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REVIEW ARTICLE: THE GINGER FAMILY: SPICING-UP THE ANTICANCER RESEARCH

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ABSTRACT

Cancer is a fatal and severe disease to the humankind. There are various potent and effective sources such as natural herbs which have various bioactive compounds to combat cancer. *Zingiber officinale* is a perennial herb of the Zingiberaceae family having various medicinal properties as well as anti-oxidant potential. The active secondary metabolites in the ginger contribute to its anti-oxidant and anti-cancer property. Various methods are used in detecting how ginger can be used as an agent to combat diseases. Cytotoxicity and antioxidant assays provide the idea about the cell-viability and anti-oxidant property of ginger. When the production of reactive oxygen species (ROSs) increases in the body, it can have various negative impacts. To nullify these impacts, ginger extract is effective on the cells. The cytotoxic nature and anti-proliferative properties of ginger directly contribute to various cellular mechanisms such as apoptosis which have a significant impact on cancer cells. The results also describe the effect of ginger on free radicals. It is concluded that ginger can be used as an alternative source of anti-cancer drugs as it has been proved to be effective in multiple studies.

***Keywords*:** Anticancer, Antioxidant, Apoptosis, Cancer, Secondary metabolites, *Zingiber officinale*

INTRODUCTION

Cancer is a severe disease of animals that occurs due to various chemical, physical and environmental changes and harm the fundamental unit of life (Sharma *et al*., 2019; Mehta *et al*., 2020). Cancer risk can be reduced if the diet that human consume contains antioxidant nutrients (Ghasemzadeh and Jaafar, 2011). Ayurveda, traditional Indian medicine, has been used in India to combat various diseases since six millennia. The ayurvedic medicines are prepared from various herbal species that help to relieve various disease symptoms and give a better quality to life. According to the worldwide cancer data statistics, lung and breast cancer are relatively more frequent worldwide, consisting of 12.3% of the total number of new cancer cases investigated in 2018. Accumulation of ROSs leads to cellular destruction due to oxidative stress and is directly linked to carcinogenesis (Ansari *et al*., 2016).

Plants are known to be a potent and productive source of anti-cancer and anti-oxidant natural compounds (Ghasemzadeh and Jaafar, 2011). Family '*Zingiberaceae*' is one of the largest family of the order *Zingiberales*. About 1300 species and 50 genera are reported under this family. This family of aromatic and rhizomatous herbs is not only effectively used in cooking as a spice but also contribute as a medicinal herb since ancient times (Kirana *et al*., 2003). 'Zingiberaceae' species are widely used as an alternative medicine to help digestion, sore throat, antiemetic, among others. Extracts of certain 'Zingiberaceae' species have analgesic properties as well (Lakhan *et al*., 2015). Various data suggest that this family of the rhizomes is significantly cultivated in the tropical and subtropical regions of Africa, Asia and America. Indian sub-continent provides favourable climatic conditions for different species of ginger. There are about 1300 species of ginger around the world among which the medicinal properties of few have been recorded. Table 1 presents some species of this family which have been used in various aspects of medicine.

State-of-the-Art

Zingiber officinale (ginger) plants of 'Zingiberaceae' family are known to be cultigen perennial plant with no record of a wild ancestor. Certain chemical factors of ginger species such as gingerol, shogaol, zingerone are known to exhibit active biological properties. The primary chemical constituents in this rhizomatous herb are carbohydrates (50-70%), lipid components (3-8%), terpene and phenols (Grzanna *et al*., 2005). The aroma and taste of ginger are because of mixtures of oils which make-up the volatile components of ginger such as shogaols and gingerols (Prasad and Tyagi, 2015). Ginger has been significantly studied for its pharmacological and biological properties *viz.* antiviral, anticancer, antitumor, antithrombotic and anticholesterolemic (Vimala *et al*., 1999). Ketone components of ginger, such as gingerol, contribute to its spicy aroma.

Anticancer Activity of Ginger Varieties

Among a large number of members under this family, only a few have attractive scientific benefits for the screening of anticancer drugs (Kirana *et al*., 2003). Ginger's bioactive and chemical components are significantly proved to be effective in preventing cancer in several experiments, such as skin carcinogenesis (Murillo *et al*. 2008). The extracts of ginger potentially kill the dividing cancerous cells and do not affect the normal cells (Elkady *et al*., 2012). The essential oils in ginger suppress the superoxides and decrease the dextran and carrageenan-induced acute inflammation by inhibiting the accumulation of reactive oxygen species (Nazhvani *et al*., 2020). The isolated polyphenols from ginger varieties inhibit the cell cycles of various tumour cells, as shown in human cancer cell lines. The secondary metabolite content in gingers, such as flavonoids make it a potential source of natural bioactive compounds. These secondary metabolites are known to be a potential carrier of anti-cancer and anti-ageing factors. Almost all of these components are significant in slowing or abolishing tumorigenesis and may trigger mechanisms that are involved in the death of cancerous cells and inhibit tumour formation (Park *et al*., 2008). Extracts derived from the raw ginger are found to have a high rate of the flavonoid components reducing the rate of cancer. The bioactive components are reported to be compounds like gingerol and shogaols which are present at lower concentrations in the fresh ginger as compared to the dried ones (Jolad *et al*., 2005; Kundu *et al*., 2009). Components like zerumbone are known bioactive components extracted from the rhizomes of *Zingiber Zerumbet*. Zerumboneis an effective chemo-preventive agent against cells of colon and skin cancer (Nakamura *et al*., 2004). It is also proved that *Zerumbone hasa* substantial inhibitory effect on liver cancer and leukaemia through induction of apoptosis (Zhang *et al*., 2012).

Table 1: Species of family "Zingiberaceae" with known medicinal properties.

Common Name	Location	Scientific Name	Medicinal P roperty	Reference
Phlai in "Thai"	Southeast Asia	*Zingiber cassumunar*	Relieving asthmatic symptoms, joint problems, menstrual disorder	(Koontongkaew *et al*., 2014)
Ginger lily, Garland flower.	Nagaland, India	*Hedychium yunnanese*	Not known	(Odyuo *et al*., 2019)
Golden cleome or yellow cleome	Asia, South America and Australia	*Curcuma angustifolia*	Treating pneumonia, diarrhoea and infectious wound	(Sharma *et al*., 2019)
Wild turmeric or Yellow Zedoary	South Asia	*Curcuma aromatica*	Diseases related to skin, cardiovascular and respiratory system.	(Sikha *et al*., 2015)
Turmeric	Southwest India	*Curcuma longa*	Positive impact on the treatment of diabetes mellitus which is a chronic disease	(Karlowicz-Bodalska *et al*., 2017)
Butterfly ginger	Tropical and sub-tropical regions of China, India and different South-East Countries	*Hedychium coronarium*	Used to treat infections of nostrils, tonsillitis and tumour.	(Pachurekar and Dixit, 2017)
Mango ginger	Asia, Africa and Australia	*Curcuma amada*	Used to treat skin diseases, asthma, hiccough and inflammation.	(Samant, 2012)
Not known	Northeast India	*Zingiber dimapurense*	Not known	(Odyuo *et al*., 2019)
Pinecone or shampoo ginger	Southeast Asia	*Zingiber zerumbet*	Used in treatment edema, stomachache, inflammation, indigestion and toothache	(Yob *et al*., 2011)
Malaysian ginger	Southeast Asia	*Zingiber spectabile*	Effective in the treatment of thrombosis, seasickness, migraine and rheumatism.	(Sirirugsa, 1999)
Chinese ginger	Southeast Asia	*Kaempferia pandurata*	Used in the treatment of asthma, diarrhoea, fever and colic disorder.	(Tanjung *et al*., 2013)
Java ginger	India, Indonesia and Malaysia	*Curcuma xanthorhiza Roxb.*	Used to treat bloody diarrhoea, dysentery, fever, stomach disorder	(Sirirugsa, 1999)
Yellow ginger lily or wild ginger	Tropical countries and the eastern Himalayas	*Hedychium flavescens*	Used as Anti-rheumatic, stimulant and anti-pyretic	(Uzma *et al*., 2016)
Red ginger	Tropical countries	*Alpinia purpurata*	Have anti-allergic, cytotoxic, anti-inflammatory properties.	(Chan and Wong, 2015)
Thai ginger	Southeast Asia	*Alpinia galanga*	Used in the treatment of problems related to indigestion, dysentery, colic, and stomach cancer	(Sirirugsa, 1999)
Aromatic Ginger	India, Indonesia and Malaysia	*Kaempferia galangal L.*	Used to treat abdominal pain, swelling and muscular rheumatism	(Sirirugsa, 1999)
Peacock Ginger	Tropical Asia	*Kaempferia rotunda L.*	Used to treat abdominal illness, gastric problem, and stomach ache	(Sirirugsa, 1999)

Other components such as Furanodiene which is a heat-sensitive sesquiterpene extracted from *Curcuma wenyujin*, are involved in the mechanism of inducing extrinsic and intrinsic apoptosis and are effective against uterine and cervix cancers. Studies have reported non-toxic and anti-tumour effects of isocurcumenol which is also a sesquiterpenoid compound isolated from the species of ginger like *Curcumazeoadria*. Isocurcumenol is known to

significantly inhibit the cell proliferation in lung-cancer, leukaemia and lymphoma (Lakshmi *et al*., 2011). Cytotoxic nature and anti-proliferative effects of ginger directly contribute to its ability to trigger cellular mechanisms leading to programmed cell death. Crude methanol extracts of ginger are proved to suppress the division of cancer cell lines such as MCF-7 and MDA-MB-231 (Elkady *et al*., 2012). Subsequently, research showed that the flavonoid components in ginger such as anthocyanin and fisetin, act as potent inhibitors of cancer cell division (Ghasemzadeh *et al*., 2012). Certain cancer studies like that of skin cancer show that the extract of ginger has a potent effect when tested on an experimental murine model. Ginger extracts inhibited the mechanisms of tumorigenesis because of the presence of specific bioactive compounds like 6-gingerol (Katiyar *et al*., 1996). In a study, the effect of ginger extract was checked on rats injected with liver cancer cells. The study revealed the antioxidant properties as well as the lipid peroxidation properties of the ginger extracts (Yusof *et al*., 2009).

The potential metabolites found in ginger's ethanolic and aqueous extracts are found to have a positive effect when administered at a proper dose and time interval. Techniques such as DAPI (4′,6-diamidino-2-phenylindole) staining show that when cancer cells are treated with ginger extracts, the cancer cells showed the condensation of nuclear components, fragmentation of DNA and formation of apoptotic bodies (Elkady *et al*., 2012). Oral squamous cell carcinoma is known to be one of the most prevalent head and neck cancer on which the ginger extracts have proven to be effective with an IC_{30} value of 58mg/mL (Nazhvani *et al*., 2020) It has been shown that ginger extract affects various families of regulatory proteins that play an essential role in the induction of apoptosis (Elkady *et al*., 2012). By using the cytotoxicity analysis, the IC_{50} value of the ginger extracts can be determined. The IC_{30} and IC_{50} value is that concentration of the extract, which prevents the growth of 30% and 50% of the cancer cells in culture, respectively (Kirana *et al*., 2003). Reactive oxygen species which are continuously formed by the human body are responsible for cellular destruction and progression of tumorigenesis (Ahmad *et al*., 2006). Thus, tissues can be protected by using various extracellular anti-oxidant produced by natural sources such as ginger.

The results of various experiments provide us with scientific evidence of impacts of extracts of different varieties of ginger on a panel of cell lines. It has been suggested that when the cancer cell lines are treated with the ginger extract, there is cell death in a dose-dependent manner of cancer cells. However, the normal cells remain relatively unaffected. When the comparisons are made between the IC_{50} values of aqueous and ethanol extract studies, show that the ethanol extract are more anti-proliferative than that of aqueous extract (Elkady *et al*., 2012); Ansari *et al*., 2016). A study on MCF7 cell line established that curcumin which is ayellow pigment extracted from *Curcuma longa*, has anti-proliferative effects on the MCF7 cell lines (Koohpar *et al*., 2015). Different parts of the plant *Zingiber officinale* are known to have a different composition of phenolic and flavonoid components. The polyphenolic components of ginger extract are known to have significant antioxidant properties due to the redox potential, which helps in neutralizing and absorbing the free radicals (Ghasemzadeh and Jaafar, 2011). Various studies also showed that quercetin, a flavonoid component of the ginger extract, hasan anti-cancer activity which stops the division of cancer cells (Elattar and Virji, 2000). Extract of the aerial part of the ginger plant is more potent in terms of antioxidant property than that of rhizomes (Rahman *et al*., 2011). From a study on the antioxidant properties of curcumin, at least 50% inhibition of liposome peroxidation was seen when cell lines were treated with the alcoholic extract of about 100µg/mL (Ramsewak *et al*., 2000). According to the available data, significant inhibition of the DPPH radicals was observed in cells treated with extracts of different varieties of ginger. Some of them showed good antioxidant properties whereas others were comparatively ineffective. The alcohol or aqueous extract of ginger thus can be utilized as a free-radical scavenger and also as a primary anti-oxidant (Ghasemzadeh and Jaafar, 2011). Alcohol extract includes the compounds containing phenols and hydroxy-phenols in addition to glycosides, acids or sugars which contribute to the antioxidant property of the species (Kikuzaki and Nakatani, 1993).

The alcohol extract of ginger also shows an anti-proliferative effect on the human cancer cell lines MCF-7, HeLa and MDA-MB-231. The study performed the colony formation assay that measures explicitly the capability of the cancer cell to proliferate in an indefinite and unrestricted manner to undergo neoplastic transformation (Elkady *et al*., 2012; Ansari *et al*., 2016). When treated with the methanol or ethanol extract of ginger, the cells showed slower proliferation and growth. Most flavonoid components are considered to be a major cause of inhibition of the growth of cancerous cells at a concentration range from 1 to 100 mM (Verschoyle *et al*., 2007). When the ginger species are analyzed, it is reported that the ginger species contain significant concentration of fisetin and anthocyanin which have various biological effects on cancer cells (Ghasemzadeh *et al*., 2012). MTT assay was carried out to estimate the cytotoxicity of ginger extract on different cancer cell lines. Effects of components like zerumbone on cancer cell has also been tested using the MTT assay. Studies showedthat when pancreatic cancer cells like PANC-1 were treated with Zerumbone, it significantly reduced the rate of division of the cancerous cells as compared to the untreated cells (Zhang *et al*., 2012). Work done by (Ramsewak *et al*., 2000) on cytotoxicity of curcumins evaluated the effect of curcumin and showed potentcytotoxic activity against the leukemia cell lines like RPMI-8226 and SR.

The morphological characteristics of apoptotic cells were also observed in the cancer cell lines treated with an appropriate concentration of ginger extract. These characteristics include membrane blebbing, condensation of nuclear components and appearance of apoptotic bodies in the cells (Kirana *et al*., 2003). However, the cells untreated with the ginger extract(s) showed normal morphology and growth. These results suggest that ginger extracts inhibit the division of cancer cells resulting in the appearance of apoptotic bodies. Induction of apoptosis is a potent indicator of an effective chemotherapeutic agent against cancer. When the cells were stained with Hoechst stain and visualised under the microscope, the cancer cells treated with the extract showed blue-colored patches indicative of chromatin condensation(Lakshmi *et al*., 2011). Studies on DNA laddering showed that DNA isolated from the untreated cells showed intact DNA on an agarose gel, whereas fragmented DNA bands were observed in the treated cells (Islam *et al*.,

2018). The DNA fragmentation is a characteristic feature of apoptosis (Nagata, 2000). Mitochondria are known to be primary producers of the ROS (Dewaele *et al*., 2010). Data from various studies have shown that the ROS production is suppressed in the cell lines treated with the alcoholic extract of ginger, owing to the anti-oxidant property of the ginger (Park and Pezzuto, 2002). Several studies suggested that cyclin D1 is over expressed in certain cancer cell lines and contributes to carcinogenesis via cell cycle progression at G1/S checkpoint (Gillett *et al*., 1994; Dickson *et al*., 1995). Western blotting analysis of ginger extract-treated cells showed reduced expression of cyclin D1 (Elkady *et al*., 2012). This decline in Cyclin D1 in return, increased the expression of p21 (cip/kip) which is a potent regulator of CDKs and thus plays an essential role in inhibiting cancer progression (Prall *et al*., 1997). It has also been suggested in studies that the transcription factor NFkB which is a pro-inflammatory protein, can trigger tumorigenesis when activated by certain agents (Aggarwal, 2004). The results obtained by (Habib *et al*., 2008)) scientifically proves that the extract of ginger inhibits the over expression of NFkB and TNF in the rats which are injected with ethionine to induce liver cancer. This study is an evidence of the chemo protectant potential of the ginger extracts.

CONCLUSION

The published literature has provided us considerable evidence about ginger and its organic compounds which have an inhibitory effect in the carcinogenic process. Nowadays, ginger is not only preferred for preventing motion or travel sickness but is now also used in cancer chemoprevention. Because of the low-cost, abundance and safety, intensive research is being conducted on ginger and has been exploited for activities like antibacterial, anti-atherosclerotic, anticancerous, antifungal and hypoglycemic. Moreover, ginger is a part of the diet and has additional advantages as it contains various dietary constituents with the ability to improve the degree of protection. In future research should be conducted to understand how environmental factors and genetic variability influence the anti-cancer potential of ginger and its components. Furthermore, clinical trials are also required to gain more information regarding the effectiveness of ginger against cancer as well as other diseases.

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Conflict of Interest

The authors declare no conflict of interest

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