Chapter 15
Gambogic Acid and Its Role in Chronic Diseases

Manoj K. Pandey, Deepkamal Karelia and Shantu G. Amin

Abstract Kokum, a spice derived from the fruit of the *Garcinia hanburyi* tree, is traditionally used in Ayurvedic medicines to facilitate digestion and to treat sores, dermatitis, diarrhoea, dysentery, and ear infection. One of the major active components of kokum is gambogic acid, also known as guttic acid, guttatic acid, beta-guttilactone, and beta-guttiferin. Gambogic acid's anti-proliferative, anti-bacterial; antioxidant and anti-inflammatory effects result from its modulation of numerous cell-signaling intermediates. This chapter discusses the sources, chemical components, mechanism of action, and disease targets of the kokum spice.

Keywords Neutraceuticals · Dietary agents · Gambogic acid · Kokum · Cancer · Signal transduction pathways

15.1 Introduction

Mother Nature has gifted us a variety of natural agents, including nutraceuticals. One of the well-known nutraceuticals is Gambogic acid (GA), which is a xanthonoid derived from the brownish or orange resin from *Garcinia hanburyi* (Fig. 15.1). *Garcinia hanburyi* is a small to medium-sized evergreen tree with smooth gray bark, and it is native to Cambodia, southern Vietnam, and Thailand. *Garcinia indica*, primarily of Indian origin, is known by many names: bindin, biran, bhirand, bhinda, kokum, katambi, panarpuli, ratamba, amsol, and tamal. In English language, it is commonly known as mangosteen, wild mangosteen, red mango, Hanbury's Garcinia, gambojia, gamboge, and Indian gamboge tree. Germans called this gummi-gutti.

The *Garcinia indica* seed contains 23–26 % oil, which is used in confectionery, medicines, and cosmetics. It is used in curries and other dishes as a slightly bitter spice, a souring agent, and as a substitute for tamarind.

M.K. Pandey (✉) · D. Karelia · S.G. Amin
Department of Pharmacology, College of Medicine, Pennsylvania State University, 500 University Dr., Hershey, PA 17033, USA
e-mail: mkp13@psu.edu

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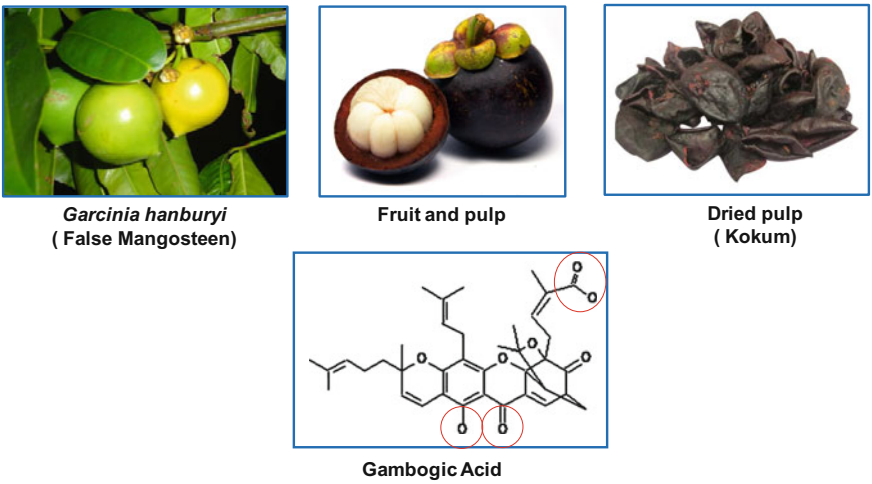

Fig. 15.1 Plant species and fruits by which gambogic acid is derived. *Highlighted circles* on GA structure indicate the most common sites for novel derivative generation

In traditional medicine, such as ayurveda, kokum is prescribed for edema, rheumatism, delayed menstruation, constipation and other bowel complaints, and intestinal parasites. The extract of *Garcinia cambogia* is used as an herbal appetite suppressant and weight-loss supplement.

In last decades, worldwide extensive studies have been performed on Gambogic acid to understand its full potential as therapeutic agents against variety of diseases including chronic diseases such as cancers which is summarized in following sections.

15.2 Physciochemical Properties of GA

GA is also chemically called as Guttic acid, Guttatic acid, beta-Guttilactone, and beta-Guttiferin. The molecular formula and weight of GA is $C_{38}H_{44}O_8$ and 628.76, respectively. The appearance of this xanthone is amorphous orange solid. The core of GA is known as xanthone core and contains a unique 4-oxatricyclo [4.3.1.03,7] decan-2-one scaffold [1, 2]. Earlier studies regarding its structural activity relationships (SAR) revealed that the C¼C bond of the α,β-unsaturated ketone in GA is critical for its antitumor activity, while the HOC(6), C(8)¼O, and C(30)OOH groups could tolerate a variety of modifications Fig. 15.1 [3, 4]. Along these lines various modifications have been performed to make GA as a better antitumor agent [5, 6].

15.3 Modulation of Cell Signaling Pathways by GA

Enthusiasm shown by researchers from around the globe clearly suggests that GA has been one of the "hot" nutraceuticals. GA has shown to be effective on different chronic diseases (Sect. 4.1 covers different chronic diseases), but its effect on cancer has been studied the most. Almost a decade ago our group showed that the anti-inflammatory and anticancer response of GA is associated with its inhibitory response on Nuclear Factor-Kappa B (NF-κB) [7], since then plethora of studies suggest that GA regulates several key signaling pathways. GA exhibits anti-proliferative, antioxidant, and anti-inflammatory effects by modulating cell signaling pathways, enzymes, and molecular targets, such as epigenetic regulators, protein kinases, transcription factors, inflammatory biomarkers, and growth regulators. Through microarray analysis, GA modulates many gene products [8, 9] (Table 15.1).

15.3.1 GA Inhibits Signaling of Nuclear Factor-Kappa B (NF-κB)

The transcription factor NF-κB is one of the major mediators of inflammation and is linked with many diseases including cancer, diabetes, arthritis, and neurological disorders. Therefore, an agent that can suppress NF-κB activation has potential for clinical use against various chronic illnesses. GA suppression of NF-κB activation induced by TNF-α, LPS, and various agents [7, 10] leads to the suppression of NF-κB regulated products, such as cyclooxygenase type 2 (COX-2), inducible nitric oxide synthase (iNOS), and survival proteins [7, 10, 11]. These actions give it great potential as a broad-spectrum clinical agent.

15.3.2 GA Inhibits Phosphatidylinositol 3'-Kinase/Protein Kinase B (PI3K/Akt)

Serine/threonine-specific protein kinase B, commonly designated Akt, is a central regulator of widely divergent cellular processes, including proliferation, differentiation, migration, survival, and metabolism [12, 13]. Akt is activated by a variety of stimuli, through growth factor receptors, in a PI3K-dependent manner [12, 13]. Frequently in human cancer, normal signaling along the Akt/PKB/phosphatase, and tensin homolog (PTEN) pathway is disrupted [14]. Akt plays important roles in development, progression, and resistance to chemotherapy in cells [12, 13]. Blocking Akt signaling can mediate apoptosis and inhibit the growth of tumor cells in vitro [14]. GA inhibits Akt activation, which leads to inhibition of tumor cell proliferation and survival [15–19].

Table 15.1 A list of molecular targets of Gambogic acid

Transcription factor
Nuclear factor—kappa B ↓
STAT-3 - ↓
STAT-5 ↓
Inflammatory cytokines
IL-6 ↓
Tumor necrosis factor alpha↓
Enzymes
Cyclooxygenase-2 ↓
Inducible nitric oxide synthase↓
Matrix metalloproteinase↓
Src homology 2 domain-containing typrosine phosphate 2↓
Kinases
Focal adhesion kinase↓
Janus kinase ↓
Mitogen-activated protein kinase ↓
Protein kinase A↓
Protein kinase B↓
Protein kinase C↓
Growth factors
Vascular endothelial growth factor ↓
Receptors
Chemokine (C-X-C motif) receptor 4 ↓
Transferrin receptor ↓
Adhesion molecules
Endothelial leukocyte adhesion molecule-1
Intracellular adhesion molecule-1 ↓
Anti-apoptotic proteins
B-cell lymphoma protein-2 ↓
Bcl-xL ↓
Inhibitory apoptosis protein-1 ↓
Mcl-1 ↓
Survivin ↓
Others
Cyclin D1 ↓
Heat shock protein 90 ↓
Heat shock protein 70 ↑

15.3.3 GA Inhibits Mitogen-Activated Protein Kinase (MAPK)

MAPKs are evolutionarily conserved enzymes that play a key role in the inflammatory stimuli and environmental stresses that lead to the activation of three independent pathways: p44/42 MAPK extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2), c-Jun N-terminal kinase, and p38 MAPK [20]. In vitro studies of several cancer cells showed that GA inhibits MAPK pathways [21]. Moreover, this phytochemical also inhibited ERK in HT-29, HepG2, KBM5, and NCI-H460 cancer cells [22–24].

15.3.4 GA Inhibits Src

The Src family of proteins consists of eight non-receptor tyrosine kinases characterized by a common structure [25]. Src kinases are involved in signal transduction pathways that are triggered by a variety of surface receptors, including receptors for tyrosine kinases, integrin, and antigens, as well as receptors coupled with the G-protein [25, 26]. As a consequence of changes observed in protein expression and kinase activity in cancer cells, the Src family has been implicated in the development of cancer [25, 26]. This prompted the design of specific inhibitors, the most common of which are adenine mimetics, to treat solid tumors and leukemia clinically [25, 26]. In addition, some of the Src kinases expressed in hematopoietic cells play pivotal roles in lymphocyte maturation and activation [25]. This finding encouraged the development of safe and effective Src-specific inhibitors that are currently in clinical trials as immune-suppressants for the treatment of immunological disorders [15, 27]. Separate research showing that GA inhibits Src in PC3, and K562 cells suggests that GA may also have clinical potential against cancers and immunological disorders in which Src plays a pivotal role [15, 16].

15.3.5 GA Inhibits Signal Transducer and Activator of Transcription-3 (STAT-3) Pathways

Proteins in the STAT family are among the best studied of the latent cytoplasmic signal-dependent transcription factors [28–30]. In vitro studies of the MCF-7, MCF-10A, U266, and MM1.s cell lines suggest that GA modulates the nuclear translocation and DNA binding of STAT3 and inhibits genes modulated by this transcription factor [28, 31].

15.3.6 GA Inhibits Chemokine X-Receptor 4 (CXCR4) and Downstream Signaling Pathways

Chemokine receptors belong to class A seven transmembrane G-protein-coupled receptors and consist of 350 amino acids on average. Primary receptors are defined as CXCR, CCR, CR, or CX3CR [32]. The function of atypical chemokine receptors is to modulate immune responses by scavenging, sequestration, buffering as well as intracellular transport of chemokines from inflammatory sites [33–35]. The receptor CXCR4 is expressed on almost all of the hematopoietic cells, embryonic pluripotent, and tissue-committed stem cells, allowing them to migrate and invade along CXCL12 gradients. In malignant cells the chemokine receptor that is most commonly found is the receptor CXCR4 [34, 36]. At least 23 different types of tumor cells from human cancers of epithelial, mesenchymal and hematopoietic origin express CXCR4 [37]. In cancer, CXCL12 plays a role in the mobilization and recruitment of these cells to the inflammatory tumor microenvironment, neo-angiogenic niches, supporting revascularization, tumor growth, and metastasis [32, 38]. Thus an inhibitor of CXCR4/CXCL12 axis will inhibit tumor metastasis, GA is one of those inhibitors. Recently, we showed that GA directly interacts with CXCR4 and inhibits the migration of multiple myeloma cells [17]. We further demonstrate that GA inhibits CXCR4 regulated pathways and suppresses the bone loss [17]. Overall, GA has a tremendous potential to be used a therapeutic agent.

15.3.7 GA Inhibits CBP/p300 Histone Aceyltransferase (HAT) and Histone Deacetylase (HDAC)

The process of histone acetylation and deacetylation in eukaryotic cells alters chromatin structure and thereby modulates gene expression [39]. HATs and HDACs are classes of enzymes that effect histone acetylation [40]. These enzymes can also acetylate and deacetylate several nonhistone substrates, which can have functional consequences. Altered HAT and HDAC activities can lead to several diseases, ranging from cancer to neurodegenerative disorders. Therefore, HAT and HDAC inhibitors are being developed as therapeutic agents. GA inhibits HAT and HDAC activity in A549 lung cancer cells [41]. These activities of GA demonstrate its great potential as a therapeutic candidate.

15.3.8 GA Inhibits the Activation of Focal Adhesion Kinase (FAK)

FAK is a 119- to 121-kDa non-receptor protein kinase widely expressed in various tissues and cell types [42]. Several studies showed that FAK plays an important role

in integrin signaling [43–45]. Once activated, whether by integrin or non-integrin stimuli, FAK binds to and activates several other molecules, such as Src, Src adaptor protein p130Cas, the growth factor receptor-bound protein 2 (Grb2), PI3K, and paxillin, and thus promotes signaling transduction [44, 46–50]. In a recent study, FAK was held responsible for uninhibited proliferation, protection from apoptosis, invasion, migration, adhesion, and spread, as well as tumor angiogenesis [46, 47]. Our group showed that GA modulates the tyrosine phosphorylation of FAK and subsequently induce apoptosis by downregulating Src, ERK, and Akt signaling in prostate cancer PC3 cells [16].

15.3.9 GA Inhibits iNOS

iNOS is expressed in a variety of cell types, particularly inflammatory cells, in response to diverse pro-inflammatory stimuli [51–53]. iNOS, which may be induced by bacterial LPS or its derivative lipid A, is expressed by a variety of solid tumors and generates high levels of nitric oxide inside tumor cells [10]. In vitro studies showed that GA inhibits LPS- and interferon-gamma-induced iNOS in RAW246.6 cells [10].

15.3.10 GA Induces the Production of Reactive Oxygen Species (ROS)

ROS have been linked with various cell signaling pathways [54, 55]. GA, induces the production of ROS [56].

15.3.11 GA Inhibits COX-2

Overexpression of COX-2 is associated with many cancers and is linked with tumor cell proliferation and suppression of apoptosis [57, 58]. Therefore, COX-2 inhibitors have great potential in the treatment of cancers and inflammatory conditions, as evidenced by the U. S. Food and Drug Administration's approval of celecoxib, a known COX-2 inhibitor, for the treatment of various inflammatory conditions [59]. GA, too, has been shown to inhibit COX-2 activation induced by TNF-α in KBM5 leukemic cells [7].

15.3.12 GA Inhibits Matrix Metalloproteinase 7 & 9 (MMP-7 & 9)

Also known as matrilysin, MMP-7 is a "minimal domain" MMP that exhibits proteolytic activity against components of the extracellular matrix [60–62]. MMP-7 is frequently overexpressed in human cancer tissues and is associated with cancer progression [63]. Therefore, MMP-7 inhibitors have great potential in the treatment of cancer [64]. The studies showed that GA inhibits the expression of MMP-7 in breast cancer cells like MDA-MB-231 and MDA-MB-435 [65, 66], further supporting the idea that GA may be effective against breast cancer in humans.

15.3.13 GA Inhibits Tubulin

Microtubules are a major component of the cytoskeleton. They are important in many cellular events and play a crucial role in cell division [67]. As such, microtubules are a highly attractive target for anticancer-drug design. Tubulin-binding agents, also called anti-microtubule or microtubule-targeted agents, are widely used chemotherapeutic drugs with a proven clinical efficacy against breast, lung, ovarian, prostate, and hematologic malignancies, as well as childhood cancers [68, 69]. Research has shown that GA belongs to this class of agents because it inhibits microtubule assembly and prevents cell division [20].

15.3.14 GA Inhibits Expression of Cyclin D1

The sequential transcriptional activation of cyclins, the regulatory subunits of cell cycle-specific kinases, is thought to regulate progress through the cell cycle [70]. Thus, cyclins are potential oncogenes, and overexpression of cyclin D1 or amplification at its genomic locus, 11q13, is commonly seen in breast cancer, head, and neck cancer, non-small-cell lung cancer, and mantle cell lymphoma [71, 72]. GA has been shown to inhibit Cyclin D1 in several cancers including leukemia and multiple myeloma [7, 31].

15.3.15 GA Induces Cleavage of Poly(ADP-Ribose) Polymerases (PARPs)

PARPs are cell signaling enzymes present in eukaryotes and are involved in poly (ADP ribosylation) of DNA-binding proteins [73]. Pharmacological degradation of PARP-1 may enhance the activity of antitumor drugs by inhibiting necrosis and

activating apoptosis [74]. In vitro studies have shown that GA induces PARP degradation and enhances apoptosis in T98 glioma, HeLa, non-small lung cancer A549 and NCI-H460, breast cancer, and multiple myeloma cells [7, 11, 17, 22, 24, 31, 66, 75–77].

15.3.16 GA Inhibits Tumor Necrosis Factor-α (TNF-α)

TNF-α is a vital member of the multifunctional superfamily of TNFs and plays important roles in immunity and cellular remodeling, as well as apoptosis and cell survival [78]. Because TNF-α is a key player in inflammation and cancer, several efforts are underway to develop therapeutic TNF-α antagonists. Two such antagonists are from the *Garcinia* species. At a dose of 5 μM, both GA and cambogin inhibited the release of TNF-α by LPS-activated macrophages [79, 80], suggesting another mechanism for their antitumor activity.

15.3.17 GA Inhibits the Expression of Bcl-2 Family Proteins

The bcl-2 gene family consists of at least 25 genes that are proapoptotic or anti-apoptotic and share at least one of the four characteristic BH domains [81]. The anti-apoptotic protein bcl-2, which displays sequence homology in all four domains (i.e., BH1–BH4), promotes cell survival [82]. Increased expression of the bcl-2 protein commonly occurs in human malignancies and is associated with disease maintenance and progression, resistance to chemotherapy, and poor clinical outcome. Antisense oligonucleotides targeting bcl-2 have been shown to facilitate apoptosis in various tumor types [83]. Therefore, bcl-2 inhibitors have great potential in the treatment of cancer. In vitro and in vivo studies showed that GA inhibits bcl-2 expression in MGC-803, HL-60, MCF-7, A375M, SMMC-7721, BGC-823, Jeko-1, and K562 [15, 84–88].

15.3.18 GA Induces BID

Pro-apoptotic BID activates the multi-domain bcl-2 family members bcl-2–associated X protein (BAX) and bcl-2 homologous antagonist killer (BAK) [89]. Activation of either BAX or BAK produces an allosteric conformational change and releases cytochrome *c* [90]. This means that compounds that can induce BID could be very useful in the treatment of cancer. GA and its derivative GA3 are such inducers because these agents activate BID and induces apoptosis in cancer cells [91].

15.3.19 GA Induces BAD

BAD is proapoptotic and proliferative, suggesting that the cell cycle functions of the multi-domain bcl-2 family members [89]. BAD antagonizes both the cell cycle and anti-apoptotic functions of bcl-2 and bcl-xL through BH3 binding [89]. Overexpression of the BH3-only molecule BAD renders the cell unable to arrest in G0 and persistently activates cdk2 [92]. Previous study showed that GA in combination with nanoparticle Fe3O4 activates BAD and induces apoptosis in LOVO cells [93].

15.3.20 GA Inhibits Cytochrome c

Cytochrome *c*, an intermediate in apoptosis, is released by the mitochondria in response to proapoptotic stimuli. The studies have shown that GA, induces the expression of cytochrome *c* in colorectal cancer HT-29, bladder cancer T24 and UMUC3, breast cancer MDA-MB-231, and human hepatocellular carcinoma cells [94–96].

15.3.21 GA Induces the Activation of Caspase-3 and Caspase-9

Caspases play a central role in mediating various apoptotic responses. In vitro and in vivo research of GA has shown that it induces the activation of caspase-3 and caspase-9 in various cancer cells including glioma, osteosarcoma, non-small lung cancer, leukemia, lymphoma, breast cancer, pancreatic cancer, melanoma and multiple myeloma and, induces apoptosis [7, 11, 17, 22, 24, 31, 66, 75–77].

15.4 Role of GA in Chronic Diseases

Extensive studies from past one decade have shed light on GA's potential as anti-inflammatory and anticancer agents. So far the focus of the studies have been to identify the molecular targets by which GA exerts its effects, primarily on cancer cells. However, a very recent study showed that GA could be used as an anti-psoriatic agent [97]. Importantly, the molecular mechanism by which GA mediates its effect strongly suggest that it could be used for the prevention and treatment of many organ and tissue disorders, which are associated with inflammation and oxidative stress. GA alleviates oxidative stress, inflammation in chronic diseases and regulates inflammatory and pro-inflammatory pathways related with most chronic diseases.

15.4.1 Cardiovascular Diseases

Cardiovascular Diseases (CVDs), including heart disease, vascular disease and atherosclerosis, are the most critical current global health threat. Epidemiological and clinical trials have shown strong consistent relationships between the inflammation markers and risk of cardiovascular diseases [98]. It is widely appreciated that the key mechanisms in the development of CVDs are inflammation and oxidant stress, activation of pro-inflammatory cytokines, chronic transmural inflammation, and C reactive protein (CRP) [99]. Thus cytokines, other bioactive molecules, and cells that are characteristic of inflammation are believed to be involved in atherogenesis. An elegant recent study by Liu et al. [100] showed that GA inhibits pressure overload or isoproterenol infusion-induced cardiac hypertrophy and fibrosis, through the inhibition of the proteasome and the NF-κB pathway, suggesting that GA treatment may provide a new strategy to treat cardiac hypertrophy and changes in myocardial NF-κB signaling [100].

15.4.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) could give rise to a systemic chronic inflammatory disorder and may impact many organs and tissues but mainly attack flexible (synovial) joints [101]. It was reported that oxidative stress made an important contribution to joint destruction in RA [102]. ROS is a significant mediator that activates a variety of transcription factors including NF-κB and AP-1, thus regulating the expression of over 500 different genes, such as growth factors, chemokines, cell cycle regulatory molecules, inflammatory cytokines, and anti-inflammatory molecules [103]. Therefore, transcription factors and genes, involved in inflammation and antioxidation, are suspected to play a crucial adjective function in RA. The main treatment of RA is to reduce arthritis reaction, inhibit disease development and irreversible bone destruction, protect the joints and muscle function, and ultimately achieve complete remission or low disease activity. Treatment principles include patient education, early treatment, and combination therapy [104, 105]. Drug therapy includes nonsteroidal anti-inflammatory drugs (NSAIDs), slow-acting antirheumatic drugs, immunosuppressive agents, immune and biological agents, and botanicals. NSAIDs are most common. Our earlier studies strongly suggest that GA is one of the NSAIDs with anti-inflammatory and antioxidant actions both in vivo and in vitro and could be used effectively as anti-RA agent. Recent studies of Cascao et al. [106] support our hypothesis. By using rat RA model, this group showed that GA inhibits RA by inhibiting the levels of cytokines and key inflammatory molecules [106].

15.4.3 Diabetes and Obesity

Type 2 diabetes is a chronic disease where cells have reduced insulin signaling, leading to hyperglycemia, and long-term complications, such as heart, kidney, and liver disease. Recently, more and more studies have shown the critical roles of oxidative stress and inflammatory reactions in the pathogenesis of diabetes. Studies have shown that AMP-activated protein kinase (AMPK) plays a key role in maintaining intracellular and whole-body energy homeostasis. Activation of AMPK has been shown to ameliorate the symptoms of type 2 diabetes and obesity. In vitro studies by Zhao et al. [107] demonstrate that GA, activates AMPK by increasing the phosphorylation of AMPKα and its downstream substrate ACC in various cell lines [107]. This group also showed that GA induced activation of AMPK was associated with increased intracellular ROS level. Collectively, these results suggest that GA may be a novel direct activator of AMPK and could be used as anti-diabetic agent. However, further studies are required to fully evaluate this function of GA.

15.4.4 Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by thick, red, and scaly lesions on any part of the body, which affects approximately 2 % of the population worldwide [108]. Many cytokines, including interleukin-23(IL-23), IL-17A, TNF-α, IL-6, IL-1β, and IL-22, are also involved in the pathogenesis of psoriasis [109]. Along these lines a recent study showed that GA could be used as an anti-psoriatic agent [97].

15.4.5 Cancer

Inflammation plays key roles in all the ways of tumorigenesis and therapy response [110]. Activation and interaction between STAT3 and NF-κB are very vital in the control of cancer cells and inflammatory cells [111]. TNF-α, VEGF, IL-10, MMP-2 and MMP-9, MCP, CD4+ T, AP-1, Akt, PPAR-γ, MAP kinases, and mTORC1 are also important linking factors between inflammation and cancer [111]. It has been shown that GA suppresses the growth of various cancer cells such as non-small cell lung cancer [112], human hepatocellular carcinoma [113], oral squamous cell carcinoma [114], human breast cancer [86], human malignant melanoma [115], human gastric carcinoma [116], and human leukemia cancer [7] and multiple myeloma [31, 117]. A variety of mechanisms have been proposed by which GA inhibits the proliferation of cancer cells and induces apoptosis. These include inhibition of antiapoptotic proteins Bcl-2 [86, 88] and survivin [118]; induction of apoptosis-associated proteins p53 [119], bax, and procaspase-3 [115]; activation of

c-*jun*-NH2-kinase, p38 [20], and GSK-3β [15]; inhibition of topoisomerase II by binding to its ATPase domain [120], downregulation of the MDM2 oncogene and subsequent induction of p21 [119]; suppression of LPS induced COX-2 [10]; and downregulation of human telomerase reverse transcriptase [121]. It has also been shown that GA directly binds to c-myc [122], transferrin receptors [123], and CXCR4 [124]. Recently, a proteomic approach revealed that GA suppresses expression of 14-3-3 protein sigma and stathmin [116]. We have shown earlier that GA inhibits NF-κB and its regulated gene products in human myeloid leukemia [7]; STAT3 and its regulated gene products in MM [31]. Most recently, we showed that GA interacts with CXCR4 and inhibits chemotaxis and osteoclastogenesis in MM [124]. Recently, it is shown that GA is a novel tissue specific proteasome inhibitor, with potency comparable to bortezomib [25]. In addition, recent studies have shown that GA is bioavailable, less toxic, effective, and inhibits development of tumors in animal models, and most importantly it has been approved for phase 2 clinical trial in solid tumors [4, 121, 125, 126]. Since, GA modulates the expression of proteins plays important role in survival, migration, invasion and chemoresistance of multiple myeloma cells (Fig. 15.2), we have been working on the development of GA as anti-myeloma agent.

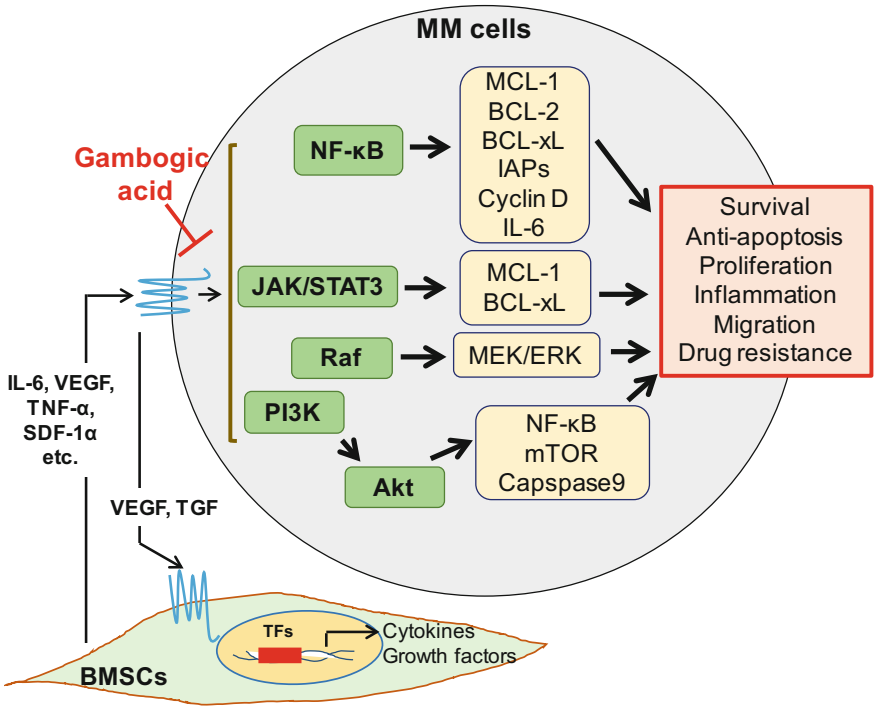

Fig. 15.2 Intimate relationship between multiple myeloma and bone marrow microenvironment. Bone marrow stromal cells secrete cytokine a growth factors, these growth factors activates several pathways in multiple myeloma. Gambogic acid targets these pathways

15.5 Biological Activities of GA in Animal Models

Besides the extensive in vitro demonstrations of GA's anti-proliferative effects, numerous other studies have evaluated its efficacy in various animal models in vivo (Table 15.2). The in vivo studies have investigated the effects of GA on tumor angiogenesis and the biomarkers COX-2 and VEGF in prostate carcinoma [16]. One group demonstrated that systemic administration of GA for 3 weeks to athymic mice bearing non-small lung NCI-H1993 xenografts significantly inhibited tumor growth [127]. Meanwhile, others have shown that GA can suppress the growth of cervical carcinoma [128], modulate the growth of colorectal cancer [129], modulate the growth of prostate cancer in rodents [16], inhibit the growth of human B-cell lymphoma by inducing proteasome inhibition [130] in nude mice, and inhibits hepatocellular carcinoma, multiple myeloma, bladder cancer tumor growth, in part by suppressing angiogenesis, and inducing apoptosis [7, 11, 17, 22, 24, 31, 66, 75–77]. More recent studies have evaluated GA's chemosensitizing effects [118]. Our group evaluated the chemosensitizing effect of GA in combination with paclitaxel, TNF-α, 5-FU on multiple myeloma [7]. Together, these in vivo animal studies clearly suggest GA's anticancer potential when administered either alone or in combination with currently employed chemotherapeutic agents.

Table 15.2 A list of studies describing antitumor effects of gambogic acid in animals

Tumor	Cell line	Route	Dose (mg/kg)	Model	References
Lung	SPC-A1	i.v.	4, 8	Xenograft	[121]
	NCI-H1993	i.p.	10, 20 or 30	Xenograft	[127]
	NCI-H1975	i.v.	8	Xenograft	[137]
	A549	i.p.	8, 16 and 32	Xenograft	[134]
Gastric cancer	BGC-823	i.v.	8	Xenograft	[85]
Cervical carcinoma	HeLa cells	i.p.	2	Xenograft	[128]
Chronic myeloid leukemia	KBM5	i.p.	3	Xenograft	[24]
Liver	HepG2	i.v.	1.5	Xenograft	[132]
Ovarian	SKOV3		1.0	Xenograft	[133]
Breast	MDA-MB-231	i.v.	4 and 8	Orthotopic	[94]
Hepatoma	H22	i.v.	2, 4 and 8	Xenograft	[125]
	H22	p.o.	12.5, 25, 30 and 50	Xenograft	[125]
	SMMC-7721	i.v.	2, 4, and 8	Xenograft	[131, 136]
Melanoma	B16-F10	i.v.	0.375, 0.75, and 1.5	Orthotopic	[135]
Colon	HT-29	i.v.	5, 10 and 20	Xenograft	[129]

15.6 Biological Activities of GA in Humans

There are no clinical studies so far in USA, however in China GA is in Phase II clinical trial [4, 121, 125, 126]. The plethora of studies clearly suggest GA's potential as anticancer agent. It the opportune time to seriously consider this xanthone in clinical trial especially in USA.

15.7 Conclusions

The spice derived from kokum, the fruit of *Garcinia indica*, is used in Indian cuisines and Ayurvedic medicine. The main component isolated from kokum is GA, which demonstrates thrust quencher, antioxidant, antimicrobial, antiulceration, and anticancer properties. Although GA is a potent, biologically active compound, only a number of studies are carried out in animals and none have been done in humans. Because of its diverse range of biological activity in vitro, more in vivo and clinical studies are warranted to establish its true usefulness as a clinical therapeutic agent in a variety of human diseases.

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