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The Iκb-NF-κb-Complex As A Common Target of Boswellic Extracts and Boswellic Acids in Chronic Inflammatory Diseases, Diabetes Mellitus and Cancer

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Abstract

Boswellic extracts and some of its ingredients, especially boswellic acids, have been shown to be effective in inflammatory diseases, diabetes mellitus and cancer. Though clinical studies are rare in case of diabetes mellitus and cancer, preclinical studies suggest, that boswellic extracts and some of its active constituents, use a variety of targets and mechanisms of action, that could attack these disorders. One common target is NF-κB.

In inflammatory diseases these targets are the immune competent cells [suppression of proinflammatory cytokines via inhibition of NF-κB activation], the complement system [inhibition of C3-convertase] the arachidonic acid cascade [especially inhibition of 5-LO] and last not least antioxidative effects and inhibition of proteolytic enzymes.

In case of diabetes mellitus, secundar targets are insulitis and insulin resistance. Both cases are related to the suppression of proinflammatory cytokines. As far as insulitis is concerned, boswellic extracts and boswellic acids [AKBA, KBA] prevent infiltration of immune cells into pancreatic islets, causing inflammation and finally ß-cell death and insulin deficiency. Insulin resistance which is closely related to overweight, inflammation of visceral adipose tissue here, infiltration of immune cells is associated with release of proinflammatory cytokines into blood where they produce insulin resistance in peripheral tissues.

As far as the effects of boswellic extracts and active constituents in cancer are concerned, they are inhibiting proliferation/growth, apoptosis, angiogenesis and migration/metastasis. Here, inhibition of signal pathways [ATM/P53; Aurora B/TOP2A; p21/FOX M2/cyclin B1; P13 K-AKT; STAT3; Erk ½; Wnt/ß-catenin], growth factors [EGRF; VEGF; BFGF; HGF], receptors [AR; DR5], enzymes [topoisomerases; caspases; Cde 2; Cde 25; Pin 1] and proteins [BCL-2; cyclin family] have been reported. In some of these targets, where nuclear factor kappa B [NF-κB] has emerged to be a major regulator, inhibition of its seems to be a important mechanism of this anticancer activity.

Conclusion

Inhibition of the phosphorylation of the IKB-NF-κB complex by IKKB, appears to be a major common mechanism of boswellic extracts and boswellic acids in the anti-inflammatory antidiabetic and anticancer activity.

From the preclinical data discussed in this review boswellic extracts and boswellic acids seem to be a promising option for the treatment of the forementioned diseases. However, well designed clinical studies must follow.

Key words: Chronic inflammations; Diabetes mellitus; Cancer; Frankincense; Boswellic extracts; Boswellic acids; Targets of actions; NF-κB common target.

Introduction

Chronic inflammations, diabetes mellitus and cancer are diseases where overexpression of cytokines from immune competent cells and tumor cells play an essential role in the pathophysiology of these disorders [3, 4]. In clinical studies boswellic extracts have been shown to be effective in bronchial asthma [24], rheumatoid arthritis [16], ulcerative colitis [23] and Crohn's disease [20]. Moreover, there is one study reporting improvement of blood glucose and HbA1c in type 2 diabetes [5] and another describing reduction of cerebral edema in patients with glioblastoma [7].

The resin ob Boswellia species has been used for thousands of years in different cultures: in India called salai guggal, in western countries called olibanum and/or frankincense. Remedies containing preparations from frankincense were prescribed by famous physicians including Hippocrates, Celsus, Galenus and others for treatment of tumours, edemas and inflammatory diseases such as diarrhoea and diseases of the respiratory tract [43]. Olibanum was also known as a remedy in Europe from ancient times till the beginning of the 20th century. Then it

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disappeared from the list of medical prescriptions, since scientific evidence for any therapeutic efficiacy was missing.

This changed when Singh et al [66] reported anti-inflammatory activity of an extract from the gum resin of Boswellia serrata in animal experiments and when inhibiton of leukotriene synthesis was shown 1991 by Ammon et al [2]. In the meantime many studies dealing with pharmacological effects, pharmacological active principles,

Mechanisms of actions, molecular targets and therapeutical efficacy of boswellic extracts [BE] and boswellic acids [BA] have been published. In these respect inflammatory diseases, diabetes mellitus and cancer were of special interest.

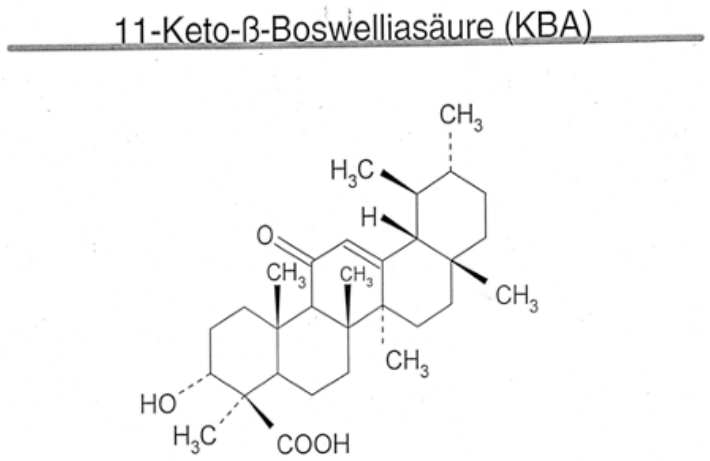

Figure 1: Chemical structure of 11-Keto-ß-boswellic acid

This review summarizes present knowledge about actions, mechanisms of actions and molecular target of boswellic extracts [BEs] and boswellic acids [BAs] in chronic inflammatory diseases, diabetes mellitus and cancer with special respect whether or not BEs and BAs share a common molecular target in these disorders, i.e. the dissociation of NFκB from its complex with IκB.

Chronic Inflammatory Diseases

The Immune System

Chronic inflammatory diseases are closely related to disorders of the immune system, where Th1-lymphocytes, monocytes and macrophages express proinflammatory cytokines including IL-1, IL-2, IL-6, TNF-α and IFN-γ, which are related to the chronicity of inflammation of different tissues.

Effects of Boswellic Extracts

Chervier et al. [10] studied the effect of an extract from Boswellia carterii on the production of TH-1 and TH-2 cytokines by murine splenocytes. The use of an extract with sesame oil - as a solvent - resulted in a concentration dependent inhibition of IL-2 and IFN-γ and a concentration dependent potentiation of IL-4 and IL-10, which are anti-inflammatory cytokines. Gayathri et al. [19] observed that a crude methanolic extract from Boswellia serrata [BS] inhibited TNF-α, IL-1 B and IL-6 in cultured Peripheral Blood Mononuclear Cells [PBMC]. In an arthritis model of rats doses of 100 and 200 mg/kg once daily for 21 days resulted in significantly reduced levels of inflammatory mediators [IL-1ß, IL-6, TNF-α, IFN-γ and PGE2] [73]. Observations on Th1/Th2 cytokines also revealed marked down regulation of IFN-γ and IL-12. Employing an acetone extract from Boswellia carterii Fan et al. [17] in an adjuvant arthritis model in lewis rats 900 mg/kg for 10 consecutive days, observed significant decrease of arthritic scores. This was associated with suppression of local tissue IL-1B and TNF-α.

Effects of Boswellic Acids

Inhibition of TNF-α and its signaling has been recognized as a highly successful strategy for the treatment of chronic inflammatory diseases such as rheumatoid arthritis. Previously it has been shown by Syrovets et al [69]. that acetyl-α-BA and AKBA in LPS-stimulated human monocytes inhibited the generation of TNF-α in concentrations between 1 and 10 μM. AKBA was found to be the most active compound. The effect was mediated by an indirect inhibition of NFκB and subsequent downregulation of TNF-α expression. Searching for compounds that are equally efficient as glucocorticoids but with less side affects Morsy et al.

[46] compared boswellic acid with the classical glucocorticoid fluticasone. Interestingly boswellic acid showed docking results with glucocorticoid receptor compatible to fluticasone as well as similar anti-inflammatory effects in cotton pellet – induced granuloma in rats by decreasing IL-6 and TNF-α.

These data indicate that BEs and BAs are capable of carrying out anti-inflammatory activities at sites where chronic inflammation is present by switching off the action of proinflammatory cytokines through inhibition of their gene expression.

Other targets of Boswellic extracts and Boswellic acids

Beside the inhibitory action of boswellic extracts and boswellic acids on inflammatory factors of the immune system both also inhibit other factors which are direct related to the inflammatory process.

Arachidonic Acid Cascade

Inflammation in characterized by five symptoms, i.e. pain, rednes, heat, edema and disturbed function of tissues. These symptoms are caused by metabolites of the arachidonic acid cascade i.e. prostaglandines and leukotrienes. Prostaglandines sensitize nociceptors and induce heat by increasing blood flow, whereas leukotrienes are mainly responsible for the development of edemas by increasing permeability of capillaries, sensitazion of nociceptors

and chemotaxis of white blood cells. Arachidonic acid cascade is activated via the membrane enzyme phospholipase A2, [PLA2] which is the initial step following injuries, infections, toxins ect. to start production of prostaglandines and leukotrienes by the action cyclooxigenases [COX] and 5-lipoxigenase [5-LO].

COX-Products

Effects of Boswellic Extracts

After in vitro stimulation human platelets with Ca-ionophor A 23187, a boswellia extract reduced 6-keto-PKF-1α synthesis, which is a product of COX-1, up to 50 % at a concentration of 100 µg/ml [2]. In another in vitro model an extract from resin of Boswellia frereana suppressed cytokine IL-1A-induced PGE2-synthesis and COX-2 [6]. Moreover, microsomal prostaglandin E synthase 1 is inhibited by a methanol extract of Boswellia serrata [55]. In this context it should be mentioned that so far extracts of boswellic resins showed no immediate analgetic effects if compared to aspirin a well known COX inhibitor.

Effects of Boswellic Acids

As far as boswellic acids are concerned some of this group interfered with the COX-system. In an assay that used human platelets acetyl-11-keto-ß-boswellic acid [AKBA] produced 50 % inhibition of 12-hyroxyheptadecatrienoic acid [12-HHT] formation, a COX-product at a concentration of 10 µM. Acetyl-boswellic acid [ABA] did not show such an effect. Inhibition of COX products by AKBA was also observed by Siemoneit et al [64, 65], using the human platelet model. In this study BAs, preferably AKBA, inhibited COX-1 product formation with an IC50 ~ 6µM.

5-LO-Products

BEs and BAs not only affect formation of COX products, but also to a much larger extend, inhibit leukotriene B4 [LTB4] synthesis [2]. This observation indicating that certain BAs are responsible for this effect, received large attention by the scientific community.

Effects of Boswellic Extracts

Using polymorph mononuclear neutrophils [PMN] Ammon et al. [2] studied the effect of a boswellia extract on synthesis of LTB4 after stimulation with the calcium ionophore A 231876. PMNs contain 5-LO but no COX. It was observed that the extract in a concentration-dependent manner inhibited production of LTB4 and 5-hydroxyeicosatetraenoic acid [5-HETE] which is a metabolite of the 5-LO-cascade. 50 % inhibition accured at a concentration of 30 µg/ml, which is by far less than its effect on prostaglandin synthesis

Effects of Boswellic Acids

Concerning the actions of BAs, Safayhi et al. [56] reported BAs to be specific, non-redox inhibitors of 5-LO. In this study, isomers of α- and ß BAs and their acetyl derivates were isolated from the oleogum resin of Boswellia serrata [BS]. It was shown that BAs partly decreased the formation of LTB4 in calcium ionophore-stimulated PMN in a concentration-dependent manner. AKBA was most effective with an IC50 value of 1.5 µM. Fisher et al. [18], showed that inhibition of 5-LO-product formation by non redox-type inhibitors depends on the activation pathway of 5-LO. In this connection the authors suggest enzyme activation involving 5-LO phosphorylation events specifically and strongly alters the susceptibility of 5-LO toward non redox-type inhibitors in intact cells. AKBA and some other BAs are non-redox-type inhibitors of 5-LO. In addition to BAs other triterpene acids from frankincense inhibit 5-LO product formation and cathepsin G [34].

The Complement System

The complement system is part of the non-specific humoral defence. It is an important link between immune- and inflammatory reactions.

Effects of Boswellic Acids

As early as 1987, inhibition of the guinea pig complement system by α-BA and ß-BA in concentration range between 5 and 100 µM was reported by Wagner et a [75]. Anticomplementary activities of a mixture of BAs were also described by Kapil and Moza [31]. They observed that BAs inhibited the in vitro

immunohemolysis, which was found to be due to inhibition of C3 convertase of the classical complement pathway. The threshold concentration for inhibition was 100 µg per 0.1 ml diluted buffer added to the assay. Thus, at least in vitro BAs can suppress the conversion of C3 into C3a and C3b and therefore its proinflammatory actions of this system.

Proteolytic Enzymes

Another factor in the inflammatory process is the release of proteolytic enzymes from PMN which are involved in the destruction of cartilage.

Effects of Boswellic Extracts

Tausch et al. [71] observed that BAs suppressed the proteolytic activity of cathepsin G in a competitive reversible manner with an estimated IC50 value of 0.6 µM. The same effect was observed in humans after oral administration of a BE.

Effects of Pentacyclic Triterpenes

Human leucocyte elastase [HLE] is a serine protease produced and released by PMN. Using pure HLE, Safayhi et al. [23] screened several pentacyclic triterpenes for inhibitory actions on HLE. In this study AKBA decreased the activity of HLE with an IC50 value of roughly 15 µM. Among the pentacyclic triterpenes, tested in concentrations up to 20 µM, substantial inhibition by ß-BA, amyrin and ursolic acid was observed.

Oxygen Radicals

Effects of Boswellic Extracts and Boswellic Acids

Oxygen radicals who are produced in PMN through the action of leukotrienes are also involved in cartilage destruction in rheumatoid arthritis. Heil et al. [26] studied the effects of BEs and AKBA on SOD-quenchable O2 – radical formation in intact PMNs and in a cell-free system. AKBA [IC50 ~ 10 µM] and extracts [IC50 ~ 13 µg/ml] consistenly inhibited phorbol-12-myristate-13-acetate [PMA]-stimulated NADPH oxidase activity in rat peritoneal PMNs and reduced n-formyl-methionyl-leucyl-phenylazanin [f-MLP] and PMA-induced oxidative burst in stimulator-sensitive human blood PMN preparations. In a model of experimental colitis, [25] an extract from BS produced reduced lipid peroxidation, nitric oxide and INOS.

Concluding remarks

The anti-inflammatory actions of boswellic extracts and pharmacological active constituents including boswellic acids use different targets within an inflammatory process.

They concern:

- immune competent cells: by inhibition of NF-κB activation resulting in inhibition of the expression of proinflammatory cytokines

- complement system: by inhibiting the enzyme C3-convertase

- arachidonic acid cascade: by inhibiting prostaglandine – and leukotriene synthesis

- proteolytic enzymes: by inhibition of cathepsin G and human leucocyte elastase

- oxygen radicals: by inhibition of stimulated NADPH oxidase activity

Diabetes Mellitus

Diabetes mellitus is a metabolic disease where hyperglycemia and hyperlipidemia are the major disorders. These are caused by insufficient insulin actions, be it the consequence of damaged insulin secretion from the islets of Langerhans or insulin resistance of peripheral insulin-dependent tissues. Impaired insulin secretion follows the inflammation of pancreatic islets [insulitis] where, due to derangement of the immune system [autoimmune diabetes], invasion of T-lymphozytes and macrophages destroy insulin-producing ß cells, leading to Type 1 diabetes and late-onset autoimmune diabetes of adults [LADA].

Quite different in its origin is type 2 diabetes. Here, environmental factors, including overweight and muscular inactivity, are associated with insulin resistance. In a later stage, pancreatic islets also become insufficient in producing insulin.

In both cases – autoimmune- and type 2 diabetes - the actions of proinflammatory cytokines play a crucial role.

At presence there exist no efficient treatments against autoimmune diabetes [type 1 and LADA] and insulin resistance concerning the suppression of proinflammatory cytokines.

The anti-inflammatory properties of BEs and BAs especially regarding factors of the immune system – i.e. proinflammatory cytokines – raised the question, about whether or not Type 1, LADA and insulin resistance [Type 2], may be candidates for boswellic extracts and boswellic acids.

Autoimmune Diabetes [Type 1 and LADA]

In type 1 diabetes and LADA overexpression of proinflammatory cytokines in immune-competent cells results in insulitis by the infiltration of macrophages and T- lymphocytes into islet tissue, leading to ß-cell death through the action of TNF-α and IFN-γ.

Thus, in patients with Type 1 diabetes, Cnop et al. [12] reported an increase in NFκB, IFN-γ, TNF-α, IL-1 and IL-2 in splenocytes and PMBCs.

In mice, Diaz-Ganete et al. [15] induced Type 1 diabetes by the administration of a cytokine cocktail, containing IL-1ß, IFN-γ and TNF-α. In this model, ghrelin, which is a peptide that stimulates cell proliferation and inhibits apoptosis in several tissues,

including the pancreas, down regulates the apoptotic actions of the cytokines and restores insulin secretion in response to glucose.

Considering this situation, some studies using extracts from the resin of Boswellia serrata and boswellic acids have been performed in animal models of autoimmune diabetes, including the administration of multiple low doses of streptozotocin [MLD-STZ] in mice and the non obese diabetic [NOD] mouse.

The MLD-STZ Model

Applying this model, Shehata et al. [60] administered 50 mg// kg of streptozotocin [STZ] i.p. for five days to male mice. Five days after the last injection of STZ, the authors observed an increase in proinflammatory cytokines, i.e., IL-1A, IL-1B, IL-2, IL-6, TNF-α and IFN-γ in the blood, infiltration of CD3 lymphocytes into pancreatic islets, some periinsular apoptotic cells and a small but significant increase in blood glucose that further increased in the subsequent 25 days.

Effects of Boswellic Extracts

When in addition to STZ the animals received 150 mg/kg i.p. for 10 days of a boswellic extract containing 4.66% AKBA and 5.48% KBA 10 days after starting the experiments, no increase was observed in the proinflammatory cytokines in the blood. Furthermore no infiltration of CD3 lymphocates into pancreatic islets and the appearance of periinsular apoptotic cells could be detected. Regarding blood glucose levels, no increase appeared at day 10, and no significant increase was detectable even after week four. The data suggested that the extract must have interrupted the STZ signal at a very early step in the expression of proinflammatory cytokines, possibly at the level of NFκB. This interpretation is in line with Cuaz, Perolin [14], reporting the inhibition of NFκB by boswellic acids. Consequently, there was no infiltration of CD3 lymphocytes into islet tissue, i.e., no damage to insulin-producing ß-cells and therefore no hyperglycemia.

Effects of Boswellic Acids

Of special interest among boswellic acids are ß-boswellic acids, which include ß-boswellic acid [ß-BA], acetyl-ß-boswellic acid [A-ß-BA], 11-keto-ß-boswellic acid [KBA] and AKBA.

Using the same protocol as for the boswellic extracts, only the keto-forms, i.e., KBA [7.5 mg/kg i.p.] and AKBA [15 mg/kg i.p.], significantly reduced the STZ-mediated increases in proinflammatory cytokines [IL-1A, IL-1B, IL-2, IL-6, IFN-γ, TNF-α] in the blood. Consequently, there were no infiltration of CD3 lymphocytes into pancreatic islets and the appearance of peri-insular apoptotic cells. Regarding the blood glucose levels, KBA was most effective in inhibiting STZ-mediated hyperglycemia. ß-BA and A-ß-BA showed no effect [61]. From these data, in the MLD-STZ model, KBA and AKBA apparently play important roles in the BE to prevent autoimmune diabetes in this model. However, it is possible that other ingredients of the resin may exhibit a protective action.

The NOD Mouse Model

In contrast to the MLD-STZ model where a chemical agent, i.e. STZ, produces a short – lasting but severe and rapid action on immune-competent cells, the initiation of autoimmune diabetes in the NOD mouse is quite different and due to a genetic disorder. Here, some female animals develop insulitis, which starts about 4 weeks after birth [81]. Due to the slow progression of the inflammatory process, it takes about 18 weeks until damage of the ß-cells leads to insulin deficiency and consequently to an increase in blood glucose.

Effects of KBA

Accordingly the control animals used in the study of Shehata [62] showed that in 7 weeks compared to 4 weeks old mice, there were significant infiltration CD3 lymphocytes into pancreatic islets. In this model, the authors administered KBA at a dose of 7.5 mg/kg i.p. daily from week 4 to week 7. This treatment caused significant inhibition of CD3 lymphocyte infiltration into pancreatic islets and the appearance of periinsular apoptotic cells.

Case Report

Clinical studies dealing with BEs and BAs in diabetes mellitus are missing so far. There is only one case report. Here, Schrott et al. [58] treated a LADA patient for 8.5 weeks with a boswellic extract preparation [Indian Boswellia™] containing 3.6% KBA and 1.4% AKBA. This patient, while being also under treatment with insulin, was assayed for a marker of insulitis, i.e. tyrosine phosphatase A2 antibody [IA2 – A]. Before treatment with Indian Boswellia™ [three times 800 mg daily], IA2 – A was assayed to be 25 K/U/1. After 8.5 weeks treatment with the Boswellia preparation, this marker decreased to 10 K/U/1, suggesting reduction of the islet inflammatory process.

Type 2 Diabetes

Type 2 diabetes as well as the metabolic syndrome [MetS] are metabolic diseases with a genetic background, were excess nutrition, obesity, lack of physical activity are the major reasons. There is general agreement that these factors are responsible for the insulin resistance of peripheral tissues. Under physiological conditions, adipose tissue – especially visceral adipose tissue – plays an essential role in insulin sensitivity of peripheral tissues by secreting adiponectin, which acts as a sensitizer for insulin. In adipose patients, the release of adiponectin is diminished, resulting in decreased insulin sensitivity. Moreover, as shown in previous publications and as discussed below, proinflammatory cytokines derived from immune-competent cells seem to play a

major role in insulin resistance.

In this connection, Janochova et al. [30] interprete an association between visceral fat and insulin resistance as follows: The storage capacity of hypertrophic adipocytes in obese patients is limited. Overload leads to increased apoptosis of adipocytes that in turn stimulates infiltration of immune cells, particularly macrophages into visceral adipose tissue. These cells produce proinflammatory cytokines.

Considering a role of proinflammatory cytokines in type 2 diabetes, it appears logical that drugs decreasing their expression from immune competent cells should be effective in the treatment of Type 2 diabetes and MetS.

While the association of proinflammatory cytokines with insulin resistance is obvious, chronic inflammation in Type 2 diabetes is proposed also to affect the pancreatic islets. The nature of islet inflammation and its effect on islet function in Type 2 diabetes was studied by

Butcher et al. [8] Human islets from organ donors with or without type 2 diabetes were examined. They found that islets from Type 2 diabetic patients displayed higher chemokine ligand 2 [CCI2] and TNF-α expression than islets from healthy persons. The elevated total islet leucocyte content and proinflammatory mediators correlated with islet dysfunction, suggesting that heterogenous insulitis occurs during the development of Type 2 diabetes.

Animal Studies with Boswellic Extracts and Boswellic Acids

Effects on Insulin Resistance

In rats receiving high calory diet to archieve overweight, extracts from boswellia gum resin significantly reduced hyperglycemia and the increased levels of IL-1ß, TNF-α and IL-6. The results were interpreted to be mediated by suppression of insulin resistance as a consequence of TNF-α and IL-1ß reduction along with increasing adiponectin [21, 22]. Studiing the effects of boswellic acids in a rat model of diet-induced non alcoholic fatty liver disease a 5 weeks treatment with 125 or 250 mg/kg boswellic acids, Zaitone et al. [86] reported improved insulin sensibility accompanied with reduced serum levels of TNF-α and IL-6.

Effects on α-Glucosidase

α-Glucosidase is an enzyme that cleaves oligo – and disaccharides in the gut. Inhibitors of the enzyme delay absorption of carbohytrates, reducing postprandial blood glucose peaks. A classical inhibitor of α-glucosidase in the therapy of diabetes mellitus is acarbose.

Previously Ur Rehmann et al. [74] reported that the resins of Boswellia species contain a variety of di – and triterpenes causing inhibition of α-glucosidase, the IC50 of the most potent substances varied in the range from 15,0 to 80,3 μM.

Clinical Studies with Boswellic Extracts

In a randomized, double-blind, placebo-controlled trial, Azedmehr et al. [5] studied the effect of the gum resin of Boswellia serrata in 71 patients with type 2 diabetes. All patients were also under treatment with metformin. The intervention group, in addition to metformin, received 400 mg of the resin orally twice daily for 12 weeks. Compared with the placebo group [metformin only], in the verum group, there was a significant decrease in the fasting blood glucose, HbA1c and serum insulin. Moreover, a reduction of serum cholesterol, LDL and triglycerides was reported. No adverse effects of the resin were observed.

In another double-blind, randomized and placebo-controlled study [44] with type 2 diabetics, although there was a considerable reduction in the intervention group the gum resin of Boswellia serrata was not found to be significantly effective in fasting blood glucose, HbA1c and triglycerides, when given orally twice daily at 250 mg for 8 weeks in addition to their routine anti-diabetic treatment.

Nevertheless, this discrepancy between the study of Azedmehr et al. [5] and that of Mehrzadi et al. [44] could be explained by the higher dose of the resin, used by Azedmehr et al. [5] i.e. 400 mg twice daily and the longer treatment [12 weeks] than the dose of 250 mg twice daily for 8 weeks, employed by Mehrzadi et al. [44] And it should be mentioned that in other clinical trials, as far as chronic inflammatory diseases are concerned, the daily dose was three times 400 – 800 mg of an extract of the resin [58].

Though, more preclinical and clinical evidence is required, it is possible, that also in type 2 diabetes, boswellic resin/extracts or boswellic acids, may prevent insulin resistance/insulitis via inhibition of the expression of proinflammatory cytokines. and therefore type 2 diabetes.

Concluding remarks

Preclinical studies suggest that boswellic extracts and boswellic acids prevent Type 1 – and Type 2 – diabetes mellitus using two peripheral targets:

- Pancreatic islets: by preventing insulitis and ß-cell death

- Peripheral tissues: by prevention of insulin resistance

In both cases the common target is suppression of expression of proinflammatory cytokines through inhibition of NF-κB activation.

Cancer

In the past, preparations from the gum resin of Boswellia species have been frequently used in the treatment of tumors including cancer [43]. At present there are increasing numbers of publications dealing with the effects of boswellic extracts and its active ingredients, including certain boswellic acids on tumor cells in vitro and in animals.

[Table 1] In this connection it appears that in an extract several compounds with antitumor activity are present, acting in a synergistical manner [28].

Table 1: Antitumor Effects of Boswellic Extracts and Ingredients (Ammon 2019 b)

HL-60 Leucoma cells:	Boswellic extracts AKBA A-ß-BA A-α-BA
Prostata Carcinoma cells:	Acetyl boswellic acids AKBA Acetyl lupeolic acid
Glioblastoma cells:	AKBA Derivatives of boswellic acids
Meningioma cells:	AKBA
Myeloma cells:	AKBA
Hep-G2 cells:	Fraction of boswellic acids
Mamma carcinoma cells:	Boswellic extracts AKBA
Colon carcinoma cells:	Boswellic extracts Boswellic acid
Pancreas carcinoma cells:	AKBA Analogues of boswellic acids
Lung carcinoma cells:	11-Carbonyl-ß-boswellic acid

Pathophysiology of cancer is characterized by proliferation of tumor cells, angiogenesis, antiapoptosis and migration of tumor cells forming metastases. These processes are initiated via activation of different signals or signal pathways respectively.

Antitumour Actions

The mechanism of antitumor action of boswellic extracts and boswellic acids is quite different from that of present chemotherapeutics, which in most cases is a singular one i.e. inhibition of synthesis of nucleinic acids, antibody effects or inhibition of enzymes.

In contrast, boswellic extracts and boswellic acids take several targets such as proliferation, apoptosis, vascularization and metastases by simultaneous blocking several signals/signal pathways. In this context NF-κB plays a well known function in the regulation of expression of genes involved in many processes that play a key role in the development and progression of cancer such as proliferation, migration and apoptosis.

Proliferation

Cell Cycles, Effects of Boswellic Acids

Inhibition of proliferation of tumor cells is an important antitumor effect of boswellic extracts and boswellic acids, meaning division of tumor cells during cell cycle. Cell cycle consists of four phases where G1- S- and G2/M phases are of special interest. In this context it should also be mentioned, that BAs may not only inhibit proliferation of tumors, but also reactivate tumor suppressor genes [63].

G1-Phase

During the phase G1 synthesis of m-RNA and proteins for preparation of mitosis takes place.

Here, Yuan et al. [84] reported that in human colon carcinoma cells AKBA caused arrest of the G-1-phase by inhibition of proliferation and by causing apoptosis through modulation of endothestial growthfactor [EGRF] and the ATM/p53 signal pathway. This pathway participates in arresting G-1-phase.

S-Phase

The S-phase is characterized by DNA-synthesis. Using HL-60-tumor cells Yuan et al. [83] observed, that AKBA diminished the S-phase, inhibited proliferation and caused apoptosis.

G2/M-Phase

In the G2/M-phase of the cell cycle, where devision of the nucleus occurs, a variety of different signal transaction pathways is involved. Employing glioma cells, Li et al. [37] observed arrest of cell cycle in G2/M-phase by AKBA through inhibition of different signal pathways such as downregulation of Aurora B/TOP2A [Aurora B – mitotic serine/threonine – kinase] [TOP2A-DNA=topoisomerase 2A] signal pathway as well as via regulation of the P21/FOXM2/cyclin B1 pathway. In this pathway FOXMJ as a transcription factor regulates the expression of genes of the cell cycle.

An arrest of the G2/M-phase was also reported in pancreas cells by a boswellic analogue. In this case there was decreased expression of mitotic factors of the cyclin family [cyclin A, cyclin B, cyclin E] and other factors [53].

Signal transduction pathways: Effects of Boswellic

Extracts and/or Boswellic Acids

P13K-AKT-signal pathway [P13K = Phosphoinosid-3-kinase; AKT-proteinskinase B]. In many tumours this pathway causes increase of proliferation and reduces apoptosis. Wang et al. 2018 [78] reported inhibition of phosphorylation and proliferation of tumor cells by boswellic acids and Liu et al. 2019 [41] using AKBA showed inhibition of proliferation and induction of apoptosis in prostate carcinoma cells with an IC50 of ~17 μM. By disrupting P13/AKT/Hsp -90 cascade and inhibiting NF-κB a novel cyano derivative of 11-keto-ß-boswellic acid induced apoptosis in cancer cells and inhibited proliferation with 48h, IC50 of 0,67 μM in HL-60 cells [33].

STAT-3 signal pathway [signal transduction and activator of transcriptions] causes cell proliferation, angiogenesis, and migration of tumor cells/metastasis and inhibits apoptosis], STAT-3 is activated by IL-6. Inhibition of this pathway has been shown by AKBA and BA [41, 47] through inhibition of phosphorylation of intermediates of this pathway.

Cdc2, Cdc25 [Celldevision Cycle 2 and 25]

These are enzymes [phosphatases] which play a role, when cells are in mitosis while splitting phosphate groups from cell devision inhibiting factors, thus supporting proliferation.

Pin1 [protein interaction in mitosis]

Pin 1, a prolyl-isomerase, controls phosphorylation of prolin. This enzyme is a molecular target in the search of anticancer drugs. As shown later AKBAs bioavailability is very low. Taking this into account Huang et al., 2018 [29] synthetized some derivatives of AKBA Most of them showed excellent inhibition of Pin 1 and proliferation of prostate carcinoma cells. The most effective compound exhibited an IC50 of 0.48 μM.

Erk 1/2 [extracellular signal – regulatory kinase ½]

Erk ½ improves live of cells especially tumour cells. Erk-kinases are phosphorylating enzymes regulating activity of other enzymes. In 2002 Park et al [49]. Reported, that AKBA [10 μM] inhibited Erk ½ signal in meningioma cells in vitro, which caused cell death after less than 24 hours.

AR [Androgen Receptor]

A further target of AKBA, to inhibit tumor proliferation, is the androgen receptor. Androgen receptor-mediated signaling is crucial for the development and progression of prostate cancer. AKBA inhibits cellular proliferation of prostate cancer. Among other anti- cancer effects AKBA also caused a decrease of AR expression at RNA and protein levels [82].

Topoisomerases: Effects of Boswellic Extracts and Boswellic Acids

Topoisomerases are enzymes playing a role in cell devision by splitting ester bindings at the level of DNA, followed by recombination. Inhibition of topoisomerases leads to DNA disorders and cell death.

In this connection inhibition of topoisomerases 1 and 2 by a boswellia extract [76], AKBA [27] as well as A-ß-BA, A-α-BA and AKBA [68] were reported. These results were confirmed by Zhao et al. [85], using melanoma – and fibrosarkoma cells and Shao et al. [59] showed that in HL-60 cells various boswellic acids inhibited DNA-RNA – and protein synthesis in the range between 0.6 and 7.1 μM of IC50. Topoisomerase I and II inhibition and apoptosis were also reported in HL-60 cells and other tumor cells using a propionyloxy derivative of 11-keto-ß-boswellic acid. The IC50 values varied between 5.95 and 15.9 μg/ml. [9]

The data discussed so far indicate, that boswellic extracts and certain boswellic acids produce inhibition of enzymes and a variety of signals and/or signalpathways being responsible for proliferation of tumor cells. They also indicate that some of these signal pathways in addition to their inhibitory action on cell proliferation also affect apoptosis, vascularization and migration.

Apoptosis

Apoptosis, the programmed death of cells, is also a target for boswellic extracts and boswellic acids. In tumor cells their capapility to produce apoptosis is limited. This is due to increased expression of antiapoptotic proteins. Besides boswellic extracts, a variety of incredients of these extracts has been shown to exhibit apoptotic activity.

As discussed below, there is a variety of targets how boswellic acids induce apoptosis. However, the central target seems to be NF-κB. Thus down regulation of NF-κB and PARP [Poly-ADP ribose polymerase:] helps damaged cells to repair themselves. A novel 3-α-butyryloxy-ß-boswellic acid was found to be associated with apoptosis and in vivo tumor regression [54]. In this sense it is interesting to note, that AKBA potented apoptosis, inhibited invasion and abolished osteoclastogenesis by suppressing NFκB and NFκB – regulated gene expression [70]. Employing four different pancreas carcinoma cell lines Park et al. [50] reported that AKBA induced inhibition of proliferation, correlated with an inhibition of constitutively active NF-κB and of NF-κB regulating gene expression. AKBA also induced apoptosis.

DR 5: Effect of AKBA

An extracellular signal, which acts on a membrane death receptor 5 [DR 5] via intracellular cascade activates proteases [caspases], that initiate cell death. Studying the effect of AKBA, Lu et al. [42] observed switch of this signal pathway.

Wnt/ß-Catenin Pathway: Effects of AKBA

Wnts are glycoproteins, which act as ligands in order to stimulate receptor mediated transductions. Among others they participate in proliferation, migration and viability of cells and

play also a role in tumors. In human gastric carcinoma cells Zhangh et al. [87] studied the effect of AKBA on this signal pathway in vitro and in vivo in mice. In this study they observed inhibition of this pathway, increase of caspase 3 and 9 and reduction of tumor growth. Modulation of Wnt/ß-catenin pathway and induction of apoptosis by AKBA was also reported by Wang et al., [79] in intestinal adenomatous polyposis of mice. AKBA in a study of Zhang et al., [87] also showed inhibition of gastric carcinoma growth through modulation of the Wnt/ß-catenin signaling pathway. Upon AKBA treatment of human gastric carcinoma cells, ß-catenin expression in nuclei was inhibited and membrane ß-catenin was activated. In APC [Min/+] mice AKBA was found to inhibit Wnt/ß – catenin and NF-κB / COX-2 signaling pathways and adenomatous polyposis [39].

Caspases

Caspases are enzymes that activate apoptosis. Most studies have been performed using AKBA and its action on caspases 1, 3, 8, 9. As could be expected, there was activation of apoptosis in a variety of tumor cells.

An activation of caspase 3 was observed in colorectal carcinoma cells, using an extract of Boswellia resin by Ranjbarnejad et al., [55]. Most studies, however, have been performed using AKBA. As could be expected AKBA produced apoptosis in Hep G2-cells [40] and gliomablastoma cells [37].

Activation of caspases 3, 8, 9 in Hep-G2-cells was also observed, employing KBA [40]. Not to forget that, as shown in pancreatic carcinoma cells, the volatile oil of frankincense can activate caspases [48].

BCL-2 [anti apoptotic protein]

There is another possibility of BEs and BAs to induce apoptosis, which is the inhibition of a signal pathway that prevents apoptosis. Such an effect was observed by Thummuri et al. [72] in mamma carcinoma cells and cervical carcinoma cells by Khan et al. [32]. Here, a decrease of the expression of antiapoptotic effects BCL-2 occurred.

Vascularization

Growth of tumors strongly depends on oxygen. Since tumours per se cannot produce blood vessels they stimulate angiogenesis in surrounding connecting tissue. In this process the vascular endothelial growth factors [VEGFs] play an essential role. Expression of VEGFs is stimulated by the hypoxy-induceable factor-1 [HJF-1] which is produced by tumor cells, suffering from oxygen deficiency. Under this aspect Ranjbarnejad et al. [55] observed, that a boswellic extract as well as AKBA reduced VEGF in colon carcinoma cells. In an Ehrlich tumor cell model in mice BA decreased VEGF and TFN-α level, as well as peritoneal angiogenesis. The expression of BAX [Bel-2-Associated X Protein] and Caspase 3 increased, suggesting drug induced tumour cell apoptosis through activating the proapoptotic bel-2

Family and caspase 3 [1] Inhibition of HJF-1[Hypoxy-Incluceable Factor-1] by AKBA was also reported by Lakka et al., [36].

Metastases

As discussed before, some signal transduction pathways causing proliferation of tumour cells, also initiate cell migration and metastases have been shown to respond to boswellic extracts and AKBA thus protecting from tumour metastases. Besides, this BEs and BAs also seem to act by further mechanism i.e. inhibiting growth factors related to metastases. Park et al., [50] showed suppression of invasion of pancreatic cancer cells through downregulation of CXCR4 chemokine receptor expression by AKBA.

BFGF [Basis Fibroblast Growth Factor]

One of the growth factors of metastases is BFGF, which in addition is also an inductor of tumor-mediated angiogenesis. This factor was reported to be suppressed following parenteral application of 10 mg/kg AKBA per day in mice [67] .

HGF [Hepatocyte growth factor]

There is an interesting study performed by Parand Ali [37]. Administering the hepatic growth factor [HGF], the authors initiated invasion of mamma carcinoma cells. Simultaneous application of an extract of Boswellia frereana suppressed this effect.

Concluding remarks

Extracts from the gum resin of Boswellia species and a variety of pharmacological acting compounds including boswellic acids and derivatives exert their antitumor actions by interfering with different targets, which are:

Proliferation / growth of tumors

Apoptosis of tumor cells

Angiogenesis of tumors

Migration of tumor cells /metastasis

It appears that active ingredients of an extract not only simultaneously attack different targets, but also act in a synergistic way among each other.

The anticancer actions of boswellic extracts and active components interfere with a big variety of targets related to proliferation, apoptosis, angiogenesis and metastases:

Here, the majour antitumor effect of boswellic extracts and boswellic acids appears to be their inhibitory action on activation of NF-κB thus suppressing gene-expression of tumor related

proteins and signal transduction pathways which could be:

ATM/P53; Aurora B/TOP2A; p21/FOX M2/cyclin B1; P13K-AKT;

STAT3; Erk ½; Wnt/ß-catenin.

Growth factors: EGRF, VEGF, BFGF, HGF.

Receptors: AR, DR5.

Enzymes: Topoisomerases, Caspases, Cde2, Cde 25, Pin 1

Proteins: BCL-2, Cyclin family

Frequently inhibition of phosphorylation of enzymes is a mechanism of action of boswellic extracts and ingredients. This holds also for a major regulator of cellular transformation, proliferation, cell survival, angiogenesis and invasion/metastasis, which is the nuclear factor Kappa B [NF-κB]. According to Yadav et al., [80] its inhibition has the potential to both prevent and treat cancer.

Finally it should be confessed, that the preclinical studies with BAs have been performed with doses/concentrations in vitro that hardly will be achieved in vivo. Thus, as discussed before, at present many attempts are undertaken to improve the bioavailability of AKBA.

For this reason i.e. to decrease IC50 but to increase bioavailability of AKBA, Meka et al., [45] synthesized new analogues of AKBA and evaluated their anti-inflammatory activities.

Among others, an example is the introduction of an amino group in position 2 that led to significantly improved cytotoxic activity [13].

Interestingly some clinical studies have shown BEs to be effective expecially in chronic inflammatory diseases: Probably this is due to multicomponent composition of the BEs and multi targets of the single components.

NF-κB as a common target of boswellic extracts and constituents in chronic

Inflammatory diseases, diabetes mellitus and cancer

Genetic expression of factors being responsible for inflammation, diabetes and cancer and their inhibition by BEs and constituents has been discussed several times in the review. This is the occasion to discuss the molecular target of these actions.

The expression of cytokines is initiated by nuclear transcription factor – κ B [NF-κB]. Activation of NF-κB results from phosphorylation reaction, induced by intracellular protein kinase [IKK]. The phosphorylation dissociates the inhibitory protein IKBα from the inactive IKBα-NFκB complex.

Boswellic extracts and 11-keto-ß-boswellic acids inhibit the

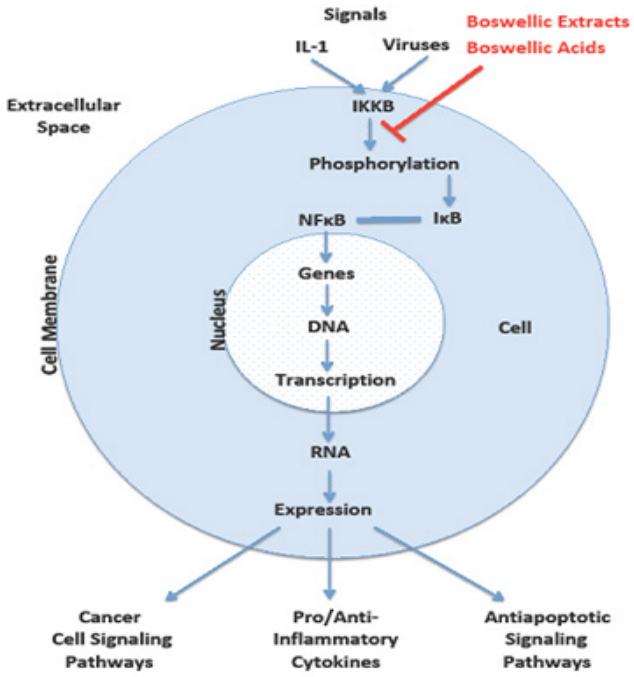

Figure 2: Activation of Nuclear Transcription via NF-κB in immune competent and cancer cells. Inhibitory actions of boswellic extracts and boswellic

phosphorylation of this complex and therefore its dissociation, avoiding the expression of cytokines involved in chronic inflammatory diseases, diabetes mellitus and cancer.

Moreover, in this context, frequent inhibition of phosphorylations of enzymes is a target of BEs and ingredients [11, 41, 47, 49, 38].

Conflict of interest

There is not any conflict of interest in the fields of chronic inflammatory diseases, diabetes mellitus and cancer.

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Abbreviations

α-BA:	α-Boswellic Acid
A-α-BA:	Acetyl-α-boswellic acid
A-ß-BA:	Acetyl-ß-boswellic acid
ABA:	Acetyl-boswellic acid
AKBA:	0-Acetyl-11-keto-ß-boswellic acid
BA:	Boswellic Acid
BAX:	Bel-2-Associated X Protein
BCL-2:	Antiapoptotic Protein
BE:	Boswellic Extract
BFGF:	Basis Fibroblast Growth Factor
BS:	Boswellia Serrata
ß-BA:	ß-Boswellic Acid
CCL2:	Chemokine Liand 2
COX:	Cyclooxigenase
DNA:	Desoxy Ribonucleic Acid
DR5:	Death Receptor 5
EGRF:	Endothelial Growth Factor
f-MLP:	n – Formyl-methionyl-leucyl-phenylazanin
5-HETE:	5-Hydroxyeicosatetraenoic acid
HGF:	Hepatocyte Growth Factor
12-HHT:	12-Hydroxyheptadecatrienoic acid
HJF-1:	Hypoxy-Induceable Factor – 1
HLE:	Human Leukocyte Elastase
IA2-A:	Tyrosine Phosphatase A2 - Antibody
IFN-γ:	Interferon – γ
IKKB :	I-Kappa B – Kinase, phosphorylates IKB
IKB:	I-Kappa B inhibits NFKB
IKK:	Intracellular Protein Kinase
IL-1:	Interleukin – 1
IL-1A:	Interleukin – 1A
IL-1B:	Interleukin – 1B
IL-1ß:	Interleukin – 1ß
IL-2:	Interleukin – 2
IL-4:	Interleukin – 4
IL-6:	Interleukin – 6
IL-10:	Interleukin – 10
IL-12:	Interleukin - 12
INOS:	Inducible nitric oxide synthesis
KBA:	11-keto-ß-boswellic acid
LADA:	Late-onset Autoimmune Diabetes of Adults
LDL:	Low Density Lipoprotein
5-LO:	5-Lipoxigenase
LPS:	Lipopolysaccharide
LTB4:	Leukotriene – B4
Mets:	Metabolic Syndrome
MLD:	Multi Low Doses
m-RNA:	Messenter Ribonucleic Acid
NADPH:	Nicodinamide Adenine Dinucleotide Phosphate Hydrogen
NF-kB:	Nuclear Transcription Factor B
NOD:	None Obese Diabetic
PARP:	Poly – ADP Ribose Polymerase
PBMC:	Peripheral Blood Mononuclear Cell
PGE2:	Prostaglandine E2
PLA2:	Phospholipase A2
PMA:	Phorbol-12-myristate-13-acetate
PMN:	Polymorph Mononuclear Neutrophils

STZ:	Streptozotozin
TNF-α:	Tumour Necrosis Factor – α
TH-1;	TH-1-Lymphocytes
TH-2:	TH-2-Lymphocytes
VEGF:	Vascular Endothelial Growth Factor

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