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Amelioratic Effects Of Boswellic Acid On Various Diseases

Mohammed saud shabab alotaibi[1], Mansour Salem Ayidh Algethami[2], Waleed muqbil almuqbil[3], Khaled Saad Alzhrani[4], Nawaf Farhan R Alruwaili[5], Ibrahim Rashed Alghonaim[6], Abdulrhman Maqham M Almutairi[7], Hayyan Hussain Hamza Alsulaymani[8], Ahmed Ali Hanash Alzahrani[9], Meshal Fahid Jumaan AlZahrani[9]

Abstract

Phytomedicines are effective & have little adverse effects, particularly boswellic acids (BAs), are increasingly being used to treat complex diseases like cancer. Oleogum resin, often known as frankincense, is extracted from Boswellia plant species & used to produce BAs. The frankincense combination contains a range of BAs, each having its unique potential for treating certain tumours. This study examines the features of BAs, their anti-cancer properties, mechanisms, & role of semi-synthetic derivatives of Bas in cancer treatment. It also investigates the biological origins of BAs, conservation strategies, & biotechnology's capacity to conserve & boost BA production in vitro. The review assesses that BAs & semi-synthetic derivatives are effective against a wide variety of cancer cell types. The review is beneficial to researchers seeking greater information on BAs & BA-based medicines for effective & affordable cancer therapy. BAs are postulated as potential therapy for brain cancer because of their ability to suppress the growth of cells; relocation; cancer metastases; angiogenesis; & cause cancer cell death.

Introduction

Boswellic acid

The recent identification of numerous chemical compounds derived from plants with anti-cancer capabilities has resurrected a[1]ncient herbal remedies via contemporary understanding. The discovery of anticancer compounds like vinblastine, vincristine, & taxol paved the way for the creation of new phytochemical anti-cancer medications (**Dhyani et al., 2022**). In the past few years, the discovery of phytochemicals that might have anticancer capabilities that have no or few side effects has grown. Boswellic acids, a group of compounds originating from the Boswellia plant, are commonly used to treat a number of chronic illnesses. These include

[1]Pharmacy technician,King Abdulaziz Specialist Hospital in Taif, Saudi Arabia.
[2]Pharmacy technician,Sharia Health Centre, Saudi Arabia.
[3]Pharmacists, Ministry of health, Saudi Arabia.
[4]Assistance pharmacist, Hada Health Center, Saudi Arabia.
[5]Pharmacy technician, Thadiq General Hospital, Saudi Arabia.
[6]Pharmacy technician, Price salman bin Mohammed Hospital, Saudi Arabia.
[7]Pharmacist Assistant, Al Muthanna General Hospital, Saudi Arabia.
[8]Pharmacy technician at Ibn Sina Hospital, Saudi Arabia.
[9]Technician Pharmacy,Qilwah General Hospital, Saudi Arabia.

hemolytic, spasmolytic; antiviral; antiinflammatory; hepatoprotective; gastroprotective; & antibacterial properties. (**Hussain et al., 2017**).

Boswellic acids (BAs) are pentacyclic triterpenes derived from Frankincense trees. Boswellia serrata, commonly referred to white guggal, Indian olibanum, Salai Guggal, & dhup, is the most important source of BAs, & B. carteri (**Roy et al., 2019**), B. sacra; & B. papyrifera; are other sources (**Al-Harrasi et al., 2019**). Gum resins produced by Boswellia species are frequently utilised in an array of uses; involving adhesives; cosmetic preparations; coating materials; & incense for cultural events & ceremonies. It is one of the most essential & frequently utilised chemicals used in conventional Ayurvedic & Unani therapies, which are particularly effective in treating a wide range of inflammatory; gastrointestinal; hormonal; & microbiological diseases. (**Trivedi et al; 2023**).

BAs originated from the gum resin frankincense, containing essential oil, mucus, & a lipophilic component. The grades & contents of this resin vary depending on the species of Boswellia utilised to extract it. (**Saraswati & Agrawal, 2012**). Boswellia gum resin consists of 12 different kinds of BAs, among them β-BA; A-β-BA; KBA; & AKBA. These BAs exhibit a wide range of pharmacological properties, such anticancer, antiangiogenic, antitumor, apoptotic induction, antiproliferative, & antiinflammatory activity. However, not all BAs possess equal activity or efficacy (**Yadav et al., 2012**). For instance, KBA & AKBA; are particularly efficient at suppressing the production of cytokines & enzymes that encourage responses to inflammation. As a consequence, they have been regarded beneficial treatment for an array of chronic illnesses. (**Roy et al., 2019**).

BAs have been found to assist with the prevention & treatment of tumours including breast; bladder; cervix; prostate; colorectal; head & neck; liver; lung; & pancreatic (**Roy et al., 2019**). To boost the anti-cancer activity of the varied BAs, numerous semi-synthetic derivatives having chemotherapeutic potential against distinctive malignant human cell lines were generated. Depending on the sort of cancer cells targeted as well, BAs use mode of action such as apoptosis, reducing malignant cell angiogenesis; restricting blood flow to tumour tissue; & down-regulating AKT phosphorylation to avoid cancer spread. (**Uthaman et al., 2012**).

Description of Boswellic Acid & related its Derivatives

For centuries, frankincense (olibanum) collected from the Boswellia tree, namely B. serrata, has been utilised because of a source of BA. Other species assessed were B. sacra, B. papyrifera, & B. carteri, all of which are employed as BA sources globally. (**Al-Harrasi et al., 2019; Bongers et al., 2019**). The resin of the Boswellia tree is a mixture of essential oil (5%-9%) & mucilage (6%-20%), which is the largest component of the BAs & comprises the surrounding 25%-35% of the resin acid combination. (**Al-Harrasi et al., 2021**).

BAs are useful organic acids that include a pentacyclic triterpene and β-carboxyl group at the C-4 position. BAs are separated into two categories: β-BAs & α-BA. Ursane-type boswellic acids (BA, KBA, ABA, & AKBA) have a triterpene backbone. Oleanane-type boswellic acids include α-BA, α-KBA, α-ABA, & α-AKBA. (**Al-Harrasi et al., 2019; Al-Harrasi et al., 2021; Schmiech et al., 2021**) (Figure 1).

The resin comprising the BAs is extracted from the Boswellia tree from wounding subsequent to tapping. These processes of extraction created a chain of signals in the Boswellia tree, encompassing gene expression & endogenous BAs manufacturing in the injured section

of the tree; at last giving rise to the clumpy frankincense (**Khan et al. 2018**). However; the BA quantity of Boswellia resin differs both between & within species. Bas; their precursor quantity, & the types of BAs recognised in the resin of B. serrata; B. sacra; & B. papyrifera showed greatly different. (**Paul, 2012**). According to **Paul's (2012)** study, B. papyrifera had higher β-AKB amounts while a smaller amount of different BAs & metabolites that are secondary; where as B. serrata had reduced β-KBA & β-AKBA quantities with greater amounts of α-BA & β-BA. The micro & macroclimatic conditions that the Boswellia trees are placed have an important impact on the BA content within a species. (**Park et al., 2011**).

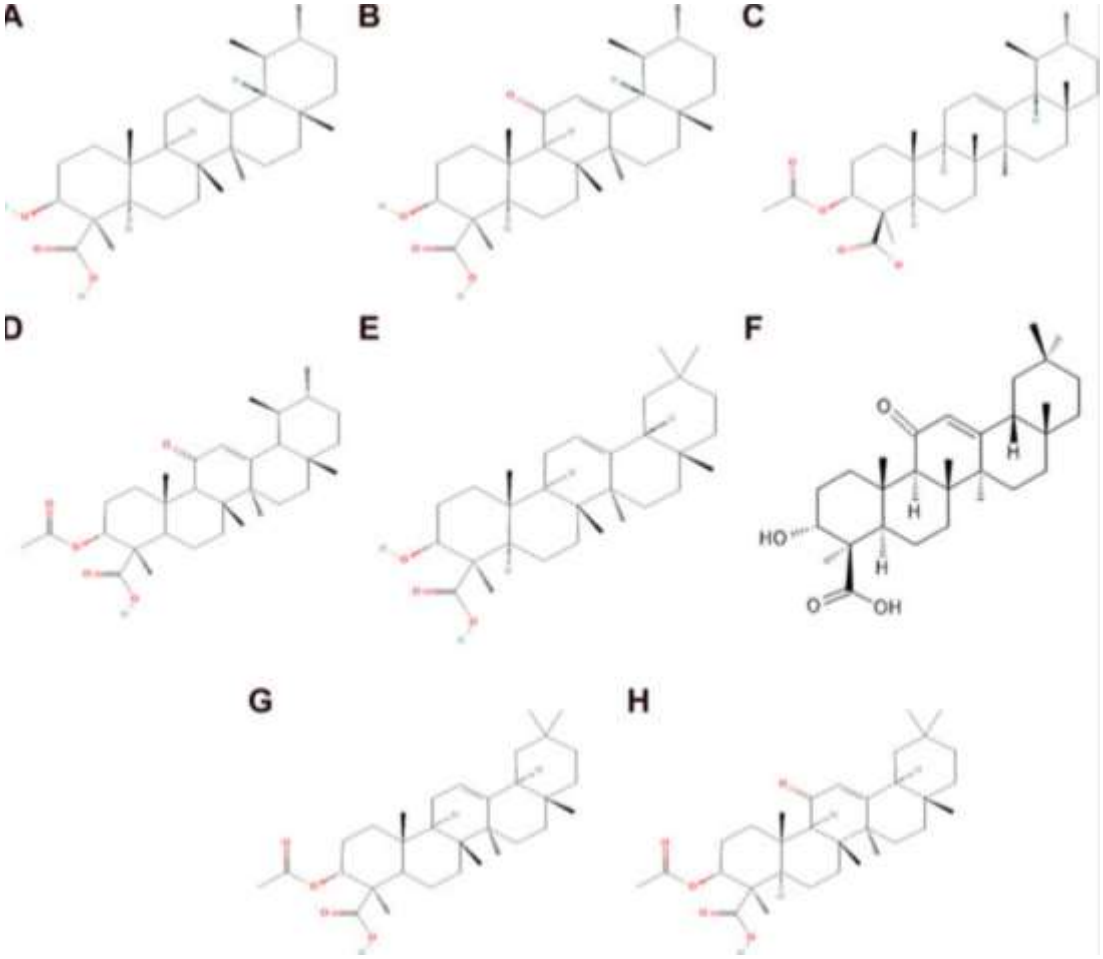

Figure 1. Ursane & oleanane-type boswellic acid chemical structure (Trivedi et al; 2023)

(A) β-BA; **(B)**11-Keto-β-Boswellic acid; **(C)** Acetyl-β-Boswellic acid; **(D)** Acetyl-11-Keto-β-Boswellic acid; **(E)** α-BA; **(F)** 11-Keto-α-Boswellic acid; **(G)** Acetyl-α-Boswellic acid; & **(H)** Acetyl-11-Keto-α-Boswellic acid.

The BA content of the resin varied extensively among Boswellia spp. populations (**Al-Harrasi et al., 2018**). B. sacra roots lacked BAs (**Paul, 2012**); whereas leaves had small quantities of β-ABA & β-AKBA. Amyrins are BAs manufactured via the terpenoid

biosynthetic pathway (MVA); which is the immediate precursor of boswellic acids. The chemical precursors of α-boswellic acid are oleananes & ursanes.

The main challenge with most BAs is their relatively low bioavailability; especially with AKBA & KBA; extending worries about the pharmacological relevance of their beneficial properties in animal & human investigations (**Du et al., 2015**). BA derivatives as a have been produced to discover novel efficient drugs; specifically anticancer; & tumour suppressors. (**Serbian et al., 2018; Shamraiz et al., 2020**).

Pharmacological & pharmaceutical consequences of BA.

BAs have been established to have a broad spectrum of biological & pharmacological effects; including antiinflammatory; immunomodulatory; antioxidant; anticarcinogenic; anticancer; & neuroprotective activities. They have been tested in clinical & preclinical research & have been shown to be helpful for the management of acute & chronic inflammatory disorders such as rheumatoid arthritis; inflammatory bowel disease; osteoarthritis; & asthma. (**Ebrahimpour et al; 2017**).

BAs are also gaining favour in the treatment of numerous tumours; as they exert anticancer & anticarcinogenic attributes using a range of biochemical pathways. AKBA has been discovered to trigger apoptosis in pancreatic & gastric tumours via p53 independent pathways. It also decreases the expression of protein kinase B & NFκB. In experimental animals, it reduces the growth & spread of human cancers of the pancreas via controlling NFκB-regulated genes comprising COX2; MMP9; CXCR4; & VEGF. (**Ebrahimpour et al; 2017**).

Furthermore; in their anticancer activities, BAs have been reported to offer protection against oxidative damage in cell lines & animal models. They boost antioxidants levels of enzymes & stimulate the Nrf2/antioxidant responses element-regulated pathways. The clinical effectiveness of a medication is measured by its bioavailability, which involves its absorption, distribution, metabolism, & elimination. The blood-brain barrier (BBB) is thought to act as a further obstacle for medical drugs in the brain's nervous system; assisting preserve brain homeostasis through restricting the escape of multiple ions & molecules. The latest study is focusing on brain illness methods of treatment; emphasising on the pharmacokinetic properties of BAs & their beneficial effect on neurological disorders. (**Roy et al; 2016**).

Mechanisms of the antitumor effects of boswellic acid

BAs have been explored for generations & have recently been demonstrated to be powerful in fighting cancer in both vitro & in vivo. Various the isomers & acid extracts possess anticancer properties via various routes in a variety of carcinomas. BAs stimulate or block an array of targets; notably angiogenesis enzymes; topoisomerases; 5-lipoxygenase (5-LO); cytochrome P450; & mitogen activated protein kinase (MAPK, notably p38). (**Iram et al., 2017**).

B. serrata gum resin extract (methanolic) comprises triterpenoids comparable β-boswellic acid & its analogues. **Huang et al. (2000)** discovered that naturally produced b-BA triterpenoids & their derivatives were employed in traditional medicine for the treatment of cancer. A number of scientific investigations have found that Boswellia's pentacyclic triterpenes constitute some of the most promising anticancer medications. (**Al-Bahlani et al., 2020**).

Inhibiting topoisomerase I & IIa suppresses the proliferation & growth of cells & encourages apoptosis through a caspase 8 dependent the mechanism in human leukaemia; hepatoma; colon; & a range of cancer cell lines (**Suhail et al., 2011**). Furthermore, a chemoproteomic study employing mass spectrometry demonstrated that b-BAs interact with ribosomal proteins; inhibiting protein synthesis & hence affecting cancer progression (**Casapullo et al., 2016**). Morphological modifications were seen in HL-60 cells treated with AKBA; a cell apoptosis marker. **Hoernlein et al. (1999)** reported that BA, 3-O-acetyl-β-boswellic acid, AKBA, & 3-O-acetyl-11-keto-boswellic acid suppressed DNA; RNA; & protein synthesis in human leukaemia HL60 cells in a way that was dose-dependent.

In vitro; AKBA showed cytotoxic efficacy in opposition to three resistant to treatment triple-negative breast cancer cell lines (TNBC) & caused apoptosis in MDA-MB-231, xenografts (**Schmiech et al., 2021**). AKBA reduced cell viability in the H460, H1299, A549, & BEAS-2B cell lines. Cell cycle arrest occurred in A549 cells during the G0/G1 phase, which hindered clone formation & encouraged cellular death. It also affected the level of expression of LC3A/B-I, LC3A/B-II, & Beclin-1 proteins, while combating the PI3K/Akt signalling pathway. It also blocked protein expression & autolysosome assembly. (**Lv et al., 2020**).

The newly synthesised & characterised β-isomer, 11-keto-boswellic acid (KBA), had fatal effects towards several resistant to treatment triple-negative breast cancer (TNBC) cell lines in vitro, induced apoptosis in MDA-MB-231 xenografts in vivo. (**Schmiech et al., 2021**).

β-BA reduces malignant breast cancer by suppressing glycolysis & reducing ATP generation in MCF-10AT cells, without compromising normal MCF-10A. It additionally seems to reduce glycolysis, which activates the AMPK pathway while suppressing the mTOR pathway, thereby decreasing MCF-10AT development. Studies on molecular docking suggest that β-BA may target GLUT1. GLUT1 forced expression may restore glycolysis restrictions & activate survival checkpoints in MCF-10AT. (**Bie et al., 2022**).

Another study investigated the impact of β-BA & AKBA on acute inhibition of growth in nine adult glioma stem-like cells & five glioblastoma-initiating cell lines. The same study looks into anticlonogenic qualities & the usage of temozolomide (TMZ) or irradiation. The results were consistent with previous studies that demonstrated BA cytotoxicity in glioblastoma at low molecular concentrations. A serious synergistic effects was also observed when irradiation was combined combined transcranial magnetic stimulation (TMS) (**Schneider & Weller, 2016**). The schematic representations in Figures 2 & 3 depict the specific mechanism of action of BAs as promising therapies for cancer.

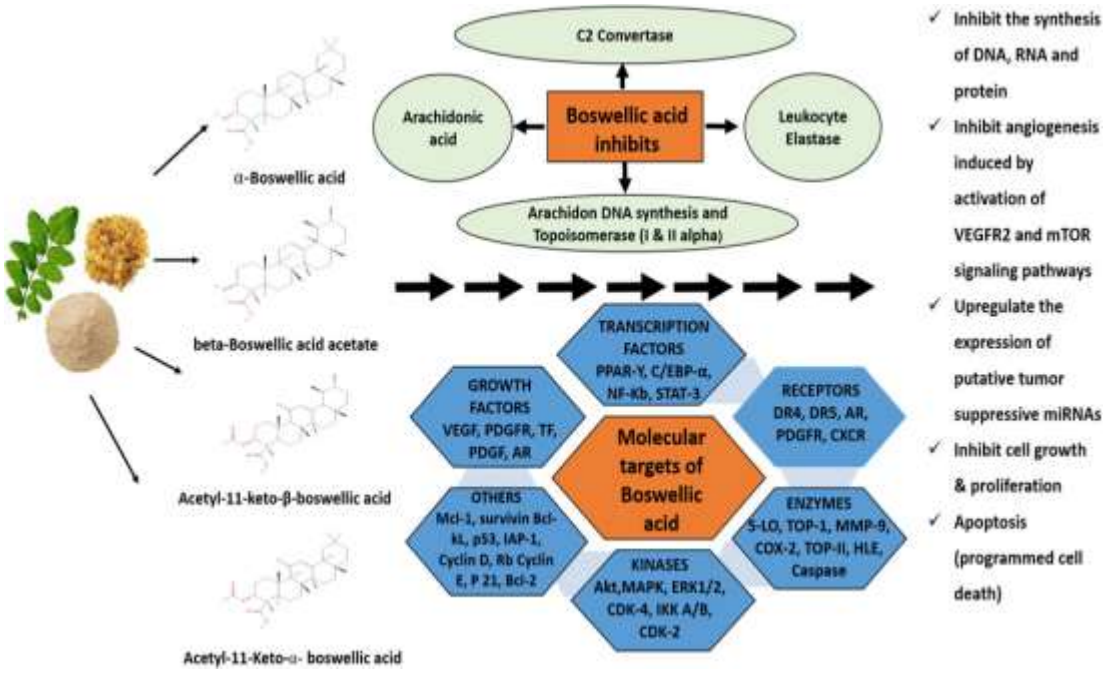

Figure 2. Diagram showing the processes of boswellic acids isolated from the plant Boswellia serrata. (Trivedi et al; 2023)

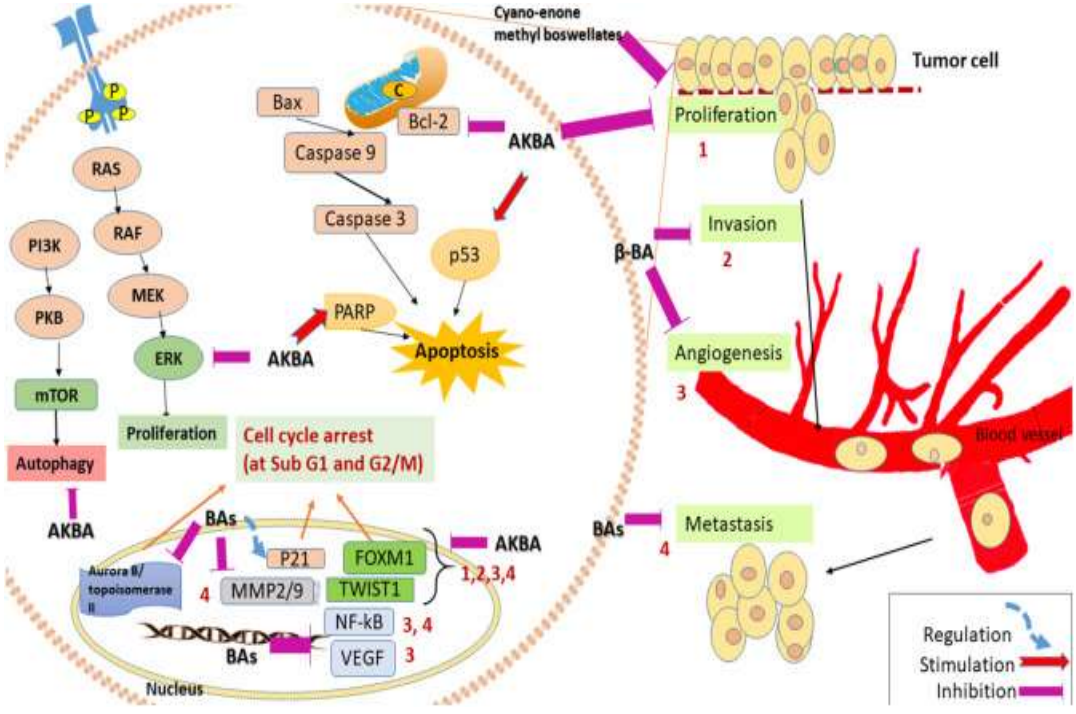

Figure 3: Mode of action of antitumor activity of boswellic acid (Arezoo et al; 2023)

Ischemic injury

A stroke that is ischemic is a sudden neurological condition caused by a blockage in the flow of blood to brain tissue. Over the past decade, research has established that antioxidants (BAs) have neuroprotective properties in ischemic brains. Pretreatment with AKBA (20 mg/kg) reduced the number of infarctions in stroke & protected against ischemia-like conditions caused by oxygen glucose depletion of primary neurons in the cortex & PC12 cells. Ischemia & reperfusion insults boost the production of reactive oxygen species (ROS), causing oxidative damage in tissue in the brain. Antioxidants treatment has been proposed as a neuroprotective treatment for strokes that are acutely ischemic. In a rat model of cerebral ischemia/reperfusion, BAs that include AKBA (20 mg/kg), KBA (25 mg/kg), & β-BA counteract damage caused by oxidation by targeting the Nrf2-HO-1 pathway & raising the levels of antioxidant enzymes. Ischemia; also, can be correlated with a significant reduction in brain antioxidant enzymes for detoxification; including glutathione peroxidase; glutathione reductase; & SOD. BAs stimulate antioxidant enzymes; which help to reduce intracellular oxygen free radicals; lipid peroxidation; & oxidative DNA damage. (**Sadeghniaet al; 2017**)

Ding et al. studied the neuroprotective benefits of an AKBA nanoformulation (10 mg/kg); against cerebral ischemia reperfusion injury. Nanoparticles have been shown to inhibit apoptotic cell death by replenishing proinflammatory signals; & antioxidants. BAs have shown promise in protecting against BBB damage; with in vitro studies showing that AKBA decreased C3aR expression; & ERK1/2; phosphorylation after ischemia.

AKBA effectively alleviated biochemical & behavioural symptoms following traumatic brain & nerve injury. Giving rats oral doses of AKBA in conjunction with piperin improved oxidative & proinflammatory markers, as well as neurotransmitters such in rats' hippocampus & cortex. It had been speculated to concentrate on Nrf2 & NFkB. A further investigation discovered that AKBA decreased brain edoema, BBB disruption, & vestibular impairment following brain injury. Excitotoxicity, defined as neuron overexcitation in clefts of synapses due to glutamate excessive amounts, has been related to neurodegenerative illnesses such as ischemia. BAs defend against excitotoxicity; a single investigation found that AKBA decreased oxidative & nitrosative damage in brains of kainic acid-treated rats by reducing peroxidation of lipids & levels of nitrite while increasing SOD & glutathione levels. When coupled with nimesulide & rofecoxib; AKBA improved the duration of clonic movement while reduced mortality rates. (**Ahmad et al; 2019**)

BAs are hypothesised to protect neurons against excitotoxicity-induced degeneration. Studies conducted in vitro have shown that AKBA's antioxidants & anti-apoptotic properties relate to their anti-excitotoxic affect on glutamate cytotoxicity. AKBA stimulates apoptotic enzymes in neuron-like PC12 & Neuro2a cells treated to high glutamate concentration. KBA decreases the release of glutamate in the rat hippocampus, which could be related to its defence against excitotoxicity. AKBA is also helpful with peripheral nerve damage, such as speeding up neurological recovery & minimising pathological changes in sciatic nerve injuries. It promotes Schwann cells to grow & stimulates the ERK signalling cascade in brain regeneration. BAs reduce the amount of infarcts & rupture the BBB in ischaemic brains. These compounds' neuroprotective properties may be linked to their potential to decrease oxidative stress, modify inflammatory & cytotoxic messengers in neurons, & activate the Nrf2/HO-1 & NFkB pathways. (**Rajabian et al; 2020**)

Other neuropathological conditions

Research suggests that BAs, specifically βaminobutyric acid (AKBA), possess important neuroprotective effects. AKBA has been demonstrated to postpone taking care of oneself in Aβ-injured rats, decrease immobility duration, & affect glutamate; kynurenine; & monoamine levels. It also impacts GFAB protein & NFkB levels in the hippocampus & cortex of Aβ-treated rats. AKBA has also been shown to improve immobility time & exploratory behaviour in glutamate or GABA abnormalities produced by chronic mild stress. This suggests that AKBA could represent a useful adjuvant therapy for depression in early stages of Alzheimer's disease. AKBA also improves the antinociceptive effects of COX inhibitors in acetic acid-induced writing, tail immersion, & tail flick tests. β-BA enhances mesencephalic neuron derivation from embryonic stem cells, leading to better released dopamine & protection against damage from oxidative stress. This suggests that BAs could be playing an effect in Parkinson's treatment with stem cells. (**Gunasekaran et al; 2021**)

Amyotrophic lateral sclerosis, also known as ALS is a progressive illness of the neurological system affecting voluntary motor neurons. Methylmercury induced neurotoxicity results from an imbalance in pro & antioxidative equilibrium. Researchers showed that AKBA alleviated ALS-like symptoms in mice by blocking the Nrf2/HO-1 pathway. BAs are hypothesised to protect against neurodegenerative because they have immunomodulatory, antiinflammatory, antioxidant, & antiexcitotoxic characteristics. They promote neurogenesis & synaptogenesis after brain trauma, enhance neurotrophic factors, & control enzymes including MMP2/9, CREB1/2, CaKMII/IV; & AChE. Preclinical data indicates that BAs may decrease neurodegeneration & cognitive decline, but additionally research & clinical studies are required to confirm their efficacy. (**Obrador et al; 2020**)

Anti-inflammatory activity

The antiinflammatory qualities of incense & its constituents assist in the management of immune disorders. The fascinating bioactivities of oleogum resins from B. carterii & B. serrata, the most extensively researched frankincense species, in addition to those from B. dalzielii & B. sacra, essential oils derived from B. dalzielii's leaves, & bark extracts from B. elongata, show that antiinflammatory benefits are not limited to a single Boswellia species. (**Siddiqui 2021**).

Exposure to frankincense & its constituents lowered oxidative stress. Reactive nitrogen species, ROS, or lipid peroxidation have all been shown to be at low levels. In the context of the immune system, neutrophilic granulocyte invasion, mast cell stabilization; T effector differentiation; immune cell penetration into inflamed cells; & leukocyte-endothelial cell adhesive interactions have all been significantly reduced. (**Beghelli et al. 2017**).

Studies indicates that BA suppresses inflammatory substances & routes; such as prostagl&ins (PGs); histamine; leukotrienes; & interferon (IFN)-γ. Additionally, it inhibits LOX; cytokines; TNF-α; COX-2; & iNOS activity. Furthermore, BA enhanced free oxygen radicals while improving antioxidant defence through catalase; peroxidase made from glutathione; & superoxide dismutase. (**Governa et al. 2018, Loeser et al. 2018**)

BA suppresses the transmission of signals & transcription factors, such as ERK1/2, NFκB, IKK, & MAPK, contributing to its antiinflammatory effects. Additionally, BAs may decrease the activity of STAT3, JNK, SMAD2/3/4/7, & IL-1 receptor associated kinases. (**Governa et al. 2018, Liu et al. 2018**).

Boswellia extracts & chemical compounds have been utilised for the treatment of a variety of illnesses; including rheumatoid arthritis; osteoarthritis (**Yu et al. 2020**); gastric colitis (**Gupta et al. 2001**); & autoimmune encephalomyelitis (**Nadeem et al. 2022**); in addition to allergic asthma (**Liu et al. 2015**); non-alcoholic fatty liver disease; & fibrosis of the kidneys. (**Zaitone et al. 2015, Liu et al. 2018**).

Conclusion

Boswellic acids (BAs): Due of their efficiency & minimal risk of side effects, phytomedicines are increasingly being used to treat complicated illnesses such as cancer; brain illness; & inflammation. Oleogum resin; sometimes called as frankincense; is extracted from the Boswellia plant species in order to make BAs. The frankincense combination possesses a number of Bas; each with a unique potential for healing certain tumours. Our investigation focuses on the features of BAs; their anticancer properties; mechanisms; & the role of semi-synthetic compounds in cancer treatment. It also investigates the biological basis of BAs; conservation strategies; & biotechnology's potential to conserve & improve in vitro BA synthesis. The review finds that BAs & semi synthetic compounds work against a diverse range of cancer cell types. The review concludes that BAs & semi-synthetic derivatives are effective against a wide variety of cancer cell types. The review is valuable for researchers interested in learning more about BAs & BA-based drugs for cancer therapy that is both efficient & cost effective. BAs have been postulated as a potential therapy for brain tumours due to their ability to decrease cell proliferation migration; metastasis; angiogenesis; & apoptosis.

References

A. Rajabian, H.R. Sadeghnia, A. Hosseini, S.H. Mousavi, M.T. Boroushaki 3-Acetyl-11-keto-β-boswellic acid attenuated oxidative glutamate toxicity in neuron-like cell lines by apoptosis inhibition J. Cell. Biochem., 121 (2) (2020), pp. 1778-1789

Agrawal, S. S., Saraswati, S., Mathur, R., & P&ey, M. (2011). Antitumor properties of Boswellic acid against Ehrlich ascites cells bearing mouse. Food Chem. Toxicol. 49 (9), 1924–1934. doi:10.1016/j.fct.2011.04.007

Al-Bahlani, S., Burney, I. A., Al-Dhahli, B., Al-Kharusi, S., Al-Kharousi, F., Al-Kalbani, A., et al. (2020). Boswellic acid sensitizes gastric cancer cells to Cisplatin-induced apoptosis via p53-mediated pathway. BMC Pharmacol. Toxicol. 21, 64–10. doi:10.1186/s40360-020-00442-1

Al-Harrasi, A., Hussain, H., Csuk, R., & Khan, H. (2019). Chemistry of boswellic acids & other terpenoids. In (pp. 9–66). doi:10.1016/B978-0-08-102441-6.00002-5

Al-Harrasi, A., Khan, A. L., Asaf, S., & Al-Rawahi, A. (2019). "Frankincense tree physiology & its responses to wounding stress," in Biology of genus Boswellia Editors A. Al-Harrasi, A. L. Khan, S. Asaf, & A. Al-Rawahi (Berlin, Germany: Springer International Publishing), 53–70. doi:10.1007/978-3-030-16725-7_4

Al-Harrasi, A., Khan, A. L., Rehman, N. U., & Csuk, R. (2021). Biosynthetic diversity in triterpene cyclization within the Boswellia genus. Phytochemistry, 184, 112660. doi:10.1016/j.phytochem.2021.112660

Al-Harrasi, A., Rehman, N. U., Khan, A. L., Al-Broumi, M., Al-Amri, I., Hussain, J., et al. (2018). Chemical, molecular & structural studies of Boswellia species: β-Boswellic aldehyde & 3-epi-11β-Dihydroxy BA as precursors in biosynthesis of boswellic acids. PLoS One 13 (6), e0198666. doi:10.1371/journal.pone.0198666

Arezoo Rajabian, Mohammadreza Farzanehfar, Hossein Hosseini, Fahimeh Lavi Arab, Ali Nikkhah, Boswellic acids as promising agents for the management of brain diseases, Life Sciences, Volume 312, 2023, 121196, ISSN 0024-3205, https://doi.org/10.1016/j.lfs.2022.121196.

Beghelli D, Isani G, Roncada P, &reani G, Bistoni O, Bertocchi M, Lupidi G, Alunno A (2017) Antioxidant & ex vivo immune system regulatory properties of Boswellia serrata extracts. Oxid Med Cell Longev 6:1–10

Bie, F., Zhang, G., Yan, X., Ma, X., Zhan, S., Qiu, Y., et al. (2022). β-Boswellic acid suppresses breast precancerous lesions via GLUT1 targeting-mediated glycolysis inhibition & AMPK pathway activation. Front. Oncol. 12, 896904. doi:10.3389/fonc.2022.896904

Bongers, F., Groenendijk, P., Bekele, T., Birhane, E., Damtew, A., Decuyper, M., et al. (2019). Frankincense in peril. Nat. Sustain. 2 (7), 602–610. doi:10.1038/s41893-019-0322-2

C.L.C. Almeida-da-Silva, N. Sivakumar, H. Asadi, A. Chang-Chien, M.W. Qoronfleh, D.M. Ojcius, M.M. Essa Effects of frankincense compounds on infection, inflammation, & oral health Molecules, 27 (13) (2022), p. 4174

Casapullo, A., Cassiano, C., Capolupo, A., Del Gaudio, F., Esposito, R., Tosco, A., et al. (2016). β-Boswellic acid, a bioactive substance used in food supplements, inhibits protein synthesis by targeting the ribosomal machinery. J. Mass Spectrom. 51 (9), 821–827. doi:10.1002/jms.3819

Dhyani, P., Quispe, C., Sharma, E., Bahukh&i, A., Sati, P., Ch& Attri, D., et al. (2022). Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine & vincamine. Cancer Cell International 22, 206. doi:10.1186/s12935-022-02624-9

E. Obrador, R. Salvador, R. López-Blanch, A. Jihad-Jebbar, S.L. Vallés, J.M. Estrela Oxidative stress, neuroinflammation & mitochondria in the pathophysiology of amyotrophic lateral sclerosis Antioxidants, 9 (9) (2020), p. 901

F. Aqil, R. Munagala, J. Jeyabalan, M.V. Vadhanam Bioavailability of phytochemicals & its enhancement by drug delivery systems Cancer Lett., 334 (1) (2013), pp. 133-141

Governa P, Marchi M, Cocetta V, De Leo B, Saunders PTK, Catanzaro D, Miraldi E, Montopoli M, Biagi M (2018) Effects of Boswellia Serrata Roxb. & Curcuma longa L. in an in vitro intestinal inflammation model using immune cells & Caco-2. Pharmaceuticals (Basel, Switzerl&)

Governa P, Marchi M, Cocetta V, De Leo B, Saunders PTK, Catanzaro D, Miraldi E, Montopoli M, Biagi M (2018) Effects of Boswellia Serrata Roxb. & Curcuma longa L. in an in vitro intestinal inflammation model using immune cells & Caco-2. Pharmaceuticals (Basel, Switzerl&)

Gupta I, Parihar A, Malhotra P, Gupta S, Lüdtke R, Safayhi H, Ammon HP (2001) Effects of gum resin of Boswellia serrata in patients with chronic colitis. Planta Med 67:391–395

H.R. Sadeghnia, F. Arjm&, A. Ghorbani Neuroprotective effect of Boswellia serrata & its active constituent acetyl 11-keto-β-boswellic acid against oxygen-glucose-serum deprivation-induced cell injury Acta Pol. Pharm., 74 (3) (2017), pp. 911-920

Hoernlein, R., Orlikowsky, T., Zehrer, C., Niethammer, D., Sailer, E., Simmet, T., et al. (1999). Acetyl-11-keto-β-boswellic acid induces apoptosis in HL-60 & CCRF-CEM cells & inhibits topoisomerase I. J. Pharmacol. Exp. Ther. 288 (2), 613–619.

Huang, M. T., Badmaev, V., Ding, Y., Liu, Y., Xie, J. G., & Ho, C. T. (2000). Anti-tumor & anti-carcinogenic activities of triterpenoid, β-boswellic acid. Biofactors 13 (1-4), 225–230. doi:10.1002/biof.5520130135

Hussain, H., Al-Harrasi, A., Csuk, R., Shamraiz, U., Green, I. R., Ahmed, I., et al. (2017). Therapeutic potential of boswellic acids: A patent review (1990-2015). Expert Opin. Ther. Pat. 27 (1), 81–90. doi:10.1080/13543776.2017.1235156

Iram, F., Khan, S. A., & Husain, A. (2017). Phytochemistry & potential therapeutic actions of boswellic acids: A mini-review. Asian Pac. J. Trop. Biomed. 7 (6), 513–523. doi:10.1016/j.apjtb.2017.05.001

K. Bairwa, S.M. Jachak Nanoparticle formulation of 11-keto-β-boswellic acid (KBA): anti-inflammatory activity & in vivo pharmacokinetics Pharm. Biol., 54 (12) (2016), pp. 2909-2916

K. Gerbeth, J. Hüsch, G. Fricker, O. Werz, M. Schubert-Zsilavecz, M. Abdel-Tawab. In vitro metabolism, permeation, & brain availability of six major boswellic acids from Boswellia serrata gum resins Fitoterapia, 84 (2013), pp. 99-106

Khan, A. L., Mabood, F., Akber, F., Ali, A., Shahzad, R., Al-Harrasi, A., et al. (2018). Endogenous phytohormones of frankincense producing Boswellia sacra tree populations. PLOS ONE 13 (12), e0207910. doi:10.1371/journal.pone.0207910

Liu M, Liu T, Shang P, Zhang Y, Liu L, Liu T, Sun S (2018) Acetyl-11-keto-β-boswellic acid ameliorates renal interstitial fibrosis via Klotho/TGF-β/Smad signalling pathway. J Cell Mol Med 22:4997–5007

Liu, J.-J., Nilsson, A., Oredsson, S., Badmaev, V., & Duan, R.-D. (2002). Keto-& acetyl-keto-boswellic acids inhibit proliferation & induce apoptosis in Hep G2 cells via a caspase-8 dependent pathway. Int. J. Mol. Med. 10 (4), 501–505. doi:10.3892/ijmm.10.4.501

Loeser K, Seemann S, König S, Lenhardt I, Abdel-Tawab M, Koeberle A, Werz O, Lupp A (2018) Protective effect of Casperome®, an orally bioavailable frankincense extract, on lipopolysaccharide- induced systemic inflammation in mice. Front Pharmacol

Lv, M., Shao, S., Zhang, Q., Zhuang, X., & Qiao, T. (2020). Acetyl-11-Keto-β-Boswellic acid exerts the anti-cancer effects via cell cycle arrest, apoptosis induction & autophagy suppression in non-small cell lung cancer cells. OncoTargets Ther. 13, 733–744. doi:10.2147/OTT.S236346

M. Zhao, J. Ma, M. Li, Y. Zhang, B. Jiang, X. Zhao, L. He Cytochrome P450 enzymes & drug metabolism in humans Int. J. Mol. Sci., 22 (23) (2021), p. 12808

N.K. Roy, A. Deka, D. Bordoloi, S. Mishra, A.P. Kumar, G. Sethi, A.B. Kunnumakkara. The potential role of boswellic acids in cancer prevention & treatment Cancer Lett., 377 (1) (2016), pp. 74-86

Nadeem A, Ahmad SF, Al-Harbi NO, Sarawi W, Attia SM, Alanazi WA, Ibrahim KE, Alsanea S, Alqarni SA, Alfardan AS, Bakheet SA (2022) Acetyl-11-keto-β-boswellic acid improves clinical symptoms through modulation of Nrf2 & NF-κB pathways in SJL/J mouse model of experimental autoimmune encephalomyelitis. Int Immunopharmacol 107:1–8

P. Bagul, K.S. Khomane, A.K. Bansal Investigating permeability related hurdles in oral delivery of 11-keto-β-boswellic acid Int. J. Pharm., 464 (1–2) (2014), pp. 104-110

P. Krüger, R. Daneshfar, G.P. Eckert, J. Klein, D.A. Volmer, U. Bahr, M. Abdel-Tawab. Metabolism of boswellic acids in vitro & in vivo Drug Metab. Dispos., 36 (6) (2008), pp. 1135-1142

Park, B., Sung, B., Yadav, V. R., Cho, S. G., Liu, M., & Aggarwal, B. B. (2011). Acetyl-11-keto-β-boswellic acid suppresses invasion of pancreatic cancer cells through the downregulation of CXCR4 chemokine receptor expression. Int. J. cancer 129 (1), 23–33. doi:10.1002/ijc.25966

Parmar, S., & Easwaran, H. (2022). Genetic & epigenetic dependencies in colorectal cancer development. Gastroenterol. Rep. 10, goac035. doi:10.1093/gastro/goac035

Paul, M. (2012). Chemotaxonomic investigations on resins of the frankincense species Boswellia papyrifera, Boswellia serrata & Boswellia sacra, respectively, Boswellia carterii: A qualitative & quantitative approach by chromatographic & spectroscopic methodology. Saarbrücken, Saarl&, Germany: Saarl& University.

Ranjbarnejad, T., Saidijam, M., Moradkhani, S., & Najafi, R. (2017). Methanolic extract of Boswellia serrata exhibits anti-cancer activities by targeting microsomal prostagl&in E synthase-1 in human colon cancer cells. Prostagl. other lipid Mediat. 131, 1–8. doi:10.1016/j.prostagl&ins.2017.05.003

Roy, N. K., Parama, D., Banik, K., Bordoloi, D., Devi, A. K., Thakur, K. K., et al. (2019). An update on pharmacological potential of boswellic acids against chronic diseases. Int. J. Mol. Sci. 20 (17), 4101. doi:10.3390/ijms20174101

S. Ahmad, S.A. Khan, A. Kindelin, T. Mohseni, K. Bhatia, M.N. Hoda, A.F. Ducruet Acetyl-11-keto-β-boswellic acid (AKBA) attenuates oxidative stress, inflammation, complement activation & cell death in brain endothelial cells following OGD/reperfusion Neuromol.Med., 21 (4) (2019), pp. 505-516

S. Ebrahimpour, M. Fazeli, S. Mehri, M. Taherianfard, H. Hosseinzadeh. Boswellic acid improves cognitive function in a rat model through its antioxidant activity:-neuroprotective effect of boswellic acid J.Pharmacopuncture, 20 (1) (2017), p. 10

S. Ebrahimpour, M. Fazeli, S. Mehri, M. Taherianfard, H. Hosseinzadeh Boswellic acid improves cognitive function in a rat model through its antioxidant activity:-neuroprotective effect of boswellic acid J.Pharmacopuncture, 20 (1) (2017), p. 10

S. Sharma, V. Thawani, L. Hingorani, M. Shrivastava, V. Bhate, R. Khiyani Pharmacokinetic study of 11-keto β-boswellic acid Phytomedicine, 11 (2–3) (2004), pp. 255-260

Schmiech, M., Ulrich, J., Lang, S. J., Büchele, B., Paetz, C., St-Gelais, A., et al. (2021). 11-Keto-α-boswellic acid, a novel triterpenoid from Boswellia spp. with chemotaxonomic potential & antitumor activity against triple-negative breast cancer cells. Molecules 26 (2), 366. doi:10.3390/molecules26020366

Schneider, H., & Weller, M. (2016). Boswellic acid activity against glioblastoma stem-like cells. Oncol. Lett. 11 (6), 4187–4192. doi:10.3892/ol.2016.4516

Serbian, I., Wolfram, R. K., Fischer, L., Al-Harrasi, A., & Csuk, R. (2018). Hydroxylated boswellic & glycyrrhetinic acid derivatives: Synthesis & cytotoxicity. Mediterr. J. Chem. 7 (4), 286–293. doi:10.13171/mjc74181121-csuk

Shamraiz, U., Hussain, H., Ur Rehman, N., Al-Shidhani, S., Saeed, A., Khan, H. Y., et al. (2020). Synthesis of new boswellic acid derivatives as potential antiproliferative agents. Nat. Prod. Res. 34 (13), 1845–1852. doi:10.1080/14786419.2018.1564295

Shao, Y., Ho, C.-T., Chin, C.-K., Badmaev, V., Ma, W., & Huang, M.-T. (1998). Inhibitory activity of boswellic acids from Boswellia serrata against human leukemia HL-60 cells in culture. Planta medica. 64 (04), 328–331. doi:10.1055/s-2006-957444

Siddiqui A, Shah Z, Nargis Jahan R, Othman I, Kumari Y (2021) Mechanistic role of boswellic acids in Alzheimer's disease: Emphasis on anti-inflammatory properties. Biomed Pharmacother 144:1–11

Suhail, M. M., Wu, W., Cao, A., Mondalek, F. G., Fung, K.-M., Shih, P.-T., et al. (2011). Boswellia sacra essential oil induces tumor cell-specific apoptosis & suppresses tumor aggressiveness in cultured human breast cancer cells. BMC complementary Altern. Med. 11, 129–214. doi:10.1186/1472-6882-11-129

Syrovets, T., Gschwend, J. R. E., Buchele, B., Laumonnier, Y., Zugmaier, W., Genze, F., et al. (2005). Inhibition of IkappaB kinase activity by acetyl-boswellic acids promotes apoptosis in &rogen-independent PC-3 prostate cancer cells in vitro & in vivo. J. Biol. Chem. 280 (7), 6170–6180. doi:10.1074/jbc.M409477200

T. Sharma, S. Jana Investigation of molecular properties that influence the permeability & oral bioavailability of major β-boswellic acids Eur. J. Drug Metab. Pharmacokinet., 45 (2) (2020), pp. 243-255

Takahashi, M., Sung, B., Shen, Y., Hur, K., Link, A., Bol&, C. R., et al. (2012). Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 & miR-200 microRNA family. Carcinogenesis 33 (12), 2441–2449. doi:10.1093/carcin/bgs286

Trivedi VL, Soni R, Dhyani P, Sati P, Tejada S, Sureda A, Setzer WN, Faizal Abdull Razis A, Modu B, Butnariu M & Sharifi-Rad J (2023) Anti-cancer properties of boswellic acids: mechanism of action as anti-cancerous agent. Front. Pharmacol. 14:1187181. doi: 10.3389/fphar.2023.1187181

Trivedi VL, Soni R, Dhyani P, Sati P, Tejada S, Sureda A, Setzer WN, Faizal Abdull Razis A, Modu B, Butnariu M & Sharifi-Rad J (2023) Anti-cancer properties of boswellic acids: mechanism of action as anti-cancerous agent. Front. Pharmacol. 14:1187181. doi: 10.3389/fphar.2023.1187181

Uthaman, S., Snima, K., Annapoorna, M., Ravindranath, K., Nair, S. V., & Lakshmanan, V.-K. (2012). Novel boswellic acids nanoparticles induces cell death in prostate cancer cells. J. Nat. Prod. 5, 100–108.

V. Gunasekaran, J. Avarachan, A. Augustine, A. Khayum, A. R 3-O-acetyl-11-keto-β-boswellic acid ameliorates acquired, consolidated & recognitive memory deficits through the regulation of hippocampal PPAR γ, MMP9 & MMP2 genes in dementia model Heliyon, 7 (12) (2021), Article e08523, 10.1016/j.heliyon.2021.e08523

Wang, D., Ge, S., Bai, J., & Song, Y. (2018). Boswellic acid exerts potent anticancer effects in HCT-116 human colon cancer cells mediated via induction of apoptosis, cell cycle arrest, cell migration inhibition & inhibition of PI3K/AKT signalling pathway. J. BUON 23 (2), 340–345.

Y. Ding, Y. Qiao, M. Wang, H. Zhang, L. Li, Y. Zhang, A. Wen Enhanced neuroprotection of acetyl-11-keto-β-boswellic acid (AKBA)-loaded O-carboxymethyl chitosan nanoparticles through antioxidant & anti-inflammatory pathways Mol. Neurobiol., 53 (6) (2016), pp. 3842-3853

Yadav, V. R., Prasad, S., Sung, B., Gelovani, J. G., Guha, S., Krishnan, S., et al. (2012). Boswellic acid inhibits growth & metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive & angiogenic biomarkers. Int. J. cancer 130 (9), 2176–2184. doi:10.1002/ijc.26251

Yu G, Xiang W, Zhang T, Zeng L, Yang K, Li J (2020) Effectiveness of Boswellia & Boswellia extract for osteoarthritis patients: a systematic review & meta-analysis. BMC complement med ther 20(1):1–16

Zaitone SA, Barakat BM, Bilasy SE, Fawzy MS, Abdelaziz EZ, Farag NE (2015) Protective effect of boswellic acids versus pioglitazone in a rat model of diet-induced non-alcoholic fatty liver disease: influence on insulin resistance & energy expenditure. Naunyn-Schmiedeberg's Arch Pharmacol 388:587–600