Modulation of cell signaling pathways by Phyllanthus amarus *and its major constituents: potential role in the prevention and treatment of inflammation and cancer*

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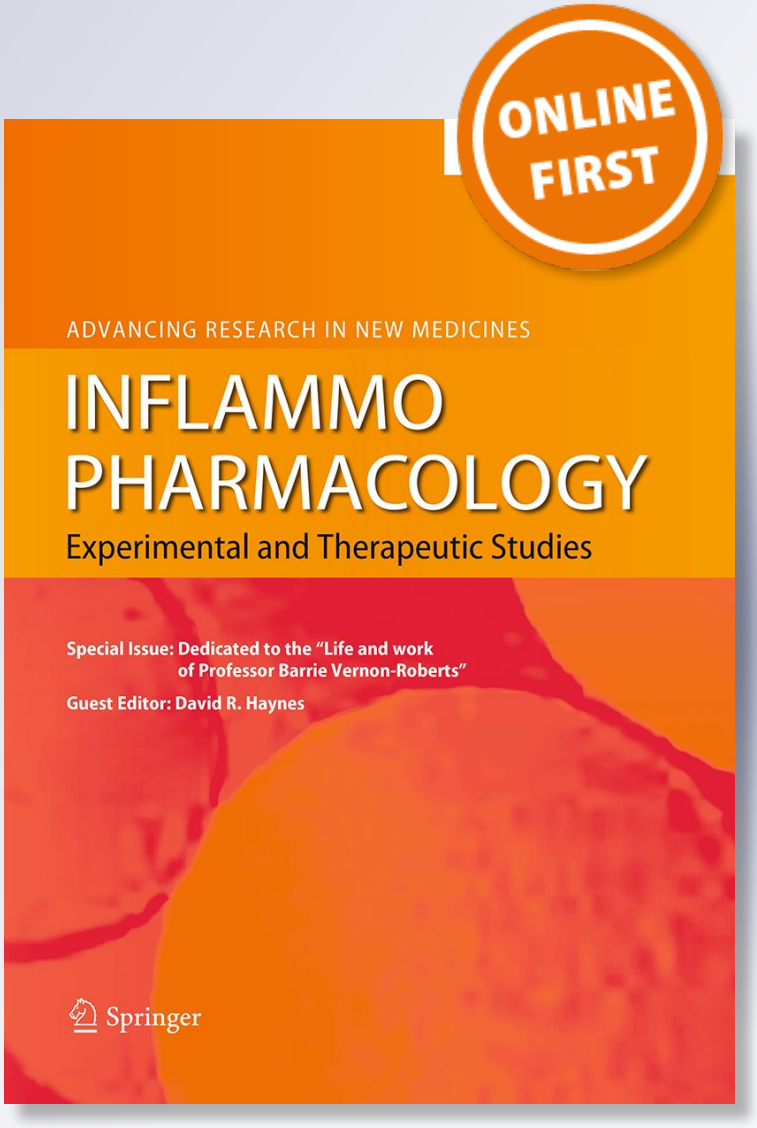

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REVIEW

Modulation of cell signaling pathways by *Phyllanthus amarus* and its major constituents: potential role in the prevention and treatment of inflammation and cancer

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Abstract

The causal and functional connection between inflammation and cancer has become a subject of much research interest. Modulation of cell signaling pathways, such as those involving mitogen activated protein kinases (MAPKs), nuclear factor kappa β (NF-κB), phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt), and Wnt, and their outcomes play a fundamental role in inflammation and cancer. Activation of these cell signaling pathways can lead to various aspects of cancer-related inflammation. Hence, compounds able to modulate inflammation-related molecular targets are sought after in anticancer drug development programs. In recent years, plant extracts and their metabolites have been documented with potential in the prevention and treatment of cancer and inflammatory ailments. Plants possessing anticancer and anti-inflammatory properties due to their bioactive constituents have been reported to modulate the molecular and cellular pathways which are related to inflammation and cancer. In this review we focus on the flavonoids (astragalin, kaempferol, quercetin, rutin), lignans (phyllanthin, hypophyllanthin, and niranthin), tannins (corilagin, geraniin, ellagic acid, gallic acid), and triterpenes (lupeol, oleanolic acid, ursolic acid) of *Phyllanthus amarus*, which exert various anticancer and anti-inflammatory activities via perturbation of the NF-κB, MAPKs, PI3K/Akt, and Wnt signaling networks. Understanding the underlying mechanisms involved may help future research to develop drug candidates for prevention and new treatment for cancer and inflammatory diseases.

Keywords *Phyllanthus amarus* · Secondary metabolites · Anti-inflammation · Anticancer · Signaling pathways

Introduction

The relationship between tumor development and inflammation has long been acknowledged. It is currently clear that inflammatory cells affect tumor progression (Balkwill and Mantovani 2001). In the initial neoplastic development, these cells are intense promoters of tumors, delivering a condition for tumor development, encouraging genomic instability and angiogenesis promotion. Production of cytokines, inflammatory cells, and chemokines can impact the entire tumor organ, managing the development, migration, and differentiation of all cells in the tumor microenvironment, as well as neoplastic cells, fibroblasts, and endothelial cells. Soon after in the process of tumorigenesis, neoplastic cells likewise redirect the mechanism of inflammation such as selectin–ligand binding, production of matrix metalloproteinase (MMP), and chemokine function to support neoplastic spread and metastasis. This might be part of an effort by the tumor to destabilize the functions of immune cells

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(Coussens and Werb 2002). However, the intake of inflammatory cells may be counterproductive for the development of the tumor, and furthermore it may represent an attempt by the host to suppress the tumor development. In this manner, inflammation and cancer are connected via histopathology, inflammatory profiles, epidemiology, and the adequacy of anti-inflammatory prophylaxis. These perceptions have given impulse to examine and suggest the semantics and mechanisms of the connection between inflammation and cancer. One proposal is that the inflammatory and immune systems may hinder cancer progression (Rakoff-Nahoum 2006).

Over the last decade, imperative progress has been made in our understanding of the molecular mechanisms underlying cellular responses to extracellular signals. In various ailments, it has been identified that cell signaling mechanisms play important roles by inducing cell survival and apoptosis. Many signaling pathways that are involved in cellular transformation have been investigated to develop treatment strategies that target these specific signaling molecules or their downstream effectors. Broad examinations over the decades have revealed a significant number of vital signaling pathways in cancer-associated inflammation. Signaling pathways connecting inflammation and tumor have been distinguished: the intrinsic pathway, which is influenced by hereditary actions that cause neoplasia; and the extrinsic pathway, which is caused by inflammatory surroundings and predisposition to cancer. Inflammation is part of the tumor microenvironment and a known sign of cancer. Connection between intrinsic and extrinsic signaling pathways comprises transcription factors [e.g., nuclear factor kappa β (NF-κB)] which control the inflammatory reaction through soluble proteins (cytokines, chemokines) as well as cell machinery (e.g., tumor-related macrophages), signal transducer and activator of transcription 3 (STAT3), and stimulating tumorigenesis (Rius et al. 2008; Yu et al. 2009). Documented evidence suggested that constant inflammation stimulates genetic instability. Important highlights of cancer-associated inflammation comprise infiltration of leukocytes, generally tumor-related macrophages (TAM); existence of cytokines, e.g., tumour necrosis factor alpha (TNFα), interleukin-6 (IL-6), interleukin-1 (IL-1), or chemokines, e.g., CXCL8 and CCL2; also the event of angiogenesis and remodeling of tissue (Mantovani et al. 2008; Del Prete et al. 2011).

Undoubtedly treatment for inflammation is effective against early neoplastic development and malignant conversion. Additional evidence has supported the utilization of non-steroidal anti-inflammatory drugs (NSAIDs) in counteracting spontaneous tumor development in individuals with familial adenomatous polyposis (FAP) (Ulrich et al. 2006). The activation of chronic inflammation can raise the risk of cancer, e.g., in microbial infections, autoimmune disease, and cryptogenic inflammatory ailments of indeterminate origin. The solidest evidence for inflammation-related cancer in humans was revealed when long-term treatment with anti-inflammatory drugs brought about diminished numbers of mutations or less appearance of new tumors (Del Prete et al. 2011).

Presently, the modulation of signal transduction pathways by natural products has gained increasing attention among scientists. Hence, there are newly emerging opinions to treat chronic diseases such as inflammation and cancer by controlling the cellular signaling pathways using various bioactive compounds of natural origin. Modulation of signal transduction pathways is therefore valued as an attractive approach for drug discovery and development. Here, we review the role of *Phyllanthus amarus* Schum. & Thonn. and its active compounds in targeting several cell signaling pathways, namely those involving NF-κB, mitogen activated protein kinases (MAPKs), phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt), and Wnt.

Phyllanthus amarus Schum. & Thonn.

The abundant presence of a wide range of phytochemicals in *P. amarus* produce various types of biochemical and pharmacological activities. Several studies reported the presence of various compounds including alkaloids, flavonoids, lignans, ellagitannins, triterpenes, polyphenols, sterols, and volatile oils, as listed in Table 1 (Calixto et al. 1998). The details underlying the mechanisms of biological and pharmacological effects of the phytochemicals for the prevention and treatment of cancer and inflammation are not well understood, but prevailing literature proposes that the compounds modulate a wide array of crucial molecular targets (Fig. 1) (Kassuya et al. 2003; Londhe et al. 2012).

Anti-inflammatory and anticancer properties of *Phyllanthus amarus*

Several in vitro and in vivo studies using various extracts of *P. amarus* have indicated its strong anti-inflammatory and anticancer activities; however, most of these studies were carried out using the crude extracts of the plant and the bioactive compounds were not identified. Standardized hexane and aqueous/ethanol extracts of *P. amarus* at different doses inhibited endotoxin-induced nitric oxide synthase (iNOS), cytokines, and cyclooxygenase 2 (COX-2) production in vitro and in vivo via the NF-κB pathway (Kiemer et al. 2003). The extracts inhibited LPS-induced production of prostaglandin E_2 (PGE_2) and NO in RAW 264.7 macrophages and rat Kupffer cells (KC). *P. amarus* suppressed induction of IL-10, IL-1β induction and interferon-g in human whole blood. The extracts inhibited the

Table 1 Major phytoconstituents isolated from *Phyllanthus amarus*

Sl. no	Chemical group	Constituents	References
1	Alkaloids	Epi-bubbialine, isobubbialine, norsecurinine, 4-methoxynorsecurinine, phyllanthine, securinine, phenazine, securinol, dihydrosecurinine, tetrahydrosecurinine	Houghton et al. (1996) and Singh et al. (2008)
2	Flavonoids	Astragalin, quercetin, quercetin-3-*O*-β-D-glucopyranoside, rutin, isoquercitrin, quercitrin, kaempferol	Nara et al. (1977), Foo and Wong (1992), Thyagarajan and Jayaram (1992), Foo (1993), Londhe et al. (2009), and Bagalkotkar et al. (2006)
3	Lignans	Phyllanthin, hypophyllanthin, niranthin, nirtetralin, phyltetralin, hinokinin, 5-demethoxyniranthin, isonirtetralin, lintetralin, dimethylenodioxyniranthin, isolintetralin	Huang et al. (2003), Kassuya et al. (2005), Maciel et al. (2007), and Shanker et al. (2011)
4	Ellagitannins and tannins (phenolics and benzene derivatives)	Corilagin, gallic acid, 4-*O*-galloylquinic acid, 1,6-digalloylglucopyranose, ellagic acid, gallocatechin, geraniin, amarulone, repandusinic acid, phyllanthusiin A, B, C, D, melatonin, amariin, amariinic acid, and furosin	Foo and Wong (1992), Foo (1993), and Calixto et al. (1998)
5	Steroidal compounds	Stigmasterol, β-sitosterol, daucosterol, amarosterol A and B, campesterol, 5,6-dihydrostigmasta-22-en-3β-ol, estradiol, isopropylcholesterol, stigmasterol acetate, and stigmast-4-en-3-one	Kuttan and Harikumar (2011)
6	Terpenes and terpenoids	1-Galloyl-2,3-dehydrohexahydroxydiphenoylglucose, 1-galloyl-2,4-(acetonyldehydrohexahydroxy diphenoyl)-3,6-hexahydroxydiphenoylglucopyranoside, oleanolic acid, ursolic acid, lupeol, lupeol acetate, phyllanthenol, phyllantheol, farnesyl farnesol	Foo and Wong (1992), Foo (1993), and Londhe et al. (2009)
7	Volatile oil	Linalool, phytol	Foo and Wong (1992), Foo (1993), and Londhe et al. (2009)

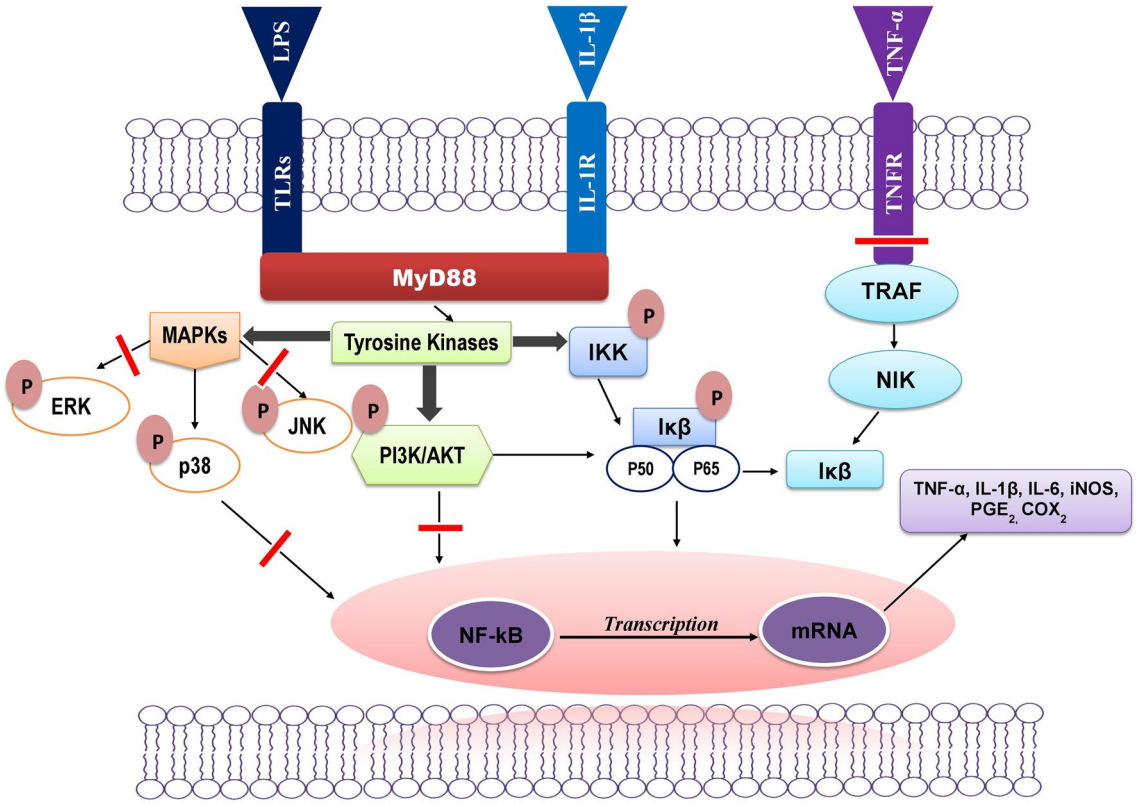

Fig. 1 Effects of major bioactive metabolites of *P.* amarus on the MAPK, NF-κB, and Akt signaling pathways. The short, thick red lines show the inhibition of the signal transduction pathways. MAPK mitogen activated protein kinase, NF-κB nuclear factor kappa β, PI3K/Akt phosphatidylinositol 3-kinase and protein kinase B, P phosphoryl group. (Color figure online)

lipopolysaccharide (LPS)-induced secretion of TNFα in RAW264.7 and human whole blood, and in galactosamine-sensitized BalbA2 mice (Kiemer et al. 2003). The in vitro and in vivo data on the inhibition of TNFα production provided evidence that *P. amarus* extracts exerts strong anti-inflammatory effects.

Male Swiss albino rats orally administered 100 mg/kg of *P. amarus* hexane extract exhibited reduction of allodynia and edema against intraplantar injection of complete Freund's adjuvant (CFA) (Kassuya et al. 2003). The methanol and aqueous extracts of the plant suppressed rat paw edema at 42% with respect to control within 3–8 h (Raphael and Kuttan 2003). Similarly the hexane extract and lignan-rich fraction of the plant inhibited carrageenan-induced paw edema and neutrophil influx and also inhibited the tissue level of IL-1β (Kassuya et al. 2006). Administration of 200 mg/kg of aqueous leaf extract of the plant orally to rats inhibited carrageenan-induced paw edema (Iranloye et al. 2011). *P. amarus* extract and niranthin also decrease the specific binding of platelet-activating factor (PAF) in mouse cerebral cortex membranes (Kassuya et al. 2006). Male Wistar rats fed orally with 250 mg/kg of 75% methanol extract of *P. amarus* markedly suppressed bradykinin, carrageenan, prostaglandin E_1 (PGE_1) and serotonin-induced paw edema (Mahat and Patil 2007). Recently, our laboratory observed that *P. amarus* ethanol extract exerted anti-inflammatory action via inhibition of MAPKs, NF-κB, and PI3K/Akt pathways in LPS-induced U937 human macrophages (Harikrishnan et al. 2018a). Pretreatment of the cells with *P. amarus* significantly reduced mRNA transcription of pro-inflammatory markers. The phosphorylation of IκB kinase alpha/beta (IKKα/β), NF-κB(p65), and IkBα phosphorylation was downregulated and the IkBα degradation was restored in a dose-dependent manner. *P. amarus* also inhibited Akt, ERK, JNK, and p38 MAPKs phosphorylation and downregulated the expression of Toll-like receptor 4 (TLR4) and myeloid differentiation primary response protein MyD88. Similarly, *P. amarus* extract inhibited the LPS-induced neuroinflammation and cognitive dysfunction in male Wistar rats (Alagan et al. 2019). LPS-induced memory impairment of the rats was effectively protected after administration of 200 and 400 mg/kg of *P. amarus* extract for 14 and 28 days. The extract given at similar doses also significantly decreased IL-1β, TNFα, and iNOS release in the brain tissue. CD11b/c integrin expression, NO level, and synaptophysin reactivity were also reduced as compared

with those in the LPS-challenged group. These studies provide strong evidence that the extracts of *P. amarus* have strong anti-inflammatory properties.

Phyllanthus amarus extract was shown to possess anticancer effects by inhibiting the solid and ascites tumor development in mice induced by Dalton's lymphoma ascites (DLA) cells and inhibiting cell growth and induced apoptosis in DLA cells through activation of caspase-3 and downregulation of Bcl-2 (Harikumar et al. 2009). Abhyankar et al. (2010) reported that the extract of *P. amarus* hairy root induced apoptotic cell death in human breast cancer. Treatment of male Wistar rats with *P. amarus* aqueous extract (150 and 750 mg/kg) resulted in reduced levels of carcinogen-metabolizing enzymes, tumour incidence, and liver cancer markers levels in *N*-nitrosodiethylamine (NDEA)-induced hepatocarcinogenesis (Jeena et al. 1999). The protective effect of 150 mg/kg of *P. amarus* aqueous extract against NDEA-induced hepatocellular carcinoma in Wistar rats was similarly reported by Rajeshkumar and Kuttan (2000). Administration of *P. amarus* aqueous extract significantly increased the survival of animals harboring hepatocellular carcinoma. Similarly, oral treatment of 150 and 750 mg/kg of *P. amarus* in Balb/c mice extract for 8 weeks at three times a week resulted in antitumor and anticarcinogenic action (Rajeshkumar et al. 2002). *P. amarus* extract (250 and 750 mg/kg body weight) administered orally to Balb/c mice for 5 days prior to whole body radiation and for 1 month after radiation could protect the animals from radiation-induced cellular damage (Kumar and Kuttan 2004). Rats administered intraperitoneally with 250 and 750 mg/kg of 75% methanol extract of *P. amarus* for 14 days remarkably reduced gastric neoplasms and exhibited potent antiproliferative activity (Raphael et al. 2006). *P. amarus* aqueous and methanol extracts were shown to suppress breast carcinoma MCF-7 and lung carcinoma (A549), and showed the capability of inducing apoptosis in association with antimetastatic activity. These anticancer activities were proposed to be contributed by the polyphenol constituents of the extracts (Lee et al. 2011).

Modulation of cell signaling pathways by major components of *Phyllanthus amarus*

The flavonoids (astragalin, kaempferol, quercetin, rutin), lignans (phyllanthin, hypophyllanthin, and niranthin), tannins (corilagin, geraniin, ellagic acid, gallic acid), and triterpenes (lupeol, oleanolic acid, ursolic acid) found as major components of *P. amarus* have been reported to exert their various anticancer and anti-inflammatory activities via perturbation of the NF-κB, MAPKs, PI3K/Akt, and Wnt signaling networks (Table 2).

Flavonoids

Flavonoids are polyphenolic compounds which are commonly present in the plant kingdom especially fruits, vegetables, grains, barks, roots, stems, and flowers (Umesh et al. 2018). The flavonoids astragalin, kaempferol, quercetin, and rutin present in *P. amarus* have been widely reported for their anti-inflammatory and anticancer properties (Table 1).

Astragalin

Astragalin or kaempferol 3-glucoside is a naturally occurring flavonoid found in various medicinal plants including *P. amarus, P. niruri*, *Cuscuta chinensis*, and *Cassia alata* (Nara et al. 1977; Bagalkotkar et al. 2006; Riaz et al. 2018). Astragalin exerts a wide array of biological and pharmacological activities including antioxidant, anti-inflammatory, antidiabetic, cardioprotective, neuroprotective, anticancer, anti-obesity, and anti-ulcer properties (Bıtıs et al. 2010; Burmistrova et al. 2011; Bainey and Armstrong 2014; Kim et al. 2017). Astragalin exhibits these multiple pharmacological activities by regulating and modulating molecular targets including transcription factors, kinases, enzymes, inflammatory cytokines, and cell adhesion proteins (Riaz et al. 2018). Studies on LPS-induced J774A-1 mouse macrophages have shown that astragalin inhibited the expression of inflammatory mediators including COX-2, iNOS, IL-1β, IL-6, TNFα, and production of NO. In addition, this study also confirmed that astragalin suppressed the production of inflammatory molecules by inhibiting the NF-κB signaling pathways (Kim and Kim 2011).

Another investigation on an LPS-induced murine model of acute lung injury and mastitis found that astragalin lessened the inflammatory response by suppressing the release of MPO and pro-inflammatory cytokine expression. The anti-inflammatory response of astragalin proceeded via suppression of the LPS-activated NF-κB signaling pathway, as it was involved in easing the IκBα degradation (Soromou et al. 2012; Li et al. 2013a). Astragalin also modulated NF-κB and MAPK signaling pathways in leptospira-activated inflammation in epithelial and uterine cells of mice (Zhang et al. 2017). Similarly, LPS-induced inflammatory signaling in mouse mammary epithelial cells showed that astragalin efficiently produced anti-inflammatory effects by downregulating the TLR4-mediated NF-κB and MAPKs (phosphorylation of ERK and p38) signal transduction pathways. Moreover, astragalin inhibited COX-2, IL-6, TNFα, and iNOS in a dose-dependent manner (Li et al. 2014). Additionally, astragalin ameliorated

Table 2 Key cell signaling networks modulated by the major constituents of *Phyllanthus amarus*

Phytoconstituents	Mechanism	References
Corilagin	Inhibits NF-κB pathway	Zhao et al. (2008), Dong et al. (2010), and Gambari et al. (2012)
	Inhibits the activation of p-ERK, Smad2, and p-Akt in ovarian growth cells	Jia et al. (2013)
	Inhibit of NEMO, P-p38, TNFα, NF-κB, and IL-6	Guo et al. (2015)
	Regulates Bax and inhibits Bcl-2	Deng et al. (2018)
Gallic acid	Suppresses of NF-κB action, Ras, Rac1, Cdc42, RhoA, PI3K, RhoB, and p38	Javelaud et al. (2002) and Park et al. (2007a, b)
	Represses the activation of NF-κB-dependent p65 acetylation	Choi et al. (2009)
	Diminishes the expression of IL-6 and TNFα	Kuppan et al. (2010)
	Downregulates Ras/MAPK and PI3K/Akt pathways	Lu et al. (2010) and Liao et al. (2012)
Ellagic acid	Inhibition of p38, JNK and ERK1/2 MAPKs and NF-κB pathways	Edderkaoui et al. (2008) and Rosillo et al. (2011)
	Downregulates the expression of Wnt signaling	Anitha et al. (2013) and Fang et al. (2015)
Geraniin	Modifies the pro-inflammatory cytokines secretion	Okabe et al. (2001), Kolodziej et al. (2001), Fujiki et al. (2003), and Park et al. (2007a, b)
	Alteration in Bax and Bcl-2 expression	Li et al. (2013a, b)
	Downregulating the gene expression of low-density lipoprotein receptor-related protein 6 (LRP6), β-catenin, T cell factor 4 (TCF4), frizzled-2, and lymphoid enhancer-binding factor 1 (LEF1)	Li et al. (2018)
Astragalin	Inhibits expression of TNFα, IL-6, IL-1β, NO, COX-2, PGE_2, and iNOS by downregulating NF-κB	Kim and Kim (2011), Soromou et al. (2012), Li et al. (2013a, 2014), Zhang et al. (2017), and Ma et al. (2015)
	Downregulates expression of p38MAPK, ERK, and JNK signaling molecules	Zhang et al. (2017) and Li et al. (2014)
Kaempferol	Inhibits the production of COX-2	Basu et al. (2017), Lee et al. (2010a), Kim et al. (2015), and Park et al. (2011)
	Downregulates TNFα, IL-1β, IL-6, MCP-1, PGE_2, and NO	Kim et al. (2015), Chen et al. (2012), and Tang et al. (2015)
	Inhibits AP-1 and PI3K/Akt signaling pathway	Kim et al. (2015), Tang et al. (2015), and Lee et al. (2010b)
	Suppresses MAPKs and NF-κB-related signaling molecules	Lee et al. (2010a), Pang et al. (2006), Kim et al. (2015), Chen et al. (2012), Park et al. (2011)
Quercetin	Downregulates NF-κB signaling pathway	Granado-Serrano et al. (2010), Zhang et al. (2015), Hwang et al. (2009), and Ward et al. (2018)
	Supresses MAPK and PI3K/Akt signaling molecules	Granado-Serrano et al. (2008), Ward et al. (2018), Guo et al. (2017), Lee et al. (2010c) and Endale et al. (2013)
	Inhibits Wnt/β-catenin signaling pathway	Park et al. (2005) and Mojsin et al. (2013)
Rutin	Suppresses the production of IL-1β, IL-6, TNFα, myeloperoxidase (MPO), reactive oxygen species (ROS), COX-2, and iNOS	Su et al. (2018), Yeh et al. (2014), Kyung et al. (2008), Nafees et al. (2015), Choi et al. (2014), and Yoo et al. (2014)
	Downregulates NF-κB, p38 MAPK, JNK, ERK activation	Yeh et al. (2014), Kyung et al. (2008), Nafees et al. (2015), Choi et al. (2014), Li et al. (2017a, b), Song et al. (2018), and Yoo et al. (2014)
Phyllanthin, hypophyllathin, and niranthin	Downregulates COX-2, TNFα, PGE_2, IL-1β, TLR4, and MyD88 signaling molecules	Harikrishnan et al. (2018a, b, c) and Krithika et al. (2016)
	Blocks the MAPK, NF-κB and P13K-Akt signaling pathways	
Lupeol	Inhibits production of pro-inflammatory markers (PGE_2, TNFα, IL-1β)	Fernández et al. (2001), Vasconcelos et al. (2008), and Lee et al. (2016)
	Downregulates PI3K/Akt, NF-κB, and MAPK signaling pathways	Saleem et al. (2004), Saleem et al. (2005), Lee et al. (2007), and Prasad et al. (2009)

Table 2 (continued)

Phytoconstituents	Mechanism	References
Oleanolic acid	Inhibits the production of pro-inflammatory cytokines and CAM molecules	Yang et al. (2012), Lee et al. (2013), Martin et al. (2014), and Wang et al. (2013b)
	Suppresses NF-κB signaling pathway	Lee et al. (2013)
	Diminishes production of iNOS, NO, COX-2, matrix metalloproteinase-9 (MMP-9), cyclin D1, Jun, Fos, and p65	Shishodia et al. (2003), Suh et al. (1998), Ryu et al. (2000), and Subbaramaiah et al. (2000)
	Downregulates the activation of MAPKs signaling molecules	Subbaramaiah et al. (2000)
	Inactivates Wnt signaling pathway by inhibiting Myc and cyclin D1	Zhang et al. (2016)

endotoxin-activated apoptosis in airway epithelial cells by controlling oxidative stress-mediated MAPK signaling pathways (Cho et al. 2014). Astragalin also alleviated IL-1-induced inflammation in human articular chondrocytes by actuating peroxisome proliferator-activated receptor gamma (PPARγ), which consequently blocked the IL-1-stimulated NF-κB and MAPKs signaling pathways (Ma et al. 2015).

Kaempferol

Kaempferol or 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one is a naturally occurring phytoestrogen and a common dietary flavonoid. It has been proposed to possess a wide range of pharmacological activities such as anti-inflammatory, antioxidant, antitumor, and antiatherogenic properties. It is present in *P. amarus* and widely available in other medicinal plants and dietary products such as cabbage, broccoli, apples, strawberries, and tea (Patel et al. 2011; Calderon-Montano et al. 2011). The ability of kaempferol to modulate multiple signaling pathways is extensively acknowledged. Kaempferol alleviated COX-2 expression in IL-6-activated monocytic THP-1 cells or carrageenan-induced mouse paw tissues. Interestingly, this study found that kaempferol suppressed the COX-2 expression via blocking the nuclear localization of major transcription factors NF-κB and STAT3 which were accountable for COX-2 expression in inflammatory cells (Basu et al. 2017). Similarly, another study reported that kaempferol mitigated the COX-2 protein and gene expression in UVB-induced skin epidermal cells via deactivating MAPKs signaling pathway and SRC kinase activity (Lee et al. 2010a). Likewise, kaempferol also diminished the translocation of NF-κBp65 from cytoplasm to nucleus and thereby suppressed the production of inflammatory markers (IL-6 and MCP-1) in TNFα-induced MC3T3-E1 osteoblast-like cells (Pang et al. 2006).

Another study proved that the inhibitory effects of kaempferol on inflammatory markers including NO, PGE_2, TNFα, and COX-2 were attributed to its anti-inflammatory properties. In addition to suppression of inflammatory markers, kaempferol suppressed NF-κB and AP-1 transcriptional activity by directly targeting kinases (SRC, SYK, IRAK1, IRAK4) which were important for NF-κB and AP-1 activation (Kim et al. 2015). An in vivo study reported that kaempferol exerted its anti-inflammatory properties by suppressing inflammatory mediators in LPS-activated acute lung injury. The possible mechanisms are linked with the inactivation of NF-κB and MAPKs signaling pathways (Chen et al. 2012). Kaempferol has been known to exert anti-inflammatory and antioxidative activities by controlling age-associated NF-κB signaling pathway and the expression of pro-inflammatory genes by inhibiting age-activated NADPH oxidase activation. Moreover, kaempferol also inhibited proteins related to NF-κB signaling pathway via blocking NF-κB–DNA binding and blunting the expression of the NF-κB p65 subunit (Kim et al. 2010). An investigation on anti-inflammatory effects of kaempferol on LPS + ATP-induced cardiac fibroblast reported that the cells treated with kaempferol diminished the release of IL-6, IL-18, IL-1β, and TNFα by downregulating the activation of Akt and NF-κB signal transduction pathways (Tang et al. 2015). Park et al. (2011) demonstrated that kaempferol was able to act as a neuroprotectant in LPS-triggered microglia cells by suppressing the synthesis of inflammatory markers and inactivating TLR4-mediated NF-κB signaling and MAPKs phosphorylation. Beside NF-κB and MAPKs signaling, a study reported that kaempferol also suppressed the transformation of EGF-stimulated JB6 Pþ cells by inhibiting PI3K/Akt signaling mechanism and consequently inactivated NF-κB and AP-1 activities (Lee et al. 2010b).

Quercetin

Quercetin [2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-chromen-4-one] is a dietary polyphenol widely spread in food sources such as citrus fruits, red onions, apples, tea, capers, and berries. It is also a major polyphenol in

P. amarus (Patel et al. 2011). Quercetin exerts various biological activities including anti-inflammatory, antioxidant, anticancer, antidiabetic, and neuroprotective properties. Numerous in vitro anticancer activities of quercetin have been found including HepG2 cell death by activating AP-1/JNK signaling pathway and inactivating NF-κB transcription factor (Granado-Serrano et al. 2010). Also, quercetin inhibited HepG2 cell growth by downregulating signaling proteins such as PI3K/AKT and ERK which were associated with cell survival and activated the JNK signaling pathway (Granado-Serrano et al. 2008). Moreover, quercetin promotes apoptosis in CACO2 and SW-620 cells by downregulating NF-κB signaling event (Zhang et al. 2015). In addition, inhibition of TGFβ1 signal transduction pathway and stimulation of P13K/Akt pathway by quercetin lessened the profibrotic effects in mice models induced with CCl_4 (Zhang et al. 2015). A study on TNFα -activated JB6 P+ mouse epidermal cells demonstrated that treatment with quercetin blocked the production of MMP-9 and the cell migratory phenomena by directly inhibiting PI3K/Akt activity, and successively inactivated NF-κB and AP-1 instigation (Hwang et al. 2009).

Quercetin was able to exert anticancer properties in prostate cancer cells by controlling ROS production as well as MAPK, PI3K-Akt, and NF-κB signal transduction pathways (Ward et al. 2018). Quercetin pretreatment also averted the development of LPS-induced abnormal bone in chronic inflammatory diseases by increasing the ERK phosphorylation and decreasing the p38 activation (Guo et al. 2017). Likewise, quercetin plays an important role in preventing lipid accretion and obesity-associated inflammation by controlling the expression of MAPKs signaling proteins in macrophages and adipocytes (Guo et al. 2017). The pretreatment with quercetin decreased the COX-2 expression in arsenite-induced rat liver epithelial cells by downregulating PI3K/Akt signaling pathway (Lee et al. 2010c). Quercetin has been shown to exert anti-inflammatory effects on LPS-induced RAW 264.7 cells by suppression of SYK- and SRC-mediated PI3K-(p85) tyrosine phosphorylation and following TLR4/MyD88/PI3K complex establishment which inactivated the downstream signaling pathways (Endale et al. 2013). Besides that, an in vitro study demonstrated that quercetin was capable of inhibiting the active binding of β-catenin and TCF in SW480 cancer cells which led to the downregulation of Wnt/β-catenin signaling machinery (Park et al. 2005). Likewise, an investigation by Mojsin et al. (2013) and colleagues found the complete reduction of Myc in quercetin-treated pluripotent embryonal carcinoma nt2/d1 cells, which suggested the occurrence of significant inhibition of canonical Wnt signaling pathway.

Rutin

Rutin or quercetin-3-rhamnosyl glucoside is a polyphenolic flavonoid widely present in citrus fruits, wine, tea, and buckwheat seeds. Rutin exhibits diverse biological and pharmacological properties such as anticancer, anti-inflammatory, and antihypertensive effects. Numerous anti-inflammatory effects of rutin have been proposed including downregulation of IL-1β, IL-6, and TNFα by deterring the production of NF-κB and its signal transduction pathway in an LPS-primed rat mastitis model (Su et al. 2018). Production of pro-inflammatory cytokines (IL-1β, IL-6, and TNFα) and MPO activity in LPS-primed acute lung injury rats were ameliorated by rutin. It also inhibited the phosphorylation signaling proteins associated with NF-κB and MAPKs signaling events (Yeh et al. 2014). The process of osteoclast development in RANKL-induced bone marrow cells was inhibited by rutin via downregulating the instigation of NF-κB and subsequently reducing ROS and TNFα production (Kyung et al. 2008). The administration of rutin repressed the manifestation of COX-2, NF-κB, iNOS, and p38 MAPK in mice induced with cyclophosphamide (Nafees et al. 2015). Similarly, rutin acted as a neuroprotective agent in rats with spinal cord injury by modulating p38 MAPK signaling pathway. Moreover, rutin prevented the inflammatory responses in UVB-induced mouse skin by lessening the expression of COX-2 and iNOS by inhibiting p38 MAPK and JNK activation (Choi et al. 2014).

In another study, rutin suppressed COX-2 by downregulating Raf/MEK/ERK and Akt signaling events (Choi et al. 2013). The powerful effect of rutin on signaling proteins such as NF-κB and p38 blocked the progression of lung cancer (Li et al. 2017a). Administration of rutin exerted neuroprotection in rats induced with isoflurane by controlling JNK/p38MAPK/ERK signaling pathway to prevent neuroapoptosis (Li et al. 2017b). Similarly, another study demonstrated that rutin showed neuroprotecive effects on spinal cord cells by attenuating the activation of pro-apoptotic proteins through downregulating p38 MAPK signaling pathway (Song et al. 2018). Rutin attenuated the phosphorylation of ERK and p38 in high glucose-induced human monocytic THP-1 cells to prevent the glycotoxin-associated inflammation (Wu et al. 2009). Rutin also exerted anti-inflammatory effects in high mobility group box 1 (HMGB1)-stimulated HUVEC cells and mice by attenuating the synthesis of IL-6 and TNFα and instigation of NF-κB and ERK (Yoo et al. 2014).

Tannins

Tannins are widely present in various plant species. In *P. amarus*, tannins are present in hydrolyzable form like ellagitannins which are further divided into tannin precursors

(ellagic acid, gallocatechin, gallic acid), simple tannins (4-*O*-galloylquinic acid and 1,6-digalloylglucopyranose) and complex tannins (amariin, geraniin, geraniic acid B, corilagin, isocorilagin, amariinic acid, elaeocarpusin, furosin, amarulone, repandusinic acid A, melatonin, phyllanthusiin A, B, C, and D) (Patel et al. 2011). Among these, corilagin, ellagic acid, gallic acid, and geraniin are associated with anti-inflammatory and anticancer activity via inhibiting signaling pathways.

Corilagin

Corilagin is a gallotannin phenolic compound which acts as a major bioactive compound in numerous plant species. It is widely reported to have several pharmacological actions like antioxidant, antitumor, hepatoprotectivity, and anti-inflammatory. Upregulation of pro-inflammatory cytokines and mediators such as IL-6, TNFα, IL-1β, iNOS, and COX-2 in LPS-induced mouse macrophage cells (RAW 264.7) was reduced by treatment of corilagin through inhibition of NF-κB pathway (Zhao et al. 2008). Corilagin suppressed cytokines (IL-12, IL-1, IL-18, TNFα and IFN-α/γ) and iNOS release in the *Leishmania major*-tainted RAW 264.7 macrophage cell line (Kolodziej et al. 2005). Corilagin also reduced the herpes simplex infection 1 (HSV-1)-stimulated inflammatory response in mouse brain via stimulation of apoptosis of infected microglial cells and suppression of the release of NO, IL-1β, and TNFα (Guo et al. 2010). Likewise, in HSV-1-induced encephalitis, corilagin has an inhibitory effect on TLR2 and other inflammatory signals likes NEMO, p38, P-p38, TNFα, NF-κB, and IL-6 (Guo et al. 2015). Moreover, inhibition of pro-inflammatory cytokines through suppression of DNA double-strand breaks (DSBs)-primed NF-κB pathway was reported in BV2 murine microglial cells (Dong et al. 2010). Similarly, corilagin inhibited Aβ25–35-stimulated neurotoxicity and dysfunction through hindrance of NF-κB signaling pathway (Youn et al. 2016). Altogether, documented evidence showed that corilagin possesses robust anti-inflammatory action.

Corilagin hindered the growth of Hep3B hepatocellular carcinoma. In addition, corilagin lessened the release of TNFα in cancer cells. It was assumed that TNFα induced the development and progression of early malignant tumor cells (Komori et al. 1993). Treatment of corilagin in cystic fibrosis bronchial IB3-1 cells revealed the suppression of NF-κB–DNA interactions and altered the IL-8 gene expression (Gambari et al. 2012). On the contrary, investigations showed that the antitumor activity involved in signaling events was influenced by corilagin treatment. Corilagin stimulated the apoptosis of tumor cells through upregulation of Bax and inhibition of Bcl-2 in SGC-7901 gastric carcinoma and Hep-2 human laryngeal carcinoma cell lines (Deng et al. 2018). Moreover, corilagin decreased the mitochondrial transmembrane potential and expanded the rate of release of cytochrome *c*, accordingly prompting apoptosis of SGC-7901 gastric carcinoma cells via the mitochondrial apoptotic pathway. Corilagin also inhibited the activation of p-ERK, Smad2, and p-Akt, in ovarian growth cells (Hey and SKO-v3ip) via suppression of TGFβ, which finally prompted the apoptosis of tumor cells (Jia et al. 2013). Accumulating evidence clearly supports that corilagin is an active compound which exhibit anti-inflammatory and anticancer activities.

Gallic acid

Gallic acid (GA) or 3,4,5-trihydroxybenzoic acid is present in several herbs and has anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, anticancer, and antidiabetic properties. GA has been widely studied for its anti-inflammatory and anticancer activities. It has been reported that GA repressed the activation of NF-κB-dependent p65 acetylation and generation of inflammatory markers. The acetylation of p65 controlled the biological effects of NF-κB, together with the translation, DNA restricting movement, and IκBα gathering. The low acetylation rate of p65 brought about the entire loss of activity of NF-κB, showing that its acetylation is important for the signaling events mediated by NF-κB. Subsequently, studies proposed that interference in the specific acetylation of p65 with molecules such as GA may be considered as another class of anti-inflammatory drugs (Choi et al. 2009). 4-*O*-Methylgallic acid (4-OMGA) is one of the principal metabolites of GA and, in vivo, its level in urine and plasma is quickly augmented after oral treatment with GA (Shahrzad et al. 2001). Therefore, 4-OMGA has been broadly investigated for its anti-inflammatory impact and its molecular mechanism in endothelial cells (HUVEC) driven by TNFα. The metabolite decreased the manifestation of VCAM-1 and ICAM-1 and in addition monocyte attachment to HUVEC treated with TNFα by hindering the action of NF-κB (Lee et al. 2006). The structure of the 4-OMGA is like the GA ester of epigallocatechin-3-gallate (EGCG), which suppress inflammatory gene activation by repressing the activation of signaling pathway identified with NF-κB (Na et al. 2006).

Kuppan et al. (2010) revealed that treatment with GA diminished the expression of IL-6 and TNFα from human monocytes. In addition, Kim et al. (2005) found that GA hindered the mast cells derived from inflammation by suppressing pro-inflammatory cytokines. Yoon et al. (2013) investigated the impact of GA on rheumatoid arthritis (RA) and found that the levels of various vital pro-inflammatory mediators of RA fibroblast-like synoviocytes were substantially inhibited by the treatment. The initiation of NF-κB as an important event of inflammation is a typical element of numerous neurodegenerative illnesses. In the brains of patients with Alzheimer's disease (AD), initiation of NF-κB

is prevalent in neurons and glial cells in zones with senile plaques containing amyloid-β (Aβ). Furthermore, the Aβ additionally seemed to activate NF-κB, which in the end prompts increased cytokine generation in neurons and glial cells (Mattson 2000; Kim et al. 2011). Kim et al. (2011) discovered that treatment with GA quashed the initiation of NF-κB induced by Aβ and cytokine generation in microglia via hypoacetylation, which finally prompted the diminution of neurotoxicity initiated by Aβ. Additionally, GA had a restorative effect on Aβ-initiated cognitive impairment. Moreover, GA treatment inhibited the neuronal cell death via in vivo acetylation of NF-κB and the downregulation of the cytokine levels.

GA also has powerful inhibitory impacts on AGS cell migration, a human gastric adenocarcinoma, by quashing the activation of MMP-2/MMP-9 and cytoskeletal F-actin. The antimigratory impact of GA may indicate the suppression of NF-κB action and different proteins identified with metastasis and cytoskeletal reorganization signaling pathways, together with Ras, Rac1,Cdc42, RhoA, PI3K, RhoB, and p38. NF-κB is retained in the cytoplasm through connections with an inhibitor of NF-κB (IκB). Upon separation, NF-κB transfers to the core and induces tumour cell proliferation, angiogenesis, and metastasis. A few workers have reported that the amount of IκB could control NF-κB nuclear translocation and subsequently effect the activation of MMP-2 in human cell lines (Javelaud et al. 2002; Park et al. 2007a, b). It was proposed that the increase in cytoplasmic IκB could encourage its binding to NF-κB and after that repressed the NF-κB action. Akt, in its turn, when initiated may straightforwardly tie to IKK unblocking it, finally triggering the destruction of IκB. When treated with GA the protein levels of PI3K, AKT-1, and p-Akt diminished accordingly in a dose-dependent way. These outcomes showed that GA might upsurge IκB binding to NF-κB at which point it suppresses the PI3K/Akt pathway and thereby avoids metastasis of AGS cells. These outcomes emphasize the therapeutic capability of GA to govern tumor metastasis over its inhibitory impact on the motility of AGS cells. An expected mechanism of the suppressive impacts of GA on AGS cells may be somewhat through the Ras/PI3K/Akt signaling pathway. Furthermore, the elevated levels of cytoplasmic IκB, which suppressed transcriptional factor NF-κB and diminished MMP-9 and MMP-2 activity, increased the antimetastatic impact (Ho et al. 2013).

The association among GA and the inhibition of cell migration and metastases can be showed by some specific enzymes linked to cell invasion. It has been demonstrated that GA could suppress the expression of p-ERK, ADAM17, and p-Akt. In addition to the suppression of its expression, the action of ADAM17 was decreased by GA. With respect to the protein engaged in cell survival, GA essentially repressed the phosphorylation of individuals from both Ras/MAPK and PI3K/Akt signaling transduction pathways, which have been implicated in cell invasion, proliferation, and survival. These discoveries support the notion that suppression of ADAM17 by GA may be in charge of diminished insensitivity via the downregulation of Ras/MAPK and PI3K/Akt pathways (Lu et al. 2010). Moreover, GA has various antimetastatic effects and can possibly be an antimetastatic agent for prostate cancer. The potential mechanism for GA to hinder migration and invasion in PC-3 (human prostate growth) cells might be via quashing of ERK, PKC, JNK, p38, and PI3K/Akt signaling pathways and NF-κB causing hindrance of MMP-9 and MMP-2. Hindrance of ribonucleotide reductase and cyclooxygenases (COXs) in vitro in human HL-60 promyelocytic leukemia cells was documented (Madlener et al. 2007). Elevated COX-2 seems to be implicated in the expansion of cancer by advancing cell division and apoptosis inhibition (Tang et al. 2002; Rizzo 2011).

Further findings confirmed that GA repressed mass cell-derived inflammatory allergic responses by blocking histamine release and pro-inflammatory cytokine expression and furthermore proposed the mechanism of action (Kim et al. 2005). GA may regulate through hindering the p38, PKC, JNK, and PI3K/Akt signaling pathways and lessening the level of NF-κB protein, resulting in the inhibition of MMP-9 and MMP-2 of PC-3 human prostate growth cells (Liu et al. 2013). GA likewise inhibited the activities of Akt, PKC, and IKK in an in vitro kinase assay. Migration and invasion ability of U-2 OS cells was suppressed by GA, and it diminished MMP-2 and MMP-9 protein and mRNA levels and secreted enzyme activity in vitro. Liao et al. (2012) proposed that potential signaling pathways of GA-hindered migration and invasion in U-2 OS cells might be expected to downregulate the PKC, hindering MAPK and PI3K/Akt, resulting in inhibition of MMP-2 and MMP-9 expression. On the basis of the documented suggestion, it was confirmed that GA possesses potent anti-inflammatory and anticancer activities.

Ellagic acid

Ellagic acid (EA) is one of the common polyphenolic compounds in herbs especially fruits, nuts, seeds, and berries, e.g., pomegranates, strawberries, raspberries, and blackberries. EA has anticarcinogenic, antioxidant, antiatherosclerosis, anti-inflammatory, antihepatotoxic, anti-HIV replication, and antifibrosis properties (Ahad et al. 2004). Various studies have revealed the immunomodulatory and anti-inflammatory properties of polyphenolic compounds. Numerous studies have shown suppressive effects of polyphenols on the release of biomarkers for inflammation (Handa et al. 2002; Rogers et al. 2005). In particular, EA inhibits IL-1β and TNFα-induced initiation of AP-1 and MAPK in pancreatic stellate cells in vitro (Masamune et al. 2005). EA reduced the

neutrophil infiltration and pro-inflammatory proteins COX-2 and iNOS via inhibition of p38, JNK, and ERK1/2 MAPKs and NF-κB pathways in a rat model of Crohn's disease (Rosillo et al. 2011). Anti-inflammatory action of EA led to downregulation of iNOS, TNFα, COX-2, and IL-6 because of NF-κB suppression and it exerts a chemopreventive effect on colon carcinogenesis in rat. A study also demonstrated that EA induced apoptosis and diminished the proliferation in pancreatic cancer cells. Although EA has no direct impact on mitochondria, it stimulated the mitochondrial depolarization, discharge of cytochrome *c*, and activation of caspase. Furthermore, it induced mitochondrial death by diminishing the NF-κB pathway (Edderkaoui et al. 2008). Pretreatment with EA diminished pro-inflammatory cytokines (IL-1β and TNFα) in the serum, TGFβ and fibronectin in the renal tissue, and also blocked the high glucose-primed NF-κB activation in the rat NRK 52E proximal tubular epithelial cells (Ahad et al. 2014). It also decreased human prostate tumor xenografts in immunodeficient mice by repressing inflammatory and angiogenic pathways (Albrecht et al. 2004). EA has been shown to regulate the Wnt signaling pathway via suppressing the expression of β-catenin and upregulating the degradation by increasing the p-β-catenin and axins in colon cancer cells (Fang et al. 2015). Similarly, EA modulated Wnt signaling in an animal model of oral oncogenesis by downregulating the expression of Wnt-associated molecules, namely Fz, Dvl-2, and GSK-3b (Anitha et al. 2013).

Geraniin

Geraniin is among the hydrolyzable tannins commonly present in various plants ranging annual herbs to woody shrubs or trees. It has several well-documented bioactivities like antioxidant, anti-inflammatory, anticancer, antihypertensive, antihyperglycemic, antidiarrheal, anesthetic, and antimicrobial. Addition of geraniin to hydrogen peroxide-induced human hepatocarcinoma cells was shown to upgrade the glutathione (GSH) level. It also diminished the level of intracellular ROS and cell death in a time- and concentration-dependent manner. Geraniin induced Nrf2, a transcriptional factor which controls different detoxifying antioxidant genes, probably by means of ERK1/2 and PI3K/Akt signaling (Wang et al. 2015). The anticancer activity of geraniin has likewise been perceived in utilizing adenocarcinoma tumor cell xenografts onto nude mice (Li et al. 2013b). A few mechanistic activities have been suggested for the anticancer activities of geraniin. Firstly, treatment with geraniin stimulated the cancer cells and led to apoptotic cell death in a dose- and time-dependent manner (Lee et al. 2008). It might be expected that unrestrained overproduction of free radicals drives the pathogenesis of various immune and inflammatory diseases such as RA, AD, cardiovascular disease, diabetes mellitus, and Parkinson's disease (Valko et al. 2007). The antioxidant activity of geraniin has been documented by means of its ability to scavenge the free radicals. A few investigations have demonstrated that geraniin treatment on murine macrophages modified the secretion of pro-inflammatory cytokines, e.g., IL-8, TNF, and interferon (Okabe et al. 2001; Kolodziej et al. 2001; Fujiki et al. 2003; Park et al. 2007a, b). Additionally, geraniin modulated the release of inflammatory mediator-producing enzymes like iNOS and 5-lipoxygenase (5-LOX) (Pan et al. 2000). Besides, geraniin compromised the action of NF-κB (cellular inflammatory response) in activated macrophages (Park et al. 2007a, b). Then again, previous study on treatment with geraniin in macrophages showed stimulatory effects in yeast phagocytosis in contrast to no treatment (Ushio et al. 1991). In view of this result, geraniin seems to have dual actions (immunostimulating and immunosuppressing). Both activities require additional evidence to delineate the modulation of immune reactions by geraniin.

Geraniin treatment extraordinarily decreased the outflow of RANKL-induced osteoclast-particular genes, restrained NF-κB and ERK signaling pathways, and blocked the action of important osteoclast transcriptional factors, Fos and NFATc1 (Xiao et al. 2015). Kang et al. (2011) concluded that geraniin hindered the mitochondria-dependent pathway through apoptosis of cells which was activated by gamma-radiation-prompted oxidative stress. Later in vivo study by Bing et al. (2013) revealed that geraniin hindered apoptosis of splenocytes, irradiated with gamma radiation, and moreover proliferation of cells was stimulated. A cytotoxicity study showed that geraniin enhanced apoptosis of A549 human lung adenocarcinoma cells, where it was shown that the cell growth was arrested in the S phase of the cell cycle. The signaling pathways prompting apoptosis of A549 cells were observed as an alteration in Bax and Bcl-2 expression, thereby resulting in interruption of the membrane of mitochondria and liberated cytochrome *c* which initiated caspase-dependent apoptosis (Li et al. 2013b). Interestingly, geraniin also supported the proliferation and differentiation of osteoblasts by activating the Wnt signaling pathway via downregulating the gene expression of LRP6, β-catenin, TCF4, frizzled-2, and LEF1 while upregulating axin2 (Li et al. 2018). Similarly, another study reported that geraniin exerted osteogenic effects on bone marrow mesenchymal stem cells by enhancing the gene and protein expression of β-catenin which led to the initiation of Wnt/β-catenin signaling pathway (Mo et al. 2018). On the basis of these studies, geraniin is a good candidate for anti-inflammatory and anticancer agents.

Lignans

Lignans are a family of polyphenols formed by the dimerization of two phenylpropanoid units. Lignans are generally present in natural products including cereal, soy beans,

vegetables, and fruits. *P. amarus* is rich in lignans such as phyllanthin, hypophyllanthin, niranthin, nirurin, phyltetralin, isolintetralin, and nirtetralin. Among them, phyllanthin, hypophyllanthin, and niranthin have been widely reported for their anticancer and anti-inflammatory properties. (Patel et al. 2011).

Phyllanthin, hypophyllanthin and niranthin

Phyllanthin, hypophyllanthin, and niranthin are among the common lignans of *Phyllanthus* species (Patel et al. 2011). Limited evidence documents their anticancer and anti-inflammatory properties. Recent studies reported the anti-inflammatory effects of 80% ethanol extract of *P. amarus* and its bioactive compounds, phyllanthin, hypophyllanthin, and niranthin, on LPS-activated U937 macrophages (Harikrishnan et al. 2018a, b, c). These studies found that the extract and compounds suppressed the expression of COX-2 and synthesis of inflammatory mediators including TNFα, PGE_2, and IL-1β in a dose-dependent manner. Furthermore, these lignans downregulated the activation of upstream signaling molecules (TLR4 and MyD88) which were fundamental for the activation of inflammatory signaling pathways (MAPKs, NF-κB, PI3K/Akt). Thus, these studies concluded that phyllanthin, hypophyllanthin, and niranthin suppressed the gene expression of TNFα, COX-2, and IL-1β in human macrophages by downregulating the initiation of MAPKs, NF-κB, and Akt (Harikrishnan et al. 2018a, b, c). Krithika et al. (2016) reported that phyllanthin has a strong in vivo inhibitory effect on CCl_4-mediated lipid peroxidation and hepatic fibrosis by inhibiting the expression of TNFα and prevented the activation of NF-κB in the hepatic tissue, and pro-fibrotic factor TGFβ1 mediating inflammatory signaling. As phyllanthin, hypohyllanthin, and niranthin are active marker compounds of *P. amarus* for anti-inflammatory activity, it is suggested for researchers to focus on these lignans for effective anti-inflammatory activity.

Triterpenoids

Triterpenes are chemical compounds with a molecular formula of $C_{30}H_{48}$ comprising three units of terpene or six units of isoprene. Triterpenes are found in animals, plants, and fungi. In *P. amarus*, lupeol, oleanolic acid, and ursolic acid were reported as major triterpenoids.

Lupeol

Lupeol is a pentacyclic triterpenoid and widely present in plant species especially in fruits and vegetable with various pharmacological effects like anti-inflammatory, antioxidant, antiarthritic, and antitumor. Pretreatment with lupeol resulted in anti-inflammatory activity by reducing the secretion of PGE_2 in A23187-stimulated macrophages (Fernández et al. 2001). Likewise, $CD4^+$ T cell-mediated cytokine production was suppressed by lupeol treatment in a mouse model. Additionally lupeol reduced the levels of cellularity and eosinophil in the bronchoalveolar fluid and therefore it reduced the mucus production and lung inflammation (Vasconcelos et al. 2008). Moreover, lupeol reduced TNFα, IL-1β, and NF-κB pathway in LPS-induced macrophages (Lee et al. 2016). Administration of lupeol against 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced markers resulted in inhibition of PI3K activation, Akt phosphorylation, NF-κB, IKKα initiation, and degradation and phosphorylation of IkBα in skin carcinogenesis (Saleem et al. 2004). Furthermore, lupeol hindered the growth of pancreatic cancer cells via NF-κB-mediated modulation by Ras-induced pathways like PpKCalpha/ODC, PI3K/Akt, and MAPK signals (Saleem et al. 2005; Lee et al. 2007; Prasad et al. 2009).

Oleanolic acid

Oleanolic acid (OA) is a pentacyclic triterpenoid generally present in fruits, leaves, and stem bark of herbal plants. OA is well known for its biological effects such as antioxidant, antitumor, anti-inflammatory, antidiabetic, and antimicrobial activity (Wang et al. 2010, 2013a; Jesus et al. 2015; Zhu et al. 2015). Various investigations have detailed the anticancer activity against cancer growth in various models. For instance, OA hindered the proliferation of transplanted tumor in liver hepatocellular cells (HepG2) through upregulation of the tumor protein (p53), cell cycle arrest, and COX-2-facilitated initiation of mitochondrial apoptotic pathway (Wang et al. 2013a). In human bladder growth cells, OA repressed cell proliferation and upgraded cell apoptosis via Akt/mTOR/S6K, and ERK1/2 inhibition (Mu et al. 2015). An OA derivative, oleanolic acid methyl ester, exhibited cytotoxic effects on human cervical growth cells (HeLa) via promotion of apoptosis and generation of ROS in a time- and concentration-dependent manner (Song et al. 2014). OA exerted its anti-inflammatory action by hindering release of LPS that affects HMGB1. HMGB1 is a protein which upregulates the pro-inflammatory cytokines and expression of cell adhesion molecules (CAMs) (Yang et al. 2012). Likewise, Lee et al. (2013) proposed that OA lessened the pro-inflammatory reactions through downregulation of NF-κB expression and also TNFα in vivo and in vitro which was induced by LPS. In a mouse model of autoimmune myocarditis, OA promoted anti-inflammatory cytokines, reduced the production of pro-inflammatory cytokines, and lessened the other symptoms (Martin et al. 2014). Moreover, OA mitigated the hepatic insulin resistance by calming anti-inflammatory activity by decreasing the levels of IL-1, IL-6, and TNFα in mice livers (Wang et al. 2013b). Taken together, oleanolic

acid therefore has strong evidence for anti-inflammatory and anticancer activities.

Ursolic acid

Ursolic acid (UA) is a pentacyclic triterpenoid carboxylic acid which is generally distributed in fruits and other plant species. UA has well-documented for anticancer, anti-inflammatory, antioxidant, and antimutagenic effects. Pretreatment with UA in RAW264.7 mouse Mb diminished the expression of iNOS and COX-2 by suppressing the NF-κB. Likewise, UA firmly hindered the production of NO in a similar cell line (Suh et al. 1998; Ryu et al. 2000). Furthermore, UA treatment in human mammary epithelial cells repressed TPA-mediated initiation of COX-2 and PGE_2 synthesis. Similarly, UA hindered the activation of protein kinase C, extracellular signal regulated kinase 1/2 (ERK1/2), Jun NH2-terminal kinase 1/2 (JNK1/2), and p38 mitogen-activated protein kinase (MAPK) against TPA. Moreover, COX-2 promoter was blocked as the activator protein-1 bonded to the promoter (Subbaramaiah et al. 2000). These results are helpful for understanding the anti-inflammatory activity of UA. Shishodia et al. (2003) studied the expression of specific oncogenes like COX-2, MMP-9, cyclin D1, Jun, and Fos which were suppressed via hindering NF-κB and P65 phosphorylation in UA treatment. In murine pMØ, UA especially enhanced ATP binding cassette transporter-mediated IL-1β emission at levels of transcription, translation, and post-translation probably through the generation of intracellular ROS and ended in initiation of ERK1/2, p38 MAPK pathways and caspase-1 (Ikeda et al. 2007). Correspondingly, triterpenoid-initiated IL-6 and macrophage migration inhibitory factor (MIF), yet not TNFα, release of protein, with a mechanism that probably related to the release of IL-1β, since IL-6 was already revealed to be induced by ROS production, and also the ERK1/2, p38 MAPK, and NF-κB signaling pathways (Kanakaraj et al. 1998; Yu et al. 2005), and MIF generation was hindered by ROS-initiated ERK1/2 (Fukuzawa et al. 2002). The antiproliferative properties of UA on human osteosarcoma cells were regulated by suppressing the transcriptional event of β-catenin/TCF-4 reporter. Furthermore, UA also inhibited the expression of β-catenin protein in the nucleus, whole cell, and cytoplasm. In addition, the downstream signals participating in Wnt signaling pathway such as Myc and cyclin D1 were also inhibited by UA treatment in a dose-dependent manner (Zhang et al. 2016).

Conclusion

Modulating the signal transduction pathways by using bioactive compounds of natural origin is valued as an attractive approach for drug discovery and development. Plant extracts and their metabolites that are able to modulate inflammation-related molecular and cellular pathways are sought after in anticancer drug development programs. Thus treating chronic diseases such as inflammation and cancer by controlling the cellular signaling pathways using various natural bioactive compounds will be a newly emerging approach in drug discovery. In this review we have focused on the various anticancer and anti-inflammatory activities of flavonoids, tannins, and triterpenes of *P. amarus*. Various studies have demonstrated that the flavonoids (astragalin, kaempferol, quercetin, rutin), lignans (phyllanthin, hypophyllanthin and niranthin), tannins (corilagin, geraniin, ellagic acid, gallic acid), and triterpenes (lupeol, oleanolic acid, ursolic acid) could effectively suppress the development and progression of inflammation-related cancer by modulating cell signaling pathways in particular those involving NF-κB, JAK-STAT3, MAPK, PI3K/Akt, and Wnt (Fig. 2). These pathways interact with each other and contribute to the development of inflammatory networks whereas these networks also play a significant role in carcinogenesis. Hence understanding the mechanisms involved in inhibiting these signaling pathways by using *P. amarus* and its bioactive compounds will provide useful information

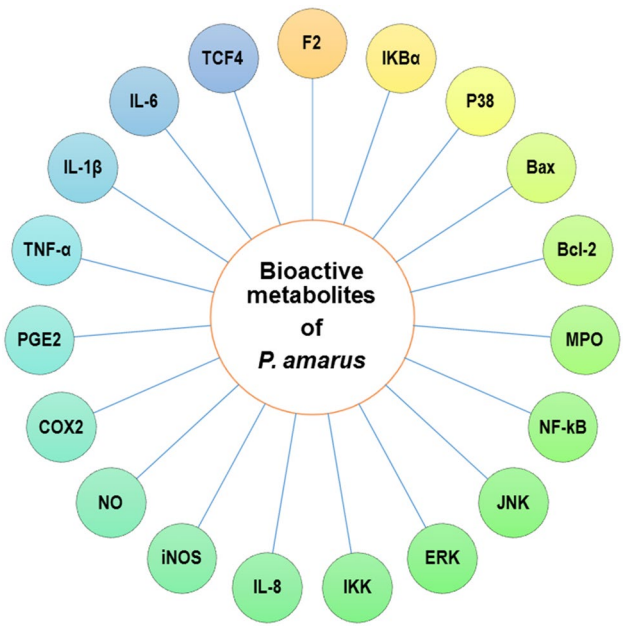

Fig. 2 Key signaling mediators downregulated by bioactive metabolites from *P. amarus* in cellular and animal models. Bax Bcl-2-associated X, Bcl-2 B cell lymphoma 2, COX-2 cyclooxygenase 2, ERK extracellular signal-regulated kinases, IL interleukin, IκBα nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha, IKK IκB kinase, iNOS inducible nitric oxide synthase, JNK Jun N-terminal kinase, MAPK mitogen activated protein kinases, MPO myeloperoxidase, NO nitric oxide, NF-κB nuclear factor kappa β, PGE2 prostaglandin E2, TCF4 transcription factor 4, TNF-α tumor necrosis factor alpha

for future research to develop drug candidates for prevention and new treatment for cancer and inflammatory diseases.

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Compliance with ethical standards

Conflict of interest All authors declare that they do not have any conflict of interest.

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