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Anthocyanin as Colorectal Anticancer: A Brief Review

Dimas Sunaraya Oktavianus Siwanahono, Selvi Apriliana Putri, and Minda Azhar*

Biochemistry Laboratory, Department of Chemistry

Faculty of Mathematics and Natural Science,

Universitas Negeri Padang, Indonesia

ABSTRACT

Colorectal Cancer (CRC) is dangerous cancer that causes many cases of death in the world. This cancer spike occurred in 2020 with 1.15 million cases and is expected to increase in 2040 by 1.92 million CRC cancer cases. Some of the most popular drugs used for CRC chemotherapy are 5-Fluorouracil, Oxaliplatin, and Irinotecan. The effects caused by chemotherapy using synthetic drugs are loss of appetite, fatigue, vomiting, numbness, hair loss, and low blood cell count. Anthocyanins are a group of flavonoid compounds and polyphenols with antioxidant, antimutagenic, and anticancer activity that can be developed as CRC anticancer. Anthocyanins do not cause side effects in CRC patients. This article is a review of anthocyanin activity to reduce the risk of colorectal cancer (CRC) in terms of molecular mechanisms, the proliferation ability of cancer cells, and promoting apoptosis of CRC cells.

Key Words: Anthocyanins, Apoptosis, Colorectal Cancer, Proliferation.

1. INTRODUCTION

Colorectal Cancer (CRC) is one of the dangerous cancers that can cause many cases of death. Colon cancer can spread to the ovaries, lungs, and other parts of the digestive system if not treated immediately [1]. The United States with 0.16 million CRC cases in 2020 increased to 0.21 million CRC cases in 2040. In 2020 with a total of 0.56 million CRC cases in China is predicted to increase in 2040 with a total of 0.91 million CRC cases [2].

The process of development of CRC causes histological, and morphological changes and is followed by genetic mutations that can occur over a period of years [3]. CRC symptoms can be indicated by adenomatous precursor lesions involving mutations of the tumor supersor gene of adenomatosis polyposis coli (APc). Chronic inflammation with oxidative tissue damage is thought to contribute significantly to colorectal carcinogenesis [4].

Age is also one of the factors that cause an increased risk of CRC. People with a 50-year-old of are at 15 times higher risk compared to 20-year-olds. The risk of CRC cases is dominated by men at 31%, while women are at 24% [5]. Unhealthy lifestyles can increase the risk of CRC such as smoking, consumption of large amounts of alcohol, unhealthy diet, lack of physical activity, and obesity [6]

Cancer screening is one of the popular methods in recent years and is widely used to detect CRC cancer [5]. Cancer screening has the ability to prevent morbidity, mortality, and treatment costs due to cancer by detecting significant lesions before it becomes cancerous and early-stage cancer before it spreads beyond the intestinal wall [3].

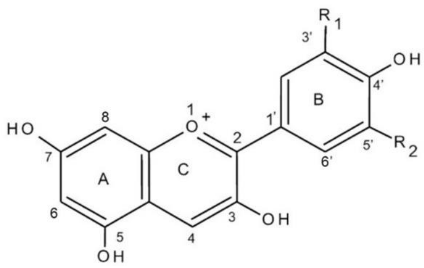
In patients experiencing a diagnosis of CRC, it is possible to be given a series of operations [7]. Chemotherapy can be applied to patients who have CRC because it can kill cancer cells. Chemotherapy can produce meaningful damage to cancerous DNA by initiating cell cycle cessation and DNA repair [8]. The most popular drugs in the CRC chemotherapy method are 5-Fluorouracil, Oxaliplatin, and Irinotecan. Chemotherapy effects are caused such as loss of appetite, experiencing fatigue, vomiting, numbness, hair loss, and low blood cells [5]. The financial burden is also an important consideration that burdens the treatment of patients with late-stage CRC diagnosis. Chemotherapy is also associated with toxicity and resistance effects that result in the patients of CRC sufferers. Anthocyanins are present as an alternative in CRC cancer therapy that does not cause side effects in CRC patients [1].

Research on natural products that are able to inhibit and prevent CRC has been widely developed from the group of flavonoid compounds [9], polyphenols [10], saponins [11] which are able to work at the molecular level by playing a role in inhibiting CRC cell proliferation and affecting the apoptosis of cancer cells [10]. Anthocyanins are a group of flavonoid and polyphenol compounds with antioxidant, antimutagenic and anticancer anti-inflammatory activities [13]. Anthocyanins have the potential to be developed as anticancer CRC [12]. Eating natural fruits and vegetables containing anthocyanins can lower the risk of CRC [14]. Anthocyanins are safer than drugs that are already available on the market. Anthocyanins are able to accelerate the development of CRC by promoting the apoptosis of cancer cells and inducing a cycle of cessation of CRC cancer cells. In CRC therapy required drugs that do not cause side effects in patients [15]. This article aims to review the anticancer activity of anthocyanins In terms of the potential molecular mechanisms of cancer cell proliferation capabilities and promoting apoptosis of CRC cells from articles published mostly from 2017 to 2022.

2. RESULTS AND DISCUSSION

2.1 Anthocyanins

Anthocyanins in general can be found in their derivative forms such as cyanidin, delphinidin, pelargonidin, malvidin, peonidin, and petunidin (Figure 1). The anthocyanin in plants that contains the most is cyanidin-3-glucoside [21]. A Meta-analysis study showed that anthocyanins have an important role in the prevention of CRC. The results of the study confirmed that consuming anthocyanins was inversely proportional to the risk of colon cancer [12].



Antocyanidins	R1	R2
Pelargonidin (Pg)	H	H
Cyanidin (Cy)	OH	H
Delphinidin (De)	OH	OH
Peonidin (Pn)	OCH_3	H
Petunidin (Pt)	OCH_3	OH
Malvidin (Ma)	OCH_3	OCH_3

Figure 1. The structure of anthocyanins and their derivatives [20]

2.2 Source of Anthocyanins

The presence of anthocyanins in nature is very abundant, especially in plants. More than 600 types of anthocyanins have been identified for their presence in nature [21]. Anthocyanins are abundantly contained in fruits (grapes, blueberries), flowers (hibiscus flowers, red roses), and vegetables (red cabbage or purple). Anthocyanins are found in many layers of their skin more precisely in the epidermis and hypodermal. Anthocyanins are also found in the entirety of its fruits (berries and cherries). In red fleshy apples, anthocyanins are found in the flesh of the fruit [22].

Anthocyanins in nature are widely found mainly in fruits, flowers, leaves, roots, legumes, cereals, and tubers. Anthocyanins (Figure 2) in oranges with the main structure of Cyanidin-3-O glucoside, while in black currants it is Cyanidin-3- 0 rutinoside. In black chokeberry, it contains a lot of Cyanidin-3-0-galactoside, while in Chicory there is delphinidin 3-O (6-O-malonyl-β-D-glucoside)-5-O- β-D-glucoside [13]. Purple eggplants contain delphinidin-3-O (p-coumaroyl rutinoside)-5-O-glucoside, while in strawberries there is pelargonidin-3-O-glucoside [13].

2. 3. Anthocyanins Activity as Anti-Colorectal Cancer

CRC is a health problem that has caused many deaths to date [1]. Anthocyanins show the ability to cause apoptosis in CRC cells and reduce the proliferation of CRC cells [23]. Animal models of CRC testing have also been widely developed that are almost the same as CRC in humans which allows in-vivo tumor analysis to be performed [24]. In-vitro models can analyze tumor specifics [25]. In-silico testing models can also analyze CRC cells [26]. Widely used carcinogen methods and cells for analyzing CRC are Azoxymethane (AOM), Dextran Sulpate Sodium (DSS), and HTC-116/HT-29 [27]. Extracts from anthocyanins (Table 1.) show anticancer activity in CRC prevention in terms of the ability to reduce proliferation cell and promote apoptosis of CRC cells.

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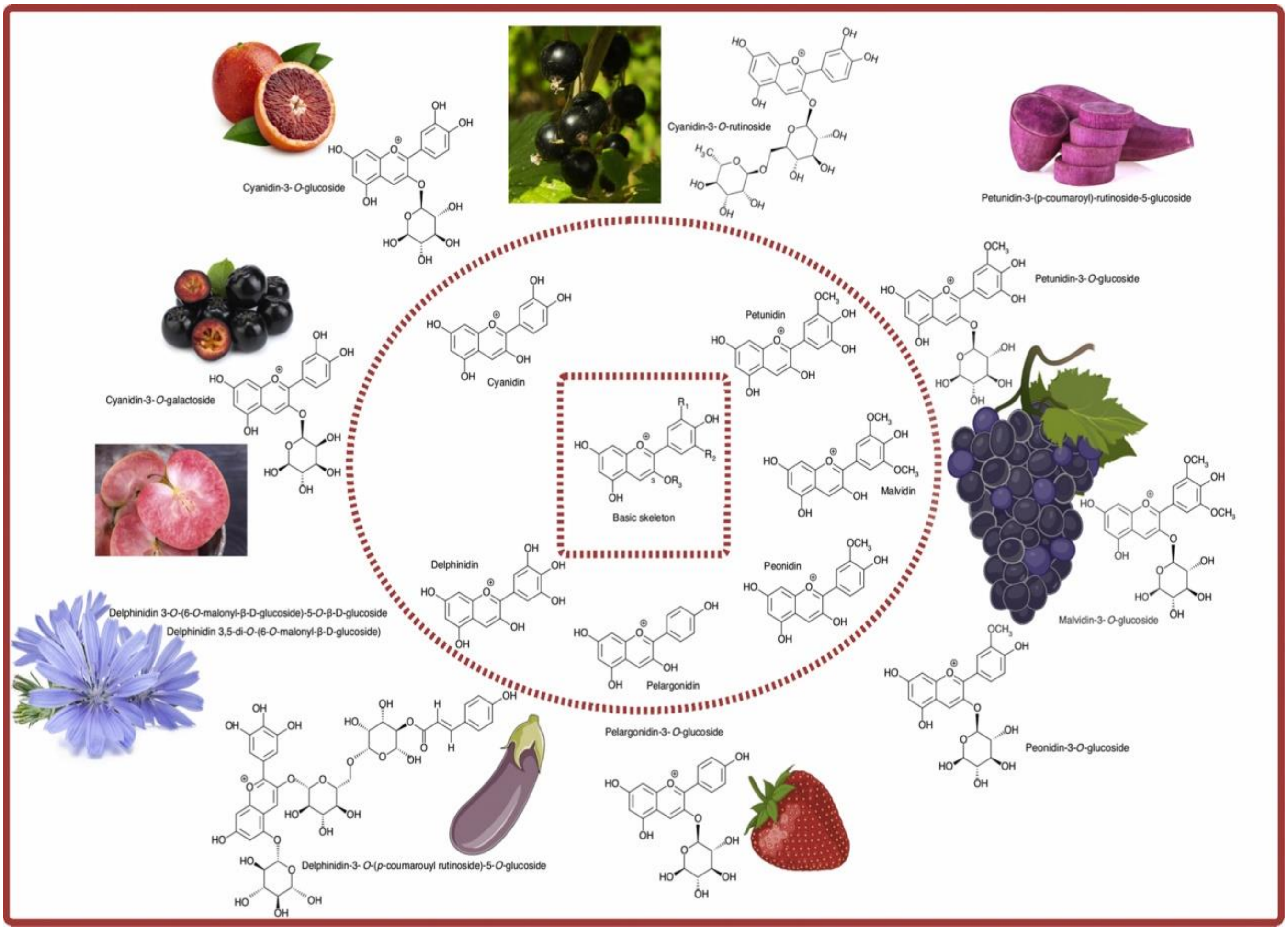

Figure 2. Structure of anthocyanin [13]

Table.1. Sources of Anthocyanins and Anticancer colorectal Activity

Anthocyanin Sources	**Molecular Activity of Anthocyanins as Colorectal Anticancer**		
	Test Model	***Findings***	***Year/ References***
Bilberry	Azoxymethane (AOM)/Dextran Sulphate Sodium (DSS) mouse	Inhibits the growth of CRC cells and cell proliferation	2017/ [30]
Pomegranate	N-Methylnitrosourea and 5-Fluororacil (5FU) rat	Reduces tumor cell proliferation and promotes apoptosis of CRC cancer cells	2017/ [28]
Purple fleshy potatoes	Gastrointestinal (GI), CRC cells CaCO-2/CCD-112-CON Vitro	Inhibits cell growth CaCO-2 cancer and reduce CRC proliferation	2017/ [26]
Sweet Potato	Azoxymethane (AOM) mice	Reducing the number of intestinal adenomas initiated by the SL222 sweet potato diet	2017/ [29]
Blueberries and Strawberries	Ozoxymethane (AOM)/ Dekstran Sulphat Sodium (DSS) rat	Reduces the number of colon tumors and CRC cell proliferation	2018/ [31]
Black Raspberries	Azoxymethane (AOM)/Dextran Sulphate Sodium (DSS) mouse	mIR-24-1-5p reduces and modulates CRC cell growth and inhibits CRC cell proliferation Reduces cancer cell	2018/ [34]
Black currant	Human colon cells (NCM460), CRC HT-29 cancer cells in- vitro	proliferation in the G0/G1 phase and promoting apoptosis of CRC cancer cells by	2018/ [35]

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		metalloproteinase MMP-2/MMP-9	
Acai Palm	1,2 Dimethylhydrazine (DMH)/ Acid 2,4,6 Trinitrobenzene (TNBS) rat	Reducing the motility of CRC cells, cell proliferation and reduced total Aberrant Crypt Foci (ACF)	2018/ [32]
Red Wine, Sorghum, and Black Lentil	Normal human colon cells (CCD-33Co), CRC cells HT-29/HTC-116 In-Silico	Inhibits the development of HT-29/HTC-116 cancer cells and increases cancer cell apoptosis	2018/ [33]
Bergamot	F344/Ntac-APC 1137 Rat	Reduces the development of CRC acneldlspromotes apoptosis cancer	2019/ [37]
Blackthorn	HTC-116 and 5-Fluororacil (5FU) mice	Inhibits the growth and polymerase of HCT-116 cells and promotes apoptosis of CRC tumor cells	2019/ [23]
Grape	Caco-2/HTC-116 in vitro	Reduces the growth and proliferation of HTC-116 cancer cells and increases Ptg2 Caco-2 cells Inhibits the proliferation of CRC cells	2019/ [36]
Apple	Azoxymethane (AOM) rat	as well as promoting cell apoptosis cancer	2020/ [38]
Black Carrot	HT-29/MCF-7 in-Vitro	Reduces CRC cell proliferation and MCF-7	2020 [25]
Bambara Beans	HT-29 Cell and Caco-2 in-vitro	Reduces HT- CRC cell proliferation 29/Caco-2	2021/ [41]
Black Chokeberry	Azoxymethane (AOM)/Dextran Sulphate Sodium and Caco-2 mouse	Inhibits the proliferation of Caco-2 cells and lowering cytokines	2021/ [39]
Black Raspberry	Azoxymethane (AOM)/ 5-fluororacil (5-FU) mouse	Reduces cell proliferation and reduce the number of CRC tumors	2021/ [24]
Flower Borago	HT-29 Cell in-vitro	Reduced HT-29. cell proliferation CRC	2021/ [42]
Purple Potatoes	Dextran Sulphate Sodium (DSS) mice	Reduced intestinal cells in expression mRNA-17 and IL-6/IL-1β proteins	2021/ [40]

Anthocyanins from several sources and anti-colorectal cancer activity

2.3.1. Apple

Cyanidin-3-O-galactoside (Cy3gal) as the main content of anthocyanins has a responsible molecular activity in reducing the proliferation of CRC cells in Azoxymethane (AOM) mice. Dietary supplements with apples can inhibit CRC cells by up to 41.3% which initiates gene expression to promote CRC cell apoptosis. Cy3gal may reduce colon carcinogenesis [38].

2.3.2. Bilberries

Bilberry is rich in anthocyanins with a molecular activity that reduces the proliferation of CRC cells by preventing tumor formation. Testing was performed with a mouse model of Azoxymethane (AOM)/Dextran Sulphate Sodium (DSS). In mice, anthocyanins provide a significant effect in preventing the growth of CRC [30].

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2.3.3. Bambara Beans

Bambara from the Fabeccea family is found in South Africa and is rich in anthocyanins containing Malvanidin-3-O-β-Dgloplyraside/Cyanidin-3-O-β-Dgloplyrasaide. Bambara has antioxidant and anticancer activity tested with HT-29/Caco-2 colon cancer cells in vitro that can reduce and inhibit the proliferation of CRC cells. bambara has the potential for natural therapies to prevent CRC [43].

2.3.4. Bergamots

Anthocyanins from bergamot have molecular activity, namely CRC anticancer activity. Mouse test model F344/Ntac-APC1337 significantly reduces the proliferation of CRC cells by increasing p53 expression and lowering the expression of the Survinn gene. Bergamot is an important candidate in CRC preventive therapy [37].

2.3.5. Black Chokeberry

Black chokeberry is a fruit rich in anthocyanins with anticancer activity CRC and associated with polyphenols. anticancer activity of Black Chokeberry with a model of Azoxymethane (AOM)/Dextran Sulphate sodium (DSS) and Caco-2 mouse cells was used to evaluate the anticancer activity of Black Chokeberry. Reduces the proliferation of Caco-2 cancer cells through decreased expression of cytokines, and glutaminase in natural therapies for the prevention of CRC [39].

2.3.6. Black Raspberries

Anthocyanins from black raspberry have anticancer activity as evidenced by using a mouse model of Azoxymethane (AOM)/5-Fluorouracil (5-FU) that can reduce the proliferation of CRC cells through inhibition of EZH2/AKT expression. Black raspberry is a strong candidate for CRC therapy [34].

2.3.7. Black Carrot

Anthocyanins from black carrots are encapsulated in Halocyte Nano Tubes (HNT) which have CRC/MC-7 anticancer activity and are good carriers of cancer drugs. In vitro Gastrointestinal (GI)/HT-29 model, Black Carrot reduces HT-29 cell proliferation and becomes an important candidate as a cancer drug carrier in CRC prevention therapy [25].

2.3.8. Blackcurrant

The molecular activity of blackcurrants containing anthocyanins plays an important role in inhibiting the proliferation of HT-29 CRC cells such as in the colon by modulating Reactive Oxygen Species (ROS). An in-vitro colon model (NCM460)/HT-29 promotes apoptosis of CRC cells by increasing the expression of Matrix Metalloproteinase (MMP-2/MMP-9). Black currant can prevent CRC cancer as well as is associated with CRC preventive therapy [35].

2.3.9. Blackthorn

Dietary anthocyanin supplements from blackthorn provide a significant molecular level impact by being able to inhibit the proliferation of CRC cells assisted by the Neutraceutical Activate Complex (NAC). By testing, 5-fluorouracil (5-FU)/HTC-116 mice were responsible for inhibiting cancer cell growth by up to 35% and producing by promoting apoptosis of HTC-116 cells [23].

2.3.10. Black Lentil and Red Wine, Sorghum.

Anthocyanins from black Letil, Sorghum, and red wine had a molecular impact when tested with the HT-29/HTC-116 in- silico testing model that reduced cancer cell proliferation by inhibiting tyrosine kinase and increasing CRC cell apoptosis. The end result of anthocyanin extracts of sorghum and lentils has the most impact in reducing the growth of CRC cells [33].

2.3.11. Blueberries and Strawberries

The main anthocyanin content of Cyanidin-3-glucoside (59%)/Pelagornidine-3-glucoside (41%) of strawberries and blueberries has molecular activity in the prevention of CRC. Testing with the Axozymethane (AOM) and Dextran Sulphate Sodium (DSS) models of mice (Hundred Nogecius F344) had an unexpected effect on the number of CRC tumors by inhibiting the polyferase activity of cancer cells and Ferric Reduction Ability of Plasma (FRAP) thus, Anthocyanins play an important role in the prevention of CRC [31].

2.3.12. Borago Flower

Borago (*Borago Officinalis*) from the family Boraginaceae contains the main anthocyanins Petunidin-3-5-glucoside/delphinidin-3-5- glucosides with antioxidant activity [44] and anti-colorectal activity. Testing with a model of HT-29 in vitro colon cells was able to lower cell proliferation [42].

2.3.13. Grape

The main anthocyanin content of Flav-3-olds from Grape is rich in the ability and anticancer activity of CRC. Testing with the Caco-2/HT-29 in-vitro model was able to inhibit the growth of tumor cells molecularly by lowering the expression of the MYC gene in HT-29 cells [36].

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2.3.14. Palem Acai

The main anthocyanin content of Cyanidin-3-rutinoside (C3R) from the acai tree has a fairly serious impact with its molecular mechanism in reducing the number of tumors, with a 1,2-dimethylhydrazine (DMH)/2,4,6-trinitrobenzene (TNBS) mouse testing model reducing the number of tumors and reducing CRC cell polyferase with tumor suppressor AKT3 in the Wnt pathway [32].

2.3.15. Purple Potatoes

Purple sweet potatoes are rich in anthocyanins with the main content of Petunidin-3-rutinoside-5-glucoside. Petunidin-3-rutinoside-5- glucoside can induce colitis with DSS models in mice. Inflammation of the colon can result in colon cancer. Colitis therapy with anthocyanins is one of the alternatives to reduce the risk of colon cancer growth [40].

2.3.16. Purple Fleshy Potatoes

Purple fleshy potatoes with a molecular mechanism rich in anthocyanins inhibit the growth of CaCO-2 cancer cells in an in-vitro gastrointestinal (GI) model. Anthocyanins with an important role in tumors and CaCO-2 cells can be found in superior meat potatoes [26].

2.3.17. Sweet Potato

Dietary sweet potato supplements rich in anthocyanins had an effect on CRC by lowering CRC cell proliferation in mouse APCMIN models. The influence of dietary sweet potato supplements significantly played an important role in reducing the amount of CRC adenoma in rats [29].

3. Molecular Mechanism of Anthocyanins as Colorectal Anticancer

3.1 Antiproliferation-anthocyanin activity

Anthocyanins with CRC anticancer activity can reduce growth and inhibit cell proliferation by various molecular means such as A/B/E cycline modulation that inhibits various pathways; kinase, MAPK [13]. Various plants rich in anthocyanins such as; Sorghum and black lentils have been linked to HCT-116/HT-29 cancer cells which show an important role in initiating cell proliferation. Anthocyanins were associated with decreased expression of the IAP-2/XIAP protein that inhibited the EGFR pathway resulting in the proliferation of CRC cells [[16]. Anthocyanins from purple shoot tea extract inhibit the proliferation of HT-29 CRC cells by reducing cyclin D/E expression [45]. CRC cell proliferation initiated by anthocyanins can block colonic epithelial cells by reducing the number of CRC carcinogenic cells [27].

3.1 Apoptosis of CRC cells

Programmed cell death (PCD) is associated with the term cancer cell apoptosis characterized by cell shrinkage [46]. Anthocyanins can promote CRC cell apoptosis by inhibiting various pathways; AMPK, PI3K/AKT, and STA3 resulting in a decrease in the number of tumors [47]. Poly adenosine diphosphate ribose polymerase (PARP) by inducing Bax/BCL-2 expression may promote CRC cell apoptosis from anthocyanin-rich purple shoot tea [45]. Cyanidin-3-galactoside from apples reduces the protein matrix of metalloproteinases associated with CRC cell apoptosis [38]. Anthocyanins can initiate apoptosis of cancer cells in p53 stem cells by inhibiting Bax and cytochrome C. Apoptosis of HTC-116 cancer cells by inhibiting STAT-3 and p-EKI 1/2 proteins [48]. Anthocyanins can promote apoptosis of CRC cells capable of initiating cancer cell death.

4. CONCLUSION

This article is a review of articles published mostly from 2017 to 2022 that discuss anthocyanins with anticancer activity in an effort to reduce the risk of colorectal cancer. The ability of anthocyanins in terms of molecular mechanisms inhibits the proliferation of cancer cells and promotes opoptosis of CRC cells. Anthocyanins have molecular activity in the prevention of colorectal cancer and have the potential to be strong candidates in natural therapies to prevent CRC.

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*Corresponding author, Email: minda@fmipa.unp.ac.id

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