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Mini-review

The potential role of boswellic acids in cancer prevention and treatment

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ABSTRACT

Despite the extensive research carried out in the field of cancer therapeutics, cancer is one of the most dreadful diseases in the world with no definitive treatment to date. The key attributes responsible for this are the various limiting factors associated with conventional chemotherapeutics that primarily include adverse side-effects and development of chemoresistance. Hence, there is an utter need to find compounds that are highly safe and efficacious for the prevention and treatment of cancer. Boswellic acid, a group of pentacyclic compounds, seems to be promising enough due to its inherent anti-cancerous properties. Considering this perspective, the present review highlights the established studies related to the anti-cancer potential of boswellic acid against different cancer types. The molecular mechanisms underlying the targets of boswellic acid that are accountable for its potent anti-cancer effect are also discussed. Overall, this review projects the pieces of evidence that reveal the potential of boswellic acid as a suitable candidate that can be appropriately developed and designed into a promising anti-cancer drug.

Introduction

Cancer is one of the most dreadful diseases in the world, with an estimation of approximately 14.1 million new cases and 8.2 million deaths in the year 2012. Considering the advances made in the area of cancer diagnostics and therapeutics, cancer statistics remain unaffected as implied by Globocan 2008 when cancer incidence was 12.7 million and death due to cancer was 7.6 million [1,2]. The conventional chemotherapeutic agents that are being used presently are often associated with several side effects [3,4]. Development of chemoresistance further complicates the process of treating this dreadful disease [5,6]. To overcome these problems, the focus needs to be shifted to the natural compounds that can function effectually in the treatment of cancer with fewer side effects. Nature is the enormous source of countless drugs with immense potential against various human ailments including cancer [7,8]. As a matter of fact, about 50% of pharmaceuticals are derived from botanicals, and this vast reserve is yet to be explored for the isolation of novel chemotherapeutic agents for better treatment modalities [9–11]. The inherent anti-cancer properties of the natural products [12,13] come from a variety of phytochemicals such as sesquiterpenes, flavonoids, alkaloids, diterpenoids, and polyphenolic compounds present in diverse fruits, vegetables, and medicinal plants [14,15]. *Boswellia serrata,* commonly known as Indian olibanum, salai guggal, loban, or kundur, is one such medicinal plant that has been shown to exhibit immense potential in combating cancer.

Abbreviations: AKBA, 3-acetyl-11-keto-β-boswellic acid; APC, activated protein C; AR, androgen receptor; BA, beta-boswellic acid; BAX, BCL2-associated x protein; BC-4, boswellic acid acetate; BCDD, butyl 2-cyano-3, 11-dioxours-1, 12-dien-24-oate; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BE, Boswellin; BOBA, 3-α-butyryloxy-β-boswellic acid; BSE, *Boswellia serrata* extracts; C/EBP-α, CCAAT/enhancer-binding protein alpha; CDK, cyclin-dependent kinase; CEMB, cyano enone of methyl boswellates; C-KβBA, 3-cinnamoyl-11-keto-β-boswellic acid; COX, cyclooxygenase; CXCR, chemokine, cxc motif, receptor; DMBA, 7, 12-dimethylbenz[a]anthracene; DNA, deoxyribonucleic acid; DR, death receptor; *EGR*, extract from gum resin; Erk, extracellular signal-regulated kinase; HLE, human leucocyte elastase; HSC, hepatic stellate cells; IKK, inhibitor of kappaB kinase; IL, interleukin; K-BA, keto-beta-boswellic acid; KMT, Korean medicine therapy; LO, lipooxygenase; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; Mcl-1, myeloid leukemia cell differentiation protein 1; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; MM, multiple myeloma; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kappa beta; PARP, poly (ADP-ribose) polymerase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositide 3-kinases; PKBA, propionyloxy derivative of 11-keto-β-boswellic acid; PMNL, polymorphonuclear leucocyte; POBA, 3-α-propionyloxy-β-boswellic acid; PPAR-γ, peroxisome proliferator-activated receptor gamma; SAMD14, sterile alpha motif domain containing 14; SHP-1, Src homology region 2 domain-containing phosphatase 1; SMPD3, sphingomyelin phosphodiesterase 3; Sp1, specificity protein 1; *STAT-3*, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; TPA, 12-O-tetradecanoylphorbol-13-acetate; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

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It is a moderate-large sized branching tree belonging to Burseraceae family and is found in dry mountainous regions of India, Northern Africa, and the Middle East. This family of Burseraceae includes 17 genera and 600 species of plants that are wide-spread throughout the tropical regions. The genus *Boswellia* comprises around 25 species distributed widely in Arabia, northeastern coast of Africa, and India [16]. It has a profound application as a traditional remedy for various ailments, especially inflammatory diseases including asthma, arthritis, cerebral edema, chronic pain syndrome, chronic bowel diseases, cancer, and some other illnesses [17,18]. The gum resin of *B. serrata* and *carteri* species contains pentacyclic triterpenic acids, namely boswellic acids (α,β,γ boswellic acid), acetyl-β boswellic acid, 11-keto-β-boswellic acid, acetyl-11-keto-β-boswellic acid, and their derivatives that exert anti-inflammatory properties to the plant (Fig. 1) [19–21].

Molecular targets of boswellic acid

Boswellic acid (BA) exerts its potent anti-cancerous effect through modulation of multiple molecular targets such as kinases, transcription factors, enzymes, receptors, growth factors, and others involved in cell survival and proliferation (Fig. 2). It was reported that BA modulates the process of apoptosis through its supportive or inhibitory regulation upon these molecular mediators (Fig. 3). Altmann et al. have shown that 11-keto-BAs can stimulate mitogen-activated protein kinases (MAPK) and mobilize the intracellular $Ca^{(2+)}$ that are important for the activation of human polymorphonuclear leucocytes (PMNL) [22,23]. In another study on the cytotoxic action of acetyl-11-keto-beta-boswellic acid (AKBA) on meningioma cells, it was found that AKBA prohibited the phosphorylation of extracellular signal-regulated kinase-1 and -2 (Erk-1/2) and impaired the motility of meningioma cells stimulated with platelet-derived growth factor BB [24]. In the case of colon cancer, BA treatment on HCT-116 cells led to a decrease in cyclin D, cyclin E, and Cyclin-dependent kinases such as CDK2 and CDK4, along with significant reduction in phosphorylated Rb (pRb) [25]. A study by Syrovets et al. reported the effect of BA on NF-κB, a transcription factor associated with malignant phenotype as well as chemoresistance of various cancers, and showed that LPS-triggered induction of TNF-alpha in monocytes is dependent on IKK activity and via their direct inhibitory effects on IkappaB kinase (IKK), AlphaBA, and AKbetaBA, convey inhibition of NF-kappaB and subsequent down-regulation of TNF-alpha expression in activated human monocytes [26]. Acetyl-beta-boswellic acid and AKBA were found to inhibit proliferation and elicit cell death in chemoresistant androgen-independent PC-3 prostate cancer cells *in vitro* and *in vivo* by inhibiting constitutively activated NF-kappaB signaling by intercepting the activity of IkappaB kinase (IKK) [27]. The TNF and chemotherapeutic agents' induced apoptosis was potentiated by AKBA, while the TNF induced invasion was suppressed. Also, an inhibition of receptor activator of NF-kappaB ligand-induced osteoclastogenesis was observed. It was also reported that AKBA does not affect the binding of NF-kappaB to the DNA directly but sequentially inhibits TNF-induced activation of IKK, IkappaBalpha phosphorylation, IkappaBalpha ubiquitination, IkappaBalpha degradation, p65 phosphorylation, and p65 nuclear translocation [28]. Furthermore, AKBA an analog of BA exhibited anti-inflammatory and anti-atherogenic effects in LPS-challenged $ApoE^{-/-}$ mice via inhibition of NF-κB and down regulation of MCP-1, MCP-3, IL-1alpha, MIP-2, VEGF, and TF [29]. In pancreatic cancer cell lines, AKBA inhibited the constitutive expression of NF-κB and caused suppression of NF-κB regulated genes such as *COX-2*, *MMP-9*, *CXCR4*, and *VEGF* [30]. A comparative study checking the prevention of intestinal adenomatous polyposis in $APC^{Min/+}$ mice between AKBA and aspirin revealed that AKBA has higher potential via modulation of the Wnt/β-catenin pathway, and NF-κB/COX-2 pathway in adenomatous polyps [31]. Recently, an extract containing boswellic acid was found to ameliorate schistosomiasis liver granuloma and fibrosis by downregulating NF-κB signaling in mice, and subsequent reduction in the expression of VEGF, TNF-α, and MCP-1 [32]. AKBA is also responsible for down-regulation of PPAR-γ and C/EBP-α in a dose and temporal dependent manner in mature adipocytes, ultimately leading to lipolysis [33]. Treatment with 3-α-Butyryloxy-β-boswellic acid (BOBA), a semi-synthetic analog of BA, was shown to induce cancer cell apoptosis and resulted in tumor regression through down-regulation of NF-κB and PARP cleavage induction [34]. The activation of signal transducers and activators of transcription-3 (STAT-3), a transcription factor, is associated with survival, proliferation, chemoresistance, and angiogenesis of tumor cells, including human multiple myeloma (MM). An extensive study carried out by Kunnumakkara et al. revealed that the constitutive activation of STAT-3 in human MM cells could be inhibited by AKBA by the induction of Src homology region 2 domain-containing phosphatase 1 (SHP-1), which is responsible for dephosphorylation of STAT-3. Additionally, the inhibition of STAT3 activation by AKBA resulted in suppression of genes involved in cell proliferation, survival, and angiogenesis [35]. Acyl derivatives of BA function as potent inhibitors of NF-κB and STATs, as evinced by their wide range of cytotoxicity against various human cancer cell lines including HT-29 colon, SW-620, Colo-205, Hep-2 larynx, DU-145, and prostate PC-3 [36]. The derivatives of BA, such as AKBA, boswellic acid acetate, and a propionyloxy derivative of 11-keto-β-boswellic acid (PKBA; a semisynthetic analog of 11-keto-β-boswellic acid), have been reported to influence the activity of topoisomerase I and II, thus leading to induction of apoptosis in different cancer cell lines [37–39]. 5-lipooxygenases (5-LO), responsible for catalyzing the synthesis of leukotrienes from arachidonic acid and human leucocyte elastase (HLE), and serine proteases involved in several inflammatory processes, is considered to be a potent molecular target of BA derivatives [19,40–42]. It is well established that the signals promoting the mitogenic response of hepatic stellate cells (HSCs) due to liver injury are activated with the dimerization and auto-transphosphorylation of platelet-derived growth factor receptor (PDGFR) upon binding with platelet-derived growth factor (PDGF), and thus contributes to the development of hepatic fibrosis. BA up-regulates SHP-1 with subsequent dephosphorylation of PDGFR-β and downregulation of PDGF-dependent signaling after PDGF stimulation, thereby exerting an anti-proliferative effect on HSCs [43]. In the case of prostate cancer, AKBA targets different receptors that include androgen receptor (AR), death receptor 5 (DR5), and vascular endothelial growth factor receptor 2 (VEGFR2), and leads to the inhibition of proliferation of prostate cancer cells via apoptosis induction and suppression of angiogenesis [44–46].

Role of boswellic acid in cancer prevention and treatment

The anti-cancer potential of boswellic acid is well evidenced by several *in vitro*, *in vivo*, and *clinical* studies in different cancers that implicate its inhibitory actions against different hallmarks of cancer such as survival, proliferation, angiogenesis, invasion, and metastasis (Tables 1–3).

Prostate cancer

BA has been proven to possess efficacy against prostate cancer. AKBA has been shown to inhibit proliferation and elicit cell death in chemoresistant androgen-independent PC-3 prostate cancer cells *in vitro* and *in vivo*. It can also inhibit constitutively active NF-κB signaling by intercepting the IkappaB kinase (IKK) activity. The constitutively over-expressed and NF-κB-dependent antiapoptotic proteins Bcl-2 and Bcl-xL were down-regulated due to the impaired phosphorylation of p65, resulting in reduced nuclear translocation of NF-κB proteins. It is associated with the reduced