**Mahmood et al., Afr J Tradit Complement Altern Med. (2016) 13(2):176-184**
http://dx.doi.org/10.4314/ajtcam.v13i2.21

# ANTIVIRAL EFFECTS OF GREEN TEA (*CAMELLIA SINENSIS*) AGAINST PATHOGENIC VIRUSES IN HUMAN AND ANIMALS (A MINI-REVIEW)

**Muhammad Shahid Mahmood[1], José L. Mártinez[2], Azhar Aslam[1], Azhar Rafique[3], Raúl Vinet[4], Claudio Laurido[5], Iftikhar Hussain[1], Rao Zahid Abbas[6], Ahrar Khan[7] & Shahid Ali[1]**

[1]Institute of Microbiology, University of Agriculture, Faisalabad, 38040-Pakistan, [2]Vicerrectoria de Investigación, Desarrollo e Innovación, Universidad de Santiago de Chile - Santiago, Chile, [3]Department of Zoology, Wildlife and Fisheries GC University Faisalabad, 38040-Pakistan, [4]Facultad de Farmacia, Universidad de Valparaíso & Centro Regional de Estudios en Alimentos y Salud (CREAS), Chile, [5]Facultad de Química y Biología, Universidad de Santiago de Chile, [6]Department of Pathobiology, University College of Veterinary and Animal Sciences, The Islamia University of Bahawalpur, Pakistan, [6]Department of Pathobiology, University College of Veterinary and Animal Sciences, The Islamia University of Bahawalpur, [7]Department of Pathology, University of Agriculture, Faisalabad, 38040-Pakistan

**Corresponding author: Muhammad Shahid Mahmood: shahiduaf@gmail.com, José L. Martinez: joseluis.martinez@usach.cl**

## Abstract

**Background**: Tea is the second most addictive worldwide after formulations containing caffeine in carbonated beverage. Green tea is made from leaves of the *Camellia sinensis* plant. In the repertoire of traditional Chinese medicine, green tea beverages have played a fundamental role associated with their culture. It has been suggested that green tea has a number of positive health benefits that are reviewed and discussed in this minireview.
**Materials and Methods**: We performed a search using the key words "green tea" AND "antiviral" covering the last 10 years. The consulted data based were PubMed, ISI Web of Knowledge, Scopus, Reuters and Thomson.
**Results**: The results of the searching greatly support that green tea presents both antibacterial and antiviral effects. The beneficial effects of green tea are mainly attributed to the presence of a type of polyphenols known as catechins and formed by several isomers including (-) - epigallocatechin gallate (EGCG), (-) - epigallocatechin, (-) - epicatechin gallate, (-) -epicatechin, and (+) - catechin. The catechins in green tea have a wide range of antiviral activity against a variety of viruses that act by interfering with its replication cycle.
**Conclusion:** A detailed information on the antiviral activity of green tea in a number of different viruses show a promising future as a popular drink and also as a potential therapeutic agent.
**Key words:** antiviral activity, *Camellia sinensis*, catechins, green tea, tea, virus

## Introduction

Viral infections are among the most common types of infections encountered by mankind. Treating viral infections is limited by the availability of drugs. Drugs approved so far have limited applications due to comparatively inferior cure rates, their side effects and the rapid accumulation of drug resistant mutants (Piret and Boivin, 2011). The insufficient therapeutic applications of these agents including interferon and nucleotide analogs have strengthened the search for alternative antiviral agents for the treatment of viral infections (Xu et al. 2008; Jin, 2013; Hameed and Ahmed, 2014).

Undoubtedly, tea is the most frequently consumed beverage on a global basis, second only to water (Steinmann et al. 2013). The customary consumption has long been attributed to various health benefits, including chemo-preventive efficacy and its use has been cited as early as in China in 3000 BC or even earlier (Suzuki et al. 2012). *Camellia sinensis*, used in traditional Chinese medicine, is considered to have beneficial properties for human and animal health including cardioprotective, anti-carcinogenetic and anti-infective effects (Lee et al. 2002).

The green tea is a product of the plant *Camellia sinensis* that is dried and steamed to avoid fermentation (Chacko et al. 2010). The flavonoids present in the green tea have two aromatic rings, A and B with hydroxyl groups (Hara, 2011). Most of the health benefits of green tea can be attributed to its polyphenols that comprise 25 to 35% in composition. These polyphenolic compounds are also known as catechins under the group of flavones, which are a subtype of flavonoids (Meltzer et al. 2009). The major catechin in green tea is (-)-epigallocatechin gallate (EGCG) (Figure 1), which make up about 59% of the total catechins of green tea leaves. Other catechins in green tea are (-)-epigallocatechin (EGC) (19%) (Figure 2), (-)-epicatechin-gallate (ECG) (13.6%) (Figure 3), and (-)-epicatechin (EC) (6.4%) (Figure 4) (McKay and Blumberg, 2002; Tran, 2013; Jin, 2013) and (+)-catechin) (Figure 5).

Green tea polyphenols are best known for their diverse biological and pharmacological activities, including anti-oxidative (Song et al. 2005), anti-proliferative (Yang et al. 2002; Conde et al. 2014; Gao et al. 2015) anti-inflammatory, antibacterial (Anita et al. 2015), antifungal (Yiannakopoulou, 2012), and antiviral activities (Araghizadeh et al. 2013). Evidence shows that green tea is also

http://dx.doi.org/10.4314/ajtcam.v13i2.21
effective against hypercholesterolemia and hyperglycemia (Yousaf et al. 2014). In this sense, *in vitro* preparations like isolated aorta have made an invaluable contribution to phytopharmacology (Vinet et al. 2012) with important results (Vinet et al. 2014; Fuentes et al. 2015).

Green tea polyphenols harbors a wide spectrum of activities against different ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses (Lin et al. 2013). The antiviral property of polyphenols is due to their antioxidants nature, inhibition of the enzymes involved in viral replication and to their cell membrane disruption. The green tea polyphenols also avert viral penetration and binding to cells triggering the self-defense of the host cell influencing the activity of a variety of signal transduction pathways (Friedman, 2007). EGCG can inhibit the invasion of human umbilical vein endothelial cells (Yamakawa et al. 2004), prevents tumor blood vessel growth (Pfeffer et al. 2003), protects human retina cells, ocular neovascularization and vascular permeability (Lee et al. 2014), inhibits fibrillogenesis of chicken cystatin (Wang et al. 2015) and offers protection against mutagenesis (Lee et al. 2003).

The foremost objective of this minireview is to amalgamate, summarize and elucidate the widely divergent information available on green tea and its derivative compounds, and their effects on various pathogenic viruses in human and animals.

## Antiviral Effects of Green Tea

### Adenovirus

Adenoviruses (Ads) are involved in a variety of human and animal pathologies (Whickam, 2000). Intermittent shedding of Ads establishes a persistent asymptomatic infection (Garnett et al. 2002). Adenoviruses infect the lining of the eyes and intestine causing conjunctivitis and gastroenteritis respectively. They also colonize on mucous membranes of respiratory and urinary tracts and cause other symptoms (Friedman, 2007). Adenoviruses proteases, involved in cancer metastasis, are inhibited by green tea catechins (Weber et al. 2003). Green tea and, in particular, EGCG inhibit one or more late steps of virus infection against adenovirus and are efficiently taken up by the cells (Williams et al. 2000). This sensitivity may be mediated by the inhibition of some cellular processes that depends on viral infection. Antiviral properties of EGCG have been demonstrated at various levels, including direct inactivation of the virus particle, inhibition of the protease adenain and inhibition of intracellular growth *in vitro* (Weber et al. 2003). Aslam et al. (2015), report antiviral activity of green tea and its isolated catechins against the fowl adenovirus type-4 through *in vitro* in cell culture and *in vivo* in broiler chickens against IBH-HPS virus challenge.

### Hepatitis B Virus

It is estimated that about 40% of the worldwide human population suffers from hepatitis B virus (HBV) (Shepard et al. 2006). In Asia, 5% of the population is chronically infected with HBV and infection is considered endemic (Lee, 1997). Catechins have shown to be active in several models of inflammatory liver injury and often used in the treatment of human liver diseases such as hepatitis C and alcoholic cirrhosis (Gloro et al. 2005). Green tea extract (GTE) reveals a prevailing inhibitory effect on the expression of hepatitis B surface antigen (HBs Ag) and hepatitis B e antigen (HBe Ag). Evidence has shown that HBe Ag plays a role in viral persistence. It has been suggested that HBe Ag endorse HBV chronicity by acting as an immune-regulatory protein (Chen et al. 2005). Recent results demonstrated that GTE had an inhibitory effect on intestinal α-glycosidases that is important for processing glycoproteins and glycolipids in viruses (Zhong et al. 2006). EGCG significantly inhibits the replicative intermediates DNA (RI DNA) synthesis, which reduces the production of covalent closed circular DNA (He et al. 2011). Pang et al. (2014) demonstrated that EGCG has a strong anti-HBV activity through decreasing the secretion of HBs Ag and HBe Ag *in vitro*. Huang et al. (2014) suggested that new strategies could be used in combination with other antiviral drugs to reduce the emergence of resistant viruses.

### Hepatitis C Virus

Hepatitis C virus (HCV) infection is a serious health hazard globally. More than 160 million people worldwide are chronically infected with HCV (Lavanchy, 2011). Chronic hepatitis caused by HCV infection leads to the higher occurrence of progressive liver diseases, including hepatocellular carcinoma, cirrhosis and fibrosis (Lin et al. 2013). However, effective therapies are highly expensive and hence these out of reach of most of the patients. These are further burdened with side effects such as anemia appearance and resistant variant, which limit the effectiveness of these remedies (Salloum and Tai, 2010).

EGCG has been shown to inhibit HCV entry into target cells and prevents cell-to-cell spread between adjacent cells (Ciesek et al. 2011). In a cell-free system, EGCG also inhibits the major HCV NS3/4A serine protease and NS5B polymerase (Roh and Jo, 2011). It was reported that EGCG inhibits the entry of HCV pseudo and cell culture-derived particles independent of HCV genotype (Calland et al. 2012; Colpitts and Schang, 2014). EGCG also inhibits the replication cycle (Chen et al. 2012). It has been demonstrated that EGCG cleared the HCV at 50 µM after three passages in human cells (Calland et al. 2012). In general, green tea gallate catechins are inhibitors of hepatitis C virus (Fukazawa et al. 2012).

### Influenza Virus

Influenza is one of the most common and severe viral diseases, causing varying degrees of systemic symptoms, such as mild fatigue, respiratory failure and even death (Wen et al. 2012). Anti-influenza drugs, $M_2$ channel blockers and sialidase inhibitors (Deyde et al. 2009), are effective if administration follows immediately after infection (Carr et al. 2002). Therefore, there is a need to develop new antiviral agents for therapeutic uses (Sahaa et al. 2010).

The survival rate of experimental animals challenged with influenza virus was significantly enhanced when they were previously treated with EGCG at 40 mg/kg body weight (Liu et al. 2013). In Madin Durby Canine Kidney (MDCK) cells, EGCG at 20 nmol/l suppressed the level of reactive oxygen following influenza A infection (Ling et al. 2012). The green tea extract inhibited the replication of influenza viruses by preventing acidification of intracellular compartment, such as lysosomes and endosomes (Lee et al.

http://dx.doi.org/10.4314/ajtcam.v13i2.21
2012; Matsumoto et al. 2012). Hydrolysable tannins obtained from the tea plant inhibited the influenza virus in the early stage of infection (Sahaa et al. 2010). It has been demonstrated that consumption of catechins for 5 months produced significant inhibitory effects on influenza virus infection, and they were well tolerated (Matsumoto *et al*. 2012). Yang et al. (2014) compared *in vitro* antiviral activity of various components of green tea in influenza virus A and B. Green tea has been reported to inhibit influenza A virus replication, effect mediated by the binding of catechins to the active pocket in the endonuclease domain of the viral RNA-dependent RNA polymerase. Since this enzyme is highly conserved among influenza A virus variants, the catechins extract could become an anti endonuclease herbal drug (Bustamante and Morales, 2012).

**Human Immunodeficiency Virus (HIV)**

HIV-1 is the etiological agent of acquired immunodeficiency syndrome (AIDS) belonging to the Lentivirus group of the family *Retroviridae*. HIV infects $CD4^+$ T-lymphocytes, resulting in its depletion and leading to the development of immunodeficiency. EGCG acts as an allosteric reverse transcriptase inhibitor of HIV-1 infection decreasing the p24 antigen concentration (Li et al. 2011). EGCG inhibits HIV-1 by directly interacting with the D-1 domain of CD4 and the pocket that binds gp120 (Williamson et al. 2006). In the presence of EGCG, viral transcription is affected by decreasing the expression of the messenger ribonucleic acid (mRNA) (Yamaguchi et al. 2002). EGCG has also shown the ability to inhibit the HIV-1 integrase protein (Jiang et al. 2010). HIV infection leads to severe complications affecting the central nervous system (McArthur et al. 2010). EGCG and EC are candidates for the treatment of neurological complications of HIV infection due to their simple structure and ability to penetrate the blood-brain barrier (Nath et al. 2012).

**Bovine Coronavirus**

Bovine coronavirus (BCV) is the causal pathogen for diarrhea in cattle, which often result in remarkable economic losses (Traven et al. 2001). For the treatment of BCV infection in farm animals, green tea polyphenols have a promising future. The antiviral activity of EGCG molecules depends on the interaction involving S1 proteins of BCV. EGCG inhibits BCV more efficiently in the bovine intestinal tract, where the temperature of approximately 37 ºC is appropriate for the antiviral efficacy of EGCG against BCV.

**Epstein–Barr virus**

Epstein-Barr virus (EBV) is a human herpesvirus that selectively binds to and infects human B-lymphocytes (B-cells), causing mononucleosis (Bravender, 2010). EGCG controls the expression of EBV lytic protein including EA-D, Zta and Rta (Chang et al. 2003). EGCG directly inhibits the transcription of EBV immediate early gene before EBV-encodes polymerase and causes the arrest of EBV lytic cascade. EGCG arrests epidermal growth factor stimulated at the mid G1 phase of breast epithelial cells and prevents cells from entering the S phase. EBV immediate-early gene may be regulated by EGCG via cell cycle control (Liberto and Cobrinik, 2005). EGCG decreases the phosphorylation and commencement of extracellular signal-regulated kinase 1/2 (ERK1/2), which efficiently restrain the constitutive EBV infection at the gene transcription level, and DNA and protein level (Liu et al. 2013). EGCG inhibits the EBV infection through the EBV induced B-cell outgrowth and B-lymphocyte transformation (Choi et al. 2009).

**Enterovirus 71**

Enterovirus 71 (EV71) belongs to the family *Picornaviridae*, having non-enveloped RNA genome causing outbreaks occasionally worldwide (Racaniello, 2001). EGCG and ECG inhibit EV-71 replication and formation of infectious progeny virions. The effect of EGCG on EV71 infection is produced by reducing the oxidative stress associated with the infection and by inhibiting the enhanced EV-71 replications in G6PD-deficient cells (Ho et al. 2009). It has been proposed that the potent antioxidant activity of EGCG and ECG against infections caused by EV 71 is due to the presence of the gallate group and the trihydroxy-B ring having free radical scavenging activity. Accordingly, a positive correlation between the antioxidant effects of catechins and their antiviral activities has been suggested (Ho et al. 2009).

**Herpes Simplex Virus**

Herpes simplex virus (HSV) is one of the most widespread human infectious diseases causing genital infection with HSV-2 or oral infection with HSV-1 (Oliveira et al. 2013). EGCG operates its antiviral activity through oxidation and dimerization by oxidative reactions, which disrupt the HSV envelope (Sang et al. 2005). EGCG is stable at vaginal pH and shows a potential as a candidate for use as a topical microbicide to trim down the transmission of HSV. EGCG also potentially interrupt the synergistic association between the HSV and HIV infection with direct effects on the virion itself (Isaacs et al. 2008). This interruption results in a reduction of the spread of HSV *in vivo* (Isaacs et al. 2011). Prodelphinidin B-2 3′-O-gallate obscured the HSV-2 reproduction in Vero cell without considerable adverse effects on the growth and cell viability (Cheng et al. 2002). EGCG modified with palmitate enhanced the activity of EGCG as a promising antiviral agent against HSV-1 infection (Oliveira et al. 2013) and lipophilic EGCG effective treatment against HSV as a topical application (Zhao et al. 2012). Also, dimmers of EGCG inactivate HSV-1 and HSV-2 more successfully between pH 4.0 and 6.6 than the monomer of EGCG. This mechanism may be more effective in reducing the spread of HSV *in vivo* because predilection sites of HSV are skin and vagina where pH is considerably low (Isaacs et al. 2011).

http://dx.doi.org/10.4314/ajtcam.v13i2.21

**Feline Calicivirus (FVS) A Surrogate of Norovirus and Other Virus Infections**

Norovirus fits into the family of Caliciviridae, which is the basis for the outbreak of gastroenteritis in human and is considered a major cause of food-borne pathogens worldwide and associated with severe childhood diarrhea (Payne et al. 2013). The causes is typically mild self-limiting and associated with symptoms lasting 24-48 h. Chronic persistent infections can be fatal in children (Payne et al. 2013). Twenty-one million cases occur annually with 800 deaths (Hall et al. 2012). Hydrolysable tannin of green tea elicits the reduction of four or more $log^{10}$ in norovirus load (Ueda et al. 2013). Catechin also shows activity against the FCV, which is the surrogate of norovirus. Among catechins tested, EGCG showed the most effective antiviral activity with a half-effective concentration ($EC_{50}$) of 12 mg/ml with relatively low cytotoxicity with a half-cytotoxic concentration ($CC_{50}$) of 320 mg/ml (Oh et al. 2013). Catechin ointments prepared from GTE have been shown to inhibit the human papillomavirus (HPV) at concentrations from 160 to 360 µM (Tyring, 2012). Human T-cell leukemia caused by human T-cell lymphotropic virus type-1 (HTLV-1) may also be treated with EGCG as well as green tea extract as a whole (Araya et al. 2011). Green tea is reported to reduce the HTLV-1 provirus in peripheral blood lymphocytes in the HTLV-1 carrier (Sonoda et al. 2004), that downregulates the protein expression of an anti-apoptotic member (Harakeh et al. 2008). Recent studies have shown that (-)-epigallocatechin gallate (Figure 1) is a major compound to norovirus (Ryu et al. 2015).

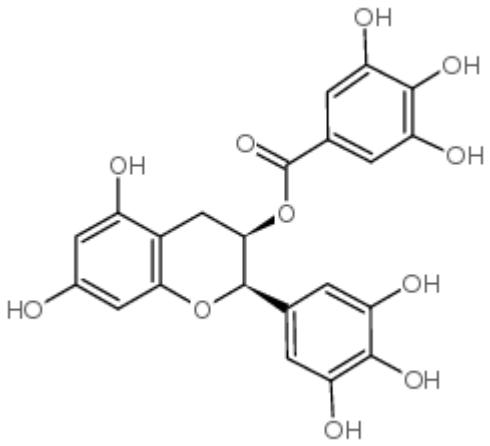


**Figure 1**

**Chikungunya Virus Infection**

CHIKV is a mosquito-transmitted alphavirus that causes chikungunya fever in humans. The disease is characterized by a sudden onset of fever, headache, malaise, arthralgia or arthritis, myalgia, and lower back pain (Suhrbier et al. 2012; Weaver et al. 2012). After the acute phase, polyarthritis can be recurrent and may persist for several years after infection, which is a serious public health problem. *Aedes albopictus*, the mosquito, inhabits temperate regions, including Europe and USA (Tsetsarkin et al. 2007), reported in Caribbean where they have been introduced (Bajak, 2014; Kuehn, 2014). There is no vaccine or medicine for this disease. Recent studies show that the main components of green tea, catechin and EGCG inhibit virus CHIKV infection (Weber et al. 2015).

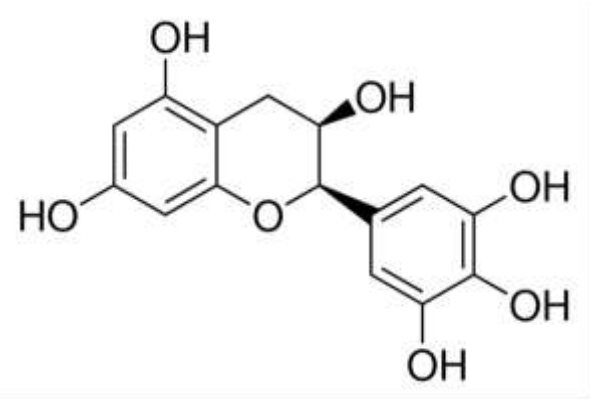


**Figure 2.**

http://dx.doi.org/10.4314/ajtcam.v13i2.21

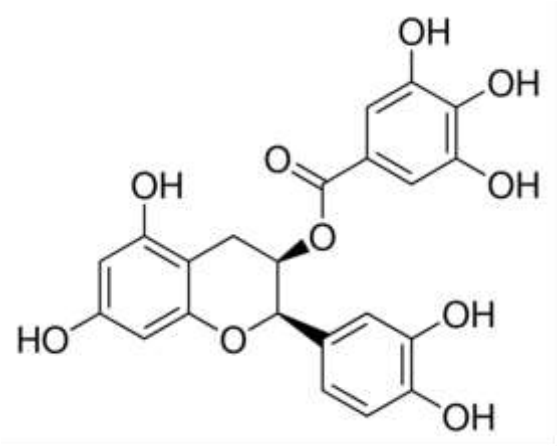


**Figure 3**

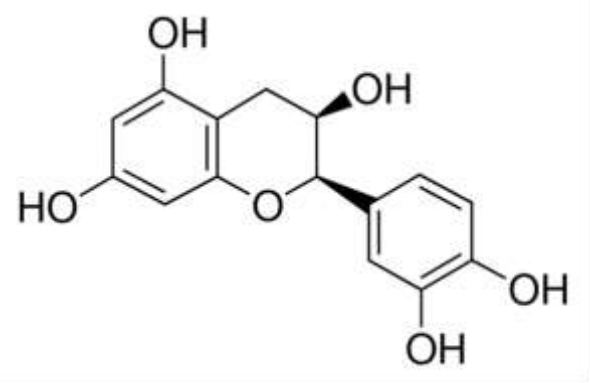


**Figure 4**

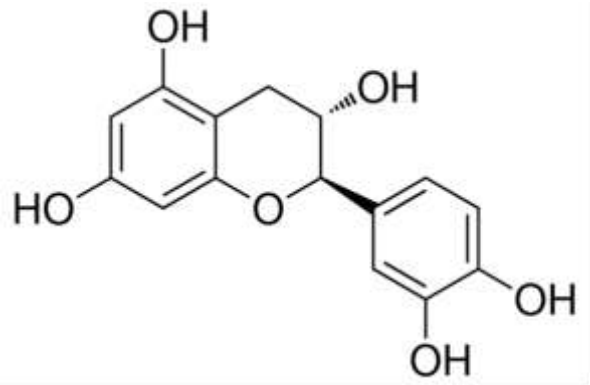


**Figure 5**

**Conclusions and Future Prospects**

The development of resistant mutants of viruses limits the use of presently accepted drugs and constantly challenges us to develop new drugs and formulations for the control and proliferation of viruses. Natural products and derivatives afford an outstanding resource for developing new and effective antiviral compounds to treat a variety of viral diseases, particularly in developing countries. The medicinal effects of polyphenolic compounds present in green tea have a history dating back approximately 5000 years. Green tea provides a dietary source of biologically active compounds that have shown efficacy in prevention of a number of viral diseases in humans and animals. These polyphenolic compounds, particularly catechins inhibit viral infections by inhibiting viral entry, reverse

transcriptase of HIV, HCV protease and several other associated enzymes. However, most of these findings regarding antiviral effects have been based on primarily *in vitro* chemical assays. There is a need to elucidate further and develop animal model systems to articulate precisely the pathways and mechanisms involved in the antiviral effects of green tea and its ingredients, and its precise therapeutic effects *in vivo*. Recently, EGCG were investigated using the rotavirus as a model of enteric virus system in cell culture without cytotoxicity showing not adverse effects at the concentration assayed (Lipson et al. 2015).

## References

1. Anita, P., Sivasamy, S., Kumar, P.D.M., Balan, I.N. and Ethiraj, S. (2015). *In vitro* antibacterial activity of Camellia sinensis extract against cariogenic microorganisms. J. Basic Clin. Pharm. **6:** 35 - 39.
2. Araghizadeh, A., Kohanteb, J. and Fani, M.M. (2012). Inhibitory Activity of Green Tea (*Camellia sinensis)* Extract on some clinically isolated cariogenic and periodontopathic bacteria. Med. Princ. Pract. **22:** 515 - 529.
3. Araya, N., Takashi, K., Sato, T., Nakamura, T., Sawa, C., Hasegaw, D., Ando, H., Aratani, S., Yagishita, N., Fujji, R., Oka, H., Nishioka, K., Nakajima, T., Mori, N. and Yamano, Y. (2011). Fucoidan therapy decreases the proviral load in patients human T-lymphotropic virus type-1-associated neurological disease. Antivir. Ther. **16:** 89 - 98.
4. Aslam, A., Mahmood, M.S., Hussain, H. and Khan, N. (2014). Evaluation of antiviral effect of epigallocatechin gallate, epigallotechin, epicatechin gallate and green tea extract against fowl adenovirus-4. Pakistan J. Zool. **46:** 1283 - 1294.
5. Bajak, A. (2014). US assesses virus of the Caribbean. Nature **512:** 124 - 125.
6. Bravender, T. (2010). Epstein–Barr virus, cytomegalovirus, and infectious mononucleosis. Adolesc. Med. State Art. Rev. **21:** 251 - 264.
7. Bustamante, S. and Morales M. (2012). Te verde, fitomedicamento contra la influenza A: rol de las catequinas. Bol. Latinoam. Caribe Plant Med. Aromat. **11:** 106 - 110.
8. Calland, N., Albecka, A., Belouzard, S., Wychowski, C., Duverlie, G., Descamps, V., Hober, D., Dubuisson, J., Rouille, Y. and Seron, K. (2012). (-)-Epigallocatechin-3-gallate is a new inhibitor of hepatitis C virus entry. Hepatol. **55:** 720 - 729.
9. Carr, J., Ives, J., Kelly, L., Lambkin, R., Oxford, J., Mendel, D., Tai, L. and Roberts, N. (2002). Influenza virus carrying neuraminidase with reduced sensitivity to oseltamivir carboxylate has altered properties in vitro and is compromised for infectivity and replicative ability in vivo. Antivir. Res. **54:** 79 - 88.
10. Chacko, S.M., Thambi, P.T., Kuttan, R. and Nishigaki, I. (2010). Beneficial effects of green tea: A literature review. Chinese Med. **5:** 3 - 13.
11. Chang, L.K., Wei, T.T., Chiu, Y.F., Tung, C.P., Chuang, J.Y., Hung, S.K., Li, C. and Liu, S.T. (2003). Inhibition of Epstein–Barr virus lytic cycle by (−)-epigallocatechin gallate. Biochem. Biophys. Res. Commun. **301:** 1062 - 1068.
12. Chen, M., Sallberg, M., Hughes, J., Jones, J., Guidotti, L.G., Chisari, F.V., Billaud, J.N. and Milich, D.R. (2005). Immune tolerance split between hepatitis B virus precore and core proteins. J. Virol. **79:** 3016 - 3027.
13. Chen, C., Qiu, H., Gong, J., Liu, Q., Xiao, H., Chen, X.W., Sun, B.L. and Yang, R.G. (2012). (-)-epigallocatechin-3-gallate inhibits the replication cycle of hepatitis C virus. Arch. Virol. **157:** 1301 - 1312.
14. Cheng, H., Lin, C. and Lin, T. (2002). Antiviral properties of prodelphinidin B-2 3′-*O*-gallate from green tea leaf. Antiviral. Chem. Chemother. **13:** 223 - 229.
15. Choi, K.C., Jung, M.G., Lee, J.C., Kwon, S.H., Kang, H.B., Kim, M.J., Cha, J.K., Kim, Y.J., Jun, W.J., Lee, J.M. and Yoon, H.G. (2009). Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. Cancer Res. **69:** 583 - 592.
16. Ciesek, S., Hahn, T.V., Colpitts, C.C., Schang, L.M., Friesland, M., Steinmann, J., Manns, M.P., Ott, M., Wedemeyer, H., Meuleman, P., Pietschmann, T. and Steinmann, E. (2011). The Green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. Hepatol. **54:** 1947 - 1955.
17. Colpitts, C.C. and Schang, L.M. (2014). A small molecule inhibits virion attachment to heparin sulfate- or sialic acid-containing glycans. J. Virol. **88:** 7806 - 7817.
18. Conde, V.R., Alves, M.G., Oliveira, P.F. and Silva, B.M. (2015). Tea (Camellia sinensis (L.): a putative anticancer agent in bladder carcinoma?. Anticancer Agents Med. Chem. **15:** 26 - 36.
19. Deyde, V.M., Nguyen, T., Bright, R.A., Balish, A., Shu, B., Lindstrom, S., Klimov, A.I. and Gubareva, L.V. (2009). Detection of molecular markers of antiviral resistance in influenza A (H5N1) viruses using a pyrosequencing method. Antimicrob. Agents Chemother. **53:** 1039 - 1047.
20. Friedman, M. (2007). Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. Mol. Nutr. Food Res. **51:** 116 - 134.
21. Fuentes, O., Cespedes, C., Sepulveda, R. (2015). Aristotelia chilensis, rutin and quercetin amielorates acute vascular endothelial dysfunction in rat thoracic aorta exposed to oxidative stress. Bol. Latinoam. Caribe Plant. Med. Aromat. **14**: 11 - 21.
22. Fukazawa, H., Suzuki, T., Wakita, T. and Murakami. Y. (2012). A cell-based, microplate colorimetric screen identifies 7,8-benzoflavone and green tea gallate catechin as inhibitors of the hepatitis C virus. Biol. Pharm. Bull. **35:** 1320 - 1327.
23. Gao, F., Li, M., Liu, W.B., Zhou, Z.S., Zhang, R., Li, J.L. and Zhou, K.G. (2015). Epigallocatechin gallate inhibits human tongue carcinoma cells via HK2-mediated glycolysis. Oncol. Rep. doi:10.3892/or.2015.3727.
24. Garnett, C.T., Erdman, D., Xu, W. and Gooding, L.R. (2002). Prevalence and quantitation of species C adenovirus DNA in human mucosal lymphocytes. J. Virol. **76:** 10608 - 10616.

25. Gloro, R., Hourmand-Ollivier, I., Mosquet, B., Mosquet, L., Rousselot, P., Salame, E., Piquet, M.A. and Dao, T. (2005). Fulminant hepatitis during self medication with hydroalcoholic extract of green tea. Eur. J. Gastroenterol. Hepatol. **17:** 1135 - 1137.
26. Hall, A.J., Curns, A.T., McDonald, L.C., Parahar, U.D. and Lopman, B.A. (2012). The roles of *Clostridium dificile* and norovirus among gastroenteritis-associated deaths in the United States, 1999-2007. Clin. Infect. Dis. **95:** 216 - 223.
27. Hameed, H. and Ahmed, S.I. (2014). The role of chemical and herbal antipathogenic compounds in the prevention of quorum sensing-dependent pathogenicity of *Pseudomonas aeruginosa* - A review. Pak. Vet. J. **34:** 426 - 431.
28. Hara, Y. (2011). Tea catechins and their applications as supplements and pharmaceutics. Pharmacol. Res. **64:** 100 - 104.
29. Harakeh, S., Abu-El-Ardat, K., Diab-Assaf, M., Niedzwiecki, A., El-Sabban, M. and Rath, M. (2008). Epigallocatechin-3-gallate induces apoptosis and cell cycle arrest in HTLV-1-positive and-negative leukemia cells. Med. Oncol. **25:** 30 - 39.
30. He, W., Li, L., Liao, Q., Liu, C. and Chen, X. (2011). Epigallocatechin gallate inhibits HBV DNA synthesis in a viral replication-inducible cell line. World J. Gastroenterol. **17:** 1507 - 1514.
31. Ho, H., Cheng, M., Weng, S., Leu, Y. and Chiu, D. (2009). Antiviral effect of epigallocatechin gallate on enterovirus 71. J. Agric. Food Chem. **57:** 6140 - 6147.
32. Huang, H.C., Tao, M.H., Hung, T.M., Chen, J.C., Lin, Z.J. and Huang, C. (2014). (-)-epigallocatechin-3-gallate inhibits entry of hepatitis B virus into hepatocytes. Antiviral Res. **111:** 100 - 111.
33. Isaacs, C.E., Wen, G.Y., Xu, W., Jia, J.H., Rohan, L., Corbo, C., Maggio, V.D., Jenkins, E.C. and Hillier, S. (2008). Epigallocatechin gallate inactivates clinical isolates of Herpes Simplex virus. Antimicrob. Agents Chemother. **52:** 962 - 970.
34. Isaacs, C.E., Xu, W., Merz, G., Hillier, G., Rohan, L. and Wen, G.Y. (2011). Digallate dimers of (-)-epigallocatechin gallate inactivate Herpes Simplex virus. Antimicrob. Agents Chemother. **55:** 5646 - 5653.
35. Jariwalla, R.J., Roomi, M.W., Gangapurkar, B., Kalinovsky, T., Niedzwiecki, A. and Rath, M. (2007). Suppression of influenza A virus nuclear antigen production and neuraminidase activity by a nutrient mixture containing ascorbic acid, green tea extract and amino acids. Biofactors **31:** 1 - 15.
36. Jiang, F., Chen, W., Yi, K., Wu, Z., Si, Y., Han, W. and Zhao, Y. (2010). The evaluation of catechins that contain a galloyl moiety as potential HIV-1 integrase inhibitors. Clin. Immunol. **137:** 347 - 356.
37. Jin, S. (2013). Therapeutic potential of natural catechins in antiviral activity. JSM Biotechnol. Biomed. Engineer. **1:** 1002.
38. Kuehn, B.M. (2014). Chikungunya virus transmission found in the United States: US health authorities brace for wider spread. JAMA **312:** 776 - 777.
39. Lavanchy, D. (2011). Evolving epidemiology of hepatitis C virus. Clin. Microbiol. Infect. **17:** 107 - 115.
40. Lee, H.J., Lee, Y.N., Youn, H.N., Lee, D.H., Kwak, J.H., Seong, B.L., Lee, J.B., Park, S.Y., Choi, I.S. and Song, C.S. (2012). Anti-influenza virus activity of green tea by-products *in vitro* and efficacy against influenza virus infection in chickens. Poult. Sci. **91:** 66 - 73.
41. Lee, H.S., Jun, J.H., Jung, E.H., Koo, B.A. and Kim, Y.S. (2014). Epigallocatechin-3-gallate inhibits ocular neovascularization and vascular pwermeability in human retinal pigment epithelial and human retinal microvascular endothelial cells via suppression of MMP-9 and VEGF avtivation. Molecules **19:** 12150 - 12172.
42. Li, S., Hattori, T. and Kodama, E.N. (2011). Epigallocatechin gallate inhibits the HIV reverse transcription step. Antivir. Chem. Chemother. **21:** 239 - 243.
43. Liberto, M. and Cobrinik, D. (2005). Growth factor-dependent induction of p21 (CIP1) by the green tea polyphenol, epigallocatechin gallate. Cancer Lett. **154:** 151 - 161.
44. Lin, Y., Wu, Y., Tseng, C., Lin, C., Chen, W., Hsu, Y. and Lee, J. (2013). Green tea phenolic epicatechins inhibit Hepatitis C virus replication via cycloxygenase-2 and attenuate virus-induced inflammation. Plos ONE **8:** 544-66.
45. Ling, J.X., Wei, F., Li, N., Li, J.L., Chen, L.J., Liu, Y.Y., Luo, F., Xiong, H.R., Hou, W. and Yang, Z.Q. (2012). Amelioration of influenza virus-induced reactive oxygen species formation by epigallocatechin gallate derived from green tea. Acta Pharm. Sin. **33:** 1533 - 1541.
46. Lipson, S.M., Ozen, F.S. Louis, S. and Karthikeyan, L. (2015). Comparison of alpha-glucosyl hesperidin of citrus fruits and epigallocatechin gallate of green tea on the loss of rotavirus intectivity in cell culture. Front. Microbiol. **6:** 359 doi:10.3389/fmicb.2015.00359
47. Liu, S., Li, H., Chen, L., Yang, L., Li, L., Tao, Y., Li, W., Li, Z., Liu, H., Tang, M., Bode, A.M., Dong, Z. and Cao, Y. (2013). (-)-Epigallocatechin-3-gallate inhibition of Epstein–Barr virus spontaneous lytic infection involves ERK1/2 and PI3-K/Akt signaling in EBV-positive cells. Carcinogen. **34:** 627 - 637.
48. Matsumoto, M., Takao, M., Furukawa, S. and Ohori, H. (2005). Inhibitory effects of epigallocatechin gallate on the propagation of bovine coronavirus in Madin-Darby bovine kidney cells. Mol. Nutr. Food Res. **51:** 116 - 134.
49. Matsumoto, Y., Kaihatsu, K., Nishino, K., Ogawa, M., Kato, N. and Yamaguchi, A. (2012). Antibacterial and antifungal activities of new acylated derivatives of epigallocatechin gallate. Frontier Microbiol. **53:** 1 - 10.
50. McArthur, J.C., Steiner, J., Sacktor, N. and Nath, A. (2010). Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. Ann. Neurol. **67:** 699 - 714.
51. Meltzer, S.M., Monk, B.J. and Tewari, K.S. (2009). Green tea catechins for treatment of external genital warts. Am. Obstet. Gynecol. **200:** 233 - 237.
52. Nath, S., Bachani, M., Harshavardhana, D. and Steiner, J.P. (2012). Catechins protect neurons against mitochondrial toxins and HIV proteins via activation of the BDNF pathway. J. Neurovirol. **18:** 445 - 455.
53. Oh, E., Kim, K., Shin, S.B., Son, K., Lee, H., Kim, T.H., Kim, Y., Cho, E., Kim, D., Lee, E., Lee, M., Shin, I. and Kim, J.H. (2013). Antiviral activity of Green tea catechins against feline calicivirus as a surrogate for norovirus. Food Sci. Biotechnol. **22:** 593 - 598.

54. Oliveira, A., Adams, S.D., Lee, L.H., Murray, S.R., Hsu, S.D., Hammondc, J.R., Dickinson, D., Chen, P. and Chu, T. (2013). Inhibition of herpes simplex virus type 1 with the modified green tea polyphenol palmitoyl-epigallocatechin gallate. Food Chem. Toxicol. **52:** 207 - 215.
55. Pang, J.Y., Zhao, K.J., Wang, J.B., Ma, Z.J. and Xiao, X.H. (2014). Green tea polyphenol, epigallocatechin-3-gallate, possesses the antiviral activity necessary to fight against the hepatitis B virus replication *in vitro*. J. Zhejiang Univ.Sci. B (Biomed. Biotechnol.) **15:** 533 - 539.
56. Payne, D.C., Vinje, J., Szilagyi, P.G., Edwards, K.M., Staat, M.A., Weinberg, G.A., Hall, C.B., Chappell, J., Bernstein, D.I., Curns, A.T., Wikswo, M., Shirley, S.H., Hall, A.J., Lopman, B. and Parashar, U.D. (2013). Norovirus and medically attended gastroenteritis in U.S. children. N. Engl. J. Med. **368:** 1121 - 1130.
57. Piret, J. and Boivin, G. (2011). Resistance of herpes simplex viruses to nucleoside analogues: mechanism, prevalence and management. Antimicrob. Agents Chemother. **52:** 459 - 470.
58. Racaniello, V.R. (2001). Picornaviridae: The viruses and their replication. In Fields' Virology 4th ed.; Fields, B.N., Knipe, D.M., Howley, P.M. and Griffin, D.E. Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA. p 685.
59. Roh, C. and Jo, S.K. (2011). (2)-Epigallocatechin gallate inhibits hepatitis C virus (HCV) viral protein NS5B. Talanta **85:** 2639 - 2642.
60. Ryu, S., You, H.J., Kim, Y.W., Lee, A., Ko, G.P., Lee, S.J. and Song, M.J. (2015). Inactivation of norovirus and surrogates by natural phytochemicals and bioactive substances. Mol. Nutr. Food Res. **59:** 65 - 74.
61. Sahaa, P.K., Takahashia, T., Kurebayashia, Y., Fukushimaa, K., Minamia, A., Kinbarac, N., Ichitani, M., Sagesakac, Y.M. and Suzukia, T. (2010). Antiviral effect of strictinin on influenza virus replication. Antiviral. Res. **88:** 10 - 18.
62. Salloum, S. and Tai, A.W. (2010). Treating hepatitis C infection by targeting the host. Translat. Res. **159:** 421 - 429.
63. Sang, S., Lee, M.J., Ho, C.T. and Yang C.S. (2005). Stability of tea polyphenol (-) epigallocatechin-3-gallate and formation of dimers and epimers under common experimental conditions. J. Agric. Food Chem. **53:** 9478 - 9484.
64. Shepard, C.W., Simard, E.P., Finelli, L., Fiore, A.E. and Bell, B.P. (2006). Hepatitis B virus infection: epidemiology and vaccination. Epidemiol. Rev. **28:** 112 - 125.
65. Song, J.M., Lee, K.H. and Seong, B.L. (2005). Antiviral effect of catechins in green tea on influenza virus. Antiviral. Res. **68:** 66 - 74.
66. Sonoda, J., Koriyama, C., Yamamoto, S., Kozako, T., Li, H.C., Lema, C., Yashiki, S., Fujiyoshi, T., Yoshinaga, M., Nagata, Y., Akiba, S., Takezaki, T., Yamada, K. and Sonoda, S. (2004). HTLV-1 provirus load in peripheral blood lymphocytes of HTLV-1 carriers is diminished by green tea drinking. Cancer Sci. **95:** 596 - 601.
67. Steinmann, J., Buer, J., Pietschmann, T. and Steinmann, E. (2013). Review. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. Br. J. Pharmacol. **168:** 1059 - 1073.
68. Suhrbier, A., Jaffar-Bandjee, M.C. and Gasque, P. (2012). Arthritogenic alphaviruses (mdash) an overview. Nat. Rev. Rheumatol. **8:** 420 - 429.
69. Suzuki, Y., Miyoshi, N. and Isemura, M. (2012). Health-promoting effects of green tea. Proc. Jpn. Acad. Ser. B 88.
70. Tran, J. (2013). Green tea: a potential alternative anti-infectious agent catechin and viral infections. Adv. Anthropol. **3:** 198 – 202.
71. Traven, M., Naslund, K., Linde, N., Linde, B., Silvan, A., Fossum, C., Hedlund, K.O. and Larsson, B. (2001). Experimental reproduction of winter dysentery in lactating cows using BCV comparison with BCV infection in milk-fed calves. Vet. Microbiol. **81:** 127 - 151.
72. Tsetsarkin, K.A., Vanlandingham, D.L., McGee, C.E. and Higgs, S. (2007). A single mutation in chikungunya virus affects vector specificity and epidemic potential. Plos Pathog. **3:** e201.
73. Tyring, S.K. (2012). Effect of sinecatechins on HPV-activated cell growth and induction of apoptosis. J. Clin. Anesthet. Dermatol. **5:** 34 - 41.
74. Ueda, K., Kawabata, R., Irie, T., Nakai, Y., Tohya, Y. and Sakaguchi, T. (2013). Inactivation of pathogenic viruses by plant-derived tannins: strong effects of extracts from Persimmon (*Diospyros kaki*) on a broad range of viruses. PLoS ONE **8:** e55343.
75. Vinet, R., Knox, M., Mascher, D., Paredes-Carbajal, C., Martinez, J.L. (2012) Isolated aorta model and its contribution to phytopharmacology. Bol. Latinoam. Caribe Plant. Med. Aromat. **11:** 35 - 45.
76. Vinet, R., Araos P, Gentina, J.C., Knox, M., Guzmán, K. (2014). *p*-Coumaric acid reduces high glucose-mediated impairment of endothelium-dependent relaxation in rat aorta. Bol. Latinoam. Caribe Plant. Med. Aromat. **13**: 232 - 237.
77. Wang, N., He, J., Chang A.K., Wang, Y., Xu, L., Chong, X., Lu, X., Sun, Y., Xia, X., Li, H., Zhang, B., Song, Y., Kato, A. and Jones, G.W. (2015). (-)-epigallocatechin-3-gallate inhibits fibrillogenesis of chicken cystatin. J. Agric. Food Chem. **63:** 1347 - 1351.
78. Weaver, S.C., Osorio, J.E., Livengood, J.A., Chen, R., Stinchcomb, D.T. (2012). Chikungunya virus and prospects for a vaccine. Expert Rev. Vaccines **11:** 1087 - 1101.
79. Weber, J.M., Ruzindana-Umunyana, A., Imbeault, L. and Sircar, S. (2003). Inhibition of adenovirus infection and adenain by green tea catechins. Antiviral. Res. **58:** 167 - 173.
80. Weber, C., Sliva, K., von Rhein, C., Kümmerer, B.M. and Schnierle, B.S. (2015). The green tea catechin, epigallocatechin gallate inhibits chikungunya virus infection. Antiviral Res. **113:** 1 - 3.
81. Wen, J., Zhao, S., He, D., Yang, Y., Li, Y. and Zhu, S. (2012). Preparation and characterization of egg yolk immunoglobulin Y specific to influenza B virus. Antiviral. Res. **93:** 154 - 159.
82. Whickam, T.J. (2000). Targeting adenovirus. Gene Ther. **7:** 110 - 114.
83. Williams, S.N., Shih, J., Guenette, D.K., Brackney, W., Denison, M.S., Pickwell, G.V. and Quattrochi, L.C. (2000). Comparative studies on the effects of green tea extracts and individual tea catechins on human CYP1A gene expression. Chem. Biol. Interact. **128:** 211 - 229.

84. Williamson, M.P., McCormick, T.G., Nance, C.L. and Shearer, W.T. (2006). Epigallocatechin gallate, the main polyphenol in green tea, binds to the T-cell receptor, CD4: potential for HIV-1 therapy. J. Allergy Clin. Immunol. **118:** 1369 - 1374.
85. Xu, J., Wang, J., Denga, F., Hua, Z. and Wang, H. (2008). Green tea extract and its major component epigallocatechin gallate inhibits hepatitis B virus *in vitro*. Antiviral Res. **78:** 242 - 249.
86. Yamaguchi, K., Honda, M., Ikigai, H., Hara, Y. and Shimamur, T. (2002). Inhibitory effects of (-)-epigallocatechin gallate on the life cycle of human immunodeficiency virus type 1 (HIV-1). Antiviral. Res. **53:** 19 - 34.
87. Yang, Z.F., Bai, L.P., Huang, W.B., Li, X.Z., Zhao, S.S., Zhong, N.S. and Jiang, Z.H. (2014). Comparison of *in vitro* antiviral activity of tea polyphenols against influenza A and B viruses and structure-activity relationship analysis. Fitoterapia **93:** 47 - 53.
88. Yiannakopoulou, E.C. (2012). Recent patents on antibacterial, antifungal and antiviral properties of tea. Recent Patents on anti-infective Drug Discovery **7:** 60 - 65.
89. Yousaf, S., Butt, M.S., Suleria, H.A. and Iqbal, M.J. (2014). The role of green tea extract and powder in mitigating metabolic syndromes with special reference to hyperglycemia and hypercholesterolemia. Food Funct. **5:** 545 - 556.
90. Zhao, M., Jiang, J., Zheng, R., Pearl, H., Dickinson, D., Fu, B. and Hsu, S. (2012). A proprietary topical preparation containing EGCG stearate and glycerin with inhibitory effects on herpes simplex virus: case study. Inflamm. Allergy Drug Target **11:** 364 - 368.
91. Zhong, L., Furne, J.K. and Levitt, M.D. (2006). An extract of black, green, and mulberry teas causes malabsorption of carbohydrate but not of triacylglycerol in healthy volunteers. Am. J. Clin. Nutr. **84:** 551 - 555.