Review

Antimicrobial potential of epigallocatechin-3-gallate (EGCG): a green tea polyphenol

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Abstract: The compounding problem of microbial resistance has become a global threat nowadays and demands urgent attention. Given the limited number of clinically proven drugs available, reversion towards compounds from natural resources have become renewed source of interest. Utilization of novel and potent antimicrobial agents with different targets can act as accessories to antibiotic therapy. Considerable amount of research has been conducted on the various advantages of secondary metabolites produced by different plants. Among these, polyphenols have come into sight over the past few decades as a potential source to promote human health. This article summarizes the various health benefits of EGCG, the major component of green tea polyphenols with more emphasis on the anti-microbial properties of EGCG.

Keywords: EGCG, green tea, polyphenols, catechins

Introduction

A huge amount of research has been conducted on the various advantages of secondary metabolites produced by different plants. Among these, polyphenols have come into sight over the past few decades as a potential source to promote human health. A number of clinical trials have shown wide range of biological and pharmacological properties of polyphenolic compounds such as anti-microbial, anti-carcinogenic, anti-oxidative, anti-allergic, anti-cardiovascular [1], anti-diabetic [2], anti-inflammatory [3], anti-hypercholesterolemic (lipid clearance) [4], anti-atherosclerosis, anti-hypertensive [1], anti-mutagenic [5], anti-aging [6], decreased risk of osteoporotic fractures [7], neuroprotective [8] and immunomodulatory effects [3]. Being an incredible source they are considered safer and metabolize better than conventional pharmaceutical drugs since these compounds are derived from natural food products [9]. The development of resistance to various commercial anti-microbial drugs drives the increased use of these natural polyphenols in recent years. Polyphenols are major dietary constituents of many food items and beverages. Tea (*Camellia sinensis*, family Theaceae) is the second most consumed plant-based (Table 1) beverage in the world preceded by water and is cultivated in about 30 countries in the world [1, 5, 10]. On the basis of method of post-harvest processing, tea can be divided into four categories namely black tea (aerated or oxidized), green tea (non-aerated), white tea and oolong tea (semi-aerated or partially oxidized) [10]. The antimicrobial potential of EGCG, the major component of green tea polyphenols, is the focus of this article.

Chemical composition of green tea

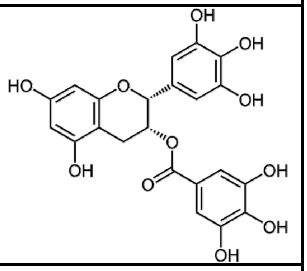
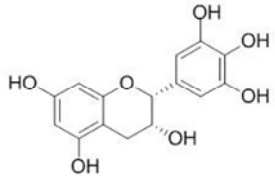
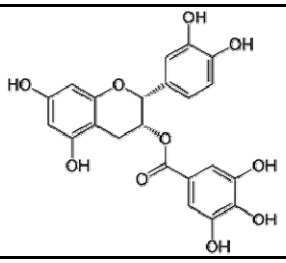
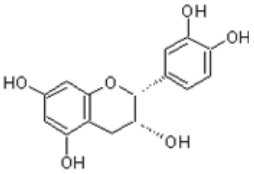
Green tea in general refers to the product which is derived from fresh tea leaves after some modifications like steaming or drying at elevated temperature. The main component of polyphenols is catechins and its oxidation is avoided in the above processing [3]. The amount of catechins is higher in green tea (Fig 1) in comparison to the other varieties. Common green tea is rich source of dietary flavonoids which are classified as catechins (C), (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC) [1] (Table 2). EGCG has been declared as safe

compound by the US Food and Drug Administration [12] and it is the most active and characteristic component found only in green tea. The natural product EGCG forms 50-80% of catechins in green tea, representing 200–300 mg in a brewed cup of green tea while other catechins are found in lower abundance in green tea which includes catechin gallate, gallocatechin, gallocatechin gallate, epigallocatechin digallate, methylepicatechin and methyl EGC [3]. Some flavanols such as quercetin, kaempferol, myricetin, and their glycosides are also present in tea. Other component like threonine which is responsible for the characteristic flavor, is present 4-6% weight of dried tea [13].

Table 1. Phylogenetic classification of green tea

Kingdom	**Plantae**
Order	**Ericales**
Family	**Theaceae**
Genus	**Camellia**
Species	***C. sinensis* [8]**

Table 2. Chemical structures of different catechins in green tea.

Catechins in Green Tea	Chemical Structure
Epigallocatechin-3-gallate(EGCG)	
Epigallocatechin (EGC)	
Epicatechin-3-gallate (ECG)	
Epicatechin (EC)	

Health promoting activities of EGCG

EGCG is the most abundant, potent polyphenol and is responsible for most of therapeutic benefits (either clinical, animal or cell culture studies) of green tea (Fig 2). It has various medicinal potentialities which include anti-microbial properties against resistant microorganisms on which it acts by either disrupting the cell membrane, inhibiting the biosynthesis of the cell constituents, cell signaling or DNA damage (described in following sections). The most important antioxidant property is very crucial in treating chronic diseases which are related to oxidative stress, cardiovascular, neurodegenerative diseases and cancer. Research on this property revealed information about its anti-cardiovascular and anti-hypertensive activity which enables EGCG to prevent platelet aggregation, lower cholesterol level and inhibit lipid peroxidation [14]. In vitro studies of mouse model, it induces lowered risk of cancer development by binding to various key proteins, thus affecting the signaling pathways followed by growth inhibition due to apoptosis or suppression of angiogenesis and metastasis [1, 15]. EGCG is also beneficial for preventing aging of brain and other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as depicted from mouse model studies [8, 14]. It also shows anti-hypercholesterolemic (anti-obesity) activity and promotes weight loss through fat oxidation [16]. Animal studies have demonstrated that EGCG is an efficient agent in preventing the development of diabetes, type 1 or type 2 [2]. EGCG increases lysosomal acidification, regulates autophagy and lipid clearance in liver due to its anti-steatotic property [4]. EGCG, in dose dependent manner can reduce the release of cytokines/chemokines responsible for inflammation showing anti-inflammatory property [3, 17]. Its anti-allergic property strongly inhibits activation of mast cells and expression of high-affinity IgE receptor, which produces an allergic reaction on exposure to certain foreign antigens [18].

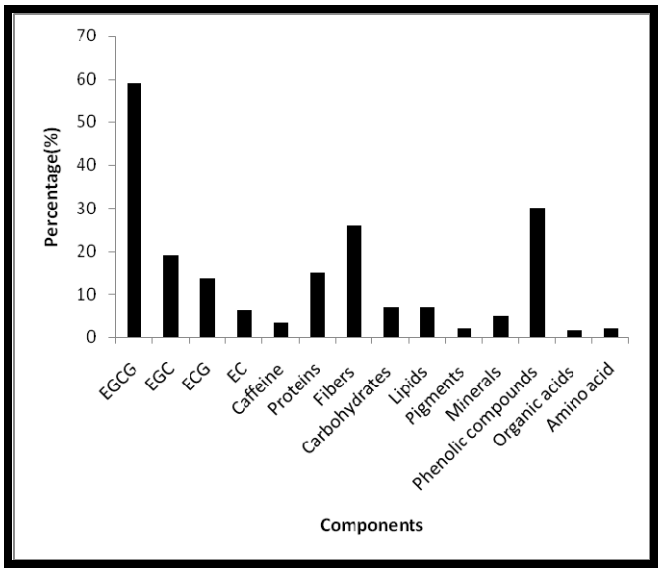


Fig. 1. Percentage of different components of green tea [11].

Antimicrobial potent of EGCG

Natural products have emerged as rich sources of antimicrobial agents efficient against a wide variety of microorganisms. Tea polyphenol EGCG have broad antimicrobial spectrum such as antifungal [*Candida spp.(C. albicans, C. glabrata),* dermatophytes *(Trichophyton mentagrophytes*, *T. rubrum*)], antibacterial (methicilllin resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia, Mycobacterium tuberculosis, Helicobacter pylori, Streptococci spp., Clostridium spp., Bacillus cereus, Salmonella spp., Mycoplasma pneumonia)* and antiviral [*Orthomyxoviridae* (Influenza virus) and *Flaviviridae* (hepatitis C), hepatitis B virus, herpes simplex virus, Human Immunodeficiency Virus and adenovirus] effects. The following section will review the various antimicrobial potential of EGCG (Fig. 3).

Antifungal activity of EGCG

More than 600 different fungi are reported to cause common to fatal infections in human. The increasing number of immunosuppressed patients and advancements in the medicinal fields contributes to the incidence of invasive fungal infections. The effects of EGCG are generally studied against yeast strains such as *Candida spp. (C. albicans, C. glabrata)* and dermatophytes (*Trichophyton mentagrophytes*, *T. rubrum)*.

C. albicans is a polymorphic and commensal organism found to be a member of human's normal microbial flora. Nosocomial infections or hospital acquired infections (HAI) are the fourth most leading cause of diseases and *C. albicans* is known to cause approximately 80% of fungal HAI which are major cause of morbidity and mortality. About 90-100% of mucosal infections and 50-70% of Blood Stream Infections (BSI) are generally caused by *C. albicans* [19]. These fungal infections are generally treated by antifungal mainly azoles such as fluconazole and itraconazole which inhibits sterol biosynthetic pathway. In antifungal therapy, these azoles have less toxicity against the fungal strains, hence providing poor fungicidal activity with increased side effects. Due to enhanced antimicrobial resistance there is a need of developing effective natural antifungal agents which are less toxic and safer [21]. Various in vitro studies using clinical isolates of *C. albicans, C. tropicalis,* etc., indicated that EGCG shows antifungal effects against resistant *Candida* species and might be an alternative agent for treating candidal infections. The ability of *C. albicans* to adhere to other cells, various hosts, medical and surgical devices contributes to its colonization and pathogenicity by biofilm formation which is highly resistant to several antifungal agents. In an in vitro study, Evensen and Braun [22] showed that at physiological concentration (1 µmol/ml), green tea polyphenols cause metabolic instability with EGCG being most potent among them. Biofilm formation of *C. albicans* was impaired by EGCG which contributed to both structural and metabolic disruption [23]. Another common mechanism of action of antifungal agents is that they physically bind to ergosterol, disturbing the osmotic integrity and hence create pores. This causes intracellular ions (potassium and magnesium) to leak out, therefore killing the cell and EGCG is known to enhance this activity due to its synergistic effect [24]. Some research groups have shown even antifolic activity of EGCG against dihydrofolate reductase (DHFR) by inhibition of this crucial enzyme for the biosynthesis of purines, pyrimidines and various amino acids resulting in disturbing the growth of fungal cells [25]. In vitro study by Hirasawa & Takada [20] showed the antifungal effects of EGCG both individually and in combination with antimycotic drugs against *C. albicans*. They found that EGCG has a pH dependent effect shows more strong action at basic pH such that the microbial inhibitory concentration was decreased by 10 times at higher (~2.0 mg/L at 8.0 pH) than at lower (~1024 mg/L at 6.0 pH) pH. The pH dependent effect holds true when it was used in association with commercial antifungal drugs where it enhanced their activity with lesser dose.

Dermatophytosis is another most common and widespread infectious diseases that is yet to be solved. It is caused by dermatophytes, particularly *Trichophyton mentagrophytes*, *T. rubrum* which were shown to have sensitivity to EGCG (MIC_{50}, 2-4 µg/ml, MIC_{90}, 4-8 µg/ml) [26]. In vitro study by Toyoshima [27] showed antifungal effects of EGCG against clinical isolates of *T. mentagrophytes*. They reported that inhibition of germination of conidia was followed by some morphological changes like deformation, swelling, granular accumulation and inhibited hyphal growth.

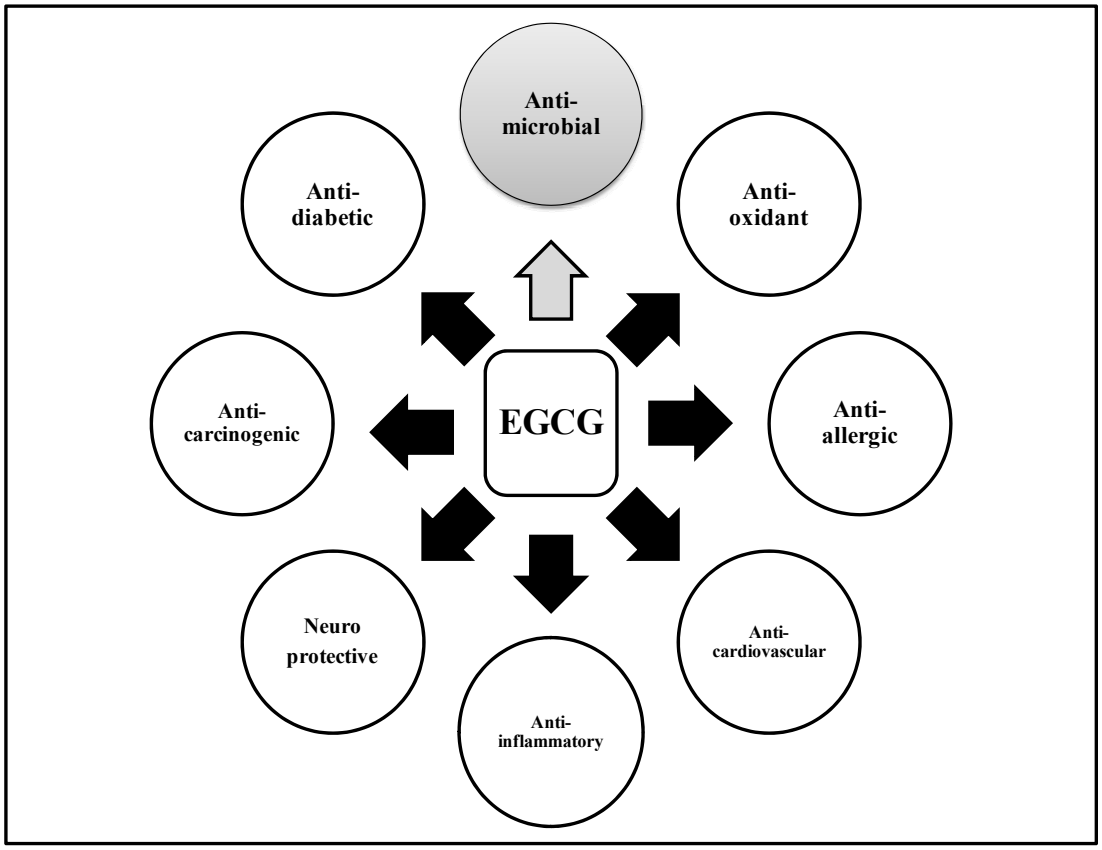


Fig. 2. Health benefits of epigallocatechin-3-gallate (EGCG).

Antibacterial activity of EGCG

Bacterial infections are offering extensive challenge to health care and a major cause of morbidity and mortality. Due to bacterial resistance to antibiotics over the past decade, treatment of these infections has become even more challenging. The effects of EGCG are generally studied against bacterial strains such as (methicillin resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia, Mycobacterium tuberculosis, Helicobacter pylori, Streptococci spp.*).

Staphylococci species (methicillin resistant *Staphylococcus aureus*) is major cause of severe, acute and chronic HAI. The activity of β-lactams (antibiotics such as methicillin) was found to be enhanced by EGCG. The biological activity of EGCG was investigated against clinical isolates of *S. aureus* and the in vitro study suggested that binding of negatively charged EGCG to positively charged lipids of the cell membrane, damages the membrane structure or fragments the lipid bilayer causing intramembranous leakage [28]. It has also been reported that EGCG inhibited (MIC_{50}, 10 µg/ml) the penicillinase activity of peptidoglycan of bacterial cell membrane by binding to it either directly or indirectly, hence keeping the penicillin away from inactivation [29]. EGCG was also found to decrease or inhibit biofilm production by *S. aureus* [30]. EGCG have been reported to inhibit the growth of Gram-positive and Gram-negative bacteria. *Stenotrophomonas maltophilia* is an environmental Gram-negative (multiple drug resistant) organism which is commonly associated with respiratory infections in humans. EGCG can lead to bacterial cell death by inhibiting bacterial DNA gyrase, thus preventing DNA supercoiling [31]. DHFR is a key enzyme that reduces 7, 8-dihydrofolate (DHF) to 5, 6, 7, 8-tetrahydrofolate (THF). This NADPH- dependent reduction reaction is involved in nucleotide biosynthesis. EGCG shows antifolate activity against DHFR and hence leads to the disruption of DNA synthesis. An in vitro study on mechanism of action of the EGCG against clinical isolates of *S. maltophilia* (MIC range, 4 to 256 µg/ml) revealed that the primary target of their anti-bacterial activity is phospholipids of the bacterial membrane, hence kills the cell by membrane disruption [32, 33].

Helicobacter pylori is known to be a major causative agent of chronic gastritis, peptic ulcer and can also lead to the development of gastric cancer. From in vitro studies, it had been proved that EGCG is natural and safe having physiochemical stability in stomach acid, which makes it an effective alternative therapeutic agent for treatment of the above mentioned gastric diseases at an inhibitory concentration of 100 µg/ml against clinical isolates of *H. pylori* [34]. EGCG blocks TLR-4 (toll like receptor) glycosylation, stimulated by *H. pylori* infection, which disturbs *H. pylori*- induced host cell signaling and protects from gastric cytotoxicity [35]. Studies indicated that EGCG is responsible for the inhibition of bacterial adhesion to human cells by *Streptococci* species (*S. mutans, S. pyogenes*) and induces cell death [36].

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (MTB) which is seventh leading cause of death worldwide and is estimated to kill more than 2 million people every year. Induction and activation of reactive oxygen species (ROS) and pro-inflammatory cytokine TNF-α (tumor necrosis factor) respectively is significant for proliferation of MTB in host cells Peripheral Blood Mononuclear cells (human monocytes). Fatima et al. [37, 38] in an in vitro study, revealed that due to its antioxidant property, EGCG is an inhibitor of ROS and reactive nitrogen intermediates (RNI) pathways. It also shows better inhibition of TNF-α and MTB 85B gene expression (MIC, 5 µg/ml) than other first line antibiotics, thus proving EGCG to be safe, economic and natural therapeutic agent for treatment of TB.

Antiviral activity of EGCG

The effects of EGCG are generally studied against bacterial strains such as (Hepatitis C Virus, Human Immuno deficiency Virus, Influenza viruses, Hepatitis B virus,

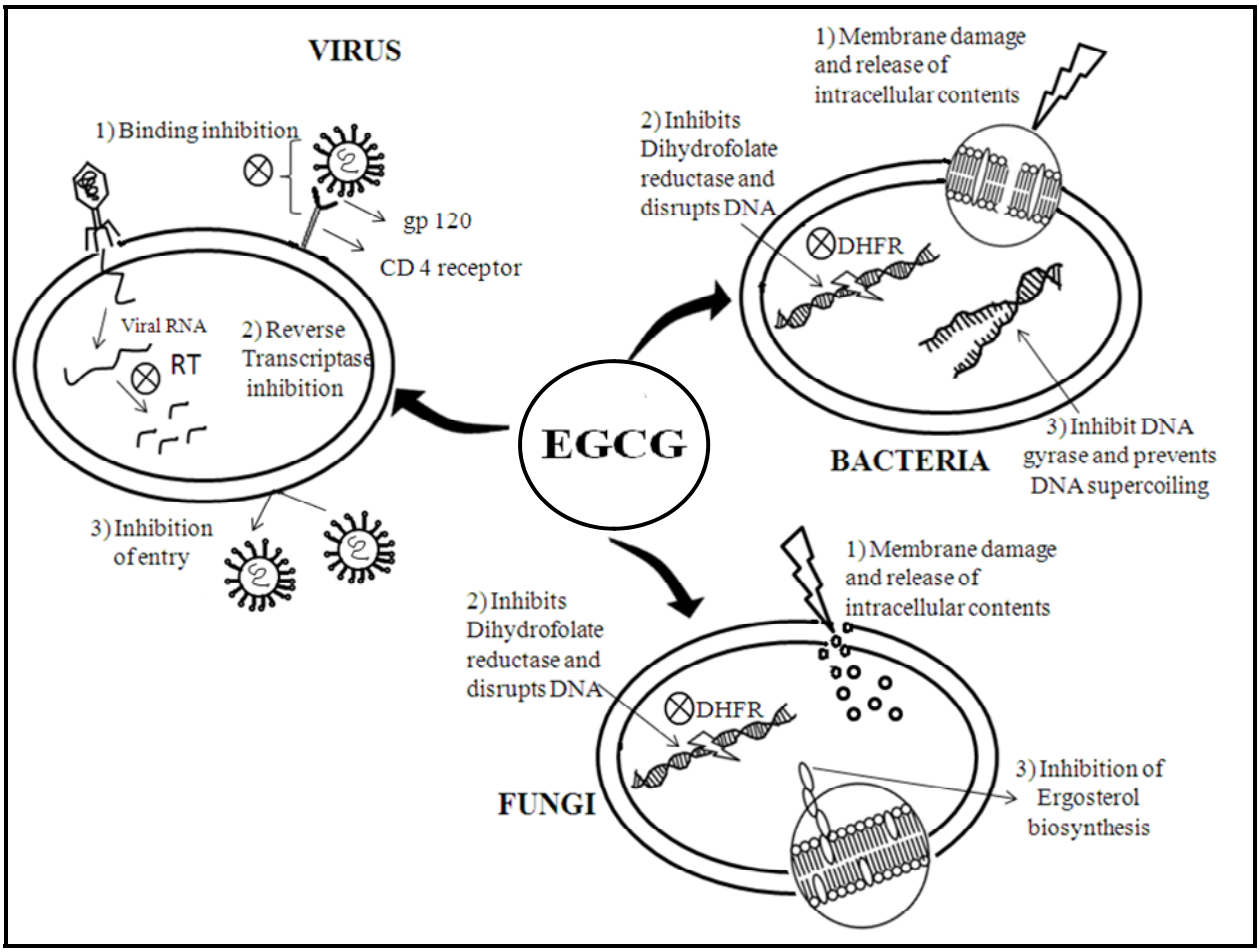


Fig. 3. Antimicrobial actions of EGCG.

Enterovirus, Adenovirus, Epstein–Barr virus, Herpes Simplex Virus). Hepatitis C Virus (HCV) is an RNA virus which chronically infects about 160 million individuals. It is a member of *Flaviviridae* family and is associated with life-threatening diseases like cirrhosis, liver failure and hepatocellular carcinoma [39]. HCV infection can be spread via cell to cell transmission. Entry of virus is a multistep process which involves endocytosis and fusion of the viral membrane with the host membrane. EGCG can prevent this cell-cell transmission due to a unique potential of inhibiting the attachment of HCV and its entry into the host cell by impairment of virus binding to the cell, thereby preventing its RNA replication. Moreover, single dose concentration of EGCG ranging from 50-1600 mg is sufficient to inhibit the HCV and safe for human volunteers as reviewed by Steinmann [23, 40, 41]. It is responsible of increasing the lipid droplet formation and impairment of lipoprotein secretion in hepatocytes, both of which are crucial for the life cycle of HCV [42].

Human Immunodeficiency Virus-1(HIV-1) is a lentivirus which is estimated to infect about 33 million people worldwide. It is the major causative agent of AIDS and belongs to the *Retroviridae* family. It is a major cause of morbidity and in the absence of effective vaccine or cure, antiretroviral treatment is the best option [43]. EGCG affects each step of the HIV life cycle, from cell attachment, entry of virus, replication cycle to the expression of mRNA. It also interferes with the infectivity of the virus by binding to the surface of viral envelope and deforming the phospholipids followed by lysis of the virus particle [44, 45]. The attachment of the gp120 envelope protein to the CD4 receptor on T-helper cells initiates the entry of HIV-1 into the host. EGCG blocks the interaction of gp120 and CD4 and prevents the attachment of HIV-1 virions [46]. This tea catechin inhibits reverse transcriptase (RT) which catalyses the conversion of RNA into DNA and integrase enzyme which splice synthesized DNA into host cell genome [11, 45]. EGCG also inhibits the viral production from infected cells and the level of expression of viral mRNA.

Influenza viruses (Influenza virus A and B) are members of *Orthomyxoviridae* family and are a major cause of respiratory diseases in human. Influenza A viruses are single stranded, segmented RNA viruses with envelope. The various antiviral drugs used to treat diseases caused by this organism are amantadine and rimantadine etc. However, many viral strains have developed resistance to these drugs and therefore, EGCG has emerged as a potent source of antiviral agent. It was reported for the first time in 1993 that EGCG was able to alter the physical integrity and agglutinate the virus preventing them from adsorbing on MDCK cells (Madin-Dardy Canine Kidney) [47]. It also ceased the growth of influenza virus by inhibiting the acidification of intracellular compartments like endosomes, lysosomes etc. [48] and inhibited the entry by binding to haemagglutinin [49]. Another virus against which EGCG exerts its antiviral activity is Adenovirus of *Adenoviridae* family, a non-enveloped virus composed of a nucleocapsid and a double-stranded linear DNA genome. Approximately 5–10% of upper respiratory infections in children are caused by this organism. Weber and co-workers [50] concluded that EGCG inactivated adenoviruses and inhibited the viral protease activity. It was found to be most effective during the transition from early to late phase of the infection and also inhibited the late stages of viral infection followed by its intracellular growth. Enterovirus 71 is a single stranded RNA virus belonging to *Picornaviridae* family and causes life threatening hand, foot and mouth disease (HFMD), cutaneous and neurological diseases. EGCG exerts its antiviral activity by inhibiting the viral replication and subsequent formation of progeny virus [51].

Hepatitis B, which affects over 300 million people all over the world, is caused by Hepatitis B virus (HBV) which is a small enveloped virus from the *Hepadnaviridae* family. It can be transmitted parentally, sexually and perinatally [52]. In a dose dependent manner, EGCG was capable of reducing the expression of HBV specific antigens, the levels of extracellular HBV DNA and inhibit the replication of intracellular replicative intermediates resulting in a reduction in cccDNA production (covalently closed circular DNA) [53].

Analysis of antiviral effect of EGCG on Epstein–Barr virus (EBV), a herpes virus of *Herpesviridae* family, demonstrated that it inhibited the transcription of immediate-early genes and expression of the lytic proteins, thus blocking the EBV lytic cycle [54]. It is associated with Burkitt's lymphoma, nasopharyngeal carcinoma, T-cell lymphoma and Hodgkin's disease [55]. Another virus from the *Herpesviridae* family, Herpes Simplex Virus (HSV) causes a sexually transmitted Herpes simplex disease at 65-90% rates all over the world [23]. As no vaccine is currently available for treatment, EGCG was characterized against HSV to study its antiviral effects in Vero cell lines and was found to affect prior to infection, having no effect on the viral production [12].

Conclusion

The recent research have reveal that green tea has proved its potentials ranging right from antimicrobial to antioxidant, neuroprotective to skin and hair care, and many more, posing as a "natural boon to human being". Despite EGCG being safe in nature, it suffers with few limitations viz. low absorption, poor membrane permeability, metabolic transformations and unstability [56]. Moreover, even antagonistic action of EGCG has been reported with anticancer drugs [57]. However, with their unique biochemical profiles, they have even managed to contribute to the enhancement of the activity of different standard drugs. This has not only grabbed the attention of common people but also nailed its position as an alternative remedy for different chronic life-threatening infections.

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Conflict of interests

The authors declare no conflict of interest.

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