REVIEW: The Role of Nutritional Bioactives for Modulation of Inflammation Resolution

OVERVIEW

Inflammatory pain is a prominent health burden that impacts the lives of countless individuals. To research the effect of herbs on acute pain symptoms, an herbal blend of curcumin derived from *Curcuma longa* and *Boswellia serrata* (Boswellia) within black sesame seed oil was clinically studied and shown to noticeably reduce muscular pain within 63 minutes,[1] which is a similar time-to-effect as acetaminophen.[2] This combination of curcumin and Boswellia extracts, Rhuleave-K™, features innovative SpeedTech™ technology, which combines particle micronization within a phospholipid-rich* sesame seed oil delivery system[3] to enhance curcumin and Boswellia absorption.[4]

BACKGROUND INFORMATION

Understanding the inflammatory process

Inflammation is an adaptive response caused by harmful stimuli, such as tissue damage in the body.[5]

The process of inflammation is mediated in four stages facilitated by:

1. **Cell receptors** that induce intracellular inflammatory signalling (e.g. toll-like receptors [TLRs], NOD-like receptor pyrin domain containing 3 [NLRP3]).[5]
2. **Messenger proteins** that relay these signals into cell nuclei (e.g. peroxisome proliferator-activated receptor gamma [PPAR-γ] and IkappaB kinase [IKK]).[5]
3. **Inflammatory** transcription factors that enter nuclei and interact with deoxyribonucleic acid (DNA), such as nuclear factor kappa B (NFκB),[5] to stimulate the transcription of:
4. **Effector mediators** that are released into tissue, including:[5]
   - Proinflammatory cytokines (e.g. interleukin 1, 1β, and 6 [IL-1], IL-1β and IL-6], and tumor necrosis factor alpha [TNF-α])
   - Proinflammatory enzymes (e.g. cyclooxygenases [COX] and lipoxygenases [LOX]), which promote arachidonic acid inflammatory pathways (e.g. prostaglandin, thromboxane, and leukotriene activity)

These inflammatory mediators act upon immune and vascular cells at the site of tissue damage, which promote the cardinal signs of inflammation in response to injury: heat, swelling, redness, and pain.[6]

A natural alternative for acute pain

To alleviate the symptoms of acute inflammation, acetaminophen and nonsteroidal anti-inflammatories (NSAIDs) are among the most widely used analgesics globally.[7] However, for many individuals who take these over-the-counter (OTC) medicines, complete relief may be difficult to achieve with a single agent.[7] Moreover, single doses above maximum recommendations (i.e. > 400 mg of ibuprofen [NSAID] and > 1,000 mg of acetaminophen may result in higher risks of adverse events.[7†] Providing a natural option, curcumin and Boswellia within Rhuleave-K has been shown to relieve musculoskeletal pain within 63 minutes.[1] Moreover, these analgesic herbs have been shown to achieve comparable outcomes to acetaminophen[2] and NSAIDs.[8,9] As such, this combination can offer individuals an effective alternative to OTC pain treatments.

Enhanced herbal efficacy with SpeedTech

Unique to the manufacture of Rhuleave-K, proprietary SpeedTech technology[‡] enhances curcumin and Boswellia absorption, helping to overcome the low bioavailability of these extracts.[10,11] By combining natural ingredients through a high-speed milling process, SpeedTech micronizes botanical particles within a phospholipid-rich base of sesame seed oil[3] to create a highly bioavailable dispersion of active compounds. For this reason, specialized SpeedTech technology can maximize the anti-inflammatory benefits of curcumin and Boswellia extracts in Rhuleave-K for greater clinical effects (**Figure 1**).[4,11,12,13]

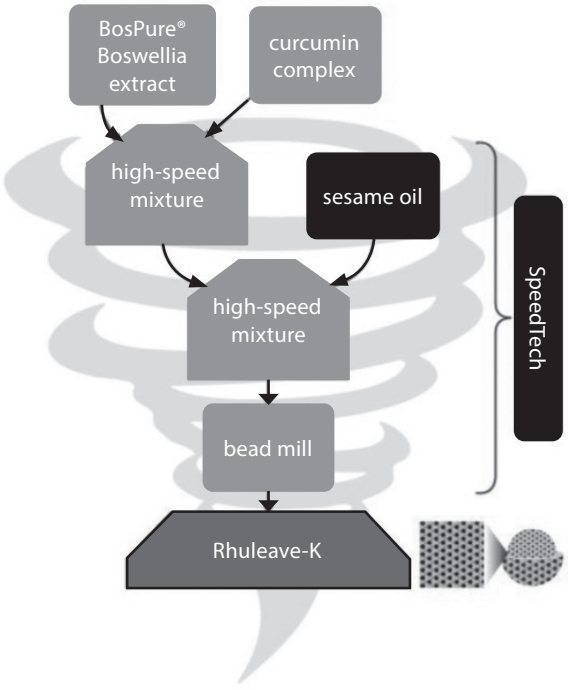

Figure 1: Pain reduction with Rhuleave-K is comparable to 1,000 mg of acetaminophen.[3]

ACTIONS

Anti-inflammatory

Boswellia and curcumin possess therapeutic actions that target several stages of inflammation. For example, **Boswellia** inhibits intermediate messenger molecule IKK *in vitro*, thereby limiting its effect on promoting NFκB activation.[14] Subsequently, Boswellia downregulates proinflammatory cytokines, including TNF-α, IL-1, and IL-6, which may help to mitigate acute inflammatory pain.[11] Additionally, Boswellia blocks the activity of the enzyme, 5-LOX,[11,15] thereby reducing leukotriene B4 synthesis *in vitro*, which plays a key role in attracting proinflammatory cells into tissues (e.g. neutrophils and eosinophils).[16] In animals, these properties have been shown to achieve greater anti-inflammatory effects in combination with COX inhibitors, highlighting the adjunctive treatment benefits of Boswellia.[17]

Curcumin also moderates the inflammatory response.[5] Specifically, curcumin binds to TLRs and PPAR-γ, which inhibit NFκB and other transcriptional signalling molecules that promote inflammatory pathways (e.g. Janus kinase [JAK] and signal transducer and activator of transcription [STAT]).[5] Through these mechanisms, curcumin has been observed to lower

cytokine levels, such as TNF-α, IL-1, IL-1β, IL-6, and IL-8.[5,18] Moreover, through downregulating transcriptional mediators, curcumin reduces the expression of COX-2 and 5-LOX *in vitro*, which promote the release of proinflammatory prostaglandins and leukotrienes.[19,20] This dual action of curcumin on both these enzymes may provide potential advantages over NSAIDs that target COX-2 pathways alone.[19] Interestingly, human studies have shown curcumin-containing extracts to reduce COX-2 levels as effectively as to NSAIDs,[21] further supporting the benefits of curcumin compared to OTC pain relief.

Analgesic and antinociceptive

Through targeting sensory pain receptors (nociceptors), analgesic agents can help to reduce pain perception. This in turn can help minimize pain sensitivity.[22,23] **Curcumin** has been shown to reduce nociception via transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1), which are linked to heightened pain sensitivity.[24,25] In addition, curcumin also stimulates adenosine triphosphate (ATP)-sensitive potassium channels that block nociceptor activation, which further dampens pain transmission.[26] Further to this, evidence indicates that curcumin can activate alpha 7 nicotinic acetylcholine receptors (α7-nACh), also associated with reducing nociceptive pain.[27] Demonstrating these effects, curcumin has been shown to limit pain sensitivity following injury in animals,[28] supporting its analgesic properties.

CLINICAL APPLICATIONS

Acute pain

Human clinical data support the efficacy of curcumin and Boswellia extracts in **Rhuleave-K**, which is comparable to a single dose of acetaminophen (paracetamol). This was demonstrated in a randomized open-label study conducted in 88 healthy subjects (mean age 42 ± 12 years) with grade 1 musculoskeletal strain.[2§] Individuals received 1,000 mg/d Rhuleave K (equivalent to 266 mg/d curcumin and 1,000 mg/d Boswellia extract; n=44) with breakfast or 1,000 mg of acetaminophen (n=44) and were monitored over six hours daily for seven days. Outcomes of the study revealed Rhuleave-K offered equal benefit to acetaminophen (p<0.001), achieving noticeable pain relief within 2.5 hours (**Figure 2**). After six hours, Rhuleave-K reduced total pain by 53.1% versus 55.4% in the pharmaceutical group, and lowered pain intensity by 37.7% comparable to acetaminophen (38.6%). Further, natural treatment improved pain quality and intensity after seven days by 71.8%, similar to OTC pain relievers (73.6%).[2]

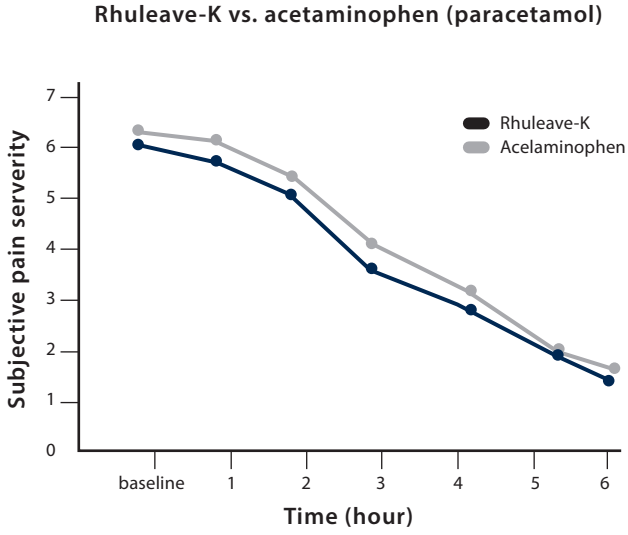

Figure 2: Pain reduction with Rhuleave-K was comparable to acetaminophen (p<0.001).[2]

The fast-acting benefits of Rhuleave-K were documented in 232 healthy individuals (mean age 36.4 years) with exercise-induced muscle pain. These patients received either Rhuleave-K (n=116) or placebo (n=116) and were monitored over six hours.[1] Results revealed a reduction of severe pain from greater than 74% to less than 3% in the head, neck, upper and lower limbs, torso, and back (p<0.001). This demonstrated a relative > 95% improvement in pain with Rhuleave-K, while no significant relief occurred in the placebo group. Researchers also observed that perceived pain relief occurred around 63 minutes with active treatment. Further, complete pain relief in the head, neck, upper and lower limb, torso, and back was achieved in 3.1 hours.[1] As such, these studies support the anti-inflammatory effects of curcumin and Boswellia extracts in Rhuleave-K.

Clinical evidence also supports the use of **curcumin** to minimize muscle pain following exercise. In a systematic review and meta-analysis of randomized-controlled clinical trials, researchers analyzed data from 159 participants (aged 19.5 to 35.5) with muscle soreness.[18] These individuals received 150 mg/d to 6,000 mg/d of curcumin featuring enhanced bioavailability. Pooled statistics revealed that 150 mg/d to 180 mg/d of curcumin achieved a near significant effect in reducing muscle soreness (p<0.051). Further evaluation revealed this effect was significant in reducing pain in untrained individuals (p<0.001) following resistance exercise (p<0.001) after 72 and 96 hours (p<0.034; p<0.001).[18]

Additionally, **curcumin** has also been observed to reduce inflammatory arthritic pain.[8,21] For instance, in a randomized double-blind, placebo-controlled trial, 24 rheumatoid arthritis patients (mean age 36) received 250 mg of curcumin twice daily** or placebo for 90 days. Results from this study revealed a 78.1% improvement in joint tenderness and a 80.4% reduction in swelling versus 4.4% and 3.7% improvement in the placebo group respectively.[29] Collectively, this research indicates that curcumin and Boswellia extracts can deliver fast-acting pain relief.

Table 1: Clinical evidence for ingredients contained within Rhuleave-K

Rhuleave-K			
CONDITION	**DOSE + FORM**	**INTERVENTION**	**OUTCOME**
Healthy subjects (mean age 42 ± 12 years) with grade 1 musculoskeletal strain (< 5 loss of function[30]) experiencing acute pain rated 60% to 65% (n=88)[2]	Single dose 1,000 mg/d Rhuleave-K (equivalent to 266 mg/d curcumin + 1,000 mg/d Boswellia) with breakfast vs. 1,000 mg acetaminophen (paracetamol)	7 days; randomized open-label study	Pain reduction from baseline with Rhuleave-K was comparable to acetaminophen (p<0.001). Both products achieved noticeable pain relief within 2.5 hours. Within 6 hours, Rhuleave-K achieved a **53.1% reduction in total pain** comparable to 55.4% with acetaminophen, as well as **37.7% improvement in pain intensity vs. 38.6% with acetaminophen**. After 7 days, Rhuleave-K improved pain quality and intensity by 71.8% compared to 73.6% in the acetaminophen group.[2]
Healthy subjects (mean age 36.4 years) with exercise-induced acute muscle pain (grade 1) rated at 80% (n=232)[1]	Single dose 1,000 mg/d Rhuleave-K (equivalent to 266 mg/d curcumin + 1,000 mg/d Boswellia) vs. placebo	6 hours; randomized double-blind placebo-controlled study	**Pain rated between 74% to 86%** in the head, neck, upper and lower limbs, torso, and back was **reduced down to 0% to 3%** after six hours with Rhuleave-K (p<0.001), improving relative pain scores by >95%. No significant pain relief was observed in the placebo group. **Perceived pain relief occurred around 63 minutes** with Rhuleave-K. **Complete pain relief** with Rhuleave-K in the head, neck, upper and lower limb, torso, and back **occurred around 3.1 hours.**[1]
Curcumin			
159 participants (aged 19.5 to 35.5) with exercise-induced muscle damage and delayed-onset muscle soreness (DOMS)[18]	150 mg/d–6,000 mg/d curcumin featuring enhanced bioavailability delivery systems	24 hours to 56 days; systematic review and meta-analysis of randomized-controlled clinical trials	Pooled data analysis revealed that <180 mg/d of curcumin across 4 clinical trials achieved a near significant effect in reducing muscle soreness in adults (p<0.051). Further analysis found curcumin to effectively reduce muscle soreness in untrained individuals (p<0.001), in response to resistance exercise (p<0.001) after 72 and 96 hours (p<0.034; p<0.001).[18]
937 patients (age >40+) with degenerative knee osteoarthritis and rheumatoid arthritis rated >50% severity[8]	500 mg/d-1,500 mg/d of mixed curcuminoids or isolated curcumin extract vs. NSAIDs or placebo	4 to 12 weeks; systematic review and meta-analysis of randomized-controlled clinical trials	Meta-analysis data revealed **no significant difference in subjective pain outcomes between turmeric extracts/curcumin with pain medication** (i.e. 800 mg/d to 1,200 mg/d of ibuprofen and 50 mg/d to 100 mg/d of diclofenac sodium; p<0.10).[8]
80 patients (mean age 64) with mild to moderate knee osteoarthritis[21]	30 mg TDS of curcuminoids (predominantly curcumin) vs. 25 mg TDS diclofenac sodium (NSAID)	28 days; randomized single-blind study	Effects of curcumin-containing extract on reducing inflammatory enzyme activity (COX-2) (that precipitates osteoarthritic knee pain) was comparable to NSAIDs (p<0.001).[21]
36 patients (mean age 36) with rheumatoid arthritis with "high disease activity level"[31] using validated disease activity scale[29]	250 mg BD dose of curcumin (n=12) vs. 500 mg BD dose of curcumin (n=12) vs. placebo (n=12)	90 days; randomized double-blind, placebo-controlled clinical trial	Outcomes revealed that 250 mg BD of curcumin within an enhanced bioavailability delivery system led to a 78.1% reduction in joint tenderness and lowered swelling by 80.4%. Comparable outcomes were observed in the 500 mg BD group, resulting in an 88% reduction in tenderness and 84.8% less swelling (p<0.001). Outcomes in the placebo group were minimal, lowering joint tenderness by 4.4% and swelling by 3.7% (p>0.05).[29]

Although natural and generally safe, the ingredients turmeric/curcumin, Boswellia, and sesame may interact with certain medications and conditions.

Contraindications

- **Allergy or hypersensitivity:** Contact dermatitis and a single case of anaphylaxis has been reported from turmeric, which contains curcumin.[32] Sesame may also cause anaphylaxis in those who are allergic.[33,34,35] Avoid if allergic or hypersensitive to turmeric, curcuminoids, or sesame.

Cautions—moderate level

- **Anticoagulant/antiplatelet drugs:** The curcuminoids in turmeric have antiplatelet effects.[32,36] Concomitant use alongside anticoagulant or antiplatelet agents such as aspirin and warfarin might increase the risk of bleeding.[37] Use with caution, and for patients taking warfarin, monitor international normalized ratio (INR).
- **Antidiabetic drugs:** Clinical research shows that sesame seed oil can reduce plasma glucose and HbA1c levels; therefore, there may be an additive effect with antidiabetic drugs.[38,39] Monitor patients with concurrent use.
- **Bleeding disorders:** Due to the antiplatelet properties of turmeric, which contains curcumin, there have been safety concerns with regard to the risk of increased bleeding tendency in patients with bleeding disorders.[32,37] Studies are limited; however, it still warrants caution in situations that carry a high risk of bleeding, such as hemorrhagic stroke and postoperative events. To minimize the risk of exacerbation of these serious bleeding events, it is recommended to discontinue the use of curcumin during acute bleeding episodes.
- **Chemotherapy/radiotherapy:** It has generally been thought that antioxidants may interfere with chemotherapy and/or radiotherapy by decreasing the efficacy of the treatment. However, review studies have found that antioxidants are safe to use in conjunction with these treatments.[40] Given the serious nature of the condition, it is still advisable to check with a patient's oncologist before recommending a formula containing antioxidants, then use cautiously and only under the supervision of the oncologist.
  - While curcumin has been shown to enhance chemotherapy in ovarian cancer,[41] it may suppress chemotherapy-induced apoptosis in breast cancer: Curcumin was found to inhibit chemotherapeutic effects by reducing camptothecin-, mechlorethamine-, or doxorubicin-induced apoptosis in breast cancer cells and reducing the effectiveness of cyclophosphamide in an *in vivo* mouse model.[42] In contrast, curcumin has also been shown to augment the cytotoxic effects of other chemotherapeutic drugs, including doxorubicin, tamoxifen, cisplatin and camptothecin, 5-fluorouracil, paclitaxel, daunorubicin, vincristine, and melphalan, with no effect on the toxicity of etoposide, daunorubicin, and idarubicin.[43] Check with a patient's oncologist before recommending a formula containing antioxidants. Use with caution and only under the supervision of a patient's oncologist.
- **Surgery:** Due to the anticoagulant properties of turmeric, which contains curcumin, there have been safety concerns with regards to the risk of increased postoperative bleeding.[32,37] Studies are limited; however, it still warrants caution in postoperative events. To minimise the risk of exacerbation of bleeding events, it is recommended to discontinue the use of curcumin four to seven days before elective procedures that have a high risk for bleeding complications.
- **Warfarin:** Use cautiously in patients on this medication and monitor INR levels.
  - This anticoagulant medication is metabolized by cytochromes (CYP) P450 1A1, 1A2, 2C9, 2C19, and 3A444[45] and has a narrow therapeutic range.[46,47,48] *In vitro* evidence shows that Boswellia may inhibit the activity of CYP 1A2, 2C9, 2C19, and 3A4,[35,49] and turmeric, which contains curcumin, may inhibit CYP 1A1 and 1A2.[37,50] Theoretically, this inhibitory action could change the drug's therapeutic effect.
  - Case reports have identified increased INRs in patients taking warfarin concurrently with Boswellia. This may be due to inhibition of lipoxygenase and interferences with COX-1, as well as the aforementioned CYP interactions.[51]

Cautions—low level

- **Amiodarone:** This Class III antiarrhythmic drug is metabolized by cytochromes P450 1A2, 2C8, 2C9, 2D6, and 3A4 and by P-glycoprotein[52,53,54] and has a narrow therapeutic range.[47,48] Turmeric, which contains curcumin, inhibits the activity of P450 1A2,[37,50] and *in vitro* evidence shows Boswellia may inhibit the activity of 1A2, 2C8, 2C9, 2D6, and 3A4.[35,49] Additionally, sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] These actions may theoretically change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Antihypertensive drugs:** Sesame seed oil may lower systolic and diastolic blood pressure in people with or without hypertension. It may also add to the effect of blood pressure-lowering medication. Theoretically sesame seed oil may increase risk of hypotension when combined with hypertensive drugs.[38,58] Monitor patients with concurrent use.
- **Atazanavir:** This human immunodeficiency virus (HIV) antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and has a narrow therapeutic range.[59,60] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis):** *In vitro* studies show that Boswellia has immunostimulant properties and theoretically may exacerbate autoimmune disease symptoms.[49] Use with caution in patients with an autoimmune disease and monitor symptoms.
- **Carbamazepine:** This antiepileptic, neurotropic, and psychotropic drug is metabolized by cytochromes P450 2C8 and 3A4[61,62] and has a narrow therapeutic range.[48,63] *In vitro* evidence shows Boswellia may inhibit the activity of these enzymes,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Cyclosporine (ciclosporin):** This potent immunosuppressant antirejection drug is metabolized by cytochrome P450 3A4[64,65] and by P-glycoprotein[64,65] and has a narrow therapeutic range.[46,48] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame has the potential to affect the clearance of drugs that are

transported via P-glycoprotein.[38,57] These actions could theoretically change the drug's therapeutic effect.[38,57] Use cautiously in patients on this medication and consult the patient's specialist if prescribed to manage organ transplantation.

- **Darunavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and has a narrow therapeutic range.[59,60] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Delavirdine:** This HIV antiretroviral nonnucleoside reverse transcriptase inhibitor is metabolized by cytochrome P450 3A4 and has a narrow therapeutic range.[59,60] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Digoxin:** This cardiac glycoside drug is metabolized by cytochrome P450 3A4 and by P-glycoprotein[52,66,67] and has a narrow therapeutic range.[46,48] *In vitro* evidence shows that Boswellia may inhibit the activity of CYP 3A4,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and only under medical supervision.
- **Disopyramide:** This Class IA anti-arrhythmic drug is metabolized by cytochrome P450 3A4[52,68] and has a narrow therapeutic range.[69,70,71] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Efavirenz:** This HIV antiretroviral nonnucleoside reverse transcriptase inhibitor is metabolized by cytochrome P450 3A4 and has a narrow therapeutic range.[59,60] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Ethosuximide:** This anticonvulsant drug is metabolized by cytochrome P450 3A4[72,73] and has a narrow therapeutic range.[48,74] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Etravirine:** This HIV antiretroviral nonnucleoside reverse transcriptase inhibitor is metabolized by cytochromes P450 2C9, 2C19 and 3A4, and by P-glycoprotein[74,75] and has a narrow therapeutic range.[59] *In vitro* evidence shows Boswellia may inhibit the activity of these enzymes,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically these actions could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Flecainide:** This Class IC anti-arrhythmic drug is metabolized by cytochrome P450 2D6[76,77] and has a narrow therapeutic range.[46,71] *In vitro* evidence shows Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Fosamprenavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and by P-glycoprotein and has a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] These actions may theoretically change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Gallstones or gallbladder disease:** Turmeric, which contains curcumin, can benefit gallbladder health through promoting the flow of bile via stimulation of gallbladder contraction.[32] This stimulation of gallbladder contraction may cause problems in some patients.[36,37] Monitor patients with a history of gallbladder disease and adjust dosing or discontinue use if required.
- **Gastrointestinal irritation:** Turmeric, which contains curcumin, benefits gastrointestinal health;[32] however, in some people large doses of turmeric may cause gastrointestinal irritation (e.g. in people with history of peptic ulcers, reflux, etc.)[32,37] Due to the potential benefits in these conditions, recommend to take after food in these patients, monitor their progress, and adjust dosing down if required.
- **Immunosuppressants:** *In vitro* studies show that Boswellia has immunostimulant properties. Theoretically, Boswellia might decrease the effectiveness of immunosuppressive drugs.[49] Immunosuppressant drugs include azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate, tacrolimus, sirolimus, prednisone, and other corticosteroids (glucocorticoids). Use together only underthe supervision of a healthcare practitioner.
- **Indinavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and by P-glycoprotein and has a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] These actions may theoretically change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Levothyroxine:** This thyroid hormone is a substrate for cytochrome P450 3A4[79,80] and has a narrow therapeutic range.[81,48] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Lopinavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and by P-glycoprotein and has a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Nelfinavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochromes P450 2C19 and 3A4[82,83] and by P-glycoprotein[59,60] and has

a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of these CYP enzymes,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.

- **Nevirapine:** This HIV antiretroviral nonnucleoside reverse transcriptase inhibitor is metabolized by cytochrome P450 3A4 and has a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Olanzapine:** This antipsychotic medication is used for the treatment of schizophrenia and bipolar disorder. It is metabolized by cytochromes P450 1A2, 2C19, and 2D6[84,85,86] and has a narrow therapeutic range.[74,87] *In vitro* evidence shows that Boswellia may inhibit the activity of all these enzymes,[35,49] and turmeric, which contains curcumin, inhibits the activity of CYP 1A2.[37,50] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and only under medical supervision.
- **Perhexiline:** This antiarrhythmic drug is metabolized by cytochrome P450 2D652,[88] and has a narrow therapeutic range.[89,90] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and only under medical supervision.
- **Phenobarbital (Phenobarbitone):** This barbiturate is a widely used antiseizure medication that is metabolized by cytochromes P450 1A1, 1A2, 2C9, 2C19, and 3A4 and by P-glycoprotein[52,91,92] and has a narrow therapeutic range.[46,48] *In vitro* evidence shows that Boswellia may inhibit the activity of CYP 1A2, 2C9, 2C19, and 3A4.[35,49] Turmeric, which contains curcumin, inhibits the activity of CYP 1A1 and 1A2,[37,50] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38, 57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Phenytoin:** This antiepileptic, anticonvulsant, and anti-seizure drug is metabolized by cytochromes P450 1A2, 2C9, 2C19, and 3A4[52,93,94] and has a narrow therapeutic range.[47,48] *In vitro* evidence shows that Boswellia may inhibit the activity of these enzymes,[35,49] and turmeric, which contains curcumin, inhibits the activity of CYP 1A2.[37,50] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Procainamide:** This antiarrhythmic drug is metabolized by cytochrome P450 2D6[95,96] and has a narrow therapeutic range.[48,74] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and only under medical supervision.
- **Propafenone:** This Class IC antiarrhythmic drug is metabolized by cytochromes P450 1A2, 2D6, and 3A4[97] and has a narrow therapeutic range.[71,98] *In vitro* evidence shows that Boswellia may inhibit the activity of these enzymes,[35,49] and turmeric, which contains curcumin, inhibits the activity of CYP 1A2.[37,50] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and only under medical supervision.
- **Quinidine:** This antimalarial and Class IA antiarrhythmic drug is metabolized by cytochromes P450 2D6 and 3A4 and by P-glycoprotein[52,99] and has a narrow therapeutic range.[71,90] *In vitro* evidence shows that Boswellia may inhibit the activity of these enzymes,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Rifampicin (rifampin):** This antibiotic drug is metabolized by cytochromes P450 1A2, 2C8, 2C9, 2C19, and 3A4 and by P-glycoprotein[99,100] and has a narrow therapeutic range.[48,63] *In vitro* evidence shows that Boswellia may inhibit the activity of these enzymes;[35,49] turmeric, which contains curcumin, inhibits the activity of CYP 1A2,[37,50] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Ritonavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochromes P450 2D6 and 3A4[101,102] and P-glycoprotein[59, 60] and has a narrow therapeutic range.[59, 60] *In vitro* evidence shows that Boswellia may inhibit the activity of these enzymes,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Saquinavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and by P-glycoprotein and has a narrow therapeutic range.[59, 60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38, 57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Sirolimus (rapamycin):** This immunosuppressant antirejection drug is metabolized by cytochrome P450 3A4 and by P-glycoprotein[103,104] and has a narrow therapeutic range.[90,105] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and consult the patient's specialist if prescribed to manage organ transplantation.
- **Tacrolimus:** This potent immunosuppressant antirejection drug is metabolized by cytochrome P450 3A4[106,107] and has a narrow therapeutic range.[71,108] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[49,35] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and consult the patient's specialist if prescribed to manage organ transplant.
- **Tamoxifen:** In animal research, sesame seed reduces the tumor-inhibitory effect of tamoxifen by reducing apoptosis and increasing proliferation.

Theoretically, large doses of sesame might interfere with tamoxifen.[35,109,110] Use with caution and only under medical supervision.

- **Theophylline:** This methylxanthine drug is used for acute relief in respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. This drug is metabolized by cytochromes P450 1A1,1A2, and 3A4[111,112] and has a narrow therapeutic range.[48,63] *In vitro* evidence shows that Boswellia may inhibit the activity of CYP 1A2 and 3A4,[35,49] and turmeric, which contains curcumin, inhibits the activity of CYP 1A1 and 1A2.[37,50] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for any adverse effects.
- **Tipranavir:** This HIV antiretroviral protease inhibitor is metabolized by cytochrome P450 3A4 and by P-glycoprotein[59, 60] and has a narrow therapeutic range.[59,60] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] and sesame seed oil has the potential to affect the clearance of drugs that are transported via P-glycoprotein.[38,57] Theoretically, these actions may change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for symptom changes.
- **Valproate (sodium valproate):** This antiepileptic, anticonvulsant, and antiseizure drug is metabolized by cytochrome P450 3A4[52,113] and has a narrow therapeutic range.[70] *In vitro* evidence shows that Boswellia may inhibit the activity of this enzyme,[35,49] which theoretically could change the drug's therapeutic effect. Use cautiously in patients on this medication and monitor for any adverse effects.

Pregnancy

Caution. Safety has not been conclusively established during pregnancy. Practitioner discretion is advised when prescribing for use in pregnancy due to the following cautions:

- **Boswellia:** Evidence states that there is no increased risk of harm to the fetus from limited use in woman.[70] However, traditional text states that Boswellia is contraindicated during pregnancy.[114] A review by the Natural Standard Research Collaboration states, "reports in Indian literature say that the resin from Boswellia may be an emmenagogue and induce abortion."[115]

Breastfeeding

Limited/unavailable research. A review did not identify any concerns for use during breastfeeding;[35,38] however, safety has not been conclusively established.

Children

Limited/unavailable research. A review did not identify any concerns for use in children;[116] however, safety has not been conclusively established.

*Phospholipids possess stabilizing, emulsifying, and solubilizing properties that can enhance the delivery of therapeutic compounds.

**Curcumin within an enhanced delivery matrix format equivalent to 10-fold greater absorption than natural curcumin.

†Negative side effects associated with NSAIDs include gastrointestinal, cardiovascular, and renal side effects; negative effects associated

‡SpeedTech is a proprietary high-speed mixture method that involves specialized milling micronization technology to create a highly bioavailable dispersion of therapeutically active compounds.

§Grade 1 muscle strain is characterized by <5% loss of muscle function.

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