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SHORT COMMUNICATION

Induction of Apoptosis in BCR-ABL Fusion Associated Chronic Myeloid Leukemia Cells by *Camellia kissi* Wall. (Theaceae) Extract

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ABSTRACT

Objective: *Camellia kissi*, a prominent tea, lacks academic works. In a previous report, this plant substantially affected chronic myeloid leukemia cells. Understanding the mechanism of action of this tea species on leukemia cells will contribute to researching alternative treatment methods in the context of drug resistance in chronic myeloid leukemia, which is constantly increasing.

Materials and Methods: *C. kissi* comes from Lam Dong, Vietnam. The crude tea extract in methanol was obtained. The flow cytometry method with Annexin V and PI staining and the DNA fragmentation assays were used to indicate the apoptosis cells. The reversed transcription real-time PCR reactions were conducted to measure the mRNA level under the treatment.

Results: The results showed the apoptosis-inducing capacity of the *C. kissi* extract on K562 cells, and the impact was suggested to be through the induction of intracellular apoptosis and cell cycle arrest.

Conclusion: The apoptosis induction on K562 caused by *C. kissi* was reported for the first time. Initial recognition of the signaling pathway of inhibition is through the BCR-ABL/PTEN.

Keywords: *Camellia kissi*, Chronic myeloid leukemia, Leukemia, Gene expression.

INTRODUCTION

Leukemia is one of the most dangerous diseases, causing nearly 312,000 deaths in 2020 in the world; approximately 475,000 new cases of leukemia were recorded in the same year.[1] Asia accounts for about 50% of incidence and mortality cases.[2] Based on the cause and pathological condition, leukemia is divided into four standard types: Acute Myeloid Leukemia, Chronic Myeloid Leukemia, Acute Lymphoid Leukemia, and Chronic Lymphocytic Leukemia (CML).[3] The proportion of blood cancer groups varies depending on geographical area, in which CML accounts for about 20% of acute leukemia cases.[4] One of the essential signaling pathways in CML pathogenesis is through BCR-ABL protein fusion.[5] Continuous amplification of cell proliferation signals is the root cause of CML pathogenesis.[6] Besides the traditional treatments, targeting BCR-ABL drugs has been considered a promising treatment for CML in recent years. Drugs known as tyrosine kinase inhibitors (TKIs) that act on the protein fusion in use include Imatinib (Gleevec), Dasatinib (Sprycel), Nilotinib (Tasigna), Bosutinib (Bosulif), Ponatinib (Iclusig), and Asciminib (Scemblix).[7] However, reduced effectiveness due to drug resistance or side effects is a significant challenge in the treatment of CML.[8] For example, the accumulation of mutations in T315 causes multi-level drug resistance, so Ponatinib and Asciminib are preferred.[9] However, Asciminib causes thrombocytopenia, and Ponatinib has the risk of causing thrombosis.[10,11] Therefore, finding alternative treatment methods is necessary.

As mentioned, Asia faces a high incidence of leukemia, with rates constantly increasing. Thus, pathological studies need to be performed. Asian people have a unique living culture; they love using fresh, natural ingredients in their lives, including tea drinking culture.[12] Green tea plays a significant role in their lives and health, and it has been shown in studies to be effective on certain types of cancer, including leukemia.[13,14] *Camellia* is an outstanding tea genus with high biodiversity. Vietnam is one of the countries endowed with the most diverse of them.[15] High endemism in distribution makes some Vietnamese tea varieties be hidden from scientific research. *Camellia kissi* is one of the potential tea species, but academic information is lacking. Providing complete scientific information about bio-activity is vital in recognizing the prestige and significance of the conservation of this plant. Based on the previously published results of

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potent proliferation inhibition on CML cells, this study aims to clarify the pathway in the mechanism of proliferation inhibition of *C. kissi* on K562 cells.

MATERIALS AND METHODS

Sample Preparation

C. kissi Wall. was harvested from Lam Dong province at the location coordinates of 11.481178.108.130521, Vietnam, with voucher No. PMT-C-01. The leaves were separated and cleaned with tap water. The leaves were left thoroughly dried in an oven with a steady temperature of 40°C. The dried sample was ground into a fine tea powder. Tea powder (200 g) was mixed into 600 mL of absolute methanol (Merck, Germany). After 24 h of shaking at 180 rounds per minute, the filtrate was collected; the filtrating process broadened three more times before filtrate pooling. By using a rotary evaporator, the crude methanol extract of *C. kissi* was obtained, and the extract (abbreviated as CKE) was prepared at a concentration of 300 µg/mL by weighting and dissolving with dimethyl sulfoxide (DMSO, Sigma-Aldrich, USA).

Cell Culture Conditions

Human Chronic Myeloid Leukemic cells, K562 (ATCC®CCL-243™) were cultured in RPMI 1640 (Roswell Park Memorial Institute Medium, Thermo Scientific, USA). The medium was added with 1% antibiotic and 10% fetal bovine serum (FBS, Thermo Scientific, USA). The trypan blue (Thermo Scientific, USA) exclusion method indicated cell density during the experiments. The initial cell concentration was set at 10^5 cells/mL Sub-culturing occurred every 72 h.

Cell Morphology Changes Screening

The tests took place in 6-well plates. The test volume was 3 mL for each well with 10^5 cells/mL, and the cells were treated with CKE in different concentrations. The cells were exposed to the extract for 72 h before collection. Next, 100 µL the treated cell biomass was smeared onto a slide, and then 90% ethanol covered the slide. The cells were stained with a 2.5 mg/mL solution of Wright's eosin methylene blue (Sigma-Aldrich, USA) dissolved in absolute methanol (Merck, Germany). After 2 min of incubation, the slide was washed with Wright's buffer (solution of 6.63 mg/mL of KH_2PO_4 and 2.56 mg/mL Na2HPO4, Sigma-Aldrich, USA). The cells' morphology was observed using a microscope (Olympus LS, Japan).

Apoptosis-Inducing Test

The solution of cell biomass at the density of 10^5 cells/mL was treated with CKE at 100 µg/mL. After 24 h of incubation, the cells were collected and dyed with the ANNEX100B kit (BioRad, USA).[16] The stained cells were analyzed on a flow cytometer (Accuri C6 Plus, BD Biosciences, USA).

DNA Fragmentation Assay

The cells at density 105 cells/mL were incubated with 100 µg/mL CKE for 24 h. The cells were collected and suspended in 100 µL of Dulbecco's phosphate buffer saline (Stemcell, Singapore). And then, 300 µL of trizol (Thermo Scientific, USA) was added to the mixture. The mix was incubated at 65°C for 15 min. 400 µL of Prec Buffer was added into the mix. Centrifugation at 10,000 g was conducted for 5 min. The precipitant was collected after removing the solution. The precipitant was washed twice with the wash solution. Total DNA was dissolved in 50 µL elution buffer (Favorgen Biotech, Taiwan). 10 µL of total DNA was analyzed using 2%-agarose-gel-electrophoresis supplemented with Redsafe dye (iNtRON Biotechnology, Korea).

mRNA Level Measurement

The cells at density 10^5 cells/mL were treated with 100 µg/mL CKE for 24 h. The cells were collected and the total mRNA was extracted using the trizol reagent (Thermo Scientific, USA). In detail, cells were harvested and, in 5 min, incubated with 750 µL trizol. The mixture was mixed with 150 µL chloroform (Merck, Germany). After 2 min of incubation, centrifugation at 10,000 g was conducted for 5 min to collect the supernatant. 300 µL of isopropanol was added to the supernatant collection. Centrifugation at 10,000 g was run for 5 min to remove the supernatant. The precipitant was washed with 750 µL ethanol 70%, and the centrifugation was repeated. Total RNA was stored in the elution buffer. The gene expression was detected by the RT-qPCR method with the combination of SensiFAST cDNA Synthesis and SensiFAST SYBR® No-ROX Kits (Meridian Bioscience, USA).[16] The used primers for analysis were named in Table 1.

Statistical Analysis

The results were collected in triplicate. The data was computed and analyzed using the GraphPad Prism software version 9.0.0. The image edition was performed by using ImageJ software.

RESULTS AND DISCUSSION

In many previous papers, apoptosis induction was observed as an impact of the extracts derived from tea.[17] *Camellia* is an outstanding member of Theaceae with the most species and diverse research activities. Thus far, the apoptosis-inducing effect has been recorded on many *Camellia* species, such as *Camellia sinensis* (L.) Kuntze[18], *Camellia ptilophylla* Hung T.Chang[19], *Camellia euphlebia* Merr. ex Sealy[20], and *Camellia oleifera* C. Abel[21]. However, the report on *C. kissi* has been ignored due to rarity and endemicity. The inhibitory effect of *C. kissi* extract

Table 1. The primers used for transcriptional-level evaluation.

Target	Forward primer	Reverse primer
GADPH	GAAGGTGAAGGTCGGAGTC	GAAGATGGTGATGGGATTTC
Fas	CACACTCACCAGCAACAC	TCCTTTCTCTTCACCCAAAC
Bcl-2	AAGATTGATGGGATCGTTGC	GCGGAACACTTGATTCTGGT
Bcl-XL	GTAGAGTGGATGGTCAGTG	TTGGACAATGGACTGGTTGA
Bax	TGGCAGCTGACATGTTTTCTGAC	TCACCCAACCACCCTGGTCTT
Caspase 3	GAACTGGACTGTGGCATTGA	CCTTTGAATTTCGCCAAGAA
Caspase 8	CTGCTGGGGATGGCCACTGTG	TCGCCTCGAGGACATCGCTCTC
Caspase 9	GGTGATGTCGGTGCTCTTGA	CGACTCACGGCAGAAGTTCA
Survivin	GTTGCGCTTTCCTTTCTGTC	TCTCCGCAGTTTCCTCAAAT
BCR-ABL	CGGGAGCAGCAGAAGAAGTTGTTC	CAGGCACGTCAGTGGTGTCTCTGTG
PIK3CA	GGTTGTCTGTCAATCGGTGACTGT	GAACTGCAGTGCACCTTTCAAGC
PIK3CB	TTGTCTGTCACACTTCTGTAGTT	AACAGTTCCCATTGGATTCAACA
mTor	GCTTGATTTGGTTCCCAGGACAGT	GTGCTGAGTTTGCTGTACCCATGT
PTEN	GGTTGCCACAAAGTGCCTCGTTTA	CAGGTAGAAGGCAACTCTGCCAAA
Erk	TCAAGCCTTCCAACCTC	GCAGCCCACAGACCAAA
p38a	TGAAATGACAGGCTACGTGG	GACTTCATCATAGGTCAGGC
CDK1	GGG TCA GCT CGC TAC TCA AC	AAG TTT TTG ACG TGG GAT GC
CDK2	TCATGGATGCCTCTGCTCTCAC	TGGAGGACCCGATGAGAATGGC
CDK4	CATTGGGGACTCTCACACTCTC	ATGGCTACCTCTCGATATGAG
TP53	TGTGGAGTATTTGGATGACA	GAACATGAGTTTTTTATGGC
pRB	ACTCCGTTTTCATGCAGAGACTAA	GAGGAATGTGAGGTATTGGTGACA

on K562 in a dose- and time-dependent manner was reported in a previous study with the half-maximal inhibitory concentration of 40.01± 3.12 µg/mL.[22] In the presence of SKE, the cell's morphology reflected many surface changes, indicating the apoptosis process (Figure 1). At 50 µg/mL CKE concentration, the K562's surface became smooth-surfaced protuberance, and the cell volume decreased. The fragmentation was observed during the treatment with 100 µg/mL CKE; the apoptotic bodies showed off. The simultaneous PI and Annexin V permeability confirmed the apoptosis induction. The results in Figure 2A indicated the increase of the co-positive stained cell population from 15% to 18% after a 24-hour treatment.

The integrity of the genome, which exhibited DNA decentralization, was evaluated after 24 h of treatment with CKE. As shown in Figure 3, the smears appeared in both treatments with CKE while absent in the control. The denaturation in the genome during apoptosis was demonstrated due to the cleaving of enzymes, especially caspase-3.[23] The programmatical cleavage created multiple fragmented products with around 180 bp difference in length.[24] The propodium iodide fluorescence analysis indicated the cell cycle arrestment at the G2 checkpoint (Figure 2B). The population of the cells harboring sister chromatins increased by almost ten percent after 24-hour CKE treatment, which indicated that cell division and cell proliferation decreased. Additionally, a slight development of the S phase was also recorded. The capacity of cell cycle arrest was previously documented as the impact of *Camellia* plants, such as *C. sinensis* on human ovarian cancer cells and *C. oleifera* on human breast cancer cells.[25,26]

The mRNA levels showed the transcriptional regulation of the CKE on the K562. The 2-delta delta CT values expressed the target mRNA contents compared to the housekeeping gene *GAPDH*. The interaction of changing RNA expression of some genes in K562 caused by *C. kissi* was published for the first time. In the 24-hour experiment, the effect of the extract recorded an increase in mRNA levels of *Fas* and *Bax*, which represent a group of proteins upstream of the apoptosis signaling pathway. Besides, the decreased expression of *Bcl-2* family genes logically contributes to the perception of induction of apoptosis by CKE. Interestingly, the expression changes of *Caspase 9* and *Bcl-2* family mRNA suggest that the effector pathway may be closely linked to the mechanism of apoptosis induction by intracellular signals (Figure 4A). One of the prominent signaling pathways in CML is considered through the BCR-ABL fusion protein, which carries diverse downstream signals.[6] However, in this study, we found increased expression of *BCR-ABL* mRNA in cells but not of *Pi3K* or *MAPK* (Figure 4B). The *Pi3k* and *mTOR* were maintained during the tests but increased *PTEN* suggested an interaction pathway that requires further investigation.[27,28] Previously, the interaction between green tea and BCR-ABL was reported. The tea-derived catechins were expected to be a new inhibitor in CML treatment.[29-31]

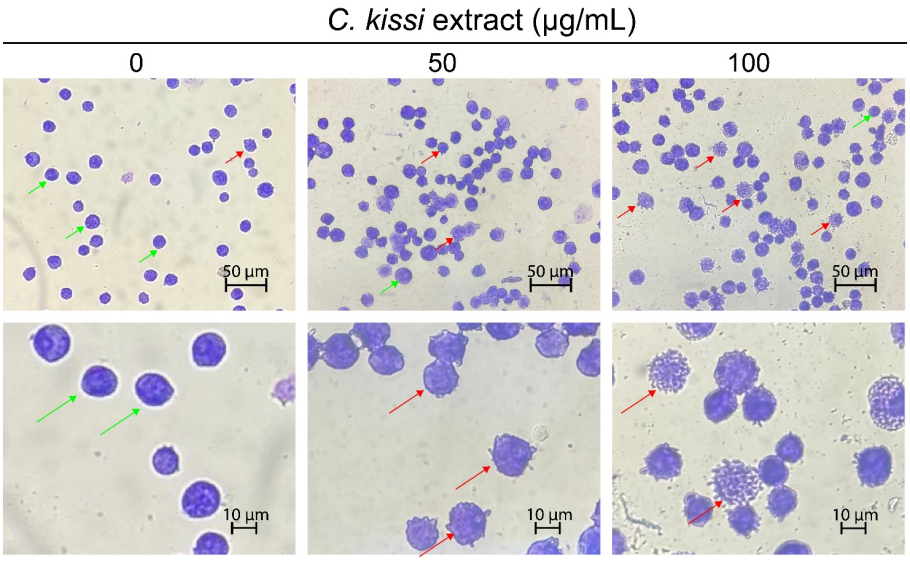

Figure 1. Cell morphology changes under the impact of *Camellia kissi* extract. The treatment at 100 µg/mL *C. kissi* extract was evaluated on K562, and the cell morphology was observed after 72 h of extract incubation. The cell morphology reflected several signs of apoptosis features, including shrinkage of the cell and smooth-surfaced protuberances (the red arrows) compared to the healthy cells (the green arrows).

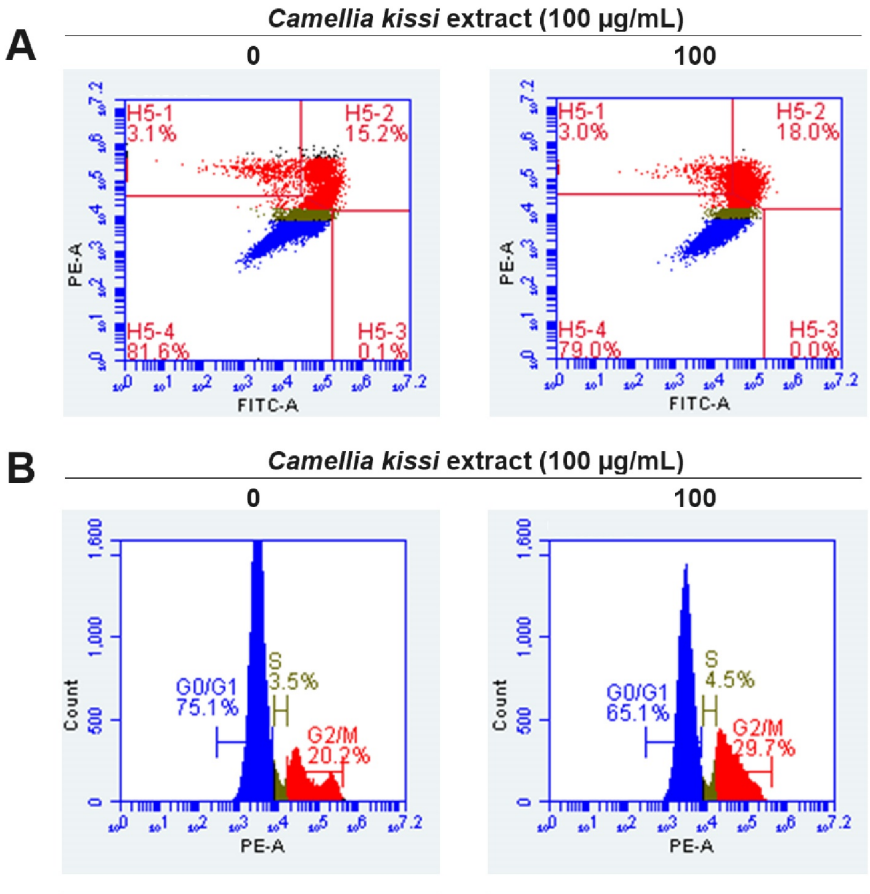

Figure 2. *Camellia kissi* extract induced apoptosis and cell cycle arrest on K562.Cells were exposed to 100 µg/mL *C. kissis* extract for 24 h before flow cytometry was performed. The results indicated the apoptosis-inducing effect of the extract, and the cell cycle was arrested at the M phase.

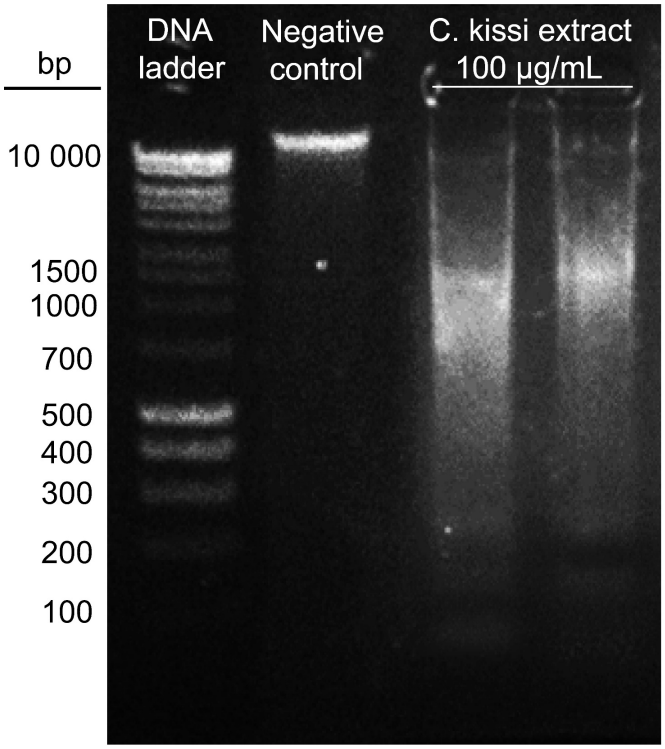

Figure 3. The DNA fragmentation under the influence of *Camellia kissi* extract. Cells were treated with *C. kissi* extract at 100 µg/mL for 24 h before DNA extraction. The 2%-agarose-gel-electrophoresis was conducted to analyze the DNA integrity. The results showed that the genome was cleaved into small polynucleotide fragments.

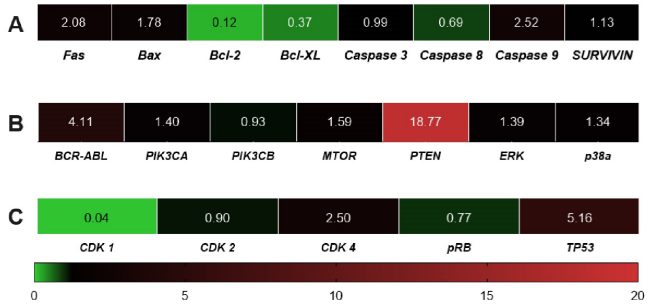

Figure 4. *Camellia kissi* extract regulated the mRNA level of several genes on K562. Cells were treated with *C. kissi* extract at 100 µg/mL for 24 h before total RNA extraction. The RT-qPCR was performed to analyze the mRNA level of several genes related to cell signaling, apoptosis, and cell cycle. The results showed that there were changes in mRNA levels in treated cells.

On the other hand, the number of cells at the G2 stage increased after 24 h of treatment, as mentioned above, for the collapse in the level of the *CDK1* described in Figure 4C, inferentially. CDK1 depletion was proposed to cause degradation of the CDK1/Cyclin A and CDK1/Cyclin B complexes, so the cells were trapped at the G2/M checkpoint.[32] Similarly, the increase in *CDK4* was also consistent with the decrease in cell number in the G1 phase under treatment. There was opposition in the expression of *TP53* and *pRB*; increased expression of *TP53* and decreased expression of pRP were observed. The increase in *TP53* was closely related to the decrease in CDK1/Cyclin B activity, leading to the cell's inability to pass the M checkpoint.[33] The results suggested the ability of *C. kissi* extract to induce K562 cell apoptosis via the intrinsic pathway through BCR-ABL/PTEN signaling. The cell arrest at G2/M was also observed as an effect of this extract. The research's development in the direction of protein analysis related to the discussed signaling pathways is necessary to have complete scientific information for this tea species.

CONCLUSION

This study documented the apoptosis-inducing ability of C. kissi leaf extract for the first time on K562 cells. The effect was considered to be mediated via the BCR-ABL pathways that led to apoptosis and G2 cell cycle arresting.

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