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RESEARCH ARTICLE

Anticancer Properties of *Alpinia officinarum* (Lesser Galangal) – A mini review.

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Abstract

Lesser Galangal (*Alpinia officinarum*) is a member of the *Zingiberaceae (*ginger) family of herbaceous plants. It typically has long green leaves and reddish white flowers and bears dark brown underground rhizomes. A native of Southeast Asia, the plant has traditionally been used as a remedy for a wide variety of maladies including abdominal pain, diarrhoea, rheumatism, hiccups, digestive problems and even cancer. The anti-cancer potential of *Alpinia officinarum*has been generating keen interest from the scientific community. There is a growing body of evidence that suggests that the plant contains potent anti-proliferative agents that may serve as a basis for anti-cancer drugs in the near future. Basic scientific research work on the plant during the past fifteen years has increased our understanding of the biochemical composition of the plant as well as the antitumor properties of its crude and purified extracts.Several anticancer studies on *A. officinarum* have focused on elucidating the molecular mechanisms underlying the preventive, protective, tumour suppressive and apoptotic activities against various types of cancers. This mini review highlights the relevant research evidence that supports the potential of *A. officinarum* as a potent anticancer agent andlooks at future prospects for development in the drive for possible application of this plant or its active agents for effective cancer treatment.

Introduction

Lesser Galangal (*Alpinia officinarum*) is a tropical perennial that is native to Southeast China and is widely cultivated as a spice throughout tropical Asia(1). It bears long, narrow green leaves and produces flowers with white petals as well as dark brown underground rhizomes having an aromatic odour. The plant usually grows to a height of approximately five feet. It belongs to the *Zingiberaceae* (ginger) family of herbaceous plants (**Fig 1A-B**).

The genus name of the plant is named after the seventeenth century Italian botanist Prospero Alpini, who first characterized the plant while the species name, galangal is thought to be derived from the Arabic translation of the Chinese word for ginger. Lesser Galangal is colloquially known by a variety of names such as India root, China root, colic root, East India catarrh, Galanga root, Blue ginger and Chinese ginger(2). It is rarely found cultivated outside of the Asian continent; however, a unique variety of the plant has been reported on the island of Jamaica(3).

Lesser galangal is of significant domestic and pharmaceutical value and has traditionally been used to treat a wide range of symptoms including abdominal pain, hiccups, vomiting and diarrhoea(4,5) . It is also extensively used as a spice in cooking **(Table 1)**. More recently, many unique biochemical compounds have been purified from *A. officinarum*(6,7). Among the most studied of these compounds are galangin and members of a class of compounds known as diarylheptanoids which have been demonstrated to have significant anti-inflammatory, anti-proliferative and anti-emetic properties (3,8–19) (**Tables 2 and 3**).

Cancer continues to be a leading cause of mortality and morbidity worldwide (20). A reliable cure is yet to be found given the fact that scientists are struggling with the ability of cancer cells to employ multiple pathways for survival. Chemotherapy is currently one of the standard approaches for eliminating cancer cells, but this carries with it a tremendous cost, namely the destruction of normal cells and accompanying emotional distress. To further compound the problem, the survival rates of patients who receive chemotherapy, especially after major surgery are unacceptably low (21,22). There is therefore an urgent need for less toxic, more efficacious therapies for manycancer conditions than are currently available.

It is an encouraging trend that interest is increasing in the search for complementary and alternative medicine (CAM) as a safer and more effective form of cancer treatment(23). Plant-derived products in particular have emerged as valuable sources of anticancer compounds which may be used to develop drugs for therapy (24,25).

Recently, the anti-cancer properties of Lesser Galangal have been the focus of many studies in the field of ethnopharmacology. Diarylheptanoids extracted from this plant have been reported to induce apoptosis in several types of tumour cells (11,14,15,17). Extracts from Lesser galangal increased the activity of certain enzymes which are known to extrude carcinogens from cells(26). Lesser Galangal has also been reported to produce anti-cancer effects against a wide variety of human cancers, including liver, colon, acute myelocyticleukemia, breast, melanoma, neuroblastoma, prostate and lung cancers(11,14,15,17).

Anti-Carcinogenic and Anti-Mutagenic Effects of Compounds derived from *Alpinia officinarum:-*

The phytochemical composition of *Alpinia officinarum* has been studied and was shown to contain high concentrations of phenols and flavonoids. The flavonol composition of a hydro-alcoholic extract by hot maceration was found to be 54 mg/g (38). Galangin, a member of the flavonol group of flavonoids is the major flavonoid in *Alpinia officinarum* and constitutes 10% of the ethanolic extract of the plant (39). Flavonoids are known to reduce the frequency of free radicals via a variety of mechanisms including direct radical scavenging, down regulation of radical production, elimination of radical precursors, metal chelation, inhibition of xanthine oxidase and elevation of endogenous antioxidants (40,41).The elimination of free radicals has been associated with a reduced risk of carcinogenesis (42). Free radicals may generate clastogenic factors that induce disruptions in chromosomal structure (43). The anti-genotoxicity of galangin has been previously reviewed and it was shown that galangin can prevent cancerous changes due to genotoxic exposure (44). An increased frequency of micronucleated reticulocytes (MN-RETs) in the peripheral blood has been associated with cytogenetic damage due to genotoxic exposure(45–47). An investigation into the levels of mitomycin C (MMC) induced MN-RETs in the peripheral blood of mice revealed that treatment with galangin prior to MMC exposure could lead to significant decreases in the frequency of MN-RETs in the peripheral blood, suggesting a protective effect ofgalangin on exposed subjects. In addition, galangin has been demonstrated to reducethe occurrence of bleomycin induced chromosomal aberrationsin mouse spleen lymphocytes (48,49). Other reports have demonstrated the anticlastogenic and antimutagenic effects of galangin. Further, in comparison to other flavonoids, galangin is among the most bioactive of the group (50).

Alpinia officinarum also contains phenylpropanoids including 1'acetoxychavicol acetate(51), which may act indirectly to protect healthy cells from cancerous changes. This compound has been demonstrated to not only discriminatorily destroy cancer cells by apoptosis, protecting normal cells (26), but also to induce glutathione-S-transferase activity in cultured hepatocytes(51). Glutathione-S-transferases (GSTs) are a family of biotransformation enzymes that can detoxify mutagenic and genotoxic compounds and therefore prevent cancerous changes from occurring. Anassociation has been observed between increased GST activity and decreased susceptibility to cytotoxic compounds. Polymorphisms that result in impaired catalytic activity of GSTs are associated with increased sensitivity to toxic compounds.However, the activity of GST increases in response to reactive oxygen species (52–54). It appears therefore, that substances that increase the activity of GST enzyme will act to prevent cytotoxic changes including cancerous transformations.

Lesser Galangal Arrests Tumor Cell Growth and Proliferation:-

A growing amount of evidence suggests that Lesser Galangal may be used as a tumor suppressor. Studies have shown that crude and purified extracts from the plant arrested the growth of cancer cell lines. The effectiveness of methanolic extracts of Lesser Galangal leaves and rhizome against acute monocyticleukemiacellsevidenced by diminished cell viabilityhas recently been reported (3). Reverse phase high performance liquid chromatography (RP-

HPLC) fractions of leaf extract, showed significant bioactivity against the leukemia cells, with minimal impact from the solvent. Bioactivity resulting in population cell death up to 99.2 +/- 3.0% was achieved by some extract fractions within 24 hours of treatment at a concentration of 0.1 mg/ml (3).

Methanolic extracts of Lesser Galangal have been demonstrated to inhibit the proliferation of breast cancer cells (MCF-7) which may be due to the induction of apoptosis (55). The plant extract is reported to inhibit cell cycle progression at the S-phase through suppression of the regulatory proteins, including E2F1, cyclin-dependent protein kinase 2 (cdk2) and cyclin A (55-58). The extract cleaves and inactivates poly ADP ribose polymerase (PARP), an enzyme that is shown to repair damaged DNA, especially single-strand DNA breaks (59-61). The cleavage of PARP is suspected to be a sign of the inability of the host cell to cope with a saturating level of unrepaired DNA injury arising from apoptosis-derived chromatin fragmentation or externally infringed genotoxic insult from the extract (55).

The occurrence of a single strand break results in the activation of PARP which then binds to the DNA and initiates the synthesis of a poly ADP ribose chain as a signal for other DNA repairing enzymes (62). This is an energy consuming process and is not energetically feasible in cells in which DNA damage is extensive. Therefore, in such cells, PARP is inactivated by caspase cleavage and the energy is instead invested in the induction of programmed cell death thus saving energy for other cells in the tissue (63). It has been shown that caspase-3 and caspase-7 are responsible for in-vivo cleavage of PARP. This cleavage occurs at aspartic acid 214 and glycine 215, resulting in 24kDa and 89kDa fragments (64). In the MCF-7 cells treated with lesser galangal extracts, molecular analysis showed a dose dependent increase in the level of a 85 kDa protein fragment representing the cleaved form of PARP, suggesting inactivation of PARP and subsequent induction of apoptosis. Treatment of the cells with the Lesser Galangal extract resulted in an increased expression of p53, a known tumor suppressor which mediates apoptosis in response to DNA damage. The extract treatment also caused an increase in the Bax/Bcl-2 ratio, which indicates a resulting mitochondrial dysfunction(55). Lesser Galangal extracts may thus be exerting their apoptotic cytotoxicity by caspase and mitochondrial dependent pathways. Observation of an increased proportion of extract treated cells in the S-phase relative to untreated cells suggests that the cytotoxicity imposed on treated cells by Lesser Galangal may be occurring during the S-phase of the cell cycle.

Most of the studies on the apoptotic effects of Lesser Galangal have been done using substances purified from the plant, most notably galangin and a group of compounds known as diarylheptanoids. Galangin extracted from *Alpinia officinarum* was shown to induce apoptosis in melanoma and colon cancer cells in a time and dose dependent manner possibly by mediating the alteration of membrane potential (35,36). Galangin also arrested the proliferation of hepatocellular carcinoma cells (HCC) apparently by inducing endoplasmic reticulum (ER) stress. In the study, suppressed proliferation was observed when galangin was used to treat hepG2, hep3B and PLC/PRF/5 cells. The levels of intracellular calcium, mitogen activated protein kinases (MAPKs) and ER proteins were assessed in an effort to understand the molecular mechanisms underlying the observed anti-proliferative activity. The results showed increased levels of ER proteins, MAPKs as well as increased free cytosolic Ca^{2+} concentration, thus confirming that ER stress was induced by the galangin treatment. It has previously been determined that prolonged ER stress may activate apoptotic pathways in cancer cells (4). Therefore, galangin's ability to induce ER stress in HCC is suggestive of its potential to act as a safe cytotoxic agent in cancer therapy.

The anticancer activity of diarylheptanoids isolated from *Alpinia officinarum* has been reported (8,9-15,17,18,28). **Table 3** summarizes the biological effects of the main diarylheptanoids purified from the plant.

Conclusion and Future Perspectives:-

Lesser galangal has been in use since ancient times, and as yet no severe harmful effect resulting from its usehas been reported. Extracts of lesser galangal appear to be able to inhibit the proliferation of tumor cells. However, it would be useful to compare the efficacy of Lesser Galangal extracts with that of standard anticancer agents to more accurately determine the pharmaceutical potential of *Alpinia officinarum.* Besides, the discriminatory tolerance of normal cells to these extracts may be a much needed positive step in the search for a safe curative treatment and management of patients in cancer therapy.

Much work has been done and more is currently being done to elucidate the molecular mechanisms underlying the observed anticancer effects of the plant. Experimental data to date suggest that Lesser Galangal products e.g. galangin and several diarylheptanoids possess potent anticancer properties. Given the fact that bioimmunotherapy is universally regarded as one of the dependable cancer treatment regimens, drugs that boost the immune system are

always in great demand. It would be useful therefore for future studies to investigate the bioimmunotherapeutic potential of Lesser Galangal, specifically looking for up regulation of markers such as CD69, CD45RO and down regulation of CD45RA and CD62L on lymphocytes, monocytes and dendritic cells. It is also important to study the synergistic effects of lesser galangal extracts with standard anticancer drugs against different cancer cell lines.

Table 1: Traditional uses of *Alpinia officinarum* (Lesser Galangal).

Galangal oil	Perfumes / bacterial infections
Powdered leaves	Treatment for halitosis
Brewed leaves / root	Respiratory, digestive and abdominal illnesses
Chopped Root	Spice in cooking

Table 2: Biological effects of Galangin

In vitro inhibition of acetylcholinesterase activity	(7,27)
Synergistic antibacterial activity against MSRA	(28–30)
Suppression of the genotoxicity of carcinogens	(31)
Inhibits lipid accumulation in adipose tissue	(32)
Cytotoxic activity in multiple cancer cell lines	(4,32–34)
Induction of apoptosis in multiple cancer cell lines via multiple mechanisms	(4,35–37)

Table 3: Some diarylheptanoids purified from *Alpinia officinarum*. Note that some diarylheptanoids have multiple biologic effects.

(5S)-5-hydroxy-7-(4-hydroxyphenyl)-1-phenylhept-3-one (5S)-5-methoxy-1,7-diphenylhept-3-one 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-4E-hepten-3-one	Antiviral	(8,9,12,13)
7-(4", 5"-dihydroxy-3"-methoxyphenyl)-1-phenyl -4-heptene-3-one 1, 7-diphenyl-5-heptene-3-one 4-phenethyl-1, 7-diphenyl -1-heptene-3, 5-dione 5-hydroxy-7-(4"-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone	Antibacterial	(18,28)
1, 7-diphenyl-3,5-heptanedione (4E)-1, 7-diphenylhept-4-en-3-one (4E)-7- (4-hydroxyphenyl)-1-phenylhept-4-en-3-one 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-4E-hepten-3-one (5R)-5-methoxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone 1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)-4E-en-3-heptanone 1,7-diphenylhept-4-en-3-one	Cytotoxic/ Anticancer	(11,14,15,17)
7-(4'-hydroxy-3'-methoxyphenyl)-1-phenylhept-4-en-3-one	Anti-inflammatory	(16)

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