Received: 26 July 2023 | **Accepted:** 04 Dec 2023 **Genel Tıp Derg. Volume** 34/**Issue** 1 (February), 38-42
DOI: 10.54005/geneltip.1333115

ORIGINAL ARTICLE

Evaluation of In Vitro Antimicrobial Activity of *Epigallocatechin Gallate* (EGCG) and Green Tea (*Camellia Sinensis*) Oil on Various Pathogens

Epigallocatechin Gallate (EGCG) ve Yeşil Çay (*Camellia Sinensis*) Yağının Çeşitli Patojenler Üzerinde İn Vitro Antimikrobiyal Etkinliğinin Değerlendirilmesi

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How to cite ?

Köksoy H, Ragbetli C. Evaluation of In Vitro Antimicrobial Activity of Epigallocatechin Gallate (EGCG) and Green Tea (Camellia Sinensis) Oil on Various Pathogens. Genel Tıp Derg. 2024;34(1):38-42.

ABSTRACT

Aim: Epigallocatechin gallate (EGCG), the polyphenolic component of Camellia sinensis catechins, and Camellia sinensis extract have broad antimicrobial activity. This study aimed to investigate the invitro antibacterial and antifungal activity of the Epigallocatechin gallate and Camellia sinensis extract.
Method: The present study tested the antibacterial and antifungal activity of Epigallocatechin gallate and Camellia sinensis extract against some gram-negative, gram-positive, and fungal isolates of American Type Culture Collection (ATCC). The minimum inhibitory concentration (MIC) of Epigallocatechin gallate (EGCG) and Camellia sinensis extract were determined for each test microorganism. In general, EGCG and Camellia sinensis extract results were found compatible. Epigallocatechin gallate and Camellia sinensis extract exhibited antibacterial and antifungal activity against all test organisms. MIC was determined visually after 16-20 hours of incubation at 37°C according to broth microdilution methods recommended by the Clinical and Laboratory Standards Institute (CLSI).
Result: The Camellia sinensis extract and EGCG MIC for gram-positive bacteria was found lower than the MIC for gram-negative bacteria and the Camellia sinensis extract MIC for C. albicans was higher than the EGCG MIC.
Conclusions: However, EGCG was more effective on C. albicans isolate than Camellia sinensis extract. Camellia sinensis extract Epigallocatechin gallate and Camellia sinensis extract may be a promising source of antibacterial and antifungal for further studies.

Keywords: Epigallocatechin gallate (EGCG), Green tea, Camellia sinensis, Antibacterial effect, Antifungal effect.

ÖZ

Amaç: Bu çalışma, Camellia sinensis çayındaki kateşinlerin polifenolik bileşeni olan Epigallokateşin gallat (EGCG) ile Camellia sinensis ekstraktının geniş bir antimikrobiyal aktiviteye sahip olduğunu incelemektedir.
Metod: Çalışma, Amerikan Tip Kültür Koleksiyonu'ndan (ATCC) seçilen bazı gram-negatif, gram-pozitif ve mantar izolatlarına karşı EGCG ve Camellia sinensis ekstraktının invitro antibakteriyel ve antifungal aktivitesini test etmiştir. Her test mikroorganizması için Epigallokateşin gallat (EGCG) ve Camellia sinensis ekstraktının minimum inhibisyon konsantrasyonu (MIC) belirlenmiştir. Genel olarak, EGCG ve Camellia sinensis ekstraktı sonuçları uyumlu bulunmuştur. Epigallokateşin gallat ve Camellia sinensis ekstraktı, tüm test organizmalarına karşı antibakteriyel ve antifungal aktivite sergilemiştir. MIC değerleri, Klinik ve Laboratuvar Standartları Enstitüsü (CLSI) tarafından önerilen çanak mikrodilüsyon yöntemleriyle, 37°C'de 16-20 saat inkübasyon sonrasında görsel olarak belirlenmiştir.
Sonuç: Gram-pozitif bakteriler için Camellia sinensis ekstraktı ve EGCG MIC değerleri, gram-negatif bakterilere göre daha düşük bulunmuştur ve C. albicans için Camellia sinensis ekstraktı MIC değeri, EGCG MIC değerinden daha yüksek bulunmuştur.
Tartışma: Ancak, EGCG, C. albicans izolatı üzerinde Camellia sinensis ekstraktından daha etkili bulunmuştur. Camellia sinensis ekstraktı ve Epigallokateşin gallat, antibakteriyel ve antifungal etkileri için ileri çalışmalar için umut vadeden kaynaklar olabilir.

Anahtar Kelimeler: Epigallocatechin gallate (EGCG), Yeşil çay, Camellia sinensis, Antibakteriyal etki, Antifungal etki.

Introduction

The problem of antimicrobial resistance causes higher medical costs, prolonged hospital stays, and increased mortality (1). Even if new drugs are developed, antibiotic and antifungal resistance will continue to be a major threat. The limited production of new antibiotics and antifungals has brought support from herbal ingredients to the agenda (2, 3). Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans are common pathogens worldwide and can cause many infections. For example, Polyphenols (tea, wine, juices) commonly found in seaweed, some plants, fruits, vegetables and beverages are natural antioxidants and antibacterials (4). EGCG and Camellia sinensis extract may work well in inhibiting bacterial growth and may have health-promoting properties. Green tea is widely known and used by people all over the world and especially in Asia due to its suggested benefits (5, 6). The chemical structure of major green tea catechins is shown in Figure 1 (7). Due to the limited production of new antibiotics and antifungals and the rapid development of resistance against the produced antibiotics and antifungals, herbal supplements are on the agenda. It is

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
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very important to evaluate the molecules to be tested more quickly and effectively as a simple, inexpensive and easy candidate that can be used to develop new antibiotics and antifungals. The antibacterial and antifungal effects of Epigallocatechin-3-gallate (EGCG) and Camellia sinensis extract on various pathogens will be examined in detail.

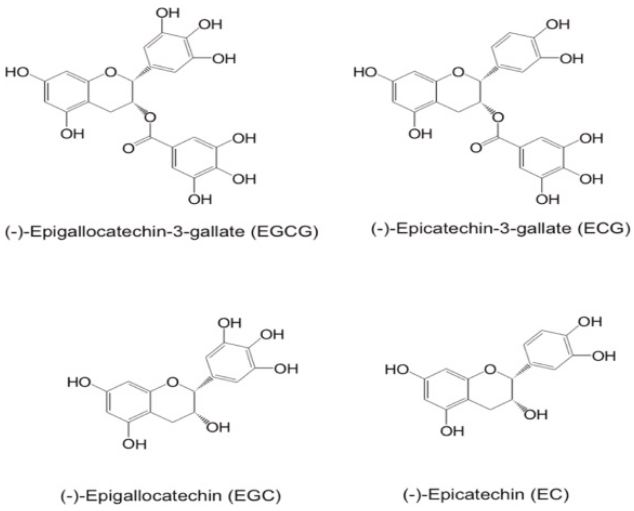

Figure 1. Chemical structure of major green tea catechins (7).

Materials and Methods

American Type Culture Collection (ATCC) strains; Staphylococcus aureus ATCC 29213, Streptococcus pyogenes ATCC 19615, Enterococcus faecalis ATCC 29212, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853 and Candida albicans ATCC 14053 were tested as microorganisms. Fresh cultures of the above-mentioned ATCC strains were tested for antibacterial and antifungal effects after 24 hours of incubation at 37°C on blood agar. The MIC of the EGCG and Camellia sinensis extract was evaluated by the broth dilution method. EGCG (Sigma, USA) in powder form with 95% purity was dissolved in normal saline and serially diluted with cation-adjusted Mueller-Hinton broth (MHB) starting from a maximum concentration of 800 µg/ml to 1.56 µg/ml. EGCG was placed on a 96-well plate. Green tea extract mainly consists of %40 polyphenols and %10 ECGG, (ONKA FARMA, Ege University Technopark) and was serially diluted. Resulting in final extract concentrations of 10000 to 20µl/ml. ATCC isolates were inoculated into each well at a concentration of 5 x 105 CFU/ml. MIC was determined visually after 16-20 hours of incubation at 37°C according to broth microdilution methods recommended by CLSI. Finally, the lowest concentration of EGCG and Camellia sinensis extract that inhibited bacterial and fungal growth was measured as MIC. All information about the participants in the study will be kept confidential and those who do not want to participate in the survey will not be forced. Permission was obtained from the ethics committee with the number 08-2022/05 on 31.08.2022.

Results

Table 1 shows the results of the antibacterial effect of EGCG and Camellia sinensis extract against all of the ATCC isolates. Camellia sinensis extract and EGCG compound showed a strong inhibitory effect against Gram-positive strains. The MIC of EGCG was 100 µg / ml for S. aureus and S. pyogenes. The EGCG MIC were 200 µg /ml for E. faecalis and E. gallinarum, 400 µg /ml for E. coli and P. aeruginosa.

Table 1: Antibacterial effect and MIC of EGCG and Camellia sinensis extract.

Microorganisms	Antibacterial effect of EGCG	MIC (µg/ml)	Antibacterial effect of C. sinensis extract	MIC (µg/ml)
S. aureus ATCC 29213	+	100	+	156
S. pyogenes ATCC 19615	+	100	+	20
E. faecalis ATCC 29212	+	200	+	78
E. coli ATCC 25922	+	400	+	500
P. aeruginosa ATCC 27853	+	400	+	1000
C. albicans ATCC 14053	+	200	+	1000

The EGCG MIC for gram-positive bacteria and C. albicans was lower than the MIC for gram-negative bacteria. The MIC of Camellia sinensis extract was 20 µg /ml for S. pyogenes, 78 µg /ml for E. faecalis, and 156 µg /ml for S. aureus. Camellia sinensis extract MIC were 500 µg /ml for E. coli,1000 µg /ml for P.aeruginosa and C. albicans. The Camellia sinensis extract MIC for gram-positive bacteria was found lower than the MIC for gram-negative bacteria and C. albicans. EGCG showed better antimicrobial activity than Camellia sinensis extract for C. albicans (Figure 2).

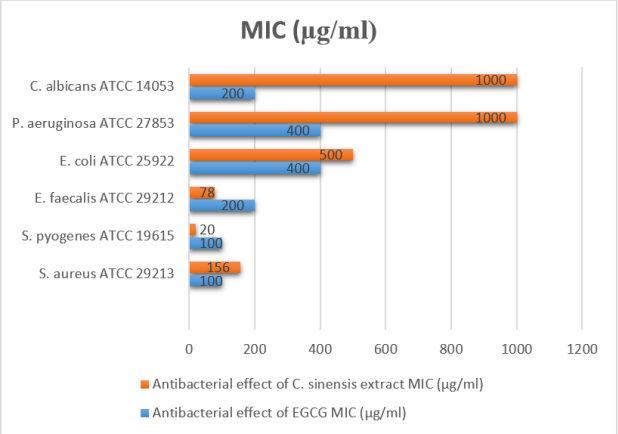

Figure 2: Comparison of Camelia sinensis and EGCG antibacterial and antifungal activity

Discussion

According to the European Food Safety Authority (EFSA), 100 mL of green tea contains 126 mg of catechin while there is 71 mg of epigallocatechin gallate per 100 mL of green tea according to the

Food and Drug Administration (FDA), (8). Green tea (Camellia sinensis) is a well-known natural source of polyphenols, including phenolic acids (caffeic acid and gallic acid) and flavonoids. These polyphenols and flavonoids are the most effective biological compound for anti-infective properties, against viruses, bacteria, and fungi (9, 10). Green tea contents exhibit broad antibacterial activity against all of these microorganisms through a variety of mechanisms, including the inhibition of cell wall and cell membrane synthesis, protein and nucleic acid synthesis, or the inhibition of metabolic pathways, such as toxins and extracellular matrix virulence factors, oxidative stress, iron chelation, and so on (11-13).

EGCG, a polyphenol abundantly found in green tea (Camellia sinensis), and Camellia sinensis extract have been recognized as having a potential antimicrobial effect. In this study, the antibacterial and antifungal activity of EGCG and Camellia sinensis extract was investigated on ATCC isolates of S. aureus, S. pyogenes, E. faecalis, E. coli, P. aeruginosa and C. albicans. This study revealed that EGCG was effective against all tested organisms, but the MIC for gram-positive strains was lower than for gram-negative strains. Camellia sinensis extract was effective in all tested microorganisms but the MIC for gram-positive strains was lower than for gram-negative strains and C. albicans (Table1). According to the results of this study, gram-positive organisms were more sensitive than gram-negative organisms to Camellia sinensis extract. The strongest activity was demonstrated against S. aureus and S. pyogenes. Higher susceptibility of Gram-positive bacteria has also been reported in some previous studies (12, 14). Gram-positive bacteria do not have this structure. When Yoda et al. in Tokyo, compared the minimum inhibitory concentrations (MICs) of EGCG against gram-positive bacteria (50-100 µg/ml), higher MICs (≥800 µg/ml) were observed against Gram-negative bacteria (15). The most resistant bacteria of E. coli and P. aeruginosa may be related to the structure of the bacterial cell wall and various cell wall components in their outer membranes, which act as a barrier. Epigallocatechin-3-gallate (EGCG) reduced not only biofilm formation but also the number of viable cells in biofilms in Stenotrophomonas maltophilia isolates insulated from cystic fibrosis patients (16) MDR Gram-negative bacterial skin infections are sometimes difficult to treat and are resistant to commonly used antibiotics. Jeon et al. MIC values of EGCG of MDR Pseudomonas aeruginosa and Escherichia coli isolated from the intensive care unit of a university hospital were measured as 200-400 ug/ml (14). In vivo, experiments support the idea that EGCG and Camellia sinensis extract may show synergy with conventional antibiotics and antifungals against Gram-negative bacteria (17-20). Zhao et al.'s study examining the synergy of Epigallocatechin gallate (EGCG) and β-Lactams, compared their MICs against Escherichia coli (more than 800 µg/ml) with their MICs against Staphylococcus aureus (MSSA and MRSA) (100 µg/ml or less) (21). Isogai et al. (2001) determined that the combination of EGCG and levofloxacin was protective against enterohemorrhagic Escherichia coli O157 in mice (22). Similarly, synergistic effects with ciprofloxacin were demonstrated in a chronic bacterial prostatitis model in rats (23). Again, EGCG has been shown to have a synergistic effect with gentamicin against MDR pathogens (6).

In this study, the antifungal effect of Camellia sinensis extracts was more effective than EGCG on C. albicans species. It reveals that the in vitro anticandidal activity of other polyphenols in green tea extract is higher than that of EGCG. The antifungal activity of green tea extract is credited to its polyphenol content and catechins (24). However, more extensive in vitro and in vivo studies should be performed for the treatment of invasive Candida infections.

In a study conducted in 2020, the antibacterial effect of EGCG (Epigallocatechin gallate) on Streptococcus suis was investigated. Streptococcus suis is a deadly zoonotic pathogen. The researchers found that EGCG at the minimum inhibitory concentration (MIC) exhibited significant inhibitory effects on S. suis growth, hemolytic activity and biofilm formation. Moreover, EGCG reduced S. suis pathogenicity in Galleria melonella larvae in vivo. To explore the underlying mechanism of EGCG's antibacterial activity at MIC, metabolomic and proteomic analyses were performed. Several differentially expressed proteins involved in DNA replication, cell wall, and cell membrane synthesis, and virulence were down-regulated in S. suis after EGCG treatment (25).

In a study focused on SARS-CoV-2, the researchers found that green tea beverage (GTB) and its main component, epigallocatechin gallate (EGCG), were highly effective in inhibiting live SARS-CoV-2 infection and human coronavirus (HCoV OC43) infection. Additionally, the study showed that GTB or EGCG efficiently blocked infection by pseudoviruses carrying spikes of the new SARS-CoV-2 variants (UK-B.1.1.7, SA-B.1.351, and CA-B.1.429). Overall, the results demonstrated the strong antiviral potential of GTB and EGCG against SARS-CoV-2 and its variants (26).

EGCG inhibits key functions of the HU protein, a crucial regulator of F. tularensis virulence, resulting in reduced F. tularensis viability. This makes EGCG a promising candidate for countering tularemia, a highly infectious intracellular bacterial disease caused by F. tularensis, and considered a potential biological weapon. In mouse models, EGCG administration delays death in F. tularensis-infected mice, indicating its potential use as a prophylactic agent against tularemia (27).

EGCG is the most promising polyphenol approved through cell culture analysis for inhibiting the entry of the Hepatitis C Virus (HCV). Consequently, various in silico techniques have been employed to identify other potential inhibitors that can mimic EGCG's behavior. As part of this effort, homology modeling of the E2 protein was performed. Homology modeling enables the generation of a 3D structural model of the E2 protein based on its sequence similarity with known

protein structures. This computational approach is crucial for designing and identifying potential inhibitors that can block HCV entry, similar to the inhibitory effects of EGCG (28).

Zhang and colleagues found that EGCG can inhibit the entry of SARS-CoV-2 into cells by suppressing ACE2 and TMPRSS2, both of which are essential for viral entry. This inhibitory effect is achieved by activating Nrf2. Additionally, EGCG can further hinder viral reproduction by inhibiting the main protease of SARS-CoV-2, which is crucial for viral replication. In summary, EGCG has the potential to block SARS-CoV-2 infection by suppressing viral entry and replication through its effects on ACE2, TMPRSS2, and the main protease (Figure 1) (7).

In breast tumors, (-)-epigallocatechin-3-gallate (EGCG), the primary catechin found in green tea, may hinder the process of carcinogenesis by targeting epigenetic alterations. Specifically, researchers identified hypermethylation of the tumor suppressor gene, signal peptide-CUB-EGF domain-containing protein 2 (SCUBE2), which suggests a potential mechanism by which EGCG exerts its anti-cancer effects in breast cancer (29).

Various recent studies on EGCG and Camellia sinensis have also been presented in the discussion section. In our study, we investigated the antibacterial and antifungal activities of these substances. As highlighted in numerous articles, both EGCG and Camellia sinensis have shown strong effects with beneficial outcomes. While our study found EGCG to be more effective, Camellia sinensis oil also demonstrated positive efficacy. Due to EGCG's antibacterial and antifungal effects against bacterial and fungal strains, it can be used alone or in combination with antibiotics to take advantage of its synergistic effects. Further studies are needed to investigate their antibacterial and antifungal activity against a wide variety of bacterial and fungal strains. In the future, more research will be required to explore the combined use of green tea extract and antibiotics and antifungals to control drug-resistant pathogens.

Author Contributions

H Köksoy: Conseptualization ideas, Methodology, Resources Writing, Preparation and Statistics C Ragbetli: Conseptualization ideas, Methodology, Validation, Verification and Preparation

Acknowledgments

In this study, we would like to thank Prof. Dr. Harun Alp, the head of the Department of Pharmacology at KMU Faculty of Medicine, for this support and efforts.

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