

## Network Analysis Reveals Tea Catechins as Multi-Target Inhibitors of Colon Adenocarcinoma

### *Network Analysis Mengungkap Katekin Teh sebagai Penghambat Multi-Target pada Adenokarsinoma Kolon*

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#### ABSTRACT

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*Colon cancer is the second most common cause of cancer death worldwide. It drives the need for effective prevention and treatment strategies, including identifying new and inventive targets for treating colon cancer. This present study evaluated the potential of tea catechins against colon adenocarcinoma in silico. The study method includes a literature review, an analysis of protein targets and protein interactions, and network analysis. The prediction analysis showed that only epicatechin-3-gallate, epigallocatechin-3-gallate, and epigallocatechin potentially target colon cancer. These compounds target six common proteins in human cancer cells, such as AURKA, CA9, SERPINE1, MET, SQLE, and VEGFA. The analysis showed that the protein targets interact strongly with various proteins in human cancer cells. Therefore, tea catechin, especially epigallocatechin-3-gallate, can be explored as a colon cancer chemopreventive agent.*

**Keywords:** Chemoprevention; Colon Cancer; EGCG; Ethnopharmacology; Tea Catechin

#### ABSTRAK

Kanker usus besar menduduki peringkat kedua sebagai penyebab kematian akibat kanker di seluruh dunia. Hal ini menggarisbawahi perlunya strategi pencegahan dan pengobatan yang efektif, termasuk mengidentifikasi target baru dan inventif untuk mengobati kanker usus besar. Penelitian ini bertujuan untuk mengevaluasi potensi katekin teh terhadap adenokarsinoma kolon secara in silico. Metode penelitian ini mencakup tinjauan literatur, analisis target protein dan interaksi protein, serta analisis jaringan. Analisis in silico memprediksi bahwa hanya epigallocatechin-3-gallate, epicatechin-3-gallate, dan epigallocatechin yang berpotensi menargetkan kanker kolon. Senyawa-senyawa ini dapat menargetkan enam protein umum dalam sel kanker manusia, seperti AURKA, CA9, SERPINE1, MET, SQLE, dan VEGFA. Analisis menunjukkan bahwa target protein tersebut berinteraksi kuat dengan berbagai protein dalam sel kanker manusia. Oleh karena itu, katekin teh, terutama epigallocatechin-3-gallate, dapat dieksplorasi sebagai bahan kemoprevensi kanker kolon.

**Kata Kunci:** Kanker Kolon; Katekin Teh; Kemopreventif; EGCG; Etno-Farmakologi

## 1. INTRODUCTION

Colon cancer, a malignant neoplasm originating in the large intestine, stands as a formidable public health concern worldwide. It is the second most common cause of cancer death worldwide (World Health Organization, 2023). The incidence varies across regions, with developed countries generally reporting higher rates.

This disparity is attributed to dietary habits, lifestyle, and genetic predisposition (World Health Organization, 2023). In Indonesia, colon cancer, while less prevalent compared to certain other cancers, is showing an upward trend (Ferlay et al., 2015). The epidemiological profile of the disease in the country is evolving due to rapid urbanization, dietary shifts towards Westernized patterns, and increasing life expectancy (Anyanwu et al., 2022).

These factors, coupled with limited awareness and access to early detection, contribute to the growing challenge of colon cancer management in Indonesia. Moreover, colon cancer risk is age-dependent. It underscores the need for effective prevention and treatment strategies. Despite advancements in medical science, the treatment of colon cancer remains a complex challenge.

Surgery, chemotherapy, and radiation therapy constitute the primary modalities. While these interventions have improved outcomes, they often encounter limitations, such as drug resistance, severe side effects, and recurrence (Azwar et al., 2021). Chemotherapy is associated with a range of adverse effects, including hair loss, vomiting, nausea, and immunosuppression, significantly impacting patients' quality of life (Anand et al., 2023).

Moreover, chemotherapy might affect non-target cells. Therefore, it is crucial to identify new and inventive targets for treating colon cancer. Ethnopharmacology has emerged as a promising avenue for novel therapeutic approaches. This discipline explores traditional medicinal practices to identify and develop new drugs. Local communities have a long history of ethnopharmacological practices, including using plants for cancer treatment (Rovik et al., 2024).

Ethnopharmacological investigations have unveiled various bioactive compounds with potential anticancer properties. These compounds often exhibit distinct mechanisms of action compared to standard drugs, potentially overcoming limitations associated with chemotherapy. Moreover, natural products are usually perceived as having fewer side effects, making them attractive alternatives or

complementary therapies (Farhan, 2022; Susilo et al., 2023).

5-Fluorouracil (5-FU) has been a cornerstone in colon cancer therapy for decades. However, the emergence of drug resistance frequently diminishes the therapeutic effectiveness of 5-FU. Also, one of the significant limitations of 5-FU is its severe toxicity (Azwar et al., 2021; Suetsugu et al., 2021). Tea catechin has attracted considerable attention for its anticancer potential.

Catechins represent a subgroup of flavonoids, highly prevalent compounds in tea. They exhibit diverse biological activities, including anti-inflammatory, antioxidant, and antiproliferative properties (Cheng et al., 2020; Farhan, 2022; Li et al., 2022). Meta-analyses indicate that green tea consumption may be associated with a reduced risk of lung and breast cancer (Guo et al., 2019; Najaf-Najafi et al., 2018; Yu et al., 2019).

Tea catechins exert anticancer effects by inducing apoptosis, inhibiting angiogenesis, and modulating key signaling pathways in cancer (Cháirez-Ramírez et al., 2021). This present study evaluated the potential of tea catechins against colon adenocarcinoma *in silico*.

## 2. METHODS

### 2.1 Literature review

In this review, we investigated bioactive compounds present in tea leaves. We compiled a list of these compounds from relevant studies published within the last decade in Scopus, Neliti, and PubMed databases. We focused our subsequent analysis on the most prevalent bioactive compounds identified. To obtain the chemical structures of these compounds, we utilized the PubChem public database (<https://pubchem.ncbi.nlm.nih.gov/>).

### 2.2 Protein and gene target prediction

*In silico* target prediction of proteins and genes was performed using the Swiss Target Prediction database (<http://www.swisstargetprediction.ch/>), which specializes in human protein targets. The canonical SMILES strings for each compound were submitted to the Swiss Target Prediction tool. The resulting predicted target data was then downloaded for further analysis.

### 2.3 Database analysis of gene expression in colon cancer patients

We investigated gene expression profiles in colon cancer patients using the online resource UALCAN (<https://ualcan.path.uab.edu/analysis.html>). This analysis was then employed to identify

genes whose expression overlapped with the predicted protein targets identified earlier. Further analysis was performed to determine common target proteins and genes at <https://www.interactivenet.net/>. The target protein of tea catechins was compared to the overexpressed genes in colon cancer.

#### 2.4 Protein-to-protein interaction

The STRING database (<https://string-db.org/>) was used to analyze protein-protein interactions. The STRING analysis employed a medium-confidence interaction network (4.00 score), further analyzed using Cytoscape software.

### 3. RESULTS AND DISCUSSIONS

The literature review revealed that the significant tea catechins include (-)-epicatechin, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epigallocatechin-3-gallate (**Figure 1**). The heatmap shows distinct gene expression patterns between normal and tumor tissues (**Figure 2**). The color scale represents the  $\log_2(\text{TPM}+1)$  values, where higher values indicate higher expression levels.

A significant upregulation of several genes was observed in tumor tissue relative to normal tissue, including CST1, MMP7, KRT23, KRT80, CA9, FOXQ1, CDH3, CPNE7, CLDN2, KIAA1199, LY6G6D, ETV4, CLDN1, NKD1, GRIN2D, C6orf223, PDX1, MMP3, GYLTL1B, MMP11, TESC, TRIM29, NKD2, MMP1, and PRSS22. These overexpressed genes may play critical roles in colon adenocarcinoma pathogenesis.

The prediction analysis showed that only epicatechin-3-gallate, epigallocatechin-3-gallate, and epigallocatechin potentially target colon cancer. These compounds target six common proteins in human cancer cells, such as AURKA, CA9, SERPINE1, MET, SQLE, and VEGFA (**Figure 3**). These six proteins were analyzed using the STRING website. The analysis showed that the protein targets interact strongly with various proteins in human cancer cells (**Figure 4**).

Colon adenocarcinoma is a prevalent form of colorectal cancer. It is a multifaceted disease characterized by aberrant cellular proliferation and the capacity for metastatic dissemination (World Health Organization, 2023). While advancements in treatment have improved patient outcomes, developing novel therapeutic strategies remains a critical challenge.

Identifying and targeting overexpressed genes and proteins in colon adenocarcinoma has

emerged as a promising approach. Traditional drug discovery often focuses on single molecular targets, neglecting the complex interplay of multiple proteins within biological networks. Network pharmacology offers a systems biology approach to identifying and prioritizing drug targets.

Identifying critical nodes and modules associated with disease pathogenesis can be performed by analyzing protein-protein interaction networks (Wang et al., 2023). This study explores the potential of tea catechins as a chemopreventive agent against colon adenocarcinoma. Natural compounds often possess multiple mechanisms of action, targeting various cancer-related pathways simultaneously.

This action might help overcome drug resistance and enhance therapeutic efficacy. Tea catechin was reported to potentially protect normal tissues from chemotherapy damage by reducing oxidative stress and inflammation (Suetsugu et al., 2021). Furthermore, some studies have suggested that tea catechins can enhance the gastrointestinal mucosal barrier, which may help prevent 5-FU-induced mucositis, a common and debilitating side effect (Azwar et al., 2021; Suetsugu et al., 2021; Susilo et al., 2023).

The prediction analysis showed that only epicatechin-3-gallate, epigallocatechin-3-gallate (EGCG), and epigallocatechin potentially target colon cancer. EGCG is the predominant catechin in fresh tea leaves, accounting for over 40% of the total catechin content (Cheng et al., 2020; Farhan, 2022; Li et al., 2022). Among other catechins, EGCG was reported to be the most biologically active (Shirakami & Shimizu, 2018).

EGCG induces apoptosis in human colon cancer cells by inhibiting ERK, activating JNK, and triggering the release of cytochrome C (Cerezo-Guisado et al., 2015). In addition, EGCG suppresses signaling pathways such as Akt, MAPK, ERK1/2, AP-1, NF- $\kappa$ B, and p38, leading to cell cycle arrest (Cheng et al., 2020). The result showed six common protein targets of tea catechin in human cancer cells, such as AURKA, CA9, SERPINE1, MET, SQLE, and VEGFA (**Figure 3**).

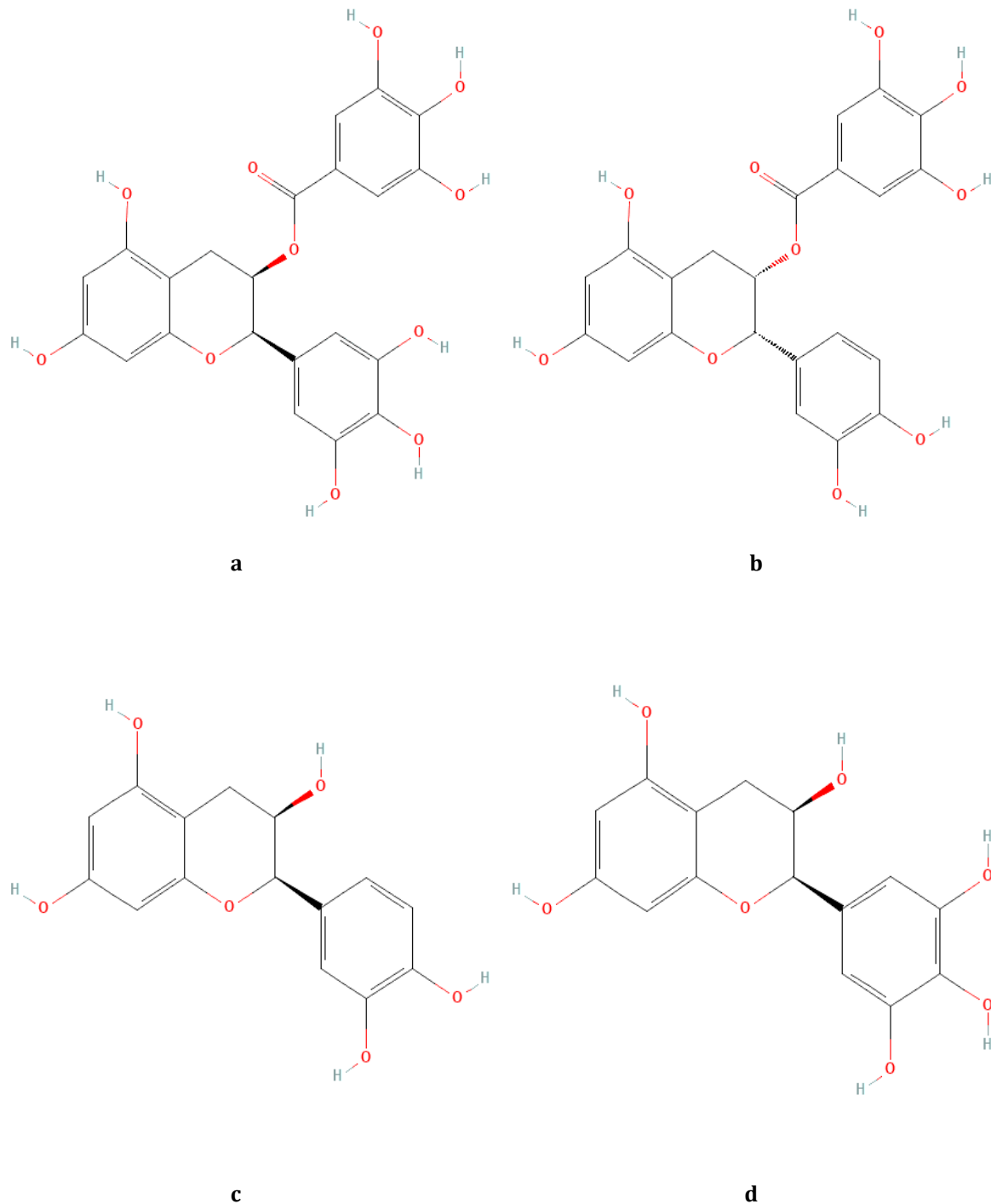
Aurora kinase A (AURKA), a serine/threonine kinase essential for cell division and chromosome segregation, is subject to stringent regulatory mechanisms. However, in many cancers, including colon cancer, AURKA is overexpressed. Its overexpression can lead to centrosome amplification, abnormal mitotic spindles, and chromosomal instability. This genomic instability can drive cancer progression

by generating genetic alterations that promote cell growth, survival, and invasion.

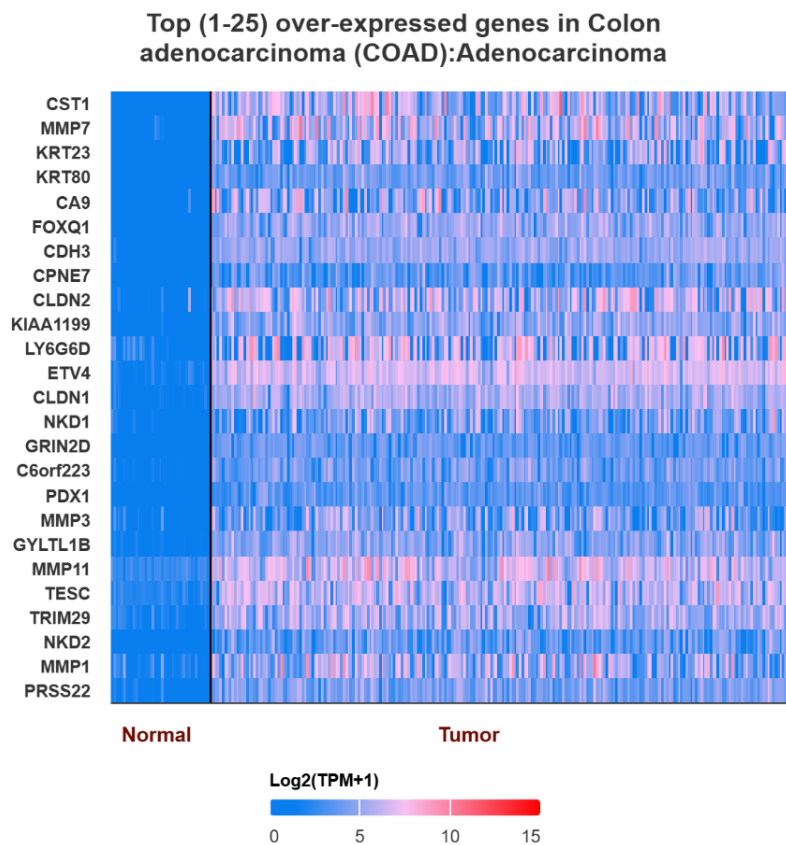
Furthermore, AURKA is a critical regulator of the G2/M phase transition within the cell cycle, which can accelerate cell cycle progression, increasing cell proliferation and cancer growth. Moreover, AURKA has been

shown to upregulate VEGF, a critical factor in forming new blood vessels in angiogenesis (Kang et al., 2024; Nikonova et al., 2013).

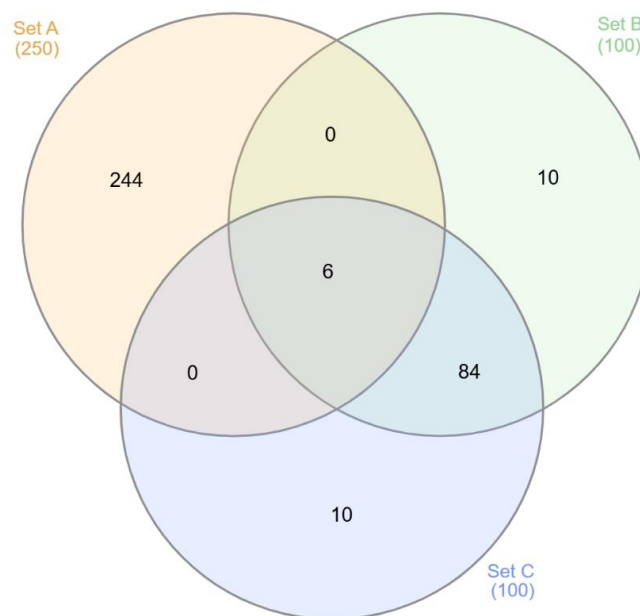
Carbonic anhydrase (CA9) is an enzyme that regulates pH balance within cells. It catalyzes the conversion of  $\text{CO}_2$  into  $\text{HCO}_3^-$ .



**Figure 1.** Chemical structure of tea catechins: a) epigallocatechin-3-gallate, b) epicatechin-3-gallate, c) epicatechin, and d) epigallocatechin. The structure was retrieved from the PubChem website.



**Figure 2.** Top 25 upregulated genes in colon adenocarcinoma patients compared to normal tissue. The analysis was performed using the UALCAN website



**Figure 3.** The typical potential target proteins of tea catechins in human cancer cells. The analysis was performed using the InteractiVenn platform. Set A: upregulated genes in colon adenocarcinoma patients; set B: protein target of epicatechin-3-gallate; set C: protein target of epigallocatechin-3-gallate



**Figure 4.** Protein-to-protein interaction network. The analysis is performed using STRING with a moderate network (4.00 score)

While essential for normal physiological functions, its overexpression in certain conditions, particularly cancer, can contribute to cancer growth and progression (Pastorekova & Gillies, 2019). Cancer growth often outpaces blood vessel formation, leading to oxygen deficiency. CA9 maintains intracellular pH, promoting cancer cell survival and proliferation (Pastorekova & Gillies, 2019).

Moreover, a study suggests that CA9 overexpression might contribute to chemotherapy resistance in colon cancer (Kováčová & Hodorová, 2021). Plasminogen activator inhibitor-1 (PAI-1 or SERPINE1) is a serine protease inhibitor with diverse functions, including regulating fibrinolysis, cell proliferation, angiogenesis, and extracellular matrix remodeling.

Its overexpression can contribute to pathological conditions. Increased SERPINE1 expression has been observed in various stages of colon cancer, from early-stage adenomas to advanced metastatic disease (Kim et al., 2022). SERPINE1 primarily functions as an inhibitor of plasminogen activators, leading to reduced

fibrinolysis. This condition contributes to cancer development and metastasis by creating a supportive microenvironment (Wang et al., 2023).

Hepatocyte growth factor receptor (HGFR or MET) is a tyrosine kinase receptor that is a key regulator of various cellular functions, including cell growth, proliferation, migration, and angiogenesis. MET initiates intracellular signaling cascades that drive these cellular responses when activated by hepatocyte growth factors (Yao et al., 2019).

Overexpression of MET has been consistently reported in various types of human cancers, including colon adenocarcinoma (Lai et al., 2021). MET activation stimulates cell growth and proliferation by activating downstream signaling pathways, including the PI3K/AKT and RAS/RAF/MAPK. MET also plays a critical role in angiogenesis, essential for forming new blood vessels that facilitate cancer invasion and metastasis.

In addition, studies suggest that MET overexpression may contribute to developing resistance to chemotherapy in colon cancer (Tang

et al., 2023; Yang et al., 2014). Squalene epoxidase (SQLE) is an essential enzyme in the cholesterol biosynthesis pathway, catalyzing the crucial conversion of squalene into squalene epoxide, an intermediate step in cholesterol synthesis. SQLE overexpression increases cholesterol biosynthesis, altering lipid metabolism within cancer cells.

This altered lipid profile can contribute to cancer growth, proliferation, and invasion (Abe et al., 2000; Du et al., 2023). Li et al. reported that squalene epoxidase increases gut dysbiosis and cancer cell proliferation, speeding up colon cancer development (Li et al., 2022). Vascular endothelial growth factor A (VEGF-A) is a potent stimulator of angiogenesis, the physiological process of new blood vessel formation.

Elevated VEGF-A expression enhances angiogenesis by promoting endothelial cell proliferation, migration, and the formation of new blood vessel structures (Clarke & Hurwitz, 2013; Hutajulu et al., 2018). This process is essential for cancer growth, providing oxygen and nutrients to the rapidly growing cancer.

Additionally, VEGF-A can induce the expression of matrix metalloproteinases (MMPs), a family of proteolytic enzymes that degrade the extracellular matrix, thereby facilitating cancer cell invasion and migration (Neuhaus et al., 2004; Yang et al., 2014).

#### 4. CONCLUSIONS

Tea catechin targets six common proteins in human cancer cells, such as AURKA, CA9, SERPINE1, MET, SQLE, and VEGFA. The analysis showed that the protein targets interact strongly with various proteins in human cancer cells. Therefore, tea catechin, especially epigallocatechin-3-gallate, can be explored as a colon cancer chemopreventive agent.

#### CONFLICT OF INTEREST

The author declares that there is no conflict of interest in this study.

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