RESEARCH PAPER

Therapeutic efficacy of BLACK TEA (*Camellia sinensis*) extract in modulating the anti-inflammatory and antifibrotic molecules in Systemic Sclerosis (Scleroderma).

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Abstract

Background: Systemic sclerosis (SSc) drives microvascular dysfunction and fibrosis via oxidative stress, impairing endothelial cells: reduced vasodilatory NO, elevated vasoconstrictors (ET-1), adhesion molecules (VCAM-1, ICAM-1), and ROS-mediated fibroblast activation into myofibroblasts. Standard treatments alleviate symptoms but neglect immune-fibrotic cascades. Black tea (*Camellia sinensis*) phytochemicals, with potent antioxidant/anti-inflammatory effects and minimal toxicity, target these mechanisms cost-effectively.

Methods: Fifteen diffuse-cutaneous SSc patients (ACR/EULAR 2013) and 10 matched controls were enrolled. Serum TGF-β, IL-6 (ELISA), and nitrite (NO biomarker) were measured. PBMCs were isolated, treated with black tea extract (Sigma-Aldrich; 250 ng/mL [IC_{25}], 500 ng/mL [IC_{50}]), and assessed after 24 hours for the levels of NO in the supernatant, TGF-β, IL-6, and collagen I mRNA (qPCR).

Results: Patients showed heightened serum IL-6 ($p<0.0001$), TGF-β ($p=0.0009$), and NO depletion ($p<0.0001$) versus controls, reflecting endothelial-fibrotic imbalance. Extract restored NO ($p<0.0001$), suppressed IL-6 ($p=0.008$), TGF-β ($p<0.0001$)—key fibrogenic signals—and collagen I ($p=0.05$), with IC_{50} outperforming.

Conclusion: Black tea extract counters SSc mechanisms by scavenging ROS, rescuing endothelial NO, and blunting TGF-β/IL-6-driven fibroblast differentiation, reducing extracellular matrix deposition. Clinically, this supports repurposing accessible antioxidants for early intervention, potentially halting progression in underserved diffuse-SSc patients. In vivo trials are essential to validate efficacy and safety.

Keywords: Systemic Sclerosis, Scleroderma, Black Tea, Camellia sinensis, Anti-inflammatory, Antifibrotic, TGF-β, IL-6, Oxidative Stress.

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Introduction

Systemic Sclerosis (SSc), or Scleroderma, is a systemic connective tissue disorder marked by progressive skin and organ fibrosis, microvascular changes, and immune system dysregulation. [1]. Despite advances in understanding its pathogenesis, the etiology of SSc remains unclear, with a notable female predominance [2]. Early stages of the disease are characterized by oxidative stress leading to endothelial dysfunction, reduced nitric oxide (NO) levels, increased endothelin-1 (ET-1), and the release of adhesion molecules like vCAM and iCAM, promoting vascular damage [3]. This vascular damage triggers the release of cytokines, chemokines, and growth factors, which attract immune cells and activate fibroblasts, causing tissue ischemia, inflammation, and fibrosis [4]

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Recent conventional therapeutic approaches for SSc typically target individual organ involvement and provide symptomatic relief for cutaneous manifestations [5] Continuous anti-cytokine treatments require prolonged clinical control, and discontinuation often leads to disease flare-ups [6]. Immunomodulatory drugs, such as Methotrexate and Cyclophosphamide, have demonstrated effectiveness in treating skin and pulmonary involvement but are associated with significant toxic side effects and require extensive monitoring [7]. Additionally, the high cost of these therapies poses a substantial burden on patients and healthcare systems [7–9].

Given these drawbacks, there is a growing interest in exploring alternative approaches that offer long-term cures and cost-effectiveness. Phytochemicals, particularly those found in black tea, have shown promise in managing various critical diseases, including cancer Pure herbal extracts and their active compounds have been identified as inhibitors of cytokine activities, suggesting their potential role in mitigating the inflammatory and fibrotic processes in SSc [10,11]. Recent research has highlighted the potential therapeutic effects of black tea in managing SSc [12–14]. Black tea (*Camellia sinensis*) contains bioactive compounds, particularly flavonoids, which have demonstrated significant anti-inflammatory, antioxidant, and anti-fibrotic properties. Black tea and its active compounds have numerous beneficial effects against inflammation, oxidative stress and diseases like cancer, autoimmune diseases, etc. Moreover, Theaflavins (3-6% of the weight of solid extract), Thearubigins (12-18% weight of solid extract) and catechins (3-10% of the weight of solid extract). During the preparation of black tea, the oxidation process converts these simple flavonoids into more complex theaflavins and thearubigins. All of these active compounds of black tea are very potent therapeutic agents [15,16]. These compounds, including theaflavins and thearubigins, inhibit key pro-inflammatory cytokines such as TNF-α and IL-1β, enhance antioxidant enzyme activity, and mitigate oxidative stress, thereby reducing inflammation and fibrosis [17]

Theaflavins, a unique class of polyphenols in black tea, have been observed to downregulate fibrotic markers such as TGF-β and collagen, suggesting their potential to reduce fibrosis in SSc [12,18]. Additionally, black tea's antioxidant properties may protect against endothelial dysfunction, a hallmark of SSc [19] Recent studies also highlight the immunomodulatory effects of black tea polyphenols, which help restore immune homeostasis disrupted in autoimmune conditions like SSc [20]

In vitro and in vivo studies, as well as clinical trials, support the anti-inflammatory and immunomodulatory effects of black tea components in managing rheumatic diseases [21] Regular consumption of black tea has been associated with a reduction in disease activity and improvement in clinical symptoms in patients with RA and SSc [22] Epidemiological studies suggest a potential link between black tea consumption and a lower prevalence of rheumatic diseases, underscoring the importance of dietary factors in managing chronic inflammatory conditions [19,22,23]

Black tea and its bioactive components offer significant therapeutic potential in regulating rheumatic diseases, particularly SSc. By integrating experimental, clinical, and epidemiological studies, this review highlights the relevance of black tea as a functional food in disease prevention and management. Future research should focus on elucidating the precise mechanisms of action and exploring the long-term benefits of black tea in clinical settings.

Methodology

Recruitment of study participants and sample collection

This *in-vitro* study was conducted at the Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata. Patients of SSc (fulfilling American College of Rheumatology criteria for SSc, 2013) were recruited from the outpatient clinic of the Department of Clinical Immunology and Rheumatology, IPGME&R. Age-sex-matched healthy individuals were included as the control group. Participants of between ≥ 18 and ≤ 55 years were included in the study. Individuals having a current or past history of tobacco usage, renal impairment, co-existence of other rheumatological diseases, hypertension, Hypothyroidism, history of diabetes, and pregnancy were excluded from the study. 5 ml of blood was collected from all recruited study participants, and the following experiments were performed according to the respective protocol. The study was approved by the institutional ethical committee, and consent was taken from all the participants.

Determination of BT Dose and Time:

Isolated PBMCs were treated with different doses of black tea extract (≤ LC50) for different periods (24, 48, and 72 hours). A cell viability assay was performed to select the appropriate dose for further experiments with the help of the MTT assay. PBMCs (1 x 10^5 cells) were plated into 96-well plates, without supplementation. Following this, procured BT was introduced into different doses and incubated for 24 and 48 hours at 37°C in 5% CO2. MTT reagent (5 mg/mL) was added to each well (final concentration 0.5 mg/mL) and incubated for 3-4 hours. After incubation, the supernatant is removed, and 100 µL DMSO is added to solubilize formazan crystals, followed by gentle shaking for 10 minutes. Absorbance is measured at 570 nm using a

microplate reader, subtracting the average blank well absorbance.

Nitrite assay (Griess assay)

One millilitre of collected blood was placed inside an EDTA vial, and it was spun at 3000 × g for five minutes to extract the plasma. After extracting plasma samples from recently drawn blood, the serum was incubated with TCA (5%) (sample: TCA, 1:9, v/v), vortexed for a short while, and then centrifuged at 1000 × g for 10 minutes to deproteinize the sample. Nitric oxide (NO) was then measured in serum sample supernatants that had undergone deproteinization. 100 µl vanadium (III) chloride (8 mg/ml) was added to each well to reduce nitrate to nitrite. Griess reagents, which included 50 µl sulphanilamide (2%) and 50 µl 0.1% N-(1-Naphthyl) ethylenediamine dihydrochloride (NEDD), were then added, and the mixture was incubated for 30 minutes at 37 ºC. A spectrophotometer (BIO-RAD) was used to measure absorbance at 540 nm. A linear standard curve generated by 0–20 µmol/l sodium nitrite was used to calculate the quantity of NO in serum samples.

Peripheral Blood Mononuclear Cell (PBMC) isolation and Culture:

PBMCs were isolated using a lymphocyte-separating medium (LSM) from the blood of the included HCs. Isolated PBMCs were then plated in tissue culture plates and grown in DMEM supplemented with 10 IU/ml penicillin, 0.1µg/ml streptomycin, 2mg/ml L-glutamine, and 10% fetal bovine serum (FBS) for the subsequent days. Treatment with black tea was done to perform the following experiments to check the therapeutic efficacy of BT on different fibrotic molecules. Cells were harvested after 24 hours of treatment with the IC_{25} and IC_{50} dosages detected from the MTT assay.

ELISA of secreted cytokine

The serum was separated from 3 ml of collected blood within the clot vial by spinning it at 3000 × g for 7 min. Serum concentrations of TGFβ and IL-6 were measured by using ELISA kits (KINESIS Dx, Los Angeles), according to the manufacturer's protocol. Translational expression of these molecules was also measured from the cell soup to assess the therapeutic efficacy of BT on these molecules.

Extraction of total RNA

Whole RNA was extracted from peripheral blood, using TRIZOL reagent (Invitrogen). Briefly, 1 ml of collected blood was incubated at room temperature with RBC lysis buffer at a 1:10 ratio. Cells were pelleted down and washed twice with 1x PBS. In ice, cells were incubated with 1 ml of TRIzol reagent and chloroform (TRIzol: chloroform = 1: 0.25). After centrifugal phase separation, total RNA was salted out with isopropanol, washed with 70% ethanol, and air-dried. Then the air-dried RNA was dissolved in RNase-free water and stored at -40 °C.**Quantitative Real-time PCR (qRT-PCR) to analyze gene expression**

Quantitative RT-PCR was done to assess the transcriptional expression of the fibrotic markers in between the HCs and patients, as well as to check the efficacy of black tea on the differential fibrotic

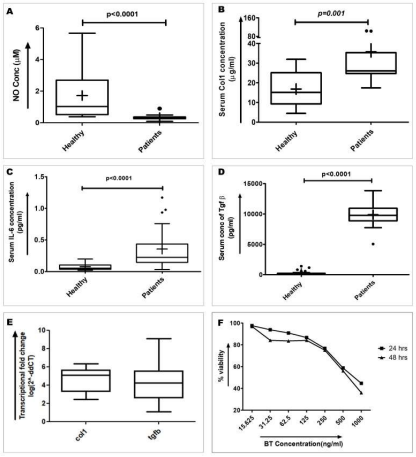

Figure 1. Fibrotic and inflammatory alterations in systemic sclerosis and the dose determination of black tea extract: Serum concentration of NO, Col I, IL-6, and TGF-β . (E) Relative transcriptional fold change of *COL1* and *TGFβ* genes [$\log_2(2^{-ddCT})$] showing enhanced fibrotic gene expression. (F) Dose- and time-dependent reduction in cell viability following black tea (BT) treatment at 24 h and 48 h." +" representing the mean value.

markers. About 2.5 µg of total RNA was treated with 1 unit of DNase-I (Roche Diagnostics, Mannheim, Germany) and first-strand cDNA was synthesized using Revert-Aid Reverse Transcriptase at 42◦C following the manufacturer's protocol (Thermo Scientific). Then the prepared cDNA was diluted (1:20) and used to quantify the expression of genes using SyBr green (Roche Diagnostics, Mannheim, Germany) and respective primer sets in Quant Studio 7 (Thermo Fisher Scientific). 18S ribosomal RNA was used as the internal control for relative quantification of expression of a gene, and each experiment was repeated twice.

Procurement of Black Tea Determination of Toxicity Level of Black Tea Extract:

Black tea extract was directly procured from Sigma Aldrich, USA, for experimental purposes. The LC50 test was conducted on the PBMCs isolated from HCs to establish the toxicity nature of black tea extract. Cell viability assay was performed to assess dead cells using the trypan blue exclusion process. Cell viability was calculated by dividing the non-stained (viable) cell count by the total cell count.

Statistical Analysis.

To assess all normally distributed data, the Shapiro-Wilk test was used. Standard deviation (SD) was used to display mean values for normally distributed variables. The Man-Whitney test for skewed data and the independent *t* test for normally distributed data were used to estimate the difference between the groups, respectively. The categorical variables were compared using the chi-square test. Every p-value less than 0.05 was regarded as statistically significant. The statistical analyses were conducted using MedcalC version 11.6 and GraphPad Prism version 5.0.

Result

Comparative analysis of the molecules responsible for vascular dysfunction and fibrosis

The serum concentration of NO was significantly lower in SSc patients compared to healthy controls

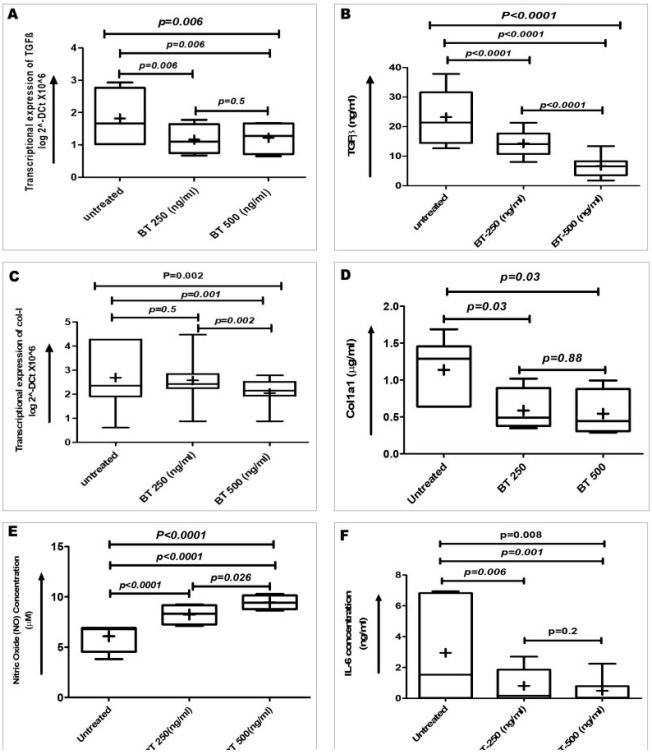

Figure 2. Antifibrotic and anti-inflammatory effect of black tea (BT) treatment. (A–B) and (C-D): Relative transcriptional and translational expression of TGFβ and Col-I, respectively, following *in-vitro* BT treatment (250 and 500 ng/ml). (E-F): the therapeutic efficacy of black tea extract in modulating serum NO and IL-6 concentration

(p<0.0001). Significantly increased serum concentration of Col-I (*p=0.001*), IL-6 (*p<0.0001*) and TGFβ (*p<0.0001*) was observed in SSc patients compared to the healthy controls. (Figure 1). Significantly elevated transcriptional fold change (6-fold and 8.5-fold) was observed regarding the expression of col-I and TGFβ (Figure 1).

Cell viability assay, dose determination of BT.

IC_{50} and IC_{25} dose of black tea was assessed by the MTT assay. Graphical representation of the MTT data revealed that 50% of cells were alive after the treatment at the dose of 500 ng/ml, and 75% of cells were alive after treatment with 250 ng/ml for 24 hours. Similar data was observed regarding the BT treatment 48 hours. Both IC_{50} and IC_{25} doses were selected for further analysis. Irrespective of time (hours), MTT data showed similar comparative viability (%), so all the following treatments were done for 24 hours. **(Figure 1).**

Assessment of the fibrotic molecules:

Transcriptional expression:

Data regarding the expression of the fibrotic marker showed significant alteration after the BT treatment. The master regulator tgf-β showed significant downregulation after the treatment (irrespective of the doses) compared to the untreated group ($p=0.006$ irrespectively). No significant differences were observed between the two treated groups regarding the mRNA expression of tgf-β ($p=0.5$). Expression of col-I showed a significant downregulation after treatment with BT (at the dose of 500 ng/ml) compared to the untreated group ($p=0.001$). No considerable differences were observed between the untreated and treatment groups with 250 ng/ml dose ($p=0.5$).

Translational expression:

Data showed TGF-β concentration was significantly lowered after treatment with BT ($p< 0.0001$, irrespective of both doses). Cell supernatant from the treatment group with BT 500 ng/ml showed a comparatively lower amount of TGF-β compared to the BT 250 ng/ml dose ($p< 0.0001$). The concentration of col-I significantly decreased irrespective of BT doses: BT 250 ng/ml ($p=0.03$) and BT 500 ng/ml ($p=0.03$). No significant differences were observed between the treated groups ($p=0.8$). Inflammatory marker IL-6 was significantly. **(Figure 2).**

Discussion

Systemic sclerosis (SSc), or scleroderma, is a systemic connective tissue disorder characterized by progressive fibrosis, microvascular changes, and immune dysregulation. Despite advancements in understanding its pathogenesis, the etiology of SSc remains unclear, with a notable female predominance. Conventional therapeutic approaches often target specific organ involvement and provide symptomatic relief but are associated with significant side effects and high costs. Consequently, there is a growing interest in exploring alternative treatments that are both cost-effective and provide long-term benefits. One promising alternative is the use of phytochemicals, particularly those found in black tea (*Camellia sinensis*), which have demonstrated anti-inflammatory, antioxidant, and anti-fibrotic properties. This study aims to evaluate the therapeutic potential of black tea extract (BT) in managing SSc by assessing its effects on key markers of fibrosis and inflammation.

The significantly lower serum concentrations of nitric oxide (NO) in SSc patients compared to healthy controls, observed in our study, align with previous research indicating endothelial dysfunction in SSc. Additionally, the increased serum concentrations of collagen type I (Col-I), IL-6, and TGF-β in SSc patients corroborate the role of these molecules in fibrosis and inflammation, providing a robust basis for exploring BT's therapeutic effects.

The MTT assay results indicated that BT at doses of 500 ng/ml (IC50) and 250 ng/ml (IC25) effectively reduced cell viability, guiding the selection of these doses for subsequent experiments. Notably, BT treatment significantly downregulated both the transcriptional and translational expression of TGF-β and COLI the key fibrotic markers in SSc, highlighting BT's potential in mitigating fibrosis. The antioxidative properties of black tea, attributed to its bioactive compounds, likely contribute to protecting against endothelial dysfunction, a hallmark of SSc. This protective effect, coupled with the immunomodulatory properties of black tea polyphenols, underscores the potential of BT in restoring immune homeostasis disrupted in autoimmune conditions like SSc. These findings are clinically significant for several reasons. First, the study highlights the potential of phytochemicals in black tea as novel therapeutic agents in managing complex diseases like SSc. The bioactive compounds of BT as inhibitors of cytokine activities suggest their role in mitigating inflammatory and fibrotic processes. Second, considering the high cost and significant side effects associated with conventional SSc therapies, black tea offers a promising, cost-effective alternative that could alleviate the financial burden on patients and healthcare systems. Finally, black tea presents a favorable safety profile compared to immunomodulatory drugs like Methotrexate and Cyclophosphamide, which require extensive monitoring due to their toxic side effects.

Conclusion:

Our study provides compelling evidence supporting the therapeutic potential of black tea in managing systemic sclerosis. By demonstrating significant reductions in key fibrotic and inflammatory markers, our findings highlight the promise of black tea as a cost-effective, natural alternative to conventional therapies. The anti-inflammatory, antioxidant, and anti-fibrotic properties of black tea bioactive compounds suggest a multifaceted approach to SSc management, addressing both the vascular and fibrotic components of the disease. Future research should focus on elucidating the precise mechanisms of action of black tea's bioactive compounds and

exploring their long-term benefits in clinical settings. Clinical trials assessing the efficacy and safety of black tea in SSc patients are warranted to validate our findings and pave the way for its integration into therapeutic protocols.

The potential efficacy of black tea as a supplement in disease prevention and management represents an exciting avenue for future investigation, offering hope for improved outcomes in SSc and other chronic inflammatory conditions.

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