Chapter 9
Curcuma and Breast Cancer: A Focus on Cell Signaling Pathways

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Abstract Cancer is a multifaceted disease characterized by deregulated epigenetic, genetic and metabolic signals which affect cellular metabolism and apoptosis. Breast cancer is regarded to be the most common malignancy in the women worldwide. The side effects of chemo-drugs such as non-selectivity, toxicity and resistance urge scientists to find more potent and safer drugs. Natural products from plants provide an extensive array of chemical scaffolds with biosafety profiles, and safer health effects. Curcuma, a genus of family *Zingiberaceae,* comprises of about 110 species natively distributed as well as cultivated in South Asia, China, Australia, Sri Lanka, West Indies, and Peru. This plant is used as a remarkable pharmacological remedy to prevent and cure various pathological disorders including cancer. The chemical constituents of this plant, terpenoids and betaketones, specifically act as the anti-breast cancer agents. Curcuma, the marvel of nature, can be regarded as panacea due to its versatile molecular targets and spacious therapeutic window.

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Various investigations on the essential oils and dry rhizome conclude that the chemical constituents of this plant e.g., curcumin, germacrone, furanodienone, bisdethoxycurcumin, demethoxycurcumin, curcumol, and aromatic turmerone are responsible for its anti-breast cancer potential. These compounds, either as single compound or in combinations with other drugs, are known to arrest cell cycle and induce apoptosis in breast cancer cells by modulating various signaling cascades including NF-κB, STAT3, PI3k/Akt/mTOR and MAPK. This book chapter intends to comprehend the biological and pharmacological mode of action of Curcuma-derived anti-breast cancer compounds in order to update the researchers and scientific community about the pharmaceutical potential of plants belonging to this genus.

Keywords Curcuma · Cancer · Cell cycle arrest · Apoptosis

1 Introduction

Cancer arises due to uncontrolled cellular proliferation (Sharma et al. 2017) caused by epigenetic and genetic mutations as well as environmental carcinogens (Perez-Herrero and Fernandez-Medarde 2015). Recent statistics about this disease acclaim it to be the second most fatal disease after cardiovascular disorders with 9.6 million deaths and 18.1 million newly reported cases in 2018 (Bray et al. 2018). Breast cancer (BC) is a multifarious disorder characterized by abrupt growth of breast cells in an uncontrolled manner ultimately leading to the formation of a lump or mass (Simos et al. 2014). It is most common malignancy in the women all over the world and is the major cause of mortality among women (Rojas and Stuckey 2016). Incidence and prevalence of BC is higher in developed countries as compared to underdeveloped countries (Ghoncheh et al. 2016). Statistical analysis provides us an insight about the facts and figures regarding increase in the incidence of breast cancer during recent years and the reasons behind this increase are reported to be the population growth (12.6%), aging (16.4%), and age related causes (4.1%) (Azamjah et al. 2019).

Despite of great advancements in the field of medicine and surgery, complete cure of cancer remains an unsolved mystery (Gupta et al. 2013). Drug discovery from natural products has emerged as a great area of research with more than 70% of anticancer drugs been isolated from natural resources (Newman and Cragg 2012). The quest for the discovery of anticancer drugs dates back to 1950s, when vinca alkaloids were first discovered from plants. Since then ~25,000 different phytochemicals have been isolated from fruits and vegetables which exert anticancer effects in humans (Sharma et al. 2017).

Curcuma, an auspicious genus of perennial rhizomatous herbs belongs to family Zingiberaceae which comprise of 110 species approximately (Rajkumari and Sanatombi 2018). There are more than 100 species which have been reported up till now. The word “Curcuma” has been originated from the Arabic word “Kurkum”,

meaning "yellow". The genus was firstly recognized by the Carl Linnaeus in 1753 (Sun et al. 2017). Most of the plants belonging to this genus are natively distributed in Southeast Asia and are cultivated on large scale in China, Indonesia, Sri Lanka, India, Peru, West Indies and Australia. Evidences show that many plants of this genus have long been employed in traditional medicines to cure various ailments (Sun et al. 2017) such as *C. longa, C. angustifolia, C. amada, C. aromatica, C. caesia,* and *C. zedoaria* (Chaturvedi et al. 2015; Sun et al. 2017). It has been reported that rhizomes are the most effective parts of these plants which exhibit a wide range of therapeutic properties to overcome the chemo-resistance against various types of cancers e.g., breast cancer, multiple myeloma, colorectal cancer, lung cancer, pancreatic cancer, oral cancer, and prostate cancer (Devassy et al. 2015; Zhong et al. 2018). This chapter focuses on the anti-breast cancer activity of plants belonging to genus Curcuma (the golden spice of South Asia) and the mechanisms lying behind their modes of action.

2 Phytoconstituents of Curcuma

Plants are the excellent reservoirs of potentially active natural compounds which endeavor them the multiple therapeutic effects against various diseases (Song et al. 2019). These natural products from plants are relatively safer than synthetic drugs in terms of efficacy, side effects and cost. The bioactive phytochemicals obtained from plants include flavonoids, alkaloids, phenolic compounds, and tannins (Edeoga et al. 2005).

Natural products are thought to be the foundation pillars regarding drug discovery since the times immemorial. In the modern times also, the therapeutic uses of traditional medicines can be never overwhelmed. The plants of genus Curcuma have also been utilized to target various diseases including breast cancer (Amalraj et al. 2017). Among all the known species of curcuma, *C. longa, C. amada, C. angustifolia, C. aromatica, C. caesia* and *C. zedoaria* are well documented in traditional system of medicines (Chaturvedi et al. 2015). Pharmacological evaluations of essential oils and pure extracts of curcuma species have recognized terpenoids and beta diketones as major bioactive classes of compounds which breast cancer by modulating different cell signaling pathways (Amalraj et al. 2017; Nair et al. 2019).

Researches to investigate the phytochemistry of 32 different plant species show that there were ~720 compounds derived from these species which include; terpenoids (529 compounds), diphenylalkanoids (102 compounds), phenylpropene derived compounds (19 compounds), flavonoids (15 compounds), steroids (7 compounds), alkaloids (3 compounds), and 44 compounds of miscellaneous origin (Sun et al. 2017). Different species of this genus have been reported to exhibit different phytochemical contents such as *Curcuma longa* contains highest phenols (curcuminoids) (Sarangthem and Haokip 2010), *Curcuma angustifolia* has highest alkaloid contents (Dutta 2015), while *C. karnatakensis* has lowest phenolic contents

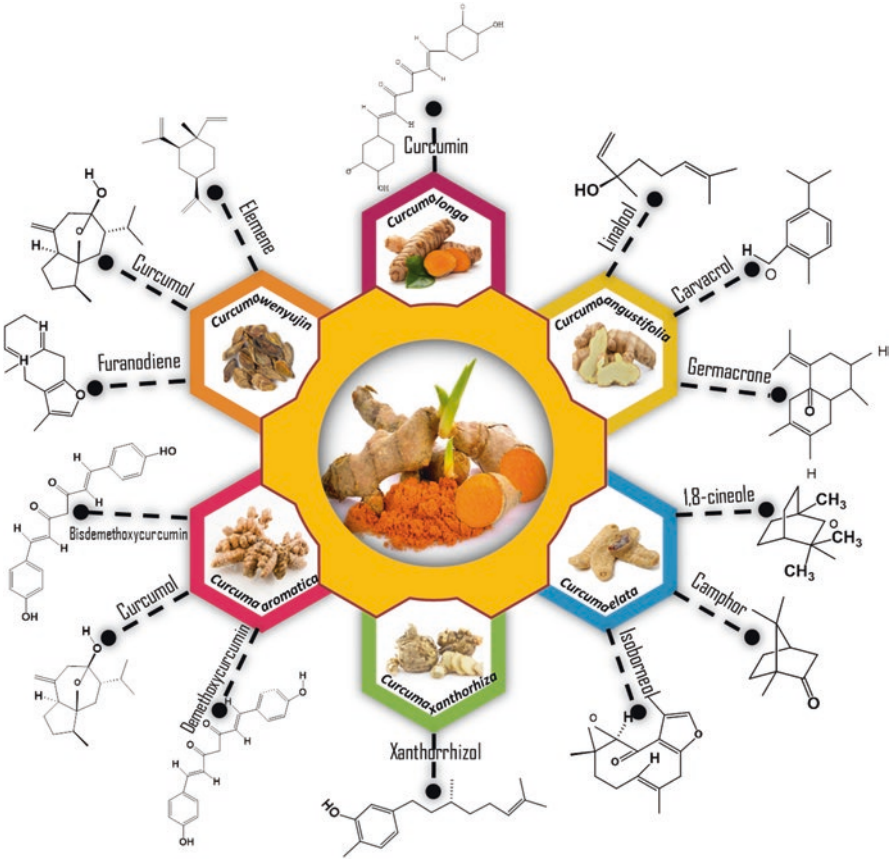

Fig. 9.1 Structural representation of anti-breast cancer compounds isolated from various species of genus Curcuma

(Tejavathi et al. 2017). Anti-breast cancer compounds isolated from various species of genus curcuma have been summarized in Fig. 9.1.

The brief account of potent compounds active against breast cancer is described here briefly:

2.1 Terpenoids

Terpenoids is a class of various non-aromatic as well as aromatic, volatile/non-volatile constituents which are pharmacologically active phytochemicals and play vital role in herbal medicine (Abdel-Lateef et al. 2016). According to an estimate, more than 30,000 terpenoids are known from plant sources exceeding over the number of alkaloids and other classes of compounds. Among the class of terpenoids in

genus curcuma, monoterpenes have been found to possess most significant anticancer activity (Pang et al. 2018). Generally, the term terpene tends to denote the compounds having integral number of C5 units. On the basis of number of C-atoms, terpenoids constitute mono-sesqui-di-tri- and isoprenoid units (de las Heras et al. 2003). Another class of compounds, beta diketones, is a main moiety of Curcuma family. It is not very common in nature but their excellent anticancer activity has made them to reach at preclinical stage of research (Kljun and Turel 2017).

2.1.1 Monoterpenes

Monoterpenes are categorized under the category of secondary metabolites. These compounds play role as a mediators among plants and their environment (Koziol et al. 2014). Several studies have documented the medicinal importance of natural and synthetic monoterpenes as antioxidant, antibacterial, anti-inflammatory and anti-cancer compounds (Moniczewski et al. 2011). Like all other terpenoids, monoterpenes are naturally derived from isopentyl-diphosphate and its allylic isomer dimethylallyl-diphosphate (Ramak et al. 2014).

There are several reported monoterpenes which are found potent against breast cancer. *Curcuma angustifolia* contain linalool and carvacrol, constituent of dried rhizome (Defilippi et al. 1991). Monoterpene constituent of *Curcuma elata* include camphene, camphor, 1,8 cineole, isoborneol and zederone (Syed Abdul Rahman et al. 2013; Ahmed Hamdi et al. 2014). Moreover, compounds such as linalool (Ravizza et al. 2008), carvacrol (monoterpenes) (Arunasree 2010), germacone (Zhong et al. 2011; Xie et al. 2014; Lim et al. 2016), and furanodiene (sesquiterpenes) (Li et al. 2011a, b) are reported to hold anti-breast cancer potential.

Linalool is an acrylic monoterpene alcohol extracted from essential oil of aromatic plants. It is reported to have antiproliferative and chemo sensitizing properties against breast cancer (Ravizza et al. 2008). Carvacrol recently captured attention of scientific community due to its high profile of biological activities. It is considered that hydrophobic interactions and hydrophilic properties of aromatic rings with OH group make it suitable antioxidant, antiproliferative and anticancer agent (Memar et al. 2017). Camphor is a transparent waxy solid with a stout aromatic odor and has a terpenoid heptanone origin (Chen et al. 2013).

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2.1.2 Sesqueterpenes

Sesqueterpenes, a sub-class comprised of three isoprene units whose formation is subjected to condensation of two precursor units, isopentenyl-diphosphate (IPP) and dimethylallyl-diphosphate (DMAPP) (Springob and Kutchan 2009; Jiang et al. 2016). Sesquiterpene lactones are the sesquiterpenes which hold a pentacyclic lactone moiety. Among these compounds, germacrone (Xie et al. 2014), furanodienone (Li et al. 2011b), zederone are cytotoxic compounds and carry potential against breast cancer.

Aromatic turmenone or 6S-2-methyl-6-(4-methylphenyl) hept-2-en-4-one is an antitumor bisabolane sesquiterpene (Afzal et al. 2013), that has been extracted from *C. longa, C. amada* and *C. wenyujin* (Park et al. 2012; Gao et al. 2014; Huang et al. 2017).

2.2 Beta-diketones

This subgroup of organic compounds possesses specific characteristics due its keto-enol tautomerism. Beta-diketone scaffold occurs naturally in curcumin and its derivatives. They are reported as ROS scavengers, anti-inflammatory, anticancer as well as chemopreventive agents with multitargeted molecular mechanisms. They influence on the signal transduction pathways (NF-κB and Nrf-2) and tumor suppressor gene p53 (Kljun and Turel 2017).

Curcumin, diferuloylmethane, has been described as chief constituent of *Curcuma longa* (Soleimani et al. 2018). It is the major anticancer compound and belongs to the polyphenols class of phytochemicals (Basnet and Skalko-Basnet 2011). Intensive investigations revealed the anticancer potential of curcumin that lies in inhibition/activation of transcription factors and tumor related proteins expression regulation (Ortega and Campos 2019). Other curcuminoids derived from *C. longa* include bisdemethoxycurcumin and demethoxycurcumin (Sasikumar 2001). Table 9.1 presents various classes of anti-breast cancer compounds isolated from genus Curcuma.

3 Anti-breast Cancer Activity of Genus Curcuma

Natural products have been utilized for the cure of various ailments and great source of drug discovery (Harvey et al. 2015). Many chemopreventive drugs are the molecules isolated from medicinal plants or their derivatives (Nageen et al. 2020). Nowaday's different chemotherapies and drugs have very confined success. These drugs are expensive and have toxic effects, so there is need of drugs that are inexpensive and less toxic (Wei et al. 2019). Cell signaling pathways are the leading pillars of cell communication as they are crucial for regulating cell proliferation and

Table 9.1 Curcuma derived compounds with their classes and natural sources

Class	Compound	Part of plant	Natural sources	Reference
Monoterpene	Linalool	Rhizome	*C. angustifolia*	Srivastava et al. (2006), Alinejad et al. (2013)
	Carvacrol	Essential oil		Sgorlon et al. (2016)
Sesquiterpene	Germacone	Dry rhizome	*C. angustifolia*	Kong et al. (2017)
	Furanodienone	Essential oil		
	Curcumol	Essential oil, dry rhizome		Ahmed Hamdi et al. (2014)
	Xanthorrhizol	Rhizome extract	*C. xanthorhiza*	Helen et al. (2012)
	Elemene	Rhizome	*C. wenjian*	Hughes et al. (2011), Liu (2013)
	Furanodiene	Rhizome		
	Zederone	Dry rhizome, essential oil, petroleum extract	*C. zedoaria*	Navarro Dde et al. (2002)
	Curdione		*C. elata*	Pimkaew et al. (2013)
	ar-turmerone	Rhizome	*C. longa*	Kocaadam and Sanlier (2017)
Beta-diketone	Curcumin	Rhizome	*C. longa*	Nabavi et al. (2018)
	Bisdemethoxycurcumin	Essential oil	*C. aromatic*	Dong et al. (2017), Liu et al. (2018)
	Demethoxycurcumin	Methanolic extract		

survival. Retrogression in these signaling pathways eventually leads to different pathological conditions incorporating cancer. Many chemopreventive and chemotherapeutic agents help to induce apoptosis in cancerous cells (Sarfraz et al. 2017).

Various studies reveal that different compounds isolated from *Curcuma*, are capable to retard the process of carcinogenesis by targeting different signaling network correlate with tumor cell proliferation. *In vitro* as well as *in vivo* studies of Curcuma derived compounds provide a clear image to researchers to investigate and summarize it deeply (Sun et al. 2017). By using high performance liquid chromatography different isolated bioactive compounds include flavonoids, terpenoids and diphenylalkanoids that were induced DNA fragmentation and leads towards the apoptosis in different cell lines of breast cancer (Zhou et al. 2016).

Carvacrol, an active constituent of *Curcuma angustifolia*, is known to exhibit cytotoxic potential against two breast cancer cell lines, MDA-MB 231 and MCF-7 (Zhou et al. 2016). Bismethoxycurcumin derived from the family *Curcuma aromatica* and it activates the p53 in MDA-MB 231 which is a tumor suppressor gene (Li et al. 2013). Curcumin isolate from fresh rhizome of *Curcuma* and it inhibits the p38MAPK and PI3K and downregulate the NF-κB (Chiu and Su 2009; Zhou et al. 2009; Palange et al. 2012). More experimentations and extensive investigations are the prerequisites to fill up the gaps regarding the molecular mechanisms by these

bioactive compounds in extrinsic as well as intrinsic mitochondrial pathways. The rhizome extracts of Curcuma (Rhizoma Curcumae) have been reported to enhance the doxorubicin activity in breast cancer (MCF-7) cells in by blocking the activity of P-gp and decreasing its expression (Zhong et al. 2018).

3.1 Curcuma and Cell Cycle Arrest

Cancer, uncontrolled cellular division, has been extensively investigated so that its cure could be found and the potential of conventional therapies could be enhanced. Natural compounds are crucial for increasing the potency of the targeted therapies. The inhibition of mitotic division declared to be promising target for chemotherapies and regulated through naturally occurring bioactive compounds (Wei et al. 2019). In cell cycle regulation different proteins and enzymes are involved such as cyclin dependent kinases (Asghar et al. 2015).

Various compounds derived from the different species of *Curcuma* have been known to arrest cell cycles at G2/G21 and M phase in breast cancer cell lines (Ravizza et al. 2008). The cell cycle arrest was found to be associated with the structural changes in tubulin proteins after which the chromosomal segregation occurred in an abnormal manner (Basile et al. 2009). In MCF-7 and BT-20 cancerous cell lines the cells are the number of cells decreased in G2/S phase after the treatment of the curcumin (Mehta et al. 1997).

With the treatment of xanthorrhizol to MCF-7 the growth was prohibited and caused the cell cycle arrest at G1 phase by increasing the level of p53 (Cheah et al. 2006). Furanodiene treatment leads the MCF-7 and MDA-MB231 towards G0/G1 phase by the hitting the molecular targets such as inhibition of the cycline D1 and CDK2 in does dependent manners (Zhong et al. 2012). The growth potential of breast cancer cell lines prohibited by the treatment of curcumol and cell cycle arrested at G1/sub G1 phase while enhanced the expression of p73, p-FAK, p-Akt and p-PI3K (Zhong et al. 2014; Huang et al. 2017).

3.2 Curcuma and Apoptosis

Apoptosis, programmed cell death, is an intricately fabricated event for cellular demise in human body which is regulated under the action of various signaling events to eliminate the harmful cells inside the body. It is essentially a vital feature of biological phenomena e.g., immune system functioning and embryonic development. Various disorders including neurodegenerative diseases and tumor formation can occur as a result of dysregulated apoptosis. Caspases are the cell death executioners which manipulate the process of apoptosis via intrinsic/extrinsic pathways (Wei et al. 2019). Chemopreventive agents which are isolated from mother nature

contribute towards the induction of apoptosis and activation of caspases (Ashkenazi 2015).

Compounds isolated from *Curcuma* exhibit great prevention against various cancer cell mainly against different cell lines of breast cancer. Cytotoxic activity of xanthorrhizol has been claimed to be responsible for causing cell death through the p53 regulation and by downregulation of Bcl-2 (Cheah et al. 2006), inhibiting the NF-κB (Palange et al. 2012), increasing proapoptic proteins, Bax (Xie et al. 2014), activation of caspase 9,3 (Zhong et al. 2011). According to the study curcumin have potential to decrease the level of c-jun/Ap-1 in MCF-7 cancerous cells (Mehta et al. 1997) and in MDA-MB 231 with the help of furanodienone HER2, Akt downregulates (Li et al. 2011a). Here further investigations are also required for the elucidation of apoptotic pathways different cancer cells via these bioactive biological compounds. Some of the anticancer agents from genus Curcuma and their molecular mechanisms have been discussed in Table 9.2.

The species belonging to genus Curcuma have been proclaimed as an attractive candidate with multitargeted chemotherapeutic effects. The anticancer property of Curcuma plants has been investigated to occur as a result of modulation of several cell signaling pathways (NF-κB, STAT3, Wnt, MAPK, and PI3K/Akt/mTOR) (Kunnumakkara et al. 2017a, b; Song et al. 2019), induction of tumor suppressor genes, alleviation of anti-apoptotic gene products (Bcl-2, XIAP, survivin, Bcl-xL), and activation of caspases (Cas-3, -7, -9) (Jiang et al. 1996; Bush et al. 2001; Chan and Wu 2004) in addition to suppression of MMPs (Fenton et al. 2002) and angiogenic cytokines (VEGF, TGF-β1) (Leyon and Kuttan 2003; Bobrovnikova-Marjon et al. 2004). Different types of cell signaling pathways, cell cycle regulators and cytokines, which are targeted by Curcuma-derived compounds have been elaborated in Fig. 9.2.

3.2.1 Curcuma and p53

Tumor suppressor gene, p53, has been reported to be involved in various cellular mechanisms e.g., repairing DNA, arresting cell cycle and inducing apoptosis. This particular gene becomes deregulated or non-functional in almost 50% of human cancers. In case of breast cancers, mutations in p53 gene are responsible for low survival rates and high resistance against conventional therapies. Hence we can conclude that targeting p53 activity is an important strategy in to treat cancer by the modulation of posttranslational modifications (ubiquitination, phosphorylation and acetylation) (Talib et al. 2018).

The phytochemical potential of medicinal herbs depends on the action mechanism of constituent molecules and moieties (Ooko et al. 2017). Curcumin induces the growth retarding effect on the breast cancer cells by acting as a proapoptotic agent (Talib et al. 2018). Linolool, a monoterpene, moderately inhibits the cancer cells proliferation by causing the programmed cell death and arresting cell cycle at increasing p53 levels and inducing cell cycle arrest at G2/M and G1 phase. An increase in the levels of p53 and p21was also noticed (Ravizza et al. 2008). In

Table 9.2 Curcuma-derived bioactive compounds with their mechanisms of action against breast cancer

Anticancer compounds	Cancer type/cell line used	IC_{50}/EC_{50}	Cell cycle arrest	Molecular targets	References
Linalool	MCF7 WT	200 μM	G2/M, G1	Bcl-xL↓, p53↑	Ravizza et al. (2008)
	MCF7 Adr^R	128 μM			
Carvacrol	MDA-MB 231	100 μM	S phase	MMP↓, PARP cleavage↑, $Caspases^{Act}$, Bcl2/Bax↓	Arunasree (2010)
Germacrone	MDA-MB-231	1.27 μM	G0/G1, G2/M, G1, G2	ERα↓, Bcl-2↓, p53↑, bax↑ PARP cleavage, Caspases 3, 7, 9^{Act}, LDH↑, Bok↑, ESR1↓, p-ATM↑, TFF1↓, GREB1↓, CCND1↓, PGR↓, CCND1 ⊥, MYC⊥, MDR1⊥, LDH release↑, p-ATR ↓, p-cdc2↓ p-Rb↓, cdc2↓, LDH1 release↑	Zhong et al. (2011), Xie et al. (2014), Lim et al. (2016), Kong et al. (2017), Al-Amin et al. (2019)
	MCF-7/ADR	180 μM			
	MCF-7	246.3 μM			
Furanodienone	BT474	---	G1	p-EGFR↓, EGFR/HER2⊥, HER2↓, Akt↓, Gsk3β↓, $p27^{kipl}$↑, ERα↓, c-Myc↓, Bcl-2↓, cyclin-D1↓	Li et al. (2011a, b)
	MDA-MB-231				
	SKBR3				
	MCF-7				
	T47D				
Bisdemethoxycurcumin	MCF-7	---	G2	$p53^{Act}$, $p21^{Act}$, $p16^{Act}$, Rb^{Act}, MMP↓	Li et al. (2013)
Demethoxycurcumin	MDA-MB-231	9 μM	---	ECM↓, MMP-9↓, AP-1↑, ICAM-1↓, CXCR4↓, NF-κB↓	Yodkeeree et al. (2010)
Curcumol	MDA-MB-231	---	G1, G1/subG1	MMP-9↓, JNK ½⊥, Akt⊥ eEF1A1↓, p73↑, $p53^{Act}$, Bak↑, PUMA↑, ABCC3↓, $NFAT^{Act}$, Cas-3 ↓, PARP cleavage↑, p-FAK, p-Akt↑, p-PI3K↑, p-p85↑, MMP-9↑, Cas-3, -7, -9^{Act}, ROS↑	Ning et al. (2016), Huang et al. (2017), Qi et al. (2017), Mbaveng et al. (2018), Zeng et al. (2020)
	4T1				
	MCF-7				

Curcumin	MDA-MB-231	20 μM	G0/G1, G2/S, G2/M	Bcl-2↓, ROS↓, Caspase-3, 9↑, MMP-3⊥, EGF↓, c-jun/Ap-1↓, Beclin1↓, PI3K⊥, uPA↓, p-ERK⊥, p-p38⊥, COX-2↓, p21/WAF/CIPI↑, p53↑, AP-1⊥, NFκB⊥, IL⊥, Cdk inhibitor↑, STAT-3⊥, p-PAR-γ⊥, NOS↓, TNFα↓, Tyr701↓, MMP-9↓, EGF↓, IL-8↓, PDGF↓, TGFα↓, VEGF↓, GH↓, pSTAT-3, Tyr694↓, JAK-2↓, caspase-3 ^{Act}, hTERT↓, p38-MAPK ^{Act}, GH↓, pSTAT-1, GCSF↓, JAK-2↓, pJAK-2↓, PIAS-3↑, SOCS-1↓, SOCSS-3↓, FAS⊥, Bax↑, Bcl-2↓, p-Akt↑, siRNA↑, Axl↓, Slug ↓, CD24 ↓, Rho-A↓, N-cadherin↓, β-catenin↓, Twistl↓ p21↑, BcL-xL↓, Bcl-2↓, p65↓, IKKα⊥, IKKβ⊥, ERK1/2^{p}↑, c-myc↓, Cyclin D1↓, bFGF↓, pSTAT-5↓, pSTAT-1	Mehta et al. (1997), Chiu and Su (2009), Zhou et al. (2009), Boonrao et al. (2010), Palange et al. (2012), Zong et al. (2012), Cine et al. (2013), Jiang et al. (2013), Kazemi-Lomedasht et al. (2013), Jain et al. (2015), Kumar et al. (2015), Kunnumakkara et al. (2017a), Coker-Gurkan et al. (2018), Gallardo et al. (2020)
	MDA-MB-453				
	MCF-10A	20 μM			
	NIH3T3				
	MCF-7	9.7 μM			
	T-47D	40 μM			
	BT-20				
	MDA-MB-468	22 μM			
	SK-BR-3				
	SK-BR-3	20 μM			
	MCF-7/LCC9	11.3 μM			
	MCF-7/LCC2	12.2 μM			
Xanthorrhizol	MCF-7	1.71 μg/mL	G1	pS2↑, PARP cleavage↑, p53↑, Bcl-2↓	Cheah et al. (2006), Anggakusuma et al. (2009)
Elemene	MCF-7			Heparanase↓, FDF-2↓, VEGF↓, p-ERK↓, p-AKT↓	Zhang et al. (2017)
	MDA-MB231				
	MDA-MB435S				
	4T1				
Furanodiene	MCF-7	75 μM	G0/G1	p-cyclin D1⊥, CDK2⊥, Rb⊥, p-Rb⊥, Bcl-xL⊥, Bad↑, Bax↑, Cas-9↑, PARP↑, I αV↓, β-catenin↓, p-Akt↓, p-PI3K/p85↓, p-FAK⊥, MMP-9↓, MMP-2↓, Cas-3^{Act}, Cas-7 ^{Act}, Bcl-xL↓, Bad↑, PARP ^{Act}, ROS↑, Cleavage of Cas-8↑, TNF-α↑, NF-κB↑, p-CDK2⊥, Akt ⊥	Yang et al. (2005), Zhong et al. (2012, 2014, 2017)
	MDA-MB231				
	MCF-7/DOX^{R}				

(continued)

Table 9.2 (continued)

Anticancer compounds	Cancer type/cell line used	IC_{50}/EC_{50}	Cell cycle arrest	Molecular targets	References
ar-turmerone	MDA-MB231		G0/G1	MMP-9 ⊥, COX-2 ⊥, p-PI3K/Akt↓, E-cadherin↑, CXCR4↑, CCR7↓, CXCR4↑, NF-κB⊥, p-ERK1/2↓	Park et al. (2012), Gao et al. (2014)
Zederone	MCF-7	>100.0 μg/mL			Syed Abdul Rahman et al. (2013), Ahmed Hamdi et al. (2014)
Curdione	MCF-7	125.6 μg/mL		Bax↑, cleaved caspase-3,-9↑, Bcl-2↓	Kong et al. (2013), Li et al. (2014)
	MDA-MB-231				
Terpecurcumin Q	MCF-7	3.9 μM	Sub G1↑	Caspases ^{Act}, Bcl-2↓, Bcl-xl↓	Lin et al. (2013), Essien et al. (2015)
	Hs578T	98.86 μg/mL			
Tetrahydrocurcumin		33.μM			Kang et al. (2014)
Curcumenol	MCF-7	9.3 μg/mL			Ahmed Hamdi et al. (2014)

Upregulation ↑, Down regulation ↓, Activation ^{Act}, Inhibition ⊥, transmembrane molecule B-cell lymphoma extra-large gene (Bcl-XL), apoptosis regulator gene (Bax), Bcl associated death protein (Bad), cyclin dependent kinase (Cdc2), poly ADP ribose polymerase (PARP), cysteine-aspartic proteases (Caspase3–9), tumor suppressor retinoblastoma protein (pRB), estrogen signaling receptor (ESR), tumor suppressor gene (p-53), serine threonine kinase protein (ATM), Tree foil factor family (TFF1), growth regulation by estrogen in breast cancer (GREB1), cyclin D1 gene for cyclin family (CCND), progesterone receptor (PGR), transcription factor encoding protoonco gene family (Myc), cyclin dependent kinase (CDK-1), intercellular adhesion molecule (ICAM)-1, epidermal growth factor receptor (EGFR), matrix metalloproteinases (MMPs), human epidermal growth factor receptor (EGFR), protein kinase B (Akt), glycogen synthetase kinase (GSK 3B), cyclin dependent kinase inhibitor-1 (P21), estrogen receptor α (ER α), tumor suppressor protein (P53), extracellular matrix (ECM), plasminogen activator inhibitor-1 (PAI-1), chemokine ligand-receptor (CXCR4), nuclear factor-κB (NF-κB), PUMA (p53 upregulated modulator of apoptosis), Jun N-terminal kinase (JNK), eukaryotic translation elongation factors 1 alpha (eEF1A1), tumor suppressor gene of P53 family (P73), cyclin dependent kinase inhibitor (P27), ATP binding cassette subfamily C member 3 (ABCC3), nuclear factor of activated T cells (NFAT), tissue inhibitor of matrix metalloproteinases (TIMP-1), reactive oxygen species (Ros), Jun Proto-Oncogene, AP-1 transcription factor subunit (c-jun/AP-1), autophagy related protein (Beclin-1), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinases (P38), protein is a marker for hormone-dependent breast tumors (pS2), endo-glycosidase expressed in mammals, (Heparinase), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2), growth hormone (GH), protein inhibitor of activated STAT (PIAS), suppressor of cytokine signaling (SOCS-2), surface antigen receptor (Fas), small interfering RNA (siRNA), receptor tyrosine kinase (AXL), member of the SNAIL family of transcriptional repressors (Slug), family of GTPases is a family of small (Rho-A), cell–cell adhesion molecule (N-cadherin), embryonic transcription factors (*TWIST*), telomerase reverse transcriptase (hTERT), nuclear focal adhesion kinase (FAK), cyclooxygenase-2 (Cox-2), Janus kinase/signal transducer and activator of transcription (JAK/STAT)

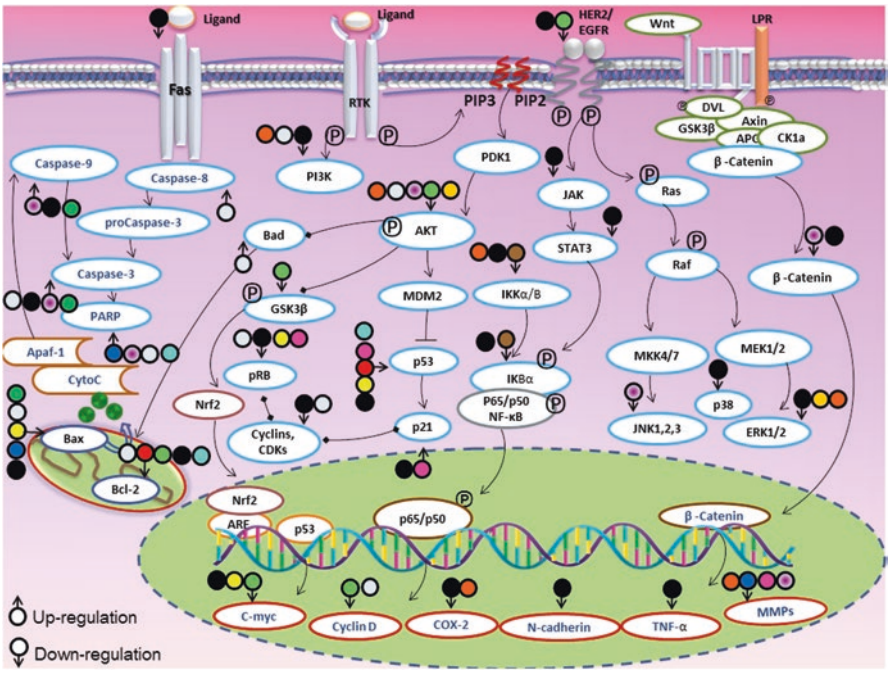

Fig. 9.2 An overview of the anti-breast cancer potential of different compounds extracted from plants of genus Curcuma. The molecular mechanism lying behind this activity involves the modulation of various cell cycle regulators, protein kinases, enzymes and hormones, and apoptosis related factors which are known to be involved in the invasion, proliferation, angiogenesis and metastasis of breast cancer. Dots of different colors symbolize the compounds given in the table below the figure

another experiment, the cytotoxic effect of germacrone was noticed on MCF-7/Adriamycin (multidrug drug resistant human breast cancer) cell line. The results elaborated that combined treatment of germacrone and adriamycin resulted in an increased cytotoxicity as compared with Adriamycin alone. The increased levels of proapoptotic proteins (p53 and bax) were also noticed (Zhou et al. 2009; Xie et al. 2014). Curcumol also activated the expression of p53 and induced apoptosis in human TNBC (triple negative breast cancer) cells (Huang et al. 2017) and is known to enhance doxorubicin sensitivity in vitro and in vivo (Zeng et al. 2020).

3.2.2 Curcuma and NF-κB

NF-κB, a proinflammatory transcription factor, is responsible for the regulation of ~500 genes which in turn control various inflammatory responses and tumor formation processes (Kunnumakkara et al. 2017a; Catanzaro et al. 2018). The alterations in the activation of NF-κB are involved in causing pathological abnormalities including cancer. Hence the modulation NF-κB is a major regime to control cancer

progression (Kunnumakkara et al. 2017a). Phytochemicals are the ray of light for the treatment of fatal calamities such as cancer.

The use of herbal medicines for the cure of cancer has been gaining a great attention due to the presence of bioactive constituents (Talib et al. 2018). Some bioactive compounds from genus *Curcuma* have been reached in the clinical trials, because of their chemotherapeutic potentials. Curcumin (diferuloylmethane) has been assumed to possess anticancer potential against breast cancer in a number of in vitro as well as in vivo experiments. Its treatments, either alone or in combination, are in Phase I/II trials against breast, colon, pancreatic, and prostate cancers targeting the molecular and transcription factors e.g., NF-κB (Zong et al. 2012; Coker-Gurkan et al. 2018). It is known to inhibit the migratory ability of human triple negative (MDA-MB231) cells by decreasing NF-κBp65 protein expression (Chiu and Su 2009). Another compound, Calebin A (4-[3 methoxy-4 hydroxyphenyl]-2-oxo-3-enebutanyl 3-[3-methoxy-4 hydroxyphenyl] propenoate), from *C. longa* is known to inhibit the activation of NF-κB by interacting with p65 protein ultimately leading to apoptosis induction (Tyagi et al. 2017). An experiment by Yodkeeree et al. (2010) stated that Curcuma derived compound, demethoxycurcumin, strongly inhibited NF-kB and expression of p65 in the nucleus of treated cells (Yodkeeree et al. 2010).

3.2.3 Curcuma and STAT3 Pathway

Signal Transducer and Activator of Transcription 3 is a transcription factor which has been reported to be involved in oncogenesis process. Its regulation is highly complex under different situations. It is involved in regulating the normal stem cells while on the other hand it is constitutively expressed in certain types of cancers. Hence its modulation can be regarded as an attractive target towards the control of cancer (Kunnumakkara et al. 2017a; Galoczova et al. 2018).

Various bioactive entities from natural plants have been proved their worth as effective anticancer agents against a variety of cancer types including breast cancer. Curcumin, a primary active ingredient from *C. longa* has been proved to be an effective modulator of JAK/STAT pathway by suppressing the phosphorylation of JAK 1, STAT 1 and STAT 3 (Li et al. 2018). Moreover, experimental evidences have stated that curcumol inhibited the Janus kinases activation and Akt signaling ultimately suppressing the breast cancer cell metastasis in triple negative breast cancer (MDA-MB231) cells (Ning et al. 2016).

3.2.4 Curcuma and Wnt Signaling Pathway

Another signal transduction pathway for the regulation of cellular development, death or demise is Wnt/β-catenin cascade, the dysregulation of which may contribute towards the spread of diseases e.g., cancer.

Curcumin, the important component of *Curcuma longa*, contributes towards the modulation of Wnt/β-catenin signaling in various types of cancers. Curcumin

treatment to MCF-7 as well as MDA-MB-231 cells, retarded Wnt/β-catenin signaling and changed the pattern of c-cyclin D1, Myc, E-cadherin, and GSK3β expression. The same bioactive compound was reported to stop the metastasis of CSCs of breast cancer by restoring E-cadherin expression, hence causing an increase in E-cadherin/β-catenin complex formation. Moreover, treatment with curcumin was investigated on ER-negative human breast cancer cells and the results elaborate that a transient increase in the level of β-catenin was noticed (Kunnumakkara et al. 2017a). Furanodiene decreased the expression of β-catenin, phosphorylation in FAK (Focal adhesion kinase), Akt and PI3Kp85, thus decreasing the tumor metastasis (Zhong et al. 2014).

3.2.5 Curcuma and MAPK Pathway

MAPK (Mitogen-activated protein kinase) pathway acts as a significant signal transduction cascade which constitutes the emerging point for other signaling pathways e.g., serine/threonine and tyrosine kinases, calcium signaling and G proteins. MAPK, the family of phosphoproteins, constitutes the signaling molecules which lead to the generation of proinflammatory mediators. Hence MAPK inhibition is thought to be an effective strategy for the control of cancer proliferation (Chauhan et al. 2018).

Curcuma longa, a widely utilized culinary spice, is utilized as anticancer agent against variety of cancers including breast cancer. Curcumin, an important constituent of *C. longa* exhibits robust potential against many diseases of malignant and non-malignant origin including cancer (Ooko et al. 2017). It modulates the MAPK pathway and induces apoptosis. Tetrahydrocurcumin, a polyphenolic compound from *Curcuma* species explicit antitumor potential in vivo by increasing Bax/ Bcl-2 ratio and activating caspase-2 as well as p38 MAPK in MCF-7 cells (Kang et al. 2014).

3.2.6 Curcuma and PI3K/Akt/mTOR Pathway

Protein kinases are involved in controlling the cellular functions e.g., RNA transcript formation, protein formation, and cellular growth by the process of phosphorylation. Their deregulations contribute towards the oncogenesis process. PI3K/Akt/mTOR signaling is stimulated to enhance the metabolism, survival and growth of cancerous cells (Asati et al. 2016). PI3K, Phosphatidylinositol-3 kinases, comprise of lipid kinase family which are able to catalyze the phosphorylation of inositol ring 3′-OH group in inositol phospholipids to generate the phosphatidylinositol-3,4,5-triphophate (Fresno Vara et al. 2004). Akt or protein kinase B is involved in various cellular events involved in the survival, progression and growth of the cell. The mutations as well as the amplifications in Akt result in the process of carcinogenesis (Fresno Vara et al. 2004; Kunnumakkara et al. 2017a).

Another kinase mTOR is also a part of cellular growth and progression machinery. The aberrations in its upstream activators as well as its downstream effectors are also found to be involved in malignant conformities (Kunnumakkara et al. 2017a).

Phosphorylation of Akt and its upstream targets EGFR, HER2 were decreased by furanodienone expose in case of HER2-overexpressing human breast cancer cells (Li et al. 2011a) while ERα negative MDA-MB-231 and MCF-7 cells responded less to furanodienone exposure (Li et al. 2011b; Zhong et al. 2012). Elemene extracted from Curcumae Rhizoma is reported to alleviate the phosphorylation of Akt and extracellular signal-regulated kinase (Zhang et al. 2017). Curcumin also inactivates the cell signaling pathways e.g., NF-kB, Src and Akt/mTOR pathways (Jiang et al. 2013). Likewise, aromatic turmerone also decreased the phosphorylation of PI3K/Akt signaling and ERK1/2 signaling (Park et al. 2012).

4 Conclusions

This book chapter aims to update the researchers and scientific community about genus Curcuma and its isolated compounds regarding their anti-breast cancer activity. The anticancer potential of this plant is attributed to the presence of bioactive terpenes and betadiketones such as curcumin, furanodienone and curcumol. These unique chemical structures have been reported as efficient modulators of several deregulated cancer signaling pathways (β-catenin, Wnt, and PI3K/Akt/mTOR signaling), apoptosis related factors (caspase-3, -7, 9, Bax, Bcl-2, and p-53), cell cycle regulators (cyclins and CDKs), protein kinases (ERK, JNK, MAPK) and transcriptional factors (NF-κB and STAT3). Being nutraceuticals, these compounds will emerge as biosafe lead candidates for cancer drug discovery. Various lines of evidences suggest that some compounds of this genus have entered into the preclinical trials which further ensure the curative potential of Curcuma derived compounds against many diseases including cancer.

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