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Cytotoxic Effects of Plant Bioactive Compounds on T47d Breast Cancer Cells Line: *A Review*

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Abstract *- The continuous cell line known as T47D cells originates from the isolation of epithelial cells from the ductal breast tissue of a 54-year-old woman with metastatic breast cancer. Numerous plant species have been employed in alternative anti-breast cancer therapy, showing advancements in recent years. The aim of this systematic review is to assess the potential bioactive compounds from herbal plant extracts and analyze the effects of herbal plants on T47D breast cancer cells. This research employs a systematic approach to gather articles, encompassing related research questions, chosen databases, keyword selection, inclusion and exclusion criteria, as well as outcomes and conclusions regarding the collected articles. From the reviewed articles, several plants exhibit anti-breast cancer activity on T47D cell lines, namely Calamintha incana, Sterculia quadrifida, Psidium guajava, Uncaria nervosa, Syzygium aqueum, Capsicum annum, Bauhinia scandens, Lansium domesticum, and Garcinia cowa due to their content of bioactive compounds such as triterpenoids, alkaloids, phenolics, flavonoids, saponins, and tannins. These bioactive compounds from the plants exert significant influence on cell cycle, proliferation, fatty acid synthesis, and apoptosis of cancer cells.*

Keywords: *Bioactive compounds, Breast Cancer, MTT assay, Review, T4D7*

INTRODUCTION

According to statistics from the World Health Organization (WHO) in 2020, the number of women diagnosed with breast cancer reached 2.3 million, causing 685,000 deaths worldwide. By the end of 2020, approximately 7.8 million women had been diagnosed with breast cancer in the last five years, making it the most common type of cancer worldwide (Arnold et al., 2022). According to Globocan data in 2020, there were 68,858 new cases of breast cancer in Indonesia, accounting for about 16.6% of the total 396,914 new cancer cases in the country. Meanwhile, the number of deaths has exceeded 22,000 cases (Ministry of Health of the Republic of Indonesia, 2022).

Currently, breast cancer treatment can be carried out by surgery, radiotherapy, and chemotherapy. However, the impact of radiotherapy and the use of chemotherapy drugs can cause side effects such as hair loss, bone marrow suppression, drug resistance, gastrointestinal lesions, neurological dysfunction, and cardiac toxicity (Hosseini and Ghorbani, 2015). Therefore, alternative treatments are needed to reduce these risks.

It is known that bioactive compounds in plants can be used as an alternative treatment because they have minimal side effects. Currently, about 20% of known plants have been used in pharmaceutical research, impacting the healthcare system in positive ways such as treating cancer and dangerous diseases (Altemimi et al., 2017). In addition, plant bioactive compounds are proven to be benefical and have biological activities such as anticancer, antioxidant, antidiarrheal, analgesic, antimicrobial, and wound healing (Ingle et al., 2017). Cancer cells' resistance to chemically synthesized drugs prompted researchers to turn to ethnopharmacognosy.

One way to predict the effect of anti-cancer drugs or plant extracts is by using cell lines. An example of a cell line used in breast cancer research is T47D. The T47D cell line has been widely used in in vitro research

because it has high homogeneity, unlimited replication ability, and easy handling. In addition, the T47D cell line is sensitive to chemotherapeutic agents and has a rapid replication ability that is suitable for cytotoxic testing (Jhofi & Hamidi., 2021).
Many plants contain natural ingredients extracted as anti-cancer drugs, but their nutritional benefits can be obtained in the form of daily nutrition. The positive benefits of plants such as fruits and vegetables as nutritional sources for health are demonstrated through the phytochemical content within them (Tusanti et al., 2014). The results of plant secondary metabolism include compounds such as alkaloids, flavonoids, phenolics, tannins, and terpenoids. These compounds have biological activities that can be utilized in medicine, for example, to treat cancer (Nurhayati et al., 2006). Therefore, a systematic review is necessary to facilitate the research of the potential of bioactive compounds contained in medicinal plants and to analyze their impact on cancer especially breast cancer using the T47D cell line.

MATERIALS AND METHODS

This study utilizes a search methodology to determine the sequence of steps, including the following: relevant scientific questions, databases to be used, selection of keywords, criteria for including and excluding information, definition of outcomes, and conclusions about the selected articles (Sampaio and Mancini, 2007).

The study applies a search method to establish the sequence of actions, including the following: connected research questions, data sources to be utilized, selection of keywords, rejection and inclusion criteria, definition of results, and closure regarding the selected articles (Sampaio and Mancini, 2007).

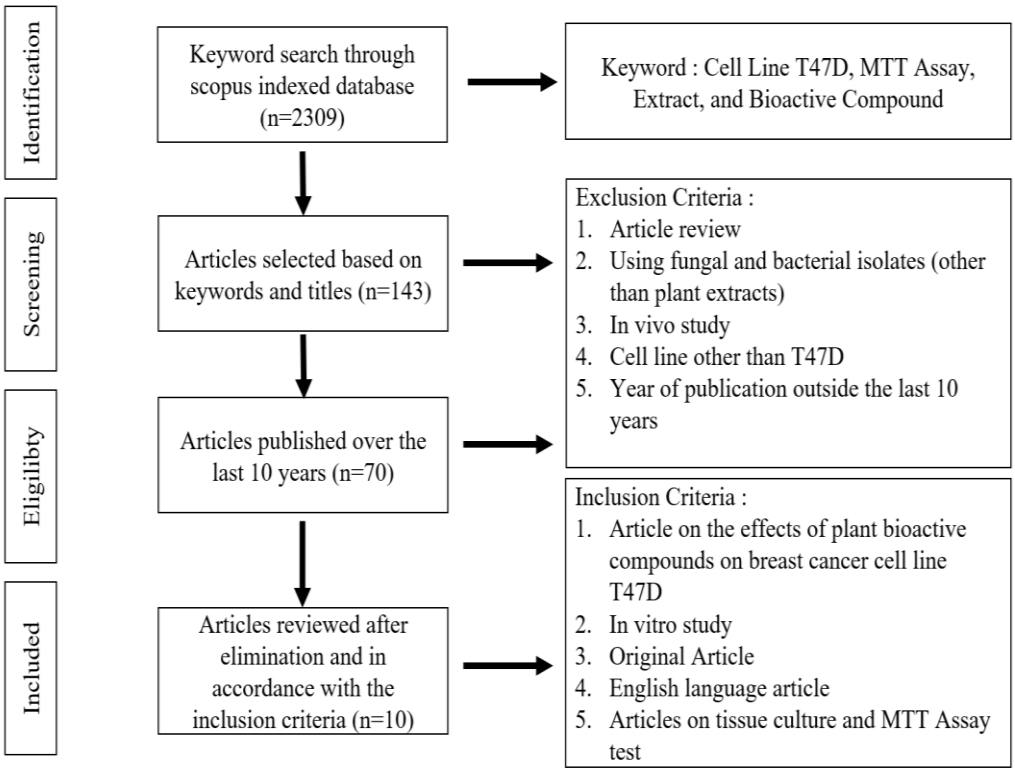
Journal searches in the Scopus database with search terms such as "T47D cell line", "Extract", "MTT assay", and "Bioactive Compound". Texts will be evaluated and selected based on set inclusion and exclusion criteria. The inclusion criteria for articles are that the journal must provide primary data on the effects of plant compounds on breast cancer using the T47D cell line. Articles must be original, in English, discuss tissue culture and MTT assay, and be in-vitro studies.

Articles not discussing plant compounds will be excluded from this review. The literature review includes journal reviews, brief reports, case reports, and clinical trial reports. In addition, there are other exclusion criteria including animal studies, the use of fungal and bacterial isolates, the use of cell lines other than T47D and publications older than 10 years. Journals that meet the requirements of keywords, title, and abstract will be thoroughly examined to understand their content and align it with the topic being studied. The analysis conducted in this article review is descriptive in nature.

RESULT AND DISCUSSION

From the initial search results in the Scopus database, 2309 titles were identified for review. After selection, 143 articles met the criteria. The criteria for articles included keywords such as “T47D cell line”, “MTT assay”, “extract”, and “bioactive compound”. The articles were further selected by observing exclusion criteria (outside the targeted articles) such as review articles, publications outside the last ten years, using fungal and bacterial isolates, in vivo studies, and other than T47D cell lines, resulting in 70 articles that met the criteria. Further selection was made by applying inclusion criteria, namely articles on the effect of bioactive plant compounds as anti-breast cancer on T47D cell line, original articles,

articles in English, in vitro studies, articles about tissue culture and using MTT assay method, resulting in 10 articles qualifying for inclusion. Graph 1 shows the flow diagram of study selection and the number of articles involved at each stage. The articles were analyzed based on the researchers mentioned, year of publication, type of compound extracted from plants, MTT Assay (IC50 measurement method), results obtained, and outcomes in Table 1."



Graph 1. Flow of Article Selection

Table 1. Inclusion Data (Article Summary)

No	Title	Plants	IC_{50}	Compound	Conclusion	Reference
1.	Chemical Composition, In vitro Evaluation of Antioxidant Properties and Cytotoxic Activity of the Essential Oil from *Calamintha incana* (Sm.) Helder (Lamiaceae)	*Essential Oil of Calamintha incana* (Sm.) Helder (Lamiaceae)	106.78 µg/mL	Phenolic compounds with benzenamine-4-methyl-3-nitro- and (2S,4R)-p-mentha-6,8-diene 2-hydroperoxide derivatives	Essential oil extracts of *Calamintha incana* (Sm.) contain diterpenes and phenolic compounds that show potential cytotoxicity in several types of cancer and non-cancer cell lines.	(Althaher et al., 2021)
2.	A Phenylpropanoid Compound from the	*Sterculia quadrifida* seeds	12.12 µg/mL	One phenylpropano	The phenylpropanoid	(Rollando et al., 2023)

No	Title	Plants	IC_{50}	Compound	Conclusion	Reference
	Seeds of *Sterculia quadrifida* and its Cytotoxic Activity			id compound, (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one	compound, (2E,4E)-1,5 diphenylpenta-2,4-dien-1-one isolated from *Sterculia quadrifida* extracts showed anticancer properties.	
3.	Exploring anticancer activity of the Indonesian guava leaf (*Psidium guajava* L.) fraction on various human cancer cell lines in an in vitro cell-based approach	*Psidium guajava* L. leaves	21.68 µg/mL (ethyl acetate fraction) and 8.92 µg/mL (n-Hexane).	Ellagitannin and Genistein	MTT testing shows that the n-hexane fraction has the best toxicity and selectivity against T47D cancer cells with an IC50 value of 8.92 and a selectivity value of >10 which is included in the good selectivity category.	(Prakoso & Nita, 2023)
4.	Cytotoxic Activity Screening of Various *Uncaria* Spp Plants on T47d Breast Cancer Cells	*Uncaria* Spp leaves	64,42 µg/mL ethanol extract of *Uncaria nervosa* leaves	Terpenoid and Alkaloid	*Uncaria nervosa* extracted with ethanol is cytotoxic and affects breast cancer cell line T47D with the best IC50 value.	(Rahmawati et al., 2023)
5.	Bioactive triterpenoids from Indonesian medicinal plant *Syzygium aqueum*	*Syzygium aqueum* stem bark	7.37 µg/mL (Alphitolic acid) and 27.51 µg/mL (Arjunolic acid)	Triterpenoids (From two compounds alphitolic acid and arjunolic acid)	Isolation of two bioactive triterpenoid compounds from *Syzygium aqueum* stem bark, namely alphitolic acid and arjunolic acid. Both compounds have toxicity against breast cancer, indicated	(Kristiani et al., 2022)

No	Title	Plants	IC_{50}	Compound	Conclusion	Reference
					by small IC50 values.	
6.	Antibacterial, Antioxidant, and Cytotoxic Flavonoid Compound from *Sterculia Quadrifida* Leaves	Leaves *Sterculia quadrifida*	25.91 µg/mL	(2E)-2-[(3,4 dihydroxy phenyl)(hydrox y)methylidene] -4,6-dihydroxy-2,3-dihydro-1-benzofuran-3-one	The compound isolated from *Sterculia Quadrifida* extract is an auron compound derivative. The compound has antioxidant, antibacterial, and anticancer activities.	(Rollando et al., 2021)
7.	Cytotoxic Effect of *Capsicum annum* L. extract on T47D Cells: In vitro Study	*Capsicum annum* L	75.81 µg/mL	Capsaicin	*Capsicum annum* extract (CAE) contains the bioactive compound capsaicin which is able to inhibit cancer cell growth and activate caspase-3 expression as a marker of apoptosis in T47D cells.	(Kurnijasanti & Fadholly, 2021)
8.	Phytochemical screening and cytotoxic evaluation of *Bauhinia scandens* leaf extracts using HeLa and T47D cell lines	*Bauhinia scandens* leaves	4.54 µg/mL	Phenols, flavonoids, saponins, tannins, alkaloids and steroids	*Bauhinia scandens* is potentially a strong candidate for anticancer agents. The cytotoxic activity of *Bauhinia scandens* leaf extract may be attributed to the total effect of the phytochemical compounds found.	(Lianah et al., 2021)
9.	A bioactive compound isolated	*Lansium domesticum* Corr fruit peel	25.56 µg/mL	Lamesticumin A	Extracts, fractions from	(Fadhilah et al., 2020)

No	Title	Plants	IC_{50}	Compound	Conclusion	Reference
	from Duku (*Lansium domesticum* Corr) fruit peels exhibits cytotoxicity against T47D cell line		(Fraksi C, *Lansium domesticum* Corr)		*Lansium domesticum* fruit peel showed cytotoxic activity against breast cancer cell line T47D.	
10	Cowanin, a Cytotoxic Xanthone from Asam Kandis (*Garcinia cowa*, Roxb.) Reduced Cell Migration and Induced Cell Cycle Arrest on T47D Human Cancer Cell	*Garcinia cowa*, Roxb stem bark	11.1 µg/mL at 48 hours incubation	Cowanin from oxygenated santones	The mechanism of cowanin's anticancer activity on T47D cell line was determined as stimulation of G0-G1 phase of cell cycle arrest and reducing migration of T47D breast cancer.	(Hefni et al., 2020)

1. Calamintha incana (Sm.)

This study revealed that the extract of *Calamintha incana* (Sm.) inhibits cell growth with an IC_{50} of 106.78 ± 5.1 µg/mL in the T47D cell line. *Calamintha incana* (Sm.) contains thousands of phytochemical compounds, such as phenolic acids and flavonoid components. The bioactive compounds of *Calamintha incana* (Sm.) are beneficial as antioxidants and have anticarcinogenic activity. Additionally, phenols and flavonoids function as free radical scavengers, reducing agents, and singlet oxygen quenchers, as well as having the ability to bind metals. Phenolates or polyphenols are significant plant secondary metabolites due to their antioxidant activity by chelating redox-active metal ions, interrupting free radical lipid chains, and scavenging hydroperoxides into reactive oxiradicals.

2. Sterculia quadrifida Seeds

The research findings revealed that the compound tested, phenylpropanoid, (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one, isolated from the chloroform fraction of *Sterculia quadrifida* seeds, shows activity against breast cancer cell lines. Specifically, this compound demonstrated inhibitory activity against 4T1, MCF-7, T47D, and MDA-MB-435 cell lines with IC_{50} values of 2.29 µg/mL, 9.93 µg/mL, 12.12 µg/mL, and 18.09 µg/mL, respectively. The compound (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one belongs to the class of phenylpropanoid compounds with a six-carbon aromatic phenyl group and a three-carbon propene tail of coumaric acid. Phenylpropanoid compounds are produced from the shikimate pathway with L-phenylalanine/L-tyrosine as precursors (Parthasarathy et al., 2018). Some studies indicate that phenylpropanoid compounds have anticancer activity through apoptosis induction. One such study by

Rollando et al., (2023) found two phenylpropanoid compounds, asaricin and isoasarone, isolated from the extract of Piper sarmentosum roots, showing cytotoxic activity against the MDA-MB-231 cell line. Both compounds can induce apoptosis by inhibiting the expression of the anti-apoptotic protein Bcl-2 and inducing the pro-apoptotic protein Bax (Rollando et al., 2023).

3. Psidium guajava L. Leaves

According to MTT assays, it was found that the n-hexane fraction has high toxicity against breast cancer cell lines with IC_{50} values for T47D, MCF-7, and HeLa being 8.92 µg/mL, 4.28 µg/mL, and 85.98 µg/mL, respectively. This is due to the presence of ellagitannin compounds in high concentration, which are believed to play a role in inhibiting cancer cell growth. Ellagitannins are known as chemopreventive agents for colorectal, skin, cervical, prostate, breast, and liver cancers (Flores *et al.,* 2015). Ellagitannins specialize in inhibiting cancer cell growth by targeting the RE+ point, where T47D cells have this point (Ismail *et al.,* 2016). The importance of RE+ in T47D cell line is associated with the expression of estrogen receptors (ER), rendering it a model for studying the effects of estrogen on breast cancer cells. The presence of RE+ in T47D cells indicates their sensitivity to estrogen and renders them suitable for investigating the effects of hormonal therapy on breast cancer cells. Furthermore, T47D serves as an ideal experimental model for elucidating the specific effects of progesterone in luminal A subtype of breast cancer (Yu et al., 2017). Moreover, this study showed n-hexane extract from *Psidium guajava* leaves contains biactive compound like genistein, which identified as playing a role in preventing the growth of breast cancer (Prakoso & Nita, 2023).

4. *Uncaria* spp. Leaves

Out of 8 samples used, leaves *Uncaria nervosa* (LUN) showed the best IC_{50} value and had the highest cytotoxic activity at 64.42 µg/ml. Previous research has shown that alkaloid and terpenoid compounds are responsible for cytotoxic activity (Abdul et al., 2022). Alkaloid compounds are regarded to possess anticancer activity and the ability to induce apoptosis through their binding to DNA, topoisomerase I, and stabilization of the cleaved topoisomerase DNA complex. The stabilization of these cleavage complexes leads to permanent damage to the double helix DNA strands, resulting in apoptosis (Yanti et al., 2021). Terpenoid compounds have been shown to inhibit NF-κB signaling, a key regulator in the pathogenesis of inflammation and cancer. Various pathways have been found to be involved in the anticancer activity of terpenoids, including apoptosis activation. Some terpenoid variations, such as monoterpenoids, act as inhibitors of NF-κB signaling through IκB degradation, DNA binding, or p65 translocation. Research reports on *Uncaria nervosa* include cytotoxic tests of methanol extracts from bark and wood. Cytotoxic tests using shrimp larvae obtained LC50 values of 1.76 and 2.66 µg/ml (Maulina et al., 2019).

5. Syzygium aqueum Bark

Research findings reveal that alphitolic acid and arjunolic acid compounds have anti-cancer activity. Alphitolic acid is an anti-inflammatory triterpene identified in *Syzygium aqueum* Bark. It acts by inhibiting Akt-NF-κB signaling pathway to induce apoptosis. Moreover, it stimulates autophagy. Alphitolic acid exhibits anti-inflammatory properties and modulates the production of NO and TNF-α (Bai et al., 2015). Alphitolic acid is this study has cytotoxic against HeLa and T47D cell lines, with IC_{50} values of 16.12 µg/mL and 7.37 µg/mL, respectively. Arjunolic acid is a saponin exhibits various

biological activities including antioxidant, antimicrobial, antibacterial, and anti-inflammatory activities. Additionally, it serves as a potent antioxidant and plays a crucial role in protecting cells and tissues against the detrimental effects of reactive oxygen species (Ghosh & Sil, 2013). Arjunolic acid has an IC_{50} of 6.74 µg/mL against HeLa cell lines and is moderately active against T47D cell lines with an IC_{50} of 27.15 µg/mL.

6. Sterculia quadrifida Leaves

Isolation from the n-butanol fraction of *Sterculia quadrifida* leaves revealed a new aurone compound named (2E)-2-[(3,4-dihydroxyphenyl)(hydroxy)methylidene]-4,6-dihydroxy-2,3-dihydro-1-benzofuran-3-one, which was tested on breast cancer cell lines including 4T1, MCF-7, MDA-MB-435, T47D, showing IC_{50} values of 4.05 mg/mL, 12.53 µg/mL, 15.38 µg/mL, and 25.91 µg/mL, respectively. Aurones are compounds resulting from the combined biosynthesis of the shikimate and acetate pathways (Kumar et al., 2020). Aurone compounds have been extensively studied and proven to have anti-cancer activity. For instance, Hamilton compounds isolated from *Uvaria hamiltonii* inhibited breast cancer cell proliferation in MCF-7 and T47D by increasing p53 gene expression (Huang et al., 1998). In another study, synthesized furoaurones, (Z)-2-benzylidenefurano[3,2-f]benzofuran-3(2H)-one, showed cytotoxic activity against the T47D cell line by inhibiting ATP-dependent enzymes (Hassan et al., 2018).

7. Capsicum annum L. Fruit

This study revealed that *Capsicum annum* extract inhibits cell growth with an IC_{50} of 75.81 µg/mL and activates caspase-3 expression as a marker of apoptosis in T47D cells. This is due to the presence of anti-cancer compounds such as capsaicin in *Capsicum annum*. Capsaicin functions as an antitumorigenic agent in human stomach cancer through the expression of proapoptotic proteins such as Bax, caspase-3, and caspase-8 (Sarkar *et al.,* 2015). Other studies reported that capsaicin activates apoptosis and cell cycle arrest in the G1 phase (Ip et al., 2012; Zhang et al., 2013).

8. Bauhinia scandens Leaves

Cytotoxic MTT assay results over 24 hours showed that *Bauhinia scandens* leaf extract suppresses cell growth with IC_{50} values of 1.95 µg/mL for HeLa cells and 4.54 µg/mL for T47D cells. This is due to the presence of anti-cancer compounds such as flavonoids, phenols, tannins, saponins, alkaloids, and steroids in the leaf extract. Flavonoids are involved in anti-cancer activities, such as inhibiting cell growth, protein kinase activity, angiogenesis, and inducing apoptosis by activating p53 protein and its target genes (Plaumann et al., 1996). Saponins can induce intrinsic or extrinsic apoptosis pathways, cell cycle inhibitors, autophagic dynamics, and inhibitors of angiogenesis and metastasis (Plaumann et al., 1996; Sobolewska et al., 2020). The cytotoxic effect of saponins may be caused by both induction of apoptosis or stimulation of non-apoptotic cell death. Tannin compounds have been proven to have strong cytotoxicity (Podolak et al., 2010). Hong et al., (2011) reported that hydrolyzed tannins extracted from *Rhizophora apiculata* bark had cytotoxic effects on HepG2 cancer cells with an IC_{50} of 12.26 µg/mL. Tannic acid is involved in inducing apoptosis in human glioma cells Hs 683 by increasing reactive oxygen species (ROS), which are responsible for inducing apoptosis in cancer cells by causing mitochondrial transition pore opening (Zhang et al., 2018).

9. Lansium domesticum Fruit Peel

In this study, the cytotoxic activity of Lamesticumin A, derived from *L. domesticum* fruit peel isolates, was shown on the T47D cell line with an IC_{50} of 15.68 µg/ml. Lamesticumin A is an onoceranoid type triterpenoid, previously isolated from *L. domesticum* twigs, which has antibacterial activity against *Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus, Bacillus subtilis, Micrococcus pyogenes,* and *Bacillus cereus* with minimum inhibitory concentrations <15 µg/ml. Lansium I-IX, other onoceranoid type triterpenoids isolated from L. domesticum leaves, have been reported to have antimutagenic activity Matsumoto et al., 2018). Boubaker et al., (2011) showed that Acacia salicina extract exhibits potent antioxidant and antimutagenic activities. The chloroform extract displays antimutagenic effects against both directly and indirectly acting mutagens, consistent with its function as a blocking agent capable of influencing the activity of enzymes involved in mutagen and carcinogen metabolism. Additionally, the tested extract demonstrates its ability to directly react with electrophilic mutagen metabolites and protect against oxidative DNA damage.

10. Garcinia cowa Bark

In this study, the cytotoxic activity of cowanin, derived from *Garcinia cowa*, was demonstrated on the T47D cell line with an IC_{50} of 11.11 + 0.13 µg/ml after 48 hours of incubation. Cowanin, obtained from the bark of the Asam Kandis tree (*Garcinia cowa* Roxb.), features hydroxy, prenyl, and methoxy groups. Research indicates that the presence of these groups can affect the compound's activity in inhibiting cancer. (Ito et al., 1998). Cowanin inhibits cell proliferation and induces apoptosis in LoVo colorectal cells, through intrinsic or mitochondrial pathway activation. Moreover, cowanin downregulates ERK and Akt signaling pathways and enhances p38 MAPK signaling regulation (Chowchaikong et al., 2018).

CONCLUSION

There are 15 bioactive compounds from various parts of plants that have been tested in vitro against the T47D cell line. These plant bioactive compounds play an essential role in the proliferation phase, cell cycle, fatty acid synthesis, and apoptosis of cancer cells. Therefore, from several studies that have been reviewed, it can be concluded that plant bioactive compounds have the potential as a source of drugs and chemopreventive agents for breast cancer.

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