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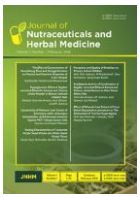

Cytotoxicity Of Moringa Plants (Moringa Oleifera L.) On Cancer Cells

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Abstract
Moringa (Moringa oleifera L.) is one of the herbal plants that grows in Indonesia. Moringa oleifera has many properties, namely that it can act as an antidiabetic, antibacterial, antitumor, antipyretic, antiepileptic, antiinflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol lowering, antioxidant, hepatoprotective, antifungal. The aim of preparing this review is to determine the cytotoxic activity of Moringa oleifera L.) and the mechanism of action of secondary metabolites that can be isolated from Moringa. The preparation of this review comes from articles obtained through the Google Scholar database , PubMed and Sciencedirect with the keywords namely " Cytotoxic AND " Moringa oleifera lam" AND Anticancer AND IC50 values ". The inclusion criteria set were original articles or articles full text in PDF format regarding the potential cytotoxic activity of the Moringa oleifera L. plant in vitro with a publication year range of 2012-2021, using the MTT assay method , has an IC value of 50 < 50 µg/mL in the leaves and seeds and has an IC value 50 < 100 µg/mL in other plant parts . From these criteria, 10 suitable articles were obtained . The results of the analysis show that the cytotoxic activity of M. oleifera against several cancer cells can be categorized as active to very active . Next, it can be seen if it has anticancer activity M. oleifera is obtained from secondary metabolites resulting from extraction M. oleifera . Secondary metabolites that have been isolated from M. oleifera is known to contain lectins, routine, quercetin, astragalin, isoquercetin, glucomoringin, 7-Octenoid Acid, Oleamide, and 1-Phenyl-2-Pentanol. This metabolite has an anticancer mechanism in the form of inducing apoptosis through : (1) ROS -mediated signaling pathways , (2) targeting the anti-apoptotic protein BCL-2 family , (3) regulation of the tumor suppressor protein p53, (4) inhibition of NF- κB, and (5) decrease in MAPK signal .

Keywords: Moringa oleifera L., cytotoxic, IC 50 , anticancer, induction of apoptosis

INTRODUCTION

The main cause of death in the world today is still cancer. According to Hanahan (2011), cancer is a disease caused by abnormal genes. Characterized by persistent proliferation signals, defective growth inhibitory genes, and absence of cell death. This is followed by uncontrolled cell replication, which stimulates angiogenesis, allowing cells to

metastasize and attack surrounding tissue (Safitri, et al. 2020). Estimates from the World Health Organization (WHO) in 2015, the first or second cause of death before the age of 70 years in 91 out of 172 countries was cancer (Bray, 2018). The World Health Organization (WHO) released data from the Global Burden of Cancer (GLOBOCAN) that up to 2018, the number of cases and deaths due to cancer was 18.1 million cases and 9.6 million deaths (Ministry of Health of the Republic of Indonesia, 2019). Next, in 2020, there were around 19.3 million new cancer cases and 10 million deaths reported by GLOBOCAN (Kubare, *et al* . 2021).

Approximately 70% of cancer deaths occur in low- and middle-income countries, possibly due to factors such as increasing pollution levels, increasing life expectancy, inadequate health facilities, and expensive anticancer drugs (Khor , *et al* . 2018). The development of cancer is common already in an advanced stage (metastasis) as well involves complex molecular mechanisms that cause problems in therapy (Apriyani , *et al* . 2019). Cancer treatment can generally be done with radiation, surgery and chemotherapy (Setiawan, 2015). However, apart from being expensive, this treatment also often causes side effects such as the spread of cancer cells to other parts, damaging healthy cells, and can cause cancer cells to mutate so that they are difficult to destroy (Muhartono, 2017). Due to the severe physical and psychological side effects of these treatment methods, developments in the field of isolation and identification of phytochemical compounds have seen increasing progress towards the application of traditional herbal medicine as a potential source of anticancer agents (Elsayed, et al. 2015). Noted that more than 60% of all existing anticancer drugs currently comes from natural sources (Khor *et al* , 2018). Various plants have shown potential as a source of anticancer compounds, one of which is Moringa (*Moringa oleifera* L.).

Moringa (*Moringa oleifera* L.) is one of the herbal plants that grows in Indonesia. Often a natural resource that is utilized for health. Different parts of the plant body such as tree bark, leaves, seeds, flowers, roots, and fruit contain a large number of phytoconstituents such as terpenoids, alkaloids, proteins, quinine, saponins, flavonoids, glycosides, tannins, steroidals, and aglycones (Paikra, 2017) . *Moringa oleifera* has many properties, namely that it can act as an antidiabetic, antibacterial, antitumor, antipyretic, antiepileptic, antiinflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol lowering, antioxidant, hepatoprotective, antifungal (Khor, 2018). Research conducted by Hussein , *et al (2014), proved that Moringa oleifera has anticancer activity on* MCF-7, HCT-116, HepG-2, Hep-2, HeLa cell lines .

This literature review was prepared in order to determine the anti-cancer activity of Moringa (*Moringa oleifera* L.) and the mechanism of action of secondary metabolites that can be isolated from Moringa which have been tested and studied by previous researchers and has been published in the available literature.

METHODS

The method for compiling *a literature review* is carried out by searching article sources from the *Google Scholar, Sciencedirect* and *PubMed databases* . The keywords used in the article search were *"Cytotoxic AND "Moringa oleifera lam" AND Anticancer AND IC $_{50}$ values"* . The process carried out in searching for articles is in accordance with **Error! R eference source not found.**.

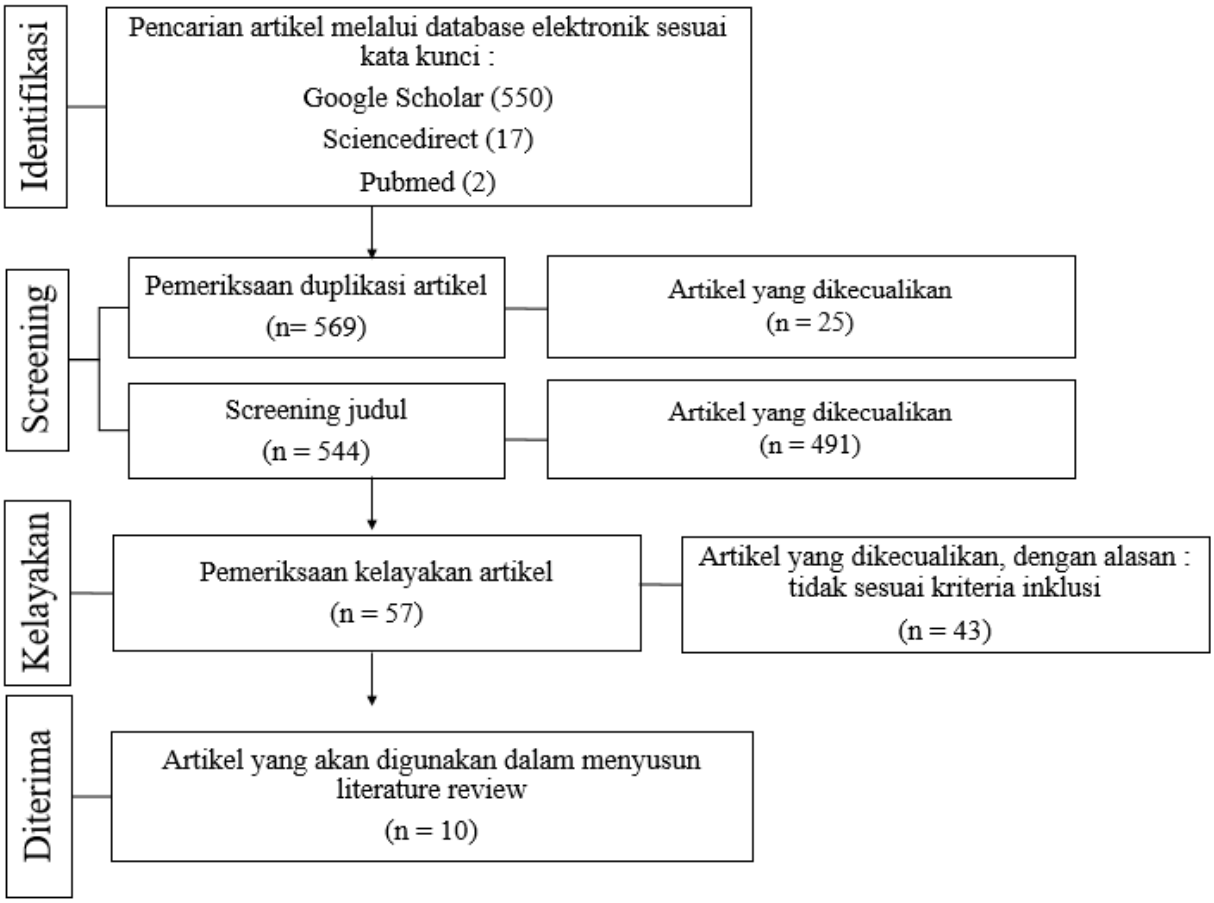

Figure 1. Literature Review Method

Articles that have been identified based on keywords are then recorded in Microsoft Excel to be screened for duplication and title suitability. At the eligibility stage, articles that have been screened are then reviewed based on inclusion and exclusion criteria . Inclusion criteria are the characteristics of the research sample that will be included in the criteria for

articles to be reviewed. The inclusion criteria set were in the form of an original article or *full text article* in PDF format regarding the potential cytotoxic activity of the *Moringa oleifera* L. plant in vitro with a publication year range of 2012-2021, using the *MTT assay method* , having an IC value of $_{50}$ < $_{50}$ µg /mL in leaves and seeds and has an IC value of $_{50}$ < 100 µg/mL in other plant parts. Exclusion criteria are characteristics of articles that are not included in the criteria for articles to be reviewed. The articles were then recorded regarding information such as the author, year of publication, plant parts used in the trials, and final results obtained from the research carried out.

RESULTS AND DISCUSSION

Search results on *Google Scholar* , *Sciencedirect* , and *Pubmed* yielded 569 articles. The articles obtained were then *screened* for duplication of articles and suitability of titles . As a result, 57 articles were found which were then checked for eligibility based on inclusion and exclusion criteria. Obtained articles that are not suitable, namely the publication time span is not in the last 10 years, are not *full* text articles, have an IC value of $_{50}$ > $_{50}$ µg/mL in leaves and seeds and has an IC value of $_{50}$ > 100 µg/mL in another section, discussing Moringa but not as an anticancer, discussing anticancer but not derived from Moringa. So we obtained 10 journals with the results in Table 1.

Table 1Article Review on Moringa (Moringa oleifera L.) In Vitro

Plant Parts	Types of Cancer Cells	Phytochemical Compounds	$_{50}$ results (µg/mL)	Reference
Leaf	Laryngeal cancer	Steroids , flavonoids and phenolics	- Hep-2 = 12.5	Krishnamurthy, *et al* . 2015
	Breast and cervical cancer	Flavonoids, saponins, alkaloids, tannins	- MCF-7 = 3.19 - HeLa = 1.68	Maqsood , *et al* . 2017
	Breast cancer	-	- T47D = 20.17	Gaffar , *et al* . 2018
	Heart cancer	-	- HepG-2 = 12.89	Nejad , *et al* . 2020
Seed	Breast, colon, liver, larynx and cervical cancer	-	- MCF-7 = 10.2 - HCT-116 = 17.9 - HepG-2 = 10 - Hep-2 = 20.6 - HeLa = 16.5	Hussein, *et al* . 2014
	Colorectal cancer	-	- T84 = 33.3 - HCT-15 = 24.6 - SW480 = 19.8	Fuel, *et al* . 2021
Flower	Cancer prostate	-	- PC-3 = 6.25	Ju , *et al* . 2018

Fruit	Colon cancer	-	- HCT116 = 6.02	Guon , *et al* . 2017
Root	U937, K562	Steroids, triterpenoids, amino acids, saponins, alkaloids.	- U937 = 8.56 - K562 = 9.12	Roy, *et al* . 2014
	Colon, liver and breast cancer	-	- Caco-2 = 32.16 - HCT-116 = 29.14 - HepG-2 = 29.1 - MCF-7 = 46.16	Abd-Rabou , *et al* . 2017

1. Cytotoxic Activity of Moringa (*Moringa oleifera* L.) Plants Against Various Cancer Cells

The part of the Moringa plant that is often studied in relation to its anticancer activity is the leaves. In 2015, Krishnamurthy et al tested the anticancer activity of Moringa leaves against laryngeal cancer cells. Fractionation was carried out and 15 fractions were obtained from the ethyl acetate extract, where the $IC_{50\ value}$ of the ethyl acetate extract was 40.2 µg/ml and of the 15 fractions studied, fraction 1 contained dichloromethane which was the most cytotoxic fraction with the smallest $IC_{50\ value}$, namely 12. 5 µg/ml. In subsequent research by Maqsood et al, 2017, it was found that the methanol extract of Moringa oleifera leaves showed an $IC\neg_{50\ value}$ with the criteria for strong cytotoxic activity. $IC_{50\ values}$ were recorded at 1.68 and 3.19 µg/ml after an incubation period of up to 72 hours for MCF-7 and HeLa cell lines. Other research has been reported by Gaffar et al, 2018, that the ethyl acetate fraction of M. oleifera leaves has an inhibitory effect on the growth of T47D cells with an IC_{50} of 20.17 µg/ml. Apart from that, the researchers also observed changes in the morphology of T47D cells using an inverted microscope. They found the shape of leaflets attached to the bottom of the wells in T47D cells that were not treated. In contrast to cells that were given treatment, it appeared that the dead cells were round, looked cloudy, and floated. These microscopic observations indicate that the ethyl acetate fraction of M. oleifera leaves has a role and effect in cell death. Next, based on the results of the MTT test on the methanol extract of Moringa leaves, it shows that there is inhibition of growth and proliferation of liver cancer cells (Nejad, et al. 2020). The highest concentration used, namely 70 µg/ml, has a cytotoxic effect similar to doxorubicin, where the cell viability of the methanol extract of Moringa leaves is 12.89 µg/ml while doxorubicin is 11.5 µg/ml.

Hussein, et al, 2014, examined the antitumor activity of M. oleifera seed essential oil which was evaluated against the following five tumor cells: MCF-7, HCT-116, Hep G2, HEP-2 and HELA. Inhibitory activity of M. oleifera essential oil against breast carcinoma cells (MCF-7), colon carcinoma cells (HCT-116), hepatocellular carcinoma cells (HepG2), laryngeal carcinoma cells (HEP-2) and cervical carcinoma cells (HELA) was detected has an $IC_{50\ value}$ of

10.2 respectively; 17.9; 10.0; 20.6 and 16.5 µg/ml. The latest research in 2021 regarding Moringa seeds was conducted by Fuel et al. The antitumor effects of the ethanol extract were evaluated in vitro with colorectal cancer (CRC) cell lines T84, HCT-15, and SW480. The IC_{50} results sequentially on T84, HCT-1, and SW480 were 33.3; 24.6; 19.8 µg/ml. So it was found that SW480 colorectal cancer cells had the highest cytotoxic activity compared to HCT-15 and T84.

Research on the cytotoxic activity of the flower parts of Moringa has been reported by Ju et al, 2018. The cytotoxicity of the ethanol extract of M. oleifera flowers was evaluated by treating PC-3 cells at a concentration range of 0.07-100 µg/mL for 24 and 48 hours using the MTT test . The results obtained show that as the concentration increases, cell death also increases. At the highest concentration, it was found that significant cytotoxic activity against PC-3 cells reached $IC_{50\ values}$ of 8.48 and 6.25 µg/mL at 24 hours and 48 hours, respectively.

Guon et al, 2017, used M. oleifera fruit in their research and the results obtained showed inhibition of HCT116 colon cancer cell proliferation in a dose-dependent manner. The percentage of cell viability of HCT116 cells treated with M. oleifera fruit decreased by 85.5%, 63.3%, and 38.5% at concentrations of 80, 120, and 1 $_{50}$ g/mL, respectively . Researchers also fractionated and isolated the compounds contained in Moringa fruit. The flavonoid compound in the form of routine was successfully isolated from Moringa fruit and showed effective cell inhibition with an IC_{50} of 6.02 µg/mL.

In contrast to Roy et al, 2014, the object studied was root bark. It was found that the ethyl acetate fraction had an IC_{50} in U937 cells of 9.73 µg/mL and K562 10.23 µg/mL and the n-butanol fraction had an IC_{50} of 8.56 µg/mL in U937 and K562 9.12 µg/ mL. Apart from researching the anticancer activity of the $IC_{50\ value}$, Roy et al obtained secondary metabolite compounds contained in Moringa root bark in the form of steroids, triterpenoids, amino acids, saponins and alkaloids. It can be said that the compounds contained here play a role in reducing the viability of cancer cells. The use of root parts has also been reported by Abd-Rabou et al (2017), by extracting Moringa roots with ethanol, it was found that the survival of the four cancer cells Caco-2, HCT-116, HepG-2, and MCF-7 with an IC of $_{50\ was\ reduced.}$ respectively 32.16; 29.14; 29.1; and 46.16 µg/mL. This study also examined the inhibitory effect exerted by Moringa root on normal cells (BHK-21). The results showed that the inhibition of BHK-21 cells was 3 times that of cancer cells. These results indicate roots Moringa has cytotoxic activity against cancer cells and has minimal effects on normal cells .

IC50 value of administering *Moringa oleifera* extract to various types of cancer cells is quite different, factors that might cause are differences in concentration, metabolites contained , and Based on the literature reviewed it can be concluded that cytotoxic activity in the leaves, seeds, flowers, fruit, and roots *M. oleifera* against several cancer cells can be categorized as active to very active. Weerapriyakul (2012) classified the cytotoxic activity of an extract against cancer cells into 3 categories (Sirait , et al. 2019). An IC50 value < 10 µg/mL is categorized as very active, the second category with an IC50 range of 10-100 µg/mL is

active, and the moderately active category if IC_{50} ranges from 100-500 µg/ mL. So *Moringa oleifera* can be further developed as a chemopreventive agent .

2. Secondary Metabolite Content Moringa plant (*Moringa oleifera* L.)

Moringa oleifera including in family *Moringaceae* is plant original Indian subcontinent and has naturalized in the area tropics and subtopics throughout the world (Farooq, *et al* . 2012). *Moringa oleifera* reported own efficacy useful pharmacology _ like anticonvulsant , antimicrobial , anticancer , and antiviral. Extracts (phytochemicals) from leaves , seeds , skin wood , and flowers *M oleifera* has used For treat a number of disease period long , incl hypercholesterolemia , pressure blood high , diabetes, insulin resistance , disease heart nonalcoholic , cancer , and inflammation (balagun 2021).

Plant can potential as treatment disease Because contain compound metabolites secondary (Salim, *et al* . 2017). There is activity anticancer in *Moringa oleifera* obtained from metabolites contained there (table 1), *Moringa oleifera* contain compound phytochemical flavonoids, alkaloids, steroids, triterpenoids, tannins, amino acids and saponins obtained in a way qualitative (Krishnamurthy *et al* ., 2015; Maqsood *et al* ., 2017; Roy *et al* ., 2014). Compound has their own mechanism as anticancer described by (Safitri , et al, 2020, Ren et al, 2003) on alkaloids during cycle cell will binds to tubulin, a protein that forms microtubules. When tubulin binds with alkaloids, will hinder deep protein polymerization microtubules, so hinder formation mitotic spindle and metabolic stop cell cycle . Cell Then undergoes apoptosis due to No capable undergo cell division. Next mechanism flavonoid compounds through induction of apoptosis viz with method hinder DNA topoisomerase I/II activity, regulates signaling pathway , reducing Bcl2 and BclXL gene expression , increased Bax gene expression and activation endonuclease .

More compounds _ Specific detected in Moringa in the form of lectin, routine , quersetin , astragalin, isoquersetin , glucomoringin , 7-Octenoid Acid, Oleamide, and 1-Phenyl-2-Pentanol (Asaduzzaman , 2017; Guon , 2017; Luz, 2017; Tragulprakseerojn , 2017; Cirmi , 2019; Wisitpongpun , 2020). As for engagement metabolites secondary that has isolated from the Moringa plant in the anticancer process that can seen in Table 2.

3. Induction Mechanism Apoptosis of Secondary Metabolites from Moringa Plants (*Moringa oleifera* L.)

In the strategy of *M. oleifera* as a potential chemopreventive agent, the compound must be involved in a pathway or mechanism with activate or inhibit carcinogen detoxification, anti-oxidant effects, tumor cell proliferation, apoptosis, inflammation, tumor angiogenesis, migration, invasion and synergistic effects (Karim 2016). Apoptosis is a physiological process death programmed cells, play a role in maintain cellular homeostasis through appointment cells that don't Again needed , experienced damage , mutation , occurs aging and not can repaired , so can preserve and maintain population cell in network (Ismail, 2019; Kou, 2018;

Muhartono , 2017). Inactivation of apoptosis is originator pathogenesis various disease like autoimmunity, ischemia , neurodegeneration and cancer (Sreelatha, 2011; Ismail, 2019). Therefore _ Therefore , induction of apoptosis can be an effective strategy oppose tumor development . Mechanism metabolites isolated secondary _ from *M. oleifera* through induction of apoptosis is presented in Table 2.

Table 2. Mechanism Metabolite Apoptosis Induction Secondary from Moringa plant (Moriinga oleifera L.)

Plant Parts	Metabolites secondary	Type Cell Cancer	Mechanism action	Reference
Seed	Lectins	Ehrlich Ascites Carcinoma (EAC)	Activation of the Bak gene with inhibition track NF- κB signaling	Asaduzzaman , 2017
Fruit	Rutin and quercetin	HCT-116	Activation of apoptosis with change expression of Bcl-2 family proteins , and activation of caspase-3, caspase-9 and PARP	Guon , 2017
Seed	Lectins	B16-F10	Trigger caspase activation (3, 8, 9) and pathways ROS production .	Luz 2017
Leaf	Astragalin and isoquercetin	HCT-116	Downregulation ERK 1/2 phosphorylation and a little subtraction AKT expression	Tragulprakseerojn , 2017
Seed	Glucomoringin	SH-SY5Y	Increase gene expression Bax , p21, p53, caspase-3, caspase-9, and inhibit NF- κB translocation with decrease in p65	Cirmi , 2019
Leaf	7-Octenoid Acid, Oleamide, 1-Phenyl-2-Pentanol	MDA-MB-231	Inhibition of Bcl-2 and activation of p53, Bax , and caspase 3.	Wisitpongpun , 2020

Extrinsic pathway in induce apoptosis using signal extracellular . Signal death cells , also known as a death ligand , binds with receptor death family that is factor tumor necrosis (TNF). Some death ligands including Fas ligand (Fas -L), TNF- related apoptosis -inducing ligand (TRAIL) and factors tumor necrosis (TNF) (Pfeffer, 2018). There is three tens member receptor family factor tumor necrosis (TNF-); eight among them contains a death domain (DD) in the tail cytosol . A number of receptor the TNF family containing this DD using caspase activation as mechanism signaling , including TNFR1/CD120a, Fas /APO1/CD95, DR3/Apo2/ Weasle , DR4/TrailR1, DR5/TrailR2, and DR6 (Hassan, 2014). Receptor death has a death

domain intracellular cells that recruit adapter proteins such as death domains related TNF receptor (TRADD) and death domain related Fas (FADD), as well as cysteine proteases such as caspase 8. Death ligand binding until death receptor produce formation of binding sites for adapter proteins and throughout known ligand- receptor -adaptor protein complexes as complex inducing signaling _ death (DISC) (Rebecca, 2011). FADD recruitment triggers pro-apoptotic pathway , while TRADD induces signal antiapoptotic . FADD attracts other DD/DED-containing proteins , such as pro-caspase-8 and -10, to push formation of death-inducing complex (DISC) in the compartment cytoplasm . In contrast , TRADD binds and forms complex I with receptor interacting protein-1 (RIP1), TNF receptor associated factor-2 (TRAF2), TRAF5 and inhibitor of apoptosis protein-1 and -2 (cIAP1/2) (Koff, 2015).

Intrinsic pathway refers to the apoptosis- mediated pathway mitochondria . Where on track This triggered by various pressure extra and intra-cellular , which includes : deprivation factor growth , excess Ca2+, molecules DNA damage , oxidant stress oxidative , irradiation , and treatment with cytotoxic drugs (jan , 2019; Pfeffere , 2018). By overall , path intrinsic regulated by the BCL-2 family of proteins. The BCL-2 protein is divided into 2 groups major , namely pro-apoptotic proteins (eg Bax , Bak, Bad, Bcl-Xs , Bid, Bik, Bim and Hrk) and anti-apoptotic proteins (e.g. Bcl-2, Bcl -XL, Bcl-W, Bfl-1 and Mcl-1). While anti-apoptotic proteins regulate apoptosis by obstruct release mitochondria from cytochrome -c, a pro-apoptotic acting protein with promote release (Rebecca , 2011). Bcl-2 and Bcl-xL (member Bcl-2 family) are anti-apoptotic proteins that prevent release cytochrome c. Cytochrome c combines with Apaf-1 and procaspase-9 for produce apoptosome . Apoptosome is multi-protein complex consisting of from complex shaped ring seven crossbar , which triggers caspase 9 followed by caspase activation of the caspase-3 signaling cascade leading to destruction cells and ends to apoptosis (Jan, 2019).

Induction of apoptosis is also associated with mechanism track mediated signaling _ species oxygen reactive (ROS). ROS mediators influence signaling intracellular , causing DNA damage and alteration epigenetics through stages cancer or tumor development , as well activate apoptotic pathway when ROS do not balanced (Karim, 2016).

CONCLUSION

Based on the literature review, it can be concluded that activity cytotoxic in parts leaves , seeds , fruit , flowers and roots M. oleifera to a number of cell cancer can categorized as active until very active based on classification by Weerapriyakul (2012). Next can is known if the anticancer activity of M. oleifera obtained from secondary metabolites resulting from the extraction of M. oleifera . Secondary metabolites that have isolated from M. oleifera It is known that there are lectins, routine , quersetin , astragalin, isoquercetin , glucomoringin , 7-Octenoid Acid, Oleamide, and 1-Phenyl-2-Pentanol . Metabolites It has an anticancer mechanism in the form of Inducing apoptosis through : (1) track ROS- mediated signaling , (2) targeting anti-apoptotic protein BCL-2 family, (3) regulation of the tumor suppressor protein p53, (4) inhibition of NF- κB , and (5) decrease MAPK signal .

Effect potential Moringa (Moringa oleifera L.) as agent chemopreventive in studies previously Still required further research regarding the anticancer activity of various compound isolated active _ from Moringa plant to find out direct anticancer mechanism. So that is known potential of Moringa in hinder or induce track certain related disease cancer .

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