JPP Journal of Pharmacy and Pharmacology

JPP 2009, 61: 1281–1293

Received February 17, 2009
Accepted May 18, 2009
DOI 10.1211/jpp/61.10.0003
ISSN 0022-3573

Review

Boswellia resin: from religious ceremonies to medical uses; a review of in-vitro, in-vivo and clinical trials

Arieh Moussaieff[a] and Raphael Mechoulam[b]

[a]Department of Plant Sciences, The Weizmann Institute of Science, Rehovot and [b]Department of Medicinal Chemistry and Natural Products, Medical faculty, The Hebrew University of Jerusalem, Jerusalem, Israel

Abstract

Objectives Despite its historical-religious, cultural and medical importance, *Boswellia* has not been thoroughly studied, and gaps still exist between our knowledge of the traditional uses of the resin and the scientific data available. Here we review the pharmacology of *Boswellia* resin and of the small molecules identified as the active ingredients of the resin.
Key findings The resin of *Boswellia* species ('frankincense', 'olibanum') has been used as incense in religious and cultural ceremonies since the beginning of written history. Its medicinal properties are also widely recognized, mainly in the treatment of inflammatory conditions, as well as in some cancerous diseases, wound healing and for its antimicrobial activity. Until recently, work on *Boswellia* focused on the immunomodulatory properties of the resin and boswellic acids were considered to be the main, if not the only, active ingredients of the resin. Hence, this family of triterpenoids was investigated by numerous groups, both *in vitro* and *in vivo*. These compounds were shown to exert significant anti-inflammatory and pro-apoptotic activity in many assays: *in vitro*, *in vivo* and in clinical trials. We recently found incensole acetate and its derivatives, which are major components of *Boswellia* resin, to be nuclear factor-κB inhibitors, thus suggesting that they are, at least in part, responsible for its anti-inflammatory effects. Incensole acetate also exerts a robust neuroprotective effect after brain trauma in mice. Furthermore, it causes behavioural as well as anti-depressive and anxiolytic effects in mice. It is also a potent agonist of the transient receptor potential (TRP)V3 channel. It thus seems that incensole acetate and its derivatives play a significant role in the effects that *Boswellia* resin exerts on biological systems.
Conclusions Altogether, studies on *Boswellia* resin have provided an arsenal of bio-active small molecules with a considerable therapeutic potential that is far from being utilized.
Keywords *Boswellia*; boswellic acids; frankincense; incensole; olibanum

Introduction

The Burseraceae family and Boswellia *species*

The Burseraceae family consists of 17 genera and 500–600 species, which are either trees or shrubs, often spiny. Many of them contain latex, gum-resins or oils, which can be strongly aromatic. This family is widespread in all tropical regions, extending into the subtropics, and is often a dominant constituent of the vegetation in dry lowland Eastern African areas. The resins of several species of this family are of considerable commercial value as raw material of incense, balm and myrrh.[1]

Boswellia species are trees or shrubs. The genus *Boswellia* Roxb. Ex Colber (1807) is centered in North-East Africa, where about 75% of the species are endemic. About 20 species are known in the dry regions of tropical Africa and in India, and one species is found in Madagascar.[1] *Boswellia* trees, when cut, exude a gum resin, which is gathered by making scrapes in the bark of the tree.[2] In Oman, where *Boswellia* trees grow and are cultivated, the pale whitish resin is either scraped off the tree with an iron implement or collected on palm mats on the ground as it drips off. Harvesting begins in December, reaching a peak from March to May.[3]

The history and applications of Boswellia *resin*

The resin of *Boswellia* species ('frankincense', 'olibanum') (Figure 1) is mentioned in numerous ancient texts. Prized by many civilizations, the resin of *Boswellia* once ranked along with gold and ivory as a precious valuable for trading and barter.[2]

Correspondence: Dr Arieh Moussaieff, Department of Plant Sciences, the Weizmann Institute of Science, Rehovot, 76100, Israel.
E-mail: arieh@weizmann.ac.il

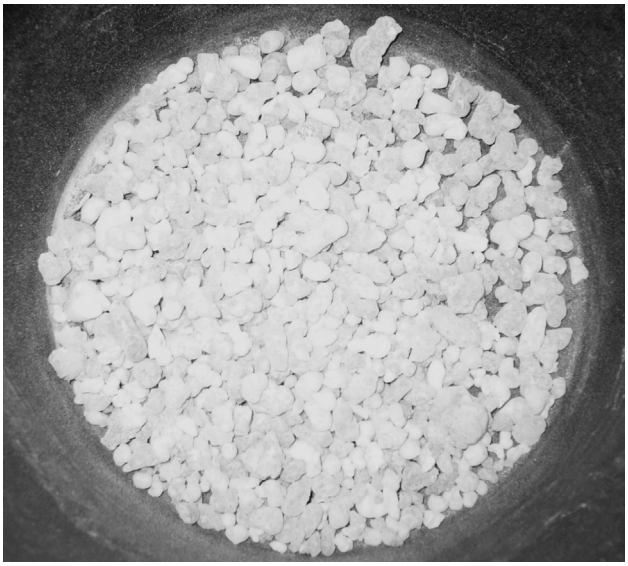

Figure 1 *Boswellia* resin, photographed by the authors

The first mention of the use of *Boswellia* resin as a drug is in the Ebers papyrus, approximately 1500 BC.[3] Early Egyptian myth describes the resin as representing the 'tears of Horus' (son of Osiris and Isis). Later texts of Greek and Roman origin describe the trade of these prized resins, which were exported to Rome, China and North Africa.[2] Dioscorides (1st century C.E.) wrote that it caused madness.[4] Celsus (2nd century C.E.) recommended that frankincense be used to treat wounds and sources of bleeding, and as a possible antidote to hemlock. If mixed with leek juice, it was thought to stop internal bleeding and superficial bruising.[2] In ancient Judea the use of the resin as incense was a central ceremony in the Temple. In the Babylonian Talmud (3rd–6th centuries C.E.) *Boswellia* resin is stated to be administered in wine to prisoners condemned to death, to 'benumb the senses' or 'not to be sorry'.[5] Based on this text, some scholars assumed that the drink given to Jesus before crucifixion contained *Boswellia* resin.[6] The work of Ibn Sina (Avicenna) of the 11th century refers to the use of frankincense in inflammation and infection of the urinary tract,[2] and suggests that 'it is beneficial for amentia and amnesia'.[7]

The uses of *Boswellia* resin for its putative psychoactive as well as its anti-inflammatory and wound healing properties extend beyond the Near East. In the Christian world its use in worship arose in the 4th or 5th century.[8,9] In Ethiopia, where *Boswellia* trees are indigenous, it is believed to have a tranquilizing effect.[10] In Kenya it is used for dressing wounds and, when mixed with sesame oil, is taken to reduce the loss of blood in the urine from schistosomiasis infestation. In India, *Boswellia* resin is widely used in the treatment of inflammatory conditions, including Crohn's disease, arthritic diseases and asthma; hence a considerable amount of work has been done on the anti-inflammatory properties of *Boswellia* (see herein). In Ayurveda, the Indian medical tradition, *Boswellia* resin is also reported to 'cause a strong action on the nervous system'.[11] In China it was a constituent of several skin remedies, including those for bruises and infected sores.[2]

Boswellia resin has various non-pharmaceutical applications. Today frankincense is widely employed as incense in catholic Christian churches as well as other religious and secular traditions. It is also an important component of perfumes and toiletries.[2] *Boswellia* resin is widely marketed as a food supplement.

The active constituents of *Boswellia* resin

More than 200 compounds have been identified in resins from *Boswellia* spp.[12] (see Hamm *et al.*[13] for examples). The long-lasting traditions of the use of *Boswellia* resin for the treatment of inflammatory conditions were successfully put to the test by many research groups that focused on boswellic acids (Figure 2). However, the use of crude extracts in inflammation-associated assays showed in some cases biphasic potentiating/inhibitory effects, contrary to the effects attained by purified compounds from these extracts,[14] and several studies indicate that the activity of *Boswellia* resin can be superior to that of purified boswellic acids.[15] These data suggest that the anti-inflammatory activity of the resin is modulated by several different constituents. When the early studies on the anti-inflammatory effects of extracts of *Boswellia* resin were performed, few constituents had been isolated and identified. Some of the major components of the resin were found to be the diterpenes incensole (Figure 3) and isoincensole, their oxide or acetate derivatives (Figure 3), and the triterpene boswellic acids, which are considered to be biomarkers of olibanum.[13]

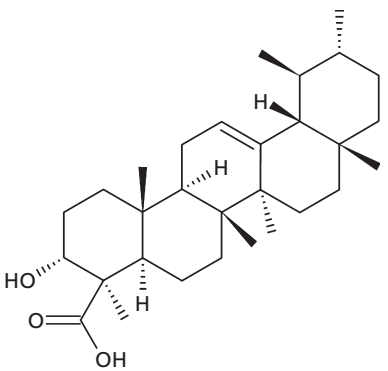

Figure 2 β-Boswellic acid

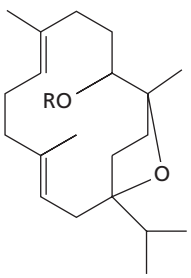

Figure 3 The structures of incensole acetate (R = Ac) and incensole (R = H)

Due to their prevalence in the resin, the pentacyclic triterpenoid boswellic acids were reported as constituents of *Boswellia* resin relatively early (see Winterstein & Stein[16]). In an attempt to identify the active components in the resin, boswellic acids were examined for their anti-inflammatory effects. From that point on, many reports have attributed the anti-inflammatory and cytotoxic properties of *Boswellia* resin solely to boswellic acids and their derivatives, specifically acetyl-β-boswellic acid (AβBA), 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid (AKBA). Pharmacological studies indicate that the β-configured derivatives exert better efficacy than the respective α-isomers. Büchele and colleagues[17] identified pentacyclic triterpenes in human plasma of patients treated with *Boswellia* resins extracts. The resins were extracted using methanol, ethanol, ethyl acetate, acetone, isopropanol, methyl ethyl ketone and hexane from various sources indicating that these compounds are bioavailable, to a certain extent at least.

After the anti-inflammatory effects of boswellic acids were established, Boden *et al.*[18] showed that 3-oxo-tirucallic acid, an additional tetracyclic triterpene isolated from *B. serrata* resin, as well as 3-acetoxy-tirucallic acid and 3-hydroxy-tirucallic acid, were biologically active. These compounds were found to act as inhibitors of 5-lipoxygenase in a cell-free assay, but in intact cells they were found to activate 5-lipoxygenase, thus exhibiting a paradoxical effect.

Given this lack of clarity as to the active ingredients of *Boswellia* resin, we initiated a bio-guided fractionation of *B. carterii* resin, aiming to identify the major anti-inflammatory constituents of the resin. Much to our surprise, while a boswellic acid mixture showed no effect on inhibitory κB (IκB)α degradation, two fractions – later shown to contain two active components, incensole acetate and its non-acetylated form incensole – inhibited IκBα degradation and nuclear factor (NF)-κB activation.[19] These compounds were previously isolated from *Boswellia* resin,[20] but no biological activity had been assigned to them before our study. *In vitro*, incensole acetate showed anti-inflammatory effects in numerous assays; *in vivo*, such an effect was seen in an anti-inflammatory paw model.[19] Robust anti-inflammatory and neuroprotective effects in mice following head trauma were also reported.[21] Incensole acetate was then found to exert anxiolytic and anti-depressive effects in mice models.[22]

Altogether, several active constituents were isolated from the resin. Importantly, one should be aware that different species of *Boswellia* contain a different mixture of active and non-active ingredients.

The immunomodulatory effects of *Boswellia* resin and its constituents

The genetic basis of the anti-inflammatory effects of a standardized *Boswellia* extract (5-Loxin) was tested in a system of tumour necrosis factor (TNF)-induced gene expression in human microvascular endothelial cells. TNF-α induced 522 genes and down-regulated over 140 genes. Of the genes induced by TNF-α, 113 genes were sensitive to treatment with *Boswellia* extract. These genes directly relate to inflammation, cell adhesion and proteolysis. The extract also prevented the TNF-induced expression of matrix metalloproteinases and the inducible expression of mediators of apoptosis. TNF-inducible expression of VCAM-1 and ICAM-1 appeared to be strikingly sensitive to the resin extract. These findings were further corroborated by realtime polymerase chain reaction (PCR) analysis.[23]

Although the anti-inflammatory activity of *Boswellia* resin probably involves boswellic acids to some extent, these were only sparsely present in some preparations used in studies that examined *Boswellia* for its immunomodulatory effects. Moreover, these extracts possessed superior activity over purified boswellic acids, suggesting that other ingredients probably contributed to the effects noted.[15] In agreement with these findings, and in contrast to the common view that boswellic acids are the only active ingredients in *Boswellia* resin, we found that incensole acetate and its derivatives are the major NF-κB inhibitory components of the resin, and may thus be the major anti-inflammatory constituents of *Boswellia carterii* resin.[19]

These effects of *Boswellia* resin and its main active constituents, boswellic acids, incensole acetate and their derivatives, are probably mediated via several, probably different, key pathways involved in inflammation and carcinogenesis. In the following sections, we shall present a summary of the effects of *Boswellia* and its active constituents via several known pro-inflammatory pathways.

Boswellia *and the nuclear factor-κB pathway*

NF-κB is an inducible transcription factor, ubiquitously expressed and involved in the activation of a multitude of genes in response to various stress stimuli. It plays a pivotal role in immune and inflammatory responses.[24,25] Several recent studies of mouse models of cancer have also provided direct genetic evidence for the critical role of NF-κB in carcinogenesis (see Pikarsky & Ben-Neriah[26]).

AβBA and AKBA inhibited constitutively activated NF-κB signalling by attenuating the activity of IκB kinase (IKK), the major regulatory enzyme in the NF-κB pathway. In lipopolysacharide (LPS)-stimulated human peripheral monocytes, acetyl-α-boswellic acid (AαBA) and AKBA down-regulate the TNF-α expression. AαBA and AKBA inhibited the phosphorylation of recombinant IκBα and p65 by IKK immunoprecipitated from LPS-stimulated monocytes. AαBA and AKBA also bound to, and inhibited the activity of, active human recombinant GST-IKKα and His-IKKβ.[27]

We re-examined different extracts (petroleum ether, ethyl acetate, methanol, ethanol–water) of the resin of *B. carterii* for their anti-inflammatory activity, using IκB degradation as a read-out system for the isolation of active constituents. We found that the petroleum ether extract inhibited the degradation of IκBα in TNF-stimulated HeLa cells. We then fractionated the active extract, and isolated its main active ingredients. Their structures were elucidated as incensole acetate and incensole. A mixture of boswellic acids did not show an effect in our model. Incensole acetate inhibited transforming growth factor β-activated kinase (TAK)/transforming growth factor β-activated kinase-binding protein (TAB)-mediated IKK activation loop phosphorylation, resulting in the inhibition of cytokine and LPS-mediated NF-κB activation. While inhibiting IKK activity in TNF-stimulated

cells, incensole acetate had no effect on IKK activity *in vitro*, indicating that the kinase inhibition is indirect. We concluded that the major NF-κB inhibitory compounds in *B. carterii* resin are the macrocyclic diterpenoids incensole acetate and incensole.[19]

The effect of incensole acetate on cytokines downstream of nuclear factor-κB activation

Incensole acetate inhibited the formation of interleukin (IL)-1β, IL-6 and TNF-α, as well as prostaglandin E2, in LPS-stimulated human peripheral monocytes.[21]

Interaction of boswellic acids with lipoxygenases

Leukotrienes play a pathological role in inflammatory diseases, such as asthma, allergic rhinitis, psoriasis and atherosclerosis[28,29] and stand in the background of other pathological condition, such as osteoporosis,[30] cancerous diseases,[31,32] asthma[33] and cardiovascular diseases.[34,35] Anti-leukotriene therapy has proven benefits in the treatment of respiratory disease.[29]

The first committed step in the synthesis of leukotrienes is the oxidation of arachidonic acid (AA) by 5-lipoxygenase.[29] Leukotrienes primarily signal through the activation of cell-surface specific G-protein-coupled receptors (GPCRs), namely BLT1 and BLT2 for leukotriene B4 (LTB4) signalling and CysLT1 and CysLT2 for CysLT signalling.[29]

Following a study by Ammon *et al.*[36] showing that *B. serrata* ethanolic extract inhibits the formation of LTB4 in rat neutrophils, Safayhi *et al.*[37] examined the effect of α- and β-boswellic acids, as well as AKBA, on the formation of LTB4 from AA in rat peritoneal neutrophils. AKBA induced the highest inhibition of 5-lipoxygenase product formation (IC50 = 1.5 μM). This inhibition probably indicates a direct interference taking place via a pentacyclic triterpene selective binding site that is different from the AA substrate binding site.[38] This study also suggests that the pentacyclic triterpene ring system is crucial for the binding of the inhibitor to the highly selective 5-lipoxygenase site. β-Boswellic acid, as well as the related pentacyclic triterpenoid amyrin, antagonized AKBA-mediated 5-lipoxygenase inhibition.

Functional groups (i.e. the 11-keto and C4-carboxylic moiety) were found to be essential for 5-lipoxygenase inhibitory activity.[39] In cytosolic fractions of differentiated HL-60 cells, Werz and colleagues[40] determined the 5-lipoxygenase inhibitory IC50 of AKBA to be 50 μM. In the same study, the authors reported an IC50 of 15 μM for intact cells. The fact that higher concentrations of boswellic acids are required to directly inhibit 5-lipoxygenase activity *in vitro* as compared with intact cells suggests that the inhibition of leukotriene formation represents interference with cellular events upstream of 5-lipoxygenase. Attempts were made to explain the discrepancies in the effects of boswellic acids on cellular versus in-vitro 5-lipoxygenase product synthesis;[15] however, no conclusive evidence has been provided so far.

The labelling of 5-lipoxygenase by a photoaffinity analogue that inhibited 5-lipoxygenase activity as efficiently as the lead compound strictly depended on the presence of free calcium ($[Ca^{2+}]$) at levels above 500 nM, and was abolished by prior incubation with a series of pentacyclic triterpenes. AA reduced photoincorporation (IC50 ~ 10 μM), whereas other long-chain fatty acids showed no effect. The inhibitory arachidonate action on labelling was not affected by blocking the substrate-binding site with a competitive inhibitor. It was suggested that AKBA binds in the presence of calcium to a site that is distinct from the substrate binding site of 5-lipoxygenase.[41]

In intact human platelets and in platelet cytosolic fractions, AKBA potently suppressed platelet-type 12-lipoxygenase product formation (IC50 = 15 μM), with higher potency for platelet-type 12-lipoxygenase in cell-free assays than crude 5-lipoxygenase.[42]

Several studies support the notion that the immunomodulatory effects of boswellic acids are not all inhibitory. Altmann and colleagues[43] found that in polymorphonuclear leucocytes (PMNLs), 11-keto-boswellic acids stimulate the formation of reactive oxygen species (ROS), and stimulate the release of AA as well as its transformation to leukotrienes via 5-lipoxygenase. Two other tetracyclic triterpenes extracted from *B. serrata* resin, 3-oxo-tirucallic acid and 3-acetoxy-tirucallic acid, were found to induce leukotriene formation in stimulated PMNLs (2.5–15 μM).[18] In contrast to their effect on cells, in cell-free 5-lipoxygenase assays, 3-oxo-tirucallic acid showed an inhibitory effect (IC50 ~ 3 μM), implying that the inductive effect is indirect.

Boswellia *and cyclooxygenase*

Boswellic acids, especially AKBA, inhibited cyclooxygenase (COX)-1 product formation in intact human platelets (IC50 = 6 μM), as well as the activity of isolated COX-1 enzyme in cell-free assays (IC50 = 32 μM).[44] This effect is reversible and is impaired by increased levels of AA as substrate of COX-1. Molecular docking of boswellic acids into X-ray structures of COX-1 yielded positive Chemscore values for boswellic acids, indicating favourable binding to the active site of the enzyme. COX-2 was less efficiently inhibited by boswellic acids.

We examined the effects of incensole acetate on COX-2 and found a significant inhibitory effect at 60 μM (unpublished data).

Boswellia *and calcium mobilization*

The activation of cellular 5-lipoxygenase depends on an increase in calcium concentration.[29] Boswellic acid induced Ca^{2+} mobilization,[43] and AKBA or 11-keto-β-boswellic acid (KBA) decreased the basal calcium concentration and prevented agonist-induced mobilization of Ca^{2+} in monocytic cells.[45]

Boswellia *and mitogen-activated protein kinases*

Mitogen-activated protein kinases (MAPKs) are fundamental regulators of immune cell functions, including proliferation, differentiation, survival and apoptosis, chemoattraction, and production of inflammatory mediators.[46]

Boswellic acids activated the p42 and p38 MAPK in isolated human PMNLs. The most pronounced activation was noted with 11-keto-β-boswellic acid and AKBA (30 μM).[47] Depletion of Ca^{2+} partially inhibited AKBA-induced MAPK, indicating that Ca^{2+} may contribute to MAPK activation by boswellic acids. Pertussis toxin, which inactivates G(i/0) protein subunits, inhibited 11-keto-boswellic acid-induced MAPK activation and Ca^{2+} mobilization, implying the

involvement of a G(i/0) protein in boswellic acid signalling.[43] Interestingly, 11-keto-boswellic acids (KBA or AKBA) evoked only moderate Ca^{2+} mobilization and activated p38 MAPK, but failed to induce phosphorylation of ERK2 or Akt, in contrast to β-boswellic acid.[48] KBA and AKBA also activated p42/44 MAPK in human PMNLs.[47]

Boswellia *and reactive oxygen species*

KBA and AKBA stimulated the formation of ROS in leucocytes,[43] causing release of AA as well as its transformation to leukotrienes via 5-lipoxygenase. The production of ROS by AKBA irreversibly inactivated the redox-sensitive 5-lipoxygenase enzyme in leucocytes. An isomeric mixture of 3α, 24-dihydroxyurs-12-ene and 3α, 24-dihydroxyolean-12-ene from *B. serrata* also caused massive elevation of the concentrations of ROS in HL-60 cells as well as in tumour cell lines such as A-549, HCT-15, Molt-4 and MCF-7 cells.

Boswellic acids and human leucocyte elastase

Human leucocyte elastase (HLE) is a serine protease produced and released by PMNLs. It has been suggested that HLE may play a role in several diseases, including pulmonary emphysema, cystic fibrosis, chronic bronchitis, acute respiratory distress syndrome, glomerulonephritis and rheumatic arthritis. It has also been suggested as a target for boswellic acids by Safayhi *et al.*[49]

Molecular targets related to drug interactions and metabolism

Boswellia spp. extracts (methanol 70% of *Boswellia* H 15 tablets) and boswellic acids potently and non-selectively inhibited the drug metabolizing cytochrome P450 (CYP) enzyme family.[50] In a set-up using a mixture of recombinant CYP enzymes, β-boswellic acid, KBA and AKBA (5–10 μM) inhibited the activity of CYP 2C8/2C9 and 3A4.

Boswellia extract, as well as the keto-boswellic acids, also inhibited the transport activity of P-glycoprotein in a human lymphocytic leukaemia cell line expressing Pgp and porcine brain capillary endothelial cells using calcein acetoxymethyl ester (calcein-AM) as P-glycoprotein substrate.[51] No effect was observed when non-keto boswellic acids were examined. These results imply that keto-boswellic acids may modulate the interactions of many drugs with P-glycoprotein at the level of the intestine and the blood–brain barrier.

The pro-apoptotic and cytotoxic effects of *Boswellia* resin

Boswellic acid derivatives induced apoptosis in several glioblastoma cell lines,[52] human leukaemia cell lines,[53–55] brain tumour cell lines,[54] liver cancer HepG2 cells,[56] colon cancer HT-29 cells,[57,58] prostate cancer cell lines,[17,59,60] human fibrosarcoma HT-1080 cells and mouse melanoma B1610 cells.[61] Interestingly, human normal lung fibroblasts did not undergo apoptosis, indicating selective cytotoxicity of AKBA towards transformed cancer cells.[62] In HL-60 and CCRF-CEM cells AKBA (IC50 = 30 μM) induced apoptosis.[53] In agreement with this study, different boswellic acids (IC50 = 0.5–7.1 μM) – with AKBA being the most potent derivative – inhibited DNA, RNA and protein synthesis in HL-60 cells.[63] In another study, addition of β-boswellic acid, 3-*O*-acetyl-β-boswellic acid, 11-keto-β-boswellic acid or AKBA to human leukaemia HL-60 cell culture inhibited DNA synthesis in the cells in a dose-dependent manner with IC50 values ranging from 0.6 to 7.1 μM.[64] Yet another study, done on boswellic acid acetates isolated from *B. carterii*, found induced differentiation and apoptosis of leukaemia cells. Based on cell morphology and nitroblue tetrazolium reduction, they were shown to induce monocytic differentiation of myeloid leukaemia HL-60, U937 and ML-1 cells at a dose lower than 24.2 μM. Ninety per cent of the cells showed morphologic changes and 80–90% of the cells showed nitroblue tetrazolium reduction.[65] Boswellic acid acetates induced apoptosis of human fibrosarcoma HT-1080 cells, as demonstrated in several assays: acridine orange fluorescence staining, Wright–Giemsa staining, electromicroscopy, DNA fragmentation and flow cytometry.[61] It was suggested that boswellic acid acetates induce myeloid leukaemia cell apoptosis by increasing the levels of death receptors and indirectly activating caspase-8.[55] However, the apoptosis exerted by boswellic acid derivatives may be a result of topoisomerase inhibition. Indeed, AKBA, but not amyrin, potently inhibited topoisomerase I from calf thymus and induced apoptosis in topoisomerase I-expressing HL-60 cells at a concentration of 30 μM.[53] Syrovets *et al.*[66] demonstrated direct binding of acetyl-boswellic acid immobilized analogue to purified human topoisomerases I and IIα with IC50 values comparable with those found for AβBA (IC50 = 10–30 μM) and AKBA (IC50 = 30–50 μM). Interestingly, AαBA was the most potent analogue (IC50 = 1–3 μM), indicating different structural requirements for target binding as compared with 5-lipoxygenase.

HCT-116 p53(–/–) cells were sensitized to the apoptotic effect of AKBA, suggesting that p21 may protect cells against apoptosis by inducing a G1 arrest. AKBA showed no p53-induced effect on the growth of the cells.[58]

Kiela *et al.*[67] postulated inhibition of the anti-apoptotic transcription factor NF-κB by boswellic acids. This assumption is strongly corroborated by the work of Syrovets and colleagues,[27,62] who suggest this pathway as another mechanism of boswellic acid-mediated apoptosis. The inhibition of NF-κB signalling in LPS-stimulated monocytes by AαBA and by AKBA is implicated to be specific by the lack of effect of the compounds on the luciferase expression driven by the interferon-stimulated response element. No effect was noted on the binding of NF-κB to the DNA.[62]

The impaired phosphorylation of p65 and the reduced nuclear translocation of NF-κB proteins were associated with down-regulation of the anti-apoptotic proteins Bcl-2 and Bcl-x(L). The expression of cyclin D1, a crucial cell cycle regulator, was reduced as well.[62] A direct inhibition of IKK activity was excluded.[68] Given the controversial data on direct IKK inhibition (Takada *et al.*[68] vs Syrovets *et al.*[27]), the search for an AKBA target upstream of IKK should be further pursued. Takada and colleagues[68] found that many anti-apoptotic genes (e.g. Bcl-2, Bcl-x_L, XIAP, survivin) were down-regulated by AKBA. They also found that AKBA modulated the expression of several anti-apoptotic gene products regulated by NF-κB. The TNF-induced Fas expression was also suppressed by AKBA.[68] When the apoptotic effects and the mechanisms of action of AKBA

were studied in LNCaP and PC-3 human prostate cancer cells, both cell lines showed a pro-apoptotic response at concentrations above 10 μg/ml. This effect was correlated with the activation of caspase-3 and caspase-8 as well as with poly(ADP)ribose polymerase cleavage. The activation of caspase-8 was further correlated with increased levels of CAAT/enhancer binding protein homologous protein and death receptor 5, but not of Fas or DR4.[60]

An improved pro-apoptotic effect of β-boswellic acid and AKBA was noted when a 4-amino analogue was prepared from the compounds, where the carboxyl group in the ursane nucleus was replaced by an amino function. These novel molecules also exhibited pro-apoptotic activity by inducing DNA fragmentation.[69]

AKBA (10 mg/kg daily) also inhibited Matrigel+bFGF-induced angiogenesis,[70] indicating that the in-vivo anti-cancerous effects of boswellic acids may involve an inhibition of angiogenesis as well as a pro-apoptotic effect.

An isomeric mixture of 3α,24-dihydroxyurs-12-ene and 3α,24-dihydroxyolean-12-ene, isolated from *B. serrata* inhibited cell proliferation in HL-60 cells (IC50 ~ 12 μg/ml) and induced apoptosis.[71]

Given our findings showing that incensole acetate, incensole and their derivatives are NF-κB inhibitors,[19] it is plausible that these components of *Boswellia* resin are also involved in its pro-apoptotic effects.

Boswellia resin constituents and transient receptor potential ion channels

Transient receptor potential (TRP) ion channels are involved in the transduction of a wide variety of sensations: mechano-sensation, vision, olfaction, taste, chemo-sensation and thermo-sensation. Members of the TRP family have been implicated in a variety of mechanical transduction processes in diverse organs and species.[72] They are widely distributed in various tissues, including peripheral neurons and the central nervous system (CNS).[73,74] These facts make TRP channels important targets for treatment of diseases arising from the malfunction of these channels.[75] Following our findings that incensole acetate elicits behavioural effects on the CNS, particularly anti-depressive and anxiolytic effects (see below),[22] we screened incensole acetate for its action on different potential pharmacological targets in the CNS. We found that incensole acetate is a potent activator of TRPV3 channels, while no (or very mild) effects were observed for other TRP channels examined. Incensole acetate did not bind to a battery of receptors, ion channels and transport proteins with known activity on the CNS. These results suggest for the first time a possible role for this channel in the CNS. Incensole acetate is currently the most potent specific modulator of the TRPV3 channel, and is hence a tool of considerable value in research on this channel, its functions and mechanism of action.

In-vivo studies on *Boswellia* gum resin and its constituents

Immunomodulatory effects of Boswellia

Agents that suppress the expression of TNF-α, IL-1β, COX-2, 5-lipoxygenase, or agents that are known to suppress the activation of NF-κB have potential for the treatment of arthritis.[76] In the case of *Boswellia* studies, anti-inflammatory in-vivo assays preceded the cellular and molecular examination. Singh and Atal[77] examined the in-vivo effects of an alcoholic extract of B. *serrata* in carrageenan-induced oedema in rats and mice and dextran oedema in rats. They found that it caused marked suppression of the carrageenan- or dextran-induced oedema, and exerted anti-arthritic activity. No analgesic or antipyretic effects were observed in this study. Many studies that followed this work corroborate the anti-inflammatory effects of *Boswellia* resin and its constituents on several inflammation models, both acute and chronic. The anti-inflammatory effect shown in these studies can be attributed, at least partially to incensole acetate, boswellic acids and their derivatives, as was determined by us[19] and by Singh and colleagues,[78] respectively, in carrageenan-induced paw inflammation assays.

A biopolymeric fraction from *B. serrata* was shown to be a potent enhancer of antigen-specific immune responses with adjuvant activity that is superior to that of the conventional adjuvant alum.[79] It potently enhanced antigen-specific Th1 (IFN-γ and TNF-α) and Th2 (IL-4) immune responses to hepatitis B surface antigen and the production of cytokines (IFN-γ TNF-α and IL-4) by spleen cells isolated from immunized animals and T-lymphocyte subsets (CD4/CD8). Total IgG and its subtypes (IgG1 and IgG2a) antibody titres in serum were significantly enhanced. A dose-related increase in the delayed hypersensitivity reaction in mice was also demonstrated following oral administration of a *Boswellia* resin extract (BOS 2000; 1–10 mg/kg).[80] These results are intriguing, and should probably be further pursued in terms of the ingredients of the resin that are responsible for them.

Boswellia *and arthritis*

Boswellia resin is marketed as an anti-arthritic herbal remedy, and several studies have examined the anti-arthritic effect of the resin and its constituents. These indicate that boswellic acids exert a beneficial effect in bovine serum albumin-induced arthritis in rabbits (see Sharma *et al.*[81]). Boswellic acids attenuated elevated levels of connective tissue metabolites (hydroxyproline, hexosamine and uronic acid) in the urine of adjuvant-induced arthritic rats, especially in the chronic phase of the disease.[82] The degradation of glycosaminoglycans was found to be reduced markedly following treatment with boswellic acids or *Boswellia* resin extract.[83] Studies done on extracts from *B. carterii* and *B. serrata* (e.g. Fan *et al.*)[84] support the notion that components of these resins may ameliorate arthritic conditions.

Boswellia *and inflammation-associated intestinal diseases*

B. serrata commercial extract (H15), as well as AKBA, significantly attenuated indometacin-induced ileitis in rats. The rats received oral treatment of extract (17.1 or 34.2 mg/kg daily) or AKBA (low dose, 3.4 mg/kg orally per day, or high dose, 5.1 mg/kg orally per day). The authors note that AKBA accounts for 2.2% of boswellic acids in the extract, and preliminary experiments with AKBA at this concentration did not achieve any significant anti-inflammatory effect.

They hence concluded that other boswellic acids in *Boswellia* extract may also have anti-inflammatory properties, and therefore the doses of AKBA given were adjusted to represent the content of all boswellic acids present in the extract (~20%). At these doses, the effects of AKBA treatment were comparable with those of the extract.[85]

Treatment with AKBA or dexamethasone significantly reduced dextran sodium sulfate -induced bowel shortening and improved histological parameters, such as cellular infiltrate, destroyed crypt architecture, colonic mucosa histological score and recruitment of adherent leucocytes and platelets into inflamed colonic venules of dextran sodium sulfate-challenged mice.[86] The treatment of colitis with AKBA (5 mg/kg daily, i.p.) also largely prevented the P-selectin up-regulation normally associated with dextran sulfate sodium colitis.[86]

Although probably not through an inflammatory mechanism, *B. serrata* extract (hydroalcoholic extract, standardized to contain 95% boswellic acids) was shown to prevent experimental diarrhoea and to normalize intestinal motility in pathophysiological states in mice without slowing down the rate of transit in control animals.[87] This inhibitory effect of *B. serrata* extract on acetylcholine-induced contractions was reduced by the L-type Ca^{2+} channel blockers verapamil and nifedipine, but not by the sarcoplasmic reticulum Ca^{2+}-ATPase inhibitor cyclopiazonic acid, by the phosphodiesterase type IV inhibitor rolipram or by the 5-lipoxygenase inhibitor zileuton.

Boswellia *and atherosclerosis*

In a study by Cuaz-Pérolin *et al.*,[88] treatment of atherosclerotic lesions in apoE–/– mice with AKBA significantly reduced lesion size by approximately 50%. Furthermore, NF-κB activity was also reduced in the atherosclerotic plaques, and a significant downregulation of several NF-κB-dependent genes, such as MCP-1, MCP-3, IL-1α, MIP-2, VEGF and TF, was noted.

AKBA did not affect the plasma concentrations of triglycerides, total cholesterol and anti-oxidized LDL antibodies. It thus seems that the anti-atherosclerotic effect observed is due to the NF-κB inhibitory effect of AKBA.

In-vivo anti-cancer studies

Huang and colleagues[64] have demonstrated the effect of methanol extract from the resin of *Boswellia serrata* on cancerous pathologies. Survival time of rats after inoculation of C6 glioma cells following administration of boswellic acids (3×240 mg/kg) was more than twice as long as that of the control group.[89] Tumour volume also decreased.

Topical application of AKBA-γ-cyclodextrin on PC-3 tumours induced concentration-dependent inhibition of proliferation as well as apoptosis. In nude mice carrying PC-3 tumours, systemic application of AKBA-γ-cyclodextrin inhibited tumour growth and triggered apoptosis in the absence of detectable systemic toxicity.[62]

The use of Boswellia *resin in the treatment of wounds*

Although *Boswellia* resin has been used as a wound healing remedy, especially as part of herbal remedy mixtures,[90] this putative feature of the resin constituents has not been examined. As the healing process of wounds is closely related to the inflammatory cascade, it is plausible that the use of the resin as a wound-healing agent is due to its anti-inflammatory qualities that indirectly improve wound healing. It may also involve antimicrobial activity (see below).

Antimicrobial activity of Boswellia *resin*

A few studies on the antimicrobial activity of *Boswellia* resin suggest that the resin indeed exerts such activity. Camarda and colleagues[91] examined the essential oils from *B. carterii*, *B. papyrifera*, *B. serrata* and *B. rivae* oleogum gum resins. *B. carterii* and *B. papyrifera* showed the best activity against fungal strains with minimum inhibitory concentration values as low as 6.2 μg/ml. Moreover, it seems that the resin of *Boswellia* species also inhibits the development of biofilms *in vitro*, as established by Schillaci *et al.*[92] They examined the anti-biofilm activity of commercially available essential oils from *B. papyrifera* and *B. rivae*. The viability of staphylococcal and *Candida albicans* biofilms was determined by methyltiazotetrazolium staining. At concentrations ranging from 217.3 μg/ml to 6.8 μg/ml, the essential oil of *B. papyrifera* showed considerable activity against both *Staphylococcus epidermidis* DSM 3269 and *Staphylococcus aureus* ATCC 29213 biofilms.

Neuroprotective effects of Boswellia *resin*

Schuhmann and colleagues (presented as an abstract)[93] suggested that the resin of *B. carterii* exhibits a neuroprotective effect after controlled cortical impact. We examined the effects of incensole acetate on the inflammatory process and on the recovery of neurobehavioural and cognitive functions following head trauma, using a mouse model of closed head injury (CHI).[21] Incensole acetate reduced glial activation, inhibited the expression of IL-1β and TNF-α mRNAs, and induced cell death in macrophages at the area of trauma in the brains of post-CHI mice. Subsequently, it inhibited hippocampal neurodegeneration and exerted a beneficial effect on functional outcome after CHI (i.e. reduced neurological severity scores and improved cognitive ability in an object recognition test). Hence, our study concurs with the results of Schuhmann and co-workers, and our findings suggest that the neuroprotective effect of *B. carterii* resin can be attributed, at least partially, to incensole acetate and its derivatives. However, unlike the data presented by Schuhmann *et al.*,[93] our data suggest that incensole acetate has no significant inhibitory effect on the post-traumatic cerebral oedema formation in mice.

The effects of Boswellia *resin on the central nervous system*

Despite its wide use and long-lasting renown, many aspects of the pharmacological activities of *Boswellia* resin have not been sufficiently studied thus far. The effects of extracts of *Boswellia* resin on the CNS have already been suggested by Kar and Menon.[94,95] They found that the non-phenolic fraction of *B. serrata* resin distillation ether extraction was sedative and analgesic in albino rats. However, until recently, no attempt was made to isolate the active ingredients responsible for this putative psychoactivity. In light of the

historical and literature data, implying the existence of psycho-active ingredients in the resin, we re-examined the effects of *Boswellia* resin and its constituents on the CNS. Our aims were to identify novel psycho-active compounds from the resin and to elucidate their mechanism of action. Using behavioural models we found that incensole acetate exerted anxiolytic- and anti-depressive effects, as well as a sedative effect; these findings were corroborated by an immunohistochemical mapping of mice brains following incensole acetate administration.[22] To pursue a mechanism of incensole acetate's central effects, we then examined incensole acetate for its binding to an array of related receptors, ion channels and transport proteins. Incensole acetate bound to none of the known pharmacological targets tested, but robustly activated the TRPV3 channel in several in-vitro assays: activated a calcium influx in HEK293 cells, and primary keratinocytes, as well as a TRPV3 current in HEK293 cells stably expressing TRPV3. We tested incensole acetate for its behavioural effects on TRPV3 null mice, and found that it exhibited no effect in the assays used to assess anti-depressive and anxiolytic effects, while retaining its sedative effect.[22] These findings may have several implications. They suggest that incensole acetate exerts anti-depressive and anxiolytic effects, thus possibly explaining the long-lasting and widespread use of *Boswellia* resin burning as a major feature of religious and cultural ceremonies. They also imply that these effects take place via TRPV3 channels in the brain, thus suggesting for the first time a role for this channel in the CNS. It is also potentially a novel prototype anti-depressant and anxiolytic drug distinct from the chemical groups of such drugs in current use. It should be noted that the finding that incensole acetate exhibits its effects on the CNS via TRPV3 channels in the brain may suggest that this channel can perhaps be used as a novel pharmacological target for the amelioration of such disorders.

Clinical trials

Ernst[96] reviewed the clinical trials that have been performed on *B. serrata* resin, and found that *Boswellia* extracts showed some promise in treating asthma, rheumatoid arthritis, Crohn's disease, knee osteoarthritis and collagenous colitis.

He concluded that 'the evidence for the effectiveness of *B. serrata* extracts is encouraging but not compelling'. Although the results in animal models are very promising, we are inclined to accept this conclusion.

Several clinical trials have been conducted with the resin of *Boswellia* spp. for its effects on chronic inflammatory conditions, as well as cancerous diseases. These studies pose methodological problems, partly because they use extracts rather than pure compounds and partly because they examine small numbers of patients. Although *Boswellia* resin seems to exert anti-inflammatory and anti-cancer effects in several clinical trials, these remain to be further corroborated and the underlying mechanisms are to be characterized.

Gupta and colleagues[97] examined the effects of *Boswellia serrata* resin (300 mg 3 times daily for 6 weeks) in patients with bronchial asthma. Seventy per cent of the patients showed improvement of the disease as shown by disappearance of physical symptoms and signs such as dyspnoea, rhonchi and number of attacks, as well as a decrease in eosinophilic count.

In a study with patients suffering from chronic colitis, *B. serrata* resin (300 mg 3 times daily for 6 weeks) was examined and compared with sulfasalazine (1 g 3 times daily for 6 weeks) which served as control.[98] The patients were then tested for stool properties and histopathology, as well as scanning electron microscopy, besides determination of haemoglobin, serum iron, calcium, phosphorus, proteins, total leucocytes and eosinophils. Out of 20 patients treated with *Boswellia* gum resin, 18 showed an improvement in one or more of the parameters. In the control group 6 out of 10 patients showed similar results. Out of 20 patients treated with *Boswellia* gum resin, 14 went into remission while in the case of sulfasalazine the remission ratio was 4 out of 10.

A *B. serrata* extract (5-Loxin) enriched with 30% AKBA reduced pain and significantly improved physical functioning, as well as pain and stiffness scores, and led to reduction of synovial MMP-3 levels in osteoarthritis patients.[99]

In another study,[100] 12 patients with brain tumours and progressive oedema were treated with *B. serrata* (H15) extract. All patients tolerated the extract well. There were no side effects and no worsening of clinical signs attributable to *Boswellia* extract. There was no tumour response to *Boswellia* extract in any patient. MRI showed a significant reduction of oedema in two of the seven patients with glioblastoma. The reduction in oedema was associated with clinical improvement. Oedema was also reduced in three of five patients with treatment-related leukoencephalopathy. All patients with leukoencephalopathy improved clinically for several months.[100]

In October 2002, *B. serrata* resin extract (orphan designation EU/3/02/117) was approved for sale by the European Commission, for the treatment of peritumoral oedema due to brain tumours. However this product was withdrawn from the Community Register of designated Orphan Medicinal Products on November 2006 upon request of the sponsor.

Adverse effects

When the effects of a *B. carterii* acetone extract on persistent hyperalgesia and oedema in rats with peripheral inflammation were examined, no noticeable adverse effects were observed in rats treated with 900 mg/kg per day for 7 days, but adverse effects in some rats were observed at 1800 mg/kg per day; in the acute toxicity study, the maximal single dose of 2500 mg/kg produced no adverse effects in the treated rats during the 14 days of observation.[101] A single case report of contact dermatitis was reported following the topical use of *B. serrata* resin in a cream made with natural plant extracts.[102] No other side effects from the topical application of *B. serrata* extract were found in this case study. Differentiated and undifferentiated keratinocytes (HaCaT and NCTC 2544) and foetal dermal fibroblasts were tested, using neutral red uptake and MTT, and DNA assays were used to compare the sensitivity of different human skin cells to *B. serrata* extract and to AKBA. These indicated that the gum resin and AKBA exert moderate to low toxicity to the skin, about similar to that of the reference compound SDS.[103] Kimmatkar and colleagues[104] found that *B. serrata* extract was well tolerated in human patients,

except for minor gastrointestinal adverse effects. No adverse effects were observed when 19 children and adolescents with intracranial tumours received *Boswellia* extract at a dose of 126 mg/kg per day for a median 9 months' application.[105] The extract was also well tolerated by all 12 patients with tumours and tumour-associated oedema in another study.[100]

Pharmacokinetic studies of *Boswellia* resin constituents

Studies in rats have presented data on the bioavailability of KBA and AKBA.[106,107] KBA and AKBA were bioavailable in female albino Wistar rats following oral administration.[106] Topical application of a methanolic extract of the gum resin of *B. serrata* on the backs of mice markedly inhibited a phorbol ester-induced increase in skin inflammation.[64] A more recent work reported that boswellic acids administered by topical application were also effective in inflammatory disorders.[108] Topical application of water-soluble AKBA-gamma-cyclodextrin on PC-3 tumours xenografted onto chick chorioallantoic membranes induced concentration-dependent inhibition of proliferation as well as apoptosis.[27] In nude mice carrying PC-3 tumours, systemic application of AKBA-γ-cyclodextrin inhibited tumour growth and triggered apoptosis in the absence of detectable systemic toxicity.[27]

Preliminary pharmacokinetic studies found only very low concentrations of KBA in human plasma after oral administration of *B. serrata* extract, ranging from 0.17 μM following a single dose administration of 786 mg,[109] to 2.7 μM subsequent to the intake of 333 mg.[110] A concentration of 0.1 μM AKBA was determined after a multiple-dose administration of 786 mg of *B. serrata* extract.[111]

Conclusions

The reputation of *Boswellia* resin as an immunomodulating agent has found support in numerous studies, some of them with crude extracts, others with pure compounds (Table 1). Boswellic acids exert diverse intracellular effects, which depend on the cell type and the chemical structure of the boswellic acid derivative. There is a considerable inconsistency between the results (particularly the IC50 values) determined in cellular and cell-free experimental settings for boswellic acids, and it seems that several different cellular mechanisms govern the imunomodulatory effects of boswellic acids.

In-vivo studies provide evidence for the anti-inflammatory activity of boswellic acids. In contrast to data from these studies, no measurable efficacy of *B. serrata* extracts was evident in a controlled trial of rheumatoid arthritis.[112] It should be noted, however, that although it was a multicentre study, it was done with a small number of patients (37).

The differences in the results of tests between the crude extract and the isolated pure compounds on 5-lipoxygenase led to an investigation of analogues of boswellic acids;[113] however, a better result than the inhibitory effect of AKBA has not yet been demonstrated. On the contrary, the tirucallic acids that were identified in an extract of *B. serrata* were found to enhance 5-lipoxygenase product formation. Thus, 3-oxotirucallic acid and 3-*O*-acetyl-tirucallic acid were found to be involved in the production of LTB4, which is considered the strongest mediator in leukotriene biosynthesis involved in some of the diseases mentioned above.[18] In some of the cell lines tested for the cytotoxic and pro-apoptotic effects of boswellic acids, the effect of the total extract was significantly more potent than pure AKBA.

These findings imply that *Boswellia* resin contains several active ingredients, boswellic acids being only some of them. Indeed, we found incensole acetate and its derivatives, which are significant components and biomarkers of *Boswellia* resin, to be the major constituents of the resin inhibiting NF-κB activation. Incensole acetate also provides potent neuroprotection, apparently via its anti-inflammatory effects on the brain.[21] We further found that incensole acetate exerts significant effects on the CNS.[22] These effects are presumably mediated via TRPV3 channels in the brain;[22] thus using incensole acetate as a powerful ligand, we were able to suggest for the first time a possible role for this channel in the CNS. As the TRPV3 channel is known to mediate sensations of warmth, it is plausible that incensole acetate and its derivatives cause a sensation of warmth, thus contributing to the feeling of exaltation in ceremonies involving burning of frankincense.

Several clinical trials with *Boswellia* extracts – many of them suffering from methodological flaws and relatively small numbers of patients – have been performed. The results of some of these studies are encouraging. However additional investigations are required to demonstrate the efficacy of extracts of *Boswellia* resin and draw conclusions regarding effectiveness and safety of *Boswellia* resin, and particularly of its constituents.

Boswellia resin has provided mankind with a potentially rich arsenal of drugs for the treatment of a variety of pathological conditions of inflammatory, carcinogenous, degenerative and mental nature. It is gratifying to realize that, after almost 40 years of research, the ancient traditions of thousands of years have found support using modern science, providing us with some novel drugs of potentially considerable importance. Moreover, following our recent study on the effects of incensole acetate on the CNS, it now seems that the pharmacological leads from *Boswellia* resin may offer insights into mammalian and human physiology, especially neurophysiology. While the incentive for research on *Boswellia* resin is obviously encouraged by the great cultural and religious importance of this resin, the pharmacological data stand very much by themselves.

Given the importance of *Boswellia* resin in religious, medical and cultural traditions, as well as the therapeutic potential of compounds isolated from the resin, the scientific data available so far seem inadequate. Despite its common use as an anti-inflammatory remedy, it is only recently that the resin has been screened for its anti-inflammatory components.[19] The information available on the anti-cancer effects of the resin is still poor, with only a few in-vivo studies. Our study on the neuroprotective effects of incensole acetate suggests that this compound and its derivatives can be utilized in several neurodegenerative diseases, and related pathologies.

It is only now that we realize that the widespread cultural and religious use of the resin is probably due to the presence

Table 1 Key papers on the pharmacology of *Boswellia* and their scientific findings

Reference	Key papers and their scientific findings
Kar & Menon[94]	Suggests a sedative activity of the resin.
Sharma *et al.*[81]	Boswellic acids significantly reduced inflammation markers and the population of leucocytes in bovine serum albumin-induced arthritis in rabbits.
Safayhi *et al.*[37,38]	Boswellic acids inhibit the formation of LTB4 in rat peritoneal neutrophils, probably by direct interference via a pentacyclic triterpene selective binding site.
Sailer *et al.*[39]	Functional groups (i.e. the 11-keto and C4-carboxylic moiety) were found to be essential for 5-lipoxygenase inhibitory activity.
Hoernlein *et al.*[53]	Boswellic acid derivatives induced apoptosis in human leukaemia cell lines. AKBA inhibited topoisomerase I from calf thymus.
Boden *et al.*[18]	3-Oxo-tirucallic acid, isolated from *B. serrata* resin, enhanced 5-lipoxygenase product formation in polymorphonuclear cells. In cell-free 5-lipoxygenase assays, 3-oxo-tirucallic acid only had an inhibitory action.
Krieglstein *et al.*[85]	AKBA significantly attenuated indometacin-induced ileitis in rats.
Büchele *et al.*[111]	Identification of pentacyclic triterpenes in human plasma of patients treated with *Boswellia* resins extracts.
Altmann *et al.*[43]	Boswellic acids induced Ca^{2+} mobilization and MAPK activation in human leucocytes.
Roy *et al.*[23]	Genetic screening of the anti-inflammatory effects of *Boswellia* resin.
Syrovets *et al.*[27,62]	Linked the anti-inflammatory and pro-apoptotic effects of AβBA and AKBA to attenuation of the activity of IKK and NF-κB activation.
Takada *et al.*[68]	Anti-apoptotic genes (e.g. Bcl-2, Bcl-xL, XIAP, survivin) were down-regulated by AKBA. A direct inhibition of IKK activity was excluded.
Poeckel *et al.*[42]	AKBA suppressed platelet-type 12-lipoxygenase product formation in intact human platelets and in platelet cytosolic fractions.
Khajuria *et al.*[79]	A biopolymeric fraction from *B. serrata* was shown to be a potent enhancer of antigen-specific immune responses with adjuvant activity that was superior to that of the conventional adjuvant alum.
Moussaieff *et al.*[19]	Identification of incensole acetate and incensole as the major NF-κB inhibitors and novel anti-inflammatory agents from *B. carterii* resin. Incensole acetate inhibited TAK/TAB-mediated IKK activation loop phosphorylation, resulting in the inhibition of cytokine and LPS-mediated NF-κB activation.
Singh *et al.*[70]	AKBA inhibited Matrigel+βFGF-induced angiogenesis.
Lu *et al.*[60]	The apoptotic effects of AKBA on human prostate cancer cells were correlated with the activation of caspase-3 and caspase-8 as well as with poly(ADP)ribose polymerase cleavage.
Moussaieff *et al.*[21]	Incensole acetate exerted a potent neuroprotective effect on mice following head trauma. This effect was concomitant with a significant anti-inflammatory effect of the compound on mice brains.
Moussaieff *et al.*[22]	Identification of incensole acetate as a novel psycho-active constituent from *B. carterii* resin with anti-depressive and anxiolytic-like effects. These effects are suggested to be mediated via TRPV3 channels in the brain.

References were sorted by year of publication, and then alphabetically by first author's name. AβBA, acetyl-β-boswellic acid; AKBA, 11-keto-β-boswellic acid; IKK, IKB Kinase; MAPK, mitogen-activated protein kinase.

of psycho-active compounds in the resin, namely incensole acetate and its derivatives.[22] Our study on the psycho-activity of incensole acetate also suggests that compounds from *Boswellia* resin may be used not only as leads for novel pharmacological therapies, but also as ligands for novel pharmacological targets to be found especially in the CNS.

We are confident that research on *Boswellia* resin and its active ingredients will gain more impact in the years to come.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Vollesen K. In: Hedberg I, Eduards S. (eds) *Flora of Ethiopia*. Ethiopia: Addis Ababa and Asmara, 1989: 442–446.
2. Michie CA, Cooper E. Frankincense and myrrh as remedies in children. *J R Soc Med* 1991; 84: 602–605.
3. Marshall S. Frankincense: festive pharmacognosy. *Pharm J* 2003; 271: 862–864.
4. Gunther RT. *The Greek Herbal of Dioscorides.* New York: Hafner, 1959.
5. Shachter J, Epstein I. (eds). *The Babylonian Talmud.* New York: Seder Nezikin, Sanhedrin tractate, The Suncino Press, 1935.
6. Koskenniemi E *et al*. Wine mixed with myrrh (Mark 15.23) and Crurifragium (John 19.31-32): two details of the Passion Narratives. *J Study New Testament* 2005; 27: 379–391.
7. Abdul Hameed H. ed. *Avicenna's Tract on Cardiac Drugs and Essays on Arab Cardiotherapy.* New Delhi: Hamdard Foundation Press, 1983.
8. *Encyclopaedia Britannica,* 15th edn. Chicago: Micropaedia, University of Chicago, 1975.
9. Uphof JC. *Dictionary of Economic Plants.* 2nd edn. Stuttgart: Medpharm GmbH Scientific Publishers, 1968.

10. Getahon A. *Some Common Medicinal and Poisonous Plants Used in Ethiopian Folkmedicine,* Mimeographed. Addis Ababa: Addis Ababa University, 1976.
11. Frawley D, Lad V. *The Yoga of Herbs: an Ayurvedic Guide to Herbal Medicine.* Delhi: Motilal Banarsidass Publications, 1997.
12. Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med* 2006; 12: 1100–1116.
13. Hamm S *et al*. A chemical investigation by headspace SPME and GC-MS of volatile and semi-volatile terpenes in various olibanum samples. *Phytochemistry* 2005; 66: 1499–1514.
14. Safayhi H *et al*. Concentration-dependent potentiating and inhibitory effects of Boswellia extracts on 5-lipoxygenase product formation in stimulated PMNL. *Planta Med* 2000; 66: 110–113.
15. Poeckel D, Werz O *et al*. Boswellic acids: biological actions and molecular targets. *Curr Med Chem* 2006; 13: 3359–3369.
16. Winterstein A, Stein G. Untersuchungen in der Saponinreihe Zur Kenntnis der Mono-oxy-triterpensäuren. *Hoppe-Seyler's Z Physiol Chem* 1932; 208: 9–25.
17. Büchele B *et al*. Characterization of 3alpha-acetyl-11-keto-alpha-boswellic acid, a pentacyclic triterpenoid inducing apoptosis *in vitro* and *in vivo*. *Planta Med* 2006; 72: 1285–1289.
18. Boden SE *et al*. Stimulation of leukotriene synthesis in intact polymorphonuclear cells by the 5-lipoxygenase inhibitor 3-oxo-tirucallic acid. *Mol Pharmacol* 2001; 60: 267–273.
19. Moussaieff A *et al*. Incensole acetate, a novel anti-inflammatory compound isolated from Boswellia resin, inhibits nuclear factor-kappa B activation. *Mol Pharmacol* 2007; 72: 1657–1664.
20. Corsano S, Nicoletti R. The structure of incensole. *Tetrahedron* 1967; 23: 1977–1984.
21. Moussaieff A *et al*. Incensole acetate: a novel neuroprotective agent isolated from Boswellia carterii. *J Cereb Blood Flow Metab* 2008; 28: 1341–1352.
22. Moussaieff A *et al*. Incensole acetate, an incense component, elicits psychoactivity by activating TRPV3 channels in the brain. *FASEB J* 2008; 22: 3024–3034.
23. Roy S *et al*. Human genome screen to identify the genetic basis of the anti-inflammatory effects of Boswellia in microvascular endothelial cells. *DNA Cell Biol* 2005; 24: 244–255.
24. Karin M. Inflammation-activated protein kinases as targets for drug development. *Proc Am Thorac Soc* 2005; 2: 386–390.
25. Perkins ND *et al*. Integrating cell-signalling pathways with NF-kappaB and IKK function. *Nat Rev Mol Cell Biol* 2007; 8: 49–62.
26. Pikarsky E, Ben-Neriah Y. NF-kappaB inhibition: a double-edged sword in cancer? *Eur J Cancer* 2006; 42: 779–784.
27. Syrovets T *et al*. Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-alpha induction in monocytes by direct interaction with IkappaB kinases. *J Immunol* 2005; 174: 498–506.
28. Wymann MP, Schneiter R. Lipid signalling in disease. *Nat Rev Mol Cell Biol* 2008; 9: 162–176.
29. Evans JF *et al*. What's all the FLAP about?: 5-lipoxygenase-activating protein inhibitors for inflammatory diseases. *Trends Pharmacol Sci* 2008; 29: 72–78.
30. Garcia C *et al*. Leukotriene B4 stimulates osteoclastic bone resorption both *in vitro* and *in vivo*. *J Bone Miner Res* 1996; 11: 1619–1627.
31. Sveinbjörnsson B *et al*. Expression of enzymes and receptors of the leukotriene pathway in human neuroblastoma promotes tumor survival and provides a target for therapy. *FASEB J* 2008; 22: 3525–3536.
32. Avis I *et al*. Inhibitors of the arachidonic acid pathway and peroxisome proliferator-activated receptor ligands have super-additive effects on lung cancer growth inhibition. *Cancer Res* 2005; 65: 4181–4190.
33. Montuschi P. Leukotrienes, antileukotrienes and asthma. *Mini Rev Med Chem* 2008; 8: 647–656.
34. Bäck M *et al*. Leukotriene B4 signaling through NF-kappaB-dependent BLT1 receptors on vascular smooth muscle cells in atherosclerosis and intimal hyperplasia. *Proc Natl Acad Sci USA* 2005; 102: 17501–17506.
35. Bevan S *et al*. Genetic variation in members of the leukotriene biosynthesis pathway confer an increased risk of ischemic stroke: a replication study in two independent populations. *Stroke* 2008; 39: 1109–1114.
36. Ammon HP *et al*. Inhibition of leukotriene B4 formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of Boswellia serrata. *Planta Med* 1991; 57: 203–207.
37. Safayhi H *et al*. Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. *J Pharmacol Exp Ther* 1992; 261: 1143–1146.
38. Safayhi H *et al*. Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-beta-boswellic acid. *Mol Pharmacol* 1995; 47: 1212–1216.
39. Sailer ER *et al*. Acetyl-11-keto-beta-boswellic acid (AKBA): structure requirements for binding and 5-lipoxygenase inhibitory activity. *Br J Pharmacol* 1996; 117: 615–618.
40. Werz O *et al*. Nonredox 5-lipoxygenase inhibitors require glutathione peroxidase for efficient inhibition of 5-lipoxygenase activity. *Mol Pharmacol* 1998; 54: 445–451.
41. Sailer ER *et al*. Characterization of an acetyl-11-keto-beta-boswellic acid and arachidonate-binding regulatory site of 5-lipoxygenase using photoaffinity labeling. *Eur J Biochem* 1998; 256: 364–368.
42. Poeckel D *et al*. Boswellic acids stimulate arachidonic acid release and 12-lipoxygenase activity in human platelets independent of Ca2+ and differentially interact with platelet-type 12-lipoxygenase. *Mol Pharmacol* 2006; 70: 1071–1078.
43. Altmann A *et al*. Coupling of boswellic acid-induced Ca2+ mobilisation and MAPK activation to lipid metabolism and peroxide formation in human leucocytes. *Br J Pharmacol* 2004; 141: 223–232.
44. Siemoneit U *et al*. Identification and functional analysis of cyclooxygenase-1 as a molecular target of boswellic acids. *Biochem Pharmacol* 2008; 75: 503–513.
45. Poeckel D *et al*. 3-O-acetyl-11-keto-boswellic acid decreases basal intracellular Ca2+ levels and inhibits agonist-induced Ca2+ mobilization and mitogen-activated protein kinase activation in human monocytic cells. *J Pharmacol Exp Ther* 2006; 316: 224–232.
46. Jeffrey KL *et al*. Targeting dual-specificity phosphatases: manipulating MAP kinase signalling and immune responses. *Nat Rev Drug Discov* 2007; 6: 391–403.
47. Altmann A *et al*. Boswellic acids activate p42(MAPK) and p38 MAPK and stimulate Ca(2+) mobilization. *Biochem Biophys Res Commun* 2002; 290: 185–190.
48. Poeckel D *et al*. Induction of central signalling pathways and select functional effects in human platelets by beta-boswellic acid. *Br J Pharmacol* 2005; 146: 514–524.
49. Safayhi H *et al*. Inhibition by boswellic acids of human leukocyte elastase. *J Pharmacol Exp Ther* 1997; 281: 460–463.
50. Frank A, Unger M. Analysis of frankincense from various Boswellia species with inhibitory activity on human drug metabolising cytochrome P450 enzymes using liquid chromatography mass spectrometry after automated on-line extraction. *J Chromatogr A* 2006; 1112: 255–262.
51. Weber CC *et al*. Modulation of Pgp function by boswellic acids. *Planta Med* 2006; 72: 507–513.
52. Glaser T *et al*. Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity. *Br J Cancer* 1999; 80: 756–765.

53. Hoernlein RF *et al*. Acetyl-11-keto-beta-boswellic acid induces apoptosis in HL-60 and CCRF-CEM cells and inhibits topoisomerase I. *J Pharmacol Exp Ther* 1999; 288: 613–619.
54. Hostanska K *et al*. Cytostatic and apoptosis-inducing activity of boswellic acids toward malignant cell lines *in vitro*. *Anticancer Res* 2002; 22: 2853–2862.
55. Xia L *et al*. Boswellic acid acetate induces apoptosis through caspase-mediated pathways in myeloid leukemia cells. *Mol Cancer Ther* 2005; 4: 381–388.
56. Liu JJ *et al*. Keto- and acetyl-keto-boswellic acids inhibit proliferation and induce apoptosis in Hep G2 cells via a caspase-8 dependent pathway. *Int J Mol Med* 2002; 10: 501–505.
57. Liu JJ *et al*. Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis* 2002; 23: 2087–2093.
58. Liu JJ *et al*. Acetyl-keto-beta-boswellic acid inhibits cellular proliferation through a p21-dependent pathway in colon cancer cells. *Br J Pharmacol* 2006; 148: 1099–1107.
59. Yuan HQ *et al*. Inhibitory effect of acetyl-11-keto-beta-boswellic acid on androgen receptor by interference of Sp1 binding activity in prostate cancer cells. *Biochem Pharmacol* 2008; 75: 2112–2121.
60. Lu M *et al*. Acetyl-keto-beta-boswellic acid induces apoptosis through a death receptor 5-mediated pathway in prostate cancer cells. *Cancer Res* 2008; 68: 1180–1186.
61. Zhao W *et al*. Boswellic acid acetate induces differentiation and apoptosis in highly metastatic melanoma and fibrosarcoma cells. *Cancer Detect Prev* 2003; 27: 67–75.
62. Syrovets T *et al*. Inhibition of IkappaB kinase activity by acetyl-boswellic acids promotes apoptosis in androgen-independent PC-3 prostate cancer cells *in vitro* and *in vivo*. *J Biol Chem* 2005; 280: 6170–6180.
63. Shao Y *et al*. Inhibitory activity of boswellic acids from Boswellia serrata against human leukemia HL-60 cells in culture. *Planta Med* 1998; 64: 328–331.
64. Huang MT *et al*. Anti-tumor and anti-carcinogenic activities of triterpenoid, beta-boswellic acid. *Biofactors* 2000; 13: 225–230.
65. Jing Y *et al*. Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leuk Res* 1999; 23: 43–50.
66. Syrovets T *et al*. Acetyl-boswellic acids are novel catalytic inhibitors of human topoisomerases I and IIalpha. *Mol Pharmacol* 2000; 58: 71–81.
67. Kiela PR *et al*. Effects of Boswellia serrata in mouse models of chemically induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G798–G808.
68. Takada Y *et al*. Acetyl-11-keto-beta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kappa B and NF-kappa B-regulated gene expression. *J Immunol* 2006; 176: 3127–3140.
69. Shah B *et al*. Cytotoxic and apoptotic activities of novel amino analogues of boswellic acids. *Bioorg Med Chem Lett* 2007; 17: 6411–6416.
70. Singh SK *et al*. Effect of acetyl 11-keto beta-boswellic acid on metastatic growth factor responsible for angiogenesis. *Vascul Pharmacol* 2007; 46: 333–337.
71. Bhushan S *et al*. A triterpenediol from Boswellia serrata induces apoptosis through both the intrinsic and extrinsic apoptotic pathways in human leukemia HL-60 cells. *Apoptosis* 2007; 12: 1911–1926.
72. Christensen AP, Corey DP. TRP channels in mechanosensation: direct or indirect activation? *Nat Rev Neurosci* 2007; 8: 510–521.
73. Smith GD *et al*. TRPV3 is a temperature-sensitive vanilloid receptor-like protein. *Nature* 2002; 418: 186–190.
74. Dhaka A *et al*. TRP ion channels and temperature sensation. *Annu Rev Neurosci* 2006; 29: 135–161.
75. Minke B. TRP channels and Ca2+ signaling. *Cell Calcium* 2006; 40: 261–275.
76. Khanna D *et al*. Natural products as a gold mine for arthritis treatment. *Curr Opin Pharmacol* 2007; 7: 344–351.
77. Singh GB, Atal CK. Pharmacology of an extract of salai guggal ex-Boswellia serrata, a new non-steroidal anti-inflammatory agent. *Agents Actions* 1986; 18: 407–412.
78. Singh S *et al*. Boswellic acids and glucosamine show synergistic effect in preclinical anti-inflammatory study in rats. *Bioorg Med Chem Lett* 2007; 17: 3706–3711.
79. Khajuria A *et al*. A new vaccine adjuvant (BOS 2000) a potent enhancer mixed Th1/Th2 immune responses in mice immunized with HBsAg. *Vaccine* 2007; 25: 4586–4594.
80. Khajuria A *et al*. Immunomodulatory activity of biopolymeric fraction BOS 2000 from Boswellia serrata. *Phytother Res* 2008; 22: 340–348.
81. Sharma ML *et al*. Anti-arthritic activity of boswellic acids in bovine serum albumin (BSA)-induced arthritis. *Int J Immunopharmacol* 1989; 11: 647–652.
82. Reddy GK *et al*. Urinary excretion of connective tissue metabolites under the influence of a new non-steroidal anti-inflammatory agent in adjuvant induced arthritis. *Agents Actions* 1987; 22: 99–105.
83. Reddy GK *et al*. Studies on the metabolism of glycosaminoglycans under the influence of new herbal anti-inflammatory agents. *Biochem Pharmacol* 1989; 38: 3527–3534.
84. Fan AY *et al*. Effects of an acetone extract of Boswellia carterii Birdw. (Burseraceae) gum resin on adjuvant-induced arthritis in lewis rats. *J Ethnopharmacol* 2005; 101: 104–109.
85. Krieglstein CF *et al*. Acetyl-11-keto-beta-boswellic acid, a constituent of a herbal medicine from Boswellia serrata resin, attenuates experimental ileitis. *Int J Colorectal Dis* 2001; 16: 88–95.
86. Anthoni C *et al*. Mechanisms underlying the anti-inflammatory actions of boswellic acid derivatives in experimental colitis. *Am J Physiol Gastrointest Liver Physiol* 2006; 290: G1131–G1137.
87. Borrelli F *et al*. Effect of Boswellia serrata on intestinal motility in rodents: inhibition of diarrhoea without constipation. *Br J Pharmacol* 2006; 148: 553–560.
88. Cuaz-Pérolin C *et al*. Antiinflammatory and antiatherogenic effects of the NF-kappaB inhibitor acetyl-11-keto-beta-boswellic acid in LPS-challenged ApoE-/- mice. *Arterioscler Thromb Vasc Biol* 2008; 28: 272–277.
89. Winking M *et al*. Boswellic acids inhibit glioma growth: a new treatment option? *Neurooncology* 2000; 46: 97–103.
90. Moussaieff A *et al*. The Jerusalem Balsam: from the Franciscan monastery in the old city of Jerusalem to Martindale 33. *J Ethnopharmacol* 2005; 101: 16–26.
91. Camarda L *et al*. Chemical composition and antimicrobial activity of some oleogum resin essential oils from Boswellia spp. (Burseraceae). *Ann Chim* 2007; 97: 837–844.
92. Schillaci D *et al*. *In vitro* anti-biofilm activity of Boswellia spp. oleogum resin essential oils. *Lett Appl Microbiol* 2008; 47: 433–438.
93. Schuhmann MU *et al*. Effect of Boswellia carterii on brain edema following contusion injury. *J Cereb Blood Flow Metab* 2005; 25: 261.
94. Kar A, Menon MK. Analgesic effect of the gum resin of Boswellia serata Roxb. *Life Sci* 1969; 8: 1023–1028.
95. Menon MK, Kar A. Analgesic and psychopharmacological effects of the gum resin of Boswellia serrata. *Planta Med* 1971; 19: 333–341.

96. Ernst E *et al*. Frankincense: systematic review. *Br Med J* 2008; 337: a2813.
97. Gupta I *et al*. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res* 1998; 3: 511–514.
98. Gupta I *et al*. Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001; 67: 391–395.
99. Sengupta K *et al*. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. *Arthritis Res Ther* 2008; 10: R85.
100. Streffer JR *et al*. Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. *Neurology* 2001; 56: 1219–1221.
101. Fan AY *et al*. Effects of an acetone extract of Boswellia carterii Birdw. (Burseraceae) gum resin on rats with persistent inflammation. *J Altern Complement Med* 2005; 11: 323–331.
102. Acebo E *et al*. Allergic contact dermatitis from Boswellia serrata extract in a naturopathic cream. *Contact Dermatitis* 2004; 51: 91–92.
103. Burlando B *et al*. Comparison of the irritation potentials of Boswellia serrata gum resin and of acetyl-11-keto-beta-boswellic acid by *in vitro* cytotoxicity tests on human skin-derived cell lines. *Toxicol Lett* 2008; 177: 144–149.
104. Kimmatkar N *et al*. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee: a randomized double blind placebo controlled trial. *Phytomedicine* 2003; 10: 3–7.
105. Janssen G *et al*. Boswellic acids in the palliative therapy of children with progressive or relapsed brain tumors. *Klin Padiatr* 2000; 212: 189–195.
106. Reising K *et al*. Determination of boswellic acids in brain and plasma by high-performance liquid chromatography/tandem mass spectrometry. *Anal Chem* 2005; 77: 6640–6645.
107. Krüger P *et al*. Metabolism of boswellic acids *in vitro* and *in vivo*. *Drug Metab Dispos* 2008; 36: 1135–1142.
108. Singh S *et al*. Boswellic acids: a leukotriene inhibitor also effective through topical application in inflammatory disorders. *Phytomedicine* 2008; 15: 400–407.
109. Sterk V *et al*. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. *Planta Med* 2004; 70: 1155–1160.
110. Sharma S *et al*. Pharmacokinetic study of 11-keto beta-boswellic acid. *Phytomedicine* 2004; 11: 255–260.
111. Büchele B, Simmet TJ. Analysis of 12 different pentacyclic triterpenic acids from frankincense in human plasma by high-performance liquid chromatography and photodiode array detection. *Chromatogr B Analyt Technol Biomed Life Sci* 2003; 795: 355–362.
112. Sander O *et al*. [Is H15 (resin extract of Boswellia serrata, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study]. *Z Rheumatol* 1998; 57: 11–16.
113. Schweizer S *et al*. Workup-dependent formation of 5-lipoxygenase inhibitory boswellic acid analogues. *J Nat Prod* 2000; 63: 1058–1061.