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A new curcumin analog, CCA-1.1, induces cell death and cell cycle arrest in WiDr colon cancer cells via ROS generation

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ABSTRACT

The new Pentagamavunone-1 (PGV-1) derivative, chemoprevention-curcumin analog 1.1 (CCA-1.1), is described as an improved physicochemical feature with similar cytotoxic activity on colon cancer cells and binding interaction to various cancer biomarkers. The current study explored the cytotoxic activity related to its ability to promote physiological changes in the WiDr colon cancer cell line. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay was used to assess the cell viability of WiDr and NIH-3T3 cells on the treatment of CCA-1.1 and PGV-1. 2′,7′-dichlorofluorescein diacetate staining, propidium iodide staining, and annexin V-PI staining were conducted to examine reactive oxygen species (ROS) level, cell cycle profiles, and apoptosis, respectively. For more examination on morphological changes, the SA-β-gal staining was used to detect senescence occurrence. We retrieved a more significant cytotoxic effect on WiDr by CCA-1.1 than PGV-1 and no effect on NIH-3T3 fibroblast cells. Our compound stimulated the arrest of the cell cycle at the G2/M phase, apoptosis, ROS generation, and senescence at an equal level to PGV-1. Altogether, these data reinforce CCA-1.1 as a viable alternative to PGV-1, attributed to its improved physicochemical features that are beneficial in designing dosage formulations for medical purposes.

INTRODUCTION

Chemoprevention-curcumin analog 1.1 (CCA-1.1) or 2,5-bis-(4-hydroxy-3,5-dimethyl benzylidene)-cyclopentanol (Fig. 1) is a new Pentagamavunone-1 (PGV-1) analog synthesized by Utomo *et al*. (2021) to construct a more compelling candidate for an anticancer drug. Recently, we reported CCA-1.1 potency on colon cancer through a bioinformatic exploration (Wulandari *et al*., 2020) and its effect against MCF-7 and T47D breast cancer cells (Novitasari *et al*., 2021; Wulandari *et al*., 2021a, 2021b). CCA-1.1 showed a better cytotoxic effect than PGV-1 on WiDr colon cancer cells (Utomo *et al*., 2021). Considering that CCA-1.1 has a similar structure backbone to PGV-1, it might have a comparable or more outstanding anticancer activity. The superiority of PGV-1 revealed a remarkable cytotoxic effect on colon cancer cells beyond many recommended drugs for treating colon cancer such as 5-fluorouracil, cisplatin, and doxorubicin (Meiyanto *et al*., 2018; Wulandari *et al*., 2018). More specifically, the antiproliferative activity of PGV-1 is related to a unique G2/M cell cycle arrest, apoptosis, senescence induction, reactive oxygen species (ROS) accumulation (Hermawan *et al*., 2011; Lestari *et al*., 2019; Meiyanto *et al*., 2014, 2018, 2019), and inhibition of nuclear

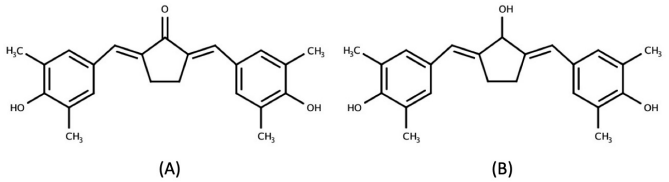

Figure 1. Structure of PGV-1 (A) and CCA-1.1 (B).

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factor kappa B, resulting in the suppression of cyclooxygenase-2 (COX-2) expression in WiDr colon cancer cells (Meiyanto *et al*., 2018). Conversely, PGV-1's limitation on physicochemical property obstructs its superiority as an anticancer candidate, and CCA-1.1 might be in place of PGV-1 to be promoted as a more effective anticolon cancer agent.

Developing colon cancer's chemotherapeutic agents with specific targets and fewer side effects remains a serious issue, which is still a crucial concern in cancer research (Ferlay *et al*., 2019) even though many attempts in recent years have been achieved to improve the outcome quality of patients (Aiello *et al*., 2019). An appropriate lifestyle might support patients to live longer with an improved quality of life (Aiello *et al*., 2019). 5-Fluorouracil (5-FU) is the first-line drug to treat colon cancer, which is usually combined with several agents as leucovorin, irinotecan, oxaliplatin, and levoleucovorin (Goto *et al*., 2019). Many clinicians also applied the combination of 5-FU and different targeted drugs, including bevacizumab, cetuximab, and panitumumab, to increase its efficacy (Li *et al*., 2011). For this concern, surgery is not the best option for colon cancer, but new therapies are still inadequate to manage cancer progression. Moreover, severe various side effects caused by several conventional drugs, such as bone marrow suppression, cardiotoxicity, and gastrointestinal toxicities, often shorten life expectancy in patients (Alessandrino *et al*., 2019). Developing a harmless drug without resistance is such a substantial issue for colon cancer treatment. PGV-1 is a possible choice for this purpose according to its safety, but CCA-1.1 may be a superior alternative.

We utilized the WiDr cell line as the representation of colon cancer, which is featured by p53 mutation, positive COX2 expression, and excessive ROS accumulation (Meiyanto *et al*., 2018). This cell line contained p21 and correlated with several drug resistance phenomena, such as cisplatin, 5-FU, and paclitaxel (Handayani *et al*., 2017; Meiyanto *et al*., 2018), making it suitable as a model for examining a candidate of a specific anticancer agent. The current study is dedicated to observing cell cycle arrest modulation, ROS generation, apoptosis, and senescence occurrence from CCA-1.1's antiproliferative effect. These results would provide supporting data for developing CCA-1.1 as a potent candidate for chemotherapy.

MATERIALS AND METHODS

Chemical compounds

CCA-1.1 and PGV-1 were synthesized by Utomo *et al*. (2021). Doxorubicin was purchased from Sigma-Aldrich.

Cell line and culture conditions

The fibroblast NIH-3T3 cells cultured in a high glucose Dulbecco's Modified Eagle Medium were contributed by Prof. Masashi Kawaichi, MD. Ph.D., Laboratory of Gene Function in Animals, NAIST, Japan. The colon cancer cells (WiDr) were acquired from the Faculty of Medicine, UGM, Indonesia, and grown in a Roswell Park Memorial Institute 1640 (RPMI-1640) medium. We added 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (Sigma), sodium bicarbonate (Sigma), streptomycin 150 µg/ml and penicillin 150 IU/ml (Sigma), and 10% v/v fetal bovine serum (FBS) (Sigma) for complementing the culture medium.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay

To assess cell viability, we utilized an MTT assay. The cells (10^4 cells/well) in 96-well plates were incubated for 24 hours with CCA-1.1 and PGV-1 at varying doses. The medium culture was replaced with an MTT reagent (Sigma). After 4 hours incubation, 100 µl of 10% sodium dodecyl sulphate (SDS) in 0.01M was added and incubated for 24 hours at room temperature, avoiding light exposure. The next day, we measured the absorbance using a microplate reader at 595 nm (BioRad).

Evaluation of cell cycle profile

Propidium iodide staining was used to assess the cell cycle profiles of WiDr cells (2×10^5 cells/well in 6-well plates) caused by compound treatment. The cell pellets were then collected and processed as a further step as mentioned in the BD Cycletest™ Plus DNA Kit instruction, following measurement using the flow cytometer BD Bioscience C6.

Staining for apoptosis detection

Authors conducted annexin V – propidium iodide (PI) staining-based flow cytometry to examine apoptosis incidence in WiDr cells. The treatment design used is similar to the cell cycle assay. The pellet cells were collected, following cell staining according to the Annexin V-FLUOS Staining Kit (Roche). The stained suspension cells were analyzed by a flow cytometer.

SA-β-galactosidase assay

Compounds at concentrations 2 and 4 µM were added to cultured 2×10^5 WiDr cells/well for 24 hours. The next day, cells were washed using phosphate-buffered saline (PBS) and fixed in 4% paraformaldehyde (Sigma). The cells were rewashed in PBS, following adding a staining solution, and placed for incubation at 37°C. Senescence cells were observed after 48 hour incubation and indicated as a green color under a light microscope (CKX-41 Olympus) (400× magnification).

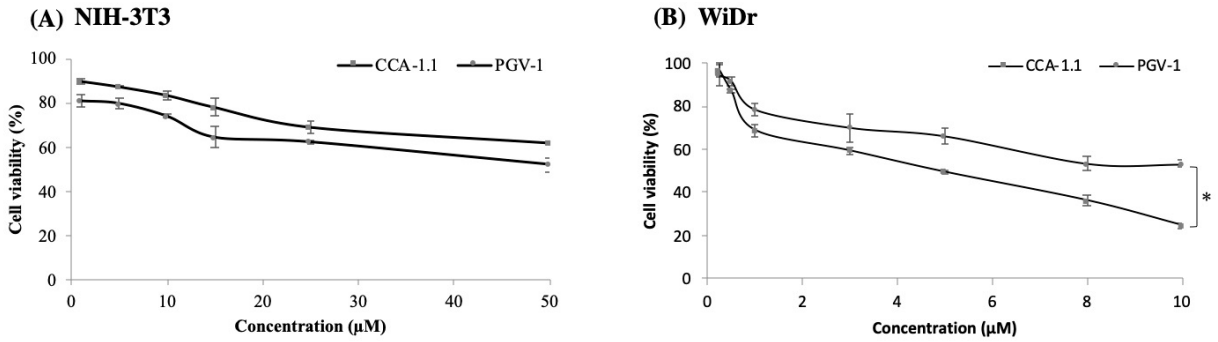
ROS level measurement

Cultured 5×10^4 WiDr cells/well in a 24-well plate were collected in 500 µl PBS containing FBS 10%, followed by 30 minutes staining with 2′,7′-dichlorofluorescein diacetate (DCFDA) (Sigma) 25 mM (incubation at 37°C, 5% CO_2 atmosphere). Following the staining incubation, cell suspension was added with samples and doxorubicin (4 hours) at selected concentrations. We utilized the BD Accuri C6™ Flow Cytometer (BD Bioscience) to analyze % fluorescein (ROS level) from 20,000 cells.

RESULTS

Cytotoxic activity

In the preliminary investigation, PGV-1 displayed an excellent cytotoxic effect compared to 5-FU on WiDr colon cancer cells (Meiyanto *et al*., 2018). Currently, we confirm that CCA-1.1 performed greatly in a dose-dependent phenomenon to treat cancer cells compared with PGV-1 against WiDr cells. CCA-1.1 was a stronger cytotoxic agent than PGV-1 ($p < 0.01$) (Fig. 2), in which PGV-1 and CCA-1.1 at a concentration of 10 µM inhibited cell growth of 47% and 73.5%, respectively. Both compounds showed no growth inhibitory effect (<5%) toward NIH-3T3 cells,



(C)

Cell lines	IC_{50} (μM)	
	CCA-1.1	PGV-1
NIH-3T3	>50	>50
WiDr	5.4	>10

Figure 2. The profile of cell viability on the treatment of PGV-1 and CCA-1.1 ($n = 3$). The results are displayed in a graph (mean ± SE). The profile on NIH-3T3 cells (A) and WiDr cells (B). The quantification of IC_{50} (μM) was presented in a table (C). Statistical analysis was conducted using Student's *t*-test (*$p < 0.01$).

a model of a noncancerous cell (Ahlina *et al*., 2020). From this result, we suggest that CCA-1.1 can possibly combat PGV-1 as an anticancer candidate, owing to the higher cytotoxic effect on WiDr cells and less toxicity on NIH-3T3 cells.

Cell cycle profile

As PGV-1 had a specific cytotoxic property against several cancer cells, we believe that CCA-1.1 would imitate its cytotoxicity. PGV-1 was shown to interrupt cell cycle progression causing arrest at the G2/M phase in WiDr cells (Meiyanto *et al*., 2014). Here, we figure out that both compounds showed similar characteristics in a cell cycle process interruption. CCA-1.1 and PGV-1 increased cell accumulation at the G2/M phase as shown in the green peak in the flow cytogram (Fig. 3) to a wider area over doxorubicin 100 nM, a chemotherapeutic drug as a positive control that triggers G2/M cell cycle arrest in cancer cells (Meiyanto *et al*., 2020; Thorn *et al*., 2011). We also spotted an accumulation at the sub-G1 phase in the treatment of CCA-1.1 (2 and 4 μM) probably representing an apoptosis incidence. We assumed that CCA-1.1 stimulates cell cycle arrest that may subsequently trigger apoptosis.

Apoptosis occurrence

We then conducted annexin V-PI staining based on a flow cytometry assay to confirm whether sub-G1 arrest caused by CCA-1.1 is indirect cell apoptosis. Apoptosis incidence mainly associates with irreversible cell cycle arrest (Foster, 2008). As the core compound of CCA-1.1, PGV-1 causes increasing apoptosis occurrence in breast cancer (MCF-7 and T47D) and colon cancer cells (WiDr) (Hermawan *et al*., 2011). We confirmed that CCA-1.1 (2 and 4 μM, 24 hours) effectually stimulates apoptosis in WiDr cells, as did PGV-1 at a similar level (Fig. 4). Considering PGV-1, which established induced cell cycle arrest accompanied by apoptosis, senescence, and ROS generation (Lestari *et al*., 2019; Meiyanto *et al*., 2019), CCA-1.1 may have an identical spectrum of activity in suppressing cancer cells. However, further investigation is required.

Cellular senescence incidence

To elucidate the correlation of cell cycle arrest and cellular senescence in the treatment of CCA-1.1, we employed Senescence-Associated (SA)-β-galactosidase assay and employed doxorubicin to trigger senescence in cells (as a positive control) (Kuilman *et al*., 2010; Yang *et al*., 2012). We demonstrated that both doses of CCA-1.1 and PGV-1 cause cellular senescence in WiDr cells ($p < 0.001$) at an equal level with doxorubicin (Fig. 5). We assumed that cellular senescence could be intrinsically related to cell cycle arrest.

Intracellular ROS level

The level of intracellular ROS plays a crucial role in senescence occurrence (Panieri and Santoro, 2016), also closely associated with the principle of the metabolic process (Davalli *et al*., 2016) and various implications of cellular stress resulting from physiological maintenance of ROS metabolic enzymes in cancer cells (Kashyap *et al*., 2019). Several studies reported that out-level ROS over the threshold causes cell death or another type of permanent cell arrest as senescence (Ikawati *et al*., 2020; Larasati *et al*., 2018). The DCFDA staining, followed by flow cytometry analysis, was used to assess the level of ROS within cells caused by CCA-1.1. We employed doxorubicin as an ROS inducer in cells (Yokoyama *et al*., 2017). We noted a significant ($p < 0.01$) elevation of ROS level caused by concentrations of both CCA-1.1 and PGV-1 at a comparable level with doxorubicin (Fig. 6). These results are well consistent with the previous report and CCA-1.1 tends to have the same feature as PGV-1 in terms of ROS generation. In addition, these results also indicate that the increasing ROS level is correlated with senescence evidence and cell cycle arrest.

DISCUSSION

CCA-1.1 and PGV-1 have a similar structure backbone, but CCA-1.1 is superior due to its improvement of solubility in

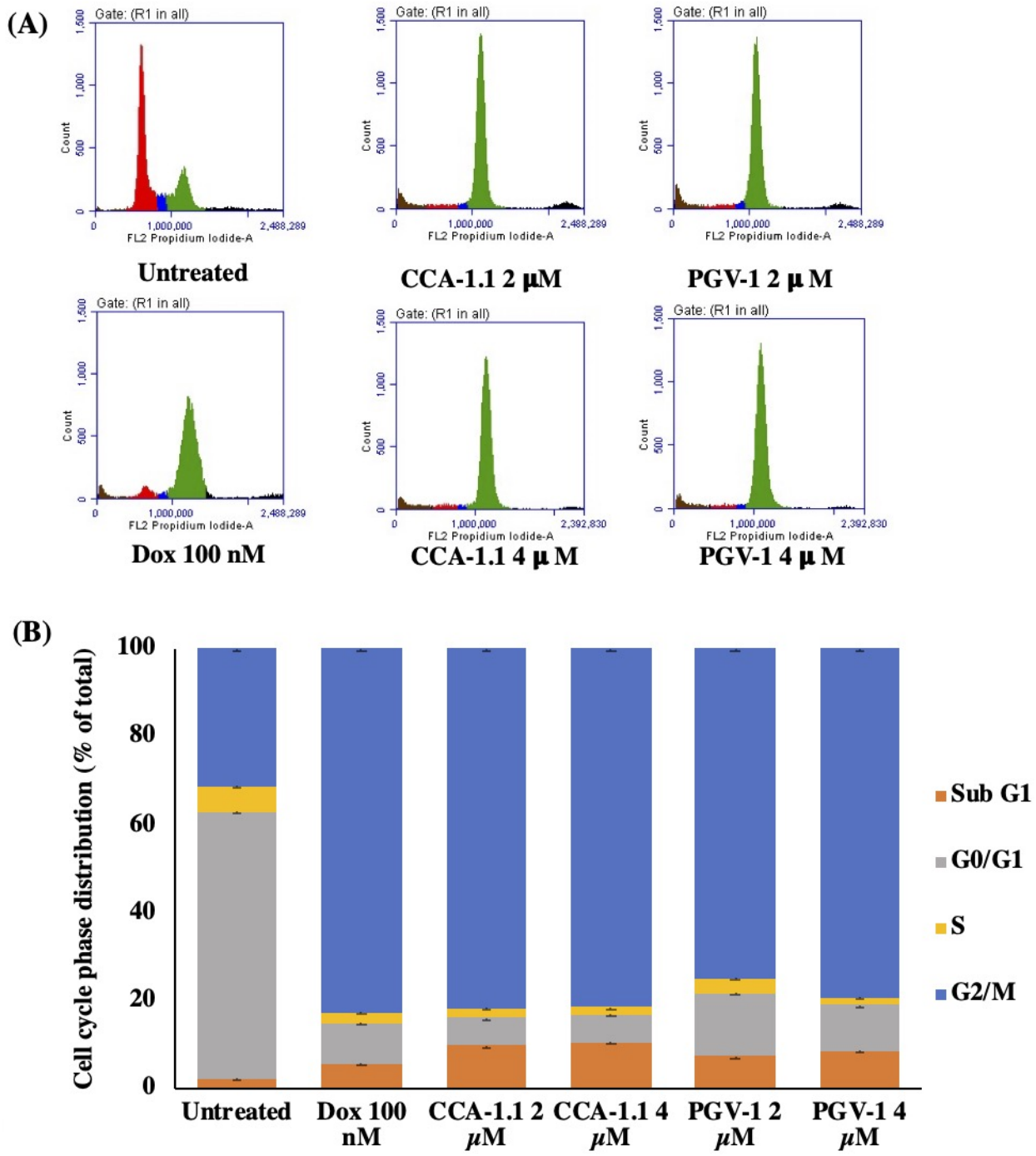


Figure 3. The modulation of cell cycle arrest on the treatment of CCA-1.1 and PGV-1 ($n = 3$). The cell cycle phase was determined by propidium iodide staining using a flow cytometer (A) as defined in the Materials and Methods section and the results are presented in a graph (mean ± SE).

aqueous solutions and stability, especially in an acidic environment, making it an auspicious candidate to combat PGV-1 as an anticancer candidate. Its stability in acidic solutions offers the possibility of CCA-1.1 to be developed as an oral anticancer drug. Additionally, CCA-1.1 had an equal or greater cytotoxicity on various types of cancer cells, including breast cancer cells (MCF-7/HER2, 4T1, MCF-7, HCC1954, and T47D), leukemia cells (K562), and colon cancer cells (Caco2 and WiDr) (Utomo *et al*., 2021). In this concern, we provided a piece of fundamental evidence through evaluating CCA-1.1's anticancer activities on WiDr cells to develop an effective candidate for colon cancer chemotherapy.

The current study disclosed the safety of CCA-1.1 on noncancerous NIH-3T3 (selectivity index > 10) cells with greater toxicity on WiDr cells than PGV-1. These results give an insight that CCA-1.1 is possibly a safe agent to treat colon cancer cells. However, whether CCA-1.1 is safe for human consumption or not, such as

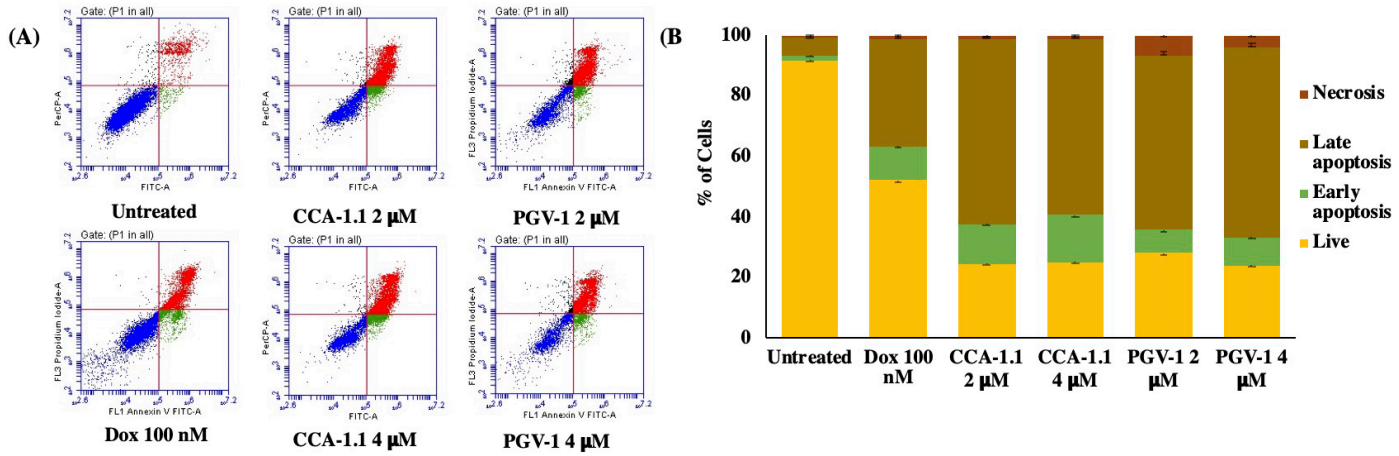


Figure 4. Apoptosis occurrence on the treatment of CCA-1.1 and PGV-1 on WiDr cells (n = 3). Apoptosis incidence was determined by annexin V-PI staining-based flow cytometry assay (A) and the % cell distribution was quantified into a graph (B) (mean ± SE).

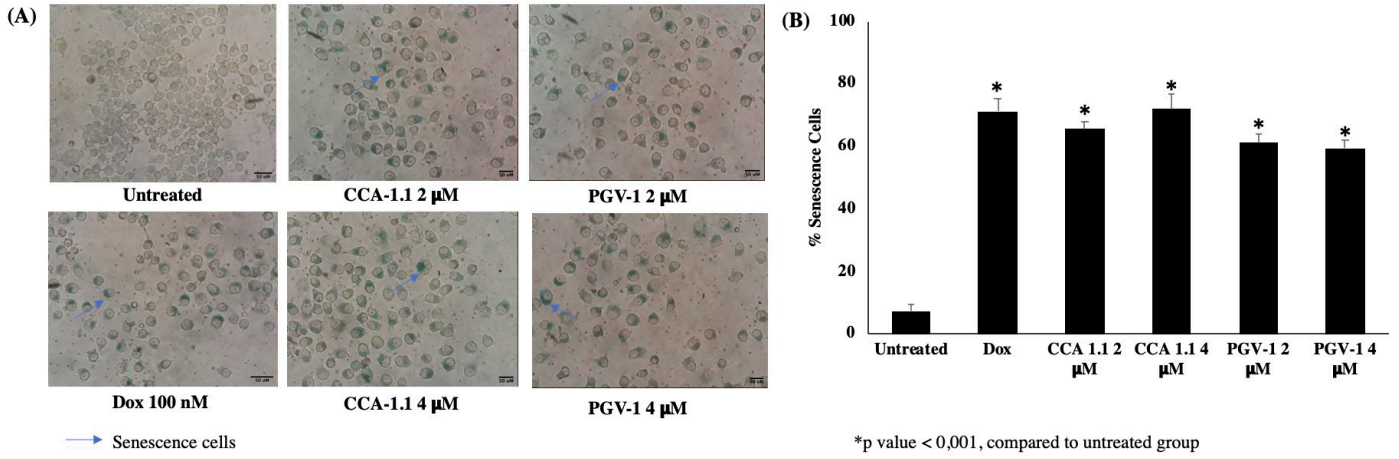


Figure 5. Senescence incidence in WiDr cells (2×10^5 cells/well/ml) on the treatment of CCA-1.1 and PGV-1 (n = 3). The morphology of senescence cells (A) was observed under a microscope and its percentages were quantified into a graph (mean ± SE). Student's t-test was used to analyze the differences between treatments (*$p < 0.001$).

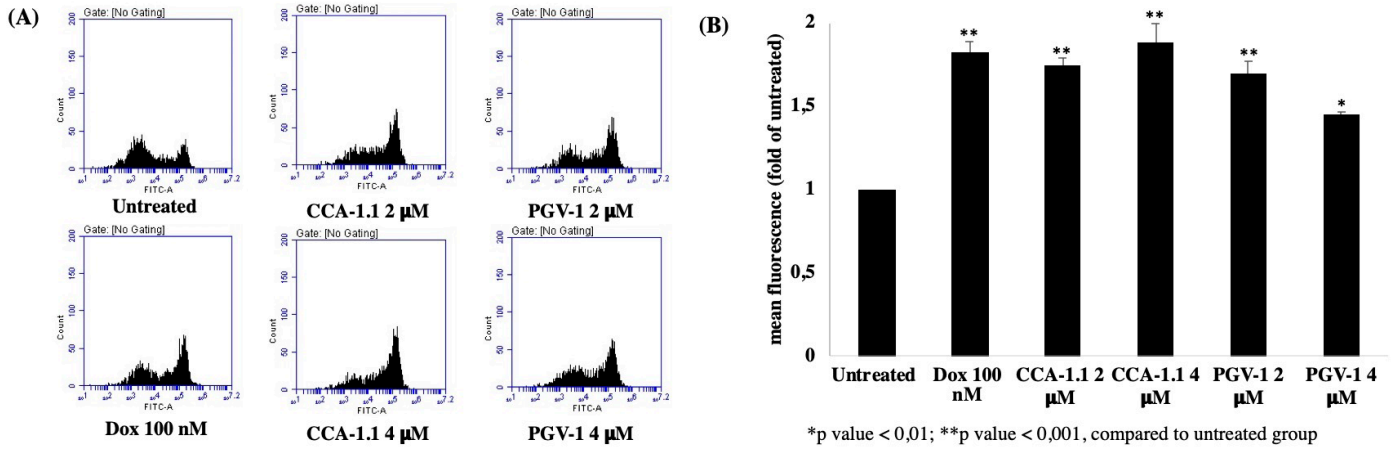


Figure 6. The level of intracellular ROS in WiDr cells on the treatment of PGV-1 and CCA-1.1 as defined in the Materials and Methods section (n = 3). DCFDA staining-based flow cytometry assay (A) was used to measure the ROS level and the results were presented as a graph (mean ± SE). Student's t-test was used to analyze the variances between treatments (*$p < 0.01$; **$p < 0.01$).

curcumin (the lead compound) which is an ingredient in a healthy drink for people (Aggarwal and Harikumar, 2009), should be explored further. The cytotoxic effect of CCA-1.1 is more reliable than that of 5-FU on WiDr cells, as previously reported (Meiyanto *et al*., 2018). Even though 5-FU is a recommended drug for colon cancer therapy, it is described to raise the resistance of colon cancers and have serious side effects to patients (Goto *et al*., 2019), such as neuropathy, cardiotoxicity, and severe bone marrow suppression. Doxorubicin, paclitaxel, and cisplatin, often used as 5-FU substitutions, were also reported to have similar severe side effects (Florea and Büsselberg, 2011; Thorn *et al*., 2011). Despite the previous report that doxorubicin (IC_{50}: 1.6 µM) is more potent than CCA-1.1 in WiDr cells (Wulandari *et al*., 2018), doxorubicin possesses disadvantages including poor solubility and instability under acidic conditions such as the gastric environment, which is not suitable for oral administration. Despite the incompatibility with its oral dosage form, doxorubicin seems to be the most suitable treatment preference since the oral route is comfortable, least invasive, and relatively nonexpensive for patients (Ahmad *et al*., 2018). A previous study stated that CCA-1.1 was stable in an acidic (gastric) environment, implying the possibility of oral use as a chemotherapy medicine. Since there are many colon cancer types with different attributes, further investigation of CCA-1.1's activities is required to evaluate the selectivity.

We noted an exciting result that CCA-1.1 mimics PGV-1-inducing cell cycle arrest at the G2/M phase, a complex and complicated stage in cell cycle progression (Rashidian *et al*., 2007). Lestari *et al*. (2019) reported that PGV-1 showed a unique inhibition of the cell cycle process at prometaphase on K562 cells (Lestari *et al*., 2019), which differs from curcumin that target anaphase (Lee and Langhans, 2012) and taxanes or vinca alkaloids that target microtubule spindles (Bates and Eastman, 2017). Defining the detailed targets of CCA-1.1 is an intriguing and challenging issue since the cell cycle elucidates various molecular pathways (Rashidian *et al*., 2007). Currently, targeting cell cycle regulators are ingenious advancements in cancer treatment (Kaldis and Richardson, 2012).

An arrest in cell cycle progression is intrinsically associated with senescence and apoptosis induction resulting in cell death in cancer cells (Foster, 2008). We presented PGV-1- and CCA-1-induced apoptosis at a similar level, and it is probably correlated with intracellular ROS elevation and senescence incidence. A balanced intracellular ROS level is needed to maintain cellular physiology and growth, especially in cancer cells. Cancer cells could undergo programmed cell death if the ROS level is higher than the threshold (Larasati *et al*., 2018). Consequently, a set of ROS metabolic enzymes in cancer cells is barely in charge to maintain an appropriate ROS level. At this point, the cytotoxic activity of PGV-1 is complemented by the initial-stage abrogation of several ROS metabolic enzymes (Lestari *et al*., 2019). Whether CCA-1.1 also mimics PGV-1 on elevating ROS levels by targeting ROS metabolic enzymes in cancer cells should be confirmed. Hence, the accumulation of ROS in cells has an opposite effect on cancer and healthy cells, where increasing ROS at an equal level in healthy cells can induce toxic possibilities in normal tissues and trigger side effects (Davalli *et al*., 2016). This was essential to explore since the increasing ROS level and senescence may appear in cancer cells and healthy cells.

Our data suggest that CCA-1.1 could be used instead of PGV-1, owing to its excellent aqueous solubility, which may be necessary for drug formulation. However, we have to note that this study was limited just to one kind of cell line, namely WiDr, a colon cell line with a particular molecular characteristic. We still need to examine this new compound against the other colon cell lines for a more comprehensive evaluation. Moreover, as the promising anticancer candidate for colon cancer, CCA-1.1 needs to be tested as a potential tumor-suppressing agent in animal models, including the safety evaluation and defining the molecular target's mechanism.

CONCLUSION

In conclusion, we determine that CCA-1.1 accomplished a greater cytotoxic effect than PGV-1 against WiDr cells with a comparable modulation on apoptosis and senescence, triggering arrest in cell cycle, and ROS elevation. Thus, promising features of CCA-1.1 are supported for developing an oral anticolon cancer drug. Some distinct potential target mechanisms have been documented for further exploration to gain a more comprehensive understanding of the anticancer mechanism of CCA-1.1.

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AUTHORS' CONTRIBUTIONS

Substantial contributions to the design and conception of the work: EM, MI, MK, and JK; acquisition of the data: FW; analysis and interpretation of data: FW, MI, JK, MK, and EM; drafting the work: FW, MI, and EM; revising the work critically: FW, MI, and EM; giving final approval of the manuscript: EM.

ETHICAL APPROVAL

This work does not involve subject experiments on animals or humans.

CONFLICT OF INTEREST

There are no conflicts of interest in this study.

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