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Analyzing the Immunomodulatory Effects of Tea Poly-Phenols and in management of COVID-19

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Abstract

This study primarily aims to co-relate the health benefits of tea intake, an accessory dietary supplement as a preventive remedy against COVID-19 and the inclusion of derivatized polyphenols in addition to the alcohol based anti-viral disinfectants providing increased longevity. A methodical exploration of databases such as ScienceDirect, Taylor & Francis Online, and Google Scholar was conducted using a variety of keyword combinations. The abstracts of all the retrieved results were scrutinized, and any studies deemed irrelevant were excluded from further assessment. Tea Polyphenols have been known to contain several defensive phytochemical compounds namely catechins, theaflavins, tannins and flavonoids. Amongst these, catechins more particularly, Epigallocatechin gallate (EGCG), a major component of green tea along with its lipophilic derivatives and theaflavins from black tea account for additional biological significance. Recent literature and molecular simulation studies have reported their potency as anti-viral agents with their effectiveness against the SARS-CoV-2, commonly known as the novel coronavirus, causing global pandemic with several deaths worldwide. Further, we emphasize on the need to explore polyphenolic compounds as adjuvants with the approved class of drugs employed for combating the severe acute respiratory syndrome (SARS) virus. This would aid in developing a novel class of drugs with plant-based compounds adding to the cumulative effect against the viral infections. Although, EGCG has been studied extensively, in vitro, and in vivo clinical studies with respect to its anti-viral capability would necessarily provide a new horizon to the scientific and medical fraternity in formulating drugs with a higher ratio of natural to the synthetic counterparts, thereby decreasing toxicity.

Keywords

Covid-19, viral infections, tea polyphenols, EGCG, theaflavins

Introduction

The World Health Organization recently announced the spread of the epidemic disease and named it as the 2019-novel coronavirus disease (2019-nCoV also known as COVID19) (1). Coronaviruses are positive sense single standard enveloped RNA viruses that are known to spread out among mammals including humans and birds. They show spherical or slight pleomorphic structure when they are viewed under an electron microscope with a genome size of 26 – 36 kb. They have more than 20,000 nucleotides, it consists of pp1a and pp1ab, two polyproteins, and is broken down by viral proteases. Alpha, beta, gamma, and delta are the four kinds of coronaviruses that are distinguished phenotypically and serologically from one another. They are reported to cause respiratory, enteric,

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hepatic, and neurologic diseases(2). The main origin of the virus is speculated to be from a bat, which later becomes transmitted to humans by several other sources(3). The symptoms associated with this viral disease include majorly throat infection, cough, runny nose, fever and respiratory related issues(4). Ever since, several stringent preventive measures are being taken in order to curb the spread of the virus. The treatment strategies mainly involved include the use of antibiotics, corticosteroids, antiviral drugs, immunomodulatory drugs and oxygen therapy based on the extent of severity. Also, vaccines are being administered to safeguard individuals and to reduce the complications posed by the contraction of the SARS-CoV-2. However, it is imperative to include supplementary drug molecules as effective remedies to limit the transmission of the disease. Plant derived compounds serve to be efficient against a wide spectrum of diseases including the ones caused by viruses. Tea polyphenols, thus are being looked upon for their anti-viral properties. Literature studies envisage epigallocatechin-3-gallate (EGCG) to be one of the major constituents present in green tea, accounting for nearly 50% to 80% of a brewed cup of green tea(5). The counter partner to EGCG is the group of theaflavins found in black tea which are fermented or oxidized forms of green tea. Both of these components found majorly in green and black tea respectively, have garnered attention for their anti-viral potency. The inhibitory effects of EGCG on a wide array of viruses make it an alternative anti-viral agent. These compounds have been proven to be essential as additional dietary supplements. Thus, as a preventive measure against the prevailing viral disease are discovery of novel and effective drugs that can significantly reduce the load of virus in the body, and other options are development of multiepitope based vaccine for the control of virus infections (6). This review discusses about the myriad of health benefits gained on regular tea consumption acknowledging the previous research and literature based studies and puts forward an overview i) focusing mainly on the two value added components: EGCG and theaflavins ii) analyzing tea polyphenols as potential adjuvants and nutraceuticals agents providing defense against the novel corona virus iii) contributing to the future perspectives that would enable further research and development in synthesizing combinatorial drugs with a major proportion of naturally derived constituents against COVID-19 (Figure 1).

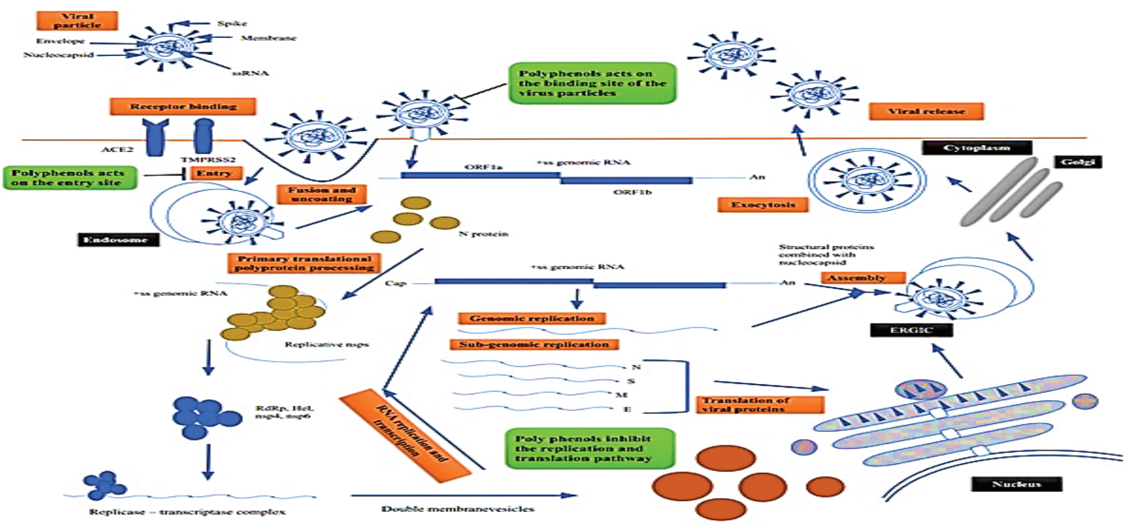

Figure 1. The SARS-CoV-2 virion and lifecycle depicting the application of polyphenols in battling COVID-19.

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Pathogenesis of Covid-19

The SARS-CoV-2 virus has a single strand and is positive RNA, with a size of around 29.9 kB. Research studies on these viral strains suggest them to be made up of four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins (7) .The pulmonary epithelial cells specifically express the much-discussed receptor ACE-2 (angiotensin-converting enzyme-2), later identified to be the functional receptor for SARS-CoV. It has been speculated that this host receptor binds the S protein to initiate the host-pathogen interaction providing viral entry(8). According to research on these viruses, type II cells' microvilli and airway cells' apical cilia may be in charge of enabling viral entry (9). There are 14 open reading frames (ORFs) in SARS-CoV-2, and these ORFs encode for 27 distinct proteins (10). Replication and transcription of the viral genome is carried out using RNA-dependent RNA polymerase (RdRP/nsp12). Nsp7 and nsp8 are the associated co-factors required during the viral RNA synthesis catalyzed by RdRP(11). COVID-19 can be divided into the following three stages based on the extent of its infection:

Stage 1: Asymptomatic phase

This is the initial stage of infection occurring in the first two days upon the entry of SARS-CoV-2. The primary receptor involved here is ACE2. According to the in vitro studies, the conducting airways are where the ciliated cells first become infected. To fully comprehend their activity in vivo, more research is necessary. The innate response is limited at this stage. Nasal swabs are used for the detection of the viral infection. These are found to be more sensitive compared to the throat swabs providing effective results on analysis using RT-PCR.

Stage 2: Upper airway tract infection

The virus continues to spread and progress in the respiratory system, intensifying the body's defenses. Beta and lambda interferons are mostly produced by the virus-infected host epithelial cells (12). The disease is restricted to this stage for the majority of the patients and could be treated with home isolation with the prescribed medication. The pathogenicity of the virus, which in extreme cases is quite comparable to that of SARS, causes coronavirus to have a substantial unfavorable impact on the respiratory system. Most COVID-19 patients only have mild side effects; approximately 4% to 5% of severe cases require hospitalization or oxygen support. Severe cases of COVID-19 can result in septic shock, acute respiratory distress syndrome (ARDS), acute renal failure, heart failure, and sepsis. Age and chronic conditions have been identified as death risk factors. A high sequential organic failure assessment (SOFA) score has been verified in recent multivariate analyses of old age and has been linked to increased mortality.

Stage 3: Lower airway tract infection

Severity increases for some patients with the development of pulmonary infiltrates, and they enter stage 3 with the symptoms of hypoxia and progression to ARDS (Acute Respiratory Distress Syndrome). The virus now infects and multiplies within the alveolar type □ cells causing apoptosis and cell death (13). Eventually it leads to the destruction of both type □ and type □ alveolar cells. The end pathological result of SARS-CoV-2 is the severe alveolar damage. Due to their weakened immune systems and less capacity to heal injured epithelium, elderly individuals are more vulnerable. Most patients initially have a fever or no respiratory symptoms at all, but as lung tissue is lost, all patients eventually have varied degrees of pulmonary abnormalities. These conditions have been documented using lung scan imaging. Also, due to reduced mucociliary clearance in such patients, the virus readily is allowed to spread the gas exchange units of the lung.

Assessment of biochemical markers in Covid-19 patients

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The timely management of Covid-19 makes the laboratory tests mandatory for controlling the viral spread and detection of the asymptomatic cases. Several serological tests are performed for monitoring the affected patients considering the associated biochemical markers. This leads to speedy isolation and in turn assists in containment of the disease (14). The laboratory parameters facilitate the understanding of the infection's severity while also predicting the likelihood that it will worsen and result in potentially fatal consequences like multiple organ failure (MOF), DIC, and ARDS (15). An elevated immune response called the cytokine storm causes damage to several tissues consequently worsening the disease progression (16). Higher blood concentrations of IFN-γ, IL6, IL10, and IL2 have been documented in severe cases. Analogously, in critically ill patients, neutrophil-to-lymphocyte ratio (NLR) and neutrophil-to-CD8+ T cell ratio (N8R) can be significant diagnostic variables. In addition, it has been noted that the serum levels of all cytokines (IL-2, IL-4, IL-10, IFN-γ, and TNF-α) except for IL-6 peak three to six days after the disease contraction (17). C-reactive protein, a plasma protein induced by different inflammatory mediators such as IL-6 is synthesized by the liver. It is used as a major clinical biomarker associated with inflammation (18). In addition to this, hepatic markers such as the alanine aminotransferase (ALT), AST and total bilirubin are routinely assessed in seriously ill patients indicating about the liver function (19). Additionally, cardiac, renal and pancreatic biomarkers are also assessed during the disease progression aiding in better treatment upon diagnosis. The elevated levels of C reactive proteins, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), creatinine kinase, alanine aminotransferase (ALT), aspartate transaminase (AST), D-dimer, and low serum albumin reported in COVID-19 patients' serological diagnosis indicate sepsis, which may eventually lead to the development of multiorgan failure upon further progression.(20). This urges the need to safeguard we and develop a strong immune system that restricts the viral growth. Literature studies have entitled tea polyphenols to be potent immunity boosters.

Health benefits of regular tea intake

Tea polyphenols have gained considerable public attention since tea consumption is directly proportional to multiple health effects. In recent years, GTCs, especially EGCG, have been recognized to contain multi-purpose bioactive molecules contributing to antitumorigenic, anti-inflammatory, antioxidative, anti-proliferative, antibacterial, and antiviral effects. Green tea has been reported to possess antiviral activity toward coronaviruses(21). In accordance with a study conducted by Mandel, the inclusion of plant flavonoids in diet, for people with known family history would aid in a prophylactic treatment prior to contracting debilitating diseases such as AD or PD(22). Recent preclinical research suggests that the green tea component EGCG may be able to enhance the pharmacological effects of existing medications when used in a combination therapy regimen. Long term green tea intake leads to decreased oxidative stress with an increase in GSH/GSSG ratio and total SOD activity. However, it decreases protein oxidation, lipid peroxidation and modulates the CREB activation. This in a cascade eventually causes prevention of age-related spatial memory decline. Furthermore, tea polyphenols are expected to find application in the food industries as food preservatives due to their antioxidant and antimicrobial activities(23). Considering their anti-microbial ability, they are being explored lately as natural agents in fighting against several viral infections including COVID-19. Formulating valuable drug regulators to tackle the cytokine driven hyper inflammatory responses for the effective management of COVID-19 becomes essential. Despite the constant efforts of the scientific community, there occurs to be a dearth of effective drugs against the viral infections. In regard to

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such circumstances, a new preventive antiviral approach with the application of tea polyphenols that turns out to be cost effective and pro environmental provides a fresh landscape in the medicinal domain. Polyphenols have been shown in earlier research to help reduce pro-inflammatory cytokines, such as kaempferol, resveratrol, epigallocatechin gallate, emodin, naringenin, apigenin, and curcumin, both in vitro and in vivo.(24, 25). Table 1 and 2 illustrate the numerous health benefits associated with the regular consumption of tea polyphenols and Table 3 highlights on the in vitro and molecular simulation studies with relevant viral molecular targets conducted recently.

Table 1. The in vitro studies evaluating anti-viral capabilities of polyphenolic compounds

Type	**Genome**	**Tea type Green/ black/ both**	**Compounds**	**Experimental Paradigm**	**Mechanism**	**Reference**
Coronavirus	ssRNA	Both	Theaflavins, EGCG	HRT-18	Neutralization Activity, molecular docking studies	(26)
Rotavirus	ssRNA	Both	Theaflavins, EGCG	BSC-1, Vero cells (ATCC CCL-81)	Neutralization Activity, anti-oxidative effect	(27)
Zika	ssRNA	Green	EGCG	Vero E6 cells	interaction of drug with the lipid envelope	(28)
Influenza A/H1N1	ssRNA	Green	EGCG	MDCK cells	Alteration in virus-host interaction	(29)
Influenza A and B	ssRNA	Black	theaflavins	MDCK cells	blockage of virus-receptor interaction and attenuation of viral replication	(30)
Dengue	ssRNA	Green	EGCG	Vero cells	causing deformation of the virus molecule	(22)
West Nile virus (WNV)	ssRNA	Green	EGCG	Vero cells (ATCC CCL-81)	Virucidal effect during the early stages of infection	(18)
Chikungunya	ssRNA	Green	EGCG	HEK 293T cells	Virus attachment inhibited	(16)
Ebola	ssRNA	Green	EGCG	HeLa cells, C57BL/6 mice	HSPA5 host factor was modulated	(31)
HIV-1	ssRNA	Both	EGCG and theaflavins	MT-2, H9/HIV-1	inhibits the entry of virus targeting gp41	(32)
HCV	ssRNA	Both	Theaflavins, EGCG	Huh-7 cells, Huh-7.5 cells	Inhibits virus- receptor interaction	(24)

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Table 2. The in vitro and in vivo studies employing major polyphenolic compounds against chronic diseases based on previous research.

Cellular function	**Polyphenol/ Compound**	**Experimental Paradigm**	**Mechanism**	**Reference**
Anti-bacterial	GTP	C57BL/6 male mice	Increased CAT, SOD in the process of ileal injury caused by Salmonella typhimurium	(33)
Anti-fungal	EGCG	M. canis, T. mentagrophytes, T. rubrum	not clearly defined	(34)
Anti-aging	epicatechin	db/db mice	Improvement in the age-related biomarkers and modulates AMPK activity	(35)
Anti-obesity	Theaflavins EGCG	C57BL6 male mice	Promotes lipid metabolism by activating AMPK, ROS mediated blocking	(36)
Anti-oxidative	EGCG	Wistar male albino rats	Increased activities of CAT, SOD, GSR	(37)
Anti-inflammatory	EGCG	Spargue-Dawley rats (contusive SCI)	Regulated expression of TNF-α IL-1β, iNOS and COX-2	(38)
Anti-hypertensive	BTP and GTP	SHRSP rats	MLC phosphorylation lowered with anti-oxidative properties	(39)
Anti-proliferation	EGCG	MCF-7, H460, and H1975 cancer cells, H460 and MCF-7 mice models	Reduces IRS-1 levels and suppresses the MAPK pathway	(40)
Anti-cancer (Breast cancer)	EGCG	MCF-7 cells	Modulation of P53/Bcl-2 signaling pathway	(41)
Positive mood	Cocoa polyphenols	Volunteers	Involvement of the GABAergic systems	(42)
Anti-anxiety	Epicatechin	C57BL/6 mice	Elevates BDNF levels and modulates neurotrophic and monoaminergic signaling pathways	(43)
Anti-depressant	GTP	Male ICR mice	inhibits the hypothalamic–pituitary–adrenal axis	(44)
Anti-diabetic	L-EGCGd	STZ-induced diabetic rats	Inhibition of α-glucosidase	(45)
Anti-atherosclerotic	EGCG	$ApoE^{-/-}$ mice (C57BL/6J)	Regulation of LXR/SREBP-1 pathway	(46)
Cytoprotective	EGCG	Vero cells (ATCC CCL-81)	Alteration of cellular redox milieu	(47)
Neuroprotective	EGCG	transgenic G93A ALS model mice	Decrease of death signals, GSK3β, cyto c, caspase-3	(48)

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Table 3. Molecular targets and inhibition of the proinflammatory biomarkers based on in vitro research and molecular simulation studies.

Drug targets	Compound	Mechanism	Reference
3CLpro/Mpro/Nsp5	EGCG, ECG, GCG TF2, TF3	Mpro-polyphenol complex (in silico docking) BE (EGCG):-7.6kcal/mol TF2: -9.8 kcal/mol TF3:-10 kcal/mol	(49)
PL^{pro}	EGCG	In silico docking studies BE:-8.601 kcal/mol	(50)
RdRp	EGCG, TF2a, TF2b, TF3	In silico studies	(51)
S protein RBD (PDB: 6VXX)	EGCG, TF	In silico studies	(52)
ACE2	EGCG, TF3	Binding with ACE2 receptor prevents viral entry, regulating ACE 2 expression	(53)
IL6	EGCG	MIF inhibition causing anti-inflammatory effect	(54)
IL-1β	EGCG	blocks IL-1β	(55)
IL-2	EGCG	Inhibits IL-2 proprietary α chains promoting T-cell regulation	(56)
IFN-γ	EGCG	Binds to SEB, neutralizes it and inhibits IFN-γ and IL-2	(57)

Tea polyphenols as anti-viral agents

Research has indicated that tea polyphenols possess antiviral capabilities against multiple viruses, such as COVID-19(34–37). The body's immunity against COVID-19 and other viral infectious diseases can be strengthened by tea polyphenol (34). Tea polyphenols have the ability to inhibit COVID-19 through a number of mechanisms, such as activating transcription factors, blocking cellular receptors, and inhibiting multiple viral targets(34). Polyphenols have an antiviral effect because of their ability to disrupt host cell defence by controlling the mitogen-activated protein kinase signal, or because of their interaction with viral protein and/or RNA through the benzene ring. Tea polyphenols have the ability to decrease vascular permeability by blocking neutrophil migration across the endothelial cell monolayer(34). Two tea-derived polyphenols, theaflavins from black tea and epigallocatechin-3-gallate (EGCG) from green tea, have been reviewed for their antiviral properties (35). It has been found that EGCG inhibits hepatitis C virus entry(38). It has been observed that theaflavin-3,3'-digallate (TF3) inhibits the virus's hemagglutinin by preventing the virus from adhering to MDCK cells (39). Tea polyphenols can also prevent and intervene in COVID-19 through the gut-lung axis(36, 37). Several such studies stating the antiviral capabilities of polyphenols have been given in Table 1 with their mechanism of action.

Multifaceted strengths with the intake of dietary polyphenols

Epidemiological studies and related meta-analyses suggest that long-term intake of diets high in polyphenols may offer protection against the development of certain chronic diseases, such as diabetes, osteoporosis, neurological diseases, and cardiovascular diseases (53-54). Tables 2 and 3 describe the in

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vitro, in vivo, and in silico studies conducted to determine the effectiveness of various polyphenols against various disease targets and their mechanisms of action. The beneficial effects of polyphenols seem to be mediated through their interactions with related machinery and cellular signaling pathways that regulate cell function in both healthy and diseased states. The capacity of dietary polyphenols to lessen the effects of oxidation on the human body, shield organs and cell structure from degradation, and preserve their functional integrity are just a few of their advantages (55).

Neurodegenerative diseases

Polyphenols have been reported to have neuroprotective properties and can contribute to reduced outcomes in neuropsychiatric disorders (56). In addition to enhancing hippocampus neurogenesis, learning abilities, memory, and mood, they can also enhance language, verbal memory, visual, and cognitive functions (56, 57). In older adults, polyphenols have the ability to improve verbal fluency, psychomotor abilities, attention speed, episodic memory, and overall cognitive performance while also modulating cerebral hemodynamics and resting regional cerebral blood flow. Pure herbal compounds, including green tea polyphenol (-)-epigallocatechin-3-gallate, resveratrol, curcumin, quercetin, and others, as well as extracts rich in polyphenols that exhibit the most promising neuroprotective effects, have been reviewed in terms of their therapeutic potential (58).

Antioxidant properties

Polyphenols act as antioxidants in the body, that is, they aid in defending the body and scavenging free radicals that harm cells (59). By scavenging reactive oxygen species (ROS) and modifying signaling pathways, they can improve cardiovascular system health outcomes and shield people from cardiovascular diseases. Polyphenols have the capacity to inhibit neuroinflammation, shield neurons from damage brought on by neurotoxins, and enhance memory, learning, and cognitive function, among other neuroprotective effects (60).

Cancer prevention

Polyphenols have been shown to have potential preventive and therapeutic effects for cancer(61). They can modulate multiple molecular events involved in carcinogenesis and have anti-inflammatory properties. Some of the polyphenols that have been studied for their anticancer properties including green tea polyphenol (–) epigallocatechin-3-O-gallate (EGCG), curcumin, resveratrol, apigenin, quercetin, and kaempferol (62). By scavenging ROS, polyphenols have the ability to prevent the growth of tumors, cause apoptosis in cancerous cells, and impede the evolution of malignancies. To increase the chemo-preventive effects of traditional chemotherapy, this type of therapeutic approach can be applied. In order to better cancer treatment and control with natural products, polyphenols can regulate important components of cancer signaling pathways. This emphasizes the significance of having a thorough grasp of these controls (63).

Cardiovascular health

It is commonly believed that polyphenols can prevent cardiovascular disease (64). Diets high in polyphenols may be linked to a lower prevalence of cardiovascular diseases, including myocardial infarction and coronary heart disease, according to epidemiological research. These substances' antithrombotic, anti-inflammatory, and anti-aggregative qualities can enhance endothelial function and prevent platelet aggregation. BPolyphenols like resveratrol, curcumin, and epigallocatechin gallate (EGCG) have been demonstrated to improve cardiovascular health by lowering reactive oxygen species (ROS) and changing signaling pathways (65). P A diet rich in polyphenols reduces the risk of cardiovascular disease, its complications, and the associated mortality. Polyphenol-rich cuisines include the French diet, which emphasizes red wine consumption, the diets of the Far East, which stress the drinking of green tea, the South Asian diet, which largely uses turmeric, and the Mediterranean diet, which emphasizes olive oil use (66).

Safety and toxicity of tea polyphenols

Despite the fact that pre-clinical model systems have demonstrated the cancer-prevention potential of tea and its polyphenols. But it's crucial to consider these substances' toxicity and safety, especially when taking large doses or using them over an extended length of time. Several clinical studies have investigated the safety and pharmacokinetics of tea polyphenols in humans. In one such study involving 40 individuals, researchers administered 800mg EGCG once/day, 400mg EGCG twice/day, 800 mg EGCG as Polyphenol E once/day, 400mg EGCG as Polyphenol E twice/day or a placebo to the 5 groups (8 individuals per group). According to the study's findings, a healthy person can safely take tea polyphenol products for four weeks at doses equal to the EGCG found in eight to sixteen cups of green tea, either once a day or in divided doses twice a day. TThe researchers also found that chronic green tea polyphenol treatment at a high daily bolus dose (800 mg EGCG or Polyphenon E once daily) increases the systemic availability of free EGCG by more than 60% (67).

In a 2018 scientific opinion, the EFSA ANS Panel examined 12 clinical studies in which participants received EGCG. The panel concluded that, as long as EGCG intake is kept to a daily maximum of 300 mg, catechins from traditional green tea infusions and reconstituted drinks with a composition equivalent to traditional infusions are generally regarded as safe under the presumption of safety. A statistically significant increase in serum transaminase, a marker of liver injury, has been observed in response to doses of EGCG taken as a food supplement of 800 mg or more per day, according to the panel's analysis of the 12 clinical studies. (68).

In a preliminary study, adult patients with solid tumors were given oral green tea extract at doses ranging from 0.5 to 5.05g/ m^2. The majority of these dose levels demonstrated mild to moderate toxicities, which were quickly reversed when the green tea extract was stopped. The highest amount that could be tolerated was 4.2 g/m^2 per day, or 1 g/m^2 three times a day. Caffeine-related toxicities, such as gastrointestinal and neurological effects, were the dose-limiting toxicities (69). Whereas EGCG levels did not accumulate or seem to be dose related, pharmacokinetic analyses revealed that caffeine levels accumulated in a dose-dependent manner. Overall, the available evidence suggests that green tea polyphenols are generally safe and well-tolerated when administered at recommended doses. However, caution should be exercised when administering high doses of these compounds, particularly in individuals with pre-existing liver or gastrointestinal conditions. Further research is needed to fully understand the safety and toxicity of green tea polyphenols in humans (70).

An alternative approach in the preparation of sanitizers

Currently, there are countless measures that are being taken in multiple ways to prevent the entry of viruses. One of the strategies majorly includes the use of alcohol-based sanitizers which in turn prove to be useful in disinfecting the skin against the micro-organisms. They are marketed under several brand labels and made available at every corner (71). However, when it comes to the formulation of these products there are still certain issues that need to be addressed with respect to their overall effectiveness, toxicity of certain ingredients, environmental pollution, and the short-term duration of their anti-microbial activity with their use(72). Therefore, there is an urgent need for an alternative approach that could certainly aid in the effectiveness, increase its longevity and at same time remain nontoxic and pro environmental. Considering the issue, are the group of compounds tea polyphenols, particularly, epigallocatechin-3-gallate (EGCG) and its lipophilic derivatives. Based on literature studies, they are found to be effective against a wide range of viral infections and have been proven to contain novel inhibitory and anti-viral properties (73). Hence, they appear to be strong contenders in developing alternative methods for formulating sanitizers with improved and better version thereby, providing long term anti-microbial effects.

Summary and future perspectives

The SARS-Co-V-2 and the identified variants remain to be the deadliest form of the viral agents, reported to have caused millions of deaths worldwide. The uncontrolled transmission of the virus via respiratory droplets and aerosols requires in depth research regarding the host-viral interactions. As a solution to combat the deadly virus, several synthetic drugs have been approved by the FDA on an urgent basis. Moreover, persistent administration of these drugs mediates immunosuppression. Also, these being synthetic in nature have been reported to have multiple side effects restricting their use during the course of the disease. In many cases, patients have been known to report other complications that include nausea, dizziness, increased uric acid levels in blood, decreased white blood cell count particularly, neutrophils, cardiac diseases, abnormal liver function tests, etc (74). Thus, the intake of higher dosage of these drugs makes the patient to have a higher probability to acquire other chronic diseases. This eventually, leads to falling into a loop where the individual becomes prone to long term illness. Regardless of the caveats, these approved drugs remain to be the only class of medicines as of now, amidst the alarming spread of the viral diseases. Research work is still in progress to comprehend about the behavior and spread of the virus along with their variants which would help in formulating broad spectrum anti-viral drugs (75). Furthermore, future studies are needed to address the amalgamative application of natural and synthetic compounds providing synergistic effects. In continuation with our purpose, the following areas necessitate to delve into the employment of polyphenols as accessory compounds against the viral infections.

i) To determine whether the molecular simulation studies can be duplicated onto animal models and further translated to human subjects. ii) To identify the possible link between tea consumption (black or green) and decreased rate of acquiring the viral infections mainly the novel coronavirus. iii) To evaluate the effectiveness of tea polyphenols as added dietary supplement and immunity boosting agents that aid against fighting the viral infections by performing thorough in vivo and cohort studies, since an effective immune system is the only structured way to overcome these diseases. iv) To implement deeper understanding in the development of combinatorial drugs comprising of natural and synthetic origins with a higher dosage of plant-based compounds and their derivatives (76).

Conclusion

The Covid-19 outbreak has turned to an international health emergency with several efforts being made worldwide to contain the spread of the disease. In this study, we shortly outline the collective health benefits with the intake of tea along with an emphasis on the prophylaxis and treatment of viral infections adding tea polyphenols as potential adjuvants in dealing against viral infections. Although, this does not in any way certainly promote their solo usage. They could only be used as supplementary agents and nutraceuticals along with the available set of precautionary measures and medications. Nonetheless, polyphenols and their derivatives in combination with the other anti-viral drugs could possibly aid in designing a novel set of medicines having both natural and synthetic origin. This would facilitate the switch to a better and improved class of drugs with lesser toxicity and better efficacy.

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Conflict of Interest

The authors declare no conflict of interest.

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