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# Cytotoxic Effect of Fenugreek (Trigonella foenum-graecum) Seed Extracts on the Wnt Signaling Pathway in the K562 Cell Line

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**Abstract**

**Objective:** Researchers have established that the fenugreek plant exhibits anti-proliferative effects against various types of cancer, highlighting its potential as a valuable source for the development of new anticancer drugs. This study attempted to assess the anti-cancer effects of fenugreek on the K562 chronic myeloid leukemia (CML) cells due to the Wnt signaling pathway.

**Materials and Methods:** The cytotoxic effect of Fenugreek was performed by 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay. We used reverse transcription-polymerase chain reaction (RT-PCR) to determine gene expression, and western blot was used to detect β-catenin, c-Jun N-terminal kinase (JNK), calcium/calmodulin-dependent protein kinase (CamK), and protein kinase C (PKC) proteins.

**Results:** The $IC_{50}$ value of fenugreek extract was 717 g/mL after 24 h, and an *in vitro* cytotoxic effect was observed on K562 cell lines. JNK, PKC, CamK, and β-catenin protein levels were reduced in fenugreek extract-treated cells by 81%, 20%, 7%, and 26%, respectively.

**Conclusion:** According to our findings, fenugreek can affect both canonical and non-canonical pathways in K562 cells, particularly via the JNK protein in the planar cell polarity (PCP) pathway. These data corroborates our hypothesis that fenugreek extract possesses adjuvant compounds beneficial for CML treatment.

**Keywords** Fenugreek · Chronic myeloid leukemia · Wnt signaling · Plant extract

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## INTRODUCTION

Chronic myeloid leukemia (CML) is a hematological malignancy characterized by the presence of Philadelphia chromosome, resulting in the expression of the BCR-ABL1 fusion protein. This oncoprotein promotes the uncontrolled proliferation and impaired apoptosis of hematopoietic cells, leading to leukemogenesis (1). Although tyrosine kinase inhibitors (TKIs) have dramatically improved CML treatment, resistance to these drugs remains a major clinical challenge (2). This resistance is partly attributed to aberrant signaling pathways, such as the Wnt/β-catenin pathway, which plays a crucial role in cellular renewal and is often dysregulated in various cancers, including CML (3). When activated, Wnt signaling prevents β-catenin phosphorylation, resulting in its accumulation and enhanced leukemia progenitor cell survival (4). As a key player in CML pathogenesis, β-catenin presents a promising therapeutic target.

Fenugreek (Trigonella foenum-graecum L.), a widely distributed plant used in traditional medicine, has garnered attention for its pharmacological properties, including anticancer effects (5). Recent studies have demonstrated that fenugreek extracts exhibit cytotoxicity in various cancer cell lines, including CML cells, through multiple bioactive compounds such as flavonoids and alkaloids (6, 7). While the therapeutic potential of fenugreek in CML has been suggested, its specific impact on Wnt signalling in this context remains unexplored. This study aims to investigate how Fenugreek modulates Wnt/β-catenin signaling in K562 CML cells, providing new insights into its potential as an adjunct therapy in overcoming TKI resistance. By evaluating the effects of Fenugreek on β-catenin expression, along with key signaling proteins such as c-Jun N-terminal kinase (JNK), calcium/calmodulin-dependent protein kinase (CamK), and protein kinase C (PKC), this research fills a critical gap in the literature regarding the modulation of Wnt pathways in CML treatment. *In vitro* studies have shown a cytotoxic effect of fenugreek extracts on several cancer cells (7).

The Wnt/β-catenin pathway is essential for the self-renewal and proliferation of leukemic stem cells (LSCs) in CML (8). Fenugreek may exert anti-leukemic effects by modulating Wnt signaling, potentially reducing LSC self-renewal and proliferation. The presence of specific miRNAs induced by Fenugreek could target Wnt signaling components, thereby influencing the pathway's activity (9).

In this work, the Wnt signaling pathway was investigated in relation to the possible anticancer effects of fenugreek extract on K562 cells. Both mRNA and protein levels demonstrated the amounts of β-catenin expression. JNK, CamK, and PKC proteins were detected by Western blot.

## MATERIALS AND METHODS

### Plant Material

Fenugreek extract was purchased from a certified company called INDUS Biotech Company (India). The extract Lot number was FE0819030016. Then, 1 mg fenugreek extract was resolved in 1 mL RPMI (1 mg/mL) and diluted at concentrations between 300 and 800 µg/mL.

### Cell Culture

Penicillin/streptomycin, L-glutamine, and fetal bovine serum (FBS) enriched RPMI medium was used to grow K562 cells that were incubated at 37 °C with 5% $CO_2$.

### 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) Cell Viability Assay

Cell counts were ascertained using a hemocytometer through the trypan blue exclusion technique. The assessment of cell proliferation and vitality was conducted using XTT test from Biological Industries, Israel. K562 cells ($5x10^3$ cells/well) were cultivated in a 96-well plate using this procedure. Subsequently, the wells received a medium containing varying doses of fenugreek extract (300, 400, 500, 600, 700, and 800 µg/mL) for a 24-h incubation period. A 50uL of the XTT solution was dispensed into each well. Following the incubation at 37 °C for 2-4 hours, the formazan crystals were assessed at 450 and 630 nm using a microplate reader (PG Instruments). Untreated cells were used as the control group. All experiments were conducted in duplicate.

### RNA Extraction, cDNA Synthesis, and Reverse Transcription-Polymerase Chain Reaction (RT-PCR) Assay

K562 cells ($1x10^6$ cells/well) were cultured in 6-well plates and exposed to half maximal inhibitory concentration ($IC_{50}$) of fenugreek extract for 24 h ($IC_{50}$=717 µg/mL). Harvesting of the cells was performed by centrifugation and the medium was removed. Thermo Scientific GeneJET RNA Purification Kit was used for RNA extraction, followed by the cDNA synthesis with A.B.T.™ cDNA Synthesis Kit. A.B.T.™ 2X qPCR SYBR-Green Master Mix was used for RT-PCR and the primer sequences are shown in Table 1. The threshold cycle (Ct) values of β-catenin in all samples were normalized to β-actin.

Table 1. RT-PCR primer sets

| Genes | Forward (5'–3') | Reverse (5'–3') |
|---|---|---|
| β-actin | CTTCCTGGGCATGGAGTCCTG | GGAGCAATGATCTTGATCTTC |
| β-catenin | TCTGAGGACAAGCCACAAGATTACA | TGGGCACCAATATCAAGTCCAA |

## Western Blot Analysis

β-actin, β-catenin, JNK antibodies were purchased from Cell Signaling Technology, USA. PKC and CaMK were obtained from Santa Cruz, USA. K562 cells (1x10$^6$ cells/well) were subjected to fenugreek extract treatment ($IC_{50}$=717 µg/mL) for 24 h, while control cells remained untreated. Following incubation, the K562 cells were collected via centrifugation, and the media was discarded. The cell lysates were prepared using RIPA lysis buffer and concentrated for 10 min at 4°C at 12,000 × g. The protein was measured using the Bradford technique and then transferred to a PVDF membrane after being loaded onto a 10% SDS-PAGE gel. Upon preliminary antibody incubation, secondary antibody treatment, and protein band detection with Luminata Forte Western HRP Substrate (Millipore, USA), the membrane was considered ready for use. All experiments were performed in duplicate.

## Statistical Analyses

We used SPSS 11 (SPSS Inc., Chicago, IL, USA) and one-way ANOVA to analyze the data. GraphPad Prism 9 from GraphPad Software, Inc. was used to construct the graphs. ImageJ was used for the quantitative evaluation of the Western blot picture (Image Media Cybernetics Inc.) ($p<0.05$).

# RESULTS

## Fenugreek Had a Cytotoxic Effect on K562 Cells

The fenugreek extract was tested for its effect on K562 cell survival. Over the course of 24 h, K562 cells were exposed to the fenugreek extract at doses ranging from 300 to 1000 µg/mL. The *in vitro* cytotoxicity of fenugreek extracts on K562 cell lines was assessed using the XTT assay. Following 24 h of treatment with the extract, a decrease was seen in the viability of K562 cells. $IC_{50}$ value of the fenugreek extract was observed to be 717 µg /mL for 24 h (Figure 1).

## The Difference in β-catenin Gene Expression Was Detected Between Fenugreek-treated and Untreated Cells

Following total RNA isolation and cDNA synthesis, expression changes of β-catenin and β-actin genes were analyzed by RT-PCR. The expression of β-catenin was diminished in the treated cells compared with the untreated cells (Figure 2).

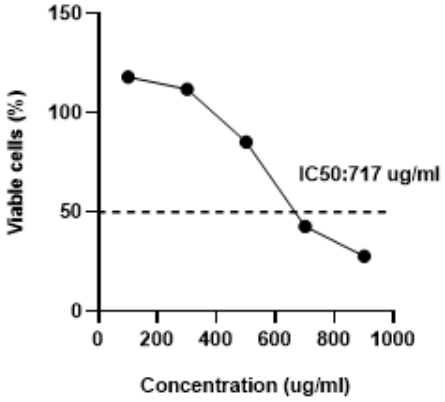



Figure 1. A 24-h XTT activity experiment evaluating the cytotoxic effects of different dosages of fenugreek on K562 cells.

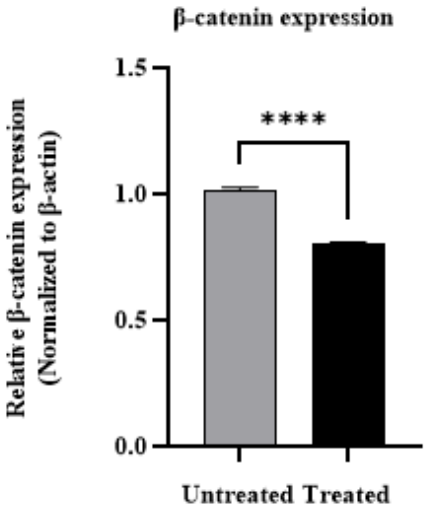



Figure 2. Effects of 717 µg/mL fenugreek extract on β-catenin gene expression of the K562 cell line at 24 h. *p<0.001. (Untreated 1.013 ± 0.012, treated 0.8 ± 0.008). Data represent the mean ± standard deviation of duplicated experiments.

## Protein Expression Changes Between the Fenugreek-treated and Untreated Groups

β-catenin, SAPK/JNK, PKC, and CAMK expression levels were normalized to β- actin levels. The SAPK/JNK p54 and β-catenin expression levels were significantly lower after Fenugreek treatment compared with the untreated group (Figure 3a, 3b).

# DISCUSSION

Tyrosine kinase inhibitors are widely used in CML therapy. However, most of the patients can develop resistance to TKI. The studies mainly focused on overcoming drug resistance and disease progression and tried to find new drug agents and

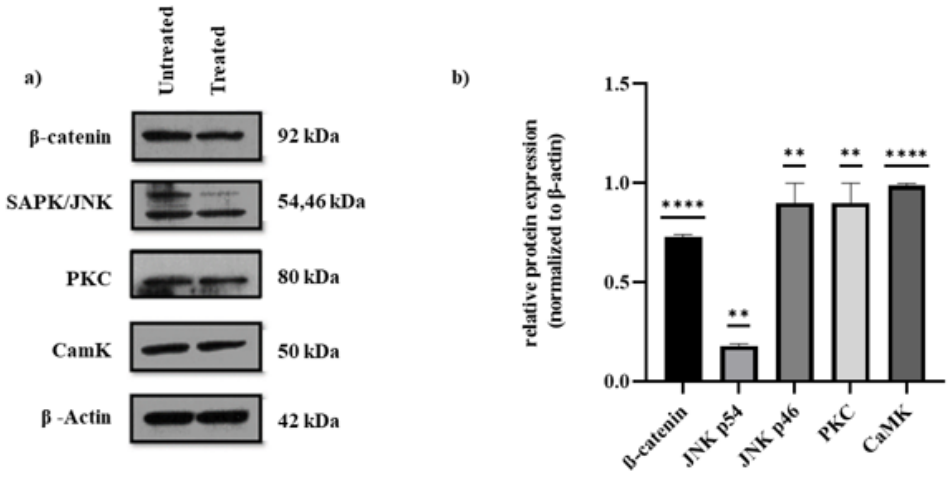



Figure 3. Analysis of fenugreek extract in K562 cells by Western blotting after 24 h of treatment ($IC_{50}$=717 µg/mL) a) Representative immunoblots of experiments. b) Relative protein expression. **p<0.01 ***p=0.005; ****p<0.001. Data represent the mean ± standard deviation of duplicated experiments.

natural additives or the effect of the combined applications (10).

Fenugreek is a medicinal plant that has been used since antiquity to treat diseases such as excessive cholesterol (11), diabetes (12), gastrointestinal disorders (13), and wound inflammation (14). Recent research has highlighted the biological activity and medicinal qualities of this species, primarily through investigations of alkaloids, flavonoids, steroids, and bioactive metabolites, including saponins and diosgenin (15). There is evidence that fenugreek possesses anti-cancer capabilities because of the functional chemical elements that it contains. Alsemari et al. demonstrated that the water extract derived from fenugreek seeds was cytotoxic on many cancer cell lines (16). Khalil et al. reported the anti-apoptotic effects of the fenugreek methanol extract in HepG2 cells ($IC_{50}$ = 1.000 µg/mL) (17). Previous research has shown that different fenugreek extracts can have cytotoxic effects and trigger apoptosis on breast cancer MCF-7 cells (18-20). Al-Oqail et al. showed the cytotoxic effect of the seed oil of fenugreek on epidermoid cancer cells and MCF-7 cells (21). We have also found that fenugreek extracts are cytotoxic to K562 cells. The Wnt signaling pathway is considered significant in controlling the mechanisms of cell proliferation, development, and differentiation (22). Abnormal Wnt signaling is associated with cancer. The effect of flavonoids such as luteolin, quercetin, trigonelline, and vitexin in fenugreek on the Wnt pathway was investigated. Chen et al. found that trigonelline reduced cell death via the Wnt pathway in human mesangial cells. They have also revealed that trigonelline modulates additional elements of the signaling cascade (23, 24). Pandurangan et al. demonstrated the effects of luteolin on human CRC cells. Research has shown that luteolin can inhibit the growth of human colorectal cancer cells by reducing β-catenin expression (25). Moreover, several effects of luteolin were demonstrated by different research groups by both *in vitro* and *in vivo* experiments (26-28).

In this study, major regulators of the Wnt signaling pathway were examined based on protein expression in K562 cells treated with fenugreek extracts. While for Wnt/$Ca^{2+}$ signaling PKC and CamKII, for Wnt/planar cell polarity (PCP) pathway JNK was investigated and for Wnt/β-catenin signaling β-catenin expressions were analyzed. In our study, we found that the expression levels of β-catenin, which is the major regulator in the canonical pathway, was decreased in K562 cells treated with fenugreek. The canonical pathway is a well-studied and proven pathway for the development of CML treatment strategies (29). Activated Wnt/β-catenin signaling promotes leukemogenesis by mediating LSC self-renewal and drug resistance (30). The BCR-ABL1 oncogene can promote β-catenin during the blast phase of the disease. Hence, the reduction in the Wnt/β-catenin pathway holds great significance in inhibiting the growth of leukemic stem cells that are associated with CML (31).

The PKC and CaMK genes play important roles in the non-canonical Wnt/$Ca^{2+}$ pathway in hematological malignancies (32). Experimental and clinical evidence both point to the possibility that PKC inhibitors could be useful in CML treatment (33). In addition, CaMKs reduce carcinogenesis and leukemia formation (34). The increased level of JNK protein in the PCP pathway was the most compelling finding after using fenugreek in CML cells. Na et al. discovered increased JNK expression in nilotinib-resistant CML cells (35). They

discovered that using a JNK inhibitor increased the sensitivity of K562 cells to nilotinib. As a result, the decrease in JNK expression observed in our findings may be important in CML progression. To determine the mechanism that is responsible for this decrease in JNK, additional research is required.

Currently, there is no available literature regarding the impact of fenugreek seed extract on the Wnt pathway in K562 cells. For this reason, our work is important to show the effect of an herbal extract on the Wnt signaling pathway. The anti-cancer properties of fenugreek seed extract will be investigated in further studies for its ingredient beneficial to CML therapy.


| | |
|---|---|
| Ethics Committee Approval | Since the study is a cell culture study, ethics committee approval is not required. |
| Peer Review | Externally peer-reviewed. |
| Authors Contributions | Conception/Design of Study- M.S., M.P.; Data Acquisition B.C.A., T.O., C.V.; Data Analysis/Interpretation: B.C.A., T.O., C.V., M.P.; Drafting Manuscript- B.C.A., C.V., T.O.; Critical Revision of Manuscript- M.S., M.P.; Final Approval and Accountability- M.S., M.P. |
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