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Understanding of genes encoding bioactive compounds from potential medicinal plants in Indonesia as cancer cell inhibitors

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Abstract. *Muflikhati Z, Sianipar NF, Syamsunarno MRAA, Anas. 2023. Understanding of genes encoding bioactive compounds from potential medicinal plants in indonesia as cancer cell inhibitors. Biodiversitas 24: 4645-4660.* Indonesia has abundant plant diversity and enormous potential to be developed as a source of medicinal plants due to the content of bioactive chemicals in them. Potential medicinal plants from Indonesia, such as *Andrographis paniculata (Sambiloto), Curcuma longa (Kunyit), Moringa oleifera (Moringa), Phyllanthus niruri (Meniran), Orthosiphon stamineus (Kumis kucing), Typhonium flagelliforme (Keladi tikus), and Zingiber officinale (Jahe),* contain bioactive compounds with mechanisms that act as anticancer. Bioactive compounds with anticancer mechanisms in plants can be controlled by specific genes. Therefore, it is important to elaborate on bioactive compounds and the genes involved. This article aims to discuss the genes encoding bioactive compounds in Indonesian medicinal plants and the mechanisms that can inhibit cancer cell growth. Several genes encode anticancer compounds, such as lectin-coding genes, the stigmasterol-coding *CYP710A* gene, the tocopherol-coding *γ-TMT* gene, the fatty acid-coding *FAD* gene, the doxorubicin-coding *DXR* gene, and the chalcone synthase-coding *CHS* gene. These genes have mechanisms to increase the expression of several apoptosis-promoting proteins, including BCL-2 family members, in several cancer cell models. This article also describes the potential utilization and creation of molecular markers linked to genes encoding anticancer chemicals and can be used as a reference for research on medicinal plants that is still limited. Knowledge of genes encoding anticancer compounds in plants can support future research in the development of cancer drugs.

Keywords: Anticancer, bioactive chemicals, genes, Indonesian medicinal plants

INTRODUCTION

Indonesia is considered a megadiverse nation because it is home to 30,000 of the world's 40,000 plant species. There is a tremendous opportunity to develop medicinal plants. About 25,000 herbal plants are selected by pharmaceutical companies, and the majority of commercially available drugs are derived from plants (Newman and Cragg 2012). Based on several studies, it is known that nearly eighty percent of the globe's population is significantly reliant on medicinal herbs for various diseases' prevention and treatment (Elfahmi et al. 2014). Plants can synthesize complex organic compounds that can be useful in biological and pharmacological activities and are suitable for development as medicinal raw materials, especially anticancer agents (Greenwell and Rahman 2015). Plants have the potential to be used as medicinal plants because of the content of bioactive compounds in them. Various bioactive compounds and anticancer components, such as flavonoids and polyphenols, as well as several compounds of the group sulfur, tannins, alkaloids, and diterpene phenolics (Yashin et al. 2017), are relatively higher when compared to vegetables, fruits, and cereals (Li et al. 2013). Medicinal plants that are widespread and easily available in Indonesia, such as *Andrographis paniculata* (*Sambiloto*), *Curcuma longa* (*Kunyit*), *Moringa oleifera* (*Moringa*), *Phyllanthus niruri* (*Meniran*), *Orthosiphon stamineus* (*Kumis kucing*), *Typhonium flagelliforme* (*Keladi tikus*), and *Zingiber officinale* (*Jahe*), contain bioactive compounds with mechanisms that can act as anticancer.

The mechanisms through which bioactive compounds act vary in their role as anticancer agents. Mechanisms that can be passed include the initiation of cell apoptosis, cell inhibition, stimulation of TNF-alpha release, cell cycle halting, and inhibition of lipoprotein oxidation (Oon et al. 2015). Through interfering in the Akt-mTOR signaling mechanism, steroid-class bioactive substances (stigmasterol) have been shown to cause apoptosis and gastric cancer cells to undergo autophagy (Zhao et al. 2021). Stigmasterol in the medicinal plant *T. flagelliforme* is considered more effective against breast cancer cells (Sianipar et al. 2021). The presence of a class of chemicals that exhibit anticancer activity allows for an increase in the value of breast anticancer activity in these extracts. Other groups of compounds, such as flavonoids in *M. oleifera*

herbal plants, can inhibit the process of carcinogenesis (Khor et al. 2018). Inhibition occurs during the stages of initiation, promotion, and progression via molecular mechanisms such as carcinogen chemical inactivation, antiproliferative, angiogenesis and cell cycle inhibition, apoptosis induction, and antioxidant action (Oršoli and Jembrek 2022).

Herbal flavonoid compounds also act as potent inhibitors of proteins that regulate intracellular transmission of signals. They suppress the activity of protein kinase C, tyrosine kinase, and lipid kinase, as well as other metabolic enzymes and protein production. Variety of factors, including their structure and cells of interest, can also arrest the cell phase during the G0 or G1 and G1/M stages. Flavonoids have also been proven in several cell types and animal models to bind to estrogen receptor type II, control and alter cell proliferation, and trigger apoptosis (Alsawaf et al. 2022). Curcumin in *C. longa*, for example, has mechanisms for causing apoptosis as well as limiting tumor growth and migration by decreasing numerous cellular signaling pathways. Curcumin has been found in various studies to exhibit anticancer action in cancers of the breast, lungs, neck and head squamous cell tumors, cancer of the prostate, and tumors of the brain (Vo et al. 2021), suggesting that it has the potential to attack various types of cancer cells.

In Indonesia, the use of medicinal plants has greatly developed into medicine. Plants such as *M. oleifera* and *C. longa* can be used as medication to boost endurance and the body's defense system against disease-causing viruses or bacteria (Tomeh et al. 2019; Vo et al. 2021). *Zingiber officinale* and *P. niruri* are also therapeutic herbs that work as immune system regulators and prevent kidney stones and hepatitis. *Typhonium flagelliforme* has also been used to treat cancer, infection, cough, and allergy problems (Sianipar et al. 2023; Farida et al. 2014; Alfarabi et al. 2015). All these possibilities are possible due to the bioactive chemicals present.

Bioactive compounds with anticancer mechanisms found in plants can be controlled by anticancer-specific genes. Therefore, it is important to elaborate on bioactive compounds with the genes involved. This article aims to find out more about specific genes that produce bioactive compounds and mechanisms for inhibiting cancer cell growth in Indonesian medicinal plants. This article also provides knowledge related to opportunities for plant development and selection using molecular markers. The information in this article can support the limited research and development base related to anticancer genes in potential medicinal plants.

DIVERSITY OF INDONESIA'S MEDICINAL PLANTS POTENTIAL AS ANTICANCER

Widely used anticancer medicines with significant adverse effects, such as cardiovascular disease and liver toxicity, after long-term use, include tamoxifen, anastrozole, and exemestane. In contrast to plants, the diversity of potential medicinal plants in Indonesia with their bioactive compounds can overcome these severe side effects, such as *Caesalpinia sappan* Linn, *M. oleifera*, and *Solanum lycopersicum* (Syamsunarno et al. 2021a; Syamsunarno et al. 2021b; Anas et al. 2022). The diversity of medicinal plants can be a promising anticancer agent.

Herbal medicine has been going on for centuries and has even evolved into a culture in Indonesia (Son et al. 2019). Plant parts that can be utilized as herbal medicines include roots, stems, leaves, flowers, fruits, seeds, and extracts that can cure or reduce various kinds of pain (Tantengco et al. 2018). Some of the bioactive compounds with potential in Indonesian medicinal plants have been presented (Table 1). In this case, some medicinal plants contain bioactive compounds from a large group of flavonoids, triterpenoids, alkaloids, polyphenols, terpenoids, phenolics, and trihydroxy lactones. These bioactive components will contribute to the improvement of the immune system and antioxidant capacity (Bala et al. 2017). Rosa et al. (2012) conducted research that indicated that antioxidant could inhibit the formation of free radicals that cause various types of diseases. This is because antioxidants can block the action of proinflammatory cytokines that cause oxidative damage. In addition, bioactive compounds can act as anticancer agents (Rosa et al. 2012).

The potential of Indonesian medicinal plants such as *M. oleifera* has been studied because they contain flavonoid-type bioactive compounds that can inhibit cancer by suppressing the cell cycle and causing apoptosis (Laouini et al. 2012). According to Jahan et al. (2018), *M. oleifera* leaves extracted using ethanol and methanol solvents and fractionated with ethyl acetate and n-Hexane at different doses of up to 250 ug/mL can inhibit cancer cell proliferation and trigger apoptosis. Similarly, *P. amarus* extract at 210 g/mL can significantly induce apoptosis in U937 and K562 cells and cause the cell cycle to be halted at the S phase of U937 cells and G0/G1 in K652 cells (Yousefvand et al. 2022). In *T. flagelliforme*, the mutant's ethyl acetate fraction test could be a possible anticancer drug by influencing cancer chemotherapy, which is critical for human health (Sianipar et al. 2020a; Sianipar et al. 2020b). One of the Indonesian medicinal plants that has been used as a cancer drug is *C. longa* (Subositi and Wahyono 2019). *C. longa* has curcumin compounds that can activate DNA damage responses, impede cell cycle progression, and cause apoptosis (Tomeh et al. 2019). Several studies have been undertaken to assess the ability of curcumin and its compounds to suppress several different carcinomas through interaction with different molecular targets.

Molecular docking and other in silico technologies have also been used to anticipate atomic-level molecular bioactivity. Docking analysis has been conducted on *T. flagelliforme* plants related to the anticancer compound stigmasterol as a ligand that could be an effective anticancer agent. The compound has been tested using MCF-7 cells and has a higher cytotoxic effect compared to the parent plant. The compound's binding to toxicity, BRCA-1, and drug-like qualities, as validated using analysis of docking, suggest that the *M. oleifera* ligand is a

potentially effective anticancer agent, similar to the findings of Balogun et al. (2021).

Indonesia has developed its use of herbal plants for a variety of medicines up to this point, which can provide value to the market for herbal medicines that is much bigger than that of other nations. In addition to other plants, ginger, galangal, turmeric, and pace are among the plant species that are frequently utilized as remedies (Yashin et al. 2017; Kumar 2021). There are three types of traditional medicine, and herbal medicine is one of them. It has been a staple of the community for many years. With support from non-clinical data and clinical data (for phytopharmaceuticals), herbal medicine can be transformed into standardized herbal medicines or phytopharmaceuticals. Ginger, galangal, and turmeric are the substances that are frequently used to make herbal medicine (50.36%, 48.77%, and 39.65%, respectively). and traditional medicine substances that are liquid or that have been packed into final products include up to 48% of these ingredients (Kusuma et al. 2020).

Indonesians frequently use herbal medicines, which are made from a collection of rhizomatous medicinal and fragrant plants that are dispersed all across the country. *Curcuma domestica* or *Curcuma longa*, also known as turmeric, which belongs to the same plant family as ginger (Zingiberaceae), has its own unique qualities. Common uses for turmeric include culinary preparation, food coloring, cosmetics, and herbal medicine preparations (Subositi and Wahyono 2019; Tomeh et al. 2019; Vo et al. 2021). The primary bioactive components of this plant work as anticarcinogens by causing cell apoptosis, which stops the spread of cancer cells. Additionally, the compounds, both in vitro and in vivo, prevent the growth of cancer in the kidneys, liver, prostate, colon, and breast. The use of this plant kind in cancer prevention and therapy appears promising (Al-asmari et al. 2015; Alsawaf et al. 2022; Greenwell and Rahman 2015).

Table 1. Content of bioactive compounds in potential of Indonesian medicinal plants

Species	Major compound(s) or group of compounds	Plant part	Biological activity	References
Typhonium flagelliforme (*keladi tikus*)	Flavonoids, alkaloids, saponin, steroids, palmitic acid, tocopherol, linoleic acid, oleic acid, stigmasterol, hexadecanoic acid, farnesol isomer a, ergost-5-en-3-ol, geranylgeraniol, β-elemene, gamma-sitosterol, eicosane, squalene	Leaves, roots, stems, and tubers	Anticancer, antibacterial, anti-inflammatory, antioxidant	Farida et al. (2014); Sianipar et al. (2016); Sianipar and Purnamaningsih (2018); Sianipar, Hadisaputri, et al. (2020a)
Moringa oleifera (*kelor*)	Flavonoid (myricetin, quercetin, and kaempferol), phenolic acid (hydroxy-benzoic acid and hydroxycinnamic acid), alkaloid, saponin, steroid, anthocyanin, tannin, and carotenoid	Leaves, seeds, bark, pods, and roots	Anticancer, antioxidant, antimutagenic, anti-inflammatory	Omodanisi et al. (2017); Abdel-Latif et al. (2018); Vergara-Jimenez et al. (2017); Syamsunarno et al. (2021)
Phyllanthus niruri (*meniran*)	Sterols, lignans, flavonoids, polyphenolic compounds, tannins, alkaloids, gallic acid, quercetin, phyllanthine, hypophyllanthin, niranthine	Leaves, roots, and stems	Anti-inflammatory, anticancer, antihepatotoxic, diuretic, antioxidant, antidiabetic	Abdel-Sattar et al. (2023); Najari Beidokhti et al. (2017); Al Zarzour et al. (2017); Ramadhani et al. (2021)
Andrographis paniculata (*sambiloto*)	Diterpenoid, flavonoid (5-hydroxy-7,8-dimethoxyflavone and 5-hydroxy-7,8-dimethoxyflavanone), steroid (ergosterol peroxide, β-sitosterol, and stigmasterol)	Whole plant	Anticancer, antibacterial, antidiabetic, antimicrobial, antioxidant, anti-inflammatory	Vetvicka and Vannucci (2021); Anoor et al. (2022); Yue et al. (2019)
Orthosiphon stamineus (*kumis kucing*)	Terpenoids, phenols (isopimaran, flavonoids, benzochromene), sinensetin, eupatorin, rosmarinic acid, and organic acid derivatives	Leaves	Anti-inflammatory, antioxidant, anticancer, antihepatotoxic, diuretic, antidiabetic, antimicrobial	Bokhari et al. (2018); Abd Razak et al. (2020); Silalahi (2019)
Zingiber officinale (*jahe*)	Phenolic, terpene, shogaol, 3-dihydro-shogaol, 1-dehydrogingerdione, gingerdiol, diarylheptanoide, mono-and diacetyl gingerdiol derivatives, and metal ether compounds	Roots and rhizomes	Anticancer, anti-inflammatory, antimicrobial, antidiabetic, antioxidant	Mao et al. (2019); Park et al. (2014); Bobde et al. (2020)
Curcuma longa (*kunyit*)	Curcuminoids, flavonoid, ar-turmerone, crude etheric, ethanolic, methyl curcumin, sodium curcuminate, volatile oil, phenolic	Leaves, rhizomes, and flowers	Antioxidant, antiviral, antineoplastic, anti-inflammatory, antibacterial, anticancer, antidiabetic, anticoagulant	Hadisaputri et al. (2015); Vo et al. (2021); Subositi and Wahyono (2019); Tomeh et al. (2019)

The Zingiberaceae family also includes *Curcuma xanthorrhiza*, often known as Java ginger, which is utilized by the local population to heal skin wounds, fever, diarrhea, stomach ailments, and constipation (Oon et al. 2015; Subositi and Wahyono 2019). The Java ginger plant's active ingredients dramatically reduce the generation of inflammatory cytokines. Additionally, it can be utilized to treat type II diabetes (Vo et al. 2021). Strong antibacterial activities and effectiveness as an enterichelmintic and skin wound healer characterize *Curcuma heyneana* (Subositi and Wahyono 2019). The Zingiberaceae family still includes *C. zedoaria*, which is closely related to *C. longa*. Traditional uses for this plant's medicinal components include treating colds, infections, vomiting, diarrhea, and vaginal discharge, in addition to relieving stomach discomfort, toothaches, blood stagnation, leucoderma, tuberculosis, enlarged spleens, and other ailments (Hadisaputri et al. 2015; Jain and Parihar 2019; Subositi and Wahyono 2019).

Due to the presence of active components in the form of sterols, terpenoids, fatty acids, sugars, and organic acids, *C. aeruginosa* has the potential to be used as a treatment for dysmenorrhea, pain, antipyretic, anti-inflammatory, flu, cough, and asthma (Hadisaputri et al. 2015; Subositi and Wahyono 2019). For cholecystopathy, flatulence, cholera, anemia, malaria, rheumatism, cholera, anorexia, arthritis, jaundice, colds, and whooping cough, *Zingiber aromativum*, also known as fragrant ginger, is frequently utilized. In the Zingiberaceae family, *Z. aromaticum* exhibits the most potent anti-carcinogenic action (Koo et al. 2013; Jain and Parihar 2019).

GENES ENCODING BIOACTIVE COMPOUNDS WITH ANTICANCER POTENTIAL

Lectin-coding genes

Lectins are non-enzyme proteins that include a minimum of one non-catalyzing site and can bind to particular targets reversibly. Several potential medicinal plants in Indonesia contain lectins, such as *Pisum fulvum* and *P. sativum* (Family: Fabaceae), *T. flagelliforme* (Family: Araceae), and *Viscum album* (Family: Santalaceae) (Yousefvand et al. 2022; Yassin et al. 2019; Sianipar et al. 2022a). Lectins can act as anticancer agents with a general mechanism through the apoptosis process in cancer cells, so that cancer cell growth is inhibited. Alfarabi et al. (2015) used the Brine Shrimp Lethality Test (BSLT) to determine the toxic effect of lectins in the *Typhonium* genus on *Artemia* sp. larvae and cancer cells to see how well they stopped cancer cells from growing. Studies on plant lectins show that these proteins are divided into seven families based on the source of lectin-producing plants. Legume lectins found in the seeds of legume plants are the first type of lectin and have been widely studied in terms of the type of lectin and the gene encoding the lectin. *Phyto-erythro agglutinating* (PHA-E) and *phyto-leuco agglutinating* (PHA-L) lectins are found in *Phaseolus vulgaris*. Both proteins are encoded by the *dlec1* and *dlec2* genes. Some potential medicinal plants in Indonesia that have lectins as anticancer compounds have been presented (Table 2).

In addition, legume plants are known to have more than one type of lectin. *Dolichos biflorus* has lectins in seeds and DB58 (found in stems and leaves). Lectins in seeds are detected at the embryonic maturation stage and are not detected at the germination stage. This lectin is not present in mature plant organs, while DB58 lectin is detected in stems and leaves during the germination stage. Both types of lectins are encoded by two genes that do not contain introns but are in the same transcriptional orientation (Katoch and Tripathi 2021). The herb *Viscum album* L. contains three types of toxic lectins in its leaves, namely MLI, MLII, and MLIII (Patel and Gupta 2017). These lectins are classified as *type 2 RIP-related lectins* and are widely used in cancer treatment. The difference between the three lectins is the molecular weight and specificity of the reaction with carbohydrate molecules. MLI is an active compound in mistletoe extract used for tumor therapy. These three proteins are encoded by the *mlIp, mlIIp,* and *mlIIIp* genes. Quantitatively, *mlIp* gene transcription is more dominant than the other two genes. *Lectin* genes were successfully detected in the potential of Indonesian medicinal plants such as *Morus* spp. (Family: Moraceae) (Wulandari et al. 2018), *T. flagelliforme* (Family: Araceae) (Sianipar et al. 2022a), and *G. max* (Family: Fabaceae) (Wang et al. 2021).

Lectin studies have evolved recently and expanded beyond their original focus on anticancer; so far, lectin genes have been studied in relation to their physiological roles, including fending off pests and getting rid of invasive pathogenic microbes. People are becoming increasingly aware of the significance of lectin research in other study domains as it continues to grow. Physiological biology and cancer research are only two examples of the many uses for plant lectins. Included among them are certain plant lectin genes that were additionally transcribed and used in the genetic engineering of plant diseases and resistance to insects, demonstrating tremendous promise for use in farming (Wang et al. 2021).

Stigmasterol-coding *CYP710A* gene

CYP710A is an enzyme involved in the formation of stigmasterol compounds. Several potential medicinal plants in Indonesia contain stigmasterol, such as *Cucumis sativus* (Family: Cucurbitaceae), *G. max* (Family: Fabaceae), *Physcomitrella patens* (Family: Funariaceae), *T. flagelliforme* (Family: Araceae), and *Zea mays* (Family: Poaceae) (Griebel and Section 2009; Cabianca et al. 2021; Aboobucker et al. 2021; Sianipar and Purnamaningsih 2018). In a study by Morikawa et al. (2006), it has been shown that Arabidopsis CYP710A1 and tomato CYP710A11 have responsibility for the C22-desaturase response with the substrate beta-sitosterol and the product stigmasterol. In *Arabidopsis*, CYP710A2 is responsible for brassicasterol production from 24-epi-campesterol and stigmasterol production from beta-sitosterol. Research by Morikawa et al. (2006) provides evidence that there is a possibility that desaturase reactions can be catalyzed by members of the CYP710A family in other plant species

besides *Arabidopsis* and tomatoes that have been studied. Sterol C22-desaturase refers to an enzyme that has the activity of catalyzing the double chain recognition reaction of sterol at location C22. A gene encoding sterol C22-desaturase is also known as the *sterol C22-desaturase* gene. The word 'C22 position' refers to the carbon corresponding to the C22 position of zymosterol. Sterol C22-desaturase activity can be measured by incubating the enzyme with a substrate in the absence of electron donors and oxygen and measuring the enzyme. Examples of electron donors are NADPH, and examples of substrates and products are ergosta-5,7,24(28)-trien-3-beta-ol and ergosta-5,22,24(28)-trien-3-beta-ol. Sterol C22-desaturase activity can be measured based on the procedure of a preceding report (Morikawa et al. 2006). The enzyme CYP710A was successfully studied in several potential Indonesian medicinal plants, such as *Solanum lycopersicum* (Family: Solanaceae) (Morikawa et al. 2006) and *Calotropis procera* (Family: Apocynaceae) (Ramadan et al. 2019a).

CYP710A11 in *S. lycopersicum* plants takes part in the steroid production process, with stigmasterol as the product (Morikawa et al. 2006). In *T. flagelliforme* plants, stigmasterol isolates have been studied, characterized, and tested on breast cancer cells by Sianipar et al. (2021). The test results show that stigmasterol is more effective against cancer cells, especially breast cancer (MCF-7). Expression analysis of stigmasterol showed that tumor necrosis factor-α (TNF-α) transcript phase could be significantly decreased (Kangsamaksin et al. 2017). The anti-inflammatory properties of stigmasterol and lupeol can inhibit the tumor growth of CCA and effectively target tumor endothelial cells (Kangsamaksin et al. 2017).

Stigmasterol, β-sitosterol, campesterol, lupeol, cyloartenol, and stigmastanol are forms of phytosterols (plant sterols*).* Some plants that have a lot of phytosterol content have been shown to have different therapeutic effects. Ethanol extract from fresh leaves of *Clinacanthus nutans* significantly inhibited superoxide formation and a substance called inhibition by active neutrophils, in addition to having anti-inflammatory and antioxidant characteristics (Alam et al. 2016). Plant sterols have been shown to prevent cancer of numerous sorts. This was proven by Sánchez et al. (2020) in a study isolating aloe vera that has angiogenic activity in vitro and recommending it for the treatment of chronic wounds. Some evidence suggests that plant sterols in such herbal extracts are agents with beneficial effects in cancer treatment. Furthermore, in addition to the *CYP710A* gene, which is involved in the plant sterol compounds sitosterol and stigmasterol, the *SMT2* gene is also involved in these compounds. However, research related to the *SMT2* gene encoding the anticancer compound stigmasterol is still limited. Stigmasterol is formed from beta-sitosterol using the sterol C22-desaturase enzyme encoded by the *CYP710A* gene. The expression of the *CYP710A* gene encoding stigmasterol in several potential Indonesian medicinal plants has been shown (Table 2).

The *CYP710A* gene is helpful for anticancer purposes as well as managing plant stress. According to Renkova et al. (2019), the presence of this gene in polyploid plants can promote the diversity of genetic pathways underlying *Triticum aestivum* plants' sterol-mediated responses to stress. The use of genes associated with stigmasterol has focused on how cold stress affects the expression of the *SMT1* and *CYP710A* genes in the roots and leaves of wheat seedlings (Renkova et al. 2019).

Tocopherol-coding *γ-TMT* gene

Tocopherol, commonly referred to as vitamin E for short, is a soluble antioxidant that is necessary in human nutrition (Willems et al. 2021). Several potential medicinal plants in Indonesia contain tocopherols, such as *Carthamus tinctorius, Cleome viscosa* (Family: Capparaceae), *Codonopsis lanceolata* (Family: Campanulaceae), *Lactuca sativa* (Family: Asteraceae), and *T. flagelliforme* (Family: Araceae) (Sianipar and Purnamaningsih 2018; Ghimire et al. 2011; Jai-uean and Sangin 2021; Matthaus et al. 2015; Tang et al. 2011). Epidemiological evidence shows that vitamin E can help prevent cancer and cardiovascular problems, improve immune system function, and prevent some age-related degenerative diseases (arthritis, spinal disorders, and cataracts). The main source of vitamin E in our diet can come from plants because tocopherols are only synthesized by photosynthetic organisms such as plants. Some potential medicinal plants that have detected the presence of the *TMT* gene are *Perilla frutescens* (Family: Lamiaceae) (Ghimire et al. 2015), *G. max,* and *Medicago sativa* (Family: Fabaceae) (Park et al. 2019; Ma et al. 2020).

Vitamin E supplements, a fat-soluble vitamin, have been utilized because of their antioxidant properties to lower the chance of cancer (Rizvi et al. 2014). Vitamin E has different variants, which are four groups of tocopherols and four groups of tocotrienols with codes α, β, γ, and δ. Alpha-tocopherol, as vitamin E 'excels' as it is more potent than other tocopherols regarding classic fertility restoration (Azzi 2019). Increased α-tocopherol concentrations can reduce the percentage of γ-tocopherol in the plasma (Huang et al. 2019). This is unfortunate because, in a variety of animal models of colon, prostate, and breast cancer, γ-tocopherol has been demonstrated to have considerably better anticancer properties than α-tocopherol (Poaty et al. 2021). γ- tocopherol can decrease cyclooxygenase-2 (COX-2) activity more effectively than α- tocopherol (Poaty et al. 2021).

Each subtype of breast cancer has a different response to recent treatments and therapies. Until now, there has been in vivo and in vitro data on prevention for each of the various cancer subtypes, especially breast cancer. The anticancer effect of tocopherol has been studied for several decades, and the results may be summarized as follows: (1) reduction of estrogen receptor; (2) expression of the PPARγ (peroxisome proliferator receptor γ); (3) activation of apoptosis; (4) anti-inflammatory and antioxidant properties, and (5) enhancement of Nrf2 activity (Das Gupta et al. 2015; Gupta and Suh 2016; Bak et al. 2018; Coelho et al. 2023). In summary, the expression of γ-tocopherol in several potential medicinal plants has been presented (Table 2).

The utilization of the *γ-TMT* gene that is being researched up to now is that it has a favorable effect on controlling the response of *Medicago sativa* to drought stress mimicked with polyethylene glycol. According to Ma et al. (2020), this reaction may be mediated by intricate processes such as scavenging systems for reactive oxygen species (ROS), stomatal growth, and other phytohormone pathways of signaling. A *γ-TMT* gene that is overexpressed can cause ROS signaling-related genes in *Codonopsis lanceolata*, which is comparable to the finding made by Tissue et al. in 2021.

According to the progress of research into *γ-TMTs* so far, *γ-TMTs* have been cloned from a variety of species and are overexpressed in several important crops (Jiang et al. 2016; Upadhyaya et al. 2021). The model plant *A. thaliana*'s γ-TMT gene (Koch et al. 2003) was used to demonstrate a significant rise in tocopherol content in soybean and lettuce seeds (Park et al. 2019). Arabidopsis seeds with overexpressed γ-TMTs have been found to have more tocopherol-supporting lipids. In growing soybean seeds, higher expression of γ-TMTs and a tight connection with high tocopherol content were noted (Park et al. 2019).

Fatty acid-coding *FAD* gene

Fatty acid desaturase (FAD) is an enzyme widely found in plants that desaturates most glycerolipids in tissues. Several potential medicinal plants in Indonesia contain fatty acids, such as *Helianthus annuus* (Family: Asteraceae), *Paeonia lactiflora* (Family: Paeoniaceae), *Ricinus communis* (Family: Euphorbiaceae), *Salvia hispanica* (Family: Lamiaceae), *Sesamum indicum* (Family: Pedaliaceae), *Spinacia oleracea* (Family: Amaranthaceae), and *T. flagelliforme* (Family: Araceae) (Yuan et al. 2019; Sianipar and Purnamaningsih 2018; Held et al. 2019; Matuszczak et al. 2020; Meng et al. 2021). Plant desaturases involved in lipid biosynthesis have been studied through isolation and characterization methods using mutant *A. thaliana*. The findings revealed the existence of four plastid desaturase locus, namely FADA (FAD4), FADB (FAD5), FADC (FAD6), and also FADD (FAD7) (Dar et al. 2017). FAD's primary job in biosynthesis is to remove hydrogen from unsaturated fatty acids in the carbon chain to produce C=C bonds. In higher plants, the only FAD known to exist in the plastid matrix is stearoyl-ACP-desaturase (SAD). All other types of desaturases belong to the integrin class and are located on the endoplasmic reticulum membrane, such as FAD2 and FAD3, and on the plastid membrane, such as FAD6, FAD7, and FAD8.

The major enzyme responsible for polyunsaturated fat synthesis in non-photosynthetic cells (plant roots and seeds developing) is FAD2 (Dar et al. 2017). As a single variant gene, the *FAD2* gene was discovered in Arabidopsis and was shown to be constitutively expressed (Peng et al. 2020). Other researchers have studied various types of FAD2 in different potential medicinal species of plants, including *Camelina sativa* (Neumann et al. 2021); *Daucus carota* L. (Dunemann et al. 2022); *Arachis hypogaea* L. (Gangadhara and Nadaf 2016); *Idesia polycarpa* (Fan et al. 2019); and *G. max* (Lakhssassi et al. 2017). *FAD2* genes have been successfully characterized in tomato (*Solanum lycopersicum)* medicine plants in terms of primary metabolism and stress response (Lee et al. 2020). Meanwhile, the gene involved in the biosynthesis of alpha-linolenic acid (ALA) has been successfully studied and researched in the potential medicinal plant *Perilla frutescens*; the gene is *FAD3* (Duan et al. 2021).

FAD3 encodes ALA in many plants and has recently been the topic of a study by Baker et al. (2016). The omega-3 fatty acid (FA) class has a primary function as a source of nutrients for plants and animals, as well as a component of lipids in the membrane, such as phospholipids, and seed lipid storage in plants, such as triacylglycerols (Manan et al. 2017). Therefore, the focus of recent research aims to replace the function of ALA in animals that cannot produce it, so ALA from plants could be a solution. ALA is essential as a precursor to signaling molecules produced from FA and for the establishment of membrane lipid fluidity in plants. ALA is also an initial step for the formation of docosahexaenoic and eicosapentaenoic acids, both of which are essential for human health, such as promoting the development of the brain, regulating body development, inhibiting aging with therapeutic effects on neurological, cardiovascular, and cerebrovascular diseases, and reducing blood pressure (Baker et al. 2016). *FAD* genes have also been widely studied regarding their potential as an anticancer agent (Table 2).

Oleic acid constitutes a few of the many remaining essential fatty acids in seed oils, and certain family members' oils are considered to include trace levels of linolenic, linoleic, and stearic acids (9-octadecenoic acid) (Duan et al. 2021). Whereas many enzymes in the FAD group change the twelve-position of 18-carbon lipids, the *Arabidopsis thaliana* FAD2 kind 12 lipid desaturases have a specific orthologous activity resulting in the synthesis of lipids unique to higher plants. Two kinds of FADs have been identified to create acetylenic linkages in plant fatty acids: a bifunctional acetyl-lipid six acetylenase/desaturase reported in moss (Duan et al. 2021) and several forms of FAD2-type 12 acetylenases found in numerous different plant groups (Dar et al. 2017). Four *FAD2* genes of soybean were recently cloned, including FAD2-1A and FAD2-1B, that participate in the breakdown of oleic acid into linoleic acid, which is found within seeds. FAD2-2 and FAD2-3, on the other hand, have been demonstrated to be constantly produced in a variety of organs (Dar et al. 2017). Simultaneous FAD2-1A or FAD2-1B mutations using promotor enzymes such as transcriptional activators (TALENs) can significantly boost soybean oleic acid content (Yuan et al. 2019). Dar et al. (2017) discovered three *FAD2* genes in Helianthus, FAD2-1 is involved in seed-specific fatty acid synthesis, while FAD2-2 and FAD2-3 are continuously produced. Additional research indicated that cherry *FAD2* genes could recover oleic acid concentrations in Arabidopsis FAD2 mutants to normal levels.

The use of high-oleic acid-content soybean oil, which produces polyunsaturated fatty acids, can help reduce health concerns (Dar et al. 2017). Researchers found that

the soybean genome has two identical copies of microsomal desaturase-6 (FAD2-1 and FAD2-2) (Lakhssassi et al. 2017). The dominant gene expression for FAD2-1 was validated throughout the seed development process, in contrast to FAD2-2, which is expressed in vegetative parts as well (Hajiahmadi et al. 2020). The FAD2-2 family's conserved sequence homology reveals numerous isoforms, including FAD2-1A, FAD2-1B, FAD2-2B, and FAD2-2C, that are almost connected with their precursor families due to ninety percent amino acid sequence identity (Dunemann et al. 2022). This validates the practical relevance and function of the FAD2-2 family and its use in peacoil generation in soybean. The *FAD2-2* gene has previously been linked to the transformation of oleic acid into linoleic acid (Lakhssassi et al. 2017). Consequently, creating FAD2-2 mutants can reduce oleic acid into linoleic acid transfer. Furthermore, a *FAD2-2* gene is expressed in practically every tissue in plants throughout the extraction of oil, with seeds having the highest level of expression (Spasibionek et al. 2020).

Twenty-four FAD members have been found and divided into four subfamilies because of the use of *FAD* genes to date in the discovery and subclassification of the *FAD* gene group of *Juglans regia* L. (walnut). According to Liu et al. 2020, of the four families, FAD3-1 is most crucial for the formation of polyunsaturated fatty acids in walnuts. FADs may play a role in cucumber's resilience to temperature stress, as evidenced by the expression patterns of *FAD* genes that are stimulated by cold and heat, but at different times for distinct FAD members (Dong et al. 2016; Dar et al. 2017).

Research on the *FAD* gene has so far shown that some plants, including carrot roots, can accumulate more polyacetylenes (PA) as a result. According to Dunemann et al. (2022), the carrot *FAD* gene of fatty acid metabolism is substantially related to the primary QTL for both of the major PAs. This discovery will support ongoing functional gene studies and a deeper examination of the genetic factors influencing PA development. Programs for breeding carrots with the goal of altering the PA concentrations in the roots will benefit from the characterization of such genes (Dunemann et al. 2022).

Doxorubicin-coding *DXR* gene

Doxorubicin (DXR) is an anthracycline anticancer drug that is an important part of several chemotherapy regimens for small-cell lung and breast cancer. Several potential medicinal plants in Indonesia contain doxorubicin, such as *Curcuma xanthorrhiza, C. longa, Z. officinale* (Family: Zingiberaceae) (Ajith et al. 2016); *Chrysanthemum indicum* (Family: Asteraceae) (Gao et al. 2018); *Cymbopogon winterianus* (Family: Poaceae) (Devi et al. 2015); *Digitalis purpurea* L. (Family: Plantaginaceae) (Rad et al. 2020); and *Santalum album* (Family: Santalaceae) (Zhang et al. 2021). DXR is the best channelizer for metastatic thyroid cancer (Venkatesh et al. 2007), although DXR can increase chromatid, micronuclei, and chromosome abnormalities, as well as single-strand and double-strand DNA breaks (Dhawan et al. 2003). The genotoxicity of anticancer medications is of particular concern due to the risk of promoting secondary malignancies. There have been many traditional medicine applications of plants. Some molecules in plants can neutralize toxicity so that they can be useful for therapeutic purposes. The Swiss rat blood micronucleus test was used to assess the toxic effects of an extract from *Copaifera langsdorffii* leaf and the effect of DXR on DNA damage. The amount of micronuclei in mice treated with *C. langsdorffii* and DXR did not decrease significantly (Alves et al. 2013).

Two isoprenoid biosynthetic routes in plants have been identified: MEP (2-C-methyl-D-erythritol 4-phosphate) in the plastid and mevalonic acid in the cytoplasm (Shen et al. 2016). Deciphering the regulation of the MEP routes has so far focused on the first two enzymes found, DXS and DXR. Several findings support the notion that DXS regulates plant isoprenoid production. The fraction of DXP employed for terpenoid synthesis is determined by the degree of DXR activeness (Koo et al. 2013). Recent research has shown that DXR regulates isoprenoid formation in crops and plays a key role in management thoughout the process (Devi et al. 2015; Gao et al. 2018; Rad et al. 2020). The *DXR* gene was extracted from *H. annuus* L. plants and evaluated for genotoxicity using micronuclei in mouse bone marrow. The results showed that there was no genotoxicity, regardless of dose, time, or gender, and that its conjunction with DXR can reduce DXR's genotoxicity (Boriollo et al. 2014). Mechanisms and cancer cell models of doxorubicin compounds in plants have been shown (Table 2).

The expression of DXR in *Mentha piperita* leaves can enhance volatile oil content by 50% and induce the production of aromatic compounds, including peppermint oil (Devi et al. 2015). DXR overexpression increased terpenoid concentration in *Tripterygium wilfordii* Hook. hairy roots, suggesting the DXR has a critical function in terpene production during the transgene stage (Alves et al. 2013). DXR upregulation can increase terpenoid synthesis in *Physcomitrella patens* Bruch & Schimper, indicating that DXR is a promising candidate for terpenoid synthesis management (Devi et al. 2015). As a result, DXR is currently establishing itself as a key research focus as a terpenoid synthesis node.

DXR genes have been used to date for anticancer, light receptivity, and signaling of hormones (alicylic acid, abscisic acid, and gibberellin), among other functions (Zhang et al. 2021). When *Santalum album* L. (sandalwood) seedlings were etiolated and exposed to light, DXR expression increased, and transgenic *A. thaliana* strains had higher chlorophyll and carotenoid levels. Methyl jasmonate (MeJA) and hydrogen peroxide were also shown to induce DXR in seedling roots. Because it directs flow to sesquiterpenoids unique to sandalwood, DXR is crucial for the manufacture of photosynthetic pigments (Zhang et al. 2021). The percentage of secretory products was strongly impacted by the MeJA administration, and the beginning effect peaked at twenty-four hours, which is compatible with DXR expression. This is similar to the study by Gao et al. (2018). DXR therefore plays a crucial role in controlling the terpenoid production

in *C. indicum* var. aromaticum. Additionally, a study of DXR expression in *Digitalis purpurea* L., a significant therapeutic crop, was conducted in vitro (Rad et al. 2020) in response to polyamines and MJ (a biotic inducer) administration. Because DXR plays a crucial upstream function in the MEP pathway, which plants use to produce secondary compounds, this study was carried out.

Chalcone synthase-coding *CHS* gene

Chalcone synthase (*CHS*) is a crucial enzyme in plants that is involved in the start of flavonoid synthetis is pathways. Flavonoids are key metabolites that occur in higher plants and have an extensive range of biological and pharmacological effects (Alsawaf et al. 2022). Several potential medicinal plants in Indonesia contain chalcone synthase, such as *Ginkgo biloba* L. (Family: Ginkgoaceae), *Grewia asiatica* L. (Family: Malvaceae), *Medicago sativa* (Family: Fabaceae), *Rheum emodi* (Family: Polygonaceae), *Scutellaria viscidula* (Family: Lamiaceae), and *Zea mays* (Family: Poaceae) (Park et al. 2021; Wani et al. 2017; Pandith et al. 2016; Lei et al. 2010; Roslan et al. 2020). The CHS enzyme is encoded by the *CHS* gene, which is a polyketide synthase type III (PKSIII) in plants. PKSIII, by combining one molecule of *p-coumaroyl* CoA and three separate molecules of malonyl-CoA can form chalcone (Koo et al. 2013).

The *CHS* genes are a multigene family with different copy numbers in several plant species. In *A. thaliana*, there is only one CHS, while *Sorghum bicolor* and *G. max* have eight CHS copies, and there are three and seventeen copies of *Vitis vinifera* and *P. patens*, respectively (Koduri et al. 2010). The *CHS* gene from *Boesenbergia rotunda* was successfully isolated, and *BrCHS* variation 2 was discovered from several regions of the *B. rotunda* plant and was effectively produced mostly in the rhizome (Roslan et al. 2020). Other potential medicinal plants, such as *Vaccinium floribundum* Kunth have been studied for the presence of the *CHS* gene with the highest expression level (143.71 ng/µl) among additional genes implicated in the production of anthocyanin biosynthesis (Chiluisa-Utreras et al. 2021).

The kinetics and modalities of drug binding, docking, and homology modeling of chalcone synthase from Indonesian medicinal plants such as *Coleus forskohlii* have been studied using computational simulations (Shen et al. 2016; Awasthi et al. 2016). Sanmugavelan et al. (2018) conducted in vitro and in silico tests of CHS on *B. rotunda* and substrate specificity to support drug development through docking methods. The medicinal potential and utility of bioactive chemicals identified in numerous CHS-related herbal plants have made CHS the most studied enzyme exclusively because it produces the backbones in the flavonoid biosynthetic pathway of different plant secondary metabolites, such as in *B. rotunda*, *Gerbera hybrida* (Deng et al. 2018), *Morus atropurpurea* (Wang et al. 2017), and *Spatholobus suberectus* (Park et al. 2017). CHS acts as an initial enzyme in catalyzing the decarboxylation and condensation interaction of malonyl-CoA substrate and p-Coumaroyl-CoA substrate, resulting in the formation of fifteen backbone structures that are the origin of various types of flavonoids (Deng et al. 2018).

CHS, as a regulator of flavonoid production, is additionally implicated in pathway control and hence plant defense (Zhu et al. 2022). CHS can be utilized as a marker of biochemistry to assess dynamic flavonoid production variations (Yin et al. 2019). Similarly, CHS overexpression increased the synthesis of silymarin, which, along with other flavonolignans, is found in capillary root systems, according to prior research on *Silybum marianum.* As a result, this provides a novel approach to enhancing silymarin production (Wang et al. 2017). *CHS* genes in numerous plant species were found and characterized (Yin et al. 2019; Roslan et al. 2020; Sukma et al. 2020; Zhu et al. 2022). In addition to genetic alterations, the generation of the corresponding secondary metabolites requires molecules that activate production. Secondary metabolite biosynthesis pathways are an important aspect of a plant's defense mechanism against diseases and herbivores. Consequently, inducing chemicals are required for their expression. Elicitors are substances that have the capacity to boost the production of genes associated with the defense pathway system. Several chemical substances, including jasmonic acid, salicylic acid, and gibberellic acid, have been investigated as well as other organisms elicitors to stimulate the synthesis of these compounds (Yin et al. 2019; Zhu et al. 2022).

The study of CHS has grown rapidly since the first isolation of the *CHS* gene by Kreuzaler et al. (1983) in *Petroselium hortense*. According to the NCBI RefSeq database, around 2000 CHS proteins from diverse species of plants have been cloned and sequenced successfully (O'Leary et al. 2016). Other CHS studies related to the number of gene families have also been developed in various plant species, like *Ipomea purpurea* and *G. hybrida* (Deng et al. 2013), which have 3 and 6 *CHS* gene families, respectively. In *Zea mays* L., 14 *CHS* gene families have been discovered (Han et al. 2016). There are 14 *CHS* genes in all that have been discovered in *G. max* (Vadivel et al. 2018) and successfully isolated in the Indonesian medicinal plant *Glycyrrhiza uralensis* (Han et al. 2016). The *CHS* gene is believed to have potential as an anticancer agent with several biological effects (Table 2).

Table 2. Genes encoding bioactive compounds from potential medicinal plants in Indonesia that can inhibit cancer cell growth.

Bioactive compound(s) or protein	Gene name	Active compound mechanism	Effect on cancer cell	Model cancer cell lines	Plant species	Plant source	References
Lectin	*Lectin*	Increase the gene expression of P53 and 1kBa and downregulate Bax and Bcl2	Antiproliferative effect, induce apoptosis, autophagy and DNA damaging effect, and cytotoxicity	MCF-7, Hepatocellular carcinoma cells (HepG2), CNE2, Hela, Sarcoma 180, HCT 116, HEP-2	*Viscum album, Pisum fulvum, Pisum sativum, Typhonium flagelliforme*	Leaves, Tubers, Seeds, Roots, Rhizomes	Sianipar and Purnamaningsih (2018); Konozy and Osman (2022); Yassin et al. (2019); Sianipar et al. (2020b)
Sitosterol, Stigmasterol, CYP710A	*CYP710A*	Inducing the caspase-3 activities and Bcl-2/Bax ratio. Enhancement of gut immune surveillance systems. Reflected in the cytokines IL-12 and IL-18 activity as well as the natural killer (NK) cells	Antiproliferative effect, induce apoptosis, autophagy	Colon cancer (HT116), breast cancer (MCF-7) and MDA-MB, hepatic cancer (HepG2), and lung cancer (A549)	*Solanum lycopersicum, Cicer arietinum, Physcomitrella patens, Calotropis procera, Cucumis sativus, Glycine max, Zea mays, T. flagelliforme*	Leaves, Roots, and tubers	Morikawa et al. (2006); Morikawa et al. (2009); Arnqvist et al. (2008); Griebel and Section (2009); Aboobucker et al. (2021); Cabianca et al. (2021); Ramadan et al. (2019b)
Gamma tocopherol	*γ-TMT*	Induce PPARγ mRNA and protein levels, glutamate cysteine ligase, Nrf2 protein levels, GST, HO-1, SOD, UGT1A1, SGTm1, HO-1, NQO1, glutathione peroxidase, catalase, and downregulate PGE2, RNS, TNF-α, COX-2, LTB4, peroxynitrite, and 8-isoprostane	Antiproliferative effect, induce apoptosis, autophagy and DNA damaging effect	Breast cancer, pancreatic cancer stem cells, mammary malignant tumor cells, colon cancer cells (SW 480), keratinocytes cells (NCTC 2544), estrogen-induced early mammary hyperplasia in ACI rats, NMU-induced mammary tumors in Sprague-Dawley rats, and prostate cancer development in male TRAMP mice	*Perilla frutescens, Codonopsis lanceolata, Cleome viscosa, Carthamus tinctorius, Glycine max, Medicago sativa, T. flagelliforme*	Leaves, Roots, Stems, and Tubers	Koch et al. (2003); Lee et al. (2010); García-Moreno et al. (2011); Tang et al. (2011); Ghimire et al. (2015); N. F. Sianipar et al. (2016); Poaty et al. (2021); Sianipar et al. (2017)

Oleic acid, decanoic acid, linoleic acid, and palmitic acid	*FAD*	Increase the expression of multiple apoptotic-promoting proteins, including members of the BCL-2 family, cytochrome c, p53, several caspases, and PPARγ activity. When cancer cells are exposed to oxidative stress, mitogen-activated protein kinases (MAPKs) are activated	Induce apoptosis, antiproliferative properties, induce autophagy,	Lung cancer (H1299), ovarian cancer (PA-1), cervical cancer (SiHa), glioblastoma (D54MG), prostate, gastric cancer, human colorectal, esophageal cancer, and breast cancer	*Sesamum indicum, Glycine max, Helianthus annuus, Spinacia oleracea, Ricinus communis, Salvia hispanica, Daucus carota, Arachis hypogaea, Triticum aestivum, Paeonia lactiflora, Camelina sativa, Linum usitatissimum, T. flagelliforme*	Rhizomes Leaves, and Tubers	Yuan et al. (2019); Held et al. (2019); Sianipar et al. (2019); Hajiahmadi et al. (2020); Matuszczak et al. (2020); Neumann et al. (2021); Meng et al. (2021); Walkowiak et al. (2022); Biswas et al. (2022); Sianipar et al. (2023)
Doxorubicin, 1-deoxy-D-xylulose 5-phosphate reductoisomerase	*DXR*	Encouraging numerous cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), activating p38-MAPK, NF- κB (nuclear factor-κB), and autophagy pathways	Induce apoptosis, autophagy, DNA damaging effect,	Colorectal cancer, MCF-7, HeLa, HepG2, gastric cancer cell lines, T47D breast cancer cells	*Copaifera langsdorffii, Curcuma xanthorrhiza, C. longa, Zingiber officinale, Chrysanthemum cinerariifolium, Digitalis purpurea, Santalum album*	Flower, Leaves, Roots and Rhizomes	Ajith et al. (2016); Rad et al. (2020); Zhang et al. (2021); Mutiah et al. (2022)
Chalcone synthase	*CHS*	Inhibit angiogenesis and induce caspase-dependent apoptosis cell death	Antiproliferative effect, cytotoxicity, immunosuppressive potential	HepG2, A549, HeLa, HL-60	*Boesenbergia rotunda, Medicago sativa, Z. mays, Ginkgo biloba, Rehum emodi, Grewia asiatica, Petroselium hortense, Scutellaria viscidula*	Leaves	Pandith et al. (2016); Lei et al. (2010); Wani et al. (2017); Roslan et al. (2020); Park et al. (2021)

FUTURE CHALLENGES: POTENTIAL UTILIZATION AND DEVELOPMENT OF MOLECULAR MARKERS

So far, Indonesian medicinal plant species identification that have the potential to be anticancer agents has generally been based on the results of microscopic morphological observations. Many Indonesian medicinal plant species with the same potential are difficult to distinguish from each other. Therefore, genes with anticancer potential in several Indonesian medicinal plants have the potential to be developed using DNA-based molecular techniques.

The understanding of molecular markers of anticancer genes can provide the basis for the selection of potential medicinal plants. Using the *FAD2* anticancer gene (Matuszczak et al. 2020; Spasibionek et al. 2020) and the *FAD3* anticancer gene (Walkowiak et al. 2022) in *Brassica napus* L. plants, two allelic mutants were found (Matuszczak et al. 2020; Spasibionek et al. 2020). Research utilizing anticancer genes using molecular marker development is still very limited, so there is an opportunity to continue with the aim of QTL (quantitative trait loci) and MAS (marker-assisted selection) on potential medicinal plants, especially in Indonesia (Chandra and Pandey 2017).

The latest generations of molecular markers, EST (Expressed Sequence Tag) and SNP (Single Nucleotide Polymorphism), have a higher level of specificity than previous-generation markers. SNP markers are often used to identify specific traits or define lineages and populations (Emanuelli et al. 2013; Inghelandt et al. 2010). It is possible to use SNP markers associated with anticancer genes in the selection of medicinal plants. Indonesian medicinal plants such as *T. flagelliforme* mutants have lectin anticancer genes, and SNP sites have been identified in some of these mutants (Sianipar et al. 2022b). Based on identified SNP sites, SNAP (Single Nucleotide Amplified Polymorphism) markers can be created. SNAP markers, which are allele-specific markers, are used to create SNP sites (Borlay et al. 2017). The potential of Indonesian medicinal plants was successfully identified using the latest markers, such as *Z. officinale*, *Leucaena leucocephala*, and *Curcuma* using EST markers (Chandrasekar et al. 2009; Jain and Parihar 2019; Faidah and Shabrina 2022), *Matricaria recutita*, and *Crepidiastrum denticulatum* using SNP markers (Do et al. 2019; Otto et al. 2017). Utilizing anticancer genes in plants, the creation of molecular markers can aid in the selection of plant candidates for use as cancer drugs. Directed mutagenesis (such as genome editing) and the TILLING (Targeting Induced Local Lesions in Genomes) method can also be utilized to aid in the research and selection of anticancer genes in medicinal plants.

Genome editing techniques such as CRISPR technology can be used for genetic manipulation such as creating knockouts, precise changes in gene regulation, and activation and repression of targeted genes. With the knowledge of genes encoding bioactive compounds in plants, editing can be done so that the compound products in plants will change. Changes in products due to editing by modifying metabolic pathways in plants can increase the content of compounds higher than in the wild type of plant. Plants that have undergone editing can be used as candidates for medicines. To date, CRISPR genome editing technology has been used to increase oleic acid content by modifying the *FAD2* gene in *B. napus* (Okuzaki et al. 2018). *C. sativa* plants successfully increased their oleic acid content from 10% to 62% with different allele combinations for three FAD2 loci (Morineau et al. 2017). Editing techniques such as genome editing and TILLING can support the development of research related to genes encoding anticancer compounds.

CONCLUDING REMARKS

Potential medicinal plants in Indonesia contain bioactive compounds that involve several genes. From the review of various sources, the *FAD* gene encoding fatty acid compounds is the most developed and has the ability to suppress cancer cells by boosting apoptosis-promoting protein expression, including cytochrome c, BCL-2 family members, numerous caspases, p53, and PPARγ activity in several cancer cell models. The genes encoding bioactive compounds mentioned in this article have the ability to block cancer cells and may be used as a reference for research on medicinal plants that is still limited. The potential utilization of molecular markers of anticancer genes can be developed in plants that have anticancer genes. Thus, development and selection related to genes encoding anticancer compounds in medicinal plants can be carried out through various techniques, such as directed mutagenesis (such as genome editing) and the TILLING method.

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