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## Review

## Tea: A native source of antimicrobial agents



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## ABSTRACT

Tea (*Camellia sinensis*) is one of the most popular nonalcoholic beverages, consumed by over two-thirds of the world's population because of its refreshing, mild stimulant and medicinal properties. It is processed in different ways in different parts of the world to give green, black, oolong, and pu-erh tea. Among all tea polyphenols, epigallocatechin-3-gallate has been responsible for much of the health promoting abilities of tea including anti-inflammatory, antimicrobial, antitumour, anti-oxidative, protection from cardiovascular disease, anti-obesity, and anti-aging properties. In the present review, the antibacterial, antiviral, and antifungal activities of different types of tea and their polyphenols are reported, highlighting their mechanisms of action and structure–activity relationship. Moreover, considering that the changing patterns of infectious diseases and the emergence of microbial strains resistant to current antibiotics, there is an urgent need to find out new potent antimicrobial agents as adjuvants to antibiotic therapy. The synergistic effect of tea polyphenols in combination with conventional antimicrobial agents against clinical multidrug-resistant microorganisms has also been discussed in this review.

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## 1. Introduction

Recently, there has been increased interest in polyphenolic compounds found in natural foods. Several of these plant foods may have beneficial effects in humans (Ferrazzano et al., 2011). Most antioxidants isolated from plants are polyphenols, which exhibit biological activities such as antibacterial, antiviral, anti-allergic, anti-inflammatory, anticancer, and immunostimulant (Scalbert, Manach, Morand, & Rémésy, 2005). The antioxidant activity of these compounds is due to their ability to stabilize or deactivate free radicals generated by a metabolic pathway within the body tissue, thereby reducing free radical-mediated degradation of cells and tissues in an organism (Staszewski, Pilosof, & Jagus, 2011). The main sources of the natural polyphenols in the daily human diet are tea, coffee, vegetables, legumes, whole-grain cereals, and fruits (Ferrazzano et al., 2011).

Tea is the most popular beverage next to water, consumed by over two-thirds of the world's population. In 2010, world tea production reached over 4.52 million tonnes. The largest producers of tea are the People's Republic of China, India, Kenya, Sri Lanka, and Turkey. Globally, India ranks second (991,180 tonnes) in tea production after China (1,467,467 tonnes) (Food and Agriculture Organization of the United Nations—Production FAOSTAT). The average estimated consumption

of tea in the United Kingdom is 644.1 tonnes every day (<http://www.statisticbrain.com/tea-drinking-statistics/>). According to UK tea council, the British drink 165 million cups of tea daily or 60.2 billion cups of tea per year (<http://www.tea.co.uk/page.php?id=237>).

Tea is used as a beverage worldwide, although consumers vary their preferences for the degree of fermentation, taste, and color. Tea is generally consumed in the forms of green, oolong, pu-erh, and black tea, all of which originate from the leaves of the plant *Camellia sinensis* L. Oolong tea is very common in many countries however, China and Japan prefer green tea over other types. Black tea is popular among Western countries and dominates the market economically whereas pu-erh tea is consumed almost exclusively in Asia (Balentine, Wiseman, & Bouwens, 1997).

Polyphenols are the most important constituents of tea leaves. Fresh green tea leaves are rich in monomeric flavanols, known as catechins, among which (–)-epigallocatechin gallate (EGCG) is found to be the most abundant. Catechins are present at levels of 30–40% of the dry weight of fresh green tea leaves (Almajano, Carbó, Jiménez, & Gordon, 2008).

In particular, *in vivo* and *in vitro* biological activities of tea flavan-3-ols include preventing generation of free radicals (Frei & Higdon, 2003), inhibition of carcinogenesis (Otsuka et al., 1998; Sato, 1999), protection from the effects of radiation (Uchida, Ozaki, Suzuki, & Shikita,

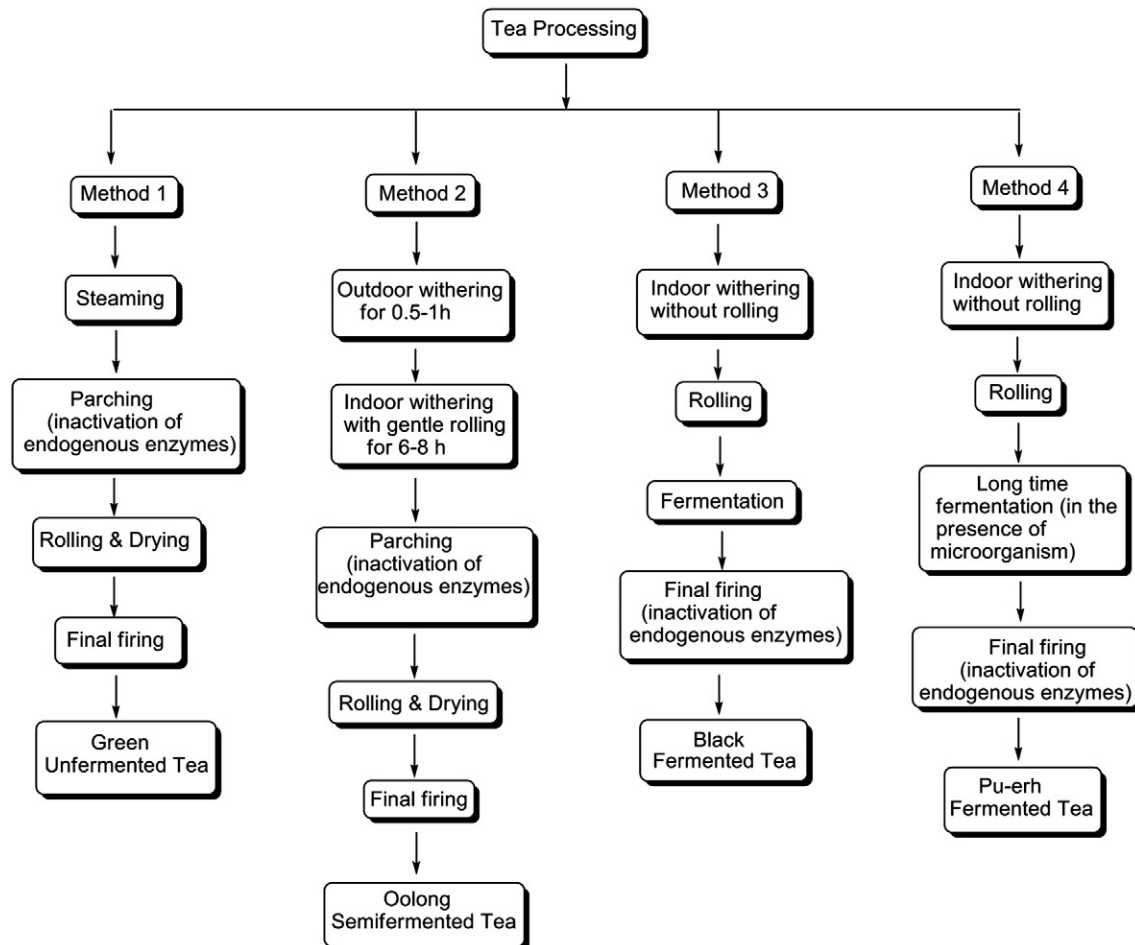


Fig. 1. Schematic diagram of the conventional manufacture process of green, oolong, black, and pu-erh tea.

1992), antimutagenic activity (Hayatsu et al., 1992), protection from cardiovascular diseases (Mukamal, Maclure, Muller, Sherwood, & Mittleman, 2002), lowering of plasma cholesterol levels (Ikeda et al., 1992), enhanced loss of body fat (Klaus, Pultz, Thone-Reineke, & Wolfram, 2005), improvement in type 2 diabetes (Shoji & Nakashima, 2006), increase of bone density (Devine, Hodgson, Dick, & Prince, 2007), protection from neurodegenerative diseases (Ramassamy, 2006), activation of leukocytes (Sakagami, Asano, Hara, & Shinamura, 1992), slowing the catabolism of catecholamines, and strengthening of capillaries ('vitamin P effect') (Min & Peigen, 1991). The potent antioxidant and antimicrobial activities of tea can be explored for its application in the food industry (Mo, Zhu, & Chen, 2008; Perumalla & Hettiarachchy, 2011).

In view of the various therapeutic activities associated with tea polyphenols, the antimicrobial activity has been much explored in recent times. The changing pattern of infectious diseases and the emergence of resistant microbial strains to current antibiotics have resulted in the need for fresh approaches to treatment of microbial infections (Taylor, Stapleton, & Luzio, 2002). Therefore, there has been an increased focus on the development of novel plant-derived antimicrobials, including polyphenols derived from tea leaves (Friedman, 2007).

This review focuses on recent findings about the antimicrobial activities of different types of tea and their polyphenols along with their synergistic effects with antibiotics. The main objective of this review is to unify and interpret widely scattered information of literature on inhibitory activities of polyphenols occurring in various types of tea leaves against bacteria, viruses, yeast, and filamentous fungi.

## 2. Types of tea and their manufacturing process

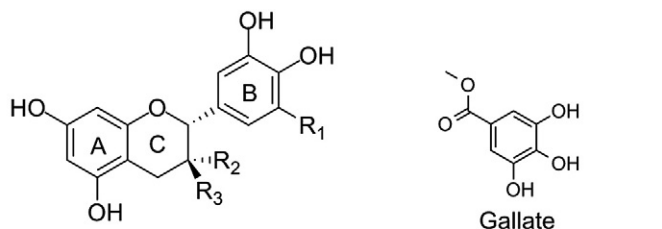
There are two major varieties used for tea, Chinese tea, *Camellia sinensis* var. *sinensis*, and Assam tea, *Camellia sinensis* var. *assamica*. Tea plants are widely cultivated in Southeast Asia, including China, India, Japan, Taiwan, Sri Lanka, and Indonesia, and in Central African countries. Tea is one of the most popular beverages in the world because of its attractive aroma, taste, and healthy effects (Lin, Lin, Liang, Lin-Shiau, & Juan, 1998). Depending on the manufacturing process, tea is classified into three major types: 'non-fermented' green tea (produced by drying and steaming the fresh leaves which inactivate the polyphenol oxidase and thus, oxidation is prevented); 'semi-fermented' oolong tea (produced when the fresh leaves are subjected to partial fermentation before drying); and 'fermented'

black tea and pu-erh tea which undergo a post-harvest fermentation stage before drying and steaming. The fermentation of black tea is due to oxidation catalyzed by polyphenol oxidase while in pu-erh tea, it is attained by using microorganisms (Bancirova, 2010). The differences between the various processes of manufacture result in differences in the polyphenolic profile among green, oolong, black, and pu-erh teas. Fig. 1 outlines the processing of the various types of tea in detail (Karori, Wachira, Wanyoko, & Ngunjiri, 2007; Wu et al., 2007).

## 3. Chemical composition of tea

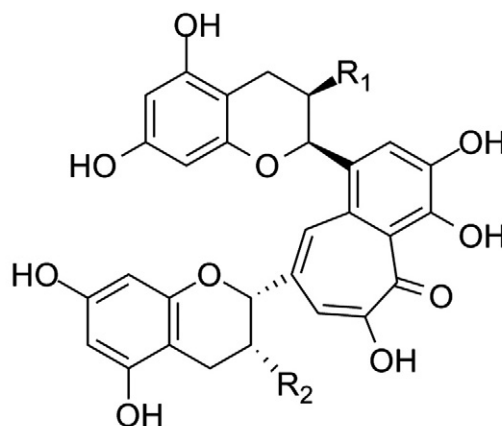
The composition of tea varies with varieties, season, age of the leaf (plucking position), climate, and horticultural practices. The chemical composition of tea is complex and includes carbohydrates, amino acids, proteins, alkaloids (caffeine, theophylline and theobromine), volatile compounds, polyphenols, minerals, and trace elements. Among these, polyphenols particularly flavonoids are important for the biological activity in tea (Cabrera, Gimenez, & Lopez, 2003).

The common flavonoids in tea are the flavan-3-ols (flavanols or flavans), which are present in relatively large amounts compared to their levels in other foods. The flavan-3-ol subclasses are ranked by degree of polymerization. The monomers include catechins (Fig. 2) such as (–)-epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin (EC), (–)-gallocatechin (GC), and (+)-catechin (C). The dimers include theaflavins (Fig. 3) such as theaflavin (TF), theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin-3,3'-digallate (TF3) and oligomers include derived tannins (thearubigins) of unknown structure. The other flavonoids including flavones (apigenin and luteolin) and flavonols (quercetin, kaempferol, and myricetin) (Fig. 4), are present in relatively lesser amount (Peterson et al., 2005). The flavonoid content of various types of tea is represented in Table 1. EGCG is the most abundant and most bioactive catechin of green tea, representing 50–80% of the total catechin content (Bansal, Syan, Mathur, & Choudhary, 2011). In the manufacturing of black tea, the monomeric flavan-3-ols undergo polyphenol oxidase-dependent oxidative polymerization leading to the formation of bisflavanols, theaflavins, thearubigins, and other oligomers (Bansal, Singla, & Boparai, 2004).



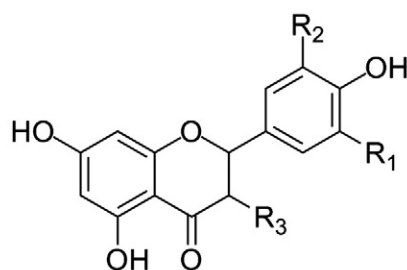
Flavan-3-ol	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
(+)-Catechin (C)	H	H	OH
(+)-Catechin-3-gallate (CG)	H	H	Gallate
(-)-Epicatechin (EC)	H	OH	H
(-)-Epicatechin-3-gallate (ECG)	H	Gallate	H
(-)-Epigallocatechin (EGC)	OH	OH	H
(-)-Epigallocatechin-3-gallate (EGCG)	OH	Gallate	H
(+)-Gallocatechin (GC)	OH	H	OH
(+)-Gallocatechin-3-gallate (GCG)	OH	H	Gallate

Fig. 2. Chemical structure of flavan-3-ols (catechins and epicatechins).



Theaflavins	R <sub>1</sub>	R <sub>2</sub>
Theaflavin	OH	OH
Theaflavin-3-gallate	Gallate	OH
Theaflavin-3'-gallate	OH	Gallate
Theaflavin-3,3'-digallate	Gallate	Gallate

Fig. 3. Chemical structure of theaflavins.



		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
Flavone	Apigenin	H	H	H
	Luteolin	OH	H	H
Flavonol	Kaempferol	H	H	OH
	Myricetin	OH	OH	OH
	Quercetin	OH	H	OH

Fig. 4. Chemical structure of flavones and flavonols.

#### 4. Pharmacokinetics and bioavailability of tea and its polyphenols

Auger, Mullen, Hara, and Crozier (2008) and Yang, Chen, and Lee (1998) reported that the bioactive constituents of green tea are absorbed upon following oral administration in a dose dependent manner. The catechins are metabolized by the liver and excreted from the body chiefly by the kidneys. After administration of a single oral dose of decaffeinated green tea (20 mg tea solids/kg) or EGCG (2 mg/kg), the maximum plasma concentrations of EGCG, ECG, and EC were found to be  $77.9 \pm 22.2$ ,  $223.4 \pm 35.2$ , and  $124.03 \pm 7.86$  ng/mL and the elimination half-lives were  $3.4 \pm 0.3$ ,  $1.7 \pm 0.4$ , and  $2.0 \pm 0.4$  h, respectively (Lee et al., 2002). Phase I clinical trials involving pharmacokinetic studies of EGCG have shown that only a small percentage of the orally administered catechin appeared in the blood. Drinking 2 cups of green tea resulted in the mean peak plasma EGCG level of  $0.17 \mu\text{M}$  after 1.5 h, and only 4% to 8% of the ingested EGCG was excreted in urine (Pisters et al., 2001).

A report by Chow et al. (2001) indicated that after ingestion of EGCG and polyphenon E (a tea polyphenol preparation) by human volunteers, plasma EGCG was mainly in the free (un-conjugated)

form. The other catechins were highly conjugated with glucuronic acid and/or sulfate groups. The major circulating metabolites of epicatechin are epicatechin-3'-O-glucuronide, 4'-O-methylepicatechin-3'-O-glucuronide, 4'-O-methylepicatechin-5- or 7-O-glucuronide, 3'-O-methylepicatechin, and 3'-O-methylepicatechin-7-O-glucuronide (Natsume et al., 2003). Microbial metabolites, namely, 5-(3',4',5'-trihydroxyphenyl)- $\gamma$ -valerolactone, 5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactone, and 5-(3',5'-dihydroxyphenyl)- $\gamma$ -valerolactone, are found mostly in conjugated forms in plasma and urine of volunteers after ingestion of green tea (Meng et al., 2002). Catechins are rapidly eliminated, and galloylated catechins were never recovered in urine due to preferential excretion of these compounds in bile (Van et al., 2001). The low bioavailability of catechins may be perhaps because of relatively low concentration of circulating catechins in relation to ingested catechins or due to rapid degradation or uptake by other tissues (Yoda, Hu, Zhao, & Shimamura, 2004).

#### 5. Antibacterial activity of tea and its polyphenols

EGCG and ECG are the most potent catechins showing antibacterial activity (Hamilton-Miller, 1995) due to the presence of galloyl moiety, which is not present in EC and EGC. Some hypotheses have been recently proposed for explaining the mechanism of antibacterial action of tea catechins. EGCG can directly bind to peptidoglycan and induce its precipitation. Therefore, the EGCG-induced damage of the cell wall and interference with its biosynthesis through direct binding with peptidoglycan are the major mechanisms for its antibacterial activity against *Staphylococcus* (Shimamura, Zhao, & Hu, 2007). Moreover, another study suggested that the bactericidal action of EGCG might also depend upon the generation of hydrogen peroxide by the reaction of EGCG with reactive oxygen species in the presence of superoxide dismutase (pro-oxidative activity) (Arakawa, Maeda, Okubo, & Shimamura, 2004). Different types of tea and their polyphenols were evaluated for antibacterial activity against various infectious agents.

##### 5.1. *Staphylococcus aureus* and methicillin resistant *S. aureus* (MRSA)

*S. aureus*, a highly pathogenic, toxin-producing, food-borne organism, and MRSA is one of the most serious pathogens to have emerged in the past 20 years. Not only  $\beta$ -lactams, which act as selective antimicrobial agents for MRSA, but also other antibiotics such as macrolides, aminoglycosides, and fluoroquinolones have limited use in the treatment of MRSA (Klugman & Koornhof, 1989). Nongalloyl analogs like EC and EGC showed enhancement of binding to staphylococcal cells and significantly increased the capacity of ECG and EGCG

Table 1

Flavonoid content of different types of tea (Peterson et al., 2005; USDA database for the flavonoid content of selected foods release 2.1., 2007).

Subclass Flavonoid		Concentration (mg/100 g dry tea)			
		Green	Black	Oolong	Pu-erh
Flavan-3-ols	(-)-Epicatechin	811.72 $\pm$ 21.10	255.19 $\pm$ 9.97	248.42 $\pm$ 16.30	81.00 $\pm$ 90.00
	(-)-Epicatechin-3-gallate	1491.29 $\pm$ 112.42	688.27 $\pm$ 28.07	627.25 $\pm$ 45.40	40.00 $\pm$ 54.00
	(-)-Epigallocatechin	2057.98 $\pm$ 103.55	956.81 $\pm$ 57.09	750.80 $\pm$ 94.10	157.00 $\pm$ 126.00
	(-)-Epigallocatechin-3-gallate	7115.98 $\pm$ 632.06	1121.92 $\pm$ 64.31	3412.62 $\pm$ 360.53	120.00 $\pm$ 126.00
	(+)-Catechin	57.12 $\pm$ 3.40	137.82 $\pm$ 4.48	30.63 $\pm$ 4.01	0.00
	(+)-Catechin-3-gallate	7.07 $\pm$ 1.83	50.83 $\pm$ 0.00	19.89 $\pm$ 0.00	No Data
	(+)-Galocatechin	258.11 $\pm$ 80.69	91.73 $\pm$ 28.84	305.69 $\pm$ 0.00	No Data
	Theaflavin	1.64 $\pm$ 0.74	159.20 $\pm$ 13.03	15.23 $\pm$ 0.00	No Data
	Theaflavin-3,3'-digallate	1.08 $\pm$ 0.63	170.77 $\pm$ 19.50	No Data	No Data
	Theaflavin-3'-gallate	0.44 $\pm$ 0.26	155.77 $\pm$ 16.10	18.62 $\pm$ 0.00	No Data
	Theaflavin-3-gallate	0.47 $\pm$ 0.32	132.25 $\pm$ 8.70	No Data	No Data
	Thearubigins	131.91 $\pm$ 131.91	5919.00 $\pm$ 563.00	No Data	No Data
	Flavones	Apigenin	12.03 $\pm$ 2.86	0.00	0.00
Luteolin		0.17 $\pm$ 0.17	0.00	0.00	No Data
Flavonols	Kaempferol	147.55 $\pm$ 4.40	126.66 $\pm$ 4.99	62.40 $\pm$ 19.67	23.00 $\pm$ 0.00
	Myricetin	104.76 $\pm$ 7.94	42.24 $\pm$ 1.23	61.85 $\pm$ 26.66	40.00 $\pm$ 0.00
	Quercetin	223.97 $\pm$ 9.60	199.75 $\pm$ 12.86	108.83 $\pm$ 40.94	52.00 $\pm$ 0.00

to reduce levels of staphylococcal oxacillin resistance (Stapleton, Shah, Hara, & Taylor, 2006). Furthermore, Shin and Chung (2007) investigated the effect of major phenolic components from tea against several pathogenic microorganisms including gram-positive strains like *S. aureus* ATCC 29213 and *Streptococcus pyogenes* 308A; and gram-negative strains like *Escherichia coli* ATCC 25922, *E. coli* 078, *Pseudomonas aeruginosa* 9027, and *Enterobacter cloacae* 1321E. The minimum inhibitory concentration (MIC) values demonstrated that both EC and EGC were considerably toxic against *S. aureus* ATCC 29213 than the other two catechins like ECG and EGCG.

The effect of extraction conditions on total polyphenolic contents, antioxidant, and antibacterial activities of black tea has been reported. Black tea was extracted for 2, 8, and 18 h with absolute acetone, dimethylformamide (DMF), ethanol, methanol, and their 50% aqueous solutions. Aqueous acetone or DMF extracts displayed the highest polyphenol contents and antioxidant activity, while absolute acetone was the least efficient solvent. *S. aureus* was found to be the most sensitive to all tea extracts, except for the methanol extract (Turkmen, Velioglu, Sari, & Polat, 2007). Similarly, Sari, Turkmen, Polat, and Velioglu (2007) screened the extracts of black tea with different solvents (acetone, DMF, ethanol, and methanol) for polyphenol content, and antioxidant, and antibacterial activities. It was found that methanol was the least efficient solvent for polyphenol extraction from black tea. All the extracts showed antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. The black tea extracts had strong antimicrobial activity against selected bacteria, except for *E. coli* O157:H7 while *S. aureus* was found to be the most sensitive to all the extracts. *E. coli* was the most resistant among bacterial strains. However, the instability of polyphenols is attributable to their oxidation; the authors examined the effects of antioxidants and inhibitors of polyphenol oxidation on the maintenance of polyphenol antibacterial activity towards MRSA. It was found that the antibacterial activity of EGCG was enhanced in the presence of ascorbic acid, and ascorbic acid was the most effective for retaining the concentration of stable EGCG (Hatano et al., 2008). Furthermore, Hua, Peng, Zeng, Yao, and Qian (2010) reported sub-minimum inhibitory concentrations (sub-MICs) of various types of tea and the main components of tea against MRSA. The MIC range of green tea was 1250–5000 µg/mL, oolong tea was 1250–5000 µg/mL, white tea was 625–2500 µg/mL, dark tea was 2500–5000 µg/mL, and black tea was 5000 µg/mL.

In another study, the relative affinity of EGCG to the cell surfaces of gram-positive and gram-negative bacteria has been studied. Highly EGCG-sensitive *S. aureus* and EGCG-resistant *E. coli* were treated with 0.5 mg/mL EGCG under pH 6.0. It was observed that attachment of EGCG was significantly lower to *E. coli* than *S. aureus* (Nakayama, Shigemune, Tsugukuni, Tokuda, & Miyamoto, 2011). Likewise, Liu et al. (2011) studied the antibacterial activity of catechins against the heterogeneous vancomycin resistant *Staphylococcus* (h-VRSA). The three catechins viz. ECG, EGCG, and EGC showed antibacterial activity against the origin (MIC = 128–512 µg/mL) and generation (MIC = 256–512 µg/mL) of heterogeneous vancomycin resistant *Staphylococcus*. The antibacterial effects of theaflavins were studied on four major bacterial strains, namely *E. coli*, *S. aureus*, *S. mutans*, and *S. sobrinus* 6715. The results indicated that theaflavins showed greater potency in the inhibition of *E. coli* and *S. aureus*, and also had an inhibitory effect on the growth and acid production of *S. mutans* and *S. sobrinus* 6715 (Jin, Wu, & Tu, 2011).

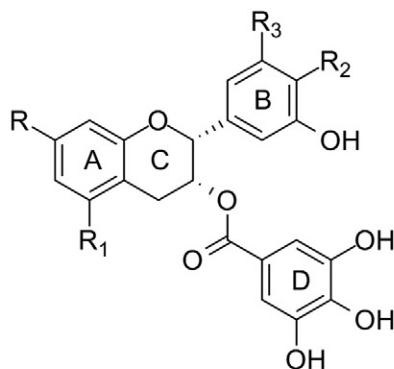
Nakayama et al. (2012) investigated the mechanism of the combined anti-bacterial effect of green tea extract (GTE) and NaCl against *S. aureus* NBRC 13276 and *E. coli* O157:H7. The authors observed that after treatment of 1 h, GTE was found to be more effective against *S. aureus* than *E. coli* O157:H7, and combined GTE/NaCl treatment caused greater cellular damage in *S. aureus* NBRC 13276 than *E. coli* O157:H7. More recently, Matsumoto et al. (2012) synthesized a series of new fatty acid esters of EGCG by lipase-catalyzed transesterification. These derivatives exhibited several-fold higher activities than EGCG,

particularly against gram-positive organisms. Among the derivatives evaluated, sub-MICs of dioctanoate **1** and palmitate **2** (Fig. 5) for 17 strains of *S. aureus* were between 4 and 32 µg/mL, although MIC of EGCG for these 17 strains was  $\geq 128$  µg/mL. The enhanced activity of the palmitate derivative against *S. aureus* was supported by its increased membrane-permeabilizing activity. The palmitate derivative showed rapid bactericidal activity against MRSA ATCC43300 at  $\geq 16$  µg/mL. The finding suggested that the addition of long alkyl chains significantly enhanced the activity of EGCG against several bacteria, particularly against *S. aureus* and MRSA.

## 5.2. *Escherichia coli*

*E. coli* is a food-borne, toxin-producing enteropathogen responsible for a hemorrhagic form of colitis, bloody diarrhea, and hemolytic uremic syndrome. Bruins et al. (2006) studied the effect of different tea types and subfractions on the intestinal fluid and electrolyte losses involved in enterotoxigenic *E. coli* (ETEC) diarrhea. Perfusion of the ETEC-infected segments with both 3 g/L green tea extract and black tea extract significantly inhibited the disturbances in fluid and electrolyte balance. Similarly, Neyestani, Khalaji, and Gharavi (2007) evaluated the microbiologic effects of black tea, compared to green tea, alone and in conjunction with selected antibiotics against *E. coli*. At a concentration of 25 mg/mL, both black tea and green tea completely inhibited *E. coli* growth after 5 and 7 h. Both tea extracts had either synergistic or antagonistic effects at different concentrations on selected antibiotics.

Cho, Schiller, Kahng, and Oh (2007) investigated the cellular responses and proteomic analysis of *E. coli* exposed to green tea polyphenols extracted from Korean green tea. The authors observed responses after exposure to tea polyphenols (TPP) like changes in cell-membrane fatty acids, presence of perforations, and irregular rod forms with wrinkled surfaces. During proteomic analysis, nine upregulated proteins were identified by exposure to TPP including chaperone protein HSP 60 and proteins involved in cellular defense mechanism, such as DNA gyrase subunit A, regulator ampC, RNA polymerase sigma factor, organic solvent tolerance protein, dihydrolipoamide acetyltransferase, superoxide dismutase, transcriptional regulator, and multidrug resistance protein K, whereas the expression of eight proteins was downregulated including chaperone protein HSP70, elongation factor EF-2, acyl-CoA dehydrogenase, enolase, succinate dehydrogenase/fumarate reductase, flavoprotein subunit, glycerophosphoryl diester phosphodiesterase, glutamate/aspartate transport system permease, and aromatic-amino acid aminotransferase. The above results indicated that *E. coli* cells stressed by exposure to TPP invest more energy in upregulating various defense mechanisms while simultaneously downregulating various metabolic and biosynthetic proteins, and provided relevant clues for understanding the mechanism of TPP-induced stress and cytotoxicity on *E. coli*. Furthermore, Lee et al. (2009) studied antipathogenic properties of green tea polyphenol EGCG at concentrations below the MIC ( $539 \pm 22$  µg/mL) against enterohemorrhagic *E. coli* O157:H7. At 25 µg/mL, the growth rate was not affected, but autoinducer 2 concentration, biofilm formation, and swarm motility decreased to 13.2, 11.8, and 50%, respectively. The black tea polyphenols reduced the expression of virulence traits of clinical isolates of *Shigella dysenteriae* and enteropathogenic *E. coli* (EPEC P2 1265) strains (Kiran et al., 2010). More recently, the antibacterial property and mechanism of a novel pu-erh tea nanofibrous membrane have been studied. In this study, pu-erh tea was used as a raw material for nanomaterial preparation and as an antibacterial agent. The results showed better antibacterial activity with smaller pu-erh tea powder (PTP) particles, the nano-sized particles had the best effects, and the MIC of nano-PTP (NPTP) was 13.5 mg/mL. Pu-erh tea in nanofibrous membranes damaged the *E. coli* cell membranes and caused leakage of potassium and enzymes (Su, Zhang, Wang, & Li, 2012).



Compound	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
1	OH	OH	OCO(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	OCO(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>
2	OH	OH	OH	OCO(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>
3	H	H	OH	OH
8	OH	OH	OH	OCO(CH <sub>2</sub> ) <sub>14</sub> CH <sub>3</sub>

Fig. 5. Chemical structure of EGCG derivatives.

### 5.3. *Helicobacter pylori*

*H. pylori* is a type 1 carcinogen and the most important risk factor for gastric cancer. Components found in green tea have been shown to inhibit bacterial growth, including the growth of *Helicobacter* (Stoicov, Saffari, & Houghton, 2009). Surh and co-workers found that green tea containing polyphenols exhibited antibacterial activity against *H. pylori*, which can be used for treating or preventing various stomach-related diseases including gastric cancer, gastric ulcer, or gastritis caused by *H. pylori* (Surh, Kang, Lee, & Park, 2006).

Stoicov et al. (2009) evaluated the effects of green tea on the development of *Helicobacter*-induced gastritis in an animal model. Furthermore, green tea consumption prevented gastric mucosal inflammation prior to exposure to *Helicobacter* infection. Recently, Ankolekar et al. (2011) investigated the effects of nine tea extracts—three different brands representing four different processed types (white, green, oolong, and black)—on the inhibition of *H. pylori* and also studied the influence of extraction time on *H. pylori* inhibition. All the 5 min extracts (extraction time—5 min) showed *H. pylori* inhibition, whereas 2 min extracts of only darjeeling black tea and tazo white tea inhibited the growth of *H. pylori*. None of the extracts inhibited the beneficial lactic acid bacteria. The authors concluded that tea could be potentially used as a low-cost dietary support to combat *H. pylori*-linked gastric diseases without affecting the beneficial intestinal bacteria.

### 5.4. *Bacillus* and *Clostridium*

The activity of tea polyphenols against the bacterial genera belonging to the Bacillaceae family (*Bacillus* and *Clostridium*) was extensively studied. Hara-Kudo et al. (2005) studied antibacterial effects of major green tea polyphenols using *Clostridium* and *Bacillus* spores. After incubation with crude catechins *C. botulinum* and *C. butyricum* spores were decreased in number while no effect was shown in *Bacillus cereus* spores. Out of six catechins investigated, ECG, EGC, EGCG, and GCG were more effective in decreasing *C. botulinum* and *C. butyricum* spore numbers. The authors observed that low concentrations of catechins, although requiring a long exposure time, inhibited the growth of bacterial spores.

The antimicrobial activities of tea catechins, theaflavins, and tea extracts have been evaluated against *B. cereus* (strain RM3190). The

results indicated that GCG, EGCG, CG, ECG, TF3, theaflavin-3'-gallate, and theaflavin-3-gallate showed antimicrobial activities at nanomolar levels, and most of the compounds were more active than current antibiotics viz. tetracycline and vancomycin, at comparable concentrations (Friedman, Henika, Levin, Mandrell, & Kozukue, 2006). In a different study, Wu et al. (2007) reported antimutagenic and antimicrobial activities of pu-erh tea. The antimutagenic activity of the water extract of pu-erh tea (WEPT) against aflatoxin B1 (AFB1) and 4-nitroquinoline-N-oxide (NQNO) was weaker than other tea extracts (green, black, and oolong) because of the least amount of total catechin in WEPT. WEPT has a potential antimicrobial effect on gram-positive *S. aureus* and *B. subtilis* than that of gram-negative *E. coli*. Juneja, Bari, Inatsu, Kawamoto, and Friedman (2007) observed in *C. perfringens* that spore germination and outgrowth were inhibited by green tea extract during abusive cooling (54.4 to 7.2 °C) of cooked ground beef, chicken, and pork. Pu-erh tea extract could significantly inhibit the growth of *Listeria monocytogenes*, *Salmonella typhimurium*, *Streptococcus faecalis*, *E. coli*, and *B. anthracis*, and their MIC values were 0.07, 0.18, 0.50, 0.42, and 0.48 mg/mL, respectively while showing weak inhibition for *S. aureus* (Hu, Jia, Qiao, Ge, & Cao, 2010).

The antibacterial activity of processed Nigerian lipton tea and South African five roses tea, extracted using distilled water, chloroform, and 70% ethanol, was determined against nine enteropathogenic bacteria—*B. subtilis*, *Proteus* species, *Enterobacter* species, *Klebsiella pneumoniae*, *E. coli*, *S. typhi*, *S. paratyphi A*, *S. arizona*, and *S. aureus*. The authors concluded that aqueous extract of lipton tea was found to be a more effective antibacterial agent than five roses tea (Ojo, Yunusa, Akindele, Vera, & Fowora, 2010). Moreover, Chan, Soh, Tie, and Law (2011) investigated the role of non-polymeric phenolic (NP) and polymeric tannin (PT) constituents in the antioxidant and antibacterial properties of six brands of green, black, and herbal teas of *C. sinensis*. Green tea inhibited the growth of all three screened gram-positive bacteria (*Micrococcus luteus*, *S. aureus*, and *B. cereus*) while black and herbal tea showed inhibition of *M. luteus* and *B. cereus*, but not *S. aureus*. Recently, Shigemune et al. (2012) investigated the mechanism of antibacterial action of EGCG against spore-forming bacteria (genus *Bacillus*). The spore count was independent of the presence of EGCG whereas, vegetative growth was suppressed by EGCG. The findings suggested that catechins did not suppress spore germination or inactivate spores

since catechins were not adsorbed by spores, and thus could not act on them.

### 5.5. *Streptococcus*

Dental caries are caused by a group of acid-producing species of the genus *Streptococcus*, in particular *S. mutans* and *S. sobrinus*, which are reported to be the major infective agents of human dental plaque. A key role in such process is played by salivary amylase, which hydrolyses food starch to oligo- and monosaccharides (e.g. maltose, glucose). The fermentation of such carbohydrates by bacterial enzymes occurring in oral cavities provokes the formation of organic acids responsible to dental caries. Ooshima (2005) studied the anti-caries activity of various types of tea and their polyphenols. The fermentation process during processing of tea results in oxidation of simple polyphenols in green tea leaves to produce more complex structures due to polymerization. The IC<sub>50</sub> of purified oolong tea polyphenol to inhibit insoluble glucan synthesis was found to be 2 µg/mL, 8 µg/mL with TF (purified from black tea leaves), 40 µg/mL with oolong tea extract, 250 µg/mL with a green tea extract, and much higher concentrations were needed with simple catechins. The author found that inhibition of glucosyltransferase activity of *S. mutans* and decreasing the surface hydrophobicity of oral *Streptococci* are responsible factors for anti-caries activity of tea polyphenols.

The inhibition of acid production in dental plaque bacteria (*S. mutans*) by EGCG was examined. After treatment with EGCG, the pH values of plaque samples from fifteen volunteers were significantly higher than those who were treated with water (Hirasawa, Takada, & Otake, 2006). Furthermore, Hassani et al. (2008) evaluated the efficacy of black and green tea extracts against *S. mutans* ATCC 25175, *S. mitis* ATCC 9811, and *S. sanguis* ATCC 10556 that are responsible for dental caries. The extracts were able to prevent the growth of oral *Streptococci*. A 1 mg/mL of black tea extract completely inhibited biofilm formation while green tea extract was unable to inhibit biofilm formation at the same concentration. The dry leaves of black tea contained more tannins than green tea and had stronger antibacterial activity (Stanczyk, Skolimowska, & Wedzisz, 2008).

The tea polyphenols extracted from Korean green tea were evaluated for their antimicrobial effects and inhibition of biofilm formation properties against twelve oral microorganisms. The authors observed various morphological changes, such as the presence of perforations, formation of cell aggregates, and leakage of cytoplasmic materials from cells treated with tea polyphenols, depending on the bacteria by scanning electron microscopy (SEM) analysis. The results concluded that tea polyphenols are effective against adherent cells of *S. mutans* and *S. sanguis*, and therefore, can be developed as a potential antimicrobial agent against oral microorganisms for the prevention and treatment of dental caries (Cho, Oh, & Oh, 2010).

Abd, Ibrahim, and Al-Atrouny (2011) evaluated the antimicrobial effect of black tea against *S. mutans* and *Lactobacillus* species in adult Egyptian citizens. The results showed that the black tea beverage had a highly significant effect on reducing the cariogenic bacterial counts. The antibacterial activity of Iranian green and black tea extracts on *S. mutans* was also studied at different concentrations (50, 100, 150, 200, 300, and 400 mg/mL). The MIC of Iranian green and black tea extracts was found to be 150 and 50 mg/mL, respectively (Naderi, Niakan, Kharazi, & Zardi, 2011). The suppression of cariogenic virulence factors of *S. mutans* by EGCG has been reported. Tea polyphenols, especially EGCG, were shown to inhibit glucosyltransferase activity and growth of *S. mutans* (Xu, Zhou, & Wu, 2011). Furthermore, Xu, Zhou, and Wu (2012) described the mechanism of inhibition of dental plaque accumulation by EGCG. They hypothesized that EGCG suppressed *gtf* genes in *S. mutans* at the transcriptional level disrupting the initial attachment of *S. mutans* and thus the formation of mature biofilms.

Recently, Cui et al. (2012) studied the comparison of morphological alterations in gram-positive and gram-negative bacteria induced

by EGCG at sub-MICs. EGCG caused aggregates in the cell envelopes of gram-positive bacteria (*S. aureus* and *Streptococcus mutans*) (Fig. 6) while it caused microscale grooves in the cell envelopes of gram-negative bacteria (*Pseudomonas aeruginosa* and *E. coli*) (Fig. 7).

### 5.6. Other bacteria

Different types of tea and their polyphenols were also evaluated for antibacterial activity against other infectious agents. Representative agents include, *Legionella pneumophila*, *Mycobacterium tuberculosis*, *Salmonella*, *P. aeruginosa*, *L. monocytogenes*, and *Vibrio cholera*.

*L. pneumophila* causes Legionnaire disease, an infection of the lungs and other organs. Few authors found that EGCG inhibited interleukin-12 (IL-12) production while enhancing tumor necrosis factor-alpha (TNF-α) production in bone marrow-derived dendritic cells infected with *L. pneumophila*. These findings suggested that EGCG had a marked effect in modulating production of immunoregulatory cytokines (IL-12 and TNF-α) in stimulated dendritic cells, which are important for antimicrobial immunity, especially innate immunity (Rogers et al., 2005). Moreover, Kobayashi et al. (2006) found that growth inhibition of *S. enteritidis* was more pronounced in black tea, oolong tea, and green tea, which contained a larger amount of catechin with galloyl moiety such as EGCG and ECG than barley tea. Out of four kinds of tea, the bacteriostatic activity of black tea against *S. enteritidis* was at the maximum due to the presence of theaflavins.

The inhibitory activity of natural products has been evaluated against the growth of *E. coli* (ATCC 25922) and *S. typhimurium* (KCCM 11862). The results concluded that natural bioactives such as EGCG and chitosan may be used as antimicrobial agents for the improvement of food safety (Kim & Kim, 2007). Similarly, Cetojevic-Simin, Bogdanovic, Cvetkovic, and Velicanski (2008) investigated antimicrobial activity of kombucha beverages made from *Camellia sinensis* L. (black tea) and *Satureja montana* L. (winter savory tea). The authors found that both kombucha beverages had the most expressive antimicrobial activity against all investigated bacteria. Black tea kombucha showed higher activity than acetic acid against *S. aureus* and *E. coli* while both kombuchas had bacteriostatic activity on *Salmonella enteritidis*.

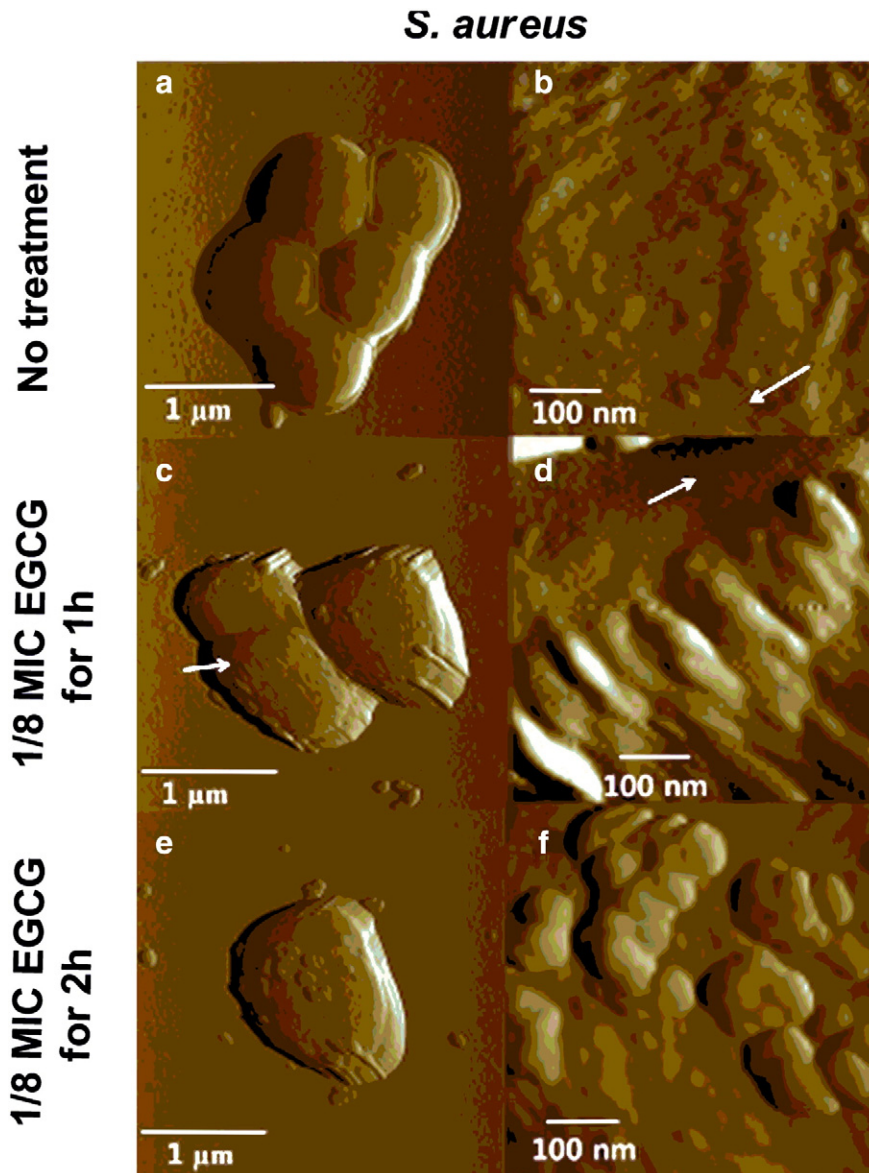
*M. tuberculosis* is a species that causes tuberculosis in humans. Lack of maturation of phagosomes containing pathogenic *M. tuberculosis* within macrophages has been widely recognized as a crucial factor for the persistence of mycobacterial pathogen. Anand, Kaul, and Sharma (2006) found that down-regulation of tryptophan-aspartate containing coat protein (TACO) gene expression by EGCG was responsible for the inhibition of *M. tuberculosis* survival. Furthermore, Sharma, Kumar, Kapoor, and Surolia (2008) reported that EGCG inhibited InhA, the enoyl acyl carrier protein reductase of *M. tuberculosis* with IC<sub>50</sub> of 17.4 µM.

*P. aeruginosa* is an opportunistic pathogen responsible for a wide range of infections. The combined effect of the cell-surface damaging compounds (surfactants and preservatives) and GTE was investigated against *P. aeruginosa*. It was found that both surfactants and preservatives enhanced the antibacterial activity of GTE at pH 5.0, 6.5, and 8.0 (Nakayama et al., 2009). Production of virulence factors and biofilm formation by *P. aeruginosa* are partly regulated by cell-to-cell communication quorum-sensing systems. Identification of quorum-quenching reagents, which block the quorum-sensing process, can facilitate development of novel treatment strategies for *P. aeruginosa* infections. It was observed that EGCG has a higher binding affinity towards enoyl-acyl carrier protein reductase (ENR) of *P. aeruginosa* and is an efficient quorum-quenching reagent (Yang, Liu, Sternberg, & Molin, 2010).

Some additional examples of antibacterial activity of tea extracts or tea polyphenols are reported in Table 2.

Kohda, Yanagawa, and Shimamura (2008) reported inhibition of intracellular survival of *L. monocytogenes* in macrophages by EGCG. Anti-*L. monocytogenes* activity of EGCG is through the inhibition of





**Fig. 6.** Topographical images of *S. aureus* treated with EGCG. Cells were: untreated (a–b); treated with 1/8 MIC (12.5 mg/L) EGCG for 1 h (c–d) and 2 h (e–f). White arrows indicate the lattice structures of the peptidoglycan layer.

hemolytic and cholesterol-binding activity of listeriolysin O, which usually disrupts the phagosomal membrane in the escaping phase of *L. monocytogenes*. Podlipnik (2009) performed docking of selected natural polyphenols to ARF (ADP-ribosylation factor) activated A1 subunit of cholera toxin (CTA1). EGCG, TF3, and 1,2,3,6-tetra-O-galloyl-D-glucose were the best binder towards the active binding site of CTA1. Tea polyphenols have been also tested as antimicrobial drugs against food-borne pathogen and food-spoilage bacteria. In a study on major food-borne pathogens, Chinese green tea extract strongly inhibited these pathogens (*E. coli* O157:H7, *S. Typhimurium* DT104, *L. monocytogenes*, and *S. aureus*). A simple and efficient reversed-phase high-speed counter-current chromatography (HSCCC) method was developed for the separation and purification of four bioactive polyphenol compounds, ECG, EGCG, EC, and caffeine (CN). Among the four compounds, ECG and EGCG were the most active, particularly EGCG against *S. aureus*. EGCG had the lowest MIC<sub>90</sub> values against *S. aureus* (58 μg/mL) and MRSA (37 μg/mL) (Si et al., 2006). Likewise, Osterburg, Gardner, Hyon, Neely, and Babcock (2009) reported that EGCG expressed bactericidal activity against multiresistant clinical isolates of *Acinetobacter baumannii* with sub-MICs ranging from 78 to

625 μg/mL, with MIC<sub>50</sub> and MIC<sub>90</sub> of 312 μg/mL and 625 μg/mL, respectively.

Tea extracts have been widely used to extend the shelf life of various foods such as fresh mutton (Kumudavally, Phanindrakumar, Tabassum, Radhakrishna, & Bawa, 2008), overnight pickled cucumber (Miyamoto et al., 2009), and Collichthys fish balls (Yi et al., 2011). Xu, Liu, Ren, and Sun (2006) reported significant bacteriostatic activities of a natural preservative (150 mg/kg nisin + 0.3% tea polyphenols) against Lactobacilli. Moreover, the combination of bacteriocin like nisin with GTE showed greater effectiveness than used alone against major foodborne pathogen like *L. monocytogenes* (Perumalla & Hettiarachchy, 2011).

## 6. Antiviral activity of tea and its polyphenols

The effects of tea and tea catechins on viruses have also been extensively studied. Some hypotheses have been recently proposed for explaining the mechanism of antiviral activity of tea catechins. EGCG inhibits viruses by direct binding to biological molecules and induces agglutination of the influenza virus thus preventing their

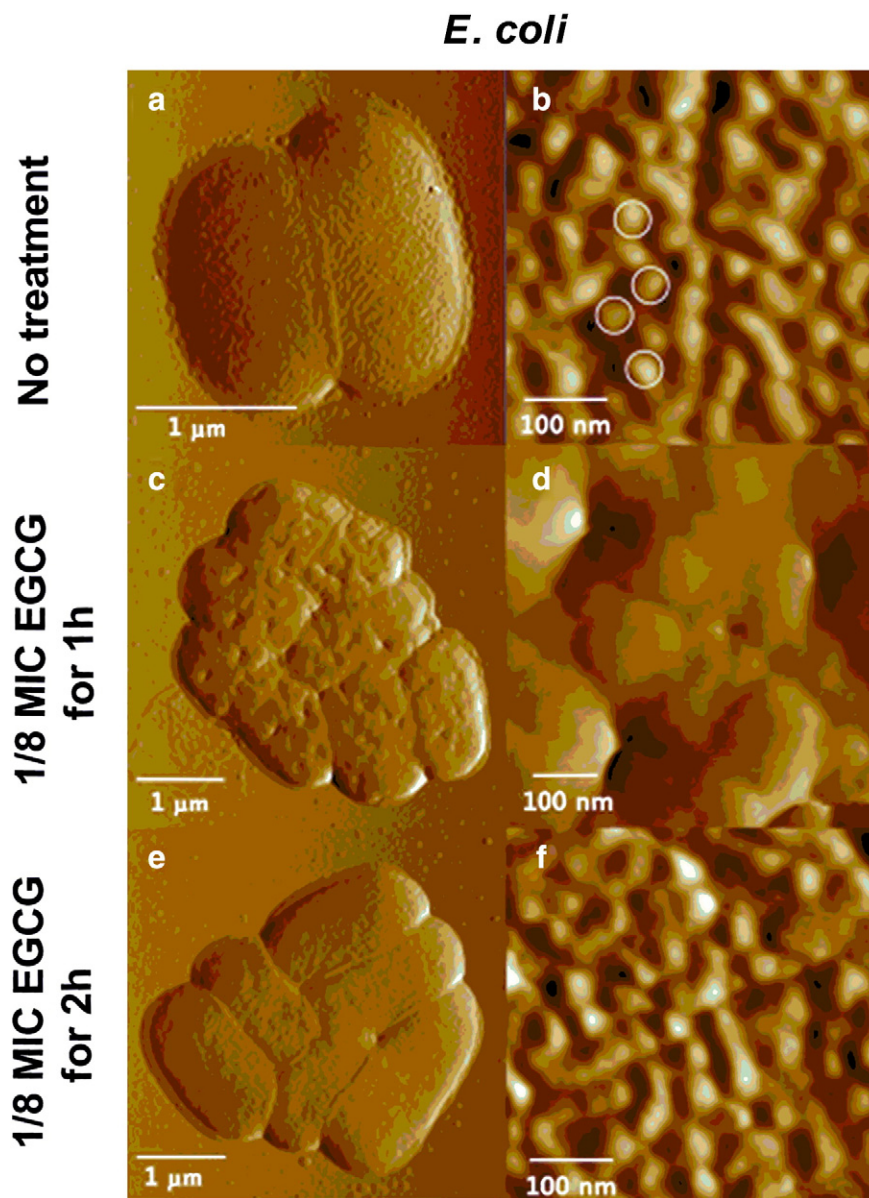


Fig. 7. Topographical images of *E. coli* O157:H7 treated with EGCG. Cells were: untreated (a–b); treated with 1/8 MIC (60 mg/L) EGCG for 1 h (c–d) and 2 h (e–f).

adsorption to target cells. In addition, the direct binding of EGCG to viral receptors on cell surfaces may also interfere with viral infectivity, following the observation that EGCG binds with CD4 cells and interferes with binding to the HIV surface protein, gp120 (Tadakatsu, Wei-Hua, & Zhi-Qing, 2007).

### 6.1. Influenza virus

Nakayama and co-workers reported that tea polyphenols greatly reduce the infectivity of the influenza virus in cell culture (Nakayama et al., 1993). Following this report, tea polyphenols have received more attention as an alternative measure against seasonal as well as pandemic influenza. Recently, Furuta et al. (2007) synthesized di-deoxy-epigallocatechingallate **3** (Fig. 5), an analog of EGCG that was evaluated for anti-influenza virus activity. The compound showed potent anti-influenza virus activity, indicating that the hydroxyl substituents on the A-ring are not crucial for anti-influenza virus activity.

Similarly, few catechin derivatives with a different alkyl chain length and aromatic ring substitutions at the 3-hydroxyl group from

EGC and (+)-catechin have been synthesized and evaluated for their anti-influenza viral activity. The derivatives carrying a chain length of 9–11 carbons such as compounds **4**, **5**, **6**, and **7** (Fig. 8), showed pronounced antiviral activity compared to those with aromatic rings. These derivatives exerted inhibitory effects on all six influenza subtypes tested including three major types of currently circulating human influenza viruses (A/H1N1, A/H3N2, and B type), H2N2 and H9N2 avian influenza virus (Song et al., 2007).

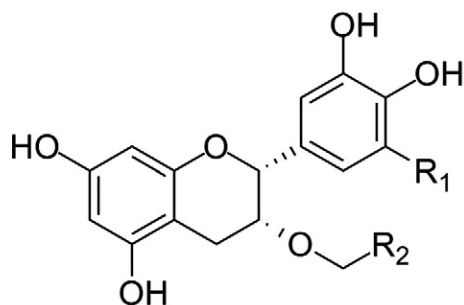
The *in vitro* inhibitory effects of EGCG on influenza virus A-induced cytopathy were observed by cytopathic effect assay (CPE). Oral administration of EGCG reduced the mortality of influenza virus A H1N1 strain-infected mice and lessened the lesion degree of mice lung tissue (Xiao, Yang, Shi, Liu, & Chen, 2008). Furthermore, Mori et al. (2008) prepared a series of fatty acid monoester derivatives of EGCG by one-pot lipase-catalyzed transesterification. The EGCG-monoesters modified with butanoyl, octanoyl, lauroyl, palmitoyl, and eicosanoyl groups were represented as EGCG-C4, EGCG-C8, EGCG-C12, EGCG-C16, and EGCG-C20, respectively. The authors showed that the anti-influenza A/PR8/34 (H1N1) virus activities of EGCG-monoesters were enhanced in an alkyl chain length-dependent manner. EGCG-C16 **8** (Fig. 5) was

**Table 2**  
Some additional examples of antibacterial activity of tea extract or tea polyphenols.

Bacterium	Tea extract or active compound (s)	Significant findings	References
<i>Staphylococcus aureus</i>	EGCG	Inhibition of staphylococcal superantigen (SsAg)-induced T-cell activation	Hisano et al. (2003)
MRSA	EGCG, ECG	EGCG (MIC = 32–64 µg/mL) more potent than ECG (MIC = 64–> 512 µg/mL)	Gibbons, Moser, and Kaatz (2004)
<i>Helicobacter pylori</i>	EGCG	Suppression of <i>H. Pylori</i> -induced gastric epithelial cytotoxicity via the blockage of toll-like receptor-4 (TLR-4) signaling	Lee et al. (2004)
<i>Streptococcus mutans</i>	Oolong tea extract	Synergistic antibacterial activity was shown by monomeric polyphenols.	Sasaki et al. (2004)
<i>Legionella pneumophila</i>	EGCG	Enhancement of <i>in vitro</i> resistance of alveolar macrophages to <i>Legionella pneumophila</i> infection	Yamamoto, Matsunaga, and Friedman (2004)
<i>Listeria monocytogenes</i>	EGCG, ECG	Inhibition of tested microorganism by complex of tea catechins (EGCG and ECG)	Patar, Nishikawa, Tanaka, Ishimaru, and Maeda (2003)
<i>Vibrio cholera</i>	Green tea extract	The MIC of 11 out of 23 strains of <i>V. cholera</i> was found to be 10 mg/mL, 4 had MIC at 20 mg/mL, 4 at 30 mg/mL, 1 at 40 mg/mL and 3 at 50 mg/mL.	Bandyopadhyay, Chatterjee, Dasgupta, Lourduraja, and Dastidar (2005)

most potent (EC<sub>50</sub> 4 µM) among EGCG monoesters, and its inhibitory effect was found to be 24-fold higher than native EGCG.

Likewise, Tan, Shi, Zhu, and Tan (2009) investigated the anti-influenza virus activity of EGCG. The effect and potency of anti-influenza virus were examined *in vitro* in cell culture. There was a close relationship between dose and efficacy of EGCG on the effect of anti-influenza virus. EGCG possessed potent inhibitory effect on influenza virus. Another study established virus inhibition activity of EGCG and EGCG-monopalmitate on avian influenza A/Duck/Hong Kong/342/78 (H5N2) virus in 11 day old chicken embryonated eggs inoculated with compound-treated or -untreated viruses. EGCG-monopalmitate showed complete inhibition while EGCG exhibited a moderate viral inhibitory effect (Kaihatsu et al., 2009). Moreover, Huang et al. (2010) performed *in vitro* and *in vivo* study on anti-influenza virus effect of tea polyphenols. EGCG and ECG showed a marked antiviral effect against influenza virus infections in MDCK cells (Madin–Darby canine kidney cells) in all influenza virus subtypes tested, including H5N1, H1N1, and H9N2 viruses and also showed an inhibitory effect on neuraminidases (NAs) from H5N1, H1N1, and H9N2 viruses. At the concentration of 1000 mg/kg/day, tea extract possessed a potent inhibitory effect on BALB/c's pneumonia consolidation infected by influenza viruses.



Compound	R <sub>1</sub>	R <sub>2</sub>
4	OH	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>
5	OH	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>9</sub> CH <sub>3</sub>
6	H	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>
7	H	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>9</sub> CH <sub>3</sub>

**Fig. 8.** Chemical structure of catechin derivatives.

A nasal inhalation containing EGCG and/or ECG has been prepared for treating common cold and influenza. The nasal preparation consisted of two parts: solid anti-influenza virus component EGCG or ECG, and liquid acetic acid–sodium acetate buffer. The inhalation containing 3.2 mg/L EGCG and 1.8 mg/L ECG showing significant inhibition against influenza virus. It has the advantages of good stability, long shelf life, rapid absorption, and good curative effect (Nie, 2010). More recently, *in vitro* anti-influenza virus and anti-inflammatory activities of TF derivatives have been reported. The results showed that all the derivatives of TF exerted significant inhibitory effects on the neuraminidase (NA) of three different subtypes of influenza virus strains (A/PR/8/34(H1N1), A/Sydney/5/97(H3N2), and B/jiangsu/10/2003) with IC<sub>50</sub> values ranging from 9.27 to 36.55 µg/mL, and they also displayed an inhibitory effect on hemagglutinin (HA) (Zu et al., 2012).

## 6.2. HIV

Among various viruses investigated for potential therapeutic targets, HIV has received the most attention. Several reports available in the literature have shown that tea polyphenols have a protective effect against HIV infection. The reports showed that green tea catechin, EGCG is the most effective compound against HIV infection. Hamza and Zhan (2006) reported a mechanism of inhibition of gp120–CD4 binding by EGCG. The authors performed extensive molecular docking, molecular dynamics simulations, and binding free-energy calculation studies to predict the most favorable structures of CD4–EGCG, gp120–CD4, and gp120–CD4–EGCG binding complexes in water. The results revealed that EGCG binds with CD4 in such a way that the calculated binding affinity of gp120 with the CD4–EGCG complex is negligible. Therefore, a favorable binding of EGCG with CD4 can effectively block gp120–CD4 binding. Similarly, Williamson, McCormick, Nance, and Shearer (2006) demonstrated binding of EGCG to the CD4 molecules at the gp120 attachment site and inhibition of gp120 binding. Molecular modeling studies suggested a binding site for EGCG in the D1 domain of CD4, the pocket that binds gp120. A 0.2 µM/L EGCG inhibited binding of gp120 to isolated human CD4+ T cells. This clearly demonstrated clear evidence of high-affinity binding of EGCG to the CD4 molecules with a K<sub>d</sub> of approximately 10 nM and inhibition of gp120 binding to human CD4+ T cells.

A docking study was performed which concluded that when HIV-1 integrase did not combine with virus DNA, the four catechins with the galloyl moiety, including CG, EGCG, GCG, and ECG, were able to bind with Tyr143 and Gln148, altering the flexibility of the loop (Gly140–Gly149), and thereby leading to an inhibition of HIV-1 integrase activity (Jiang et al., 2010). The HIV fusion-inhibiting activity of peracetate ester of EGCG 9 (Fig. 9) was investigated by computer aided molecular docking to analyze the binding sites of peracetate ester of EGCG on

gp41. The stability of EGCG was significantly enhanced after introduction of acetate protection groups on the reactive hydroxyls of EGCG. After hydrolysis, peracetate ester of EGCG inhibited HIV fusion by targeting gp41 (Yang, Li, et al., 2010).

Li, Hattori, and Kodama (2011) found that EGCG appeared to act mainly as an allosteric reverse transcriptase inhibitor with mechanisms different from those of currently approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) that directly interact with the NNRTI binding pocket. It also showed synergistic inhibition with 3'-azido-3'-deoxythymidine (AZT). Liu et al. (2005) reported anti-HIV activity of TF derivatives in black tea and catechin derivatives in green tea. The authors found that TF derivatives had more potent anti-HIV-1 activity than the catechin derivatives. They inhibited HIV-1 entry into target cells by blocking HIV-1 envelope glycoprotein-mediated membrane fusion. Computer-aided molecular docking analysis indicated that these tea polyphenols, TF3 as an example, may bind to the highly conserved hydrophobic pocket on the surface of the central trimeric coiled coil formed by the N-terminal heptad repeats of gp41. The inhibition of HIV-1 infection by natural theaflavins preparation has been reported. Tfmix is an economic natural product preparation containing high content of theaflavins with potent anti-HIV-1 activity by targeting the viral entry step through the disruption of gp41 6-HB core structure (Yang et al., 2012).

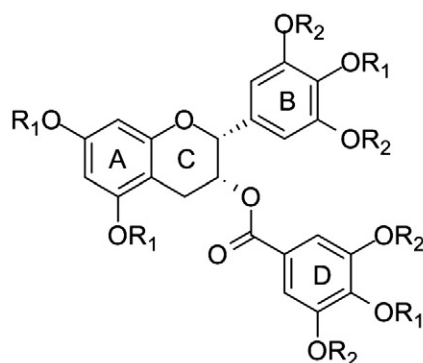
### 6.3. Epstein–Barr virus

Epstein–Barr virus (EBV) is a DNA virus belonging to the Herpesviridae family and is associated with several human malignancies, such as Burkitt's lymphoma and nasopharyngeal carcinoma. However, the expression of Epstein–Barr nuclear antigen 1 (EBNA1) is prevalent in all EBV-associated tumors and has become one of the most attractive drug targets for the discovery of anti-EBV compounds. Recently, Chen, Tsai, and Peng (2012) found that the treatment of cells with 50  $\mu$ M EGCG effectively blocked the binding of EBNA1 to oriP-DNA both *in vivo* and *in vitro*, leading to the abrogation of EBNA1-dependent episome maintenance and transcriptional enhancement. The anti-EBNA1 effects caused by EGCG ultimately impaired the persistence of EBV latent infection.

### 6.4. Hepatitis B virus

Hepatitis B virus (HBV) infection is endemic in Asia and is a major public health concern worldwide. Present treatment strategies for HBV infections are not satisfactory and the clinical limitation of current antiviral drugs for HBV, such as lamivudine, has caused rapid emergence of drug-resistant viral strains during the prolonged therapeutic treatment. The green tea extract and primary active ingredient EGCG inhibited the expression of hepatitis B antigens and the replication of HBV DNA and could be used as drugs or adjuvants for treating hepatitis B infection (Wang, Xu, Deng, & Hu, 2007). Similarly, the efficacy of a natural green tea extract (GTE) was examined against HBV in a stably expressed HBV cell line HepG2-N10. The results indicated that EC<sub>50</sub> values of GTE on HBsAg, HBeAg, extracellular HBV DNA, and intracellular HBV DNA were 5.02, 5.681, 19.81, and 10.76  $\mu$ g/mL, respectively (Xu, Wang, Deng, Hu, & Wang, 2008).

The antiviral mechanism of EGCG has been analyzed against HBV replicating cell line HepG2.117. EGCG inhibited HBV replication by impairing HBV replicative intermediates of DNA synthesis which resulted in reduced production of HBV covalently closed circular DNA (He, Li, Liao, Liu, & Chen, 2011). Recently, Pei, Zhang, Xu, Chen, and Chen (2011) studied the role of pu-erh tea extract (PTE) against HBV by using a stably HBV-transfected cell line HepG2 2.2.15. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay showed that PTE and its active components (tea polyphenols, theaflavins, and theanine) had a low cytotoxicity profile against HBV. More recently, four lipophilic ester derivatives of EGCG, namely EGCG-O-tetratearate **10**, EGCG-O-tetraeicosapentaenoate **11**, EGCG-O-tetradocosahexaenoate **12**, and EGCG-O-octabutyrate **13** (Fig. 9) were prepared and evaluated for their *in vitro* antioxidant and antiviral activities. Incorporation of long chain polyunsaturated fatty acids (PUFA), into EGCG resulted in increased peroxyl radical scavenging activity and metal chelation capacity. The EGCG-PUFA esters were found to be 1700-fold more effective in inhibiting hepatitis C virus (HCV) protease than embelin which serves as a positive control. The derivatives were also found to be  $\alpha$ -glucosidase inhibitors, suggesting their potential role as an anti-HIV agent (Zhong, Ma, & Shahidi, 2012).



Compound	R <sub>1</sub>	R <sub>2</sub>
<b>9</b>	COCH <sub>3</sub>	COCH <sub>3</sub>
<b>10</b>	H	CO(CH <sub>2</sub> ) <sub>16</sub> CH <sub>3</sub>
<b>11</b>	H	CO(CH <sub>2</sub> ) <sub>3</sub> (CH=CHCH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>
<b>12</b>	H	CO(CH <sub>2</sub> ) <sub>3</sub> (CH=CHCH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>
<b>13</b>	CO(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	CO(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>

Fig. 9. Chemical structure of EGCG esters.

### 6.5. Herpes simplex virus

Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), also known as Human herpes virus 1 and 2 (HHV-1 and HHV-2), are belonging to family, Herpesviridae, that infect humans. Both HSV-1 (which is responsible for cold sores) and HSV-2 (which causes most genital herpes) are ubiquitous and contagious. Savi, Barardi, and Simoes (2006) evaluated antiherpetic activity and genotoxicity of tea catechins and their derivatives using the MTT colorimetric and comet assays. The study showed that all compounds have antiviral activity with selective indexes varying from 1.3 to 13, depending on the tested HSV-1 strain.

Isaacs et al. (2008) observed that binding of EGCG to HSV-1 envelope glycoproteins gB and gD was responsible for anti-HSV activity. Furthermore, the *in vitro* antiviral activity and therapeutic efficacy of catechin polyphenols have been evaluated in mice infected with herpes simplex virus (HSV) and influenza virus (IFV). The *in vitro* and *in vivo* studies demonstrated that green tea polyphenols were active against HSV while failing to show any activity against IFV (Daikoku et al., 2011). EGCG inactivates HSV-1 and HSV-2 at pH 8.0 by 3 log<sub>10</sub> to 4 log<sub>10</sub> but is ineffective at pH 5.7. Recently, Isaacs et al. (2011) noticed that the EGCG digallate dimers such as theasinensin A, P2 (Fig. 10), and TF3 inactivated HSV-1 and HSV-2 viruses by 3 log<sub>10</sub> to 4 log<sub>10</sub> at pH 5.7 and as much as 5 log<sub>10</sub> at pH 8.0 while TF3 inactivated both viruses by 4 log<sub>10</sub> to 5 log<sub>10</sub> in the pH range of 4.0 to 5.7. Dimers with one gallate moiety had antiviral activity intermediate between the activities of EGCG and digallate dimers. The results concluded that digallate dimers of EGCG had excellent potential as microbicidal agents against HSV at both acidic and neutral pH.

### 6.6. Other viruses

Different types of tea and their polyphenols were evaluated for antiviral activity against other infectious agents, which include bovine coronavirus, adenovirus, tobacco mosaic virus, and cucumber mosaic virus.

The inhibitory effect of EGCG on bovine coronavirus (BCV) propagation has been investigated in Madin–Darby bovine kidney (MDBK)

cells (Matsumoto, Mukai, Furukawa, & Ohori, 2005). The authors observed that EGCG possessed a distinct anti-BCV activity and interfered with the adsorption of BCV to MDBK cells by the interaction of EGCG with BCV particles. Moreover, Furukawa, Kawabe, Ohori, Mukai, and Matsumoto (2005) developed a composition containing reduced glutathione and catechin (EGCG) against viruses belonging to the Coronaviridae and Flaviviridae family.

Some additional examples of antiviral activity of tea extract or tea polyphenols are reported in Table 3.

The importance of catechins as antiviral drugs for prevention and treatment of respiratory viral infection, avian influenza infection, respiratory syncytial infection, coxsackie infection, and adenovirus infection has been reported by authors (Yang & Shi, 2007). Recently, Zhou et al. (2008) reported the isolation and characterization of ZH14 with antiviral activity against tobacco mosaic virus. The bacterium ZH14, which was isolated from Chinese oolong tea, secreted the antiviral substances, having 94.2% virus inhibition.

## 7. Antifungal activity of tea and its polyphenols

However, not enough studies have been carried out so far on the antifungal activity of tea polyphenols. Among tea polyphenols, EGCG was the most active against *Candida albicans*.

### 7.1. *Candida albicans*

*C. albicans* is a diploid fungus that grows both as yeast and filamentous cells. It is a causal agent for opportunistic oral and genital infections in humans. *In vitro* antimycotic activity of some plant extracts have been studied towards yeast and yeast-like strains. Green tea extract exhibited broad antimycotic activity towards *Candida glabrata*, *Clavispora lusitanae*, *Cryptococcus laurentii*, *Filobasidiella neoformans*, *Issatchenkia orientalis*, *Saccharomyces cerevisiae*, and *Prototheca wickerhamii* strains. The compounds responsible for antimycotic activity were ECG and EGCG (Turchetti et al., 2005).

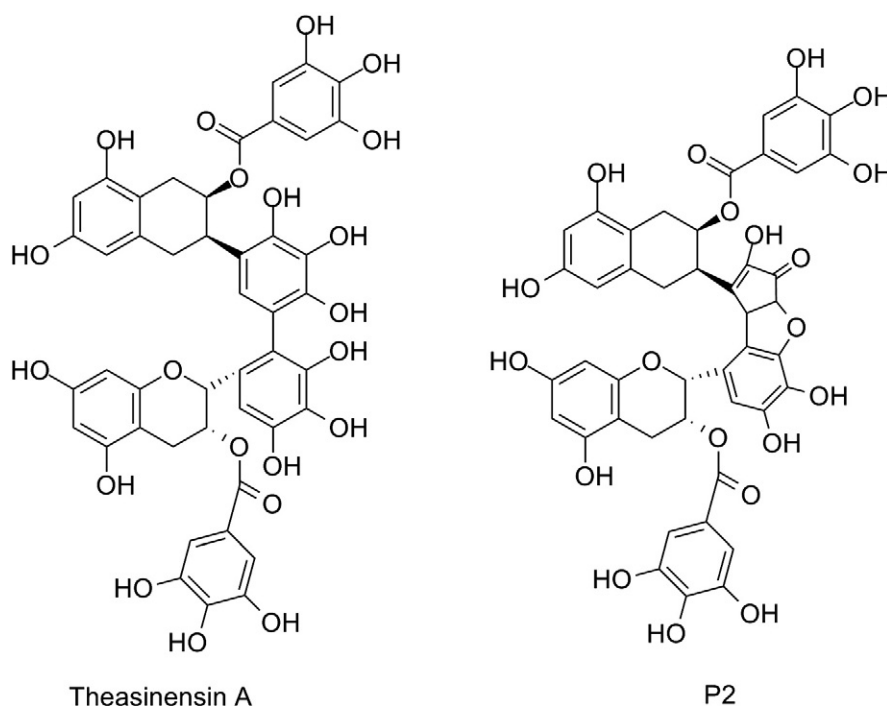


Fig. 10. Chemical structures of EGCG digallate dimers.

**Table 3**  
Some additional examples of antiviral activity of tea extract or tea polyphenols.

Virus	Tea extract or active compound (s)	Significant findings	References
HIV	EGCG	Direct binding of EGCG to CD4 and inhibition of gp120–CD4 binding.	Kawai et al. (2003)
Epstein–Barr virus	EGCG	Interference with EBV-encoding activator protein-1 (AP-1) signal transduction pathway.	Zhao et al. (2004)
Hepatitis B virus	Tea catechin	Protection of liver functions and reduction of pathological changes of the liver tissue.	Li, Zhou, and Zhang (2001)
Adenovirus	EGCG	EGCG inactivated purified adenovirions with IC <sub>50</sub> of 250 μM.	Weber, Ruzindana-Umunyana, Imbeault, and Sircar (2003)
Rotavirus	Tea polyphenol	Reduction of infectivity of rotavirus by combination of anti-retroviral agent with tea polyphenol.	Apostolides and Selematsela (2003)

Navarro-Martinez, Garcia-Canovas, and Rodriguez-Lopez (2006) elucidated the mechanism of action of EGCG against *C. albicans*. The authors demonstrated that by disturbing the folate metabolism, EGCG could inhibit ergosterol production. Furthermore, the antifungal susceptibility of 21 clinical isolates of seven *Candida* species to EGCG has been investigated. Among the tested species, *C. glabrata* exhibited the highest susceptibility to EGCG (MIC<sub>50</sub>, 0.5–1 μg/mL and MIC<sub>90</sub>, 1–2 μg/mL) compared favorably with fluconazole. Moreover, the susceptibility of *Candida krusei* strains (MIC<sub>50</sub>, 2 μg/mL and MIC<sub>90</sub>, 4–8 μg/mL) to EGCG was found to be approximately 2- to 8-fold higher than flucytosin and fluconazole (Park et al., 2006). It has been reported that EGCG treatment inhibited the hyphal formation of the yeast form of *C. albicans*, causing growth-inhibition of the candidal cells in a murine model of disseminated candidiasis. The authors also observed a synergistic effect between amphotericin B and EGCG (Han, 2007).

Few topical antifungal compositions containing polyphenols mainly EGCG with ≥98% purity have been developed. Teavigo (high-purity EGCG) showed MIC<sub>50</sub> values of 8, 0.5, and 0.125 μg/mL against *C. albicans* NBRC 0583, *C. glabrata* NBRC 0005, and *C. parapsilosis* NBRC 0840, respectively (Sugai, Park, Han, & Hyeon, 2008). Tea polyphenols showed inhibition of biofilm formation and proteasome inactivation of *C. albicans*. Cultures treated with 1.0 μM EGCG displayed a 75% reduction of viable cells during biofilm formation. Established biofilms treated with EGCG were also reduced, by 80%, as determined through XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) colorimetric assays (Evensen & Braun, 2009). Likewise, Sitheeque et al. (2009) studied antifungal activity of black tea polyphenols (catechins and theaflavins) against *Candida* species. The polyphenols showed anti-candidal activity against all tested *Candida* species and demonstrated a MIC of 6.25 mg/mL for *C. albicans*. *C. glabrata* was found to be the most sensitive species followed by *C. parapsilosis*, *C. albicans*, *C. krusei*, and *C. tropicalis*.

## 7.2. Other fungi

The tea catechin mainly EGCG and caffeine showed antifungal activity against *Trichophyton tonsurans*, *T. violaceum*, *T. rubrum*, and *T. mentagrophytes* (Matsuura, Ogawa, Goto, & Hara, 2007). Few oral cavity care compositions containing EGCG from green tea polyphenol and ε-poly-L-lysine were tested for antifungal activity. All compositions containing EGCG had significant antifungal activity in combination with ε-poly-L-lysine (Matsumura, Okazaki, Xuan, Komasa, & Sugai, 2009). Similarly, the antifungal activity of EGCG and other antifungal agents has been investigated against thirty-five clinical isolates of dermatophytes. All isolates exhibited good susceptibility to EGCG (MIC<sub>50</sub>, 2–4 μg/mL, MIC<sub>90</sub>, 4–8 μg/mL) than those of fluconazole (MIC<sub>50</sub>, 2–16 μg/mL, MIC<sub>90</sub>, 4–32 μg/mL) and flucytosin (MIC<sub>50</sub>, MIC<sub>90</sub>> 64 μg/mL) (Park et al., 2011).

## 8. Synergism between tea polyphenols and antibiotics

Current literature indicates that combined use of antibiotics and green tea polyphenols can increase the antimicrobial activity of the former through specific synergistic interactions. Tea catechin, EGCG synergized the activity of β-lactams against MRSA because of the fact that both EGCG and β-lactams directly or indirectly attack peptidoglycan synthesis (Zhao, Hu, Okubo, Hara, & Shimamura, 2001). Direct binding of EGCG with penicillinase inhibits enzymatic activity and protects the antibacterial activity of penicillin. EGCG also enhanced the activity of tetracycline in resistant staphylococcal isolates by inhibiting its efflux from bacterial cells (Roccaro, Blanco, Giuliano, Rusciano, & Enea, 2004).

### 8.1. β-lactam antibiotics

The mechanism of synergistic antibacterial action has been hypothesized between ECG/EGCG and β-lactam antibiotics against MRSA. ECG/EGCG showed synergistic effect with β-lactams against MRSA due to down-regulation of PBP2a expression and up-regulation of LytM and LgrA expression, which resulted in increased secretion of autolytic enzymes, increased mucopeptide hydrolysis, and synergism with β-lactam antibiotics in inhibiting bacterial cell wall synthesis (Hua, Peng, Huang, Yao, & Qian, 2010). The synergic anticandidal effect of EGCG has been investigated in a murine model of disseminated candidiasis caused by *C. albicans*. EGCG treatment inhibited the hyphal formation from the yeast form of *C. albicans*, causing growth-inhibition of the candidal cells. A group of mice administered with combination of amphotericin B (0.5 mg/kg) and EGCG (2 mg/kg) had a mean survival time (MST) of 42.1 days, which was approximately 30 days longer than the group receiving amphotericin B alone-received mice groups (Han, 2007).

Combination of green tea polyphenols mainly ECG/EGCG and various antibiotics exhibited synergistic antibacterial effect against MRSA. Inhibition zones of penicillin, oxacillin, ampicillin, ceftazidime, ceftazole, minocycline, and tetracycline in combination with green tea against MRSA were larger than the single antibiotics (Hua, Peng, Zeng, et al., 2010). Recently, Cho, Oh, and Oh (2011) explored the synergistic antibacterial and proteomic effects of imipenem alone and in combination with EGCG on clinical isolates of imipenem-resistant *Klebsiella pneumoniae* (IRKP). The MIC of imipenem and EGCG for 12 clinical isolated IRKP strains ranged from 8–32 μg/mL and 300–650 μg/mL, respectively. Each of the 12 IRKP strains experienced a 4- to 64-fold reduction in the MIC of imipenem upon co-incubation with 0.25× MIC level of EGCG. Compared to imipenem alone, combination of EGCG with imipenem demonstrated enhanced bactericidal activity. Two-dimensional polyacrylamide gel electrophoresis identified eight down-regulated proteins including proteins involved in energy metabolism (glyceraldehyde-3-phosphate dehydrogenase and pyruvate kinase), biosynthesis, biosynthesis of cofactor, protein synthesis (elongation factor Tu, acetyl-coA carboxylase,

molybdenum cofactor biosynthesis protein A, and 50S ribosomal protein L9), cell envelope (outer membrane protein) and DNA metabolism (single stranded DNA binding protein), and four up-regulated proteins including molecular chaperone DnaK, chaperonin GroEL, alkyl hydroperoxide reductase, and superoxide dismutase in the IRKP strain upon exposure to 1×MIC of EGCG. Analysis of the outer membrane protein profiles of IRKP cultures treated with EGCG revealed unique changes in outer membrane proteins. These outcomes demonstrated that sub-MIC exposure of EGCG dramatically affected the expression of several important IRKP proteins.

## 8.2. Other antibiotics

Other groups of antibiotics have been studied for their synergistic interactions with green tea catechins. Lee et al. (2005) observed that a combination of catechins with fluoroquinolone antibiotic ciprofloxacin acted synergistically to alleviate chronic bacterial prostatitis in rats. Hirasawa and Takada (2004) evaluated the susceptibility of *C. albicans* to green tea catechin and the synergism of the combination of catechin and antimycotics. The authors found that the combined treatment with 3.12–12.5 mg/L EGCG and amphotericin B 0.5 mg/L (below MIC) markedly decreased the growth of amphotericin B-resistant *C. albicans*. Likewise, the combined use of 12.5 mg/L EGCG and fluconazole 10–50 mg/L (below MIC) effectively inhibited the growth of fluconazole-resistant *C. albicans* by 98.5%–99.7%. These results indicated that EGCG enhanced the antifungal effect of amphotericin B or fluconazole against antimycotic-susceptible and -resistant *C. albicans*. The authors also reported synergistic effect with concomitant use of teavigo and amphotericin B, fluconazole, flucytosine, itraconazole, micafungin, or miconazole (Sugai et al., 2008).

## 9. Conclusion

In this review, we have discussed various studies exploring antimicrobial profile of different types of tea and their polyphenols. These findings could be attributed to direct action against bacteria, viruses, and fungi, as well as suppression of microbial virulence factors. However, the detailed mechanism of antimicrobial activity of tea polyphenols still remains to be explored. Based on literature, EGCG was found the most potent tea polyphenol against bacteria, viruses, and fungi. Gram-positive bacteria were more susceptible towards EGCG compare to gram-negative strains. EGCG derivatives possessing hydrophobic alkyl side chain exhibited greater potency against parent molecule (EGCG) because of increased membrane-permeability. Therefore, structural modifications could improve its activity. In addition, there is growing evidence that EGCG acts synergistically with various conventional antibiotics against multidrug-resistant microorganisms. However, the *in vivo* efficacy of EGCG appears hindered by limited absorption, presystemic metabolism, and non-specific binding with other biological macromolecules. Recently, a successful attempt was made to improve the bioavailability by nanoemulsification of green tea extract (Kim et al., 2012). The following findings therefore suggest that future investigations should be carried out to study their *in vivo* activity, toxicity, and bioavailability of tea polyphenols (specially EGCG) to determine the actual relevance in the treatment of human and animal infections.

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