



Zingiberaceae as the Family of Potential Anticancer Plants

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Abstract: The increasing number of cancer patients worldwide has encouraged developing effective and affordable anticancer drugs due to the limitations and drawbacks of chemotherapy and radiotherapy. The exploration of potential medicinal plants constitutes a common alternative for cancer treatment in many countries around the world as it is a rich source of bioactive compounds. Zingiberaceae is one of the most explored families for anticancer herbal medicine identification and characterization. The common genera in the family which have the anticancer properties are *Ginger*, *Curcuma*, *Hedychium*, *Boesenbergia*, *Alpinia*, *Etingera*, *Kaempferia*, *Globba*, *Amomum* and *Elettaria*.

Keywords: Anticancer, bioactive, phytochemicals, therapeutic, Zingiberaceae

Cancer is one of the diseases that threaten human death and important cause of death worldwide, accounting for almost 10 million deaths recently (Sung et al., 2021). Conventional methods such as chemotherapy and radiotherapy are used to treat cancer patients. These methods can cause unpleasant side effects and toxicity since they can destroy both normal cells and cancer cells. To reduce the side effects, there is a tremendous clinical need for the development of effective anticancer drugs with low toxicity. Medicinal plants have become a source of anticancer compounds because they are safe, with low side effects and are easily accessible. Natural products play an essential role in the discovery and development of anticancer agents, especially plant sourced anticancer drugs have made significant contributions to

cancer treatment and successfully used for the benefits of human health (Atanasov et al., 2021).

Zingiberaceae or Ginger family is a large family containing approximately 1600 aromatic plant species in 52 genera, most of which are rich in essential oils. The family is an important natural resource providing many useful products for food, spices, medicines, dyes, perfumes and aesthetics. Among this high number of representatives, some species have been reported for their therapeutic properties both in classical and ethno medicine. Most of the genera are widely used as traditional medicine for many treatments, such as to relieve stomachache and hemorrhoids, as a herbal compress for massage, to improve blood circulation, to relieve muscular pain, and

as a honey balm. Moreover, the rhizomes of these plants are used as spices and ingredients for cooking. Essential oils from Zingiberaceous plants have been used for mosquito control. They have demonstrated various bioactivities such as antimycobacterial, immunomodulatory, antineoplastic and anticancer (Aolga et al., 2022). The common genera in Zingiberaceae which have the anticancer potential are *Ginger*, *Curcuma*, *Hedychium*, *Boesenbergia*, *Alpinia*, *Etingera*, *Kaempferia*, *Globba*, *Amomum* and *Elettaria*.

1. Anticancer plants in Zingiberaceae

1.1. *Zingiber* Mill.

Ginger is herbaceous plant widely distributed throughout the tropical and subtropical regions and it is equally reputed for its medicinal properties. The perennial plant has annual pseudostem of about one meter tall bearing narrow leaf blades. The inflorescences bear flowers having pale yellow petals with purple edges, and arise directly from the rhizome on separate shoots. Different types of extract from the rhizome of ginger have been used in Ayurvedic and traditional herbal medicine in order to treat various disorders such as indigestion, vomiting, arthritis, rheumatism, pains, cramps, fever and infection. The main pharmacological actions of active compounds extracted from ginger root reported by in vitro and in vivo test attributed to its active phytochemicals were antiinflammatory, antioxidant, antiemetic, anticancer, anticoagulant, immunomodulatory and cardioprotective. The main phytochemical constituents of the root, the vegetal product of this plant, responsible for the therapeutic action are gingerols, shogaols, paradols, gingerdiols and

zingeronone. Regarding its anticancer properties, recent studies have indicated a beneficial effect in case of liver, endometrial, ovarian and prostate cancer. Furthermore, ginger was described as an antiemetic agent in cancer chemotherapy. Moreover, the ginger extracts show promising anticancer activity against cholangiocarcinoma (Plengsuriyakarn et al., 2012).

Anticancer activities: *Z. officinale* is the main representative of Zingiberaceae family studied for a wide range of therapeutic properties. The antitumour activity of *Z. officinale* rhizome on B164A5 murine melanoma cell line regarding both proliferation and apoptosis and the increased anticancer activity may be correlated with the higher amount of polyphenols and antioxidant capacity (Dancio et al., 2015). Moreover, *Z. ottensii* is a plant with less than 2 m in height and it is widely cultured in Southeast Asian countries including Thailand, Malaysia, Indonesia, Laos and Vietnam. It has been used as traditional medicinal herb for the treatment of gastrointestinal diseases like peptic ulcers, stomachache and constipation as well as myalgia, sprain and wounds. Crude extracts of *Z. ottensii* exhibit its cytotoxicity in HEK293T/17 cells and reduce IL-6 levels in HeLa cells. The extracts in different solvents induce anticancer activity against four strains of cancer cells, A549 cells (lung carcinoma cell lines), MCF-7 cells (breast cancer cell lines), HeLa cells (cervical carcinoma cell lines), and K562 (chronic myelogenous leukemia cell line). Among the four cancer cells, extracts of *Z. ottensii* shows the most effective in inhibiting MCF-7 (Panyajai et al., 2022).

Z. cassumunar is commonly known as

'Cassumnar Ginger'. The root is perennial, tuberous with long, white fleshy fibres, deep yellow when fresh and possessing a strong camphoraceous odour with bitterish taste. The plant has been used in folk medicine for the treatment of inflammation, sprains, rheumatism, muscular pain, wounds and asthma. Moreover, it acts as mosquito repellent, carminative, mild laxative, antidysenteric, radical scavenging and anti-malarial activity. A major part of the pale amber colour oil obtained from *Z. cassumunar* consists of terpenoids, flavonoids, alkaloids, steroids and benzenoids. It is often used as traditional medicine for inflammation, sprains, rheumatism, muscular pain, wounds and asthma (Singh et al., 2015).

1.2. *Curcuma* L.

Curcuma is a perennial, herbaceous plant that can reach a height of 1 meter and it emits numerous, edible rhizomes whose interiors are yellow or orange. The rhizomes are reduced to a powder, which is the spice called *curcuma*. The lanceolate leaves are oblong or elliptical and uniform green coloured. *C. longa*, (Turmeric), popular name-turmeric, is an aromatic, nutraceutical plant have been intensively used under different pharmaceutical formulations in Indian traditional medicine for different ailments namely wounds, acne, parasitic infection, cold and urinary tract and liver diseases. Numerous experimental studies regarding the therapeutic activity of turmeric reported a plethora of pharmacological properties of the vegetal extract including antioxidant, anti-inflammatory, antiangiogenic, antibacterial, analgesic, immunomodulatory, proapoptotic, and antihuman immunodeficiency properties. The major active compound responsible for the pharmacodynamic action is the polyphenol

curcumin. Additionally, this natural polyphenol has been described as an anticancer agent both in vitro and in vivo on a wide range of cancer types such as colon, pancreatic, liver, cervical, pulmonary, thymic, brain, breast and bone cancer. Recent studies intensively support the role of polyphenols in the prevention of degenerative diseases like cardiovascular affections and cancers. The antioxidant activity of polyphenols induces the antiproliferative and proapoptotic effect of *Curcuma* rhizome on B164A5 murine melanoma cell line (Danciu et al., 2015).

Anticancer activities: *C. zedoaria*, 'White Turmeric', is one of the important crude drugs possesses many biological activities for many therapeutic actions due to the presence of wide range of phytochemicals such as curcumin, ethyl p-methoxycinnamate, β -turmerone, β -eudesmol, zingiberene, dihydrocurcumin, furanodiene, α -phellandrene, 1–8 cineole, β -elemense and germacrone. White turmeric extract has the antitumour activity against various human cancerous cell lines of breast, cervical and lungs. Moreover, sesquiterpene compounds in white turmeric are highly active against human gastric cancer cells lines (Lee et al., 2019).

1.3. *Alpinia* Roxb.

The genus is commonly known as 'Shell ginger' which is native to Asia, Australia and the Pacific Islands. Several species are cultivated as ornamental plants in tropical and subtropical climates. It shows thick rhizome from which the lance shaped to oblong leaves are arising. The inflorescence is spike, panicle or raceme and hooded in bracts and bracteoles. The plants are generally aromatic due to the

presence of essential oils. *A. coriandriodora*, a widely cultivated perennial edible plant with the odor of coriander, is widely cultivated for its medicinal value and used as a condiment. The rhizome of *A. coriandriodora* has been used in Chinese folk medicine to treat indigestion, stomachache, cold, asthma and fever.

Anticancer activities: Phytochemical compounds like diarylheptanoids and flavonoids isolated from *A. coriandriodora* are responsible for the antioxidant and anti-inflammatory activities. Moreover, the most predominant component of *A. coriandriodora* rhizome essential oil, (E)-2-decenal, inhibits the migration and invasion ability of A549 cells via down regulation of MMP-2 and N-cadherin as well as upregulation of E-cadherin (Hong et al., 2022). *A. officinarum* is a tropical perennial species native to China. It is used to flavor food and to treat a variety of diseases. It bears long, narrow green leaves and produces white flowers and dark brown rhizomes. The phytochemical compounds of *A. officinarum* extracts have antiinflammatory, antibacterial, antioxidant, antiobesity, anticancer, enzyme inhibitory and remarkable antiviral properties. The effectiveness of leaves and rhizome extracts induces apoptosis against acute monocytic leukemia cells and breast cancer cells (MCF-7) (Ghil 2013; Omoregie et al., 2013).

A. purpurata, a traditional herbal medicinal plant, shows antidermatophytic, hepatoprotective, antimicrobial, immunostimulatory and anticancer properties. The rhizomes are used to improve appetite, taste and voice; in addition, it is used to treat headache, rheumatism, sore throat and renal

infection. The leaves and rhizomes have antioxidant, antibacterial, larvicidal, cytotoxic and vasodilator activities. The plant extracts exhibit anticancer activities against prostate cancer cells (Palanirajan et al., 2022). Likewise, *A. elegans*, 'Tagbak', is an endemic herbaceous species found at low to medium altitudes in Luzon, Polilio Islands, Mindoro and Leyte. It possesses therapeutic properties including hemoptysis, paralysis extremities, urticarial etc. The leaf extract of *A. elegans* significantly inhibits the cellular proliferation and migration at high concentrations in turn exhibits antiproliferative activity against lungs, liver and colorectal cancer cells (Lintao & Medina, 2021).

A. galanga, 'Greater galangal', is a perennial rhizomatous herb, widely cultivated in tropical areas as an essential source of cosmetics, medicines and culinary products. The species includes various bioactive compounds like diarabinoside, steroldiglucosyl caprate, galangoflavonoside and acetoxychavicol acetate. The essential oils and extracts from different parts of *A. galanga*, especially from flower, rhizome, leaf and fruit, have been used for the treatment of various diseases including stomach ache, vomiting, diarrhea, diabetes, microbial infections, bronchitis, fever and headache. The ethanolic extract of *A. elegans* contained bioactive compounds which inhibit the proliferation of breast cancer cell lines (MCF-7) with the involvements of apoptosis or programmed cell death (Samarghandian et al., 2014).

1.4. *Hedychium* J. Koenig

The genus *Hedychium* is distributed in Asia and Madagascar, and native to India, Southeast Asia and Madagascar. There are

approximately 70-80 known species that grows as herb of perennial tuberous rootstocks. Members of the genus are commonly growing up to 120-180 cm height. Some species are cultivated for the exotic foliage and fragrant spikes of flowers in shades of white, yellow and orange. Various species are used in traditional medicines for the treatment of asthma, bronchitis and gastric and eye diseases.

Anticancer activities: The ornamental ginger, *H. coronarium* (Butterfly Ginger) has the pharmacological properties including antioxidant, antibacterial, antifungal, cytotoxic, chemopreventive, antiallergic, larvicidal, antiinflammatory, neuropharmacological, fibrinogenolytic, coagulant and hepatoprotective (Chan & Wong, 2015). *H. spicatum* rhizome is described as medicine in Ayurvedic and the plant has been used in various treatments of stomachache, cough, wound ulcer, fever, respiratory problems, cancer, AIDS etc. The species also shows the antioxidant, antimicrobial, antidiabetic, hepatoprotective, antidiarrheal, analgesic, expectorant, antiinflammatory, emmenagogue, antifungal, hypoglycaemic, insect repellent, hypotensive, pediculicidal and cytotoxic activities (Bhatt et al., 2008).

1.5. *Boesenbergia* Kuntze

Genus contains more than 70 species that native to China, the Indian Subcontinent, and Southeast Asia. *B. rotunda* or 'Finger Root' is a herb with medicinal properties which grows in Southeast Asia, India, Sri Lanka and southern China. The species uses as a traditional medicine to treat rheumatism, muscle pain, gastrointestinal disorders, flatulence, stomach ache, dyspepsia and peptic ulcer.

Anticancer activities: The whole plant extract of *B. rotunda* is effective towards breast, colon, prostate, liver and lung cancers. Moreover, the rhizome possesses antileukemic property due to the occurrence of various bioactive compounds having high anticancer potential. Sakuranetin has a cytotoxic effect on B16BL6 melanoma cells, while cardamonin and pinostrobin chaconne isolated from rhizome have a cytotoxic effect on the H-29 colon cancer cell line. The anticancer activity of *B. rotunda* is strong cytotoxic and induces apoptosis of breast cancer cell lines through insilico and in vitro approaches (Widyananda et al., 2022). *B. pandurata* is known to have various pharmacological activities, mainly the anticancer property. The ethanolic extract of the plant shows strong inhibitory effects on the growth of cancer cells. Panduratin A, a chalcone derivative isolated from *B. pandurata*, inhibits the growth of MCF-7 human breast cancer and HT-29 human colon adenocarcinoma cells. In addition, rhizomes of *B. pandurata* contain active compounds with anticancer activities and have antiproliferative and apoptotic induction against HeLa and PANC-1 pancreatic cancer cell lines. Recently, the species is known to inhibit the growth of breast cancer cells and the anti-breast cancer activity is significantly influencing by the inhibition of two receptors, ER- α and HER2 (Pratama et al., 2022).

1.6. *Etingera* Giseke

The genus *Etingera* consists of more than 100 perennial herbaceous species distributed mainly in tropical regions. Some of the larger species have leafy shoots reaching almost 10 metres high, and the bases of the shoots are so stout as to seem almost woody.

Other species grows as clumps of leafy shoots; while some have long creeping rhizomes with leafy shoots, more than a metre apart. Unique and distinctive to the species is a tube that forming above the point where the base of the flower petals joins onto the plant. The main phytochemical compounds of *Etilingera* are phenolics, diarylheptanoids, flavonoids, steroids, alkaloids and terpenoids. Eight species in the genus namely *E. elatior*, *E. pavieana*, *E. brevilabrum*, *E. pyramidosphaera*, *E. megalocheilos*, *E. coccinea*, *E. fimbriobr-acteata*, and *E. corneri* are potential anticancer agents to treat human cancer.

Anticancer activities: The rhizome of *E. elatior* provides the anticancer activity; similarly the rhizome essential oil has potential against the cell lines MCF-7, HeLa and HI 60. The aqueous extract of flowers shows anticancer activity against the breast and colon cancer cell lines. Presence of lapachol, apigenin, methylated chrysin, 6,2'-dihydroxyflavone, 3-Hydroxy3, 4'-dymethoxyflavone and 4'-Hydroxy-5,7-dimethoxyflavone compounds contained in *E. elatior* provide the anticancer effect in turn help to suppress different human cancers. Moreover, *E. pavieana* rhizome extract provides an antiproliferative effect against breast adenocarcinoma MDA-MB-231, hepatoma HepG2 and cervical carcinoma HeLa and C33A. The trans-4-methoxycinnamaldehyde (4-MCA) compound blocks the cell proliferation and cancer cell colony formation by inducing apoptosis and cell cycle arrest (Wahyuni et al., 2021).

The essential oil from *E. brevilabrum* shows cytotoxic activity and inhibits cell proliferation against MCF-7, HeLa, P388 and HL 60 cancer

cell lines due to the presence of α -fenchol, elemicin, borneol, methyl isoeugenol, β -farnesene etc. similarly, the essential oil from the rhizomes of *E. pyramidosphaera* inhibits cell proliferation of MCF-7 and P388 cancer cell lines due to the presence of lauricaldehyde, 1-dodecanol, lauryl acetate, 1-tetradecanol etc. (Vairappan et al., 2012). Due to the presence of terpineol oxide, aromadendrene, aromadendrene oxide and caryophyllene, the essential oil from the rhizomes of *E. megalocheilos* obstructs cell proliferation of MCF-7, HeLa, P388 and HL 60 cells. Likewise, the essential oil derived from the rhizome of *E. coccinea* demonstrates the cytotoxic activity against the MCF-7, P388 and HL 60 cell lines with the presence of 2-Methyl-1-undecanol, 1-Dodecanol, Lauryl acetate, etc. The polyphenolic content in leaf extract of *E. fimbriobracteata* has antiproliferative effect against cervical cancer cells; beyond, rhizome of *E. corneri* hinders the growth and proliferation of MCF-7 cells (Ghazaly et al., 2020).

1.7. *Kaempferia* L.

Kaempferia is native to China, India and Southeast Asia. These gingers grow from small globular rhizomes bearing fleshy roots. The herbaceous plant has pronounced dormancy period. The short stem with two to a few colourfully marked broad leaves often carries large showy flowers. Various species of the genus are used in traditional medicines for the treatment of cold, dry cough, toothache, rheumatism and hypertension. In addition, it has been used widely as spices due to highly aromas.

Anticancer activities: *K. parviflora* is commonly known as 'Black Ginger' grown in

tropical Asia and traditionally plays an important role in treating all kinds of everyday ailments including general pains, abscess, allergy and ulcer. Extracts of *K. parviflora* also suppresses gastrointestinal ulcer formation and cancer cell growth. It inhibits cervical cancer HeLa and ovarian cancer SKOV3 cells (Paramee et al., 2018). Likewise, *K. galanga*, 'Aromatic Ginger', is one of the most economically important species known for its broad ethnomedicinal use. It has been used as a spice and traditional medicine in local communities of Southeast Asia. The rhizome extract of *K. galanga* exhibits the antiproliferative activities against various cancer cell lines. The anticancer effects have been attributed to enhanced cytotoxic T lymphocyte responses and the upregulation of proapoptotic genes (Elshamy et al., 2020).

K. rotunda is also known as an ornamental plant with silver patterned leaves and a purplish flower. It is used as ethnomedicines in wide area spreading from India to Indonesia. Some of the polyoxygenated cyclohexane derivatives of the plant have moderate cytotoxic activity and acts against pancreatic and breast cancer cell lines. Lectin in *K. rotunda* induces cell cycle arrest in colon cancer cells and Ehrlich-Lette ascites carcinoma cells via the caspase-3-dependent pathways. Likewise, anticancer compounds, kaempulchraol F and kaempulchraol L, extracted from *K. pulchra* exhibit antiproliferative activities against human pancreatic cancer cells (Win et al., 2016). Moreover, the anticancer properties of kaempfolienol and zeylenol derivatives from *K. angustifolia* acts against human promyelocytic leukemia (HL-60) and human breast

adenocarcinoma (MCF-7) cell lines (Yeap et al., 2017).

1.8. *Globba* L.

Globba ('Dancing Ladies') is the third largest genera in the Zingiberaceae family with over 100 species, distributed in tropical and sub-tropical Asia. Many of the species have the peculiar habit of producing bulbils on the inflorescence in place of the lower flowers. In some species, the bulbils are spicy and occasionally eaten. Different *Globba* species have been used for centuries to treat a variety of diseases including mouth ulcers, conjunctivitis, eye infections, asthma, leucoderma, cough, stomachache, fever and heart disease. Phytochemical compounds including humulen-6,7-epoxide, β - caryophyllene, terpineol, heptadecane, 2,6-dimethyl1,5,7-octa trien-3-ol and alloaromadendrene are prominent in *G. marantina* extract which could be a potential source of natural antioxidants for use in food, cosmetics and pharmaceuticals industries. Moreover, the main compounds of the rhizome extract of *G. candida* are levoglucosan, allylhydrazone acetaldehyde, trans-2,3-epoxybutane, butan-3-enoic acid methyl ester, 2-methylcyclopentanone and 2-n-propyl-oxetan. While the dominant contents of the leaves extract of *G. candida* are pinostrobin chalcone.

Phytochemical studies of *G. reflexa* rhizomes afford main compounds namely stearyl palmitate, villosin, coronarin D and stigmaterol that have anticancer activity against the human breast cancer, human oral epidermoid carcinoma and human small cell lung cancer cell lines. Likewise, the essential oil from *G. pendula* possesses significant cytotoxic

activity against MCF-7 and Hep3B cell lines and *G. bulbifera* ethanolic tuber extract shows good activity for protease inhibition to block the proliferation of breast cancer cell lines (Rao & Kaladhar, 2014).

1.9. *Amomum* L

The genus *Amomum* consists of over 90 species extensively distributed in Africa, Tropical Asia, Australia and the Pacific Islands. These are mostly terrestrial rhizomatous herbs showing elongate pseudostems that arise from widely creeping rhizomes. The densely flowered spike, spike like raceme or panicle type inflorescence arises from rhizomes. The seeds of *Amomum* are used as spices; similarly, other plant parts are used in traditional medicine in healing of toothache, dysentery, diarrhea, rheumatism and lung diseases (Dutta et al., 2000).

Anticancer activities: *Amomum* consumption is beneficial to health as it possesses antioxidant, cytotoxic and immunosuppressive properties. The volatile oil from *A. kravanh* induces anticancer activity in human beings (Chaothanaphat et al., 2022). The hexane and ethyl acetate extracts of *A. subulatum* exhibit maximum cytotoxic activity against human breast cancer and cervical cancer cell lines. Aculeatin A extracted from *A. aceleatum* is active against human breast cancer cells, MCF-7. Moreover, acetone extract of *A. compactum* has anticancer activity against breast cancer cells (Alkandahri, 2021); while the ethanolic extract of *A. subulatum* fruits shows cytotoxic activity against cervical cancer cell line due to the presence of proteins, terpenoids, tannins, steroids, phenols and flavonoids (Yadav, 2014).

1.10. *Elettaria* Maton

The genus is commonly known as 'Green Cardamom' or 'Queen of Spices'. The dried fruit of herbaceous perennial plant *E. cardamomum* is spicy and ethnomedicinal. It is the third most expensive spice behind vanilla and saffron. Cardamom has three sided fruits with a rough, thin and delicate outer layer and small deep-brown aromatic seeds that arranged in vertical order. It exhibits many medicinal and pharmacological activities like antiseptic, antispasmodic, anthelmintic, cephalic, antibacterial and stomachic (Singhal et al., 2022).

Anticancer activities: Cardamom phytochemicals are well known inhibitors of cancer. The plant is also able to treat or inhibit different stages of breast cancer from Stage 0 to Stage 4 due to the occurrence of cancer fighting compounds. It is not only inhibits the progression of the disease, but also prevents the breast cancer when consumed at the appropriate dosage level. Cardamom based therapy has very few side effects in turn increases the levels of tumour suppressor p53, inhibits tumour proliferation initiating cells, decreases expression of the metastasis promoter Snail1 and inhibits the epithelial mesenchymal transition. Chemical compounds in cardamom, diindolylmethane and indole-3-carbinol, prevent the growth of cancer cells including breast cancer cells. Moreover, phytochemicals such as cineole and limonene have the protective role against cancer progression (Vutakuri & Somara, 2018). Moreover, cardamom could serve as an apoptotic stimulator agent presenting a novel and potentially curative approach for cancer

treatment, inducing fewer side effects than those of the commercially used anticancer drugs (Almeer et al., 2021).

2. Outlook

Phytochemical investigations in medicinal plants reveals that many plant species have anticancer activity due to the presence of broad range of secondary metabolites or bioactive compounds. Among

the genus of Zingiberaceae, the most notable members include *Ginger*, *Curcuma*, *Hedychium*, *Boesenbergia*, *Alpinia*, *Etlingera*, *Kaempferia*, *Globba*, *Amomum* and *Elettaria* which possess various biological activities towards different human cancer cell lines. Nowadays, these species play major role in pharmaceutical and therapeutic approaches towards anticancer drug development to inhibit cancer cell proliferation and metastasis.

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