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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, 2003).

![Fig. 1. Schematic diagram of the conventional manufacture process of green, oolong, black, and pu-erh tea.](attachment:fig1.png)
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 leucocytes (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, & Ngure, 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), (−)−epicatechin (EC), (−)−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 flavonoids (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. EGC and the most abundant and most bioactive catechin of green tea, representing 50–80% of the total catechin content (Bansal, Sany, 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).
volunteers, plasma EGCG was mainly in the free (un-conjugated) EGCG and polyphenon E (a tea polyphenol preparation) by human (Pisters et al., 2001).

1.5 h, and only 4% to 8% of the ingested EGCG was excreted in urine.

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

| Flavan-3-ols                  | Concentration (mg/100 g dry tea) | Green     | Black     | Oolong    | Pu-erh    |
|------------------------------|----------------------------------|-----------|-----------|-----------|-----------|
| (-)-Epicatechin              | 811.72±21.10                    | 255.19±9.97| 248.42±16.30| 81.00±90.00|
| (-)-Epicatechin-3-gallate    | 1491.29±112.42                  | 688.27±28.07| 627.25±45.40| 40.00±54.00|
| (-)-Epigallocatechin         | 2057.98±103.55                  | 956.81±57.09| 750.80±94.10| 157.00±126.00|
| (-)-Epigallocatechin-3-gallate| 7115.98±632.06                 | 1121.92±64.31| 3412.62±360.53| 120.00±126.00|
| (+)-Catechin                 | 57.12±3.40                     | 137.82±4.48| 30.63±4.01| 0.00|
| (+)-Catechin-3-gallate       | 7.07±1.83                      | 50.83±0.00| 19.89±0.00| No Data|
| (+)-Gallocatechin            | 258.11±80.69                   | 91.73±28.84| 19.89±0.00| No Data|
| Theaflavin                   | 1.64±0.74                      | 159.20±13.03| 15.23±0.00| No Data|
| Theaflavin-3′-digallate      | 1.08±0.63                      | 170.77±19.50| No Data| No Data|
| Theaflavin-3′-gallate        | 0.44±0.26                      | 155.77±16.10| 18.62±0.00| No Data|
| Theaflavin-3′-gallate        | 0.47±0.32                      | 132.25±8.70| No Data| No Data|
| Thearubigins                 | 131.91±131.91                  | 5919.00±563.00| No Data| No Data|

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

| Apigenin                     | 12.03±2.86                     | 0.00     | 0.00     | 0.00     |
| Luteolin                     | 0.17±0.17                      | 0.00    | 0.00    | No Data  |

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

| Kaempferol                   | 147.5±4.60                     | 126.66±4.99| 62.40±19.67| 23.00±0.00|
| Myricetin                    | 104.76±7.94                   | 42.24±1.23| 61.85±26.66| 40.00±0.00|
| Quercetin                    | 223.97±9.60                   | 199.75±12.86| 108.83±40.94| 52.00±0.00|

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 EGCC, EGC, and EC were found to be 77.9±22.2, 223.4±35.2, and 124.03±7.86 nmol/mL and the elimination half-lives were 3.4±0.3, 1.7±0.4, and 2.0±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 ingested EGCC was excreted 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. EGCC 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 β-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 & Koonhof, 1989). Nongalloyl analogs like EC and EGC showed enhancement of binding to staphylococcal cells and significantly increased the capacity of EGC and EGCG.
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 EGC. 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 (Turkm, Veligyo, Sari, & Polat, 2007). Similarly, Sari, Turkmen, Polat, and Veligyo (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 S. aureus. It was found that the antibacterial activity of EGC was enhanced in the presence of ascorbic acid, and ascorbic acid was the most effective for retaining the concentration of stable EGC (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 EGC to the cell surfaces of gram-positive and gram-negative bacteria has been studied. Highly EGC-sensitive S. aureus and EGC-resistant E. coli were treated with 0.5 mg/mL EGC under pH 6.0. It was observed that attachment of EGC 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. EGC, EGC, 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. colai, 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 EGC by lipase-catalyzed transesterification. These derivatives exhibited several-fold higher activities than EGC, 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 EGC for these 17 strains was ≥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 ≥16 μg/mL. The finding suggested that the addition of long alkyl chains significantly enhanced the activity of EGC 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, Neyerstani, Khalaji, and Garhari (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, glycerophospholyl 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 anti-pathogenic properties of green tea polyphenol EGC at concentrations below the MIC (539 ± 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).
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). Suh 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* (Suh, 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, EGC, ECG, 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, EGC, 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 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 IC₅₀ 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-Atroony (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 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 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 enteridis.

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 Surloria (2008) reported that EGCG inhibited InhA, the enoyl acyl carrier protein reductase of M. tuberculosis with IC₅₀ 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
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 foodborne pathogens 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 MIC90 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 MIC50 and MIC90 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

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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.
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-epigallocatechin gallate 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
most potent (EC_{50} 4 \mu M) 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.

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_{50} values ranging from 9.27 to 36.55 \mu g/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 \mu M/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_{d} 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 (Fig. 9) was investigated by computer aided molecular docking to analyze the binding sites of peracetate ester of EGCG on...
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 μM 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 EC50 values of GTE on HBsAg, HBeAg, extracellular HBV DNA, and intracellular HBV DNA were 5.02, 5.681, 19.81, and 10.76 μg/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-tetrastearate (9), EGCG-O-tetraeicosapentaenoate (10), EGCG-O-tetracosahexaenoate (11), and EGCG-O-octabutyrate (12) (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 α-glucosidase inhibitors, suggesting their potential role as an anti-HIV agent (Zhong, Ma, & Shahidi, 2012).

| Compound | R₁ | R₂ |
|----------|----|----|
| 9        | COCH₃ | COCH₃ |
| 10       | H   | CO(CH₂)₁₆CH₃ |
| 11       | H   | CO(CH₂)₃(CH=CHCH₂)₅CH₃ |
| 12       | H   | CO(CH₂)₃(CH=CHCH₂)₅CH₃ |
| 13       | CO(CH₂)₂CH₃ | CO(CH₂)₂CH₃ |

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 antitherpetic 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 log₁₀ to 4 log₁₀ 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 log₁₀ to 4 log₁₀ at pH 5.7 and as much as 5 log₁₀ at pH 8.0 while TF3 inactivated both viruses by 4 log₁₀ to 5 log₁₀ 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 microbiocidal 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 ECGG 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 antifungal activity of some plant extracts has been studied towards yeast and yeast-like strains. Green tea extract exhibited broad antifungal activity towards Candida glabrata, Clavispora lusitaniae, Cryptococcus laurentii, Filobasidiella neoformans, Issatchenka orientals, Saccharomyces cerevisiae, and Prototheca wickerhamii strains. The compounds responsible for antifungal activity were ECG and EGCG (Turchetti et al., 2005).
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 (MIC25, 0.5–1 μg/mL and MIC50, 1–2 μg/mL) compared favorably with fluconazole. Moreover, the susceptibility of Candida krusei strains (MIC25, 2 μg/mL and MIC50, 4–8 μg/mL) to EGCG was found to be approximately 2- to 8-fold higher than fluconosin 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 MIC25 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, Silethentheque 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, & Har, 2007). Few oral cavity care compositions containing EGCG from green tea polyphenols and ε-poly-lysine were tested for antifungal activity. All compositions containing EGCG had significant antifungal activity in combination with ε-poly-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 (MIC50, 2–4 μg/mL, MIC90, 4–8 μg/mL) than those of fluconazole (MIC50, 2–16 μg/mL, MIC90, 4–32 μg/mL) and fluconosin (MIC50, MIC90 > 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 penicillin 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, Ruscian, & Enea, 2004).

8.1. β-lactam antibiotics

The mechanism of synergistic antibacterial action has been hypothesized between EGCG/EGCG and β-lactam antibiotics against MRSA. EGCG/EGCG showed synergistic effect with β-lactams against MRSA due to down-regulation of PBP2a expression and up-regulation of LmrA and LgrA expression, which resulted in increased secretion of autolytic enzymes, increased mucoprotein hydrolysis, and synergism with β-lactam antibiotics in inhibiting bacterial cell wall synthesis (Hua, Peng, Huang, Yao, & Qian, 2010). The synergic candidal 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 (Han, 2007).

Combination of green tea polyphenols mainly EGCG/EGCG and various antibiotics exhibited synergistic antibacterial effect against MRSA. Inhibition zones of penicillin, oxacillin, ampicillin, cefazidime, ceftezole, 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 (below MIC) markedly decreased the growth of amphotericin B, cell envelope (outer membrane protein) and DNA metabolism.

8.3. Other polyphenols

Bandyopadhyay, D., Chatterjee, T. K., Dasgupta, A., Lourdrujara, J., & Dastidar, S. G. (2005). In vitro and in vivo antimicrobial action of tea: the commonest beverage of Asia. Biological & Pharmaceutical Bulletin, 28, 2125–2127.

Bansal, D. D., Singla, A., & Boparai, R. (2004). Tealode in health and diseases. Natural Product Radiance, 3, 156–166.

Bansal, S., Sany, N., Mathur, P., & Choudhary, S. (2011). Pharmacological profile of green tea and its polyphenols: a review. Medicinal Chemistry Research, http://dx.doi.org/10.1007/s00044-011-9800-4.

Bruins, M. J., Cermak, R., Kiers, J. L., Van, D. M. J., Van, A. J. M. M., & Van, K. B. J. W. (2006). In vivo and in vitro effects of tea extracts on enterotoxigenic Escherichia coli-induced intestinal fluid loss in animal models. Journal of Pediatric Gastroenterology and Nutrition, 42, 459–469.

Cabrera, C., Gimenez, R., & Lopez, C. M. (2003). Determination of tea components with antioxidant activity. Journal of Agricultural and Food Chemistry, 51, 4427–4435.

Cetorjevic-Simin, D. D., Bogdanovic, G. M., Cvetkovic, D. D., & Velicanski, A. S. (2008). Antimicrobial and antimicrobial activity of traditional kombucha and Satureja montana L. Kombucha. Journal of Balkan Union of Oncology, 13, 395–401.

Chan, E. W. C., Soh, E. Y., Tie, P. P., & Law, Y. P. (2011). Antioxidant and antibacterial properties of green, black, and herbal teas of Camellia sinensis. Pharmacognosy Research, 3, 206–272.

Chen, Y. -L., Tsai, H. -L., & Peng, C. -W. (2012). EGCG debilits the persistence of EBV latency by reducing the DNA binding potency of nuclear antigen 1. Biochemical and Biophysical Research Communications, 417, 1093–1099.

Cho, Y. -S., Oh, J. -J., & Oh, K. -H. (2010). Antimicrobial activity and biofilm formation inhibition of green tea polyphenol on human teeth. Biotechnology and Bioprocess Engineering, 15, 359–364.

Cho, Y. -S., Oh, J. J., & Oh, K. H. (2011). Synergistic anti-bacterial and proteomic effects of epigallocatechin gallate on clinical isolates of imipenem-resistant Klebsiella pneumonia. Phytochemistry, 18, 941–946.

Cho, Y. S., Schiller, N. L., Kahng, H. Y., & Oh, K. H. (2007). Cellular responses and proteomic analysis of Escherichia coli exposed to green tea polyphenols. Current Microbiology, 55, 501–506.

Chow, H. H., Cai, Y., Alberts, D. S., Hakin, I., Dorr, R., Shahi, F., et al. (2001). Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenon E. Cancer Epidemiology, Biomarkers & Prevention, 10, 53–58.

Cui, Y., Oh, Y. J., Lim, J., Youn, M. E., Lee, I. P., & Huk, H. K. et al. (2012). APM study of the differential inhibitory effects of the green tea polyphenol (−)−epigallocatechin-3-gallate (ECGG) against gram-positive and gram-negative bacteria. Food Microbiology, 29, 80–87.

Daikoku, T., Horiba, K., Miyata, K., Takemoto, M., Okuda, T., Yoshida, Y., et al. (2011). Polyphenols including catechin from green tea with in vitro antiviral activity exerted anti-herpes simplex virus type 1, 2 activity but not anti-influenza virus activity in mice. Journal of Traditional Medicines, 28, 63–72.

Devine, A., Hodgson, J. M., Dick, I. M., & Prince, R. L. (2007). Tea drinking is associated with benefits on bone density in older women. The American Journal of Clinical Nutrition, 86, 1243–1247.

Evensen, N. A., & Braun, P. C. (2009). The effects of tea polyphenols on Candida albicans: Inhibition of biofilm formation and proteases inactivation. Canadian Journal of Microbiology, 55, 1039–1039.

Ferrazzano, G. F., Roberto, L., Amato, I., Cantile, T., Sangianni, G., & Ingenito, A. (2003). Antimicrobial properties of green tea extract against cariogenic microflora: an in vivo study. Journal of Medicinal Food, 14, 907–911.

Food and Agriculture Organization of the United Nations—Production FAOSTAT (Accessed on 25.07.2012).

Frei, B., & Hilgdon, J. V. (2003). Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. Journal of Nutrition, 133, 3275S–3285S.

Friedman, M. (2007). Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea and its polyphenols: a review. Medicinal Chemistry Research, 16, 1243–1247.

Furukawa, S., Kawai, H., Ohtori, H., Muki, T., & Matsumoto, M. (2005). Preventive or therapeutic combination containing glutathione and/or catechin for viral infectious diseases. In vitro and in vivo studies. PCT International Application, WO 200001261 A1 20000126.

Furuta, T., Hirooka, Y., Abe, A., Sugata, Y., Ueda, M., Murakami, K., et al. (2007). Concise synthesis of deoxyc-epigallocatechin gallate (DO-EGCG) and evaluation of its anti-inflammation activity. Bioorganic & Medicinal Chemistry Letters, 17, 3095–3098.

Gibbons, S., Moser, E., & Kaatz, G. W. (2004). Catechin gallates inhibit multidrug resistance (MDR) in Staphylococcus aureus. Planta Medica, 70, 1240–1242.
Hamilton-Miller, J. M. T. (1995). Antimicrobial properties of tea (Camellia sinensis L.). Antimicrobial Agents and Chemotherapy, 39, 2375–2377.

Hajizadeh, A., Zid, C., & Tramonti, M. (2006). How can –epigallocatechin gallate from green tea prevent HIV-1 infection? Mechanistic insights from computational modeling and the implication for rational design of anti-HIV-1 entry inhibitors. The Journal of Physical Chemistry. B, 110, 2910–2917.

Han, Y. (2007). Synergic antibacterial effect of epigallocatechin-3-O-gallate combined with amphotericin B in a murine model of disseminated candidiasis and its anticanidal mechanism. Biological & Pharmaceutical Bulletin, 30, 1693–1696.

Hara-Kudo, Y., Yamasaki, A., Sasaki, M., Okubo, T., Minai, Y., Haga, M., et al. (2005). Antibacterial action of the polyphenolic fraction from the green tea catechins. Journal of the Science of Food and Agriculture, 85, 2354–2361.

Hassani, A. S., Armiramzafari, N., Orduzadeh, N., Hamdi, K., Nazari, R., & Ghaemi, A. (2008). Volatile components of Camellia sinensis inhibit growth and biofilm formation of Staphylococcus aureus. Pakistan Journal of Medical Sciences, 24, 1336–1341.

Hatano, T., Tsgawa, M., Kusuda, M., Taniguchi, S., Yoshida, T., Shiota, S., et al. (2008). Enhancement of antibacterial effects of epigallocatechin gallate, using ascorbic acid. Phytochemistry, 69, 3111–3116.

Hayatsu, H., Inada, N., Kukutani, T., Arimoto, N., Negishi, T., Mori, K., et al. (1992). Suppression of genotoxicity of carcinogens by epigallocatechin gallate. Preventive Medicine, 21, 370–376.

He, W., Li, L. -X., Liao, G. -J., Liu, C. -L., & Chen, X. -L. (2011). Epigallocatechin gallate inhibits HBV DNA synthesis in a viral replication-inducible cell line. World Journal of Gastroenterology, 17, 1507–1514.

Hirasawa, M., & Takada, K. (2004). Multiple effects of green tea catechin on the antifungal activity of anticycotics against Candida albicans. Journal of Antimicrobial Chemotherapy, 53, S27–S29.

Hirasawa, M., Takada, K., & Otake, S. (2006). Inhibition of acid production in dental plaque bacteria by green tea catechins. Caries Research, 40, 265–270.

Hisano, M., Yamaguchi, K., Inoue, Y., Iikeda, Y., Iijima, M., Adachi, M., et al. (2003). Inhibition effect of catechin against the superantigen staphylococcal enterotoxin B (SEB). Archives of Dermatological Research, 295, 181–189.

http://www.statisticbrain.com/tea-drinking-statistics/ (accessed on 30.07.2012).

Huang, S. -H., Tang, Y. -Z., Zhou, X. -M., Xie, G., Kurihara, H., He, Z. -H., et al. (2010). Antimicrobial activity of epigallocatechin gallate against heterotrophic bacteria in aseptic ground beef, chicken, and pork. Trends in Food Science & Technology, 30, 322–331.

Hu, Y., Jia, J. -Q., Qiao, G. -C., & Ca, Z. (2010). Antimicrobial activity of pu-erh tea extract in vitro and its effects on the preservation of cooked mutton. Journal of Food Protection, 73, 170–175.

Hua, D., Peng, Q., Huang, Y., Yao, F., & Qian, Y. (2010). The mechanism of synergistic antibacterial action between ECC/EGCG and β-lactam antibiotics against MRSA. Zhongguo Canran Yu Hualiao Zazhi, 30, 123–126.

Hua, D., Peng, Q., Zeng, X., Yao, F., & Qian, Y. (2010). Antibacterial activity of green tea and its extracts against MRSA. Zhongguo Kangshengsu Zazhi, 35, 218–226.

Huang, S. -H., Tang, Y. -Z., Zhou, X. -M., Xie, G., Kurihara, H., He, Z. -H., et al. (2010). Study on anti-influenza virus effect of tea polyphenols in vitro and in vivo. Chuyue Xuebao, 30, 302–308.

Ikeda, I., Imae, S., Sasaki, E., Nakayama, M., Nagao, H., Takeo, T., et al. (1992). Tea catechins decrease micellar solubility and intestinal absorption of cholesterol in rats. Biochimica et Biophysica Acta, 1127, 141–146.

Iswa, C. E., Wen, G. Y., Xu, W., Jia, J. H., Rohan, L., Corbo, C., et al. (2008). Epigallocatechin gallate inactivates clinical isolates of herpes simplex virus. Antimicrobial Agents and Chemotherapy, 52, 962–970.

Isaka, C. E., Xu, W., Merz, G., Hillier, S., Rohan, L., & Wen, G. Y. (2011). Dilagate dimers of –epigallocatechin gallate inactivate herpes simplex viruses. Antimicrobial Agents and Chemotherapy, 55, 5364–5365.

Jang, F., Chen, W., Wu, Y. -K., Liu, S. -Y., Han, W., et al. (2010). The evaluation of catechins that contain a galloyl moiety as potential HIV-1 integrase inhibitors. Antiviral Research, 77, 347–356.

Jin, E. -J., Wu, Y., & Tu, Y. (2011). Study on antibacterial effect of theaflavins. Zhongguo Shpin Xuebao, 11, 108–112.

Juneja, V. K., Bari, M. L., Inasus, Y., Kawamoto, S., & Friedman, M. (2007). Control of Clostridium perfringens spores by green tea leaf extracts during cooking of cooled cooking ground beef, chicken, and pork. Journal of Food Protection, 70, 1429–1433.

Kalhatu, K., Mori, S., Matsumura, H., Daidoji, T., Wakamaki, C., Kurata, H., et al. (2009). Broad and potent anti-influenza virus spectrum of epigallocatechin-3-O-gallate-monogalactosyltransferase. Journal of Molecular and Genetic Medicine, 3, 195–197.

Kariot, S. M., Wachira, F. N., Wanyoko, J. K., & Ngure, R. M. (2007). Antioxidant capacity of different types of tea products. African Journal of Biotechnology, 6, 2287–2296.

Kawahara, M., Tsuo, N. H., Kitayama, J., Okaji, Y., Yazawa, K., Askage, M., et al. (2003). Epigallocatechin gallate, the main component of tea polyphenols, can bind to CD4 and interfere with gp120 binding. The Journal of Allergy and Clinical Immunology, 112, 951–957.

Kim, Y. J., Jeong, S. -J., Kim, J. H., Kim, Y., -R., Ji, H. G., & Lee, S. -J. (2012). Nonmemulsified green tea extract shows improved hypcholesterolemic effects in C57BL/6j mice. The Journal of Nutritional Biochemistry, 23, 186–191.

Kim, J. -S., & Kim, Y. (2007). The inhibitory effect of natural bioactives on the growth of pathogenic bacteria. International Journal of Food Research and Practice, 1, 273–278.

Kiran, S., Ratho, R. K., Sharma, P., Harjai, K., Capalash, N., & Tiwari, R. P. (2010). Effect of black tea (Camellia sinensis) on virulence traits of clinical isolates of Shigella dysenteriae and Escherichia coli EPEC P2 1265 strain. European Food Research and Technology, 231, 679–700.

Klaus, S., Pultz, S., Thone-Reinecke, C., & Wolfram, S. (2005). Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. International Journal of Obesity, 29, 615–623.

Klugman, K. P., & Koontz, J. (1989). Worldwide increase in pneumococcal antibiotic resistance. Lancet, 2, 444.
Yang, C. S., Chen, L., & Lee, M. J. (1998). Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer Epidemiology, Biomarkers & Prevention*, 7, 351–354.

Yang, J., Li, R.-M., Mao, Q.-C., Chen, Z.-P., Jiang, S.-B., Jiang, Z.-H., et al. (2010). HIV fusion-inhibiting activity of peracetate ester of (-)-epigallocatechin gallate and the mechanism. *Zhongguo Xinyao Zazhi*, 19, 1967–1972.

Yang, J., Li, L., Tan, S., Jin, H., Qiu, J., Mao, Q., et al. (2012). A natural theaflavins preparation inhibits HIV-1 infection by targeting the entry step: Potential applications for preventing HIV-1 infection. *Fitoterapia*, 83, 348–355.

Yang, L., Liu, Y., Sternberg, C., & Molin, S. (2010). Evaluation of enoyl-acyl carrier protein reductase inhibitors as *Pseudomonas aeruginosa* quorum-quenching reagents. *Molecules*, 15, 780–792.

Yang, Z. & Shi, L. (2007). Application of plant extract catechins in preparing antiviral drugs. *Faming Zhuanli Shenqing*, CN 1994294 A 20070711.

Yi, S., Li, J., Zhu, J., Lin, Yi, Fu, L., Chen, W., et al. (2011). Effect of tea polyphenols on microbiological and biochemical quality of Collichthys fish ball. *Journal of the Science of Food and Agriculture*, 91, 1591–1597.

Yoda, Y., Hu, Z.-Q., Zhao, W.-H., & Shimamura, T. (2004). Different susceptibilities of *Staphylococcus* and gram-negative rods to epigallocatechin gallate. *Journal of Infection and Chemotherapy*, 10, 55–58.

Zhao, W.-H., Hu, Z.-Q., Okubo, S., Hara, Y., & Shimamura, T. (2001). Mechanism of synergy between epigallocatechin gallate and β-lactams against methicillin-resistant *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, 45, 1737–1742.

Zhao, Y., Wang, H., Zhao, X.-R., Luo, F.-J., Tang, M., & Cao, Y. (2004). Epigallocatechin-3-gallate interferes with EBV-encoding AP-1 signal transduction pathway. *Zonghua Zhong Liu Za Zhi*, 26, 393–397.

Zhong, Y., Ma, C.-M., & Shahidi, F. (2012). Antioxidant and antiviral activities of lipophilic epigallocatechin gallate (EGCG) derivatives. *Journal of Functional Foods*, 4, 87–93.

Zhong, Y., Wang, H., Zhang, L.-X., Zhang, B., Wang, F., Liang, Z.-H., & Niu, T.-G. (2008). Isolation and characterization of ZH14 with antiviral activity against tobacco mosaic virus. *Canadian Journal of Microbiology*, 54, 441–449.

Zu, M., Yang, F., Zhou, W., Liu, A., Du, G., & Zheng, L. (2012). In vitro anti-influenza virus and anti-inflammatory activities of theaflavin derivatives. *Antiviral Research*, 94, 217–224.