**ABSTRACT**

**Introduction:** Cancer has been identified to be the second major cause of death internationally as exemplified by ca. 9.6 million deaths in 2018 along with ca. 18 million new patients in 2018 that have been recorded. Natural boswellic acids (BAs) and their source, frankincense, have been reported to possess in vitro and in vivo anticancer effects toward various cancer cells.

**Areas covered:** This comprehensive review focuses on the importance of boswellic acids (BAs) for the establishment of future treatments of cancer. Moreover, potent semisynthetic derivatives of BAs have been described along with their mode of action. In addition, important structural features of the semisynthetic BAs required for cytotoxic effects are also discussed.

**Expert opinion:** Numerous semisynthetic BAs illustrate excellent cytotoxic effects. Of note, compounds bearing cyanoenone moieties in ring A, endoperoxides and hybrids display increased and more potent cytotoxic effects compared with other semisynthetic BAs. Moreover, BAs have the potential to conjugate or couple with other anticancer compounds to synergistically increase their combined anticancer effects. In addition, to get derived BAs to become lead anticancer compounds, future research should focus on the preparation of ring A cyanoenones, endoperoxides, and C-24 amide analogs.

1. **Introduction**

Triterpenes having six isoprene units are quite widespread and are found in many natural sources dating from ancient times. It was later determined that these compounds are synthesized via a cascade cyclization of squalene in many plants. Furthermore, over 20,000 triterpenes have been reported from various natural sources and interestingly, most of them are found in their free form while others occur as triterpene glycosides (saponins) [1–4]. Additionally, triterpenes are widespread in various medicinal plants and in particular, in their resin, fruits, leaves, seeds, and bark of the specific herbs. Furthermore, on the basis of the number of isoprene units, triterpenoids can be classified as acyclic, mono-, bi-, tri-, tetra- and pentacyclic. On the other hand, among the triterpenoids, tetracyclic triterpenes (viz., dammaranes, protostanes, euphanes, and cycloartanes) and pentacyclic triterpenes (viz., uranes, oleananes, gammaceranes, hopanes, and lupanes) are the most studied of the triterpenes [1–4].

Pentacyclic triterpenes demonstrated interesting biological effects with some rather unique mechanisms of action. For instance, they showed antidiabetic, antitumor, antiviral, analgesic, antiparasitic, anti-inflammatory, antimicrobial, hypolipidemic effects, anti-obesity effects, and ameliorating effects [1–4]. Additionally, some pentacyclic triterpenoids are currently marketed as therapeutic agents and for instance, glycyrrhizic acid and oleanolic acid are registered as drugs for the treatment of various liver diseases. On the other hand, corosolic acid and gymnemic acids are registered as dietary supplements for diabetes while carbenoxolone and asiaticoside are used as drugs to treat gastritis and wound-healing, respectively [1–4]. Moreover, pentacyclic triterpenes are in various phases of clinical trials viz., bevirimat (PA-457), S-0139, and RTA 404 are in phase II clinical trials to treat HIV infection, cerebrovascular diseases, and multiple sclerosis, respectively. Additionally, two oleanolic acid analogs CDDO (phase I) and CDDO-Me (phase II) are in clinical trials in the USA for cancers [1,2].

It has been reported that triterpene acids possess remarkable biological effects viz., regulating blood sugar level, anti-inflammatory, antitumor, and antiviral effects. It is noteworthy that triterpene acids have attracted a fair amount of attention recently among medicinal chemists because they have selective toxic effects on various cancer cells.
while at the same time are harmless to normal cells [5]. Among the triterpene acids, boswellic acids are well-known natural products having a carboxylic acid group at the C-24 position and possessing cytotoxic, anti-inflammatory, anti-apoptotic, anti-ulcerogenic, and anti-arthritic effects [6]. Moreover, boswellic acids (BAs) showed interesting in vitro anticancer effects toward various cancer cell lines viz., bladder [7], cervical [8], brain [9], colon [10], colorectal [11], leukemia [12], liver [13], lung [14], pancreatic [15], melanoma [16], meningioma [17], myeloma [18], neuroblastoma [8], and prostate cancer [19].

Additionally, boswellic acids possess in vivo anticancer effects toward the following various cancers viz., colon cancer [20], Ehrlich tumor [21], colorectal cancer [11], glioma [14], leukemia [22], pancreatic cancer [15] and prostate cancer [19]. Most importantly, some clinical studies have also been reported in which boswellic acids have been successfully used for cancer treatment viz., brain tumor, lung cancer, and breast cancer [23–27]. Although only a few reviews have been published on the biological effects of boswellic acids [6,28–34], in this review, we provide an historical background of the structural elucidation and cytotoxic effects of the most active boswellic acid synthetic derivatives (IC_{50} ≤ 10 μM or percentage inhibition >90%).

2. History of boswellic acids (BAs)

Literature revealed that Baer [35] initiated the chemical investigations of frankincense in 1788. A century later Tschirch and Halbey published some further studies on BAs in 1898 and 1900 [36–39]. Normally these researchers divided the whole frankincense extract into neutral and acidic fractions and after various purification steps they isolated a raw product which they described as ‘Boswellic Acid.’ Although the exact chemical structure was not known at that time, they proposed the chemical formula to be C_{32}H_{52}O_{4}. After a further three decades, Winterstein and Stein [40] showed that Tschirch and Halbey’s raw product comprised of mixture of four BAs viz., α-BA, β-BA, A-α-BA, and A-β-BA. Additionally, they purified these four BAs but were unable to elucidate their chemical structures. However, they did propose the correct chemical formula to be C_{34}H_{56}O_{4}.

In 1937 Simpson [41] conducted some investigative chemical experiments on the putative β-BA and suggested that it was the β-hydroxy-acid (1) (Scheme 1). This suggested that it has a hydroxyl group at the C-3 position relative to the CO_{2}H group. However, the configuration of this hydroxyl group was still unclear. Simpson deduced this information from two oxidation reactions which he performed: firstly, the free acid gave a mono-ketone ‘nor-boswellenone (3)’ via the intermediate 2 by its decarboxylation (molecular formula: C_{30}H_{46}O) after initial treatment with CrO_{3} [42]. On the other hand, methyl β-boswellate (4; C_{31}H_{50}O_{2}) afforded the stable keto-ester 5 upon a similar treatment with CrO_{3} [41–43]. In the same year, Simpson & Williams [44] demonstrated that the putative β-BA has one double bond which was confirmed via an allylic oxidation. They deduced the presence of the double bond via oxidation of methyl acetyl-β-boswellate (6; molecular formula: C_{33}H_{52}O_{4}) with CrO_{3} which afforded methyl O-acetyl-β-boswellenolactone (7; molecular formula: C_{33}H_{52}O_{5}).

Structure elucidation of organic compounds in the last two decades has become dramatically easier because of the establishment of more advanced techniques viz., NMR, mass spectrometry (MS), and X-ray crystallography. On the other hand,

Scheme 1. Transformations of boswellic acids for early structure elucidation.
in the earlier mid-nineteenth century, it was very hard to elucidate the structure of unknown compounds. One of the methods employed to elucidate the structures of unknown triterpenes is to compare its spectral and other properties with known triterpenes. Therefore, Ruzicka and Wirz [45,46] performed experiments in order to correlate BAs with their basic cores. Based on the chemical conversions of BAs, they indicated that ß-boswellic acid and α-boswellic acid are derived from α-amyrine (an ursane type pentacyclic triterpene) and β-amyrine (an oleanane type pentacyclic triterpene) respectively. Additionally, at that time Ruzicka was also involved between 1921 and 1953 in the development of the isoprene rule [47] and based on this tremendous work he and Butenandt were awarded the Nobel Prize for Chemistry in 1939.

In 1956 Beton et al. [48] indicated that, based on their chemical experiments, the C-3 OH of boswellic acids is in the α-configuration (3α-axial) and the C-4 CO₂H group is in the β-configuration (4β-axial; above the ring). Moreover, they further confirmed via various experiments that α and β-boswellic acids are derived from β and α-epi-amyrines. Six years later, a major breakthrough came from Sharma et al. [49] who published the ¹H NMR data of various pentacyclic triterpenes including boswellic esters. One year later Budzikiewicz et al. [50] reported the first mass spectral data of various amyrine analogs and these data are still used for the structure elucidation of unknown triterpenes. After a further 15 years, Pardhy and Bhattacharyya [51] isolated four BAs viz., ß-BA (8), A-ß-BA (9), KBA (10) and AKBA (11) (Figure 1) from B. serrata and reported their ¹H NMR and mass spectral data. In 2000 the research group of Ammon [52] reported on the crystal structure of AKBA (11) while 1 year later Gupta et al. [53] reported the crystal structure of A-ß-BA (9).

3. Source of boswellic acids

In his PhD thesis, Bergmann [54] compared the Boswellia species viz., B. ameero, B. freereana, B. papyrifera, B. sacra, B. socotrena, B. carterii, and B. serrata in order to detect which of them contained BAs and in what relative amounts. He concluded that among the above-mentioned Boswellia species only B. serrata, B. papyrifera, B. carterii, and B. sacra, (Bcar) contained a BAs in high quantities. Additionally, Basar [55] also showed in her PhD thesis that B. ameero, B. papyrifera, B. frereana, B. carterii, B. socotrena B. sacra, and B. serrata contain Bas, but only in trace amounts. Additionally, Paul [43] showed that B. sacra, B. carterii, and B. papyrifera contain relatively large quantities of BAs. He further demonstrated via HPLC analysis, that B. sacra, B. carterii, and B. papyrifera contain ß-KBA in rather low amounts when compared to the ß-ß-KBA content. On the other hand, B. sacra and B. carterii samples demonstrated a big deviation regarding the ß-ß/α-ß-KBA contents. Interestingly, B. serrata contains equal amounts of ß-KBA and ß-ß-KBA and that B. papyrifera contains the most ß-ß-KBA, followed by B. sacra, and B. carterii. Paul [43] further showed that B. serrata contains the greatest amounts of α-BA and β-BA. On the other hand, B. sacra, and B. carterii contains α-BA and β-BA in differing quantities and higher than in B. papyrifera. Moreover, high quantities of α-ABA and ß-ABA were present in B. sacra and B. carterii while B. papyrifera and

B. serrata comprise similar values of α-ABA and ß-ABA but lower compared with B. sacra and B. carterii.

We have conducted evaluations for the quantification of AKBA and KBA in B. sacra by using HPLC and NIR spectroscopy [56,57]. The results showed that the methanol extract of the resin contains AKBA at a concentration of 7.0% which is the highest concentration among BAs. In addition, this AKBA concentration was followed by the epidermis (1.37%), hypodermis (0.3%), stem bark (0.2%), and essential oil (0.1%) [56] (Table 1). Surprisingly, no AKBA was present in the roots, leaves, stem, and water extracts of B. sacra. On the other hand, the MeOH extract of the resin (0.6%) of B. sacra comprises the highest amount of KBA and this compound was also present in essential oil and epidermis in equal amounts (0.1% each) [57]. Moreover, no KBA was found in the roots, cortex, leaves, bark, epidermis, and hypodermis, and neither in the water extract. Furthermore, AKBA and KBA are only present in the epidermis of the stem as well as in the resin exudate. Thus, the presence of moderate amounts of AKBA and KBA in the epidermis is perhaps due to the presence of resin-producing canals. In another report, Krohn et al. [58] showed that B. serrata contains four BAs viz., AKBA, KBA, ß-BA, and A-ß-BA (Table 1) and that the amount of ß-BA was much higher than either AKBA or KBA.

Generally, the total organic acids in the total alcoholic extracts of B. sacra and B. serrata account for around 65–70% by weight. Sometimes these percentages are misconstrued in market products because normally they claim a 70% BAs content or 30% AKBA content. This is somehow misleading because Buchele et al. [59], reported that the highest amount of BAs in B. sacra is ca. 190 mg/g (i.e. 19%) followed by B. serrata ca. 140 mg/g (i.e. 14%). To corroborate the truth of these values, Mannino et al. [60], carefully analyzed the content of BAs in B. sacra and B. serrata. Their findings showed that the ‘real content’ of BAs in B. serrata and B. sacra were 16% and 29%, respectively. Mannino et al. [60] further showed that B. sacra and B. serrata contain all six BAs viz., AKBA, KBA, ß-BA, α-BA, A-ß-BA, and A-α-BA and that a comparison between the two Boswellia species demonstrated that the composition of B. sacra has AKBA (about 10-fold), α-BA (1.5-fold) and ß-BA (1.6-fold) higher than in B. serrata.
Table 1. Amount of boswellic acids in various parts of boswellia species.

| Source     | Part/Extract      | AKBA (%) | β-BA (%) | α-BA (%) | A-β-BA (%) | A-α-BA (%) | Reference |
|------------|-------------------|-----------|----------|----------|------------|------------|-----------|
| B. sacra   | Resin/MeOH        | 7.0%      | 0.6%     | -        | -          | -          | [56,57]   |
| B. sacra   | Resin/H$_2$O      | nd        | nd       | -        | -          | -          | [56,57]   |
| B. sacra   | Essential oils    | 0.1%      | 0.1%     | -        | -          | -          | [56,57]   |
| B. sacra   | Bark/MeOH         | 0.2%      | nd*      | -        | -          | -          | [56,57]   |
| B. sacra   | Epidermis/MeOH    | 0.1%      | 0.1%     | -        | -          | -          | [56,57]   |
| B. sacra   | Hypodermis/MeOH   | 0.3%      | nd       | -        | -          | -          | [56,57]   |
| B. sacra   | Roots/MeOH        | nd        | nd       | -        | -          | -          | [56,57]   |
| B. sacra   | Stem/MeOH         | nd        | -        | -        | -          | -          | [56,57]   |
| B. sacra   | Leaves/MeOH       | nd        | nd       | -        | -          | -          | [56,57]   |
| B. sacra   | Bark/MeOH         | -         | nd       | -        | -          | -          | [56,57]   |
| B. sacra   | Resin/MeOH        | 0.09      | 1.7      | 2.6      | 0.6        | -          | [60]      |
| B. serrata | Resin/MeOH        | 0.05      | 0.2      | 1.7      | 0.8        | -          | [60]      |

Nd: not detected; *% w/w (Mean ± SD (n = 3) expressed on a dry weight basis); √: Detected but no percentage is reported

4. Isolation and partial synthesis of BAs

4.1. Isolation and extraction of BAs

In 1932 Winterstein and Stein [40] (Scheme 2) reported on the first extraction and purification of natural BAs with preparative HPLC as the final purification step [60] and many natural product chemists are still using this very similar procedure today. The Winterstein and Stein protocol includes treating the whole extract with barium hydroxide (to form barium salts) followed by treatment with acetic anhydride in order to isolate the acetylated α- and β-isomers of the BAs. In 1998 Shao et al. [12] published another protocol for the extraction of BAs from frankincense. They extracted the raw frankincense with methanol to which was added a 2% KOH solution and followed this by extraction with EtOAc. The remaining aqueous solution was then neutralized with 2% HCl and again followed by extraction with EtOAc. The combined EtOAc extract from the second treatment which contains the free BAs was washed with water and dried over Na$_2$SO$_4$ to yield the BAs after removal of the EtOAc under reduced pressure. Beton et al. [48] further modified the procedure of Winterstein and Stein [40] and obtained better results (higher quantity and purity). In 2004 Bergmann [54] reported on a new ion exchange method in his PhD thesis using the ion exchanger IRA-900. The author claimed that this process is feasible both on a laboratory as well as on a larger scale.

4.2. Enrichment of BAs

A literature survey showed that crude extracts of B. serrata and B. sacra contain the four major BAs viz. β-BA (8), A-β-BA (9), KBA (10), and AKBA (11) and that the concentrations of KBA (10) and AKBA (11) in the Boswellia extracts are low. Moreover, the generally low yields of BAs makes the purification of these four BAs very difficult. On the other hand, a pharmacological examination of the most active BAs viz., KBA and AKBA is not such a viable enterprise because of the inherent difficulties in their purification from unavoidable mixtures of various BAs (and other resin compounds) via conventional chromatographic techniques. To overcome this problem, Jauch and Bergmann [61] developed a protocol (Scheme 3) in order to enrich the BAs mixture with KBA and/or AKBA up to 100%. This involves a two-step protocol: (i) acetylation (AKBA production; A$_2$O/pyridine) or deacetylation (KBA production; KOH in i-PrOH); (ii) conversion of the BAs into KBA or AKBA via photochemical oxidation process.

5. Cytotoxic effects of semi-synthetic boswellic acids

5.1. AKBA and KBA analogs

Kaur et al. [62] prepared the ring A modified AKBA analog 14 and tested it for cytotoxic effects. Although compound 14 possesses cytotoxic effects toward HL-60 (myeloid leukemia) with an IC$_{50}$ = 5 μM it was inactive toward HeLa cells (cervical carcinoma). Csuk et al. [63] prepared the AKBA analog 15 having an endoperoxide system which showed significant cytotoxic effects toward 15 human cancer cell lines with IC$_{50}$ values in the range of 0.4–4.5 μM (Figure 2). It is noteworthy that compound 15 possesses strong cytotoxic effects toward melanoma (S18A2: IC$_{50}$: 0.8 μM), ovarian (A-2780: IC$_{50}$: 0.7 μM), and anaplastic thyroid (SW-1736: IC$_{50}$: 0.4 μM). Moreover, this compound also showed promising effects toward head cancer (A-253: IC$_{50}$: 1.3 μM), lung (A-549: IC$_{50}$: 1.3 μM), colon (DLD-1: IC$_{50}$: 1.4 μM; HCT-8: IC$_{50}$: 1.5 μM; HCT-116: IC$_{50}$: 1.6 μM; HAT-29: IC$_{50}$: 1.4 μM), and breast cancer cells (MCF-7: IC$_{50}$: 1.8 μM) [63]. In another study, peroxide BA derivative 15 also possesses potent cytotoxic effects toward A375 (EC$_{50}$: 0.9 μM), A2780 (EC$_{50}$: 0.7 μM), and S18A2 (EC$_{50}$: 0.8 μM) [64]. Moreover, KBA analog 16 illustrated cytotoxic effects toward K562, PC-3 and HL-60 with IC$_{50}$: <9 μM, and in particular against K562 (IC$_{50}$: 5 μM) [65]. On the other hand derivative 17 was only active toward K562 with IC$_{50}$: 4.9 μM [65].
In another study, Huang et al. [66] prepared a library of BA derivatives and screened them for their cytotoxic effects toward PC-3 cells. Among the tested compounds, KBA derivatives 18–20 (Figure 3) possess good effects toward PC-3 with IC₅₀ values ranging from 9.4 to 7.8 μM. Furthermore, compound 21 was the most potent with (IC₅₀: 1.82 μM) followed by 22 (IC₅₀: 3.29 μM). In this study, the parent KBA cytotoxic effects were not promising and had IC₅₀ values of 13.9 μM [66]. Quite recently we prepared AKBA derivative 23 and this compound displayed cytotoxic effects toward LNCaP with IC₅₀: 3.29 μM.
In another report, our group also prepared the pyrazine analog 24 and its semithiocarbazone analog 25 both of which possess cytotoxic effects for the two cancer cell lines, e.g. A375 (EC\(_{50}\) = 2.1 \(\mu\)M) and A2780 (EC\(_{50}\) = 9.3 \(\mu\)M) [68].

Li et al. [69] prepared the trifluoromethyl (at ring A) boswellic acid analogs 26 (PC-3: GI\(_{50}\): 3.78 \(\mu\)M) and 27 (LN\(\alpha\)P: GI\(_{50}\): 3.92 \(\mu\)M) and both compounds were effective toward PC-3 and LN\(\alpha\)P cancer cells respectively as illustrated. On the other hand, the iodo (at ring A) comprising boswellic acid analogs 28–30 possess better activities than the trifluoromethyl group. Compounds 28–30 possess significant activities toward LN\(\alpha\)P and PC-3 cells in which the GI\(_{50}\) ranged from 2.98 to 4.65 \(\mu\)M [69].

5.2. Boswellic acid amides and related compounds

Wolfram et al. [70] prepared various AKBA analogs and evaluated them for their cytotoxic effects. KBA analog 31 (Figure 4) having a (3-hydroxypropyl)carbamic group at C-4 (instead of the CO\(_2\)
H group) possesses significant cytotoxic effects toward breast cancer (MCF-7: EC\textsubscript{50} 4.5 \mu M) and ovarian cells lines (A2780: EC\textsubscript{50} 5.9 \mu M). Moreover, compound 32 having the hydroxybenzylidenehydrazine system also demonstrated activity against MCF-7 (EC\textsubscript{50} 7.1 \mu M) and A2780 (EC\textsubscript{50} 3.4 \mu M) and compound 33 possesses cytotoxic effects toward MCF-7 (EC\textsubscript{50} 8.9 \mu M) and A2780 (EC\textsubscript{50} 5.3 \mu M). On the other hand, the hydroxyl analog 34 showed significant effects toward MCF-7 (EC\textsubscript{50} 5.2 \mu M) and A2780 (EC\textsubscript{50} 3.8 \mu M), while compound 35 having an aminopropylcarbamoy moiety possesses very promising effects toward MCF-7 and A2780 with EC\textsubscript{50} 1.9 \mu M and 1.7 \mu M, respectively. Additionally, AKBA analog 36 comprising the [3-{4-[3-aminopropyl]piperazin-1-yl}propyl]carbamoy moiety possesses strong activity against MCF-7 with an EC\textsubscript{50} 1.0 \mu M [70].

Cusk et al. [71] screened boswellic acid analogs 37 and 38 toward 12 cancer cell lines and only showed significant effects toward MCF-7 with IC\textsubscript{50} 5.5 and 4.5 \mu M, respectively. Endonucleases cleave the DNA into small fragments during the cell death process and thus is an indication of apoptosis. Further study illustrated that 38 has the ability to induce apoptosis and DNA fragmentation in A2780 cancer cells. After 24 h of treatment with 38 on A2780 cancer cells, it leads to a loss of adherence and the cell to cell contact. Cusk et al. [71] further reported that a 24 h treatment of compound 38 maintains the A2780 human ovarian cancer cell membrane intact which is confirmed by the trypan blue dye exclusion assay. DNA fragmentation and the maintenance of intact cell membranes is a hallmark of apoptosis.

Compound 39 (Figure 5) possesses cytotoxic effects toward A549 and MIA PaCa-2 (pancreas) with IC\textsubscript{50} values of 6.6 and 6.0 \mu M, respectively. On the other hand AKBA analogs 40–43 showed significant effects toward MCF-7 with IC\textsubscript{50} values of <0.25, 2.0, 3.6 and 4.4 \mu M, respectively. In addition, compounds 40 and 41 possess good activity toward A549 (IC\textsubscript{50} 2.0 \mu M) and MIA PaCa-2 (IC\textsubscript{50} 6.0 \mu M) respectively [72]. Moreover, compounds 44 (IC\textsubscript{50} 1.6 \mu M) and 46 (IC\textsubscript{50} 3.0 \mu M) possess significant effects toward HL-60 while KBA analogs 45 and 47 were active toward A549 with IC\textsubscript{50} 3.1 and 2.9 \mu M, respectively. Additionally, compound 46 was active toward HL-60 (IC\textsubscript{50} 5.2 \mu M), A549 (IC\textsubscript{50} 6.9 \mu M), MIA PaCa-2 (IC\textsubscript{50} 8.7 \mu M), and MCF-7 (IC\textsubscript{50} 4.0 \mu M). On the other hand the KBA analog 42 also showed cytotoxicity against MIA PaCa-2 (IC\textsubscript{50} 8.6 \mu M), and MCF-7 (IC\textsubscript{50} 7.1 \mu M) [72].

Aberrant acetylation of tumor suppressor and cell death associated genes by histone deacetylase (HDAC) is very common in different types of tumors. HDAC regulates the mitochondrion membrane potential, cell cycle, and apoptosis [72]. Inhibition of HDAC by molecules has a direct effect on cells to
undergo cell cycle arrest and apoptosis. Sharma et al. [72] studied the HDAC inhibitory effect of compound 44. The authors noticed that compound 44 inhibits HDAC activity by 92.2% (5 µM). To correlate the HDAC inhibition of 44 with cells cycle, mitochondrial membrane potential and apoptosis, the authors checked the efficacy of compound 44 against HeLa cells. Thus, Sharma et al. [72] showed that the loss of membrane mitochondrial potential occurred when 44 was used to treat such cells and was confirmed by an Rh-123 fluorescence assay. Furthermore, the authors stated that 44 orchestrated apoptosis and cell cycle arrest at the G1 phase in HeLa cells. Taken together, the Sharma et al. findings revealed that HDAC inhibition by 44 in HeLa cells has a direct effect on the loss of mitochondrial membrane potential, cell cycle arrest, and apoptosis [72].

Two lactam analogs viz., compounds 48 and 49 (Figure 6) exhibited comparatively moderate effects toward HBE (bronchial epithelial; 48: IC_{50}: 6.1 µM; 49: IC_{50}: 5.7 µM) and K562
Moreover, the 3,4-seco compounds 50–57 (Figure 7) demonstrated more potent effects against HL60, K562, and A549 than the parent AKBA. In particular, compounds 50, 53 and 54 demonstrate much better activity toward HL-60 with IC\textsubscript{50} 4.2 and 4.0, 2.1 μM, respectively. In addition, compounds 54 and 56 demonstrated significant effects against K562 with IC\textsubscript{50} 4.1 and 4.5 μM, respectively [65]. On the other hand, the 3-amino derivative 60 showed better activity toward A-253 (sub-mandibular carcinoma; IC\textsubscript{50} 5.6 μM) [73].

Wolfram et al. [74] prepared the 1,4-diazepane analog 61 (Figure 7) which was shown to possess significant effects toward A375, A2780, HT29, MCF7, and SW1736 with EC\textsubscript{50} values ranging from 1.9 to 3.2 μM. The same authors also prepared compounds 62 and 63 and both these compounds demonstrated good cytotoxic effects toward MCF-7 with EC\textsubscript{50}: 9.8 and 7.3 μM respectively [74]. In another study, the C-24

**Figure 7.** Boswellic acid derivatives 54–63 and their cytotoxic effects.
amino derivative 64 illustrated potent inhibition toward prostatic cancer (DU145: % inhibition 94%) followed by colon (SW-620: % inhibition: 87%; 502,713: % inhibition: 86%). On the other hand, the same compound was less active toward HT-29 cancer cell (colon) line [75].

5.3. Boswellic acid derivatives with non-enolizable cyanoenones in ring A

It has been established that Michael acceptor cores are crucial structural elements for biological effects and the α,β-unsaturated carbonyl group is one of the most investigated Michael acceptor pharmacophore groups [76,77]. The insertion of this group into natural products enhances their biological effects [78,79]. Notably, the most intriguing results in this area were when the 2-cyano-3-oxo-1(2)-en group was inserted into pentacyclic triterpenoids [80–86]. Kaur et al. [62] prepared the ring A modified AKBA analog 65 and tested it for its cytotoxic effects. AKBA analog 65 (Figure 8) having the 2-cyano-1-en-3-one system in ring A possesses very strong effects toward HL-60 with IC_{50} = 0.67 μM and also showed significant activity toward HeLa (IC_{50}: 3.0 μM). It is noteworthy that compound 65 is seventeen and ten times more active than the parent AKBA toward HL-60 (AKBA: IC_{50}: 11.0 μM) and HeLa (AKBA: IC_{50}: 31.0 μM) respectively. Interestingly, compound 66 (HL-60: IC_{50} = 0.42 μM) is 57 and 4 times more active than the parent AKBA toward HL-60 (AKBA: IC_{50}: 24.0 μM) and HeLa (AKBA: IC_{50}: 35.0 μM) respectively [62].

Detailed investigations demonstrated that compounds 65 and 66 are effective in the cell cycle arrest at G0 phase. The authors treated HL-60 cells with compounds 65 and 66 and observed the percentage of cells in the hypodiploid sub-G0 DNA fraction. The data reveal that HL-60 cells treated with compounds 65 and 66 at 4 μM concentration increased the number of cells in the sub-G0 DNA fraction by 96% and 76%, respectively. Overall, compound 65 has the remarkable ability to initiate an apoptotic cascade in HL-60 cells [62]. Further propidium iodide staining reveals that a much smaller population of cells showed a positive result which indicates that compounds 65 and 66 induced cell death in HL-60 cells by apoptotic pathways. Further study revealed that compounds 65 and 66 at 0.5 μM concentration changes the nuclear morphology remarkably by inducing condensation and blebbing in HL-60 cells. This experimental result ensured that compounds 65 and 66 are indeed triggers of the apoptotic cascade [62].

Khan et al. [85] reported that compound 65 induced the accumulation of functionally active p53 in the nucleus of HPV18 HeLa cells in response to DNA damage by suppressing viral E6 mRNA expression. Moreover, their study showed that compound 65 up regulated the expression of p53/PUMA/p21 despite HeLa cells with deprivation of p-AKT and NF-κB signaling. Translocation of p53 and p21 into a nucleus through up regulation of PUMA was orchestrated by compound 65 treatment in HeLa cells. This signaling provokes activation of the caspase cascade in HeLa cells by compound 65 and is ensured by DNA fragmentation and PARP-cleavage assays. In addition, the authors demonstrated that this compound inhibits the expression of telomerase resulting in a considerable loss of aggressiveness of the late stages of cervical cancers. In vivo studies demonstrated that compound 65 exerts anticancer activity by reducing the tumor size by 48% at 30 mg/kg concentration and it clearly suggests that this compound has tremendous potential in cervical cancer treatment.

Li et al. [69] prepared derivatives 67–74 and demonstrated that these compounds possess significant cytotoxic effects toward PC-3 and LNCaP with GI_{50} values ranging from 0.04

Figure 8. Boswellic acid derivatives 64–74 and their cytotoxic effects.
to 5.37 μM. Among the tested derivatives, analogs 69 (PC-3: GI$_{50}$ = 0.18 μM; LNCaP: 0.7 μM), 73 (PC-3: GI$_{50}$ = 0.13 μM; = LNCaP: 0.67 μM) and 74 (PC-3: GI$_{50}$ = 0.04 μM; LNCaP = 0.27 μM) illustrated the most potent effects toward both cell lines. Further, in order to study the cell death mechanism induced by 74, PC3 cells were treated with different concentrations of 74. Treatment of PC3 cells with 74 at 1 μM and 2.5 μM for 12 h increased the cell number in the G2/M phase (26.1% and 27.6%, respectively) as compared to untreated cells (22.4%). This data evidenced that 74 induced dose and time-dependent cell cycle arrest in PC3 cells and it induces the occurrence of apoptosis in PC3 cells.

Molecular mechanism studies done by Li et al. 69 revealed that 74 decreased the levels of pro-caspase-3, pro-caspase-8 and pro-caspase-9 in a concentration dependent manner. Apoptosis associated molecules such as Mcl-1, c-FLIP, and NOXA expression in PC3 cells were altered by 74 treatment. Cyclin D1 plays a central role in orchestrating the cell cycle process. Kun Li et al. demonstrated that 74 treatment reduced the expression of cyclin D1 in PC3 cells in a dose dependent manner and that this could modulate the cell cycle regulator cyclin-dependent kinases (CDK4/6) 69. Moreover, it has been reported that triterpenoids having the 2-cyano-1-en-3-one pharmacophore in ring A demonstrated interesting biological effects. For instance, glycyrrhetic acid, usoric acid, betulinic acid, and betulin having this very 2-cyano-1-en-3-one pharmacophore in their ring A have developed a promising increase of the apoptotic properties of these compounds 86–88. Most importantly, the oleanolic acid analogs having the 2-cyano-1-en-3-one pharmacophore in ring A (CDDO and CDDOme) are presently in advanced phases of clinical trials for possible cancer therapy 89.

5.4. β-BA analogs

Kumar et al. 90 prepared a number of BA analogs and discovered that out of these BA analogs, 75, having a pyridine ring system at C-2, possesses remarkable cytotoxic effects toward various cancer cells viz, lung cancer (A549; IC$_{50}$: 2.3 μM), prostate cancer (PC-3; IC$_{50}$: 1.9 μM), colon cancer (HCT-116; IC$_{50}$: 1.8 μM) and breast cancer (T47D; IC$_{50}$: 1.2 μM). It is noteworthy that this compound is much more active than the parent AKBA (Figure 9). The lead compound 75, significantly inhibited colony formation in HCT-116 cells. Moreover, the induction of apoptosis was additionally evidenced by loss of mitochondrial membrane potential, DAPI staining, and ROS generation 90.

The Kumar et al. 90 study further reveals that compound 75 efficiently inhibits the colony formation of HCT-116 cells with increasing concentration of the drug. Further studies indicate that compound 75 when treated on HCT-116 cells, induced chromatic condensation and increased the formation of apoptotic bodies in a nucleus dose dependency. Initiation of DNA fragmentation accompanied with chromatin condensation is a hallmark of apoptosis induction. Kumar et al. 90 clearly demonstrated that compound 75 plays a significant role in the apoptotic mechanism of HCT-116 cells. Moreover, compound 75 diminished the RH-123 fluorescence in HCT-116 cells in a dose dependent manner and elicits depolarization of the mitochondrial membrane potential. Further study demonstrated that compound 75 induced PARP cleavage significantly and is comparable with paclitaxel. This information clearly shows that this compound is involved to a significant extent in the apoptotic mechanism. Furthermore, Kumar et al. 90 indicated that compound 75 induced the cytotoxicity by generating ROS in HCT-116 cells. In another report, compounds 76 and 77 illustrated potent cytotoxic effects toward colon cancer with percentage inhibitions of 96% and 99%, respectively. In addition, BA derivative 77 was significantly effective toward prostate cancer (DU145) with 92% percentage inhibition 75.

5.5. Hybrids and dimers

Wolfram et al. 74 prepared the hybrid compound 78 (Figure 10) comprising boswellic acid and rhodamine via a linker such as piperazine. Notably, this compound possesses potent cytotoxic effects toward epithelial (A375: EC$_{50}$: 0.51 μM), ovarian (A2780: EC$_{50}$: 0.45 μM), colorectal (HT29: EC$_{50}$: 0.50 μM), and breast (MCF7: EC$_{50}$: 0.39 μM) cancer cells. The same authors also prepared boswellic acid and rhodamine hybrid compounds 79–81 where the two units are connected directly (without linkers). Interestingly, compounds 79 and 77 demonstrated potent activities toward A375, A2780, HT29, and MCF7 with EC$_{50}$: <0.6 μM. On the other hand, hybrid compound 81 possesses effects toward A375, A2780, HT29, and MCF7 with EC$_{50}$: ranging from 1.32 to 1.71 μM 74. Quite recently, we reported that the dimer compound of boswellic acid 82 possesses cytotoxic effects toward A375, A2780, HT29, and FaDu with EC$_{50}$: ranging from 6.2 to 8.6 μM 68.
5.6. **Boswellic acid derivatives as pin1 inhibitors**

Pin1 inhibitors can be effective anticancer agents since Pin1 is aberrantly expressed in diverse tumors. Pin1 is involved in the stabilization of cyclin D1 to promote tumor pathogenesis and metastasis. AKBA is known to be an effective anticancer agent. Targeting a specific signaling pathway by AKBA is not quite straightforward. AKBA derivatives have tremendous potential to target specific signaling molecules [66]. Huang et al. [66] synthesized different AKBA derivatives and tested them for their Pin1 inhibition. Among the tested compounds, boswellic acid analog 83 (Figure 11) comprising a piperidine group, showed potent effects (IC$_{50}$ = 1.01 μM). On the other hand, compound 84 (IC$_{50}$ = 2.18 μM) bearing a piperazine group with a trifluoromethyl benzene core, illustrated lower effects compared to compound 83. The phenylamine analog 85 (IC$_{50}$ = 1.27 μM), 4-phenoxypyphenyl bearing compound 86 (IC$_{50}$ = 1.58 μM) and 4-cinnamoylphenyl comprising analog (18; IC$_{50}$ = 0.97 μM) also possess significant inhibition.

Notably, the incorporation of a 3-oxo-2-carboxymethylene core to ring A has a major impact on its inhibition activity. In particular, compound 21 (IC$_{50}$ = 0.46 μM) comprising the C-24 benzyl group, possesses potent inhibition among all the tested compounds. Moreover, inhibition effects were slightly decreased when the benzyl group is replaced by piperidine (87; IC$_{50}$ = 0.55 μM) and is further decreased when replaced by morpholine (88; IC$_{50}$ = 2.68 μM). On the other hand, compound 22 also possesses potent inhibition with IC$_{50}$ = 0.68 μM.
Detailed investigations of compound 21 demonstrated that it restricted the proliferation of human prostate cancer cells significantly by reducing the expression of cyclin D1 and further, by arresting the cells at the G0/G1 phase in a concentration dependent manner. This data clearly demonstrates that 21 destabilizes cyclin D1 by inhibiting Pin1 [66].

6. Expert opinion

The WHO has identified cancer as the second international major cause of death amounting to around 9.6 million deaths in 2018 alone. Moreover, the cancer patient’s numbers reached ca. 18 million in 2018. Cancer drug discovery has certain major limitations because the current chemotherapy drugs are associated with numerous serious issues viz., resistance development, nonspecific toxicity, and inefficiency among others. Therefore, new anticancer entities with potent selectivity, more effectiveness and having different modes of action on cancer cells are urgently required. Natural products (NPs) are intriguing sources of anticancer drugs and ca. 80% of FDA approved anticancer drugs in the last thirty years are either NPs, mimicked NPs, or NP analogs.

Boswellia species (frankincense) have been employed in traditional medicine to treat various diseases viz., constipation, flatulence, cancer, central nervous illness, amnesia, tuberculosis, bronchial and gastrointestinal infections, diarrhea, burns, stomachache, infections, bruises, eye sores, and pancreatic carcinomas [91]. Frankincense and its chemical constituents (boswellic acids) possess in vitro and in vivo cytotoxic effects toward various cancer cells. Notably, numerous clinical trials

Figure 11. Boswellic acid derivatives 83–88, 18 and 21 and their pin1 inhibition.
have been published on frankincense and boswellic acids, demonstrating the clinical effectiveness toward various diseases viz., osteoarthritis, asthma, erythematous eczema, analgesia multiple sclerosis, and plaque-induced gingivitis [91]. A limited number of anticancer clinical trials have been published about frankincense and boswellic acids, which clearly demonstrated beneficial effects with mild adverse side effects [23, 25, 91–95]. The current studies on the clinical use of boswellic acids and frankincense for cancer treatment is still an ongoing exercise. Thus, future research should focus on investigating the effects of natural/semisynthetic boswellic acids and their analogs and frankincense on tumor regression. In addition, natural/semisynthetic boswellic acids and frankincense should be investigated to determine the survival time of those patients suffering from the many and varied cancers prevalent in society today.

Numerous semisynthetic BAs have been prepared in last three decades and tested toward various cancer cell lines. Notably, these semisynthetic BAs possess better cytotoxic effects than their parent natural boswellic acids. Moreover, substitutions on the BA’s scaffold plays a very important role in enhancing their cytotoxic effects. Notably, BA analog 15 bearing an endoperoxide core between C-1 and C-9 demonstrated some of the most potent effects toward various cancer cells. In addition, a literature survey showed that glycyrrhetinic acid, oleanolic acid, and ursolic acid endoperoxides have also been reported to show significant cytotoxic effects [96]. Moreover, various natural endoperoxides have been reported to possess significant cytotoxic and antimarial effects [97]. In addition, BA derivatives having the cyanoenone chromophore in ring A were the most potent compounds (compounds 65–69, 73 and 74) which all illustrated very potent effects toward various cancer cells. Most interestingly, hybrid compounds of BAs with rhodamine also illustrated very potent effects. Lastly, C-24 amides of BAs possess a considerable enhancement in their cytotoxic effects. Based on the above-mentioned SAR results, the authors strongly suggest that there is a huge potential for future synthetic modification of the BAs scaffold for additional ring A cyanoenones, endoperoxides, and C-24 amide analogs in order to get lead molecules for future anticancer drug discovery.

Notably, combination therapy strategies are highly demanding because the synergistic responses between two active molecules are very important to be identified since they illustrate less drug resistance and toxicity. In addition, hybrid compounds of BAs with numerous anticancer drugs must be fully explored because there is the expectation that this could synergistically increase the anticancer effects even further. In addition, future research should also focus on further synthetic analogs. Despite the BAs potent activities toward various cancer cells, research output has been rather slow, which could be due to technical difficulties connected with their quantitative isolation. This is no doubt due to their very low concentration present in some Boswellia species. However, numerous methods used for their extraction and isolation, have been improved from existing old techniques. Conventional extraction/purification methods used for BAs are easier to perform and less expensive. These methods are generally limited by various inefficiencies viz., purity, thermal degradation, and extraction time.

High-speed counter-current chromatography (HSCCC) is a valuable substitute for various separation techniques viz., HPLC. HSCCC offers various crucial benefits over other chromatographic techniques viz., high recovery, no chance of degradation of compounds, high efficiency, large-scale separation, purification of polar compounds, and purification of compounds with close Rf values [98]. For large-scale extraction the Jauch and Bergmann [61] protocol is generally used in order to get the KBA (10) for further modification. Future research should focus on the isolation of the four major boswellic acids viz., β-BA (8), A-β-BA (9), KBA (10), and AKBA (11) via HSCCC techniques. By doing this, all four major BAs can be isolated and purified for detailed biological investigation as well as for future synthetic modifications.

Although there is no current proof that any BA derivative has been established as clinical candidates the current authors firmly believe that a few of the most potent semisynthetic BA derivatives mentioned in this review should be considered for further detailed investigations. For example, various semisynthetic BA derivatives illustrated IC50 values lower than 1 μM, with less toxicity, which confirm that these BA derivatives could be able to treat various cancers. Moreover, this comprehensive review on potent semisynthetic BA derivatives could be the starting point to establish further interesting studies viz., molecular docking and quantitative structure–activity relationship (QSAR). Such computational studies might serve to not only help the scientists to predict some potent BA derived anticancer lead compounds but also assess the lead compound’s pharmacokinetics profiles.

For the development of a successful lead compound, its pharmacokinetic studies should be carried out accurately. Various studies have demonstrated that AKBA and KBA are exceptionally good lipophilic drugs that result in a decrease absorption via the GIT. Moreover, both these compounds have low oral bioavailability due to their lipophilic nature. The initial pharmacokinetic investigation has led to the finding that minimum concentrations of both KBA and AKBA were present in human plasma after administration of frankincense [28]. Among pentacyclic triterpenoids, BAs are characterized by poor water solubility along with having a highly lipophilic character (log P = 7–10.3) [99]. Another study illustrated that the metabolic profiles of KBA in liver and in rat plasma were similar for both in vitro and in vivo investigations while the presence of AKBA was not detected. This study demonstrated that the administration step should be further investigated to enhance the bioavailability of boswellic acids and their synthetic derivatives [28, 100].

Various strategies have been employed to enhance the bioavailability of BAs such as administering them with anionic drugs [101] and standardized meal [102]. In addition, further protocols have been adopted to increase the BAs bioavailability including, lecithin delivery, nanoparticle delivery protocols viz., emulsions, liposomes, nanostructured lipid carriers, solid lipid nanoparticles, and micelles [28, 103–105]. Future studies should focus on enhancing the bioavailability and
pharmacokinetics of potent BA synthetic derivatives via different protocols such as nanoemulsions, micelles, polymeric nanoparticles, solid dispersions, and nanocrystals. Quite recently, it has been shown that pharmacokinetic properties of BAs have been improved via combining the BAs rich fraction with piperine [106]. The authors strongly suggest that pharmacokinetic properties of potent synthetic BAs should be improved via a combination with piperine, curcumin, or other related compounds.

In conclusion, boswellic acids illustrate real promise as pharmaceutical entities for anticancer agents. Major research requirements would be to encourage the use of BA-based anticancer lead compounds which should include the development of more advanced protocols for their large-scale production; the preparation of numerous semisynthetic BA derivatives; and to understand the exact mode of actions of the most potent BA derivatives. We believe that most of the major problems could be solved via scientific collaboration between synthetic chemists, medicinal chemists, and molecular biologists. Despite all the drawbacks and limitations mentioned above, the authors firmly believe that BA-based compounds could emerge as a privileged scaffold for the establishment of lead compounds for cancer therapy.

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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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