Potential Pharmacotherapeutic Phytochemicals from Zingiberaceae for Cancer Prevention

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Indrani Manna, Debalina Das, Sejuty Mondal, and Maumita Bandyopadhyay

Abstract

Cancer, one of the most nefarious maladies, is set to affect one in five of the global population soon. Aberrant uncontrolled cell divisions, proliferation and metastasis are hallmarks of cancer. For quite some time now, numerous cancer prevention and treatment strategies have been formulated with a capricious investment of wealth and resources. The state-of-the-art treatment procedures rely on surgeries, radiation therapies, stem cell induction in conjunction with chemotherapy, immunotherapy and hormonal therapeutics. Yet, these combined treatments are not foolproof often leading to secondary health risks, unspecific outcomes and toxicity. Plant extracts have been used to prevent and cure cancerous growth since times immemorial. In the traditional Indian pharmacopoeia, many phytochemical extracts are listed as potent pharmacotherapeutics against cancer. Zingiberaceae, one of the largest monocot families with a centre of diversity in India, is a promising source of many anti-cancerous, anti-proliferative compounds, attributable to its high polyphenol and flavonoid contents. Principal phytochemicals include curcumin, curcumol, kaempferol, zerumbone, apigenin, galangin, 6-gingerol and 8-gingerol. These compounds are reportedly effective against human colorectal, cervical, breast, lung, ovarian, gastric and liver cancers. Interestingly, the modus-operandi of each compound against cancer cells is unique: curcumin and curcumol reportedly induced apoptosis via p53 regulation and accumulation of ROS/oxidative stress or by modulation of MAPK pathway and inhibition of NF-κB; kaempferol inhibited angiogenesis by suppressing ERK-NFκB-cMyc-p21-VEGF pathway, while apigenin modulated signalling pathways that include PI3K/AKT, MAPK/ERK, JAK/STAT, NF-κB and

I. Manna · D. Das · S. Mondal · M. Bandyopadhyay (✉)
Plant Molecular Cytogenetics Laboratory, Centre of Advanced Study, Department of Botany, Ballygunge Science College, University of Calcutta, Kolkata, India
e-mail: mbbot@caluniv.ac.in

M. Kumar et al. (eds.), *Pharmacotherapeutic Botanicals for Cancer Chemoprevention*, https://doi.org/10.1007/978-981-15-5999-0_10

Wnt/β-catenin pathways and zerumbone caused apoptosis by expression of pro-apoptotic proteins like Bax via cytochrome-c dependent caspase activation, simultaneously decreasing levels of anti-apoptotic proteins like Bcl2. These phytochemicals are effective in cancer cell lines resistant to chemotherapeutic drugs like cisplatin and 5-fluorouracil. Plant-based compounds offer flexibility of usage and diversity of action, affording recourse to most of the woes left behind by systematic and commercial chemical drugs. In this context, the present chapter will thoroughly look into the pros and cons of using phytochemicals of Zingiberaceae on various cancer cell lines, delving into their mode of action, potential side effects, discussing how far research has progressed and what the immediate future holds for us.

Keywords

Cancer · Zingiberaceae · Phytochemicals · Pharmacotherapeutics · Treatment

Abbreviations

AP 1	Activator protein 1
cAMP	Cyclic adenosine monophosphate
COX	Cyclooxygenase
CREB	Cyclic AMP response element binding
EGCG	Epigallocatechin gallate
EGFR	Epidermal growth factor receptor
ERE	Oestrogen responsive element
ERK	Extracellular signal-regulated kinases
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
FOXO	Forkhead box O
FU	Fluorouracil
GSK	Glycogen synthase kinase
HDAC	Histone deacetylases
HIF	Hypoxia-inducible factor
HNSCC	Head and neck squamous cell carcinoma
IL	Interleukin
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NF κB	Nuclear factor-κB
NRF	Nuclear factor erythroid 2-related factor
NSCLC	Non-small cell lung carcinoma
PARP	Poly ADP ribose polymerase
PI3K	Phosphatidylinositol 3-kinase

PTEN	Phosphatase and tensin homolog gene
ROCK	Rho-associated protein kinase
ROS	Reactive Oxygen Species
STAT	Signal transducer and activator of transcription
TGF	Transforming growth factor
TNF	Tumour necrosis factor
uPA	Urokinase plasminogen activator
VEGF	Vascular endothelial growth factor

10.1 Introduction

Cancer is the second largest non-communicable killer worldwide after cardiovascular diseases [1]. In developed and developing countries cancer has emerged as a major concern to public health with high incidence of morbidity [2]. With the third highest number of deaths by cancer registered globally per year, number of cancer patients in India is predicted to increase by a further 25% by the year 2020 (https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/indias-share-in-global-herbal-medicinal-market-just-0-5-government/articleshow/55498419.cms).The National Cancer Prevention and Research Institute confirmed that around 1.7 million new patients would be reported in India by early 2020s, killing at least 0.8 million of those affected, at the rate of around 1300 lives lost per day according to a recent report (http://www.vims.ac.in/blog/cancer-treatment-in-india/. Accessed 07 Jan 2020). While breast cancer is most common in women, oral and lung cancer kills most cancer afflicted men in India (http://ncdirindia.org/NCRP/ALL_NCRP_REPORTS/PBCR_REPORT_2012_2014/ALL_CONTENT/PDF_Printed_Version/Chapter1_Printed.pdf. Accessed 07 Jan 2020). Against the worldwide trend, in India more women are affected by cancer than men (https://www.bbc.com/news/world-asia-india-43539369. Accessed 07 Jan 2020). Recent advancements in terms of cancer drugs and therapeutics have seen a ginormous growth and development of target oriented drugs have opened novel dimensions in cancer treatment but even the most advanced strategies are often rendered ineffective during metastasis [3]. For the last five decades, chemotherapy has been the most common treatment module for cancer patients, though more often than not, these agents cause multiple toxicities in the already cancer-ravaged weakened patients [4], inciting a range of problems like renal failures, cardiovascular problems, myelotoxicity and vasospasm, pulmonary problems, immunosuppression and alopecia [5]. Most of the common and effective chemotherapeutic drugs, like 5-fluorouracil, doxorubicin, bleomycin and cyclophosphamide, cause one or more of these above problems [6]. As recourse to such plight, multiple plant-based products have gained favour of doctors and patients alike for their promise in controlling cancerous growth, as evident in many recent studies. Interestingly, though people of different ethnicities around the world, especially in Asia, Africa and America, have used plants for curing different diseases since times immemorial, in recent times plant-based remedies have found newer proclivity, their usages having increased manifold [7, 8].

Plants have retained prominent status in human civilizations for thousands of years as chief sources of economic, industrial and commercial products. Ayurveda, the ancient Indian system of healing and well-being, is based entirely on plant products [8]. Similar plant-based medicines are prevalent in many Asian and African cultures too. Compounds extracted from terrestrial plants had long been known for their anti-cancerous properties, especially those which are now known to be rich in polyphenols, flavonoids, brassinosteroids, etc. [9]. According to a recent report, approximately 50–60% patients suffering from various cancers in the USA rely on and use plant-based compounds along with prescription drugs and conventional therapies for efficient disease mitigation [10, 11].

The most common mechanism of action of these plant-based compounds includes their effects on expression of P53 protein, NF-κB expression and beginning of apoptosis cascades, reduction of cyclin-dependent proteins like P21 and P27 expression, interfering with or inhibiting pathways like PI3K/Akt/mTOR and associated biochemical changes like reduced acid phosphatase levels and lipid peroxidation, culminating in checking cell cycle proliferation of different cancers [12].

Compounds like curcumin from turmeric, polyphenols from tea, gingerol from ginger, genistein from soybean, resveratrol from red grapes, sulforaphane and isothiocyanates from cruciferous vegetables, lycopene from tomato as well as rosmarinic acid and apigenin from members of Umbelliferae are the most sought after for anti-cancer drug development [11, 13, 14]. While traditional medicinal systems have used plant extracts for cancer treatment for a long time, the first plant metabolite to be adopted for cancer therapeutics was taxol [15].

The search for safer, selectively toxic anti-cancer plant-based drug has been a long and exhaustive one. While many metabolites, like taxol, campothecin, vinca alkaloids, were approved by FDA, USA, for human use and are routinely used as chemotherapeutic agents, they too can induce severe side effects ranging from cardiomyopathy to neurotoxicity. In fact, most anti-cancer drugs developed so far have potent cytotoxicity that would hamper a wide range of cells. In the recent years, with multiple developments, specific agents have been developed that target only tumorigenic pathways and cellular checkpoints. However, presently, many precision drugs have been designed to meet the particular needs of a patient [16]. Chemically, the secondary metabolites exuded by plants have been a wholesome source of anti-tumorigenic, anti-neoplastic compounds. The most common chemotherapeutics, namely taxanes, vinca alkaloids and anti-microtubule compounds like camptothecin and podophyllotoxins, are all originally extracted from various plants [17].

Chemopreventive compounds have been recommended by health care professionals in the recent years because of their manifold health benefits. Figure 10.1 shows a simplified diagram showing types of cancer therapies that can be achieved through plant products. With the rise in so many lifestyle disorders, use of phyto-nutraceuticals has gained much impetus. Compounds like resveratrol, genistein, eriocitrin, apigenin, rosmarine, piperine, andrographolide are some plant derived preventive compounds found mostly in leafy greens and plant-based food items that are being used extensively all across the globe [18–20].Through detailed analyses and trials, many new plant-based compounds have gained popularity, and

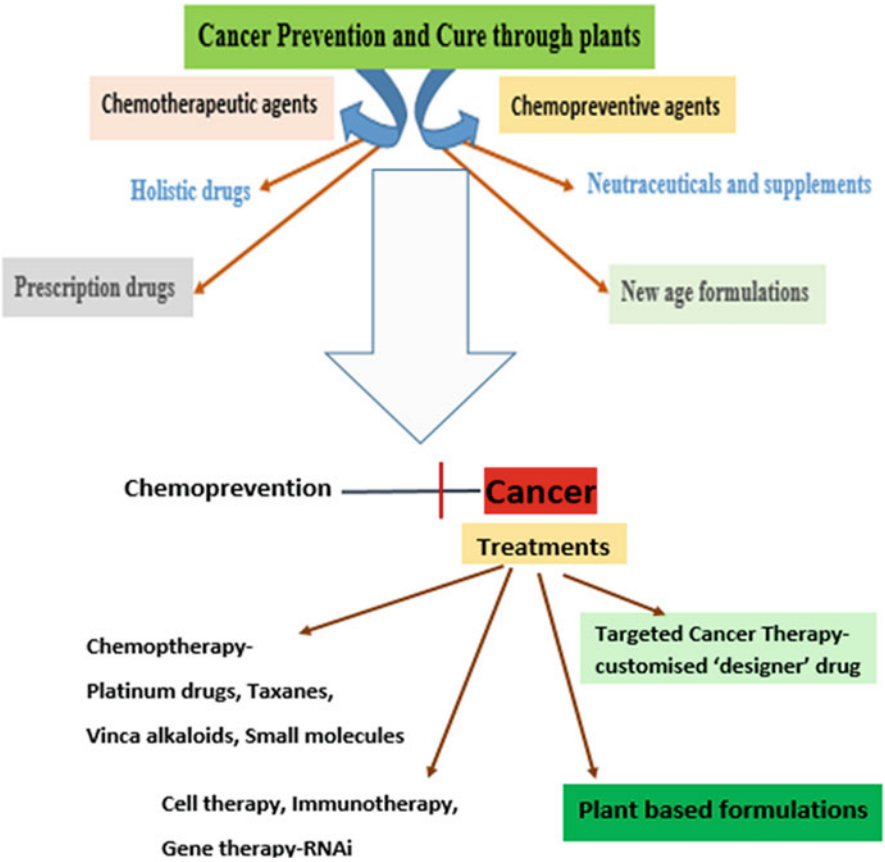


Fig. 10.1 Schematic diagram showing types of cancer therapies based on plant-based products

the global market is around $70 billion; India's share in it is, however, minute, only around 0.5% [3]. Many novel anti-cancer products are now being used in conjunction with other known drugs to better their effectiveness [21, 22]. India has a rich diverse reserve of endemic flora that has long been used as a good repertoire of many indigenous compounds with widespread health benefits.

Zingiberaceae, perhaps the most diverse family in India, has a plush variety of various chemical compounds that could potentially be used as miracle drugs to cure multiple ailments and health conditions. From diabetes to coronary dysfunction to cancer prevention and therapy, this family can provide an elixir for all. Yet it is one of the most underutilized, overlooked family, the main incentive has been put on the use of few rhizomes as herbs and spices. Few compounds like curcumin, gingerol, zerumbone and kaempferol have received both praises and flack for their astounding health benefits, but were soon relegated to obscurity. India already fares poorly when it comes to reaching out, popularizing and marketing its plant products for holistic purposes. Compared to the wide market availability and popularity of Chinese

traditional medicines, Indian products have remained underutilized. In this review, the authors would try to expound and illustrate such underutilized plants of Zingiberaceae family that have gained considerable popularity and scientific interest in the recent years.

10.2 Zingiberaceae: The Wonder Family

Zingiberaceae the 'ginger family' belongs to the order Zingiberales of the monocots and is one of the largest plant families [23], comprising of 52 genera and more than 1200 species worldwide [24]. India has one of the richest diversities of Zingiberaceae, with 20 genera and more than 200 species, including a host of endemic taxa [25]. Members of Zingiberaceae are well known for their medicinal value since times immemorial. A large variety of phytochemicals obtained from different parts of these plants possess potent anti-diabetic, anti-tumour, antioxidant and anti-cancer properties. While members of this family are characterized by presence of rhizomes and in most cases aroma in their leaves [26], chemically they are distinguished by high phenolic and flavonoid contents [27]. Phenolic compounds (phenols and flavonoids) apart from being potent antioxidants have other biological activities like anti-cancer [28, 29], anti-inflammatory [30], anti-diabetic [31] and anti-pyretic [32]. Very recently, anti-obese property of phenolic compounds was also established [33]. The most important genera of medicinal importance from this family are *Alpinia*, *Curcuma* and *Zingiber* [34, 35]. Figure 10.2 shows the diverse nature of this family via few distinct representatives.

Medicinally important phytochemicals from rhizomes and leaves of Zingiberaceae include galangin, apigenin, kaempferol, acacetin, quercetin, alpinetin, rutin, oxyphyllacinol, luteolin [36], curcumin, curcumenol, cineole, pinocembrin, cinnamic-acid, coumaric acid, eugenol, curdione, limonene, cuminyl-alcohol, turmerone, arturmerone, germacrone, ar-curcumene [37], 6-gingerol, 8-gingerol, 10-gingerol, shogaols like 6-shogaol, 8-shogaol, kaempferol, zerumbone, zingerone, zingiberene, cardamonin, α-zingiberene, β-bisabolene, β-sesquiphellandrene, β-bisabolene, β-phellandrene, kaempferol 3-glucuronide, quercetin, sabiene, 3-glucuronide, quercetin 3-glucoside, myricetin, beta-sitosterol, proglumide, convallatoxin, osthol [38]. Out of this array, the principal phytochemicals with reported anti-cancer properties are curcumin, apigenin, galangin, alpinetin, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, zerumbone, kaempferol, zingiberene, zingerone and cardamonin. However, no other secondary metabolite of Zingiberaceae can even come close to the scientific attention that curcumin has merited till date. Figure 10.2 shows some of representatives depicting the morphological diversity in this family.

The following section focuses on the different phenolics and flavonoids found in various members of Zingiberaceae that have potent anti-cancer activities.

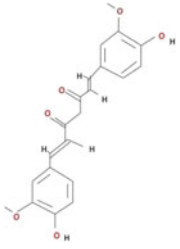
Fig. 10.2 Diversity in Zingiberaceae family—few representatives

10.3 Chemical Nature of Medicinally Important Secondary Metabolites of Zingiberaceae

Curcuma longa (L.), the golden spice of India, is one of the most important species of the genus for its utilities as medicine, spice, food, cosmetics, dye, along with myriad cultural and spiritual importance in Asian countries. Active constituents of turmeric are Curcuminoids, diarylheptanoid or diphenylheptanoid flavonoids and include curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin [39, 40]. Curcumin ($C_{21}H_{20}O_5$), chemically a diferuloyl methane or 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E), was isolated in 1815, and is the principle compound of curcuminoids [41]. Polyphenolic curcuminoids impart the characteristic yellow colour to rhizomes and extracts typically contain 71.5% curcumin (curcumin I), 19.4% demethoxycurcumin (curcumin II) and 9.1% bisdemethoxycurcumin (curcumin III) [42–44]. Apigenin (4′,5,7-trihydroxyflavone) is a dietary flavonoid usually synthesized naturally in rhizomes and leaves of different *Alpinia* species [45]. Galangin (3,5,7-trihydroxyflavone) is a naturally active flavonoid, present in high concentrations in propolis and roots of *Alpinia officinarum* [45]. Alpinetin (ALP,7-hydroxy-5-methoxyflavanone) is a medicinally important plant flavonoid isolated from *Alpinia katsumadai* [46]. The pungent phenolic substances from *Zingiber* species, gingerols and shogaols are generally extracted from *Zingiber officinale.* 6-gingerol (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone) is the most potent anti-cancer compound, while 8-gingerol [5S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) dodecan-3-one], 10-gingerol [(5S)-5-ethoxy-1-(4-hydroxy-3-methoxyphenyl)tetradecan-3-one], 6-shogaol [1-(3,4-dimethoxyphenyl)dec-4-en-3-one], 8-shogaol [1-(4-hydroxy-3-methoxyphenyl)dodec-4-en-3-one] are also promising with respect to cancer inhibition [47]. Zerumbone (2,6,9,9-tetramethylcycloundeca-2,6,10-trien-1-one), a cyclic sesquiterpene, is the main constituent of *Zingiber zerumbet* [48], which has garnered extensive attention in the recent decade for anti-cancer activities. Zingiberene (2-methyl-5-[(2S)-6-methylhept-5-en-2-yl]cyclohexa-1,3-diene) is a sesquiterpene hydrocarbon, isolated from *Zingiber officinale* [49], as is Zingerone (4-(4-hydroxy-3-methoxyphenyl)butan-2-one), a phenolic alkanone in nature [50]. Kaempferol [3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one] is a natural dietary flavonol derived from the rhizome of *Kaempferia galanga* L. [51]. Cardamonin [1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenylprop-2-en-1-one], a chalcone isolated from *Alpinia katsumadai,* is also an emerging anti-cancer phytochemical from Zingiberaceae [52].

The list of such medicinally important secondary metabolites from Zingiberaceae is literally unending with newer ones being characterized regularly. However, an exhaustive table detailing all the reported anti-cancer metabolites of Zingiberaceae, their chemical structures as well as reported activities has been compiled (Table 10.1). The following section focuses on the mode of action of some of the most important compounds that have been elucidated with rigorous scientific research spanning over decades as depicted in Fig. 10.3.

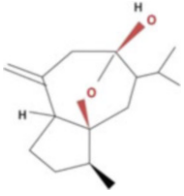
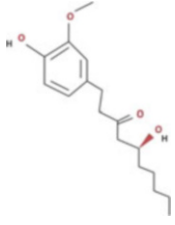
Table 10.1 Different phytochemicals from Zingiberaceae family with their potent anti-cancer activity

Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
Curcumin ($C_{21}H_{20}O_6$)  *Curcuma longa*	Gastric cancer BGC823 and SGC7901 MGC803	Decreased proliferation and inducing apoptosis Inhibition of proliferation	Modulating expression of microRNA 33b (mir-33b) Induction and apoptosis via the mitochondrial pathway	[60, 267]
	Human papillary thyroid carcinoma BCPAP cell line	Papillary thyroid cancer cell invasion and metastasis arrested	Suppression of the TGF/Smad2/3 pathway	[315]
	Head neck squamous cell carcinoma (HNSCC) Fadu cell line (hypopharyngeal cancer) and Cal27 cell line (tongue cancer)	Reduction of cell proliferation and imposes cytotoxic effect	Pro-apoptotic Bik cascade over-expression, decreased pro-survival signalling by AKT and NF-κb	[75]
	Breast cancer cell lines MCF-7 and MDAMB231	Inducing breast cancer apoptosis Inducing cell cycle arrest at the G2/M phase and late S-phase	Regulate the apoptosis-related proteins Regulating Spindle-related signalling pathways	[53, 125]
	Acute myeloid leukaemia Human trial	Attenuated the proliferation and clonogenicity of leukemic cells	Down-regulation of wt1 protein through over-expression of mir-15a/16-1	[61]
	Colorectal cancer Orthotopic mouse model	Inhibition of tumour growth and angiogenesis	Inhibition of NF-κb activation	[79]
	Bone marrow cancer Human multiple myeloma cells U266	Modulated tumorigenic proteins	Inhibition of both constitutive and inducible STAT3 activation	[109]
	Brain cancer LN229	Inhibition of growth, invasion and metastasis	Elevation of either cytostatic and/or cytotoxic effects of some EGFR kinase inhibitors through EGFR pathway	[176]

(continued)

Table 10.1 (continued)

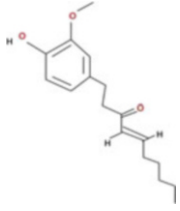
Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Hepatocellular carcinoma Mouse model	concentration- and time-dependent inhibition of migration and invasion	Signalling cascades like EGFR and CAV-1 pathways repressed	[181]
	Oesophageal cancer Raji cells	Inhibition of growth of cancer cells	Notch 1 down-regulation through repression of vital complex proteins	[226]
	Lung 95D and A549	Inhibition of NSCLC proliferation and invasion	Induction of G0/G1cell cycle arrest through MTA1-mediated deactivation of Wnt/β-catenin pathway	[259]
	Prostrate LNCaP	Decreased proliferation, colony formation and cellular motility; enhanced cell–cell aggregation	Interference between the Wnt/β-catenin signalling pathway and androgen receptors	[257]
	Ovarian OVAR3, SKOV3, HO-8910 and A2780	Reduction in mean tumour growth, decreased proliferation and lessened micro-vessel density; significant increase in apoptosis	Induction of apoptosis by down-regulation of HSP27 and HSP70 pathways	[66]
	Oesophageal squamous cell carcinoma cell line EC 109	Apoptosis	Suppression of the PTEN/PI3K/ AKT pathway	[132]
	Human leiomyosarcoma	Cancer cell repression	Modulation cross talk between signal cascades of autophagy and apoptosis	[137]
	Hepatocellular carcinoma/liver cancer SK-Hep-1 Huh7, Hep3B, HepG2 Bel7402, SGC7901, HL60 HA22T	Inhibition of both migration as well as invasion, increase in apoptosis	Decrease in Nf-kβ activation, as well as a lowering of cox-2 levels	[87]
	Pancreatic cancer (Xenograft study) Female mice model	Reduced tumour size, and inhibited tumour angiogenesis	Decrease in the expression of CD31 in addition to that of VEGF and IL-8 indicating suppression of pancreatic carcinoma growth	[83]
	Blood cancer Chronic leukaemia K562	Results in growth arrest and apoptosis	Down-regulation of JAK-STAT3 pathway by suppression of JAK2, cyclin d1 and v-src gene expression	[117]

Curcumol ($C_{15}H_{24}O_2$)  *Curcuma longa*	Nasopharyngeal—CNE-2, NPC 5-8F Breast—MDA-MB-231 Bladder—EJ, T24 Ovarian—SKOV3 Liver—HSC-T6, HepG2 Gastric—AGS MGC—803 Colorectal—LoVo, HCT-116, SW-480	Cell cycle arrest and apoptosis, inhibition of cell proliferation and invasion	Down-regulation of various signalling pathways, lowering of mitochondrial membrane potential, decrease in levels of MMP-9, decrease in levels of cyclins and CDKs	[300]
6-gingerol ($C_{19}H_{30}O_4$)  *Zingiber officinale*	Pancreatic cancer cell BxPC-3 and HPAC cell lines	Cell cycle arrest and cancer cell death	Cyclin A and Cyclin-dependent kinase (Cdk) expression were decreased p53 expression was decreased down-regulation of Rb phosphorylation up regulation of p21	[306]
	Liver cancer AH109A Hep3B PLC/PRF/5 Hep G2	Cell cycle arrest at S-phase Anti-invasive action Anti-invasive action Inhibition of metastasis Improvement of tumourmicroenvironment Apoptosis of cancer cells	Suppresses the production of Hepatocyte Growth Factor (HGF) Inhibition of phosphorylation of mitogen-activated protein kinase (MAPK) Down-regulation of PI3K/Akt signalling Inhibition of translocation of NF-κB Down-regulation of STAT3 pathway Decrease in Microvascular Structural Entropy (MSE) via p-VEGFR2/VEcadherin/β-catenin/ actin pathway Inhibition of de novo fatty acid synthesis via inhibition of carnitine palmitoyltransferase-1 activity	[100, 205, 304, 334]

(continued)

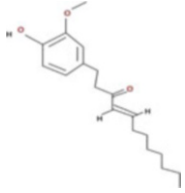
Table 10.1 (continued)

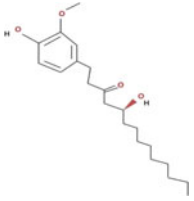
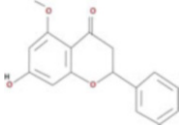
Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Colorectal cancer LoVo HCT-116, SW480, HT-29, LoVo and Caco-2	Cell cycle arrest at the G2/M phase Cell cycle arrest and apoptosis	Trigger the G2/M cell cycle Arrest via down-regulation of cyclin A, CDK2, cyclin B1 and CDK1 Suppressed cyclin D1 expression activation of PKCε and GSK3 pathways Suppresses β-catenin signalling pathway	[100, 303, 305]
	Cervical cancer HeLa, CaSki, SiHa HeLa	Decreased proliferation and apoptosis; cell cycle arrest at G2/M phase Apoptosis (through shrinkage, detachment and membrane blebbing) and cell cycle arrest	ROS generation and p53 reactivation via proteasome inhibition Up regulation of p21-p53/p21 mediated cell cycle arrest Suppression of cyclin D1 Increase in caspase 3/7 activity Down-regulation of PIK3/Akt/ mTOR	[151, 207]
	Oral cancer OSCC, KB, SCC4	Apoptosis (through shrinkage, detachment and membrane blebbing) and cell cycle arrest	Suppression of cyclin D1 Increase in caspase 3/7 activity Down-regulation of PIK3/Akt/ mTOR	[151]
	Retinoblastoma cancer cells RB355 Cell line	Apoptosis and cell cycle arrest	Upregulation of PI3K/Akt signalling pathway	[150]
	Breast cancer MCF-7	Inhibition of metastasis Improvement of tumour microenvironment	Decrease in micro vascular Structural Entropy (MSE) via p-VEGFR2/VEcadherin/β-catenin/ actin pathway	[334]

	Skin cancer Mouse skin Mouse skin	Inhibited skin tumour promotion Inhibits mouse skin tumour promotion and anchorage-independent growth of epidermal growth factor stimulated cultured mouse epidermal cells	Down-regulation of TPA-induced epidermal ornithine decarboxylase activity suppressed NF-κB DNA binding activity in mouse skin Activation of p38 MAPK	[102, 103]
	Bone cancer 143B, MG63	Inhibition of cell proliferation and apoptosis	Activation of AMP-activated protein kinase (AMPK) Activation of caspase cascades Alteration of BCl2 protein	[275]
6-shogaol ($C_{17}H_{24}O_3$)  *Zingiber officinale*	Lung cancer A549 A549	Inhibition of proliferation of cancer cells Pro-apoptotic activity induced Induction of autophagy	Modulation of STAT 3 and MAPK signalling cascade Inhibition of the AKT/mTOR pathway	[118, 154]
	Breast cancer MCF-7 and MDA-MB-231 And cancer stem cells (CSC) MDA-MB-468, MDA-MB-231, MCF-7, and T47D	Induction of autophagy in cancer cells Inhibition of cell proliferation	Modulation of notch signalling pathway Activation of peroxisomal proliferator activated receptor c (PPARc) and suppression of NF-κB signalling	[230, 281]
	Liver cancer Hep3B HepG2	Anti-invasive action Induction of apoptosis	Inhibition of phosphorylation of mitogen-activated protein kinase (MAPK) Down-regulation of PI3K/Akt signalling Inhibition of translocation of NF-κB Down-regulation of STAT3 pathway Caspase activation and endoplasmic reticulum (ER) stress signalling	[100, 280]

(continued)

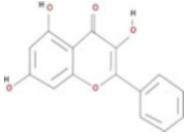
Table 10.1 (continued)

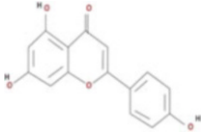
Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Squamous carcinoma SCC4	Inhibition of proliferation of cancer cells Pro-apoptotic activity induced	Modulation of STAT 3 and MAPK signalling cascade	[118]
	Colorectal cancer and colon cancer COLO 205 HT29 and HCT116	Induction of apoptosis Inhibition of cell proliferation	Fas activation, and modulation of GADD153 gene expression Mitochondrial dysfunction (loss of mitochondrial membrane potential), resulting in cytochrome-c release, Caspases activation and apoptotic death Activation of peroxisomal proliferator activated receptor c (PPARc) and suppression of NF-κB signalling	[106, 281]
	Prostate cancer DU145	Inhibition of proliferation of cancer cells Pro-apoptotic activity induced	Modulation of STAT 3 and MAPK signalling cascade	[118]
8-shogaol ($C_{19}H_{28}O_3$)  *Zingiber officinale*	Blood cancer Leukaemia cells	Induction of apoptosis	Reactive oxygen species (ROS) generation, glutathione depletion and caspase activation	[223]

10-gingerol ($C_{21}H_{34}O_4$)  *Zingiber officinale*	Breast cancer MDA-MB-231TNBC	Inhibition of cell proliferation and cell invasion Induction of apoptosis	Suppression of Akt and p38MAPK activity Mitochondrial dysfunction (loss of mitochondrial membrane potential), resulting in cytochrome-c release, Caspases activation	[152, 277]
	Colon cancer HCT 116	Induction of mitochondrial apoptosis	Down-regulation of MAPK signalling pathway	[209]
	Cervical cancer HeLa	Cell cycle arrest and apoptosis	Decrease in phosphorylation of Akt and down-regulation of PIK3/Akt/mTOR pathway and suppression of NF-κB activation	[104]
	Ovarian cancer HEY, OVCAR3, and SKOV-3	Cell cycle arrest at G2/M	Combined effects of decreased expression of cyclin B1 and D3	[307]
Alpinetin ($C_{16}H_{14}O_4$)  *Alpinia katsumadai*	Oral cancer TCA-8113 and CAL-27	Inhibition of cell proliferation	Through miR-211-5p (micro-RNA) upregulation and Notch Pathway Deactivation	[231]
	Gastric cancer AGS N87	Induction of apoptosis and cell cycle arrest at G2/M phase	By translocation of Bax and triggering mitochondrial pathway of apoptosis	[274]
	Pancreatic cancer BxPC-3	Anti-proliferative activity		[298]
	Lung cancer A549, SK-MES-1, NCI-H292, and A549/cis-diammined dichloridoplatium (CDDP)	Inhibition of lung cancer progression and increased sensitization towards chemotherapeutic drug	Inhibition of the PI3K/Akt signalling pathway	[146]
	Colorectal cancer HT-29	Cell cycle arrest at G0/G1 phase and S-phase and apoptosis	p53 mediated cell cycle arrest and Uridine-cytidine kinase 2 (UCK 2) enzyme inhibition	[314]

(continued)

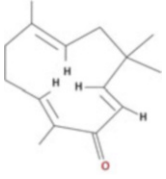
Table 10.1 (continued)

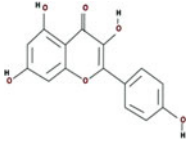
Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Ovarian cancer SKOV3	Inhibition in proliferation and migration of cancer cells, anti-invasive property	Suppression of STAT 3 signalling pathway	[120]
	Brain cancer Glioma stem cells (GSC) U-87, U-251, and U-373	Inhibition of proliferation of cancer stem cells	By suppression of notch signalling pathway	[232]
	Liver cancer	Supresses proliferation of cancer cells and sensitizes those towards chemotherapeutic agents	By the activation of Mitogen-activated protein kinase kinase-7 (MKK7)	[322]
Galangin ($C_{15}H_{10}O_5$)  *Alpinia officinarum*	Kidney cancer or renal cell carcinoma 786-0 and Caki-1 A498	Suppresses EMT and induces apoptosis Inhibition of cell migration and invasion	Increased levels of ROS Down-regulation of PI3K/AKT/ mTOR signalling pathways	[317, 318]
	Hepatocellular carcinoma	Induction of apoptosis	Mitochondrial dysfunction	[268]
	Oesophageal carcinoma Eca9706, TE-1, and EC109 nude mice with xenograft tumours	Inhibition of proliferation	Increased intracellular reactive oxygen species (ROS) levels	[289]
	Cervical cancer HeLa	Induces cell death of cancer cells	Modulating the expression of glyoxalase-1 and Nrf-2	[203]
	Laryngeal carcinoma TU212 and M4e	Suppressed proliferation	Modulation of caspase 3 and AKT signalling pathways	[249]
	Ovarian cancer OVCAR-3 A2780/CP70	Inhibition of angiogenesis	Decrease in levels of AKT	[250]
	Human nasopharyngeal carcinoma	Cell cycle arrest at S-phase	Inhibition of PI3K/AKT signalling pathway	[148]

	Breast cancer MCF-7 and T47D	Induces apoptosis	TRAIL pathway by activating AMPK	[168]
	Human fibrosarcoma HT-1080	Inhibited proliferation	Decrease in MMP-9 expression	[316]
	Brain cancer glioma cells U87, U251 and U87-luciferase and HUVECs	Suppresses EMT and inhibits angiogenesis	Down-regulation of CD44	[96, 251]
	Murine melanoma mice bearing B16F1melanoma tumour	Inhibits cancer	–	[45]
Apigenin ($C_{15}H_{10}O_5$)  *Alpinia galanga*	Breast cancer MDA-MB-231	Cell cycle arrest at G2/M phase	Histone H3 acetylation leading to p21WAF1/CIP1 expression	[302]
	Thyroid cancer (papillary thyroid cancer) BCPAP cells	Induces autophagy	Increase in acidic vesicular organelles (AVOs) formation with respect to control	[204]
	Colorectal cancer and colon cancer SW480 and HCT15 HCT-116 Cisplatin resistant colon cancer cells	Inhibition of migration and cancer cell proliferation Induces apoptosis Induction of autophagy and programmed cell death Inhibits epithelial-mesenchymal transition	Wnt/β-catenin signalling pathway repression extrinsic and intrinsic pathways of apoptosis stimulated Targeting m-TOR/PI3K/Akt signalling pathway targeting NF-κB/Snail signalling pathway	[143, 145, 263, 272, 292, 293]
	Liver cancer HepG2	Induction of autophagy and induction of apoptosis	Inhibition of PI3K/AKT/mTOR signalling pathways	[144]
	Brain cancer U87MG and U373MG	Inhibits cancer stem cell like phenotype	Suppression of c-met signalling	[232, 339]
	Bone cancer U2OS and MG63	Inhibition of proliferation and invasion of cancer cells	Suppression of Wnt/β-catenin signalling pathway	[262]
	Skin cancer B16F10 cells in mouse model	Anti-metastasis	Inhibition of STAT 3 signalling pathway	[291]

(continued)

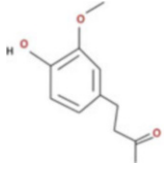
Table 10.1 (continued)

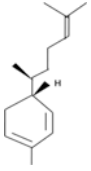
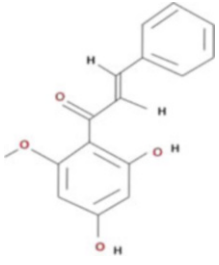
Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Cervical cancer HeLa	Inhibits formation of sphere-like cancer stem cells	Inactivation of casein kinase 2α	[338]
	Oesophageal cancer	Inhibits proliferation of tumour	Inhibits IL-6 transcription	[343]
	Prostate cancer	Inhibits metastasis	Targeting the SPOCK1-snail/slug axis-mediated epithelial-to-mesenchymal transition	[333]
Zerumbone ($C_{15}H_{22}O$)  *Zingiber zerumbet*	Prostate cancer PC3 PC-3 and DU-145	Inhibition of growth of cancer cells Increases paclitaxel sensitivity Induces apoptosis and autophagy	Inhibition of JAK2/STAT3 pathway ER stress and mitochondria insult	[123, 286]
	Kidney cancer Xenograft mice model	Inhibits proliferation and induces apoptosis	Suppression of STAT 3 signalling cascade	[124]
	Gastric cancer SGC-7901	Induction of apoptosis	upregulated Bax levels, and triggered intrinsic pathway of apoptosis	[309]
	Cervical cancer SiHa	Induces cell cycle arrest and apoptosis	Production of ROS and a loss of the mitochondrial membrane potential and triggered intrinsic pathway of apoptosis	[215]
	Oral cancer ORL-48 and ORL-115	Reduces motility and proliferation	Down regulates PI3K/ mTOR signalling	[155]
	Non-small cell lung cancer A549	Suppresses cell invasion	Inhibition of FAK/AKT/ROCK pathway	[156, 330, 331]
	Liver cancer Hep G2 Sprague Dawley Rat model	Suppression of angiogenesis Inhibition of proliferation	Inhibition of MMP-9 activity Apoptosis Anti-proliferative and anti-angiogenic effect	[248, 249]

	Colorectal cancer cells and cancer stem cells (CSC) HCT-116 and SW-48 SW480 HCT-116 and SW480	Inhibits EMT Induces cell cycle arrest and has anti-migratory effect Supresses cancer invasion and metastasis	Inhibition of β-catenin pathway through micro-RNA Decreased mitochondrial membrane potential, and activated caspase cascade (caspase 3, caspase 8 and caspase 9) Modulation of FAk/PI3k/NF-κB-uPA Pathway	[210, 260, 323]
	Oesophageal cancer EC-109	Inhibits proliferation and apoptosis	Alteration of Bcl-2 levels	[310]
	Laryngeal cancer Hep-2	Inhibits proliferation and cell cycle arrest	Down-regulation of cyclin D1	[297]
	Breast cancer	Inhibition of cancer proliferation	Targeting β-catenin of the Wnt–β-catenin pathway	[261]
Kaempferol ($C_{15}H_{10}O_6$)  *Kaempferia galanga*	Prostate cancer LNCaP	Apoptosis	Induction of caspase cascade pathway	[283]
	Skin cancer A375	Cell cycle arrest Inhibition of cell migration Induction of apoptosis	Down-regulation of PI3K/AKT/mTOR signalling pathways	[158]
	Lung cancer A549 A549	Induction of EMT Inhibition of epithelial-mesenchymal transition.	Inhibition of Akt1-mediated phosphorylation of Smad 3 Modulating the expression of E-cadherin and vimentin	[330, 331]
	Kidney cancer 786-O	Inhibition of invasion and migration	Downregulation of EFGR pathway	[191]
	Ovarian cancer A2780 CP70	Promotes apoptosis	TRAIL pathway and death receptors	[171]
	MC3T3-E1 cells		Antioxidant upheaval and mitochondrial dysfunction	[216]

(continued)

Table 10.1 (continued)

Name of phytochemical and source plant	Type of cancer and cell line/ mouse model	Therapeutic effect	Mechanism	Reference
	Colorectal cancer cells	Apoptosis	ROS induction, p53 mediated action of p38 and caspase induction	[284]
	Pancreatic cancer	Cancer cell growth and proliferation inhibited	Blocking of EFGR related signal pathway	[186]
	Human fibrosarcoma HT1080	Inhibition of proliferation	Decrease in MMP-9	[316]
	Cervical cancer HeLa SiHa	Increase in apoptosis Induced apoptosis and inhibited proliferation	Down-regulation of PI3K/AKT and telomerase pathways Disruption of mitochondrial membrane potential and the disturbance of intracellular free Ca^{2+}concentration	[157, 284]
	Lymphoma Daudi cells	Anti-proliferative activity	–	[312]
	Breast cancer MDA-MB-231	Suppresses the migration and invasion	Down-regulation of the activities of RhoA and Rac1	[328]
Zingerone ($C_{11}H_{14}O_3$)  *Zingiber officinale*	Colon cancer HCT-116 Winster rats	Induction of apoptosis – Chemopreventive efficacy	Elevation of ROS Modulation of lipid peroxidation Elevation of ROS	[220–222]
	Breast cancer MCF-7 Experimental rat	Induction of apoptosis	Activation of caspase cascade	[277]
	Liver cancer SNU182 In rat model	Suppresses invasion and migration of cancer cells EMT phenomenon suppression Modulatory effect against cisplatin and radiation induced hepatotoxicity	Inhibition of TGF-β1 pathway Modulation of, p38, MAPK, JNK, ErK1/2 signal transduction cascades	[192, 332]
	Human neuroblastoma cells BALB/c mouse tumour model BE(2)-M17	Cell cycle arrest, inhibition of mitosis	Inhibition of activity of cyclin D1	[313]

	Mouse tumour Renca cells	Suppresses angiogenesis	By inhibition of MMPs	[252]
Zingiberene ($C_{15}H_{24}$)  *Zingiber officinale*	Colon cancer HT-29	Induction of autophagy	Suppression of PI3K/AKT/mTOR pathway	[160]
Cardamonin ($C_{16}H_{14}O_4$)  *Alpinia katsumadai*	Colon cancer and colorectal cancer HCT116 and LOVO cells SW480	Induction of autophagy and inhibition of cancer progression Cell cycle arrest at G2/M Anti-proliferative action	Formation of (LC3)-I–LC3-II, an incorporation of monodansylcadaverine (MDC), a marker for the acidic compartment of AVOs Degradation of β-catenin and thereby down-regulation of Wnt/β-catenin pathway	[264, 296]
	Breast cancer MCF-7, MDA-MB-231 and BT-549	Anti-invasive property Reversal of EMT	Down-regulation of Wnt/β-catenin signalling cascades	[265]
	Lung cancer A549 xenograft in mice A549 and HK1 cells	Cell cycle modulation Caspase dependent apoptosis	Suppression of NF-κB and decrease in expression of cyclin D1 Modulator of mTOR pathway	[105, 159]
	Prostate cancer (PC) PC androgen independent DU145 and androgen dependent LNCaP	Inhibits cancer proliferation and metastasis	Modulation of STAT3 pathway	[121]
	Gastric cancer AGS, MGC-803, BGC-823	Inhibition of cancer cell proliferation	Inhibition of STAT3 activity	[122]
	Skin cancer Human metastatic melanoma cell line A375 (CRL-1619)	Inhibition of cancer proliferation	Apoptosis of tumour cells	[219]

10.4 Generalized Mode of Anti-cancer Action of Some Important Secondary Metabolites of Zingiberaceae

The molecular basis of anti-carcinogenic and chemopreventive activities of curcumin is attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators and cellular signalling molecules. Excitingly, curcumin successfully acts at all three phases of cancer, namely initiation, advancement and development, by targeting critical processes involved in cancer development and progression [53]. The anti-carcinogenic nature of curcumin has been reported in preclinical models of lymphomas, multiple myeloma, leukaemia and brain, pancreatic, gastric and colorectal cancers [54]. Curcumin has been shown to down-regulate production of pro-inflammatory cytokines tumour necrosis factor-α (TNF-α), IL-1β and inhibit transcription factors like Nuclear Factor-κB (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3) and Activator Protein-1 (AP-1), which regulate signal cascades of genes involved in the pro-inflammatory pathways and protective antioxidant functions [55] that play key roles in cancer development and progression. It also inhibits Specificity Protein 1 (Sp-1) and its housekeeping genes to prevent cancer formation, migration and invasion [56]. Inhibition of downstream gene products like c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-α, interleukins (IL) and MMP-9 demonstrates the anti-proliferative property of curcumin. In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumour growth, angiogenesis and metastasis [57]. Apart from action on STAT3 and NF-κB pathways, curcumin has been shown to inhibit cell proliferation, causing cell cycle arrest and stimulating apoptosis via modulation of other transcription factors, such as AP-1, Erg-1, p53, β-catenin, Notch-1, HIF-1 [58]. Curcumin asserts its anti-tumour activity in cancer cells by altering the deregulated cell cycle via cyclin-dependent, p53-dependent as well as p53-independent pathways. Curcumin has major positive influences on key signal transduction pathways of cell cycle and its effectiveness in animal model systems has made it eligible as a 'multiple edged sword' in combating the deadly disease—cancer [59]. Moreover recent studies show that curcumin can exert its anti-proliferative and pro-apoptotic action by modulating the expression of micro-RNA, like miR-33b, in case of gastric cancer lines BGC823 and SGC7901 [60] and down-regulation of Wt-1 protein through miR15a/16-1 in leukemic cells [61]. Figure 10.4 depicts the mode of action of curcumin.

Though many other metabolites from different members of Zingiberaceae are being investigated for their anti-cancer activities, their modes of action are not as thoroughly researched as curcumin. Induction of apoptosis by generation of oxidative stress is known to be induced by flavonoids. Galangin, 6-gingerol, 6-shogaol, zerumbone and kaempferol all reportedly induce ROS and arrest cell proliferation in different types of cancer. Another potent target of anti-cancer drugs is the mitochondria, as mitochondrial dysfunction brings on apoptosis. Galangin, apigenin, alpenitin, 6-gingerol, 6-shogaol, zerumbone and kaempferol are some of the prominent metabolites with proven capacity of inducing mitochondrial dysfunction in

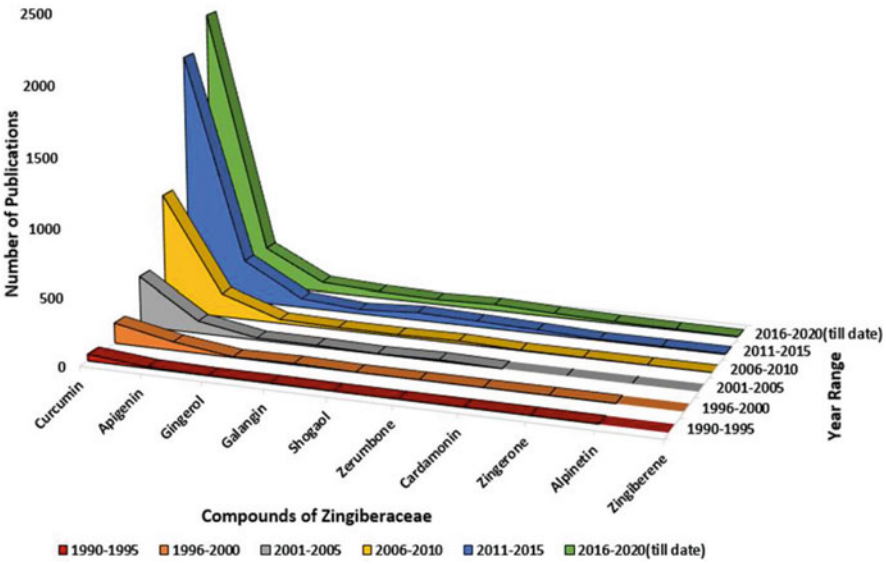


Fig. 10.3 Comparison of the number of research publications pertaining to the different anti-cancerous compounds of Zingiberaceae in the last three decades (data acquired from PubMed Central, accessed on 31 Jan 2020)

different cancer cell lines [46, 47]. Zerumbone and kaempferol are further implicated in the disturbance of the endoplasmic reticulum affecting a number of critical cellular processes that finally culminate in cell death [48, 51]. In some reports, galangin, apigenin, 6-shogaol and zerumbone are shown to interfere with autophagic cascades compromising cancer cell survival and potentiating apoptosis. Along similar lines, many of these compounds are known to modulate different cell cycle checkpoints and ushering in premature cell cycle. Probably the most interesting application of these zingiberaceous metabolites was in compromising cell adhesion and discouraging metastasis, the two most crucial requirements for proliferation of cancer [35].

In the next section, the authors have reviewed the cell signalling cascades and cellular pathways modulating different aspects of cancer induction and progression.

10.5 Cell Signalling Pathways Modulated by Zingiberaceous Metabolites Related to Their Anti-cancer Activities

10.5.1 NF-κB Pathway

Atypical activation of the NF-κB pathway has a significant role in cancer pathogenesis [62–64]. Curcumin can effectively disrupt many of integral activation steps of this pathway, thus promises to be of great use in cancer remediation. Curcumin

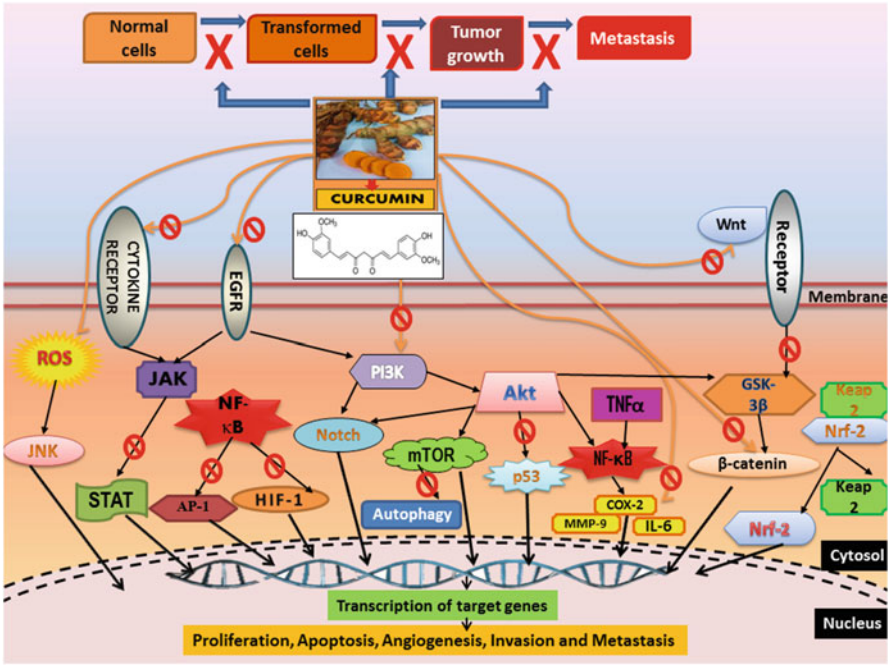


Fig. 10.4 Schematic depiction summarizing the mode of action of curcumin on cancer cells

reportedly blocked TNF-α-induced nuclear translocation of NF-κB, further compromising its DNA binding ability via inhibition of IκBα phosphorylation by down-regulating NF-κB-inducing kinase (NIK) and IκB kinase (IKK), which was followed by degeneration in the most common myeloid leukaemia cell line in human beings [65]. Similarly, curcumin is known to prevent cell proliferation, invasion, metastasis, angiogenesis as well as chemotherapy and radiotherapy resistance of numerous cancers by manifold manipulation of target molecules originally regulated through NF-κB pathway. In colon and ovarian cancer for example, curcumin induced apoptotic behaviour through inhibition of numerous genes namely survivin, BCL-2, specificity protein (Sp) transcription factors (Sp1, Sp3, and Sp4) and Sp-regulated genes, NF-κB (p65 and p50), hepatocyte growth factor receptor (c-MET), and cyclin D1, finally preventing tumorigenesis [53, 66]. On the other hand, in prostate cancer, curcumin promotes deactivation of androgen receptors and androgen receptor-related cofactors encompassing NF-κB as well [67]. Curcumin-induced down-regulation of NF-κB pathway also shows promise in treatment of lung cancer [68]. Hypopharyngeal cancer, one of the most hostile forms of head and neck malignancies with substandard prognosis [69], shows NF-κB playing a crucial link between neoplastic and inflammatory events in epithelial cells [70]. Vageli et al. [71] demonstrated in *in vitro* model that bile-related activation of NF-κB and its transcriptionally activated oncogenic factors can be inhibited by the usage of turmeric supplements (curcumin) in exposed normal human hypopharyngeal cells. Their

discovery indicated that selective dietary supplements with anti-inflammatory and anti-apoptotic properties like curcumin can suppress acidic bile-induced oncogenic mRNA phenotype in human hypopharyngeal cells and may be useful for the prevention of extra-oesophageal reflux-related hypopharyngeal neoplasia. The fact that NF-κB inhibition could effectively decrease the expression of genes with cell proliferation or anti-apoptotic function in Head and Neck Squamous Cell Carcinoma (HNSCC) and the role of curcumin in potentiating it was also supported by various reports [72–75]. In breast cancer cells, the survival signalling molecules such as NF-κB play a pivotal role in cell proliferation [76]. It was reported that curcumin was able to inhibit NF-κB expression and toggled many downstream signalling pathways, silencing inflammatory cytokines (CXCL1 and CXCL2) and upregulating expression of matrix metalloproteinase 9 (MMP-9) in breast cancer cell lines [77], as well as repression of urokinase plasminogen activator (uPA), uPA receptor (uPAR), intercellular adhesion molecule 1 (ICAM-1) and chemokine receptor 4 (CXCR4) [78] ultimately leading to inhibition of colorectal cancer as well [79]. Reports reveal that effectiveness of curcumin and its cohorts in preventing breast cancer cell growth and invasion could partially be regulated through downregulation of NF-κB signalling pathways [80] and downregulation of the insulin-like growth factor 1 (IGF-1) signal cascades [81].

Preclinical studies have demonstrated that curcumin exerts anti-cancer effects against the deadly pancreatic cancer (PC) by modulating multiple molecular targets [82]. Curcumin can hinder survival of PC cells, under both in vitro and in vivo conditions, rendering activities of essential factors and modulators of different signalling cascades like COX-2, NF-κB, CD-31, VEGF- and IL-8 useless [83]. In vitro studies have shown potent cytotoxic effects of curcumin on different PC cell lines including MiaPaCa-2, Panc-1, AsPC-1 and BxPC-3. In addition, in vivo studies on PC models have shown that the anti-proliferative effects of curcumin are caused by inhibition of oxidative stress and angiogenesis through induction of apoptosis [84, 85]. Li et al. [83] demonstrated that curcumin down-regulated NF-κB and associated growth control molecules in human pancreatic cells in a time and dose-dependent manner. These effects were accompanied by marked growth inhibition and apoptosis, which was confirmed by other studies as well [86]. In hepatocellular carcinoma liver cancer cell lines SK-Hep-1, Huh7, etc. curcumin induced decreased NF-κB expression and lowering of COX-2 levels which led to inhibition of both migration and invasion of cancer cells [87]. Jutooru et al. [88] showed that curcumin inhibited NF-κB expression and cancer cell growth by down-regulation of the specificity protein Sp1. Tolfenamic acid and dietary spice curcumin co-treatment reportedly enhanced anti-proliferative effect in PC cells through Sp1 suppression, disruption of NF-κB translocation to the nucleus and cell cycle phase distribution [89]. Marquardt et al. [90] evaluated cancer cell depleting potential of NF-κB inhibition in liver cancer achieved by its inhibitor curcumin. Their work demonstrated that blocking NF-κB specifically target cancer stem cell populations and suggest a potential for combined inhibition of NF-κB and HDAC signalling for treatment of liver cancer patients with poor prognosis. This study along with others

uncovered the potential of curcumin to diminish growth of difficult to treat hepatocellular cancer [91, 92].

The gamut of activities of other zingiberaceous metabolites echoes the action of curcumin on NF-κB. Clinical administration of extracted apigenin has shown to inhibit NF-κB activation in in vivo TRAMP mice models [93] and blocks IKKα activation as well as suppresses prostate cancer progression [94], however, apigenin did not show any inhibitory effect on NF-κB in A549-non-small cell lung cancer cell lines in human, but it did suppress translocation of NF-κB from to the nucleus [95], similar to curcumin's action as mentioned earlier. Galangin also inhibited activity of nuclear factor kappa B (NF-κB) and its binding activity to activator protein1 (AP-1) [96]. NF-κB inhibition and concomitant inhibition of MEK-ERK signalling occurred upon treatment of ovarian cancer cells with kaempferol [97, 98]. 6-Gingerol (6G), on the other hand, reportedly inhibited NF-κB activity and hence suppressed NF-κB pathway in liver cells [99, 100] and in cervical cancer cells as well [101]. Similar observations were reported in mouse skin where 6G application suppressed NF-κB DNA binding ability and activation of p53 MAPK [102, 103], as does 10-gingerol in cervical cancer according to reports [104]. Cardamonin is also known to modulate cell cycle through suppression of NF-κB and decrease in cyclin D1 expression in lung cancer A549 xenograft in mice [105]. 6-shogaol is reported to activate PPARc and suppress NF-κB expression in colorectal cancer lines HT29 and HCT116 inhibiting cancer proliferation [106].

10.5.2 STAT3 Pathway

STAT3, a pro-inflammatory transcription factor, is responsible for controlling and onset of various cancers [107]. Both chemo- and radioresistance in cancer cells are modulated by STAT3. Curcumin shows widespread success in inhibiting STAT3 activation pathway, as reported in multiple myeloma cells and both clinical trials and animal models [108, 109]. Curcumin either alone or in combination with 5-flourouracil is effective against gastric cancer and with cisplatin shows promising results in HNSCC cells by inhibiting STAT3 phosphorylation [110, 111] as well as in human non-small cell lung cancer (H460) cells [112]. In mice models, curcumin when administered intraperitoneally effectively inhibited STAT3 activation [113]. Similar results were documented in pancreatic cancer, multiple myeloma [114, 115] and dextran sulphate sodium (DSS)-induced colitis in mice model too [116]. Curcumin inhibited JAK-STAT3 phosphorylation in K562 chronic leukaemia cells through suppression of JAK2, cyclin D1 and v-src gene expression. In chronic lymphocytic leukaemia, curcumin down-regulated JAK-STAT3 pathway by inhibiting the kinase Jak 1 and influencing STAT3 phosphorylation, resulting in growth arrest and apoptosis [117].

Among the other metabolites, 6-shogaol reportedly down-regulated STAT3 pathway and suppressed breast cancer in a time-dependent manner [118]. Apigenin was also reported to suppress JAK/STAT pathway through decreased nuclear translocation of STAT3 [119]. In another study, ovarian cancer cells when treated with

alpinetin showed variations in expression levels of STAT3, pSTAT3, c-myc and surviving cells, indicating decreased phosphorylation of STAT3 and suppression of the STAT3 pathway [120]. Modulation of STAT3 pathway and inhibition of cancer cell division as well as proliferation were reported in prostrate and gastric cancer cells treated with cardamonin [121, 122]. Suppression of the STAT3 and associated pathways upon application of zerumbone is reportedly responsible for the inhibition of prostate cancer line PC3 and kidney cancer xenograft mice model [123, 124].

10.5.3 PI3K/AKT/mTOR Pathway

Curcumin exhibited remarkable anti-apoptotic effects in different malignancies through modulation of the phosphatidylinositol 3 kinase/phosphatidylinositol 3-kinase and the mammalian target of rapamycin (PI3K/Akt/mTOR) signalling cascades [125]. Curcumin induced apoptosis in HNSCLC cell line by curbing PI3K/Akt and precluding miR-192-5p [126]. In breast cancer, curcumin degraded Akt protein, inducing autophagy and inhibiting ubiquitin–proteasome pathway depending on time and dose [127, 128], hence impeding metastasis. pAkt and MAPK pathways were also down-regulated in breast cancer by curcumin [129]. Moreover, synergistic action of curcumin with PI3K inhibitors caused apoptosis in MCF-7 breast cancer cells [130]. Curcumin showed cell cycle arrest in pancreatic cells too, by inducing FoxO1 expression which in turn deregulated PI3K/Akt signalling [131] by upregulating phosphatase and tensin homolog gene (PTEN) [132] and depletion of MMP1/7 and COX-2 proteins in thyroid cancer [133]. In LoVo cell line apoptosis was brought about by upregulation of caspase-3, cytochrome-c and Bax mRNA and inhibition of Akt phosphorylation by curcumin [134]. Similarly, in Burkitt's lymphoma expression of the PI3K/Akt was inhibited by curcumin [135]. Other than these curcumin also arrested cell cycle at G2/M and induced autophagy both in vitro and in vivo in melanoma cells [136] and in uterine leiomyosarcoma growth by suppressing mTOR and S6 phosphorylation [137]. In HNSCC cells, nicotine related Akt/mTOR regulation was thwarted by this molecule [138]. Synergistic role of curcumin with ECGC and imatinib effectively inhibited uterine leiomyosarcoma cell growth and down-regulated the Akt/mTOR pathway in many cell lines [139, 140].

ATP binding sites in PI3K were blocked by flavones like apigenin, directly leading to their inactivity and deactivation of Akt as well [141]. Apigenin also effectively down-regulated Akt phosphorylation and induced over-expression of FOXO3a target genes, p21WAF1/ CIP1 and p27KIP1, thus preventing PI3K/Akt/FOXO signalling midway in many cancers like breast, colon and hepatocellular carcinoma, culminating in cell cycle arrest, apoptosis and prevention of proliferation as well [142–144]. Induction of autophagy and programmed cell death by apigenin through mTOR/PI3K/Akt signalling pathway in cisplatin resistant colon cancer cells is also reported [145]. Inhibition of lung cancer progression and increase in sensitization of lung cancer lines were shown to be executed by alpinetin via repression of the PI3K/Akt pathway [146]. Galangin decreased phosphorylation of Akt and

suppressed mTOR to ultimately down-regulate the PI3K/Akt/ mTOR pathway inducing autophagy or apoptosis in many cancer cells [147], including human nasopharyngeal carcinoma [148] and in laryngeal carcinoma TU 212 and M4e [149]. Modulation of the PI3K/Akt pathway leading to apoptosis and cell cycle arrest was shown in retinoblastoma cancer RB355 cell line upon 6-gingerol (6G) treatment [150]. In human oral and cervical cancer lines, OSCC, KB and SCC4, 6G reportedly down-regulated the PI3K/Akt/mTOR pathway [151]. 10-Gingerol is also reported to inhibit cancer by down-regulation of PI3K/Akt pathway in breast cancer cells [152] and cervical cancer HeLa cells [104, 153]. Inhibitory action of 6-shogaol against Akt/mTOR pathway was reported [154] in lung cancers. Zerumbone is also reported to inhibit the PI3K/Akt/ mTOR pathway [155]. In another study, zerumbone decreased lamellipodia formation in NSCLCs through inhibition of FAK/Akt/ROCK pathway and hence the downstream ROCK/LIMK/cofilin signalling in A549 cells [156]. Kaempferol was also found to inhibit PI3K/Akt pathway indicating a possible role in cancer therapy [157, 158]. Modulation of mTOR pathway and initiation of caspase dependant apoptosis have been reported in A549 and HK1 cells treated with cardamonin and its homologues [159]. In colon cancer HT-29 cell line, zingiberene is reported to induce autophagy through suppression of the PI3K/Akt/mTOR pathway [160].

10.5.4 Tumour Necrosis Factor Pathway

Cellular signalling pathway of TNF-related apoptosis-inducing ligand is known to be modulated by curcumin [161]. In addition to interrupting cell cycle, curcumin disrupts mitotic spindle structures, induces micronucleation and apoptosis and inhibits IL-2 gene expression, thus having immense anti-proliferative activity [162]. The multi-targeted action of curcumin is reported to be beneficial in early stages of chronic lymphocytic leukaemia. It prevents the progression of the disease, decreases CLL B-cell counts and also when administered together with conventional anti-cancer drugs, has synergistic actions in addition to lowering their dose and side effects [163]. Other studies have reported that curcumin enhanced the TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis even in TRAIL-resistant breast cancer cells [164]. In Panc-1 cells, cell death was induced by reduced production of IAP (inhibitors of apoptosis) proteins using curcumin [165]. Further, curcumin inhibited cancer progression modulating epithelial-mesenchymal transition (EMT), Cyclooxygenase 2 (COX-2) and pro effector cytokines [166, 167].

It was shown that galangin sensitized TRAIL activity leading to human breast cancer cell apoptosis through TRAIL/Caspase-3/AMPK signalling pathway [168]. Ozbey et al. [169] reported the sensitization of human liver cancer cells to TRAIL pathway induced apoptosis after treatment with apigenin. That TRAIL pathway induced apoptosis of colon cancer cells upon treatment with zerumbone was also reported [170]. Promotion of apoptosis in ovarian cancer cell lines A2780 and CP70 through the TRAIL pathway was also shown on kaempferol application [171]. Kaempferol reportedly modulates telomerase pathways too [172]. Kaempferol

decreased the expression level of human Telomerase Reverse Transcriptase (hTERT) (catalytic subunit of telomerase). As telomerase regulates ageing and hence apoptosis, decrease in expression of this gene resulted in apoptosis of cervical cancer HeLa cells [157, 173].

10.5.5 EGFR Pathway

EGFR is responsible for cellular proliferation, survival, migration, adhesion even differentiation down the cancer cascades [174], and curcumin was shown to interfere with this cascade in the cellular membrane microenvironment leading to inhibition of various enzymes in diffecent cancers [175]. In brain cancer LN229 cells, curcumin exerted anti-modulatory effects leading to cytotoxicity and inhibition of kinase inhibitors like AG494, AG1478 tyrphostins [176]. Additionally, in erlotinib-resistant NSCLC cells curcumin hindered proliferation led to apoptosis by downgrading EGFR, p-EGFR, survivin and other proteins in the pathway [177]. Further, curcumin suppressed COX-2, EGFR, ERK 1/2 activities ushering apoptosis in lung and pancreatic adenocarcinoma [178] and oral cancer as well [179]. In mice model too, it inhibited angiogenesis in cervical cancer cells, down-regulating the above-mentioned proteins [180] and curcumin-induced inactivation of EGFR and Cav-1 pathways controlled mouse hepatocellular carcinoma in a time and dose-dependent manner [181].

Curcumin induced breast cancer apoptosis by regulating expression of apoptosis-related genes. A group recently studied curcumin [182] treated triple-negative breast cancer cell lines (TNBC) and reported significant inhibition in phosphorylation levels of EGFR and downstream signalling molecules, such as ERK1/2. Another study, however, reported suppression of breast cancer cell growth due to attenuated levels of EGFR and Akt [183]. In addition, curcumin and paclitaxel synergistically inhibited growth and induced apoptosis in breast cancer cells by blocking EGFR signalling and modulating Bax/BCL-2 expression [184]. Curcumin also potentiated anti-tumour effect of gefitinib in NCSLC, both in vitro and in vivo, which was mediated through inhibition of proliferation and EGFR phosphorylation, and led to the induction of EGFR ubiquitination and apoptosis [185].

The EGFR and associated cascades are also potent targets of other zingiberaceous metabolites. While zerumbone is known to affect the MAPK/ERK cascade [186], ERK signalling pathway was also inhibited by apigenin through phosphorylation of focal adhesion kinase (FAK) and ERK, which reduced integrin protein levels and finally suppressed cancer cell migration and thereby inhibited metastasis [187]. Kwak et al. [188] proved that suppression of phosphorylation of threonine 179 residue in Smad3 linker region upon application of GA resulted in growth inhibition of human prostate cancer cells. GA strongly inhibited PKC activity and subsequently phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) to reduce cancer [189]. In another study by Dang et al. [190], it was shown that kaempferol targeted MAPK pathway by modulation of c-Met activity, while Hung et al. reported down-regulation of the EFGR pathway in kidney cancer line 786-O

which inhibited its invasion and migration [191]. Modulation of cisplatin or γ-radiation induced hepatotoxicity through the p38 MAPK/JNK/ErK1/2 signal pathway was shown in rat models treated with zingerone [192].

10.5.6 Nrf2 Pathway and ROS Induction

Nuclear factor 2-related factor (Nrf2) is a potent target for cancer chemoprevention because of its ability to regulate genes that are tangled in the electrophile and ROS detoxification cascades as well as in the repair or removal of damaged products [193]. Curcumin has shown in vivo potency to activate this pathway, renew p53 activity, thus controlling inflammatory signals [194]. Its role in prevention of metastasis in Nrf2 knockdown [195] and exerting chemoprevention in prostate cancer by epigenetic modification and activation of Nrf2-aided defence [196] is well documented. Curcumin affects down-regulation of Flap endonuclease 1 (Fen1) expression, whose over-expression promotes breast cancer, by interfering Nrf-2, eventually preventing breast cancer [197–199]. Curcumin induced apoptosis of breast cancer cells by ROS accumulation, finally leading to p53/p21- and p16/Rb-mediated breast cancer inhibition [76]. Further, in Head and Neck squamous carcinoma, tested in vivo and in vitro, curcumin improves the activity of cisplatin, reduces its chemosensitivity and helps in checking tumour proliferation by modulating pSTAT3 and Nrf2 [111] also in bladder carcinoma cells Keap1–Nrf2 pathway is hindered by curcumin along with cisplatin [200].

The generation of oxidative stress is a pivotal step for induction of apoptosis and researchers contend that flavonoids can increase ROS levels, thereby potentiating DNA damage of cancer cells. Galangin (GAL) treatment is known to induce ROS generation in cancer cells [201]. When selenium nanoparticles fused with galangin (Se@Ga) were used, ROS generation increased in liver cancer cells over controls [202]. Cancer inhibition by galangin was correlated with ROS generation in cervical cancer cells too [203]. Galangin reportedly mobilizes endogenous copper ions, which form a ternary complex with chromatin, generating ROS and inducing DNA cleavage [201]. Zhang et al. [204] showed that even low concentrations of apigenin increased ROS accumulation in human papillary thyroid carcinomas. The mechanism of generation of oxidative stress by treatment of cancer cells with gingerols is also well documented. 6-gingerol (6G) treatment of cancer cells inhibited fatty acid synthesis and subsequent malonyl-CoA accumulation, coupled to Carnitine Palmitoyltransferase-1 enzyme (CPT-1) inhibition, which triggered mitochondria mediated production of ROS in liver cancer cells [205]. Another study with 6G shows that ROS-induced oxidative stress resulted in the release of cathepsin D, a metastasis marker, into the cytosol by increasing permeabilization with consequent release of cytochrome-C [206]. 6G induced spike is ROS production was also associated with an enhanced p53 mediated G2/M cell cycle arrest in cervical cancer cells [207]. 6-shogaol induced intracellular ROS in breast cancer cells, ultimately triggering MAPK protein kinase and apoptosis [118, 208]; similarly MAPK activation in human colon cancer cells upon treatment with 10-gingerol

(10G) is reported, though the exact mechanism is not known [209]. Zerumbone (ZER) effectively increased ROS production in colorectal cancer cells in dose-dependent manner [210], and in melanoma cells as well, which in turn decreased the mitochondrial membrane potential, favouring apoptosis [211]. Zerumbone treated ROS-mediated apoptotic fate was reported in chronic myelogenous leukemic cells [212] and in cervical cancer cells [213]; though contrary reports indicate ROS-independent, thiol-dependent DNA damage and apoptosis of colorectal cancer cells [214]. Chiang et al. [215], however, reported insignificant increase in ROS production in human prostate cancer cells upon zerumbone treatment. Kaempferol (KMF) treatment significantly increased ROS production and triggered apoptosis in cancer cells. KMF reportedly inverted antimycin A (AMA)-induced toxicity by disruption of MMP and accumulation of intracellular calcium ions and ROS, via PI3K/Akt/CREB pathway [216, 217]. ROS accumulation via catalase inhibition upon kaempferol treatment is also reported [218]. ROS induction and cytotoxicity, leading to apoptosis, was shown upon cardamonin application in human tumour lines [219]. Elevation of ROS was also reported in human HCT-116 colon cancer cell lines and in Winster rats when treated with zingerone [220–222]. 8-shogaol reportedly induced cell death in leukaemia cells through ROS generation leading to glutathione depletion and caspase activation [223].

10.5.7 Notch 1 Pathway

Neurogenic locus notch homolog protein-1 (Notch 1) family members control cell fate by modulating cell differentiation, proliferation and apoptosis cascades, and are investigated as potent therapeutic targets for cancer therapy [224]. Curcumin controls Notch pathway effectively preventing cancer stem cells [225, 226]. Curcumin could effectively down-regulate this pathway in an array of cancers—colorectal, oesophageal, oral, decreasing γ-secretase complex proteins especially in oesophageal cancer [226]. Not only Notch-1 signalling but associated factors including early growth response-1 gene product (Egr-1), farnesyl-protein transferase (FPTase), telomerase, c-Myc, fibroblast growth factors (FGF) mediated cell signalling are also inhibited by curcumin [227, 228]. Curcumin reportedly blocked Notch-1 signalling pathways which play important roles in pancreatic tumour growth [229]. Only a few of the other metabolites of Zingiberaceae are known for their effects against Notch-1 signalling cascades. In a study, 6-shogaol was reported to inhibit breast cancer cells by modulation of notch signalling pathway [230]. Transfection experiments conducted with miR-211-5p and anti-miR-211-5p in oral squamous carcinomas showed that alpinetin upregulated microRNA levels and thereby suppressed Jagged-1 expression as well as Notch signalling pathways [231]. Alpinetin treated brain tumor (Glioma) of rat cells showed inhibition of Notch signaling cascade, where transcription of Notch target genes, such as HES and c-Myc, were both found to be suppressed in GSCs [232].

10.5.8 Activating Protein-1 Pathway

AP-1, a dimeric transcription factor, is involved in cellular proliferation, transformation and death [233]. Curcumin down-regulated androgen dependent and independent lines, halting transactivation of androgen receptor (AR)—AP-1, cAMP and NF-κB showcasing anti-tumour activities [234]. It also regulated pro-inflammation cytokines IL-1α, IL-1β of AP-1 and IL-6 in mice lymphoma model [235]. Curcumin reportedly induced apoptosis of monocytic leukaemia cells through AP-1 activation as well [236]. Galangin was also reported to interfere with the binding of NF-κB with AP-1 thus inhibiting cancer progression [237].

10.5.9 HIF-1 Pathway and Angiogenesis

Angiogenesis is an important physiological process promoting tumour growth and metastasis, as cancer growth depends upon establishment of new blood vessels [238]. Curcumin inhibits tumour generation via impeding Hypoxia-inducible (HIF-1α) protein [239]. HIF-1 is necessary for continual survival of cancer cells as it is crucial for glycolysis activation and also initiates angiogenesis [240]. It is known that, curcumin constrains pituitary adenoma by HIF-1α mRNA induction, while down grading aryl hydrocarbon receptors leading to inhibition [241]. Similarly, curcumin also remarkably upregulated in oral squamous cell carcinomas associated with areca quid chewing [242]. Further, curcumin and cisplatin or diamminedichloroplatinum (DDP) exerts positive additive effects in A549 cells, leading to apoptosis where HIF-1α is broken down but caspase-3 upregulated [243]. Among all the potent anti-cancer phytochemicals of Zingiberaceae, kaempferol is reported to be the most efficient in inhibiting angiogenesis. Kaempferol triggered apoptosis of Human Umbilical Vein Endothelial Cells (HUVECs) and inhibited angiogenesis [244, 245]. Kaempferol also inhibited expression of Vascular Endothelial Growth Factor (VEGF) that stimulated HUVECs and hence proved to be a key mediator of angiogenesis in ovarian cancer cells OVCAR-3 and A2780/CP70 [246]. Reports also indicate that inhibition of proliferation, migration and tubule formation in HUVEC can be achieved by zerumbone [212, 247, 248]. Similar anti-proliferative and anti-angiogenic effect of zerumbone was shown in Sprague Dawley mice model of hepatocellular carcinoma [249]. Anti-angiogenesis properties are also exhibited by galangin in ovarian cancer cells OVCAR-3 via regulation of VEGF expression [250]. Inhibition of angiogenesis and suppression of epithelial-mesenchymal transition in glioma cell lines after galangin application were reported recently [251]. Suppression of angiogenesis by inhibition of MMPs was reported in mouse tumour Renca cells after application of zingerone [252]. Angiogenesis and metastasis in orthotopic Ovarian Tumour Model through modulation of the AKT/P70S6K1/MMP-9 Pathway by apigenin is reported [253].

10.5.10 Wnt/β-Catenin Pathway

The Wnt/ β-catenin pathway with its immense importance in controlling apoptosis and cell survival [254] is known to be effectively controlled by curcumin. Migration of breast cancer stem cells was inhibited by curcumin, through reinstatement of E-cadherin expression, resulting in enhancement of E-cadherin–β-catenin complex formation [255].

Curcumin administration showed control in cell proliferation and cellular aggregation, which in turn is controlled by β-catenin transcription activity and β-catenins [256]. Hence, in Lymph Node Carcinoma of the Prostate (LNCaP) cell line, Wnt/β-catenin pathway was effectively controlled by curcumin as well [257]. Further, PLGA-CUR NPs [poly (lactic-co-glycolic acid) which are curcumin encapsulated nanoparticles, showed impressive result against prostate cancer by checking this pathway [258]. Curcumin also leads to cell cycle arrest at G0/G1-phase in Non-Small Cell Lung Carcinoma (NSCLC) cells by blocking this pathway [259].

Zerumbone reportedly inhibited Wnt/ Beta-catenin pathway to abolish cancer stem cells [260] and targeted the β-catenin disrupting the cascade in breast cancer [261], while apigenin also silences the Wnt/β-catenin signalling pathway [262, 263]. On the other hand, cardamonin is also found to exert anti-proliferative action on SW480 cells degradation of β-catenin and subsequent down-regulation of the Wnt/β-catenin signalling pathway [264]. In breast cancer lines MCF7, MDAMB231 and BT549 cardamonin showed reversal of epithelial-mesenchymal transition by down-regulation of the Wnt/β-catenin signalling pathway [265].

10.5.11 Induction of Dysfunction of Cellular Organelles

A reduction or disruption in mitochondrial function occurs as a result of loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane, altering the electron transport chain, or reducing transport of critical metabolites into mitochondria [266], which culminates in a massive upheaval of cellular homeostasis and induces apoptosis. Anti-cancer drugs thus target mitochondria for ushering apoptosis of cancer cells. Curcumin is reported to prohibit apoptosis mitochondrial dysfunction ultimately leading to cell cycle arrest in human gastric cancer cell line MGC803 [267]. Galangin (GA) induced human colon cancer cell death through alteration of mitochondria membrane potential and dysfunction. GA exposure caused release of cytochrome-C (cyt C) and apoptosis-inducing factor (AIF) from the mitochondria to the cytoplasm, and translocation of pro- and anti-apoptotic proteins across the mitochondrial membranes, increasing the ratio of pro-apoptotic protein Bax and anti-apoptotic protein Bcl-2 in hepatocellular carcinoma [268]. Molecular mechanisms of galangin treatment suppressing tumour cell growth revealed that GA increased the expression of cleaved PARP and caspase-3 in human cancer cells [268]. Depletion of mitochondrial membrane potential and translocation of phosphatidyl serine was induced by selenium nanoparticle fused

with GA triggering apoptosis [202]. Apigenin triggered both the intrinsic and the extrinsic pathways of apoptosis [269]. Apigenin caused increase in Bax/Bcl-2 ratio causing apoptosis in prostate cancer [270]; similar observations of apoptosis and a reduction in cell viability due to decreased Bcl-2 and Bcl-xL and increased active form of the Bax protein upon apigenin treatment in colon cancer are also known [271]. A dose-dependent suppression of the pro-survival member proteins, like XIAP, c-IAP1, c-IAP2, was also observed in their study. Apigenin application reduced outer membrane potential of mitochondria, leaking cytochrome-C and inducing procaspase-9 activation, through intrinsic pathway [272] and forming of Fas-associated death domain (FADD) [272]. Nonetheless, Bcl-2 and Bax activities were unaltered by apigenin [273]. Alpinetin is reported to promote Bax translocation and induction of mitochondrial pathway of apoptosis [274]. 6-gingerol too increased the ratio of Bax to Bcl2 at the messenger RNA (mRNA) level in both 143B and MG63 osteosarcoma cell lines in a dose-dependent manner [275], and also elevated levels of cleaved caspase-3, caspase-8 and caspase-9. 6G treatment of Human cervical adenocarcinoma cell (HeLa) showed a gradual decline in membrane potential of mitochondria [101]. On a similar note, caspase3 and PARP were altered to induce apoptosis with 6-gingerol. In MDAMB231TNBC, a breast cancer line, 10-gingerol caused mitochondrial dysfunction leading to cytochrome-c and caspase cascade initiation [276]. Gan et al. reported activation of caspase cascade and induction of apoptosis in breast cancer line MCF-7 after zingerone application [277]. 6-shogaol activated caspase-8, caspase-9 and caspase-3 and caused PARP cleavage in MDA-MB-231 (human breast cancer), DU145 (human prostate cancer), SCC4 (human squamous cell carcinoma), HepG2 (human hepatocellular carcinoma), A549 (human lung adenocarcinoma) and also suppressed expression of Bcl-2, Bcl-xL and Survivin in tumour tissues [278, 279]. Its effect on colorectal cancer line inducing apoptosis through mitochondrial membrane damage, cytochrome-c leakage and caspase cascade activation is also documented [106]. Zerumbone decreased mitochondrial membrane potential and pushed cancer cells towards apoptosis [280]. Mitochondrial dysfunction via elevation of ROS was induced in a variety of cancer cells upon kaempferol treatment. A study with melanoma cells showed that zerumbone efficiently inhibited mitochondrial biogenesis by suppressing activity of a mitochondrial biogenesis factor—TFAM [211]. Apoptosis of MCF-7 breast cancer cells accompanied with nuclear condensation and mitochondria dysfunction [281] and mitochondrial dysfunction via increase in ROS in colorectal cancer cells [282] were observed after treatment with kaempferol. Induction of caspase cascade was reported in prostate LNCaP cells by kaempferol culminated in apoptosis [283]. Tu et al. reported disruption of mitochondrial membrane potential and perturbation in intracellular free Ca^{+} concentration in SiHa cells treated with kaempferol inhibiting their proliferation and inducing apoptosis [284].

Endoplasmic reticulum (ER) is the principal organelle responsible for multiple cellular functions including macromolecular trafficking involving protein folding and protein translocation and maintenance of cellular homeostasis. Disturbance in the ER (a pool of free calcium ions) environment by external or internal stimuli

causes calcium depletion, altered glycosylation and oxidative stress. Experiments have revealed that galangin altered signal transduction pathways, which in turn induced ER stress and inhibited calcium channels, resulting in a significant increase of Ca^{2+} concentration in the cytoplasm and mitochondria, leading to apoptosis of hepatocellular carcinomas [285]. Zerumbone also induced a significant increase of intracellular Ca^{2+} concentration in prostate cancer cell lines, PC-3 and DU-145. Further, calpain I (calcium dependent protease) was induced upon zerumbone treatment facilitating apoptosis in those cell lines [286]. Kaempferol induced liver cancer cell death via ER stress and CHOP-autophagy signalling pathway [287].

10.5.12 Induction of Autophagy

Autophagy marks the transport and compartmentalization of cellular (cytoplasmic) material in vacuoles for degradation by lysosomal enzymes [288]. Reports show that galangin (GA) induced autophagy and apoptosis concomitantly. Beclin1, autophagy-related gene (ATG) 6, reportedly reacted to increased levels Bcl-XL and decreased Bcl-2 levels upon treatment with GA. Subsequent signal transduction cascades ultimately culminate in the formation of autophagosomes [289]. GA also induced autophagy via deacetylation of LC3 by SIRT1 in HepG2 liver cancer cells [290]. That galangin induced autophagy through upregulation of p53 in HepG2 liver cancer cells was also reported [147].

That apigenin induced autophagy was evident from presence of acidic vesicular organelles (AVOs) as well as the Atg5/Atg7 dependent autophagy marker, LC3-II [291]; reports also indicated concomitant autophagy and apoptosis upon apigenin application [292]. In macrophages, apigenin treatment upregulated Beclin 1, Atg5 and Atg7, to usher autophagy and the appearance of LC3-II in human colon carcinoma HCT-116 cells confirmed the same [293]. Vital staining with acridine orange showed accumulation of AVO (acidic vacuoles) in cytoplasm of HeLa cervical cancer cells exposed to 6G-gingerol [101]. Onset of apoptosis and mitochondrial damage was reported in U-118MG glioblastoma cells upon treatment with 6-G as well [294]. SSi6 (a 6-gingerol analogue) markedly blocked the autophagic flux and subsequently increased levels of LC3B-II, which contributed to cell death in triple-negative breast cancer cell line MDA-MB-231 [295].

6-shogaol (6-SG) induced a large number of cytoplasmic vacuoles in MCF-7 breast cancer cells. Localization of LC3 to autophagosomes in these cells was also noted in the same study [230]. AVO formation in non-small lung cancer cell line A549 cells was observed after exposure to 6-SG. Moreover, 6-shogaol mediated autophagy was blocked by 3-MA, an autophagy inhibitor, confirming that 6 SG induced autophagy in cancer cells [154]. Instances of zerumbone-induced increase of LC3-II formation indicating autophagy in human hormone-refractory prostate cancers were also reported [286]. Similarly, cardamonin is known to induce autophagy and inhibit cell cycle progression in HCT116 and LOVO cells where formation of AVOs and LC3 were also reported [296].

10.5.13 Modulation of Cell Cycle

Uncontrolled and rapid cell division is another hallmark of cancer. As evidenced, anti-cancer drugs inhibit cancer cell proliferation by modulating the cell cycle and blocking it at the G2/M or G0/G1 or the S-phase checkpoints. Reports pertaining to the cell cycle modulation by novel anti-cancer phytochemicals like apigenin, alpenitin, zerumbone and kaempferol show inhibition of the activities of some key players, namely cyclin D1, D3, E and A and cyclin-dependent kinase (CDK) 4 and CDK 6 [274, 281, 297, 298].

Inhibition of proliferation of pancreatic cancer cell lines like BxPC-3 using curcumin showed its therapeutic prospect. One of the pathways involved initiates cell cycle arrest at G2/M by preventing expression of cyclin B1/ Cyclin-dependent kinase 1 (Cdk1). Activation of ataxia telangiectasia mutated (ATM)/Checkpoint kinase 1(Chk1)/Cell Division Cycle 25C (Cdc25C) showed similar data [299]. Cell cycle arrest at different checkpoints using Aurora-A and kinase activity using Curcumin in breast cancer have also been projected [53]. Curcumol, a novel anti-cancer metabolite from *Curcuma longa*, too has been shown to be effective in arresting cell cycle and inducing apoptosis in a number of cancer lines through modulation of Cdk and p53 signalling cascades [300].

Cell cycle arrest at G2/M stage as well as G0/G1 checkpoint was shown by the treatment of apigenin on human colorectal carcinoma, prostate cancer cells, breast cancer line MDA-MB-231 and various other cancer cells [301, 302]. Similarly, G2/M transition in cell cycle and p53 reactivation via proteasome inhibition and upregulation of p21-p53/p21 by treatment of cervical cancer cells with 6-gingerol (6G) was also reported [207, 303]. Apoptotic nuclear shrinkage and membrane blebbing were shown in oral and cervical cancer cell lines upon 6G treatment [100]. Cell cycle arrest and apoptosis through modulation of cyclins by 6G have also been shown in hepatocarcinoma and colorectal carcinoma lines [304–306]. Cyclin A and CDK expression decreased via down-regulation of Rb phosphorylation and upregulation of p21 in pancreatic cancer cells upon 6G treatment [306]. Application of 10-gingerol (10G) resulted in down-regulation of the cell cycle regulatory proteins like CDK2, CDK4, cyclin D and cyclin E [152] in breast cancer cells. 10G also induced cell cycle arrest at G2/M phase in ovarian cancer HEY, OVCAR3 and SKOV3 lines due to decrease in cyclin B1 and D3 [307]. Cell cycle arrest in the G0/G1 phase by degradation of β-catenin, decreased c-myc expression and inhibition of activity of cyclins and CDKs upon treatment of cancer cells with galangin were reported [188]. Zerumbone, besides inducing cell cycle arrest of cervical carcinoma at G1 [213] and at G2/M stage [210] of cell cycle, also potentially inhibited ATM phosphorylation, and hence ATM activation, thereby sensitizing the cervical cancer cells and prostate cancer cells towards radiation [48, 215]. A combination of zerumbone and cisplatin was found to be effective in inducing cell cycle arrest in cervical intraepithelial neoplasia in female BALB/c mice [308]. Upregulation of Bax levels and alteration of Bcl levels were reported to induce apoptosis in gastric cancer SGC-7901 and oesophageal cancer EC-09 by zerumbone [309, 310]. Evidences pertaining to cell cycle arrest by kaempferol

indicate that G1 and G2/M cell cycle arrest of cancer cells take place by inhibition of cyclin A, cyclin B1, cyclin E, cyclins D1 protein expressions, as well as inhibition of CDK2 and CDK4 activities, reduction in phosphorylation of retinoblastoma (Rb) protein and lowering the expression levels of Cdc2, Cdc25C` [311]. Several cell cycle related genes like CHK1, CHK2 and p21waf1/Cip1 were found to be upregulated and p35 and cyclinB1 genes were down-regulated upon treatment with kaempferol [191]. Anti-proliferative property of kaempferol was shown in lymphoma Daudi cells by Parmar et al (2016) [312]. Zingerone is implicated in cell cycle arrest and inhibition of mitosis through suppression cyclin D1 in human neuroblastoma BALB/c mouse tumour model BE(2)-M17 [313]. Alpinetin treatment of gastric cancer lines AGS and N87 reportedly induce cell cycle arrest at G2/M phase and apoptosis by translocation of Bax and triggering of the mitochondrial apoptotic cascade [274, 298]. Moreover arrest of colorectal cancer HT-29 cell cycle at G0/G1 and S-phases by alpinetin was reported with p53 mediated cell cycle arrest and uridine-cytidine kinase 2 inhibition [314].

10.5.14 Inhibition of Cancer Cell Adhesion and Metastasis

Cell adhesion is defined as the binding capability of one cell to another cell or to the extracellular matrix (ECM), and is a critical process through which cancer cells establish new tumours in the body. Metastasis involves the over-expression of the proteolytic enzymes, such as matrix metalloproteinases (MMPs). Studies have shown that MMP-2 and MMP-9 and TPA (12-O-tetradecanoylphorbol-13-acetate) are the main players of tumour metastasis. Several reports of curcumin inhibiting multiple metastatic steps including invasion and migration exist, which include its effect on thyroid carcinoma BCPAP cell line through the TGF/Smad2/3 pathway as well [315]. Galangin effectively inhibited adhesion of TPA-treated HepG2 cells in a dose-dependent manner, further RT-PCR studies with galangin treated liver cancer cells showed alteration in F-actin pattern, inhibition of transcription of MMP 2 and MMP 9 mRNAs [237] thereby inhibiting the cell adhesion and cancer cell metastasis. Inhibition of proliferation of human fibrosarcoma HT-1080 cell lines was attributed to galangin induced decrease in MMP-9 expression as well [316]. Another investigation revealed that the anti-metastatic ability of galangin resulted from repression of ADAM9 expression in the Glioma cells [189]. It was also reported by different authors that galangin administration suppressed cancer cell migration and metastasis of renal carcinoma cell lines through increased ROS levels and downregulation of the PI3K/Akt/mTOR signalling pathway [317, 318].

Apigenin strongly inhibited tumour cell invasion and migration in a dose-dependent manner in prostate cancer cells [270]. Cell migration and invasion of human and murine melanoma B16F10 cells in mice was prevented by down-regulating STAT3 phosphorylation and its target genes MMP-2, MMP-9, VEGF and Twist1 upon apigenin treatment [319]. It has been reported that in human ovarian cancer in vitro, cellular migration and onslaught of invasion by prohibiting FAK expression thus stopping metastasis as seen in mice model when treated with

apigenin [320]. In an orthotopic colorectal cancer model, apigenin was shown to upregulated transgelin (active protein in actin cross-linking) and downregulate MMP-9 expression [321].

Alpinetin was reported to suppress proliferation and sensitize liver cancer cells towards chemotherapeutic agents by activation of mitogen-activated protein kinase kinase-7 (MKK-7) [322]. With respect to metastasis, alpinetin reportedly decreased migratory capacity of ovarian cancer cells; moreover, MMP2 and MMP9 protein expression levels were significantly decreased in alpinetin-treated cells in comparison to control cells. Conversely, tissue inhibitor of metalloproteinase TIMP1 and TIMP2 expression levels were increased in the alpinetin treated ovarian cancer cells [120]. Inhibition of invasion of glioma cancer cells by treatment with alpinetin was also reported [232]. It was found that 6G-treated liver cancer cells showed reduced metastatic burden and necrotic areas; moreover, 6G reduced the levels of MSE and improved the tumour microenvironment to inhibit metastasis. In the same study, Immunohistochemical (IHC) staining demonstrated a reduction in the expression of HIF1α, MMP2 and MMP9 in the 6G-treated cancer cells when compared to the untreated cancer cells. 6G treatment of osteosarcoma cells 143B and MG63 underwent apoptosis after inhibition of cell proliferation through activation of AMPK, caspase cascades and alteration of BCl2 levels [275].

Sithara et al. [210] studied the anti-migratory effect of zerumbone, and claimed that, colorectal cancer cells grew only in the internal space of the wound, rather spreading in form of dense cell mass with reduction in density due to zerumbone treatment. Hosseini et al. showed that zerumbone can induce suppression of cancer invasion and metastasis can be attributed to modulation of the FAk/PI3k/NF-KB-uPA pathway in human colorectal cancer lines HCT-116 and SW-48 [323]. Other studies with liver cancer cells [324], ovarian cancer cells [325] and breast cancer cells [326] also revealed anti-migratory properties of zerumbone. Kaempferol effectively blocked the development of metastatic cancer by inhibiting MMP-3 activity in highly invasive breast cancer cell line MDA-MB-231 [327] or through down-regulation of the RhoA and Rac1 cascades [328]. Migratory activity of pancreatic cancer cells was also reported to be inhibited by low doses of kaempferol, without having any cytotoxic effects on normal cells [329]. Inhibition of epithelial-mesenchymal transition through repression of multiple pathways was reported upon kaempferol treatment in A549 lung cancer cell line and human non-small cell lung cancer [330, 331]. Invasion and migration of liver cancer cells SNU182 were suppressed by inhibition of TGF-β-1 signalling pathway upon zingerone application [332].

Some important phytochemicals like apigenin [333] and 6-gingerol [334] are reported to improve the tumour microenvironment thus helping in prevention of metastasis. In prostate cancer cells, apigenin treatment induced downregulation of SPOCK1, improved tumour microenvironment bringing in reduced expressions of mesenchymal markers and significant depletion of the invasive abilities of metastatic cells [333]. 6G is known to prevent metastasis and improve tumour microenvironment through modulation of the pVEGFR2/VEcadherin/β-catenin/actin pathway [334].

10.6 Novel Anti-cancer Targets

10.6.1 Inhibition of Leukotriene Activity

The leukotrienes belong to a class of hormones which are formed by leukocytes, macrophages and other tissues in response to immunological and nonimmunological stimuli, and are found at high levels in most inflammatory lesions, probably playing an important role in cancer development as well. 6-gingerol readily suppressed Leukotriene A4 hydrolase (LTA4H) activity in human colorectal cancer cells HCT116 as well as in in vivo in nude mice under in vivo conditions [335]. As LTA4H has a positive role in carcinogenesis and is known to be responsible for anchorage-independent growth of cancer cells, this aspect of target of cancer cells might be a good strategy for inhibition of proliferation of cancers.

10.6.2 Effect on Cancer Stem Cell (CSC) and Glioma Stem Cells (GSC)

Cancer stem cells (CSCs) are chemo-resistant, self-renewing, tumorigenic sub-population of cells which are present in a very small percentage in the total tumour. CSCs reside in specified niches of the total tumour [336]. CSCs play a very important role in cancer development and progression. Hence, chemotherapeutic as well as phytochemical drugs targeting the main tumour along with their CSCs might be considered as a useful strategy to inhibit human cancers.

So far as the phytochemicals from members of Zingiberaceae are considered, only apigenin (AP), alpinetin (ALP) and 6-shogaol (6-SG) can reportedly target cancer stem cells. In ovarian cancer (SKOV3) apigenin compromised self-renewal ability of SFCs [337] and cervical cancer (HeLa) cells by downregulation of Casein Kinase 2 α (CK2α) expression [338], alpinetin suppressed proliferation and invasiveness of GSCs through suppression of Notch signalling [339]. 6-shogaol on the other hand was reported to be effective in inducing apoptosis of both breast cancer monolayer as well as the interior spheroid cells (SFCs) like cancer stem cells [230]. Apigenin can inhibit stem cell like phenotype of glioblastoma lines U87MG and U373MG by suppression of c-met signalling [232].

10.6.3 Cancer Immunotherapy

Cancer immunotherapy is the choicest of all ways to treat cancerous growth these days and is executed through upregulating the inherent immunity of a patient. A specific protein-programmed cell death 1 protein (PD1), commonly found in metastatic immune cells—T and B cells, monocytes and natural killer cells, is a means to disintegrate such immunity, with PD1/PD-L1 proteins being used for such surveillance [340]. T-regulatory cells (Tregs) are also used in an alternate strategy whereby effector T cells are prevented in the background of a hostile environment [341].

With respect to cancer immunotherapy, apigenin seems to be very promising. In a murine pancreatic cancer model, apigenin treatment enhanced CD4+CD8+ T cells and decreased the percentage of Tregs and ultimately showed prolonged mouse survival time [342]. Zerumbone is also reported to modulate CD1d expression and lipid antigen presentation pathway in breast cancer cells [280]. Recently it was shown that apigenin can inhibit transcription of interleukin-6, a potent pro-inflammatory cytokine that has a prominent presence in human oesophagus cancer patients. Repression of IL-6 transcription in human oesophagus cancer Eca-109 and Kyse-30 cells by apigenin has opened a novel dimension in cancer therapy [343]. The following table represents a summary of information known about different compounds from members of Zingiberaceae with known anti-cancer activities. Since the same compound may be present in multiple members, the major source of the particular metabolite is mentioned as the source plant in Table 10.1.

10.7 Cumulative Mechanism of Phytochemicals Towards Cancer Therapy

The intricate modulation of signal transduction pathways with a detailed study of the multi-step processes leading to cancer origin reveals that over-expression of the ligands and proteins related to respective signal transduction pathways, results in overall gain of function of distinct oncogenes and subsequently, loss of function of tumour suppressor genes, result in uncontrolled cell division, resulting in cancer. Table 10.1 summarizes the effect of the various compounds extracted from Zingiberaceae family used for cancer prevention and treatment. Elucidation of the exact modes of action and improvements in analytical techniques have also propelled a look in on many lesser known compounds like zingerone, zingiberine, cardamonin, which show promising results.

The anti-cancer phytochemicals discussed in detail here target multiple signal transduction pathways like NF-κB-IκB, PI3K/AKT/mTOR, TGF-β1/ Smad pathway, GSK3β-PKC, STAT3 and cause downregulation of the pathways. Down-regulation of NF-κB-IκB results in the decrease in activities of mitochondrial metalloproteinases (MMPs) (MMP-2, MMP-9). Down-regulation of PI3K/AKT/mTOR pathway results in elevation in levels of p53, this subsequently results in elevation of ROS levels in tumour cells (Figs. 10.4 and 10.5). The suppression of MAPK/ERK signalling pathway leads to the alteration in MMPs on the one hand, and on the other hand results in decrease of FAK activity. Inhibition of Smad pathway results in elevation in levels of Beclin 1 protein, leading towards autophagy. The suppression of the concerned signal transduction processes leads to either total inhibition or decrease in expression of genes, responsible for cell division, like c-myc, cyclins (in most cases cyclin D1). This results in cell cycle arrest of cancer cells at G0/G1 phase or G2/M phase (Figs. 10.4 and 10.5). Intracellular ROS hires the caspases and direct the cancer cells towards either extrinsic pathway for apoptosis or result in release of cytochrome-c, followed by formation of apaptosome

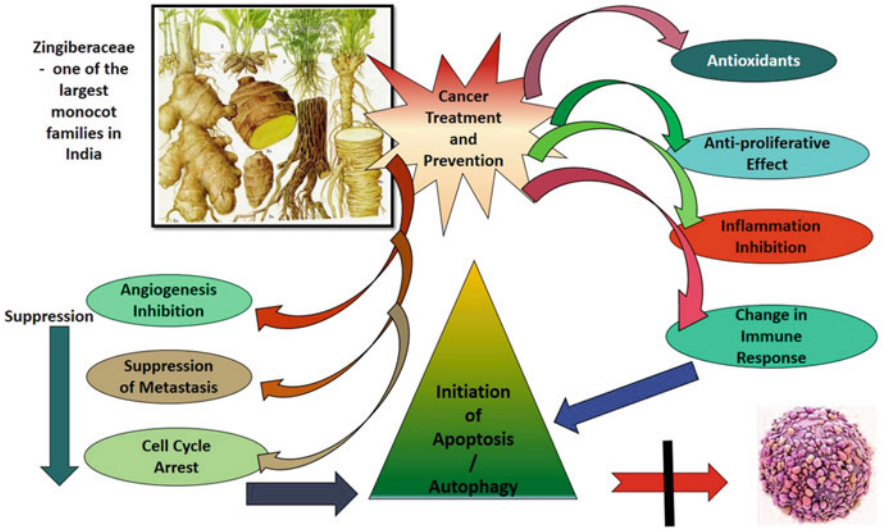


Fig. 10.5 Generalized diagram of effectiveness of the above-mentioned compounds in treating cancerous growth

and triggers the intrinsic pathway of apoptosis via mitochondrial dysfunction. On the other hand, the decrease in the MMPs and decrease in FAK activity ultimately lead towards decreased expression of F-actin and integrin protein levels, which ultimately inhibits cancer cell progression and migration (Fig. 10.5) and hence metastasis, thus the malignancy of cancer is inhibited.

10.8 Conclusion

The uses of plant-based nutraceuticals-pharmaceuticals have manifold in the recent years. People worldwide, searching for plausible solution against deadly cancers, are taking keen interest in such products as well. The age-old novelties and knowledge passed on for thousands of years are being rebranded presently to meet market trends.

The members of Zingiberaceae as discussed in the chapter have been used by the Asians for hundreds of years against a variety of diseases. The option to use easy to find, cheap herbs and rhizomes as alternatives and supplementary aids to traditional cancer medications and therapies is an exciting field. However, as discussed, bio-availability has still remained the major issue when it comes to human consumption and dose determination. Curcumin, for example, has lost some of its glory because of issues relating to bioavailability being insoluble in water. Preclinical trials with many of the compounds from the family have shown impressive result in treating or preventing angiogenesis, metastasis or tumour formation as a whole. However, clinical trials under strict control conditions should be ensured to meet the end

objective of providing safe alternative to presently available drugs with multiple side effects and toxic aftermaths. Plants for a long time have provided better alternatives; these clinical trials should ensure such standards from leading authorities like FDA. Marketing strategies should be developed to ensure that maximum number of people could get hold of such medications and supplements, in a cost effective manner. Efforts should be made to popularize local products to reach global population and share the goodness and richness of plants universally.

Conflict of Interest The authors declare that they have no conflict of interest.

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