

## Benefits of Boswellia

The popularity of boswellia, a botanical medicine discovered over three millennia ago, is now experiencing resurgence. Long recognized for its anti-inflammatory benefits, this oleogum resin also has anti-cancer and immunomodulatory properties.<sup>1</sup> Boswellia, or frankincense, harkens back to ancient India and Egypt. Frankincense was one of the four components in the medicinal “Balsam of Jerusalem” from the Franciscan Monastery<sup>2</sup> and, as noted in the Papyrus Ebers, circa 1500 BCE, had applications in Egypt for mummification, cremation, and the treatment of skin wounds.<sup>3 4</sup>

In the Indian medical system of Ayurveda, boswellia goes by the term, “salai guggul”. Its Sanskrit name, “Gajabhakshya”, suggests that human observed elephants ingesting the plant. That is, ancient Indian Ayurvedic healers witnessed these huge animals feeding on *Boswellia serrata* trees, which grow widely across the dry hills of northwest India. Coupling this observation with their knowledge of elephants’ longevity and astounding physical capacity, these early doctors began questioning whether the elephants’ dietary intake of boswellia might offer similar benefits to humans, though in much smaller amounts.<sup>5</sup>

Boswellia, or boswellic acids, exhibit potent anti-inflammatory properties, demonstrated both in vitro and in vivo. Triterpenes in boswellic acid reduce the synthesis of leukotrienes in intact neutrophils by inhibiting 5-lipoxygenase, the key enzyme involved in the biosynthesis of leukotrienes, which mediate inflammation.<sup>6 7</sup> Leukotrienes form via the lipoxygenase pathway, subsequent to the enzymatic oxidation of arachidonic acid. Certain inflammatory states, including colitis and bronchial asthma, are characterized by increased concentrations of leukotrienes. Leukotrienes incite chemotaxis, chemokinesis, superoxide radical formation, and phagocytic expulsion of lysosomal enzymes.<sup>8</sup> In cases of asthma, leukotrienes induce bronchoconstriction, increased mucus

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<sup>1</sup> Anonymous. Frankincense oil used on melanoma. *Veterinary Practice News*. March 2006; p. 38.

<sup>2</sup> Moussaieff A, Fride E, Amar Z, et al. The Jerusalem Balsam: From the Franciscan Monastery in the old city of Jerusalem to Martindale 33. *Journal of Ethnopharmacology*. 2005;101:16-26.

<sup>3</sup> Mathe C, Culioli G, Archier P, et al. Characterization of archeological frankincense by gas chromatography-mass spectrometry. *Journal of Chromatography A*. 2004;1023:277-285.

<sup>4</sup> Lemenih M and Teketay D. Frankincense and myrrh resources of Ethiopia: II. Medicinal and industrial uses. *Ethiop J Sci*. 2003;26(2):161-172.

<sup>5</sup> Sharma S, Thawani V, Hingorani L, et al. Pharmacokinetic study of 11-keto beta-boswellic acid. *Phytomedicine*. 2004;11:255-260.

<sup>6</sup> Hostanska K, Daum G, and Saller R. Cytostatic and apoptosis-inducing activity of boswellic acids toward malignant cell lines *in vitro*. *Anticancer Research*. 2002;2853-2862.

<sup>7</sup> Roy S Khanna S, Krishnaraju AV et al. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to anti-inflammatory *Boswellia*. *Antioxidants & Redox Signaling*. 2006;8(3&4):653-660.

<sup>8</sup> Roy S Khanna S, Krishnaraju AV et al. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to anti-inflammatory *Boswellia*. *Antioxidants & Redox Signaling*. 2006;8(3&4):653-660.

secretion and edema, and promote production of an eosinophil-rich inflammatory cellular infiltrate.<sup>9</sup>

Boswellia extracts cause immunomodulation by simultaneously inhibiting TH1 and promoting TH2 cytokine production.<sup>10</sup> They regulate vascular responses to inflammation<sup>11</sup> and stabilize mast cells.<sup>12</sup> In cases of intestinal inflammation, boswellic acids may modulate the adhesive interactions between leukocytes and endothelial cells, by countering the activation of leukocytes and/or down-regulating the expression of endothelial cell adhesion molecules.<sup>13 14</sup>

On the anti-cancer front, boswellic acids induce antiproliferation, differentiation and apoptosis in leukemia cell lines.<sup>15 16 17 18</sup> They exert cytotoxic effects on established human glioblastoma and leukemia cell lines, as well as on primary human meningioma cells.<sup>19</sup>

New information reveals that an extract from a related species, *Boswellia elongate*, showed significant inhibitory activity against angiotensin converting enzyme (ACE), neutral endopeptidase (NEP), and aminopeptidase N (APN).<sup>20</sup> The zinc-endopeptidases NEP and ACE work their enzymatic activity on the outer surface of certain cells and participate in the metabolism of regulatory

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<sup>9</sup> Gupta I, Gupta V, Parihar A, 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.

<sup>10</sup> Chevrier MR, Ryan AE, Lee DY-W, et al. *Boswellia carterii* extract inhibits TH1 cytokines and promotes TH2 cytokines in vitro. *Clinical and Diagnostic Laboratory Immunology.* 2005;12(5):575-580.

<sup>11</sup> Roy S Khanna S, Krishnaraju AV et al. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to anti-inflammatory *Boswellia*. *Antioxidants & Redox Signaling.* 2006;8(3&4):653-660.

<sup>12</sup> Pungle P, Banayalakar M, Suthar A, et al. Immunomodulatory activity of boswellic acids of *Boswellia serrata* Roxb. *Indian Journal of Experimental Biology.* 2003;41:1460-1462.

<sup>13</sup> Kriegelstein CE, Anthoni C, Rijcken EJM, 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.

<sup>14</sup> Anthoni C, Laukoetter MG, Rijcken E, 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.

<sup>15</sup> Jing Y, Nakajo S, Xia L, et al. Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leukemia Research.* 1999;23:43-50.

<sup>16</sup> Hostanska K, Daum G, and Saller R. Cytostatic and apoptosis-inducing activity of boswellic acids toward malignant cell lines *in vitro*. *Anticancer Research.* 2002;28:2853-2862.

<sup>17</sup> Zhao W, Entschladen F, Liu H, et al. Boswellic acid acetate induces differentiation and apoptosis in highly metastatic melanoma and fibrosarcoma cells. *Cancer Detection and Prevention.* 2003;27:67-75.

<sup>18</sup> Shao Y, Ho C-T, Chin C-K, et al. Inhibitory activity of boswellic acids from *Boswellia serrata* against human leukemia HL-60 cells in culture. *Planta Medica.* 1998;64:328-331.

<sup>19</sup> Park YS, Lee JH, Bondar J, et al. Cytotoxic action of acetyl-11-keto-beta-boswellic acid (AKBA) on meningioma cells. *Planta Med.* 2002;68:397-401.

<sup>20</sup> Oleski A, Lindequist U, Mothana RAA, et al. Screening of selected Arabian medicinal plant extracts for inhibitory activity against peptidases. *Pharmazie.* 2006;61(4):359-361.

peptides such as substance P, bradykinin, natriuretic peptide, enkephalins, and other hormonal and vasoactive peptides. Boswellia extracts thus inhibit the renin-angiotensin-aldosterone system and stimulate the kinin system and natriuretic peptides, and as a result reduce vasoconstriction, increase vasodilation, and improve sodium-water balance.

Boswellia is perceived to be a safe and effective remedy for a number of conditions. In fact, Germans with inflammatory bowel disease (IBD) placed *Boswellia serrata* extract among the top three most beneficial CAM treatments by IBD patients in Germany, along with probiotics and acupuncture.<sup>21</sup> In one study, the gum resin of *Boswellia serrata* provided improvements in patients with chronic colitis comparable or better than pharmaceutical treatment with sulfasalazine.<sup>22</sup>

Clinical studies have also shown boswellia to benefit patients with arthritis. An uncontrolled study on dogs with arthritis showed a significant reduction in the severity of clinical signs.<sup>23</sup> A human study on patients with osteoarthritis of the knee showed that boswellia decreased pain and swelling and increased range of motion and endurance.<sup>24</sup>

For cancer patients, boswellic acids may help reduce cerebral edema in patients with brain tumors, helping reduce the need for steroids and their significant adverse side effects.<sup>25</sup>

The pharmacokinetics for most herbs given to veterinary patients continue to be a mystery. In humans, one study showed that the elimination half-life for boswellia was approximately six hours, suggesting that oral administration would require dosing every six to eight hours.<sup>26</sup> The presence of food in the stomach, as well as the type of food eaten, dramatically alters the bioavailability of boswellic acids, and bile acids significantly affect their absorption.<sup>27</sup> When human subjects ingested boswellic acids with a high-fat meal, the areas under

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<sup>21</sup> Joos SS, Rosemann TT, Szecsenyi JJ, et al. Use of complementary and alternative medicine in Germany – a survey of patients with inflammatory bowel disease. *BMC Complementary and Alternative Medicine*. 2006;6:19. In press.

<sup>22</sup> Gupta I, Parihar A, Malhotra P, et al. Effects of gum resin of *Boswellia serrata* in patients with chronic colitis. *Planta Med*. 2001;67:391-395.

<sup>23</sup> Reichling J, Schmokel H, Fitz J, et al. Dietary support with Boswellia resin in canine inflammatory joint and spinal disease. *Schweiz Arch Tierheilkd*. 2004;146(2):71-9.

<sup>24</sup> Kimmalkar N, Thawani V, Hingorani L 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.

<sup>25</sup> Reising K, Meins J, Bastian B, et al. Determination of boswellic acids in brain and plasma by high-performance liquid chromatography/tandem mass spectrometry. *Anal Chem*. 2005;77:6640-6645.

<sup>26</sup> Sharma S, Thawani V, Hingorani L, et al. Pharmacokinetic study of 11-keto beta-boswellic acid. *Phytomedicine*. 2004;11:255-260.

<sup>27</sup> Sterk V, Buchele B, and Simmet T. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. *Planta Med*. 2004;70:1155-1160.

the plasma concentration-time curves and peak concentrations totaled several times higher than when the herbal preparations are taken in the fasting condition.

Another study showed that combining certain boswellic acid extracts with ethanol produced significant cellular toxicity, which was not observed in a sesame oil preparation.<sup>28</sup> This finding underscores the importance of pursuing further research in phytopharmaceuticals to ensure their safe administration. Although veterinary patients are unlikely to imbibe ethanol voluntarily, they may encounter ethanol in other herbal extracts they are taking.

Side effects of boswellic acids include abdominal discomfort nausea, epigastric pain, hyperacidity<sup>29</sup>, and diarrhea.<sup>30</sup>

Frankincense extracts, as well as boswellic acids themselves, display moderate to potent inhibition of human drug-metabolizing cytochrome P450 enzymes,<sup>31</sup> but the clinical significance and comparative effects on non-human P450 enzyme systems remain unknown.

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<sup>28</sup> Chevrier MR, Ryan AE, Lee DY-W, et al. *Boswellia carterii* extract inhibits TH1 cytokines and promotes TH2 cytokines in vitro. *Clinical and Diagnostic Laboratory Immunology*. 2005;12(5):575-580.

<sup>29</sup> Gupta I, Gupta V, Parihar A, 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.

<sup>30</sup> Kimmatkar N, Thawani V, Hingorani L 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.

<sup>31</sup> Frank A and Unger M. Analysis of frankincense from various *Boswellia* species with inhibitory activity on human drug metabolizing cytochrome P450 enzymes using liquid chromatography mass spectrometry after automated on-line extraction. *Journal of Chromatography A*. 2006;1112:255-262.