The Ginger Prophecy; A Review of the Underexplored Genus, *Hedychium* against Cancer

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Cancer, the seventh most fatal disease in the world, poses a long struggle to combat this deadly disease. Economically and pharmacologically important members of Zingiberaceae plant family have helped to eradicate a number of ailments worldwide. This review highlights gingers and their wide spectrum of medicinal values focusing on their role as anticancer agents with facts and data obtained from literature review performed using PubMed, PMC, ScienceDirect, Google Scholar in a systematic way. Among the many genera underlined in this review, several species of *Hedychium* have emerged as potential cancer treatments with remarkable activity against different forms of tumour. However this genus is not much explored to unravel its value to medical research. Several species have been found to have cytotoxic, antiinflammatory, antioxidant and antitumour activities but not many attempts made to establish the plant principles as anticancer agents.

Key words: Natural products, cancer, chemoprevention, Zingiberaceae, *Hedychium*

In the traditional medicine, plants have been used for centuries to treat various diseases[1]. Natural products from plants are also used in several therapeutic formulations[2]. These compounds belong to different chemical classes (alkaloids, phenolics, flavonoids, terpenoids) and have diverse complex chemical structures. Natural products contributed many drugs that are currently available in the market for the treatment of a number of diseases[3].

Cancer is a disease occurring at an alarming rate in the last few decades throughout the world. It is a multifactorial disease, which results in uncontrolled growth of cells and their invasion leads to the formation of tumour in the human body. There has been a steep rise in the number of cases where patients have been reported to be suffering from various kinds of cancers[4]. This may be attributed to the change in food habits, excessive consumption of tobacco and alcohol, chronic infections, exposure to harmful radiations and chemicals, industry waste/fumes or more widely due to change in lifestyle and environmental pollution[5]. Cancer is among the leading causes of death worldwide. With figures obtained from GLOBOCAN 2018, there has been 18.1 million cases of cancer incidence and 9.6 million cases of human mortality occurred due to cancers reported worldwide[6]. The mortality rate of cancer patients is enormous. The situation is much critical in economically challenged countries like Africa due to the lack of education, infrastructure, medicinal amenities, diagnostic services and high cost of the treatments[7].

Natural plant products are under exploration to discover new chemical entities as anticancer agents which is also one of the breeding areas of research in the scientific field. Natural products are inexpensive, easily available, mostly beneficial to human health, which makes their use more popular among the public generally but also easily accessible for research and at most times prove to be better forms of alternative medicine.

Among the natural plant resources, Angiosperms are a huge reservoir of products with medicinal values[8]. One such plant family with significant pharmacological gravity is the family of gingers, the Zingiberaceae, which consisted of annual or perennial herbs with creeping horizontal or tuberous rhizomes[9]. The

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family comprises of 50 genera and about 1500 species distributed throughout tropical Asia[10]. The gingers mostly need shady, humid environments with timely water showers for proper growth.

The plant family Zingiberaceae is a paramount natural resource that provides many useful products for food, spices, medicines, dyes, perfume and aesthetics[11]. It constitutes a family of rhizomatous, aromatic medicinal plants characterised by the presence of volatile oils and oleoresins[12]. The plants are widely distributed mostly in tropical and subtropical regions of Asia especially Thailand, Indonesia, Malaysia, India as well as in America and Australia[13]. *Curcuma*, *Kaempferia*, *Hedychium*, *Amomum*, *Zingiber*, *Alpinia*, *Elettaria* and *Costus* are some of the economically important genera of Zingiberaceae. These are all well known for traditional medicinal uses[12].

The rhizomes of the plants of this family are predominantly aromatic, analeptic and stimulant. They are rich sources of essential oils that consist of numerous complex terpenoid mixtures. Many terpenoid compounds with varied physiological activities, antimicrobial, antiarthritic, antioxidant, anticancer, antiinflammatory, antidiabetic, antiHIV and neuroprotectives have been identified in the essential oils of ginger plants[14]. Considering the wide range of pharmacological activities possessed by the various genera of gingers, which also makes them economically cardinal, their uses have been compiled and represented in Table 1[15-44].

Apart from the broad range of pharmacological activities possessed by the different ginger genera, many members are reported to have important anticancer activities[45]. Gingers besides being commonly used as spices and flavouring agents by local people worldwide, they are an essential and frequently available source of antiinflammatory constituents, which can be utilised to combat various forms of cancer or so as to prevent its occurrence[46,47]. These gingers could play an essential role in developing anticancer drugs. The attempt of making use of edible ginger forms to prevent or treat cancer accounts to its contribution to chemoprevention. Table 2[48-72] is a compilation of common gingers and their reported anticancer activity. The various disadvantages of chemotherapy, which involves treatment of cancers with standard chemical therapeutic drugs include several side effects like nausea, loss of appetite, hair loss, anaemia and vomiting[73]. Other than these, treatment at high cost, longer time span and the pain the patient suffers post treatment are also a matter of concern. Chemotherapy is usually clubbed with surgery and radiation therapy. In addition to that, targeted therapy[74], neoadjuvant therapy[75], immunotherapy[76], treatment with herbal medicines and natural sources

TABLE 1: GINGERS WITH PHARMACOLOGICAL AND ECONOMICAL IMPORTANCE[15-44]

Botanical name (common name)	Parts used	Bioactivity
Alpinia galanga (Linn.) Willd. (greater galangal/ blue ginger)	Rhizome	Antiinflammatory[15], antiallergic[16], gastroprotective[17], cytotoxic[18], neuroprotective effect[19]
Alpinia nigra BURTT.	Tender shoot and rhizome	Fluckicidal[20], antimycobacterial[21]
Amomum aromaticum Roxb. (Bengal cardamom)	Seeds	Antimycobacterial[21], antileishmanial[22]
Amomum subulatum Roxb. (black cardamom)	Pods	Treatment of cardiovascular diseases[23], hepatoprotective[24]
Curcuma amada Roxb.(mango ginger)	Rhizome	Cholesterol lowering activity[25], antioxidant and antibacterial[26] , antitubercular[27]
Curcuma longa L. (turmeric)	Rhizome	Antiinflammatory[28], antioxidant[29], antifungal[30], antitumour[31], antidepressant[32], antiviral effect[33], treatment of cardiovascular diseases[23]
Curcuma zedoaria Rosc. (Zedoary)	Rhizome	Antiinflammatory[34], anticancer activity [35], antiangiogenic effect[36]
Elettaria cardamomum (Green/true cardamomum)	Seeds and pods	Antispasmodic[36]
Kaempferia galanga L. (sand ginger/resurrection lily)	Leaves and rhizomes	Vasorelaxant[37], larvicidal activity[38]
Kaempferia rotunda L.(Bhumichampa)	Leaves and rhizomes	Insecticidal[39]
Zingiber officinale Rosc. (garden ginger)	Rhizome	Antioxidant[40], treatment of cardiovascular diseases[23], antiobesity[41], anticancer[42], antinausea/vomiting[43]
Zingiber zerumbet Smith. (bitter ginger)	Rhizome	Anticancer, antiinflammatory, antiHIV, antiAlzheimer's disease, multipotential bioactivities[44], antileishmanial[22]

TABLE 2: COMMON GINGERS AND THEIR ANTICANCER ROLES[48-72]

Anticancer agent	Plant source	Cancer cell line(s) tested/cancer type
Acetoxyeugenol acetate, acetoxychavicol acetate, isocoronarin D, caryolane	*Alpinia galanga* (rhizome)	HeLa, A549, HepG2, SMMC-7721[48]
Galangin	*Alpinia officinarum* (rhizome)	B16[49]
Yakuchinones A and B	*Alpinia oxyphylla*	HL-60[50] HepG2[51], HepG2, BEL-7402, SMMC-7721, Hep3B[52]
Volatile oils	*Alpinia officinarum*	A549[53]
Caffeic acid, apigenin, curcumin, pinnocambrin	*Alpinia pricei* (rhizome)	CH 27, HL 60, A 549[54]
Curcumin	*Curcuma sp* (rhizome)	Prostate cancer, MCF 7, MDA MB 231, BT474, Pancreatic, Colorectal, Daltons lymphoma cells[55,56]
Isocurcumenol	*Curcuma zedoaria* (rhizome)	A549, KB, K562[57]
Curcumin	*Curcuma zedoaria* (rhizome)	CORL 23, PC3[58]
- -	*Curcuma amada* (rhizome)	MCF 7, HBL 100, MDA MB 231[59]
Curcumol	Curcuma kwangsiensis	LoVa, SW480[60]
Curcumin	Curcuma longa	A549[61], PC3[62], melanoma[63]
A-zingiberene, gingerol	*Zingiber officinale* (rhizome)	HeLa, SiHa[64], HCT116, SW480, LoVo[65], MDA-MB-231[66]
Zerumbone	*Zingiber zerumbet* (rhizome)	CHL-1[67]
Extract	*Etlingera elatior*	B16[68]
Protocatechuic acids, syringic acid, ferulic acid, rutin, apigenin, kaempferol	*Roscoea purpurea* (rhizome)	SiHa, A 549,CHOK 1,C-6[69]
Extract	*Kaempferia parviflora*	SKOV3[70]
Panduratin A	*Kaempferia pandurata* (rhizome)	HepG2[71]
Panduratin A	*Boesenbergia pandurata* (rhizome)	MCF 7, HT 29[72]

(as complementary and alternative medicines)[77] are also used for therapeutic purpose.

In the present review, the therapeutic activity of *Hedychium* is highlighted with latest studies performed in past 10 y and related information from past two decades mostly. *Hedychium* is an important member of plant family Zingiberaceae, not explored adequately for its anticancer activity till date.

An introduction to *Hedychium*:

Among the economically known genera one such important genus is *Hedychium,* which consists of about 80 species and is among the well-known genera of Zingiberaceae because of its striking foliage, diversified flamboyant flowers and sweet aroma[78]. *Hedychium* genus is spread throughout tropical and temperate Asia (China, Indian subcontinent and Southeast Asia) and Madagascar[79-81]. The genus *Hedychium* was established by Koenig in 1783, based on the type species *H. coronarium* Koenig. Many species of *Hedychium* possess some pharmaceutical importance[82]. This makes the genus economically popular. *Hedychium* emerge during the monsoon season and hence need to be kept warm, wet and well-nourished in the summers. The plant demands well drained soil which can retain optimum moisture[83].

This review highlights the therapeutic uses of a few popular and important genera of ginger family with emphasis on *Hedychium* species and the active antitumour principles, which have been analysed and are under local use. It was observed that not many species of the genus have been examined for cytotoxic or antitumour potential. Out of the ones studied, only a few have been analysed in details but still not propelled towards development as a drug for chemoprevention. Rest of the species have only been studied at elementary level. It can be concluded conclusively that *Hedychium* is an underexplored genus with ample pharmaceutical values not discovered or utilized to its complete potential.

General medicinal values and antitumour activity of selected species of *Hedychium*:

Hedychium coronarium J. Koenig is an extremely popular medicinal plant. The plant is hardy in nature growing at high altitudes in the foothills of Himalayas extending from east Nepal through India to China. An essential oil obtained from the rhizome has anthelmintic, carminative and antibiotic properties. The common names of the plant append white ginger lily, *dolan chapa* (Bengali) and *Gulbakawali* (Hindi)[84]. The plant possesses antihypertensive and diuretic properties[85].

Different extracts of the plant exhibit antiinflammatory activity by inhibiting 5-lipoxygenase[86], possesses analgesic effects[87] and leishmanicidal activities[88]. Aqueous extract of the plant was found to lower glycaemia in diabetic rodent models[89]. Suresh *et al.*[90] showed the presence of two new labdane diterpenes along with coronarin D and C, coronarin D methyl ether, cryptomeridiol, hedychenone, pacovatinin, 6-oxo-7,11,13-labdatriene-16,15-olide, 4-hydroxy-3-methoxy cinnamaldehyde and 4-hydroxy-3-methoxy ethyl cinnamate from the plant with cytotoxic effects on A-549 (lung cancer), SK-N-SH (human neuroblastoma), MCF-7 (breast cancer) and HeLa (cervical cancer) cell lines. Similar work carried out by Zhan and colleagues showed positive cytotoxic and antiinflammatory effects of common isolates upon B16, HT-29, HeLa and HepG2 cell lines[91]. During inflammatory reciprocation, activation of the nuclear transcription factor-kB (NF-kB) is an essential step[92]. The event of activation of NF-kB transcription factor is involved in process of inflammation, cell multiplication and oncogenic operations[93].

Popular for its antiinflammatory activity, presence of 4 isolates in the plant namely 7-β-hydroxycalcaratarin A, calcaratarin A, coronarin A and E-labda-(17), 12-diene-15,16-dial were found in the plant possessing antiinflammatory potential which supports the traditional use of the plant in the prevention or treatment of various inflammatory diseases[94]. coronarin D has been shown to constrain the activation of the NF-kB pathway induced by different carcinogens and pro-inflammatory molecules and also debilitate the expression of constitutive NF-kB[95]. Chen and co-workers[96] reported that coronarin D induced ROS-mediated death in human nasopharyngeal cells by activating JNK along with inhibition of p38 MAPK whereas Giron and co-workers[95] found that coronarin D inhibits NF-kB also by down regulating IKK activation.

Panigrahy and co-workers[97] showed that different extracts from the rhizome of the plant were found to be rich in total phenolic content and antioxidant capacity. This establishes *H. coronarium* as a potential resource of bioactive molecules which may be utilized as a remedy to treat diseases which result due to oxidative stress.

In an oncology based study it was seen that the methanol extracts of *H. coronarium* exhibited anticancer activity and acts as a potent growth suppressive agent against human breast cancer MCF-7 cells *in vitro*[98]. A very recent study reported about the ethanol extracts of the plant exhibiting considerable antiproliferative effect upon HeLa cervical cancer cells. The extract treatment led to upregulation of Bax and conversely acting on Bcl2. It also led to arrest of the cell cycle at G1 phase with increased levels of p21 and p53 with downrigger of CDK4, 6 and cycD1. The extracts could activate the caspase signalling cascade with enhanced roles of caspase 9, 8 and 3. It successfully downregulated MMP2 and 9 and thus inhibited the migratory capacity of HeLa cells[99].

H. spicatum (Ham-ex-Smith) is a perpetual rhizomatous herbaceous plant. Commonly called *Shati*, *Ban Haldi* and *Kapur Kachri* (Hindi), the plant is distributed in subtropical Himalayan range including Uttarakhand, Assam, Arunachal Pradesh at fairly high altitudes and extreme cold temperatures[100]. Pharmacologically, *H. spicatum* is widely used to treat several diseases. Sravani and Paarakh[101] presented a detailed overview on the plant where they mentioned about the plant to be possessing antiinflammatory, analgesic, antifungal, hypotensive, antipyretic properties and it also helps in indigestion, bronchitis and treatment of eye diseases. The rhizome also exhibits spasmolytic, vasodilatory, hypoglycaemic, hypotensive, antimicrobial and antioxidant activities[102]. Tandon *et al.* defined the analgesic potential of the plant[103]. Decoction of the plant is used to treat cold and cough in Nepal[104].

The anticancer potentials of *H. spicatum* have been studied in the past few years. Results of the MTT assay carried out with the methanol extracts of *H. spicatum* upon HeLa cervical cancer cells presented an IC_{50} value of 48.77 ppm hinting at the plant to be a promising anticancer drug aspirant[105]. Reddy *et al.*[106] isolated two new labdane diterpenes from the plant. Compound 1 had significant cytotoxic role upon Colo 205, CHO, MCF-7 and A459 cell lines. Compound 2 showed good killing effect upon the CHO cells. Bhatt and co-workers[107] concluded that the phenolic tocopherol content in *H. spicatum* was significantly high in one year old planted rhizome. Tocopherol is a known antioxidant compound which possesses biological activities such as immune stimulation and alteration of metabolic activation of proto-oncogenes[108] and hence assists in cancer prevention.

H. thyrsiforme is synonymously called *Gandasulium thyrsiforme* (Sm.) Kuntze. The plant is localised in India, Nepal, Bangladesh and Vietnam[109]. The plant has not been evaluated for pharmacological values other than an account of its antioxidant

and anticancer activity reported by Jasril *et al.*[110]. The team analysed n-hexane and dichloromethane extracts from the rhizome of the plant. They isolated 5-kaempferol type flavonoids, 3,7,4'-trimethoxy-5-hydroxyflavone, ermanin, 3,7,4'-trimethoxy5,7-dihydroxyflavone, 3,5,7,4'-tetramethoxyflavone and 7,4'-didimethoxy-3,5-dihydroxyflavone. Compounds ermanin, 3,7,4'-trimethoxy5,7-dihydroxyflavone and 7,4'-didimethoxy-3,5-dihydroxyflavone depicted fine antioxidant property. Antitumour capability of these compounds was assessed to evaluate their inhibitory role towards activation of EBV in Raji cells. All 5 compounds showed sturdy inhibition at concentrations as low as 10 µg/ml. This study attempted to corelate the antioxidant and antitumour role of the plant rich in flavonoids as latter are well known antioxidants[111]. They also inculcate antiinflammatory, antiviral, antiangiogenic, anticarcinogenic properties[112]. With only a single evidence about the antitumour potential of the plant *H. thyrsiforme*, the plant appears to be an important natural provenance for anticancer remedies which has not faced much exploitation yet.

H. ellipticum Buch. is locally called *Pankhaful* (Hindi). The plant is localised in Nepal, Bhutan, Thailand and Vietnam[113]. The plant holds several pharmacological values. The tuber of the plant is used in the treatment of liver disorders and is contained with antiinflammatory activity[114]. The n-hexane and dichloromethane extracts of the rhizome of the plant was evaluated with good antituberculosis activity against the strain H37Ra[115]. The main essential oils from *H. ellipticum* studied using GC-FID and GC-MS by Thanh *et al.* were (11 %) β-pinene, (18.3 %) α-pinene and (40.8 %) 1,8-cineole in the roots of the plant. The leaves contained (9.2 %) bornyl acetate, (11.8 %) β-pinene and (15.9 %) nerolidol[116]. Cineole or eucalyptol is found to supress expression of COX-2 through UVB-induced carcinogenesis in HaCaT cells and also inhibit generation of prostaglandin E2 in the cells[117]. Pinene also, is found to reduce the growth of tumour in mice[118]. Nerolidol is reported to possess anticancer activity upon HeLa cancer cells with an IC_{50} as low as 1.5 µM[119]. Songsri and Nuntawong[115] reported isolation of 10 labdane diterpenoids from the rhizomes of the plant, among which, coronarin E, coronarin D, villosin, 15-methoxylabda-8(17),11,13-trien-15, 16-olide and 16-hydroxylabda-8(17),1113rien-15, 16-olide were found to possess good antitumour activity. Villosin, 15-methoxylabda-8(17),11,13-trien-15, 16-olide and 16-hydroxylabda-8(17),11,13-trien-15, 16-olide were also tested upon KB (oral cavity), MCF-7 (breast) and A-549 (lung) cancer cell lines and were evaluated to be powered with considerable cytotoxicity. According to previous and latest reports, coronarin E is shown to have positive cytotoxic effect on HL-60 (leukemic), THP-1 (leukemic), A-375 (melanoma) and A549 (lung) cancer cell lines[106]. Similarly, coronarin D was found to have induced apoptosis and G2/M cell cycle arrest in human oral cancer cell lines SAS and SCC-9[120].

H. yunnanense are perennial herbaceous plants which have rotund fleshy rhizomes. The plant is native to Vietnam, south-east and south-central China. It grows with a single inflorescence[121]. Qing *et al.*[122] prepared crude extracts of *H. yunnanense* which were tested *in vivo* for assessing the anticancer potential of yunnancoronarin A and hedychenone. It was found that the compounds showed significantly inhibitory effects on H22 tumour in ICR mice. Yunnancoronarin A displayed the strongest suppression, with the inhibitory ratio of 54.27 %. Yunnancoronarin C also showed durable anticancer effect on human breast cancer cell line MDA-MB-231 *in vitro*. Another work done by Li and colleagues[123] reported the use of rhizomes of *H. yunnanense* collected from Yunnan. The ethanol extracts were subjected to column chromatography, which eluted a novel labdane diterpene, hedychenoid B and two other known compounds hedychenone and villosin, all of which exerted cytotoxic effects against SGC-7901 (gastric cancer) cell line with extremely low IC_{50} concentrations. The latter two also showed cytotoxicity against HeLa with considerably low IC_{50} values. Evidently, the plant contained compounds with remarkable therapeutic potential but unfortunately these species were not explored to realise their medicinal potential. It can be concluded that this ginger is an important natural resource as an anticancer remedy which needs exposure by the research arena for development of better drugs against various forms of cancer.

H. forrestii is a hardy and vigorous plant with white flowers and delightful sweet fragrance. It is commonly known as Forest's hardy ginger lily. General medicinal values have not been well explored. Zhao *et al.*[124] isolated two new labdane diterpenoids, hedyforrestin D and 15-ethoxy-hedyforrestin D along with three other known compounds, yunnancoronarin A, yunnancoronarin B and yunnancoronarin C with the help of column chromatography from the ethanol extract partitioned against ethyl acetate to give a brown oil. The cytotoxic activity of these 5 compounds were

evaluated against A-549 (lung) and K562 (leukaemia) cell lines. Yunnancoronarin A and B were most active (A>B) against lung adenocarcinoma and the activity of these compounds against K562 was in the order of yunnancoronarin B>yunnancoronarin C>yunnancoronarin D>15-ethoxy-hedyforrestin D> hedyforrestin D. In reality, not much work was reported on this ginger variety thus it can be concluded that the plant possessed ample potential to be developed as an anticancer agent which requires further studies.

H. gardenerianum ex ker-Gawl is native to the Himalayas. The essential oil of the plant exhibited antithrombin and antibacterial activity[125]. Arruda *et al*.[126] studied the essential oils of *H. gardnerianum,* which exhibited antiacetylcholinesterase and antioxidant activity making the plant potentially be useful as an adjuvant in treatment of Alzheimer's disease. Kumrit *et al*.[127] reported isolation of 7 labdane diterpenes from this plant, which showed cytotoxic activity. They isolated coronarin E, coronarin A, yunnancoronarin A, yunnancoronarin B, hedyforrestin B, villosin and hedyforrestin C from the rhizome of this plant and tested the cytotoxic activity *in vitro* on lung cancer (NCI-H187) and non-cancerous Vero cells. Villosin displayed most promising cytotoxic potential with an IC_{50} of 0.40 μM against the lung cancer cells, while noncytotoxic even at higher concentrations on Vero cells. These results indicated that the lactone ring was essential for considerable cytotoxic activity. This plant species is also unexplored considering the pharmacological potential the plant holds.

The plant family of Gingers consisted of economically as well as pharmacologically important genera wherein the plants exhibit a wide spectrum of medicinal properties that include antimicrobial, antioxidant and antiinflammatory activities. These gingers are maximally found in the Asian lands and have faced much exploitation in lieu of development of natural drugs against several diseases. *Hedychium* was initially explored and its chemical constituents and pharmaceutical importance has also been depicted in various reports. This review has primarily focused on the antitumour potential of various species of *Hedychium*. *H. coronarium* is a very well-studied member with finely-established anticancer and antiinflammatory role of its active principles on various cancer forms both *in vitro* and *in vivo.* Whereas other members such as *H. thyrsiforme*, *H. gardnerianum*, *H. yunnanense* and *H. forrestii* are the least explored forms in field of cancer biology and thus they are of immense value for research to understand their antitumour potential. A common notable finding in this review is the absence of reports on *in vivo* activity and hence it is not possible to establish chemotherapeutic value of the phytoconstituents of this genus. Species other than *H. coronarium* and *H. spicatum* have not garnered much attention may be due to relative unavailability and medicinally unknown in countries other than south-east Asian countries.

The plant family of Gingers or Zingiberaceae has ample medicinal properties including anticancer capacity. *Hedychium* holds potential with its unexplored members which could make a difference in development of better chemopreventive drugs in future. *Hedychium* is a treasure plant with prepatent in the fight against prevention and treatment of cancers worldwide. *H. coronarium* is the only well studied species in the area of cancer research, while the others are under explored to identify the anticancer potential that they possess. Gain of popularity by different plant species of the genus and knowledge about their usage would provide better treatment options for cancer in near future.

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