

## Synergetic effect of NovaSOL® Curcumin / Boswellia

Inflammation is one of the major causes for the development of different diseases like arthritis, cancer, cardiovascular disease, diabetes, obesity, osteoporosis, inflammatory bowel disease, asthma, and even central nervous system-related diseases such as depression and Parkinson's disease<sup>1</sup>.

Reports in the literature suggest that almost 90% of synthetic anti-inflammatory drugs produce drug related toxicities and additional adverse effects<sup>2,3</sup>.

Consequently, an immense interest has reemerged in herbs exerting anti-inflammatory activity as a potential alternative for the prevention of inflammation with much fewer side effects. The most promising and widely used herbs in this context are *Curcuma longa* and *Boswellia serrata*.

### Curcumin

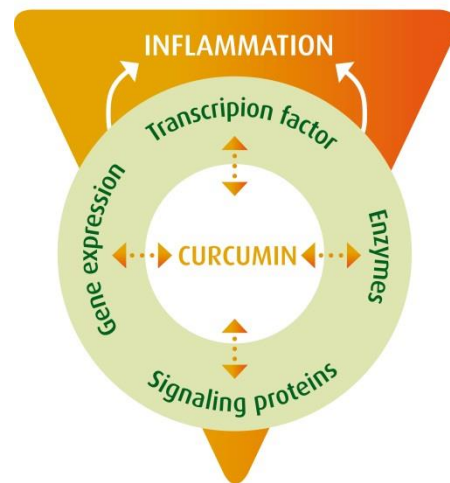
*Curcuma*, traditionally used in Ayurvedic medicine, is a well-studied compound known for its antioxidant and anti-inflammatory properties<sup>4,7</sup>. The three major curcuminoids isolated from *Curcuma longa* are curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the primary component. Numerous studies have demonstrated its activity and therapeutic effects for different health issues including joint, brain, cardiovascular and gastro-intestinal health.



Curcumin exerts its anti-inflammatory activity through multiple molecular targets and mechanisms of action. It mainly affects and

modulates the presence of proinflammatory signaling molecules and enzymes. This is done by the down-regulation of pro-inflammatory signals (cyclooxygenase-2 [COX-2], 5-lipoxygenase [5-LO] prostaglandins, leukotrienes) and cytokines (TNF- $\alpha$ , interleukin-1 beta [IL-1 $\beta$ ], interleukin-6 [IL-6], nuclear factor kappa B [NF- $\kappa$ B])<sup>7,8</sup>.

### Mechanism of curcumin to reduce inflammation



Although curcumin has exhibited much therapeutic promise, its use has been limited by its poor intestinal absorption, rapid metabolism, and limited systemic bioavailability<sup>9</sup>.

While various techniques have been developed to increase the bioavailability of curcuminoids, with the aim to obtain pharmacologically relevant blood serum levels, many are not able to accommodate high loading of curcumin, thus limiting the bioactivity of the finished products.

The NovaSOL® micellation technology based on micellar solubilisation of curcumin, has been shown to result in the largest increase of curcumin bioavailability reported to date. In a human clinical trial, where up to 185-fold larger AUC and a 455-fold higher maximum total curcumin plasma concentration (C<sub>max</sub>)

were observed for micellar curcumin compared to the native form<sup>12</sup>.



NovaSOL<sup>®</sup> Curcumin offers a liquid, soluble form of curcumin extract which results in effective blood serum curcuminoid levels at a low daily dose.

## **Boswellia**

In the last couple of years the use of *Boswellia serrate* extracts as a natural, herbal anti-inflammatory compound has gained popularity and the amount of scientific publications describing its activity has increased.

*Boswellia* extracts are shown to have positive effects in mainly joint, gastro-intestinal and respiratory health<sup>13-18</sup>.



The mechanism of anti-inflammatory activity of the *Boswellia* extract is due to the boswellic acids (BA's) which are the active principals of frankincense. It was shown that a number of pivotal enzymes in the inflammation process (5-lipoxygenase [5-LO], cathepsin G [catG], and microsomal prostaglandin-E synthase [mPGES-1]) as well as nuclear transcription

factor  $\kappa$ B (NF- $\kappa$ B) and several pro-inflammatory cytokines (tumor necrosis factor [TNF $\alpha$ ], interleukin [IL]-1 $\beta$ , IL-2, and IL-6) are inhibited by boswellic acids (BAs). Specifically 3-O-acetyl-11-keto-boswellic acid (AKBA) is the most active BA, modulating the lipoxygenase pathway of arachidonate metabolism<sup>19-21</sup>.

*Boswellia* extracts usually have poor bioavailability because of their hydrophobicity and poor water solubility. Pharmacokinetic studies conducted in human and in animal models indicate that after oral administration of *Boswellia* products, a sufficient systemic concentration of AKBA is required for its anti-inflammatory activity<sup>22-26</sup>. Poor absorption through the intestine, and/or extensive metabolism is the crucial factor affecting the systemic availability of AKBA and thus limiting the anti-inflammatory efficacy of standard *Boswellia* extracts.

By the preparation of a micellar formula in the form of liquid NovaSOL<sup>®</sup> *Boswellia*, the bioavailability is strongly increased. The administration of a *Boswellia* extract in its solubilized form is shown to result in a significant increase of BA plasma concentrations, specifically AKBA for which the bioavailability is increased up to 50 fold<sup>27</sup>.

## **Combination Curcumin / Boswellia**

While the activity of both Curcumin and *Boswellia* extracts have individually been well defined, the combination of both can further promote their multi-target anti-inflammatory activity. The diversity in the mechanism of action of these actives will result in a synergistic effect with additional benefits.



While both Curcumin and Boswellia partly affect the same inflammatory pathway by modulation of NF- $\kappa$ B and several other pro-inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$ , IL-2, and IL-6), Curcumin also acts as free radical scavenger and selectively down-regulates the activity of cyclooxygenase-2 (COX-2). Boswellia in its turn modulates the lipoxygenase pathway (5-lipoxygenase [5-LO]).

As the activity of both Curcumin and Boswellia extracts is affected by their low bioavailability, micellar solubilization also results in an increased anti-inflammatory activity of curcumin, boswellia and their combination compared to their respective native forms.

A new study shows that liquid, micellar curcumin in combination with boswellia not only increases their bioavailability, but also enhances the biological activity [28].

The combination of solubilized curcumin with boswellia resulted in a significantly more potent anti-inflammatory activity in comparison with native and standalone extracts.

#### Key features NovaSOL® Curcumin / Boswellia

- Potent anti-inflammatory combination
- High bioavailability
- Effective at low dosages
- Synergetic effect
- Strongly supported by science

#### References

1. Laveti, D., Kumar, M., Hemalatha, R., Sistla, R., *et al.* Anti-inflammatory treatments for chronic diseases: a review. *Inflamm. Allergy Drug Targets*, 2013, 12, 349-361
2. Lanas, A. Non-steroidal anti-inflammatory drugs and cyclooxygenase inhibition in the gastrointestinal tract: a trip from peptic ulcer to colon cancer. *Am. J. Med. Sci.* 2009, 338, 96-106.
3. Kandulski, A., Venerito, M., Malfertheiner, P. Non-steroidal anti-inflammatory drugs (NSAIDs) – balancing gastrointestinal complications and the cardiovascular risk. *Dtsch. Med. Wochenschr.* 2009, 134, 1635-1640.
4. Prasad, S., Gupta, S.C., Tyagi, A.K., Aggarwal, B.B. Curcumin, a component of golden spice: from bedside to bench and back. *Biotechnol Adv.* 2014, 32, 1053-1064
5. Amalraj, A., Varma, K., Jacob, J., Divya, C., Kunnumakkara, A.B., Stohs, S.J., Gopi, S. A Novel Highly Bioavailable Curcumin Formulation Improves Symptoms and Diagnostic Indicators in Rheumatoid Arthritis Patients: A Randomized, Double-Blind, Placebo- Controlled, Two-Dose, Three-Arm, and Parallel-Group Study. *J. Med. Food.*, 2017, 20, 1022-1030
6. Moghadamtousi, S.Z., Kadir, H.A., Hassandarvish, P., Tajik, H., Abubakar, S., Zandi, K. A review on antibacterial, antiviral, and antifungal activity of curcumin. *Biomed. Res. Int.*, 2014, ID186864
7. Jurenka, J.S. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. *Altern. Med. Rev.* 2009, 14, 141–153
8. Bisht, K., Wagner, K.H., Bulmer, A.C. Curcumin, resveratrol and flavonoids as antiinflammatory, cyto- and DNA-protective dietary compounds. *Toxicol.* 2010, 278, 88–100.
9. Douglass, B.J., Cloutre, D.L. Beyond yellow curry: Assessing commercial curcumin absorption technologies. *J. Am. Coll. Nutr.* 2015, 34, 347–358

10. Schiborr, C., Kocher, A., Behnam, D., Jandasek, J., et al. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Mol. Nutr. Food Res.*, 2014, 58, 516–527
11. Kocher, A., Schiborr, C., Behnam, D., Frank, J. The oral bioavailability of curcuminoids in healthy humans is markedly enhanced by micellar solubilisation but not further improved by simultaneous ingestion of sesamin, ferulic acid, naringenin and xanthohumol. *J. Funct Foods* 2015,14, 183–191
12. Kocher, A., Bohnert, L., Schiborr, C., Frank, J. Highly bioavailable micellar curcuminoids accumulate in blood, are safe and do not reduce blood lipids and inflammation markers in moderately hyperlipidemic individuals. *Mol. Nutr. Food Res.* 2016, 60, 1555-1563
13. Sander O, Herborn G and Rau R: Is H15 (resin extract of *Boswellia serrata*, 'incense') a useful supplement to establish drug therapy of chronic polyarthritis? Results of a double-blind pilot study. *Z Rheumatol* 57: 11-16, 1998 (In German)
14. Gerhardt H, Seifert F, Buvari P, et al: Therapy of active Crohn disease with *Boswellia serrata* extract H15. *Z Gastroenterol* 39: 11-17, 2001 (In German)
15. Kimmattkar N, Thawani V, Hingorani L and Khiyani R: Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee - a randomized, double-blind, placebo-controlled trial. *Phytomedicine* 10: 3-7, 2003
16. Sontakke S, Thawani V, Pimpalkhute P, et al: Open, randomized, controlled clinical trial of *Boswellia serrata* extract as compared to valdecoxib in osteoarthritis of the knee. *Indian J Pharmacol* 39: 27-29, 2007
17. Sengupta K, Alluri KV, Satish AR, et al: A double-blind, randomized, placebo-controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. *Arthritis Res Ther* 10: R85, 2008
18. Madisch A, Miehle S, Eichele O, et al: *Boswellia serrata* extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. *Int J Colorectal Dis* 22: 1445-1451, 2007
19. Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR and Ammon HP: Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. *J Pharmacol Exp Ther* 261: 1143-1146, 1992
20. Sailer ER, Subramanian LR, Rall B, Hoernlein RF, Ammon HP and Safayhi H: Acetyl-11-keto-beta-boswellic acid (AKBA): structure requirements for binding and 5-lipoxygenase inhibitory activity. *Br J Pharmacol* 117: 615-618, 1996
21. Sailer ER, Schweizer S, Boden SE, Ammon HP and Safayhi H: Characterization of an acetyl-11-keto-beta-boswellic acid and arachidonate-binding regulatory site of 5-lipoxygenase using photoaffinity labeling. *Eur J Biochem* 256: 364-368, 1998
22. Abdel Tawab M, Kaunzinger A, Bahr U, Karas M, Wurglics M, Schubert-Zsilavecz M (2001) Development of a high-performance liquid chromatographic method for the determination of 11-keto-b-boswellic acid in human plasma. *J Chromatogr Biomed Appl* 761:221–227
23. Buchele B, Simmet T (2003) Analysis of 12 different pentacyclic triterpenic acids from frankincense in human plasma by high-performance liquid chromatography and photodiode array detection. *J Chromatogr B* 795:355–362
24. Sharma S, Thawani V, Hingorani L, Shrivastava M, Bhate VR, Khiyani R (2004) Pharmacokinetic study of 11-keto-b-boswellic acid. *Phytomedicine* 11:1255–1260
25. Sterk V, Buchele B, Simmet T (2004) Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. *Planta Med* 70:1155–1160
26. Kruger P, Daneshfar R, Eckert GP, Klein J, Volmer DA, Bahr U, Muller WE, Karas M, Schubert-Zsilavecz M, Abdel Tawab M (2008) Metabolism of boswellic acids in vitro and in vivo. *Drug Metab Dispos* 36:1135–1142
27. Mona Abdel-Tawab. Enhanced absorption of boswellic acids by a micellar solubilized delivery form of *Boswellia* extract. *NFS Journal* 11 (2018) 12–16
28. T. Khayyal et Al. Micellar solubilisation enhances the anti-inflammatory activities of curcumin and boswellic acids in rats with adjuvant-induced arthritis. *Nutrition* 54 (2018) 189–196