an effective role in the inhibition of microorganism growth and also kill the bacteria through the destruction of cell wall. Currently used antimicrobial agents are effective but also cause side effect. Green tea and its constituents show a vital anti-bacterial affect and also kill pathogens. Catechin components of green tea show antibacterial activity, and EGC, EGCG and ECG constitute the most important antibacterial agents [36]. Earlier studies based on green tea were reported to have a synergistic effect with β -lactam antibiotics against MRSA [37-41]. Polyphenols, epigallocatechin gallate can reverse methicillin resistance of MRSA by inhibiting the synthesis of PBP2 [42].

Numerous findings based on green tea showed that green tea catechins, especially EGCG and ECG, showed antibacterial activity against Gram-positive and Gram-negative bacteria [443-45] and green tea can prevent tooth decay by inhibiting oral bacteria [46].

Green tea extract showed activity against MRSA and methicillin-sensitive *Staphylococcus aureus* [47] and against MDR-*P. aeruginosa* [48-49].

The antimicrobial activity of green tea showed that MIC of green tea extracts against *S. aureus* ATCC 25923 and MRSA were 400 μ g/mL and 400 μ g/mL, respectively, whereas the MIC for *P. aeruginosa* ATCC 27853 and MDR-*P. aeruginosa* were 800 μ g/mL, and 800 μ g/mL, respectively [50].

Several studies have shown that polyphenol contents of green tea inhibit the pathogenic bacterial growth such as *Helicobacter pylori*, methicillin-resistant *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Salmonella typhi*, *Shigella dysentery*, *Shigella flexneri* and *Vibrio cholera* [51-56].

S. mutans was more susceptible than periodontopathic bacteria as crude GTE produced growth inhibition zones up to 36.3 mm by ADD test and MIC was as low as 3.28 mg/ml [57] and synergistic effect of green tea extract and levofloxacin against *Escherichia coli* was observed in earlier studies [58].

Anti-diabetic activity

Diabetes is a metabolic disorder and major global health problem worldwide. Diabetes and its complication are increasing day by day worldwide. Various metabolic and genetic factors are responsible for the diabetes and its complications. A variety of medicinal plants such as olive, black seed and curcumin has shown anti-diabetic activity. Green tea and its constituents show a vital role in the control of diabetes and its complications. An important study results shows that EGCG, a major catechins modifies glucose and lipid metabolism in H4IIE cells and also noticeably increase glucose tolerance in diabetic rodents [59]. Another study showed that, green tea and its extracts were demonstrated to modify glucose metabolism beneficially in experimental models of type II diabetes mellitus [60-61]. Different studies suggested that green tea consumption is effective in lowering blood glucose in diabetic patients [62-64]. Earlier studies showed the benefits of green tea consumption and its effect in reducing the occurrence of T2D in laboratory animal studies [65-66]. EGCG, constituents of green tea enhances oral glucose tolerance in severely diabetic db/db mice and in moderately diabetic ZDF rats and furthermore, EGCG supplementation influences the expression of genes involved in glucose and lipid metabolism in the liver as well as in H4IIE rat hepatoma cells [67].

Moreover, green tea lowered blood glucose levels in diabetic db+/db+ mice and streptozotocin-diabetic mice 2-6 h after administration at 300 mg/kg without affecting serum insulin level and no effect was observed in control mice [68] and lower dose of green tea is insulinotropic while higher dose is hyperglycaemic [69]. Earlier finding has shown that green tea has been found to improve insulin sensitivity *in vivo* [70-71].

Gastro-protective effect

Numerous factors such as food ingredients, drugs, microbial agents and pro-inflammatory cytokines can cause mucosal damage, peptic ulcer and other related complications. Peptic ulcers are believed to result from the imbalance between protective and aggressive factors [72-73]. Various plants and their constituents play an important effect in the balance between protective and aggressive factors via secretion of mucin. Green tea and its constituents play an important role in the prevention of gastric ulcer but the exact mechanism behind this is not known. It is thought that inhibitory mechanism comes from the antioxidant activity of green tea. Previous findings has reported that catechins, tea component are well absorbed in the gastrointestinal tract and also interact synergistically in their disease-modifying actions; thus drinking unfractionated green tea is beneficial way to prevent gastrointestinal disorders [74].

Hepato-protective effect

Currently used medicine such as paracetamol, Ibuprofen and other drugs in the treatment of diseases are effective but also causes adverse side effect and liver damage. Paracetamol is activated and converted by cytochrome P450 enzymes to toxic metabolite NAPQI (N-acetyl-p-benzoquinoneimine) that causes oxidative stress and glutathione (GSH) depletion [75-76]. Various types of plants and traditional formulations are available for the treatment of liver diseases [77-78]. Green tea and its constituents play an important role in protection of liver damage via scavenging of free radical and also maintain the balance between free radical and antioxidant defence system.

Noteworthy studies demonstrate that daily treatment of diabetic rats by green tea extract noticeably improves antioxidant status in liver tissue and furthermore, also showed that green tea extract improved serum biomarkers of liver tissue injury and histopathologic properties of this organ [79] and 1.5 % green tea extract has the capacity to scavenge free radical and can protect against oxidative stress induced by Tamoxifen citrate (TAM) intoxication[80]. Another important results has shown that Carbon tetrachloride (CCL4)-induced fibrosis indicated by increased activities of liver enzymes and increased lactate dehydrogenase (LDH) activity, decreased liver reduced glutathione (GSH) content and green tea and selenium reduced these changes and improved the pathologic effects caused by CCL4 [81].

Neuro-protective effect

Green tea and their constituents such as theanine and catechins play a vital role as neuroprotector. The exact mechanism of action of green tea constituents as neuroprotector is not clearly understood, but it is thought that green tea shows neuroprotector effect due to the phenolic and flavonoids compounds. An important study showed death of hippocampal CA1 pyramidal neurons caused by transient forebrain ischemia in the gerbil was inhibited with the ventricular pre administration of theanine and also neuronal death of the hippocampal CA3 region by kainate was also prevented by the administration of theanine [82]. Another study has shown that the minimizing effect of green tea extract on the eicosanoid accumulation and oxidative damage in the ischemia/reperfusion-induced brain injury [83]. Previous investigation showed that tea polyphenols enhance neuroprotective effects by inhibiting polarization of mitochondrial membrane potential, increasing ATP content, and blocking cytochrome c release[84]. Others finding has shown that green tea constituents has neuroprotective effect and (-)-epigallocatechin-3-gallate (EGCG), the chief polyphenol component of green tea, has been shown to improve age-related cognitive decline and protect against cerebral ischemia/reperfusion injuries[85-86]. Earlier finding have shown that catechins, a constituents of green tea prevented neuronal cell death caused by the neurotoxins such as 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium and amyloid b-peptide (Ab)[87-90].

Cardio-preventive effect

Various medicinal plants and its constituents show an important role as cardio- protective effect via modulation of biological activities. In this vista, green tea and its constituents also shows a vital role in cardio- protection. An important cohort study on a total of 8,552 general residents was conducted on the basis of the follow-

up study and found that decreased relative risk of death from cardiovascular disease was 0.58 (0.34-0.99) for men, 0.82 (0.49-1.38) for women, and 0.72 (0.60-1.04) for members of both sexes consuming over 10 cups a day [91].

Earlier key study in diabetic rats showed that green tea treatment with dose of 300mg/kg body weight for 4 weeks can impede cardiac dysfunction by improving oxidative stress and lipid profile [92-93].

Photo-protection effect

Ultraviolet light is the most harmful to the skin [94]. Ultraviolet radiation increases oxidative stress and inflammatory process by causing excessive generation of reactive oxygen species. The antioxidants have also been shown to protect against near infrared radiation (IRA) and they are important for their central role in IRA induced adverse effects [95-96]. Medicinal plants are rich source of antioxidant and also play a key role to neutralize the adverse effect caused by free radical and also scavenging the free radical. A finding based on animal model has shown that both systemic and topical administration of green tea polyphenols and EGCG were found to protect against the UV-induced sunburn response [97], and photoprotection of the skin [98]. An interesting review summarised the photoprotective effects of green tea polyphenols [99].

Other results has revealed that skin treated with green tea extracts reduced the number of sunburn cells and protected epidermal Langerhans cells from UV damage and green tea extracts also reduced the DNA damage that formed after UV radiation [100] and treatment of GTP to human skin prevents UVB-induced cyclobutane pyrimidine dimers formation [101].

Anti-obesity effect

Green tea plays an important role as anti-obesity through the modulation of various biological activities. An important finding based on in vitro studies showed that epigallocatechin gallate (EGCG) had an inhibitory effect on acetyl-CoA carboxylase that play role in fatty acid biosynthesis [102]. Another study based on mice model was performed and results suggest that Green Coffee Bean Extract GCBE is possibly effective against weight gain and fat accumulation by inhibition of fat absorption and activation of fat metabolism in the liver [103] and other results showed that EGCG alone has the potential to increase fat oxidation in men and may thereby contribute to the anti-obesity effects of green tea [104]. A study based on obese thais was performed to investigate the effects of green tea on weight reduction and conclude that green tea reduce body weight by increasing energy expenditure and fat oxidation[105]. A previous study was performed to investigate the effects of green tea extract on the mineral, body mass, lipid profile, glucose, and antioxidant status of obese patients and results demonstrate the beneficial effects of green tea extract supplementation on body mass index, lipid profile, and total antioxidant status in patients with obesity [106]. Green tea polyphenols -targeted genes in obesity using the high-fat-diet-induced obese rat model and this finding collectively showed those beneficial effects of GTP on body weight via regulating obesity-related genes, anti-inflammation, anti-oxidant capacity, and estrogen-related actions [107].

Immunomodulatory effect

Several studies have revealed that green tea and their constituents show a pivotal role in defence against pathogens through the modulation of immune system. An important study was performed to examine the effects of epigallocatechin gallate fraction of green tea extract (EGTE) on mice for 6 weeks and its effect on innate and adaptive immune responses was measured and results demonstrated that EGTE administration showed role as increased NK cell cytotoxicity and peritoneal cell phagocytosis, splenocyte proliferation and secretion of IL-2 and IFN- γ [108]. Another study was performed on rainbow trout to study the immunomodulatory effects of decaffeinated green tea extract and findings showed that decaffeinated green tea in lower doses of administration could be optimum to enhance the immunity [109]. In addition to this, the efficacy of green tea on growth performance, immune and antioxidant systems and cytokine gene expression in rainbow trout

tissues was examined and results suggests that green tea especially at 100 mg kg⁻¹ feed effectively enhance the antioxidant system and immune system [110].

Role in dentistry/oral health

The effect of EGCG solution on dental plaque pH was investigated and found that EGCG inhibited pH fall when cariogenic bacteria grown in medium with or without sucrose that incubated with sugar [111]. A randomized, controlled, investigator-blind trial was performed to correlate the periodontal status with daily dietary intake of green tea and finding has shown positive and significant effects of oral intake of green tea on periodontal disease [112]. Earlier study was performed to assess the protective properties of green tea on oral health and finding of the study revealed significant difference among pre- and post subjects-rinsing with 2% green tea concerning *S. mutans* count in saliva and plaque, salivary and plaque pH values and Gingival Bleeding Index [113].

Effect in the eye/retinal disease

Various medicinal plants and its constituents show a role in the retinal disease or diabetic retinopathy via modulation of genetic pathways such as angiogenesis. A finding shows that pretreatment of retinal pigment epithelium cells with 50 µM EGCG significantly reduced H₂O₂-induced retinal pigment epithelium cell death [114]. Another study was performed to examine the effect of green tea (GT) on diabetes-induced retinal oxidative stress and proinflammatory parameters in rats and results of the study showed that superoxide dismutase and catalase enzymatic activities were restored close to normal in the GT-treated group and TNF-α and VEGF expression was significantly inhibited in GT-treated retinae when compared to diabetic retina [115].

CONCLUSION

Natural medicines or products from plant sources are still the mainstay of health care worldwide especially in the developing world. Earlier report based on *in vivo* and *in vitro* studies has confirmed that medicinal plants shows an important role in health management. Green tea is commonly used beverage after water has therapeutics role in diseases management. Although numerous studies has shown the beneficial effect of green tea in health management, however few studies has confirmed its exact mechanism of action in diseases control and still various studies based on animal model are needed to confirm the safe dose and bioavailability in the diseases prevention and treatment.

CONFLICT OF INTERESTS

Declared None

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