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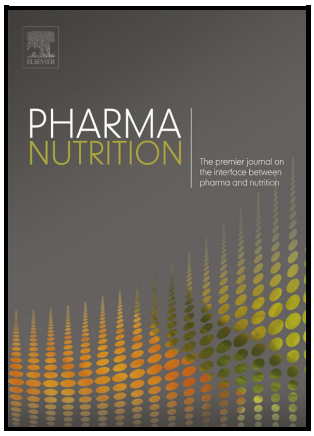

Green tea polyphenols in cardiometabolic health: A critical appraisal on Phytogenomics towards personalized green tea

Logesh Rajan, Arun Radhakrishnan, Keshav Narayan Alagarsamy, Abhay Srivastava, Sanjiv Dhingra, Anthony Booker, Viven Rolfe, Dhanabal Palaniswamy, Suresh Kumar Mohankumar

PII: S2213-4344(22)00009-3

DOI: https://doi.org/10.1016/j.phanu.2022.100296

Reference: PHANU100296

To appear in: *PharmaNutrition*

Please cite this article as: Logesh Rajan, Arun Radhakrishnan, Keshav Narayan Alagarsamy, Abhay Srivastava, Sanjiv Dhingra, Anthony Booker, Viven Rolfe, Dhanabal Palaniswamy and Suresh Kumar Mohankumar, Green tea polyphenols in cardiometabolic health: A critical appraisal on Phytogenomics towards personalized green tea, *PharmaNutrition*, () doi:https://doi.org/10.1016/j.phanu.2022.100296

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Green tea polyphenols in cardiometabolic health: A critical appraisal on Phytogenomics towards personalized green tea

Logesh Rajan[1#], Arun Radhakrishnan[2#], Keshav Narayan Alagarsamy[3], Abhay Srivastava[3], Sanjiv Dhingra[3], Anthony Booker[4], Viven Rolfe[5], Dhanabal Palaniswamy[1] and Suresh Kumar Mohankumar[6*]

1. TIFAC CORE in Herbal Drugs, Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamilnadu, India.
2. Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamilnadu, India.
3. Regenerative Medicine Program, Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, MB R3T 2N2, Winnipeg, Canada.
4. Research Centre for Optimal Health, School of Life Sciences, College of Liberal Arts and Sciences, University of Westminster, London, United Kingdom
5. Pukka herbs Ltd, Block C, The chocolate factory, Keynsham, BS31 2GN, United Kingdom.
6. Swansea University Medical School, Institute of Life Sciences, Swansea University, Singleton Park, Swansea, Wales SA2 8PP, United Kingdom.

#Authors contributed equally

*** Corresponding author**

Suresh K. Mohankumar, M.Pharm, Ph.D, PGCHE, FHEA

Associate Professor, Pharmacy-Pharmacology
Swansea University Medical School
Institute of Life Sciences
Swansea University
Singleton Park
Swansea
Wales SA2 8PP
Phone +44 07760 164415
Mail id: s.k.mohankumar@swansea.ac.uk

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Author contributions

Logesh Rajan#: Content writing & data collection

Arun Radhakrishnan#: Content writing & data collection

Keshav Narayan Alagarsamy: Literature review and content writing

Abhay Srivastava: Literature review and draft preparation

Sanjiv Dhingra: Content design & development

Anthony Booker: Content development and editing

Viven Rolfe: Content development and editing

Dhanabal Palaniswamy: Content review and editing

Suresh Kumar Mohankumar: Framework planning, Concept development, Guidance

Abstract

Cardiovascular disease is a chronic multifactorial health complication that is either directly or indirectly associated with pathophysiological mechanisms, including pro-oxidation, pro-inflammation, vascular and endothelial dysfunction, impaired platelet function, thrombosis, and others. The therapeutic options to circumvent cardiovascular complications include several phytomedicines, including green tea polyphenols. However, while many experimental and clinical studies report distinct mechanisms by which the polyphenols of green tea elicit a beneficial role in cardiometabolic health, the translation and applications of green tea polyphenols in clinics have yet to gain their optimal use on the broader population. This review critically appraises the various reported mechanisms of green tea polyphenols in modulating cardio-metabolic health and associated phyto-genomic challenges. Further, our review highlights the probability of gene polymorphic associated therapeutic variations in individuals using green tea for cardio-metabolic effects and the necessity to personalize green tea for clinical use, thereby improvising the risk-benefit ratio.

Keywords:

Green tea polyphenols, cardiovascular disease, inter-individual variability, genetic Polymorphism, phyto-genomic.

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Abbreviations

ACE - Angiotensin-converting enzyme

ADMA - Asymmetric dimethylarginine

ADP - Adenosine diphosphate

ADSC - Adipose-derived stem cells

AGEs - Advanced glycation end products

BMI - Body mass index

BW - Body weight

CAD - Coronary artery disease

COMT - Catechol-O-methyltransferase

CRB - Catechins rich beverage

CRP - C-reactive protein

CVDs - Cardiovascular disease

DBP - Diastolic blood pressure

ECs - Endothelial cells

EDHFs-Endothelium-derived hyperpolarizing factors

EDRF - Endothelium-derived relaxing factor

EGC - Epigallo catechin

EGCG - Epigallocatechin gallate

eNOS - Endothelial nitric oxide synthase

FBF - Forearm blood flow

FMD - Fibromuscular dysplasia

GTC - Green tea catechins

GTE - Green tea extract

HDLC-High-density lipoproteins cholesterol

HOMA-IR-Homeostasis model assessment of insulin resistance

ICAM-1 - Intercellular adhesion molecule-1

IEs - Idiopathic environmental intolerances

IHD - Ischemic heart disease

iNOS - Inducible nitric oxide synthase

NOS - Nitric oxide synthase

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LDL - Low density lipoprotein

LDL-C-Low density lipoprotein cholesterol

MCP-1 - Monocyte chemo attractant protein-1

MC-SF - Macrophage colony-stimulating factor

MMPs - Matrix metalloproteinases

NO - Nitric oxide

PDE-5 - Phosphodiesterase type 5

PDGF - Platelet-derived growth factor

PI3-K - Phosphatidylinositol 3-kinase

PKC - Protein kinase-C

PL - Phospholipids

RCM - Restrictive cardiomyopathy

ROS - Reactive oxygen species

SBP - Systolic blood pressure

SNP - Single nucleotide polymorphisms

TAS - Total anti-oxidant status

TC - Total Cholesterol

TG - Triglycerides

TNF-α - Tumor necrosis factor

TXA2 - Thromboxane A2

VCAM-1-Vascular cell adhesion molecule-1

VED - Vascular endothelial dysfunction

VSMCs - Vascular smooth muscle cells

WC - Waist circumference

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Introduction

Cardiovascular disease (CVD) is a chronic severe multifactorial disease that adversely affects an individual's health, well-being, and lifestyle [1]. The World Health Organisation (WHO) projected cardiovascular diseases (CVDs) as the primary cause of death globally. In 2019, around 17.9 million (32%) people died due to CVDs, and it is estimated to increase exponentially in the future [2-5]. Thus, preventing the risk of CVD is a timely task. Plant-based

bioactivities hold enormous interest in a safe alternative among various therapeutic strategies to combat CVD.

Since ancient times, tea has been consumed as a common drink by humans worldwide. The tea plant *Camellia sinensis* (L.) Kuntze Theaceae, is commonly known as tea, and it likely originates from South-West China, Indo-Burma, Tibet region, having been domesticated from the wild Camellia taliensis (W.W.Sm) Melch [6, 7]. While tea has several varieties, green tea has gained immense therapeutic interest because of its potent anti-oxidant, anti-inflammatory, anti-hypertensive, anti-diabetic, and other valuable activities [8, 9]. The primary chemical constituents of green tea are catechins, consisting of 80-90% of the total polyphenols. Among the various catechins reported in green tea, the epigallocatechin gallate (EGCG) constitutes more than 50% of total catechins. The polyphenols of green tea have shown significant cardioprotective effects under experimental conditions in cell lines, animal models, and clinical studies [10-15], suggesting its therapeutic potential in combating CVD. Of note, many epidemiological studies report that regular consumption of green tea catechins (GTC) reduces the risk of CVD [16-22]. However, despite the several pieces of evidence supporting GTC's therapeutic implications in CVD, the clinical outcomes of GTC remain mixed.

Emerging reports indicate that the effects of GTC vary with individuals due to ethnic, gender, lifestyle, cultural, environmental, and genetic differences [23-25]. This was further justified by various researchers by their experimental pieces of evidence. In 2015 a Japan-based prospective study revealed that lifestyle change, i.e., smoking, dietary habits, etc., can alter the effect of green tea in CVD management. Later in 2016, green tea failed to establish its ability to control hyperlipidemia in a clinical trial on the Chinese population[26]. However, in the same year, a clinical trial conducted on the American hyperlipidemic population established positive co-relation, which indicates the region, race associated altered effect of green tea. Inter-ethnic related differences in the pharmacokinetic profile of green tea were also explained in a systematic literature study carried out in 2021[27]. Apart from these positive outcomes, the frequency and degree of ADRs also change according to the individual variation. Even though the number of ADRs was associated with green tea consumption, liver injury is considered significant adverse effects. A systematic review on green tea supplements revealed the hepatotoxic effect of green tea and it further concluded that the adverse effect is majorly based

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on patient factors [28]. A randomized, placebo-controlled, double-blinded phase II clinical trial studied the adverse effects of sustained high dose oral green tea extract. The study strongly indicated the effect of green tea extract in liver enzyme elevation [28]. The European Food Safety Association (EFSA] Panel on Food Additives and Nutrient Sources added to Food suggested that the intake of EGCG equal to or above 800mg/day may increase the serum transaminases [29]. Likewise, few published reports indicate the population-based hepatotoxic nature of green tea. Despite these ADRs, several scientific studies reported GTC consumption's health benefits; the possible associations with gene polymorphisms were less addressed [30]. A few ancillary analysis studies suggested that the selective genes such as *SLCO1B1*1B* (rs4149056), *UGT1A1* (rs8175347), *SOD1A251G* (rs2070424), and others could influence the molecular mechanisms by which GTC elicit cardio-metabolic effects [31, 32]. Thus, it is pivotal to understand the specific genetic polymorphisms and their association with cardiovascular benefits of GTC.

Collectively, this review collates the effective mechanisms associated with cardio-metabolic health benefits of GTC and subsequently appraises the genomic factors that affect the therapeutic responses of GTCs. These genes are selectively proposed to alter the dynamics and kinetics of GTC in humans, based on the population pharmacokinetic data constructed from conventional drugs, which exhibit their action via similar pathways [33, 34].

GTCs-mediated cardiometabolic health

Conventional cardioprotective action

Many human clinical trials and cohort studies show the association between green tea consumption to CVD health [35-39]. For example, a Japanese elderly cohort study with the patient population of 14001 reported that intake of green tea of about five or more cups daily significantly reduced CVD mortality [40, 41]. Additionally, various cohort studies carried out in China and Japan further strongly explained the positive effect of green tea on CVD [42]. However, the risk of CAD was reduced only in males, whereas it was not observed in female participants [43]. Likewise, multiple clinical studies showed that consuming green tea flavonoids significantly decreased endothelium-dependent vascular reactivity and CVD parameters [44-46].

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On the contrary, some studies on specific people have also shown that green tea fails to meet the expected cardio-related positive effects. In **table 1** population-based positive, negative co-relation and the adverse effects of green tea towards various cardio-parameters were extensively reviewed.

Table 1. Population-based studies on green tea consumptions and its cardiometabolic outcomes.

Co-relation type	**Objective**	**Results& Conclusion**	**Population**	**Year**
Positive correlation *Tea consumption effects on*	BP, cholesterol, coronary and total mortality	Decreased SBP, coronary mortality rate	Norway (9,856 men and 10,233 women)	1992 [47]
	Endothelial disfunction	Reversed endothelial dysfunction.	USA (coronary artery disease patients)	2001 [48]
	BP, serum lipids, oxidative stress, and inflammatory	Significant decrease in LDL c, HDL c.	China (hypercholesterolemic patients)	2003 [49]
	4-O-methylgallic acid and hypertension	Long term intake of tea has a favorable effect on BP Reduction in SBP and DBP	Australia (greater than 70 years old women)	2003 [50]
	Hypertension	Reduction in the risk of developing hypertension	China (711 men and 796 women with no hypertension)	2004 [51]
	Anti-oxidant activity, oxidative resistance to DNA, and lipid profile	GT improved overall antioxidative status	Italy	2005 [52]
	Postprandial lipid response	Catechins reduce TG level after fat loaded	Japan (subjects with hyper	2005 [53]

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		food consumption	triacylglycerolaemia)	
	Insulin resistance and systemic inflammation	A slight decrease in BW, SBP and DBP, blood glucose, hemoglobin A1C, and insulin levels	Japan (53 males and 13 females with mild diabetes)	2005 [54]
	Endothelial function and endothelial progenitor cells in smokers	Increase in FMD and endothelial progenitor cells, prevent the cardiovascular events in chronic smokers	Korea (20 young healthy smokers)	2006 [55]
	Endothelial dysfunction	The level of O-methylase affects the improvement of FMG	Australia	2006 [56]
	Endothelial dysfunction and blood pressure	Flavonoid supplementation improved endothelial function.	———	2006 [57]
	Oxidized plasma LDL and lipid profile	Significantly decreased oxidized LDL without change in plasma LDL	Japan (10 men, 30 women)	2007 [58]
	Cardiovascular risk and body fat reduction	Reduced BW, BMI, body fat ratio, WC, body fat mass, SBP, and LDL.	Japan (women and men with visceral fat-type obesity)	2007 [59]
	Susceptibility of LDL oxidation	Decreased LDL, prevent atherosclerosis progression	Japan	2008 [60]

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	Nitric oxide and endothelin 1 Acute and chronic administration of high doses (580mg)	Enhancing the NO and decreasing the ET-1 plasma concentrations Improvement in the forearm blood flow in male smokers	Australia (Healthy men)	2008 [61]
	Endothelial function [Flow-mediated vasodilation)	Increased FMD, Acute beneficial effect on endothelial function	Greece (Male)	2008 [62]
	Vascular function and lipid peroxidation	Significant increase in brachial artery diameter, reduction in oxidized LDL and anti-oxidized LDL IgM antibodies level	Spain (Female)	2008 [63]
	Type 2 diabetes patients	Decreased WC and increased Adiponectin, useful in reducing obesity.	Japan (Patients with type 2 diabetes)	2009 (64]
	BW, lipids and lipids peroxidation	Green tea improved the metabolic syndrome in obese patients	USA (35 subjects with obesity and metabolic syndrome)	2010 [65]
	Evaluate the effects of green tea on cardiovascular disorder markers	Anti-atherosclerotic action on dysfunctional vessels in smokers	Japan (smokers)	2010 [66]
	TC and LDL and HDl	Reduced LDL cholesterol	USA	2011 [67]
	LDL, glucose and hormone level in post-menopausal women	Significant decrease in LDL.	USA (post-menopausal women)	2012 [68]

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	Insulin resistance and cardiovascular risks in obese hypertensive subjects	GTE influences blood pressure, TC, LDL-C, HOMA-IR, CRP, TNF-α, and TAS	Poland (obese, hypertensive patients)	2012 [69]
	Prevention of CVD	Black tea: Reduced LDL, SBP, and DBP Green tea: Reduced TC	UK	2013 [70]
	Insulin resistance and glucagon-like peptide 1 in type 2 diabetes patients	Decrease in insulin resistance and TG and HOMA-IR index. Increased HDL	China	2014 [71]
	Weight reduction, lipid profile, and hormone peptides (obesity-related]	Significant reduction in BW reduced LDL and TC	China (women with central obesity]	2015 [72]
	Ischemic heart disease (IHD) and cancer	Reduced risk of IHD and major coronary events	China	2017 [73]
	CVD	Reduced BP, LDL, support vascular functioning and reduced inflammation	UK	2018 [74]
	Dose response relation between green tea consumption and risk of CVDs	4% lower risk of stroke and CVD mortality, 2% lower risk of CVD events	USA	2020 [75)
	Effect of green tea consumption on blood pressure	Significant reduction in SBP and DBP	China	2020 [76]
Negative correlation *Tea consumption effects on*	Arterial stiffness and inflammation in type 2 diabetes patients	No reduction in inflammatory, lipid profiles, blood glucose, insulin resistance	South Korea	2005 [77]
	Inhibition of platelet aggregation, LDL oxidation, and matrix metalloproteinases (MMPs) activity	No reduction in the concentration of MMPs, urine 8-epi-PGF(2alpha), and platelet aggregation	Japan	2005 [78]

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	Blood parameters and metabolic parameters when consumed with low energy diet	Modest weight loss	Netherlands	2006 [79]
	Body fat and CVD and its safety in obese children	No significant weight loss. Genetic variation, dietary habits, and body composition alters the results	Eastern and western population	2008 [80]
	Obese women and related hormones	No significant reduction in BW, BMI, and WC	Taiwan (Obese women)	2008 [81]
	Insulin resistance and associated metabolic risk factors	No significant effect on insulin resistance. A modest reduction in diastolic BP	UK (obese patients: 40-65 years)	2009 [82]
	Serum lipids	No significant LDL lowering	Netherlands (67 men and 35 women)	2010 [83]
	CVD	No anti-inflammatory, anti-oxidant, antiproliferative effects.	USA	2011 [84]
	Obese, type 2 diabetic patients (EGCG 856 mg)	No significant difference between the placebo and treatment group in EC and insulin level	Taiwan	2011 [85]
Adverse effects *Tea consumption effects on*	TC, LDL, and HDL	Significant reduction in TC and LDL **Adverse effects:** Skin rashes, abdominal bloating, and gastric upset	China (1136 subjects)	2011 [86]
	Cholesterol	Visceral fat loss **Adverse effects**: Gastrointestinal symptoms (Bloating,	China (Adults)	2012 [87]

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		diarrhea, appetite change)		
	Blood pressure	Reduced SBP, TC, and LDL **Adverse effects**: High doses are associated with side effects	UK	2014 [71]
	Insulin resistance and glucagon-like peptides in type II diabetes Mellitus and lipid abnormality patients	Improved insulin decreased the level of glucagon-like peptide 1. **Adverse effects:** Epigastric dullness and mild constipation	China (92 subjects)	2014 [88]
	Weight loss	No significant weight reduction. **Adverse effects**: Mild to moderate hypertension and constipation	Canada	2014 [89]
	Blood lipids	Reduced LDL and TC. No reduction in HDL **Adverse effects**: Abdominal bloating, gastric upset and skin rashes	China	2020 [90]

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These reported data show that green tea fails to reach its positive claim in some studies and, up to some extent, leads to adverse effects. Also, multiple studies reported that regardless of age, gender, sex, etc., genetic predisposition plays a significant role in inter-individual variability. Extensive studies were carried out by analyzing genes irrespective of age, gender, sex, etc. Genetic predisposition plays a vital role in inter-individual variability. Comprehensive studies were carried out by analyzing gene age, gender, sex, etc. Genetic predisposition plays a significant role in inter-individual variability. Extensive studies were carried out by analyzing gene-related population changes with positive results [91]. An individual's genetic makeup

remains a constant variable throughout their lifespan and shows a potential impact on kinetic profile [92]. Even though various factors determine drug efficacy, genetic predisposition is considered feasible, accurate, and highly influencing compared to other factors' heterogeneity among individuals [93]. Based on the extensive referred reports and shreds of evidence, it was firmly believed that green tea exhibits significant inter-individual variability on cardio-metabolic health. These individual variabilities may result in an unexpected effect that may or may not benefit a person already at risk of cardiac health. In association with many inconsistent reported clinical interventions, the "one size fits for all" approach is a failed strategy in green tea consumption. Therefore, this helps us focus more on inter-individual variability, which can predict the efficacy of green tea usage in the treatment of cardio-metabolic disorders. This further paved the path of research towards molecular mechanism based genetic Polymorphism associated inter-individual variability

Molecular mechanisms by which GTC combats cardiometabolic diseases

Table 2. Distinct mechanisms of GTCs to combat CVD.

S. No.	Mechanism	Activity	Reference
1.	**Anti-oxidant effects**	• Increased anti-oxidant enzymes decreased pro-oxidant enzymes • Free radicals scavenging • Chelation of redox ions • Decreased OxLDL and NOX-1 enzymes	Dhalla et al., 2000[94]; Paravicini and Touyz, 2008[95]; Park et al., 2011[96]; Zinkevich and Gutterman, 2011[97]; A Islam, 2012[98]
2.	**Anti-inflammatory activity**	• Decreased cytokines, chemokines, VCAM-1, adhesion molecules, MCP-1 expression, leucocyte penetration, p38 MAPK, and NF-kappa B	Marui et al., 1993[99]; Lin and Lin, 1997[100]; Gu et al., 1998 [101]; Gerszten et al., 1999[102]; Kevil et al., 2001 [103]; Ludwig et al., 2004 [104]; Libby, 2006[105]; Suzuki et al.,

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			2007[106]; A Islam, 2012 [39]
3.	**Vascular endothelial dysfunction**	• Increased NO, eNOS, cGMP, PI3K/Akt and ET-1 activation	Dimmeler et al., 1999[107]; Schiffrin, 2001 [108]; Galley and Webster, 2004[109]; Kobayashi et al., 2005[110]; Hadi and Carr, 2005[111]; Forstermann and Munzel, 2006[112]; Basu and Lucas, 2007 [113]; Balakumar et al., 2009[114]; Islam, 2012[98]
4.	**Anti-proliferative activity**	• Decreased VSMCs proliferation, PDGF expression, degradation of matrix protein, MMP-2 and MMP-9 expression	Ross and Glomset, 1973[115]; Lindner and Reidy, 1991[116]; Schwartz et al., 1995[117]; Yamamoto et al., 2000[118]; Visse and Nagase, 2003 [119]; Ouyang et al., 2004[120]; De Donatis et al., 2008[121]; Yuan et al., 2011[122]; Yang et al., 2011[123]; A Islam, 2012[98]
5.	**Anti-platelet and anti-thrombotic activity**	• Decreased Ca^{2+} utilization, inositol 1,4,5-triphosphate, fibrinogen-GPIIb/IIIa binding, phospholipase Cγ2	Born, 1965 [124]; Kang et al., 2001 [125]; Ueno et al., 2011[126]; A

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		phosphorylation, protein tyrosine phosphorylation, arachidonic acid, and cellular prostaglandin D2 levels	Islam, 2012[98]
6.	**Reduce the production of VLDL and induce LDL expression**	• Significant down regulation of Apolipoprotein B and microsomal triglyceride transfer protein reduce VLDL • Activate peroxisome proliferator-activated receptor δ and regulatory element-binding protein 2 thereby increase the level of LDL c	Luo K et al., 2020 [127]
7.	**Reduction of cholesterol absorption from intestine**	• Targeting Low-Density Lipoprotein Receptor and down regulating Microsomal Triglyceride Transfer Protein	Pamela Mason et al., 2021 [128]

Genomic factors responsible for the inter-individual variability

Genetic polymorphism and altered activity in the human body differentiate individuals' drug responses. Any polymorphism that influences the mediators in a drug action pathway or the drug-metabolizing enzymes determines the drug response. The inter-individual variability constructed the path towards genomic variation-based drug action science. The concept of pharmacogenomics has existed since ancient times. The Greek philosopher Pythagoras reported that only a micro-set of people suffered from fatal hemolytic anemia [129]. Later, modernization of science-supported his claim by identifying genetic polymorphism associated with glucose-6-phosphate dehydrogenase. This initiation, along with the human genome project, widened the scope of pharmacogenomics in medical research.

Pharmacogenomic factors are regarded as critical in cardiovascular therapy. For instance, one of the metabolizing enzymes, *CYP2C19,* was 40% low functional in the Hawaiian population. Such polymorphisms influenced clopidogrel's therapeutic outcome in the Hawaiian population [130].

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Most cardiometabolic medicines are predominantly affected by ABCB1 [efflux pump) polymorphism, specifically C3435T, which results in an average 72% risk when comparing individuals with CT/CC genotype. [131-134]. In addition, various other genes *VKORC1, CYP2C19*2, CYP3A4, HMGCR13, SLCO1B1, NEDD4L, CACNA1C, CACNB2*, and *KCNMB1*, were related to change in cardiovascular drug PK-PD profile [135]. **Figure 1** shows the association of molecular mechanisms of green tea polyphenols with genetic polymorphism-linked inter-individual variations in protecting cardio-metabolic health.

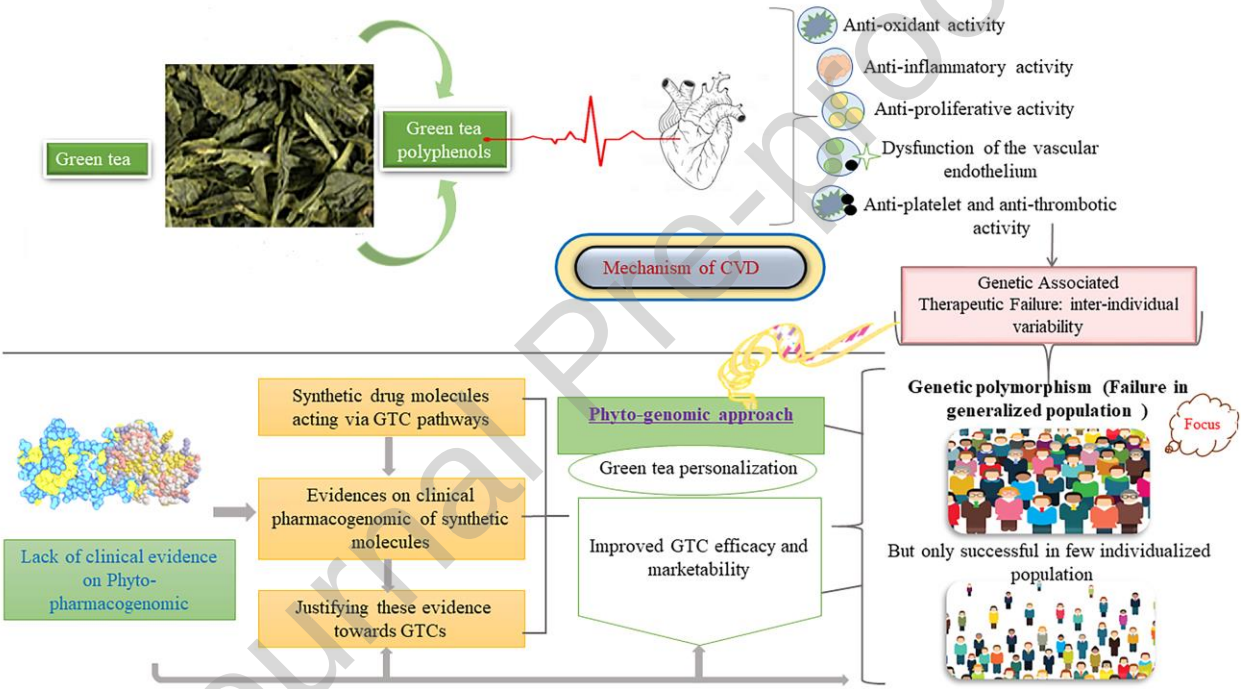

Figure 1. Association of molecular mechanisms of green tea polyphenols with genetic polymorphism-linked inter-individual variations in protecting cardio-metabolic health (insert here)

Some direct correlation studies on green tea catechins pharmacogenomic profiles were performed on various populations, which provided a favorable report on inter-individual variability. Investigation revealed that the individuals with polymorphisms in the gene T allele of *MRP2 -24C* present in the *ABCC2* gene reduced the efficacy of EGC. Bruhn and co-workers studied the polymorphisms of drug transporters ABCB1, ABCG2, ABCC2, and ABCC3 and

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their impact on drug bioavailability with respect to the clinical relevance of EGC [136]. It was also found that *SLCO1B1* gene coding for OATP1B1 has been involved in EGCG and EGC clearance. There was a 30% reduction in clearance for homozygous individuals with the C allele of *SLCO1B1* 521T>C *SLCO1B1*5* and a 35% reduction in wild-type clearance when compared to the *SLCO1B1* 388A>G allele. Konig *et al.,* reported that the clearance of EGC was reduced in the wild type compared to the variant allele *SLCO1B1*1B* found in individuals [137]. Gong and his co-authors worked on the impact of genetic variation in OATP transporters on EGC disposition and response [138]. While considering the phase II enzymes in the biotransformation of green tea catechins SULT1A1, COMT, UGT1A1, there was less impact on the kinetics of EGC. Twenty-four human volunteers, 14 women and 10 men with *COMT* SNPs, were studied in Berlin to determine the effect of EGCG on *COMT*. 24% lesser bioavailability of EGC was identified with individuals having low activity genotype Met/Met of *COMT*. 26% clearance reduction in the *UGT1A1*(rs8175347) wild-type carriers were identified. The activity of catechol-O-methyltransferase was not impaired by high doses of epigallocatechin-3- gallate EGCG *in vivo* [139]. In a randomized controlled cross-over trial, the influence of COMT Val/Met genotype was observed. The homozygous group with high activity G allele had a lesser urinary accumulation of EGC and 4'-O-methyl EGC. In contrast, the individuals with a minimum of one low activity A allele had a Higher EGC and 4'-O-methyl EGC in urine [140]. A population-based case-control study performed on Asians from Los Angeles suggested the *COMT* genotype influences the change in green tea's polyphenol bioavailability. The results revealed that the low-activity COMT genotype carriers excreted fewer polyphenols in urine, implying that they may retain more tea polyphenols in their bodies and get more health advantages[141, 142]. On the other side, a study conducted in the United Kingdom with twenty participants recruited 10 of each homozygous COMT genotype. A preliminary investigation of the impact of *COMT* genotype on the absorption and metabolism of green tea catechins was studied on the population and demonstrated no significant variation in absorption and elimination of EGCG in *COMT* polymorphism [143]. A population nutrikinetic study conducted in German people, 84 healthy volunteers on the effect of EGCG and EGC, indicated the use of oral contraceptives and inherent genetic variations in *MRP2* and *OATP1B1* impact their pharmacokinetics [144]. Whereas the genes *MRP2, MRP2, ABCB, ABCC, and ABCG* are related to a transmembrane protein specifically involved in the efflux of drug molecules, including EGCG and EGC. Hence,

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polymorphism in this protein will enhance the elimination rate and thereby reduce the efficacy of green tea. On the other hand, the genes *OATP1B1* and *SLCO1B* are related to influx protein, which takes the drug for hepatic metabolism. Polymorphism in these genes can alter the pharmacokinetic profile of EGCG and EGC [145]. Similarly, various studies have suggested significant pathways involved in the metabolism of catechins are glucuronidation (4''-O-glucuronidation, 3'-O-glucuronidation, 7-O-glucuronidation), sulfation (O-sulfation), o-methylation (4'-O-methylation, O-methylation), and ester hydrolysis. The isozymes involved in the enzymatic hydrolysis are SULT1A1, SULT1A3, UGT1A8, UGT1A9, UGT1A3. Polymorphism in these enzyme-related genes may also alter the pharmacokinetics of catechins [146].

The significant genetic polymorphism involved in altering the effect of GTCs is shown in **table 3.**

Table 3. Genetic Polymorphism involved in GTCs.

S. No	Genetic Polymorphism	Drug	Effect	Year	Reference
1.	*SLCO1B1*	EGCG and EGC	Involvement in clearance	2000	König et al., 2000[137]
2.	*MRP1, MRP2 and Pgp*	Green tea catechin	Involvement in the absorption and excretion of GTCs	2008	Kadowaki et al., 2008[147]
3.	*COMT*	EGCG	Not impaired by high doses of EGCG	2010	Lorenz et al., 2014[139]
4.	*COMT*	tea polyphenols	Influence in bioavailability.	2010	Inoue-Choi et al., 2010 [39]
5.	*SLCO1B1*1B*	EGC	Reduced clearance	2012	Gong and Kim, 2012 [138]
6.	*COMT SNPs*	EGC, EGCG	Reduced bioavailability	2010	Inoue-Choi et al., [141]

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7.	*MRP2-24C, ABCC2, ABCB1, ABCG2, ABCC2 and ABCC3*	EGC	Reduced efficacy of EGC	2014	Bruhn and Cascorbi, 2014[136]
8.	*MRP2 and OATP1B1*	EGCG and EGC	Impact in pharmacokinetics	2018	Scholl et al., 2018[144]

At present surplus, clinical-cum-pharmacogenomic information is available on FDA-approved synthetic molecules. Based on this evidence, we are hypothesizing the EGCG associated cardiometabolic genetic polymorphism. EGCG action in the body happens through NOS, CAT, and GPX. EGCG inhibits inducible nitric oxide synthase (iNOS), Lipoxygenase, cyclooxygenase, xanthine oxidase, etc. Hence the SNPs in these components affect the activity of EGCG in an individual.

The induction of NOS is one of the mechanisms by which EGCG produces its anti-oxidant activity. A cohort study conducted in 2015 reported the influence of nitric oxide synthase *NOS* polymorphisms *NOS2A* −2.5 kb(CCTTT)$_n$, Ser608Leu and *NOS3* −786(T>C) of nitrite/nitrate levels in inflammatory disorders accounting to 107 multiple chemical sensitivity, 89 fibromyalgia/chronic fatigue syndrome, 108 suspected multiple chemical sensitivity patients and 196 healthy subjects. *NOS3* –786(TT)was associated with higher nitrite/nitrate levels in study subjects with idiopathic environmental intolerances IEs. In a study performed in 2017, polymorphic effects of NOS and nitric oxide levels in chronic periodontitis, rather than the polymorphic variations, gender was the contributing factor for the differences in nitric oxide concentration. Concomitantly in Brazilian individuals, SNPs in -1026(AC) and +2087(AG)SNPs had a significantly higher level of nitric oxide but were not associated with chronic periodontitis (148]. These polymorphisms determine the levels of NOS in individuals, hence the effect of a drug acting through NOS mechanisms. Another enzyme involved in the pathway of EGCG is Lipoxygenase. Lipoxygenase catalyzes the conversion of arachidonic acid to leukotriene A4. Polymorphisms in Lipoxygenase extensively influence the action of Leukotriene receptor antagonists and leukotriene synthesis inhibitors[149]. Around 2002, US-based researchers came up with the concept, ser529 gene polymorphic *COX-1, PLA1/A2* polymorphic gene-related glycoprotein GP Ia/IIa may result in the maximized chance of resistance in aspirin action and

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thereby enhanced ischemic cardiac events [150]. EGCG produces its anti-oxidant effects, reduces oxidative stress and inflammation by inhibiting the enzymes such as inducible nitric oxide synthase (iNOS), Lipoxygenase, cyclooxygenase, xanthine oxidase, etc and thereby supporting cardio-health. Pharmacokinetically higher the inhibition better the action, but the above discussed pharmacogenomic variation will affect EGCG binding affinity which further results in inter-individual variations in EGCG action. Similarly, in a clinical trial it was found that the variability in drug response is also associated with non-steroidal anti-inflammatory drugs due to *COX-2* polymorphisms. In 2017, Lee *et. al.* found celecoxib produced inhibitory action in 2h in all subjects, the area under the curve was significantly less for rs689466 GG genotype compared to other groups [151]. SOD, GPX, and CAT are the major anti-oxidant enzymes and the anti-oxidant activity of EGCG is through the induction of these enzymes. *SOD1* A251G*(*rs2070424) polymorphism was observed in 56.3% of females and 43.7% males in a study of 494 Turkish subjects in 2017 [152]. The association of CAT enzyme expression during a pathological condition depends on various factors such as TNF-α, PPARγ, CpG islands hypermethylation, and p53 protein. Polymorphisms in the *CAT* gene contribute to variation in the enzyme levels and activity during pathological conditions, such as asthma, insulin resistance, hypertension, dyslipidemia, vitiligo, and hypertension. Polymorphisms -262 C/T and -844 A/G influence the gene expression and its activity. Physical activity, age, seasonal variations, and several chemical compounds further influence the expression of CAT [153]. In 2018, the effect of polymorphism in CAT, SOD, and GPX enzymes in clinical, anthropometric, and biochemical outputs was studied in obese patients under dietary intervention in a clinical trial. There was a significant difference in outcomes between genotypes. Genotypes rs7943316 SNPs− 21A>T CAT and rs4880 47C>T *SOD2* significantly affected clinical, anthropometric, and biochemical outcomes compared to other groups [154]. Apart from CAT, SOD, GPX enzymes, it was identified that catechin also exhibits its action by inhibiting MMP-2; this paved the pathway for analyzing gene Polymorphism associated with MMP-2. Around 2017, Andrea R *et al.*, worked on MMP-2 polymorphism associated with drug resistant hypertension in the Brazilian population in a cross sectional study and concluded the result stating GCC and GCT haplotype of -735C/T *MMP-2* may critically be associated with drug failure in hypertension, and this justifies the chances of genetic level change in *MMP-2* can further affect catechin action [155].

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EGCG induces vasorelaxation by increasing NO production by activating eNOS, which is responsible for the highest production of NO and has an extensive impact on the cardiovascular system. eNOS polymorphisms impact the response of drugs angiotensin II receptor antagonists, beta-blockers, statins, diuretics, angiotensin-converting enzyme inhibitors acting via NO signaling [156]. A clinical study by Silva *et al.*, in 2013 presented anti-hypertensive elanapril response better in patients with rs2070744 polymorphism. But there were responders and non-responders to the drug even though they possessed the same4b/4a and Glu298Asp polymorphism. Therefore, the 2996A/G Polymorphism in *eNOS* was responsible for enhancing beta-blockers and angiotensin II receptor blockers [157]. Diuretic hydrochlorthiazide action is modulated by the effect *eNOS(*Glu298Asp) polymorphism. Glu polymorphic individuals are significantly more responsive to hydrochlorothiazide than individuals with ASP polymorphism [158]. A study in 2003 demonstrated the effect of polymorphism in eNOS inhibitors, the Phosphodiesterase type 5 PDE-5 which are used in the treatment of erectile dysfunction since the drug acts by increasing cGMP levels in tissues in the absence of NO. Homozygous subjects of Glu298Asp Polymorphism are less responsive to sildenafil [159]. Calcium channel blockers such as nifedipine can enhance the NO bioavailability and endothelial function [160, 161]. A randomized clinical trial conducted in 2012 reported the polymorphic effects of NO_3 with stroke, and the glu298asp G>T variant resulted in mortality while comparing amlodipine with lisinopril [162]. Further, EC maintains the angiotensin- II and thereby balances the vascular tone, but in 1999, researchers conducted a clinical experiment with losartan, revealing a change in drug action associated with Ang II type 1 receptor genetic polymorphism. The study was conducted on 66 healthy Caucasian populations, para amino Hippurate and inulin clearance were used as a tool to measure renal hemodynamic function [87]. This analysis specified that EC following angiotensin mechanism may face gene-based variation in drug action similar to losartan.

The drug examples specified in the above sections were acting via one of the paths followed by GTCS to produce its cardiometabolic action. Hence there exists a possibility either the same polymorphic effects will affect the response of green tea. These possibilities will necessitate the personalization of green tea use to achieve maximum benefits. Further on, understanding green tea's challenges and opportunities from industrial perspectives will broaden the scope for real-time implementation for the benefit of the society.

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Real-Time implementation: Challenges and opportunities

Globally, tea is one of the most highly consumed beverages. Multiple tea-producing countries and processing industries economically support this vast market size. Based on a 2014 survey, the global cultivation area of tea was around 3.8 million hectares. The productivity was about 5.6 million metric tons, including multiple verities and species of tea worth billions of dollars[163]. This growing market supported certain tea varieties to transit from commercial drink to health drink, and at present organic tea, white tea, etc., are typically considered a nutraceutical health drink. Based on these statistics, we can forecast the growth of the green tea market as a nutraceutical benefiting both producers and consumers. Hence, integrating the phytopharmacological knowledge with pharmacogenomics is regarded as an important way forward as it could advance the personalization of green tea for enhanced cardiometabolic outcomes. However, phyto-genomic approach towards green tea personalization also faces numerous challenges. The non-specific cardiometabolic pathway of GTCS makes it challenging to predict and narrow down the influencing gene. Gene-related experiments are expensive, which in turn may increase the product cost, stringent regulations on phytochemical-based clinical trials, lack of extensive clinical data, etc. Transdisciplinary approaches with the support of phytochemical industries, clinical researchers, and the technology sector can resolve these challenges, resulting in next-generation personalized green tea for a specified population.

Conclusion

Green tea and its polyphenols such as catechins and EGCG especially have gained attention in targeting CVDs. The mechanism by which green tea exerts cardio-metabolic effects includes anti-oxidant, anti-inflammatory, vascular endothelial dysfunction, anti-proliferative, antiplatelet and anti-thrombotic activities. Apart from its application towards CVDs, green tea also possesses various other applications in diabetes, cancer, and other minor benefits such as headaches and better digestion etc., towards human health. However, in this review, we have extensively collated published literature on green tea with its role in preventing CVDs; most clinical studies suggest a complete reduction in CVDs. On the other hand, some interventional studies possess the hepatotoxic effect of green tea consumption.

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Further, there are also mixed data about the effects of the consumption of green tea on cardiac risk factors from observational and intervention studies. We firmly believe that green tea exhibits significant inter-individual variability on cardio-metabolic health based on many heterogeneously reported clinical interventions. This further paved the research to focus on genetic polymorphism associated with inter-individual variability. Polymorphisms of *NOS, COX 1, COX 2, SOD, CAT*, etc. have been modifying the conventional drug's efficacy via cardiometabolic pathways. This evidence indicates the probability of polymorphic effects in individuals using green tea for cardio-metabolic effects and the necessity to individualize green tea therapy.

Conflict of Interest

The authors declare no conflict of interest.

Financial disclosure

I certify that no financial and/or material support was received for this research and/or the creation of this work

Acknowledgment

We highly acknowledge the TIFAC CORE in Herbal Drugs, JSS College of Pharmacy, Ooty and JSS Academy of Higher Education and Research for providing us the infrastructure and generous supports. Mr. Logesh R. receives senior research fellowship from the Indian Council of Medical Research ICMR with reference no. 45/43/2018/MP/BMS/dt. 05.12.2018.

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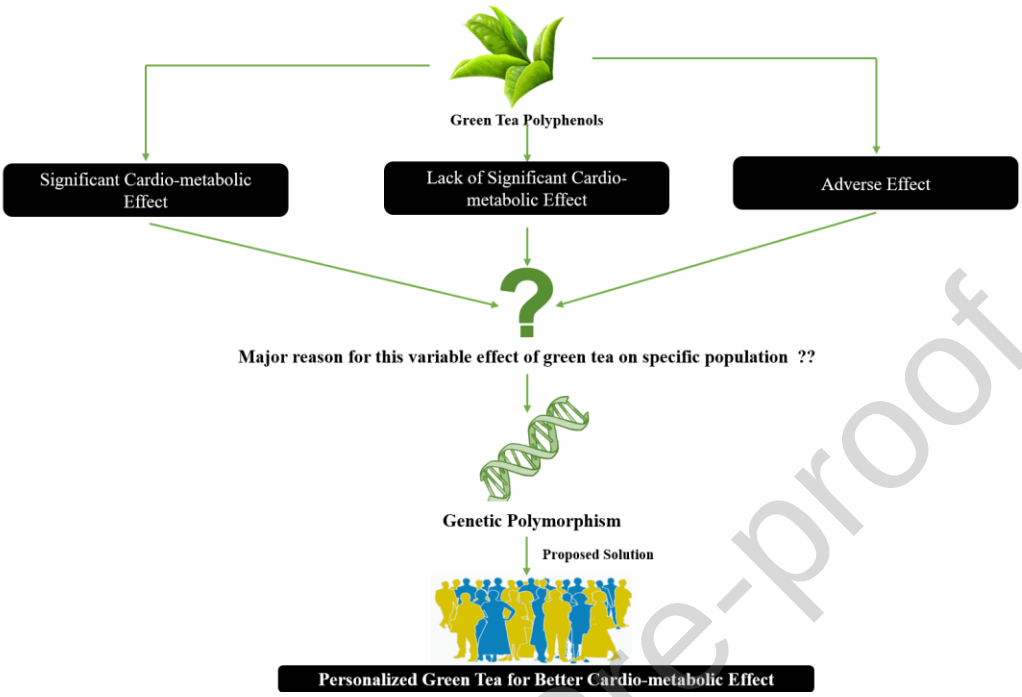
Graphical abstract



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Highlights

- Cardiovascular disease (CVD) is a chronic severe multifactorial disease that adversely affects an individual's health, well-being, and lifestyle.
- Polyphenols of green tea elicit a beneficial role in cardiometabolic health. The mechanism by which green tea exerts cardio-metabolic effects includes anti-oxidant, anti-inflammatory, vascular endothelial dysfunction, anti-proliferative, antiplatelet and anti-thrombotic activities.
- Green tea exhibits significant inter-individual variability on cardio-metabolic health based on many heterogeneously reported clinical interventions.
- Polymorphisms of *NOS*, *COX 1*, *COX 2*, *SOD*, *CAT* etc. has been modifying the efficacy of the conventional drug acting via cardiometabolic pathways.
- Polymorphic effects in individuals using green tea for cardio-metabolic effects and other benefits and the necessity to individualize green tea therapy. Personalizing GTC therapy in cardio-metabolic health can regulate the risk-to-benefit ratio that could result in better market viability.