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Cytogenotoxicity Test and Biological Evaluation of *Curculigo latifolia* Extract with Bioindicators *Allium cepa* L. var. aggregate

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Abstract

Curculigo latifolia plants have secondary metabolites that can suppress cell division. Compounds that suppress cell division can be used as anticancer drug candidates. This research aims to determine the effect of *C. latifolia* root extract on cell division and genotoxic effects using bioindicator *A. cepa* L. var. aggregatum. This study was conducted experimentally with a completely randomized design (CRD) using 6 treatment levels and 5 replications. The treatment levels in this study were K (water), K + (H2O2 300 Mm), K - (H2O2 26 hours + water 46 hours) and a combination of treatments at P1, P2, and P3 with H2O2 immersion (26 hours) and continued immersion of *C. latifolia* root extract concentrations of 400 µg mL^{-1}, 600 µg mL^{-1} and 800 µg mL^{-1} (46 hours). The roots of *A. cepa* from the soaking treatment of *C. latifolia* extract were used to make preparations using the squash method. The results of the ANOVA test showed that the administration of *C. latifolia* root extract had a significant effect on the mitotic index and cell abnormalities ($P<0.05$). P1 had the most effective value in reducing the mitotic index and cell chromosome abnormalities.

Keywords: *Allium cepa* L. var. aggregatum; Cell abnormalities; Cell division; *Curculigo latifolia*; Mitotic index.

INTRODUCTION

The Indonesian Ministry of Health released data on cancer rates in 2022 of 136 people per 100 thousand population and ranks 8th in Asia-Southeast (DinKes NTB, 2024). Cancer is a disease that can cause death, but is not an infectious disease. Cancer is characterized by uncontrolled abnormal cell division due to loss of cell control mechanism (Lestari et al., 2020). Various cancer treatments have been carried out, one of which is treatment with chemotherapy (Indra et al., 2022). However, chemotherapy treatment can provide side effects that are toxic to normal cells (Mahmoud & Abdelrazek, 2019). Due to the side effects caused by chemotherapy treatment, some researchers began to be directed to the bioactive components of plants in efforts to find and study anticancer activity (Rahayuningsih et al., 2021).

Curculigo genus plants are one of the plants that belong to the Hypoxidaceae family (Syabana et al., 2015). Curculigo genus plants play a role as antioxidants, antiinflammation, antitumors, anticancers and antidiabetics (Zabidi et al., 2021). Some species of Curculigo plants such as *C. orchioides, C. capitulate, C. pilosa* and *C. latifolia* (Nie et al., 2013). *C. latifolia* is a plant that contains secondary metabolites such as flavonoids, alkanoids, terpernoids, phenols and tannins (Haryanto et al., 2023). Plants that have active compounds are tested for cytotoxicity and genotoxicity (Rahayuningsih et al., 2023). As a major step in the search for anticancer compounds (Çelik & Aslantürk, 2010).

Cytotoxicity and genotoxicity tests are tests to determine how effective the compound is in inhibiting cell division and to determine the effect on healthy cells through chromosomal abnormalities (Rahayuningsih et al., 2022). The use of *A. cepa* L. var. aggregatum as a bioindicator because it has a division profile similar to multicellular systems (Kannangara et al., 2015). It is similar to mammals such as mice (Bonciu et al., 2018), has a low chromosome number (2n=16) (Olusola & Solomon, 2018), and has easily observable assay parameters such as root growth, mitotic index and cell structure due to chromosomal aberrations (Fujiwara & Hagan, 2014). Cytotoxic and genotoxic test research on Jatropha mollissima (Pohl) plants has toxic and genotoxic effects along with the increase in concentration used, namely at an extract concentration of 0.01 mg/mL with a mitotic index of 44.09% and at an extract concentration of 1 mg/mL has a mitotic index of 21.04% while the genotoxicity test results at an extract concentration of 0.01 mg/mL have damage of 2.91% and a concentration of 1 mg/mL with damage of 4.04% (Dias et al., 2019).

Research on *C. latifolia* plants against cytotoxic and genotoxic tests on bioindicators of *A. cepa* L. var. aggregatum needs to be done because this plant is a plant that has anticancer potential and no research has ever been done related to cytotoxic and genotoxic tests to determine the effect on inhibition of cell division and the effect on cell damage bioindicator *A. cepa* L. var. aggregatum. This research aims to determine the effect of *C. latifolia* root extract on cell division and genotoxic effects using bioindicator *A. cepa* L. var. aggregatum.

MATERIALS AND METHODS

This research was conducted at the Biology Laboratory, Faculty of Science and Technology, Universitas Muhammadiyah Bandung. This study used an experimental method with a completely randomized design (CRD) pattern.

Procedures

Extraction of C. latifolia plant roots

The source of the extract came from the roots of *C. latifolia* plant. Samples were washed and dried for 8 days in the sun covered with a black cloth. Samples are made simple using copper and a blender. Simple is carried out maceration extraction using 96% ethanol solvent for 3x24 hours with a sample: solvent ratio (1: 8 b / v). Then the macerate is filtered using filter paper followed by concentration using a rotary evaporator at 50oC until the solvent evaporates (Wendersteyt et al., 2021).

Bioindicator Induction Treatment of A. cepa L. var. aggregatum

A. cepa L. var. aggregatum came from farmers of Cupunagara Village (Bank Desa), then cleaned and grown to 2mm root length. The soaking technique was carried out on a bottle, the soaking was divided into 6 treatments with 3 controls and 3 treatments as follows: each treatment consisted of five *Allium cepa* L. var. aggregatum induced for 26 and 46 hours, in K (Water), K+ (H2O2), K- (H2O2 Water combination), and treatments P1, P2, and P3 administration of hydrogen peroxide (H2O2) 300 mM (26 hours) with a combination of extracts of *C. latifolia* Dryand ex. W. Aiton at concentrations of 400µgmL^{-1}, 600µgmL^{-1} and 800µgmL^{-1} for 46 hours (Akinboro & Jimoh, 2021 modified). Total soaking 72 hours (three days).

On the 3rd day of soaking, *A. cepa* L. var. aggregatum was harvested at 12.00 (Akwu et al., 2019). Then, the roots were cut along 3 mm and the root length was averaged. The roots were put into a fixation solution (ethanol (3): glacial acetic acid (1)). The roots were ready to be used for preparation.

Preparation with Squash Method

The roots of *A. cepa* L. var. aggregatum were put into the fixation solution for at least 24 hours, then put into 70% ethanol for 10 minutes, and then transferred to 1 N HCl hydrolysis solution for 1 hour (60 minutes). Roots that have been hydrolyzed for 60 minutes are inserted into a new tube and stained consisting of acetocarmine and methylene blue 1% in a ratio of 2: 1 are homogenized and kept for 24 hours then the roots are transferred to the glass object and then closed using cover glass and pressed (Squash) until the cells spread evenly and then observed under a microscope (Abdullah et al., 2017 modified).

Preparations that have been made are observed using a 40x10 magnification microscope and then the calculation of mitotic index and cell abnormality: The following is the calculation formula for IM and AS according to Sabeen et al. (2019).

Calculation of mitotic index percentage (MI)=$\frac{number\ of\ dividing\ cells}{total\ number\ of\ cells}$ 100%

Cell abnormality calculation formula% (CA)=$\frac{number\ of\ aberrant\ cells}{total\ number\ of\ cells}$ $x100\%$

Data Analysis

Data analysis used a one-way ANOVA statistical test. Mitotic index data and cell abnormality have significant values, so the Tukey HSD test is continued further. Data analysis using SPSS version 16.

RESULTS AND DISCUSSION

Effect of *C. latifolia* extract on cell division of bioindicator *A. cepa* L. var. aggregatum

Based on the results of the study, water control has the highest mitotic index value of 49.61%, K- (H2O2 + water) has a value of 44.72% and K + is 39.70%. In the treatment of a combination of 300 mm H2O2 (26 hours) with C. latifolia extract (46 hours), a concentration of 400µg / ml (P1) with a mitotic index value of 32.70%, which was able to reduce 7% of the positive control (Table 1). The results of the ANOVA test on the mitotic index in each treatment had a significant value ($p< 0.05$). In the Tukey HSD further test P1, P2 and P3 have similarities with K+. Meanwhile, K water has the highest mitotic index value.

Table 1. Effect of *C. latifolia* on the mitotic index in cells of *A. cepa* L. var. Aggregatum.

Treatment	In	Cell Division (Mitotic)				Total cells observed	MI (Mean±SD%)	Reduction %
		P	M	A	T			
K: Air	989	881	22	14	57	1963	49.61±0.81^{c}	-
K+: H_2O_2 300Mm	986	779	3	4	41	2083	39.70±0.74^{ab}	-
K-: H_2O_2 300Mm + air	977	921	8	3	29	2049	44.72±0.51^{bc}	-
P1: H_2O_2 300Mm+E 400µgmL^{-1}	1205	604	5	7	21	1948	32.70±0.60^{a}	16.91
P2: H_2O_2 300Mm + E 600µgmL^{-1}	959	594	18	8	34	1768	36.99±1.83^{a}	12.62
P3: H_2O_2 300Mm+ E 800µgmL^{-1}	965	751	16	11	40	1931	42.37±0.87^{ab}	7.24

Note: E: *C. latifolia* extract, In (Interphase), P (Prophase), M (Metaphase), A (Anaphase), T (Telophase)
The mean followed by the same letter indicates the treatment gives the same effect with α=0.05.

Effect of *C. latifolia* extract on cell abnormality of *A. cepa* L. *var. Aggregatum*

Based on the observation, there are normal and abnormal cells. Normal cells consist of interphase, prophase, metaphase, anaphase and telophase, while in cell abnormalities, there are nuclear lesions, giant nuclear, stickiness*, extended interphase, micronuclear*, *extended cell and dislocation spindle* (Figure 1).

Interphase is the stage of the cell cycle when the cell prepares to divide and is characterized by a clearly stained cell nucleus (Figure A). Prophase is the first stage in cell division; the prophase stage is characterized by chromatids beginning to form and the cell nucleus losing its identity (Figure B). Metaphase is characterized by the appearance of chromosomes that are thickened and aligned on the metaphase plate (Figure C). Anaphase is characterized by chromosomes that are at different poles with the same number (Figure D). Telophase is characterized by the formation of two identical daughter cells and the cell nucleus is clearly visible (Figure E).

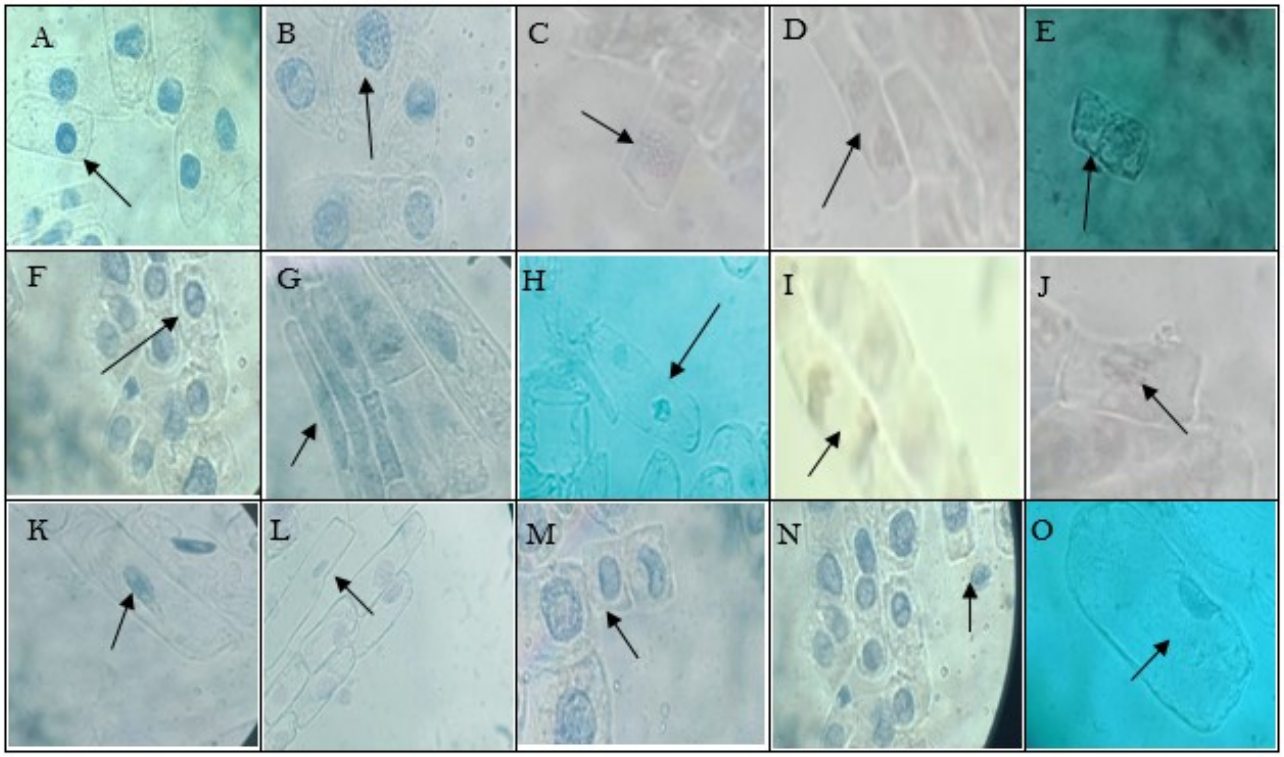

Figure 1. Observation of Normal Cells and Abnormal Cells at 1000x magnification using acetocarmine staining and methylene blue 1%.
Note: A. interphase, B. Prophase, C. Metaphase, D. Anaphase, E. Telophase, F. Nuclear lesions, G. Giant nucleus, H-I. Binucleated, J. Stickiness, K-L. Extended interphase, M-N. Micronucleus, dan O. Extended cells and dislocation of the spindle.

The results of the genotoxicity test with the aim to determine the effect of *C. latifolia* extract on cell abnormality are in (Table 2). Based on the results of the study, the percentage of cell abnormality obtained in K+ is 13.04% in the treatment of P1-P3 ranging from 5.42%-9.40% with the highest abnormality of K+ and the least abnormality in P1. P1 is the most effective concentration when compared to the others because P1 is able to reduce

55.44% of K+. Based on the ANOVA test, the percentage of cell abnormality is significant (P< 0.05). Based on Tukey HSD further test, P1 has a smaller value than K+ (Table 2). P2 and P3 had no significant difference from each other but were significantly different from K+. P1 has a significant difference with K +.

Table 2. Effect of *C. latifolia* on cell abnormality of *A. cepa* L. var. Aggregatum.

Treatment	Nuclear lesions	Giant Nuclear	Binuclear	Stickiness	Ext. interphase	micronuclear	Ext cell and dislocation of spindel	Amount cell abnormal	Cell abnormal (mean+sd)%	Reduction (%)
K:Air	0	0	0	0	0	0	0	0	0^{a}	-
K+: H_2O_2 300Mm (+)	78	50	8	1	32	40	63	272	13.04 ± 1.3^{d}	-
K-: H_2O_2 300Mm+air	35	54	23	1	40	28	30	211	9.81 ± 0.66^{c}	24.77
P1:H_2O_2 + E400 µgmL^{-1}	28	24	4	0	20	13	17	106	5.42 ± 1.40^{b}	58.44
P2:H_2O_2 + E600 µgmL^{-1}	26	41	4	3	25	14	42	155	8.70 ± 2.97^{c}	33.29
P3:H_2O_2 + 800 µgmL^{-1}	38	40	8	5	34	17	40	182	9.40 ± 1.77^{c}	27.92

Note: -E: Extract of *C. latifolia,* ex: Extended
The average of the results followed by the same letter indicates that the treatment gives the same effect with $\alpha = 0.05$.

Discussion

Several previous studies on cytotoxic tests using the bioindicator *A. cepa* L. var. aggregatum found effective results in *Rhizophora apiculata* plant extract, namely at a concentration of 500 ppm with an IM of 10.7% which was able to reduce 41.95% from the negative control of 52.65% (Rahayuningsih et al., 2021). *Avicennia marina* extract has an effective concentration to reduce IM 1000 ppm, namely 24.7% which can reduce 33.47% from K- 58.17% (Rahayuningsih et al., 2022).

The decrease in the mitotic index in this study is possible because *C. latifolia* contains secondary metabolites such as flavonoids, tannins, alkaloids, phenols, and terpenoids. Alkaloid compounds are secondary metabolite compounds that interfere with the cell cycle in the metaphase phase (Phase M) by binding to tubulin in a different place with taxanes, which can then prevent polymerization and microtubule assembly, which results in the termination of metaphase and causes apoptotic cells (Puri et al., 2023). Phenol compounds can cause inhibition of cell cycle phases, namely in the G1, S, S-G2 and G2 phases by downregulating cyclin and cyclin-dependent kinases (CDKs) by inducing the expression of P21, P27 and P53 genes (Dai & Mumper, 2010).

Flavonoid compounds act as antioxidants, inhibit cell proliferation by inducing cell cycle arrest in the M/G phase and induce autophagy and apoptosis in human breast cancer cells (Zhang et al., 2018). Tannin compounds have the ability to inhibit the cell cycle by disrupting the synthesis process and causing cell damage and activating apoptosis while tetanoid compounds have the ability to be cytotoxic which causes neoplastic lines by inhibiting cellular activity and activating apoptotic cells (Chudzik et al., 2015).

Cell abnormalities consist of nuclear lesions characterized by damage to the cell nucleus due to failures that occur in G1, S and G2 phases that can cause damage to the nucleus (Fibras, & Amon, 2014). Giant nuclear is characterized by the cell nucleus having a giant or large size many times that of normal cells (Vazhangat & Thoppil, 2016). Stickiness is characterized by chromosomes sticking to each other forming bridges caused by degradation, sticky chromosomes or depolymerisation of chromosomal DNA (Rahayuningsih et al., 2022). Micronucleus is characterized by small cell nuclei caused by unbalanced chromosome division at the anaphase phase, causing the chromosomes to have a very small size (Imaniar & Phatmawati, 2014).

Binuclear is characterized by the number of cell nuclei more than one occurs due to failure in the telophase phase, namely the formation of cell plates so that the cell nucleus is more than one (Sabeen et al., 2020). Extended interphase and extended cell and dislocation spindle are characterized by cell nuclei that change shape to oval and move position to the edge of the cell. Cell damage can occur from the side effects of secondary metabolites that have OH groups such as phenols, flavonoids and tannins which can cause damage to the S phase by breaking the hydrogen chain in DNA or causing mutations in genes (Rahayuningsih et al., 2023).

The use of positive control H2O2 because H2O2 is a substance or chemical compound that has the ability to damage or is toxic to cells (Akwu et al., 2019). The high percentage of cell abnormality is influenced by the provision of high concentrations. In research with a similar method, namely the combination of sodium azide and *Aloe vera* extract, it was found that the higher the concentration of extract given, the higher the cell abnormality value obtained by the 50% extract treatment,

namely 0.41%, while at a concentration of 6.25%, namely 0.29% which can reduce 42.27% of K + 0.55% (Akinboro & Jimoh, 2021). Research with *Avicennia marina* (Forks.) extract has the smallest abnormality concentration at 125 ppm which is 17.75% while at concentrations of 550, 500, and 1000 ppm are 21.5%; 28%; and 36.3% (Rahayuningsih et al., 2022). At the same time, *Rhizopora styliosa* Griff extract has a decrease in abnormality from the positive control of 52.33% in fractions F6, F7, and F8 (flavonoid compounds from KLT results) with a percentage of abnormality of 9.67%, 9.33% and 9.33%. F2, F3 and F4 (terpenoids and steroids) are 8.33%, 16.3% and 13.3% (Rahayuningsih et al., 2023).

CONCLUSIONS

Based on the results of the study, it can be concluded that *C. latifolia* extract has a cytotoxic effect on H2O2 in suppressing cell division (Mitotic index) and cell abnormality with the optimal concentration in treatment P1 with a mitotic index percentage value of 32.70% and has the least effect of 5.42%.

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