Tea Polyphenols as Natural Products for Potential Future Management of HIV Infection – An Overview

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Abstract

Belonging to the Lentivirus genus of animal retroviruses, human immunodeficiency virus (HIV) is the etiological agent of acquired immunodeficiency syndrome (AIDS) which attacks cells of the immune system including CD4⁺ T lymphocytes, monocytes, macrophages and dendritic cells. A rapid progression to immunodeficiency and the higher transmissibility of HIV-1 compared to HIV-2 are hallmarks of the worldwide spread of AIDS. Conventional HIV treatments are limited by drug toxicity and by multi-drug resistance, caused by the high genetic variability of HIV. This has led researchers into new areas of drug discovery in search of novel therapeutic molecules. Accumulating evidence indicates that tea polyphenols possess a range of beneficial properties including anti-cancer, anti-inflammatory, anti-oxidative, neuro-protective, anti-bacterial, anti-fungal and anti-viral effects. The anti-HIV infection potential of tea polyphenols has been confirmed by several preclinical studies. This suggests that polyphenol-rich extracts of tea could be used as dietary supplements as part of a combined therapeutic regimen with conventional anti-HIV drugs. Phenolic structures may also be considered as backbones for the discovery of a new generation of anti-HIV remedies. This review provides a perspective on the anti-HIV activity of tea polyphenols and their development as a possible source of future drugs for the therapy of HIV/AIDS.

Keywords: AIDS, Catechin, HIV, Polyphenol, Phytomedicine, Tea, Theaflavin

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1. Introduction

1.1 HIV Aetiology and Pathophysiology

Human Immunodeficiency Virus (HIV) is a member of the Lentivirus genus, part of the Retroviridae family of enveloped, single-stranded, positive-sense RNA viruses that are characterized by replication in a host cell through the process of reverse transcription. HIV is the etiological agent of Acquired Immuno Deficiency Syndrome (AIDS) which infects cells of the human immune system including CD4+ T lymphocytes, monocytes, macrophages and dendritic cells. As a zoonotic disease HIV/AIDS is thought to be derived from simian immunodeficiency viruses that infect West African primates. Common chimpanzees (Pan troglodytes) and western lowland gorillas (Gorilla gorilla gorilla), and sooty mangabey monkeys (Cercocebus atys), are recognized as the original source of HIV-1 and HIV-2, respectively. Of the two major types of HIV, such intrinsic features of HIV-1 as a greater rate of transmission than HIV-2 and driving a quicker loss of host immunocompetence have enabled it to become the principal cause of AIDS around the world. M, N, O and P are the four identified groups of HIV-1 that are isolated from chimpanzees and gorillas. Of these, group M, which comprises nine subtypes: A-D, F-H, J and K, is known to be responsible for the global HIV pandemic. This group was transmitted to humans in West-Central Africa approximately 100 years ago.

The globalization of HIV-1 may be due to the high mutation and recombination rates of the nine subtypes of group M caused by the Reverse Transscriptase (RT) enzyme. The number of infections caused by recombinants is reported to have increased from 17% over the period 2000-07 to at least 20% by 2011. Drug injection with contaminated shared needles, unprotected sexual contact, percutaneous blood exposure, mucous membrane exposure to contaminated blood or other body fluids, mother-to-child transmission and receipt of contaminated blood products are all identified as major routes of HIV transmission. After gaining entry into the body via one of these routes, each virion attacks a CD4+ T lymphocyte, its main target, with the assistance of chemokine co-receptors such as CCR5 or CXCR4. The virus genome is released into the host cell and viral RT converts viral RNA into double stranded DNA. This new viral DNA is concealed within the DNA of the host cell by another HIV enzyme named integrase. In this way, transcription of the host cell's DNA during cell division causes spread of the virus within the host’s body.

1.2 HIV Epidemiology

It is estimated that worldwide over 35 million people live with HIV, of whom 69% are resident in sub-Saharan Africa where 1 in every 20 adults is HIV-positive. As far back as 2009 6% of Kenyan adults (15-49 years) were infected with HIV-1, with a difference between urban (10%) and rural areas (5.6%). Furthermore, the Centers for Disease Control and Prevention estimate that currently approximately 50,000 people contract HIV each year in the USA. Another report from 2015 indicated that in China 501,000 people had HIV/AIDS among whom 205,000 were living with AIDS.

1.3 Current Treatment of AIDS Complications

There are more than 25 Anti-retroviral (ARV) drugs licensed for HIV therapy which are divided into several groups including nucleoside RT inhibitors (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine), nucleotide RT inhibitor (tenofovir), non-nucleoside RT inhibitors (nevirapine, delavirdine, efavirenz and etravirine), protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir), fusion inhibitor (enfuvirtide), co-receptor inhibitor (maraviroc) and integrase inhibitor (raltegravir). Several side effects including constipation, fever, liver disorders, muscular dystrophy, lipoatrophy, metabolic disorders, blood disorders, hypersensitivity reactions, peripheral neuropathy, hyperlactaemia, pancreatitis and mitochondrial toxicity, as well as multi-drug resistance and toxicity caused by the high genetic variability of HIV have limited long term treatment with the aforementioned ARV drugs. Thus, screening of alternative drugs such as plant metabolites used as natural products would appear necessary due to their therapeutic activities with lesser or no side effects. Against this background, the principal purpose of this review is to provide an overview of recent findings on anti-HIV activity of polyphenols extracted from different types of tea.
2. Health Benefits of Tea Polyphenols as Dietary Natural Products

Recently, polyphenols have been recognized as extremely important plant-derived dietary compounds due to producing a vast range of effects considered to be beneficial to humans. This comprises antioxidant, antibacterial, antiviral, anti-allergic, anti-colitis, anti-inflammatory, anti-arthritis and anti-cancer activities21–25. Among several polyphenol sources in the human diet, tea is one of the most consumed beverages around the world as a result of the pleasant taste, attractive aroma and health-promoting effects. Depending on the degree of processing and fermentation, tea is divided into green tea, which is consumed mostly in South East Asian countries, black tea, which is commonly consumed in the Indian subcontinent and Western societies, and Pu-erh, white, yellow and oolong teas that are produced and drunk mainly in China26. There are many reports about consumption of tea worldwide. The UK Tea Council claims that British people drink 60.2 billion cups of tea per year27. Worldwide, over 4.52 million tons of tea were produced in 2014 28. In addition to the abundant distribution of polyphenols in this plant species, tea is also a leading natural source of caffeine, a psychoactive alkaloid that acts as a stimulant and, if taken at a bioactive dose, can show beneficial effects on wellbeing29.

While used as a routine part of the human diet, tea has attracted scientific attention due mostly to its highly active antioxidant and anti-inflammatory polyphenolic compounds, especially catechins29. The European Food Safety Authority reported that each 100 ml of green tea contains about 126 mg of catechin derivatives30. Several beneficial properties have been attributed to tea polyphenols, including anti-cancer31,32, anti-diabetic33, anti-oxidative34, cardioprotective35 and neuroprotective36 activities, as well as antibacterial37, antifungal38 and antiviral39,40 functions. Considering the high content of antioxidants and anti-inflammatory components, including flavonoids, tea could be introduced as a suitable beverage for the prevention of chronic inflammatory and oxidative stress-related conditions41.

3. Anti-HIV Activity of Tea Polyphenols

3.1 Green Tea Polyphenols

Green tea originates in China and is prepared from leaves of the evergreen shrub Camellia sinensis that have undergone minimal oxidation during processing. Monomeric flavanols, recognized as catechins, are the most important polyphenols with several beneficial therapeutic properties such as prophylactic effects on atherosclerosis, anti-oxidative stress, anti-ulcer, anti-bacterial and anti-cancer activities42-47. Catechins constitute 30-40% of the dry weight of fresh green tea leaves48, including (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epigallocatechin gallate (EGCG) as main catechin derivatives, and also (-)-catechin gallate (CG), (-)-gallocatechin (GC), (-)-gallocatechin gallate (GCG), (-)-epigallocatechin 3,5-digallate (EGCDG) and 2',2”-bis epigallocatechin digallate (BGCDG) as minor ingredients40. EGCG is the most frequent catechin derivative of green tea polyphenols49.

The immunoregulatory effects of green tea extracts have been reported50-53. A dose-dependent decrease in histamine production was noted for rodent peritoneal mast cells incubated with green tea polyphenol50. Further experiments by these authors showed that the altered histamine release was due to a green tea extract-mediated decrease in cAMP and calcium levels which leads to an NFκB and p38 MAPK-dependent inhibition of the pro-inflammatory cytokines TNF-α and IL-650. Green tea components are reported to have immunoregulatory activity. EGCG was effective at suppressing peripheral blood mononuclear cell proliferation and IFN-γ production51. They can also change the profile of pro-inflammatory cytokines secreted by lymphocytes52. Neutrophils were modulated by green tea polyphenols through suppression of the TLR-4/NFκB p65 signal activation pathway53.

EGCG inhibits HIV-1 replication in several steps of the virus life cycle by interfering with RT and protease activity, blocking gp120-CD4 interaction via binding to CD4 and destroying virions54-58. Several investigations have demonstrated that green tea catechins, especially EGCG, possess anti-HIV activity. For instance, it was
shown that EGCG inhibits the infectivity-enhancing property of Semen-derived Enhancer of Virus Infection (SEVI) at non-toxic concentrations, treatment with 0.4 mM of EGCG reducing the average rate of infection by 70.6% (p < 0.0001)\(^5\). SEVI and also semen-mediated enhancement of HIV-1 infection may be inhibited by EGCG without cellular toxicity. In addition, the formation of fibril is abrogated completely by treatment with high concentrations of EGCG (10 and 20 mM EGCG)\(^6\). Furthermore, it has been reported that blockade of antibody and glycoprotein 120 through binding of EGCG to CD4\(^+\) T cell is another anti-HIV mechanism of this molecule\(^5\). Prevention of attachment of HIV-1-glycoprotein 120 to CD4 has a key role in inhibition of HIV-1 infection by EGCG\(^6\). Also, inhibition of HIV-1 p24 antigen production across a broad spectrum of both HIV-1 clinical isolates and laboratory adapted subtypes (B, C, D and G) has been observed following application of EGCG at a concentration of 6 \(\mu\)mol/L.

Inhibition of HIV-1 infection by EGCG is not a consequence of cytotoxicity, cell growth inhibition or apoptosis, indicating the specificity of the inhibitory potential of EGCG for HIV-1 infectivity\(^6\). Treatment of HIV-1 Tat transgenic mice with EGCG at a dose of 300mg/kg/day caused a reduction in Glial Fibrillary Acidic Protein (GFAP) associated neuronal loss\(^6\). EGCG both mildly reduced activated microgliosis and enhanced neuron survival. Antiviral activity of EGCG occurs by interacting with several steps of the HIV-1 life cycle. A destructive effect on virions, post-adsorption entry and RT in acutely infected monocytoid cells were observed at concentrations of EGCG greater than 1 \(\mu\)M\(^6\). However, suppression of protease kinetics was identified at EGCG doses higher than 10 \(\mu\)M. Moreover, inhibition of virus production by THP-1 cells chronically infected with HIV-1 was promoted by liposome modification of EGCG in a dose-dependent manner. Following EGCG treatment of THP-1 cells inhibition of viral mRNA production was observed in lipopolysaccharide (LPS)-activated chronically HIV-1-infected cells; however, inhibition of viral mRNA production in unstimulated or LPS-stimulated T-lymphoid cells (H9) was not observed\(^6\). Another \textit{in vitro} study showed that EGCG strongly inhibited the replication of HIV as determined by RT and p24 assays performed on cell supernatants\(^5\). Among catechin derivatives including ECG, EGC, EGCG and Green Tea Extract (GTE) with HIV-1 RT inhibitory activity, EGCG and ECG were recognized as highly potent HIV-1 RT inhibitors\(^8\). In addition, reduction by EGCG of HIV neurotoxicity in the presence of IFN-\(\gamma\) via inhibition of Janus Activating Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway has been demonstrated \textit{in vivo}\(^6\).

### 3.2 Pu-erh Tea Polyphenols

Pu-erh tea is a dark, aged tea that is produced in Yunnan province, China, from a large-leaved variety of tea plant, \textit{Camellia sinensis assamica}, following a two-step process of microbial fermentation by organisms such as the mould \textit{Aspergillus sp.} and oxidation\(^6\). Several beneficial activities of Pu-erh tea are documented, including prevention and treatment of cancer, heart diseases, rheumatoid arthritis and immune disease such as AIDS\(^7\). Due to its inhibitory effect on HIV replication Pu-erh tea extracts may be used as a dietary supplement or a natural product administered to HIV patients\(^6\). Water and ethanol extracts of Pu-erh tea (WEPT and EEPT), as well as fermented Pu-erh tea (FPT), possess anti-HIV activity with low cytotoxicity. The WEPT showed better anti-HIV activity than EEPT. Furthermore, this activity of the FPT’s water extracts was better than that of the untreated Pu-erh tea. As shown in Table 1, it has been reported that HIV-1\(_{\text{RGL}}\) and HIV-2\(_{\text{CBL-20}}\) infections can be inhibited by Pu-erh tea extracts. Pu-erh tea reduced p24 antigen expression in HIV-1\(_{\text{IIIB}}\) acutely infected C8166 cells and HIV-1\(_{\text{KM018}}\) infected peripheral blood mononuclear cells. The fusion between normal C8166 cells and HIV-1 chronically infected H9 cells was blocked by Pu-erh tea. The synergistic anti-HIV activity of Pu-erh tea in combination with the antiretroviral medication azidothymidine (AZT) was noted although no inhibitory effects on RT activity were observed\(^6\).

### 3.3 Black Tea Polyphenols

Chinese black tea is made from the small-leaved \textit{Camellia sinensis sinensis} and is more oxidized and stronger in flavour compared to other varieties of tea. Theaflavins are polyphenols that are found naturally in black tea and which constitute approximately 2% of its dried water extract. Anti-bacterial, anti-viral, anti-inflammatory, anti-oxidative and anti-tumour activities have been...
## Table 1: Summary of evidence of anti-HIV effects of tea polyphenols based on preclinical research studies.

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<tr>
<th>Polyphenol</th>
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<th>Virus</th>
<th>Model</th>
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<td>Green</td>
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<td>Green, Oolong, Black</td>
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<tr>
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<tr>
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<td>Not defined</td>
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<td>EGCG</td>
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Abbreviations: AZT: 3'-azido-3'-deoxythymidine; C8166, H9, MT-2 & MT-4: human T cell leukemia or lymphoma cell lines; EC50: effective concentration 50%; EEPT: ethanol extracts of Pu-erh tea; EGCG: (-)-epigallocatechin-3-galllate; FPT: fermented Pu-erh tea; GFAP: glial fibrillary acidic protein; GTE: green tea extract; GTLPT: green tea-like Pu-erh tea; HIV: human immunodeficiency virus; JAK: Janus-activating kinase; LPS: lipopolysaccharide; PAP: prostatic acid phosphatase; PBMC: peripheral blood mononuclear cell; RT: reverse transcriptase; SE: human semen; SEVI: Semen-derived enhancer of virus infection; 6-HB: six-helix bundle; STAT: signal transducer and activator of transcription; Tat: trans-activating protein; TFmix: an economical natural preparation containing 90% theaflavins; THP: monocyteid; WEPT: water extracts of Pu-erh tea.
reported as properties of major theaflavin derivatives in black tea including theaflavin (TF1), theaflavin-3-gallate (TF2A), theaflavin-3’-gallate (TF2B) and theaflavin-3,3’-digallate (TF3)\textsuperscript{70-73}. It is known that theaflavins in black tea possess anti-HIV-1 activity through inhibition of virus entry into target cells by interfering with glycoprotein 41 six-helix bundle formation\textsuperscript{40}. Due to higher anti-HIV activity of black tea theaflavins in comparison to green tea catechins, extracts of the former are leading candidates for a new generation of anti-HIV-1 herbal therapy\textsuperscript{74}. Theaflavins and catechins both inhibit HIV-1 entry by targeting glycoprotein 41 between the N- and C-peptides\textsuperscript{40}. Amongst eight examined tea polyphenols, TF2B had the predominant anti-HIV activity followed in decreasing order by TF3, BEGCG, TH2A, EGCDG, GCG, TF1 and EGCG. Furthermore, the most inhibitory effect on HIV-1-mediated cell-cell fusion has been attributed to TF3 followed by GCG, TF2B, BEGCG, EGCDG, TH2A, TF1 and, poorly, EGCG. In contrast, neither inhibition of HIV-1-mediated cell-cell and virus-cell fusions, nor inhibitory activity against HIV-1 replication have been observed for some other tea polyphenols including (-)-catechin, CG, GC, EC, ECG and EGC\textsuperscript{40}.

It is thought that the mechanism of anti-HIV activity of tea polyphenols is not via specific interaction or interference with co-receptor binding. According to molecular docking analysis TF3 may bind to a highly conserved hydrophobic pocket that is located on the surface of the central trimeric coiled-coil of glycoprotein 41\textsuperscript{40}. Another in vitro investigation using p24 production and luciferase assays demonstrated that a natural preparation containing 90% theaflavins (TFmix) had a strongly anti-HIV-1 effect on both laboratory-adapted and primary HIV-1 strains possessing low cytopathicity\textsuperscript{75}. Inhibition occurred at viral entry of the host cell by targeting glycoprotein 41 and blocking membrane fusion. While RT activity of the virus is also suppressed by TFmix, the IC\textsubscript{50} for this inhibition is approximately 8-fold higher than that needed for inhibition of glycoprotein 41 6-HB formation, thus indicating that RT is not a primary target for TFmix\textsuperscript{74}. In an animal model of arthritis black tea also showed anti-inflammatory activity\textsuperscript{76}, demonstrating the immunomodulatory properties of theaflavins, which may be considered as complementary to their apparent protective effect against HIV-1 discussed here.

4. Discussion

According to the World Health Organization, around 71 million persons have become infected with HIV since records began, of whom 34 million patients have died due to AIDS-related illnesses, with a further 36.9 million individuals identified as carrying HIV at the end of 2014\textsuperscript{77}. Current medicaments for AIDS include nucleoside RT inhibitors, nucleotide RT inhibitor, protease inhibitors, fusion inhibitors, co-receptor inhibitors and integrase inhibitor\textsuperscript{17}, but which in some patients may cause a range of adverse side effects like liver disorders, muscular dystrophy, metabolic disorders, blood disorders, hypersensitivity reactions, pancreatitis and mitochondrial toxicity\textsuperscript{1,18,19}. Multi-drug resistance and toxicity linked to the high genetic variability of the virus are additional limitations of conventional HIV treatments that collectively have prompted renewed efforts to discover novel therapeutic options.

Since ancient times humans have used plant-derived agents as treatments for various infective diseases and other ailments. The wealth of botanical-based therapies that are both efficacious and safe has prompted research to screen different known medicinal plants for anti-HIV activity, of which different types of tea – with their broad range of polyphenols as an active ingredient – could be considered as among the most important\textsuperscript{41}. Green, Pu-erh and black teas contain such phenolic compounds as ECG, EGC, EGCG, GCG and TF which have demonstrated anti-HIV activity in several in vitro and in vivo studies (Table 1). While both are classified as flavonoids, green tea polyphenols consist mostly of EGCG and other catechin gallates, whereas theaflavins are the main constituents of black tea.

These two main categories of tea polyphenols are involved in cellular pathways such as JAK/STAT\textsuperscript{64}, as well as in different steps of cell-cell and virus-cell interactions\textsuperscript{40}. They show anti-viral and immunomodulatory effects on HIV-induced infection via different mechanisms including inhibition of virus replication, of HIV-induced cytopathic activities, and of antigen and RT expression, prevention of virus attachment and destruction of virions. Tea polyphenols also show activities against HIV infection in concentrations that are non-toxic for eukaryotic cell lines\textsuperscript{61}. Pu-erh tea has been studied mostly in the form of crude extracts and isolated compounds.
were not assessed; however, these preparations were successful in demonstrating anti-HIV properties.

Figure 1 illustrates the chemical structure of each of the tea polyphenols with anti-HIV activity most relevant to future drug preparation. As one of the most significant properties of polyphenols, anti-oxidant effects are likely to play a crucial role in their noted anti-retroviral activities. In addition, an immunomodulatory effect could be one of the mechanisms involved in the anti-HIV function of these molecules.

5. Conclusion

Taking into account the collective body of research discussed herein, it is proposed that tea polyphenols and polyphenol-rich extracts could be used in future as dietary supplement in combination with conventional anti-HIV medicines. Phenolic structures may also be considered as scaffolds for the discovery of a new generation of anti-HIV drugs. Since investigations of the protective effects of specific tea polyphenols in humans are either limited or have not yet taken place, there is a pressing need to undertake detailed clinical trials in order to attain sufficient and robust data to either support or refute the predicted possible beneficial role of tea polyphenols in the therapy of HIV-infected patients.

6. Conflict of Interests

The authors do not have any conflict of interest to declare. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

7. References

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30. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the substantiation of health claims related to Camellia sinensis (L.) Kuntze (tea), including catechins in green tea and tannins in black tea, and protection of DNA, proteins and lipids from oxidative damage (ID 1103, 1276, 1311, 1708, 2664), reduction of acid production in dental plaque (ID 1105, 1111), maintenance of bone (ID 1109), decreasing potentially pathogenic intestinal microorganisms (ID 1116), maintenance of vision (ID 1280), maintenance of normal blood pressure (ID 1546) and maintenance of normal blood cholesterol concentrations (ID 1113, 1114) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010; 8:1463.


