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Applications and Implications from Epigallo Catechin Gallate (EGCG) in Green Tea

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ABSTRACT

Epigallo catechin gallate (EGCG), a catechin bioactive component found in green tea, has been used widely as a popular beverage in Asian nations for centuries. According to a summary of five years' worth of recent papers, EGCG has a wide range of positive benefits including anticancer, anti-cholesterol, cardiovascular agent, anti-virus, antioxidant, and adjuvant treatment agent. The purpose of this literature review is to get more knowledge on EGCG, the most prevalent catechin derivative found in green tea. A substance with significant antioxidant capabilities, EGCG has a wide range of applications. However, EGCG also has a number of drawbacks in addition to its benefits, such as low stability, poor absorption, and the requirement for a daily intake restriction because it acts as a pro-oxidant and can be harmful if consumed in excess. As a result, authors attempt to mitigate undesirable effects and discover a way to maximize EGCG benefits through additional study that serves as research material. Furthermore, we are becoming research subjects in order to against the negative effects of EGCG, such as how to use probiotics to boost the absorption of EGCG during digestion.

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1. Introduction

Green tea has been extensively consumed as a beverage in Asian countries for centuries. Green tea has various health benefits, such as cancer prevention, obesity, diabetes, and neurodegenerative diseases. Green tea and its extracts are rich in polyphenolic compounds, most of which are flavanols, commonly known as catechins (Cao et al., 2016).

The most important catechins evidenced in several studies with teas (*Camelia sinensis*) are as follows: (-)-catechin (C), (-) catechin gallate (CG), (-)-epicatechin (EC), epicatechin gallate (ECG), (-)-gallocatechin (GC), (-)-epigallocatechin (EGC) and (-)-epigallocatechin gallate (EGCG). The concentrations of these compounds may vary primarily about the region of production, the stage of maturation of the plant, and the processing conditions (Sanlier et al., 2018).

Green tea contains approximately 50% of catechin called (–)-epigallocatechin-3-gallate (EGCG). EGCG has the remarkable potential to scavenge radicals and chelate metal ions. These abilities could be ascribed to the presence of dihydroxy and trihydroxy groups in A ring, B ring, and D ring. See the figure 1 below (Gan et al., 2018)

EGCG, the most abundant (approximately 50%) and active catechin present in the green tea extract (GTE), displays a wide range of beneficial effects including anti-inflammatory, anti-carcinogenic, anti-microbial, immune modulating effects (Xing et al., 2019), anti-obesity (L.-C. Wang et al., 2018) and others as attached.

Research on fermented tea to increase the value of the tea leaves especially for their stability and absorption ability in the gut system. They used a variety of probiotics and had good results. In a recent study, it was stated that fermented green tea can increase its biostability and absorption as shown in the research were fermented green tea with various probiotics such as *Levilactobacillus brevis* (Jin et al., 2021), SCOBY (Kaewkod et al., 2019), *Lactobacillus paracasei* subsp. paracasei NTU (L.-C. Wang et al., 2018), *S. thermophilus* (108 -–109 CFU/ml) and *Lactobacilllus* spp. (106 – 107 CFU/ml) (Muniandy et al., 2017), *Saccharomyces cerevisiae* (R. Wang et al., 2020), *Streptococcus thermophilus* and *Lactobacillus bulgaricus* (Gülfem et al., 2018), *Lactobacillu*s sp (Chatterjee et al., 2018), *Lactobacillus acidophilus* (Najgebauer-Lejko, 2014), *Streptococcus thermophilus* (ST) and *Lactobacillus bulgaricus* (Romero et al., 2021) and *Lactobacill*i spp. and *Bifidobacteria* spp (Rha et al., 2019).

Summarized from the 5-year recent articles will be shown. Besides the benefits, there are some negative impacts of consuming green tea in exceed that can be overcome with further research that we are learning to be research material. EGCG has a broad variety of advantageous effects, such as cardiovascular, anti-cancer, anti-cholesterol, antioxidant, and adjuvant therapeutic agents. In addition to its advantages, green tea consumption has certain drawbacks, such as poor stability and absorption. Since it is a prooxidant, green tea has a daily intake limit that should be adhered to to avoid EGCG becoming a hazardous agent. More study is being conducted to improve the effectiveness of green tea, which has a high EGCG content. Fermented green tea is one approach being investigated, it has been demonstrated to improve the health of the digestive tract. This is because fermented tea contains probiotics that can increase the bioaccessibility (biostability and absorption) of EGCG in green tea. This study aims to look for other probiotics that has a great impact on increasing health as in fermented green tea.

2. Methods

This study used literature study methods. The Impact (application and implication) of EGCG from green tea from many sources will be described below.

2.1 *The Application of EGCG from Green Tea From Many Sources*

Green tea has been associated with various health benefits, such as cancer prevention, obesity, diabetes, and neurodegenerative diseases (Cao et al., 2017).

As Anticancer

EGCG has emerged as a chemo-preventive product with anticancer activity for its ability to target several oncogenic signaling pathways and it has been recently tested in various phases of clinical trials (Farooqi et al., 2020).

As Anti-cholesterol

Consumption of green tea EGCG resulted in a significant reduction of LDL-C and the effect size was slightly dependent on the baseline lipid level of the subjects (Momose et al., 2016). A double-blind, randomized, placebo-controlled trial further confirmed the benefit of EGCG on blood lipids in healthy postmenopausal women (Samavat et al., 2016).

As Cardiovascular agent

A meta-analysis evaluated the association between green tea intake and risk of cardiovascular diseases or ischemic related diseases. The study provided evidence that consumption of green tea is associated with favorable outcomes (Pang et al., 2016).

As Antivirus

Green tea polyphenols are known to possess antiviral activities against a wide range of DNA and RNA viruses. Among natural catechins, EGCG was found to be the most potent virus inhibitor and the 3-galloyl and 50-OH groups appear crucial for this activity(Kaihatsu et al., 2018 , X u et al., 2017).

As Antioxidant

α-lipoic acid to catechins is effective for its stabilization. BP-4, a soluble UVB filter, can stabilize EGCG to produce effective anti-oxidants (Bae et al., 2020). EGCG reduced the secretion and production of melanin in human melanoma cells in skin hydration that measured anti-oxidant and pigmentation properties. EGCG increased hyaluronic acid synthase gene expression and cell proliferation (Kim et al., 2018).

EGCG-5′-O-α-glucopyranoside (EGCG-5′Glu), an EGCG derivative, has anti oxidative effects in both cell-free and cellular systems. EGCG-5′Glu restores reactive oxygen species (ROS)-mediated cell viability, regulates caspases and cell survival molecules, and increases cell proliferation by modulating NF-κB activity (Han et al., 2018).

As Adjuvant therapies

Cooperative interaction of two or more agents could target more signaling pathways, thus effectively improving agent chemo sensitivity, reducing untoward effects of treatment, expanding the scope of action, and showing higher therapeutic outcomes (Pathak et al., 2018). EGCG could also up regulate Copper transporter 1 (CTR1) expression through the stimulation of ROS (Chen et al., 2020).

Many studies found that EGCG inhibits signal transducer and activator of transcription (STAT)1/3 and also nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factors, whose activities are crucial in a multiplicity of downstream pro-inflammatory signaling pathways so can be proposed as a supplementation therapy with EGCG in COVID-19 patients (Menegazzi et al., 2020).

2.2 *Negative Impact of EGCG from Green Tea*

The biological activity of EGCG comes from a large number of active phenolic hydroxyl groups with molecular structure, which are widely used in food industry. Especially in recent years, some studies have confirmed that EGCG has good healthcare effects, including antioxidant (Kim et al., 2018) and antitumor (Huang et al., 2017).

Poor Stability

Many studies have confirmed that the bioavailability of EGCG is related to its stability. Poor stability was an important reason for the low utilization rate (Zhang & Zhang, 2018). The blood-brain barrier (BBB) is a kind of selective diffusion barrier, which can restrict some substances in the blood to enter the brain tissue and maintain a relatively constant internal environment. After oral administration, EGCG was metabolized into GA and EGC in the small intestinal microbial environment, while the resulting EGC further divides into EGC-M5 in the large intestine environment. Unno et al., (2017) reported the results of BBB permeability of EGCG within 0.5 h.

Compared with smaller molecular size GA (MW170.12), the BBB permeability of the molecular size EGCG (MW458.372), EGC (MW306.27), and EGC-M5 (MW208.07) were decreased by 57.54%, 47.35%, and 43.31%, respectively. The results showed that the molecular weight of EGCG and its metabolites was smaller and its permeability was higher. In addition, the BBB permeability of EGCG may also be affected by hydrophobicity (Pervin et al., 2017); The less polar molecules were, the greater their absorption of brain tissue (Figueira et al., 2017; Squillaro et al., 2018). Therefore, the structural modification of EGCG could not only improve the stability of EGCG in the gastrointestinal tract but also affect its absorption.

Poor Absorption

Oral EGCG enters the intestine through the stomach. Part of the EGCG that entered the intestine was absorbed into the blood and then transported to other organs or parts. Therefore, only part of EGCG could play its biological function. Most EGCG entered the excretion system through bile and then was excreted. Most of the EGCG was not absorbed by the intestine, entered the large intestine, and was excreted by feces. From oral administration to excretion, only a few EGCG have biological effects Another study reported that the blood concentration of EGCG peaked from 1 to 2 h after ingestion when oral EGCG was absorbed by the intestine (Law et al., 2017).

Glycoside modification refers to the selective attachment of one or more hydrophilic monosaccharides to eight phenolic hydroxyl groups of EGCG. At present, the most common modification is to improve the bioavailability of EGCG.

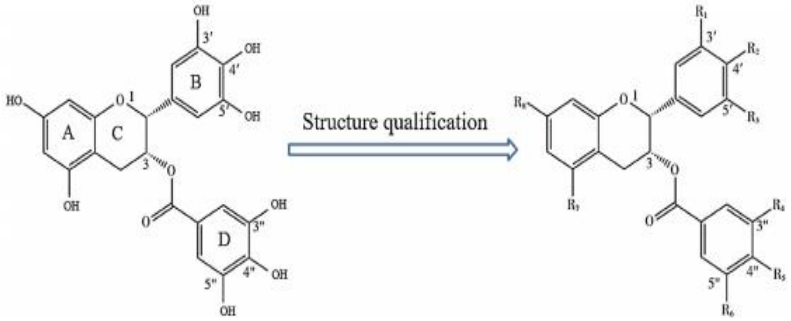

Figure 1. Schematic diagram of EGCG modification (note: In the process of structural modification of EGCG, X represents methyl, acyl, and glycosides, respectively (Dai et al., 2020)).

As prooxidant

Besides as an antioxidant, EGCG could also function as a prooxidant under certain. Its pro-oxidant effects on the cells were evidenced as oxidative damage to the cell structures, including DNA and lipids (Ouyang et al., 2020).

3. Results and Discussion

3.1. EGCG content

Green tea generally contains catechins, namely Epigallocatechin gallate/EGCG, Epicatechin gallate /ECG, Epigallocatechin EGC, and Epigallocatechin/EC. EGCG as a source of catechins is abundant in green tea and EGCG is found most abundantly in green tea compared to other plants which are beneficial for health (Bae et al., 2020); (Shen et al., 2012). Here, the information includes about catechins type and % content in thick extract.

Types of Catechins and Their Levels in Green Tea

Catechin components	Green tea (% weighed from thick extract)
Epigallocatechin gallate (EGCG)	20,3
Epicatechin gallate (ECG)	5,2
Epigallocatechin (EGC)	8,4
Epicatechin (EC)	2,0

(Cataldo, 2014)

Epigallo catechin-3 gallate (EGCG) > Epicatechin gallate (ECG) > Epigallo catechin (EGC) > Epicatechin (EC) > Catechin (C) are the catechin compounds in green tea that contain hydroxyl groups that are positively correlated with the antioxidant activity of phenolic compounds (Bernatoniene & Kopustinskiene, 2018). The most prevalent component of green tea, EGCG, is the subject of both in vitro and in vivo research. Although EGCG has highly potent antioxidant properties, it is typically unstable and poorly absorbed once it reaches the digestive system (Pedro, 2020).

The dried leaves of green tea (7380 mg per 100 g), white tea (4245 mg per 100 g), and black tea (936 mg per 100 g) all contain significant amounts of EGCG. Through the use of polyphenol oxidases, the catechins in black tea are mostly transformed into theaflavins and thearubigins (Bhagwat et al., 2011). Apple peel, plums, onions, hazelnuts, pecans, and carob powder (109 mg per 100 g) contain trace quantities (Lorenz et al., 2009).

According to a review from 2018, consuming too much EGCG can be harmful to the liver. The risk of liver damage could grow with a daily intake of 800 mg or higher, according to the European Food Safety Authority in 2018 ((ANS) et al., 2018).

Taken as a pill or capsule The recommended daily intake of EGCG is 338 mg, although drinking tea is safe at 704 mg. The amount of EGCG in 100 mL of green tea is around 70.2 mg (or 165 mg per cup). However, consumption of EGCG that does not exceed the recommended standard dose will have a significant impact on the health of the human body (Hu et al., 2018).

3.2 Intake limit of EGCG Consumption

A tolerable upper intake level of EGCG, based on animal and human data. The need for establishing tolerable upper intake levels for bioactive nutrients and used EGCG as one example of an approach on how to assess the safety of bioactive dietary components. A tolerable upper intake level of 300 mg/day of EGCG, based on human data in healthy adults in a fed state, and an acceptable daily intake (ADI) of 4.6 mg/kg per day, derived from animal toxicity data (Yates et al., 2017).

In a safety assessment of green tea supplements, proposed a tolerable upper intake of 300 mg EGCG/person and day, based on clinical trials that did not report liver effects (using a twofold safety margin), and NOAELs from animal studies with dietary administration of green tea catechins (using a safety factor of 100) (Dekant et al., 2017).

The National Food Administrations of Norway, Sweden and Denmark requested the Commission to initiate the procedure under Article 8 of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to food for the intake of catechins, and in particular EGCG in green tea extracts used in the manufacture of food supplements and in green tea infusions, because of safety concerns on the potential risk to consumers associated with the intake of these substances. These concerns – cases of liver toxicity possibly associated with the intake of green tea catechins – are outlined in the scientific opinion on green tea extracts and green tea infusions carried out by the National Food Institute of the Technical University of Denmark and in the safety assessment on levels of EGCG in green tea extracts used in food supplements carried out by the Norwegian Institute of Public Health (ANS) et al., 2018).

3.3 Future Perspectives

To overcome the negative impact of EGCG with further research we are learning to be research material, such as how to increase the absorption of EGCG in digestion with probiotics (L.-C. Wang et al., 2018). Even though EGCG has highly potent antioxidant properties, it tends to be unstable once it enters the digestive tract due to its limited bioaccessibility. One way to boost bioaccessibility is by fermenting green tea with probiotics. Probiotics are anticipated to improve bioaccessibility. Probiotics are a class of food that contains living, non-pathogenic bacteria that, when administered to people or animals, assist the host by balancing the microbiota in the digestive system and enhancing overall body health (Fuller, 1989; Syukur et al., 2022).

4. Conclusion

Based on the results of our study, EGCG in green tea displays a wide range of beneficial effects including anti-cancer, anti-cholesterol, cardiovascular agent, anti-virus, antioxidant, and adjuvant therapy agents that are summarized from the 5-year recent articles. Besides the benefits, there are some negative impacts of consuming green tea including poor stability, poor absorption, and as a prooxidant needs a daily intake limit to prevent exceeding consumption. To make green tea more effective that contain great EGCG inside, more research is being done. One method being explored is fermented green tea contains probiotics inside, which has been shown to enhance digestive system health with increasing

bioaccessibility. This study compares using green tea with many probiotic and further research to look at other probiotics that have a great impact as in fermented green tea.

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