Curcumin H2O SAP and Curcumin SAP

Science-based curcumin with targeted therapeutic solutions

Curcumin, the major bioactive curcuminoid has poor oral bioavailability owing to its low water solubility, rapid biotransformation via phase II metabolism and systemic elimination. NFH offers two unique formulations **Curcumin H2O SAP** (prepared using a proprietary process) and **Curcumin SAP** for improved bioavailability and targeted therapy

Curcumin H2O SAP-100% WATER SOLUBLE CURCUMINOIDS

- Readily absorbed with excellent plasma bioavailability and stability
- >20 folds better absorption compared to regular curcuminoids
- Higher cellular uptake and efficacy at low doses

Curcumin H2O SAP:

- Supports cancer therapy.
- Improves mitochondrial dynamics.
- Improves rheumatoid arthritis and autoimmune conditions.
- IS a neuroprotective.
- Fosters optimal insulin and lipid metabolism.

Curcumin SAP (with added Piperine):

- Inhibits hepatic and intestinal glucuronidation and elimination of curcuminoids.
- Improves bioavailability of curcuminoids.
- Helps manage inflammatory bowel diseases.
- Supports colon cancer therapy.

ACTIVE INGREDIENTS

Curcumin H2O SAP

Curcumin, 10% water soluble curcuminoids (*Curcuma longa* extract)..... 500 mg

Contains no: Gluten, soy, wheat, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.

Curcumin SAP (with added Piperine)

Turmeric (*Curcuma longa*) extract, 95% curcuminoids ..... 500 mg
Piperine (from *Piper nigrum*) ..... 5 mg

Contains no: Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.

Other ingredients: Vegetable magnesium stearate and silicon dioxide in a vegetable capsule composed of vegetable carbohydrate gum and purified water.

These products are non-GMO.

Curcumin H2O SAP and Curcumin SAP each contain 90 capsules per bottle and deliver curcuminoids (curcumin I, demethoxycurcumin, and bisdemethoxycurcumin)

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

DIRECTIONS FOR USE

Adults: Take 1–2 capsules daily or as directed by your healthcare practitioner.

CAUTIONS AND WARNINGS

Do not take **Curcumin H2O SAP/Curcumin SAP** concurrently with chemotherapy, as it may interfere with the activity of chemotherapy drugs. **Curcumin H2O SAP/ Curcumin SAP** may be taken before and after completion of chemotherapy protocol.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for each product lot number of **Curcumin H2O SAP and Curcumin SAP** have been tested by an ISO 17025 accredited third-party laboratory for identity, potency, and purity.

NFH®

351, Rue Joseph-Carrier, Vaudreuil-Dorion, Quebec, J7V 5V5
T 1 866 510 3123 • F 1 866 510 3130 • nfh.ca

For healthcare professional use only.

SCIENCE-BASED CURCUMIN EXTRACT FROM TURMERIC ROOT

Turmeric (*Curcuma longa L.*) is a medicinal plant reputed for it's use as a spice and herbal remedy in China and India for over 2000 years.[1, 2] In Ayurvedic medicine, turmeric is used for common eye infections, wounds, respiratory ailments, and childbirth.[2] Recent research on this vibrant yellow spice has revealed its numerous beneficial properties, including anti-inflammatory, antioxidant, immunomodulatory activities that have been demonstrated in pre-clinical and human clinical trials.[1, 2] It has also demonstrated antithrombotic and antiplatelet activity, and the therapeutic efficacy of curcumin against various human diseases — including cancer, cardiovascular diseases, diabetes, arthritis, neurodegenerative diseases including Alzheimer's disease,[1] and Crohn's disease — has been very well documented.[1, 2] These medicinal properties of turmeric are mainly attributed to bioactive polyphenolic compounds called curcuminoids which include three principal components namely curcumin (diferuloylmethane; 77%), demethoxycurcumin (also known as curcumin I; 17%) and bisdemethoxycurcumin (also known as curcumin II; 6%).[3] Curcuminoids are obtained from dried rhizomes of turmeric and exert significant anti-inflammatory and cardioprotective effects.[4]

CURCUMIN-PIPERINE SYNERGY

Combination of curcumin/curcuminoids and piperine from *Piper nigrum* extract has been clinically shown to increase the bioavailability of curcuminoids by almost 20 folds.[5] Researchers reported the specific increase in bioavailability of curcumin itself and not its phase II metabolites. The rapid biotransformation of curcumin via phase II metabolism lowers the bioactivity of curcumin. Piperine is known to inhibit the formation of phase II metabolites by inhibiting hepatic and intestinal glucuronidation.[6] Simultaneous consumption of 5 mg of piperine along with curcuminoids has shown to increase the bioavailability of curcumin.[6] In addition, the thermogenesis activity of piperine facilitates sustenance of the metabolic process and enables better absorption of nutrients in the intestine.[5, 6]

COLON AND DIGESTIVE HEALTH

Inflammatory Bowel diseases

Curcumin has been known to promote colon health by playing a key role by modulating NF-κB pro-inflammatory cytokines and the IL-6/STAT3 signaling pathway and could be therapeutically useful in several colonic inflammatory diseases, such as inflammatory bowel disease (IBD; ulcerative colitis and Crohn's disease).[7] Two clinical studies have evaluated the use of curcumin in IBD in 99 patients with UC and CD.[7, 8] As an adjunct to mainstream therapy (sulfasalazine (SZ) or mesalamine (5-aminosalicylic acid [5-ASA] derivatives or corticosteroids), curcumin dosed at 1100-2000 mg/day over 2-6 months duration has been shown to significantly improve patient symptoms in UC/CD patients compared to the placebo and enabled dosage reduction of corticosteroids or 5-ASA derivatives.[7, 8] Researchers reported that in the small study of 10 patients, some patients even stopped taking corticosteroids or 5-ASA.[7] Researchers also noted that curcumin had better clinical efficacy over placebo in the prevention of relapse and was well-tolerated.[8] Based on this evidence, curcumin could be a promising and safe therapy for maintaining remission in patients with IBD and can be used as a steroid-sparing induction agent in mild to moderate colitis or as an adjunct to maintaining remission in patients non-responsive to immunomodulators.

Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer deaths in Canadian men and women.[9] Risk factors for the disease include advancing age, colorectal polyps, inflammatory bowel disease, a diet high in red meat, physical inactivity, obesity, and type II diabetes.[10] Curcumin has been shown to attenuate the progression of CRC by acting on multiple molecular processes to arrest the cell cycle, inhibit the inflammatory and oxidative stress responses, and slow angiogenesis.[11, 12, 13] An *in vitro* study examining metastatic colon cancer cell lines HCT-116 and SW480 discerned that inhibition of the cancer cell proteasome, leading to suppression of cell proliferation and subsequent apoptosis, could be one of the mechanisms for the chemopreventive roles of curcumin in human colon cancer.[14]

Curcumin also modulates other key players involved in carcinogenesis, such as cyclooxygenase-2 (COX-2), matrix metallopeptidases 2 and 9 and tumor necrosis factor α-induced vascular cell adhesion molecule.[15] In two separate clinical trials, the effect of curcumin on malignancies and tumor marker levels in fifteen patients with advanced CRC refractory to standard chemotherapies was explored.[16] Patients were administered a standardized *C. longa* extract in capsule form (at doses ranging from 440 to 2200 mg/d, corresponding to 36-180 mg of curcumin) for up to 4 months. *C. longa* extract was well-tolerated, and dose-limiting toxicity was not observed. In a follow-up second dose-escalation study where doses were increased to 0.45 and 3.6 g/d for 4 months, decreases of 62% and 57% in inducible plasma prostaglandin E2 (PGE2) levels were observed.[16] PGE2 is an end product of cyclooxygenase that has been shown to stimulate the growth of human colorectal cancer cells.[16] In another study evaluating the effects of curcumin levels in the colorectum and the pharmacodynamics of curcumin in 12 patients with confirmed CRC, a dosage level of 3.6 g of curcumin was reported to be pharmacologically efficacious in reducing M1G levels, but not COX-2 levels in malignant colorectal tissue.[17] Noteworthy, curcumin levels were found to be highest in the normal tissue of the cecum and the ascending colon as opposed to the transverse colon, the splenic flexure and the descending colon, which suggests a local effect.[17]

Curcumin has been observed to act as an adjunct in combination with other agents for the prevention and treatment of CRC.[18] Familial adenomatous polyposis (FAP) is an autosomal-dominant disorder characterized by hundreds of colorectal adenomas that eventually develop into CRC. In one study, supplementation with the curcumin-quercetin combination (480 mg and 20 mg, respectively), for 6 months suppressed adenomas in patients with FAP evidenced by the reduction in size and number of ileal and rectal polyps.[18] In another study, oral curcumin supplementation at 4 g/day for 1 month significantly reduced the number of abnormal crypt foci. Curcumin has demonstrated the potential to be beneficial in all 3 stages of carcinogenesis.[19] A recent cell culture study found that curcumin selectively destroys colon cancer cells sparing normal cells by increasing the level of the growth arrest and DNA-damage-inducible protein (GADD45-α), which is known to be activated during DNA damage. Interestingly, curcumin was found to not trigger the increase of the same protein in normal cells.[20] These observations suggest the potential chemopreventive role of curcumin in colon cancer.

CURCUMIN WATER SOLUBILITY AND BIOAVAILABILITY

A crucial aspect of nutrient metabolism is it's bioavailability and the clinical efficacy of curcumin has been limited due it's poor bioavailability stemming from its instability at low intestinal pH values, and low water solubility.[3] Also, curcumin undergoes rapid metabolism resulting in conjugation and systemic elimination. Daily doses of up to 12 g in healthy adults have consistently been well tolerated with no dose-limiting toxicity.[2, 3] However, curcuminoids are hydrophobic, and numerous studies report low plasma and tissue levels even with high-dose supplementation that may be due to poor absorption, rapid metabolism, and rapid systemic elimination.[3] Despite this, the clinical efficacy of curcumin cannot be denied: even studies that report minimal curcumin absorption have shown significant therapeutic effect.[3] The challenge is to get curcumin into circulation and usually curcumin is reported to be stable in plasma and even accessible to other tissues in the body such as the brain. Several approaches exist that help improve plasma bioavailability of curcumin and increasing the water solubility of curcumin is suggested to increase bioavailability by multiple folds, up to the order of > 20 folds.[3] Water-soluble curcumin (10%) is prepared by emulsification of turmeric oleoresin with polysorbate and subsequent dilution with maltodextrin and dissolution in water followed by spray drying. This water-soluble form has greater stability and enhanced plasma bioavailability for targeted health benefits. Recently, water soluble forms have demonstrated their potential to help prevent muscle damage and attenuate oxidative stress by regulating the nuclear factor-κB and nuclear factor (erythroid-derived 2)-like 2 pathways and improve the exercise induced inflammation in an *in vivo* model.[21] The study also suggests that the water soluble curcumin could positively modulate mitochondrial biogenesis, thereby opening a plethora of mitochondria targeted health applications.[21]

In another study using an experimental type-1 diabetes animal model, researchers demonstrated that a small dose of water-soluble curcumin profoundly reduced plasma glucose and improve insulin responses in addition to improving the lipid profile and oxidative status.[22] Notably, water soluble curcumin was found to retain the essential potencies of natural curcumin.[22] Overall, existing evidence supports the potential benefits of water soluble curcumin in terms of improved cellular uptake and efficacy at low doses.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease, causing progressive joint destruction, deformity and disability, and that afflicts approximately 1% of the Canadian population.[23] In a double-blind crossover study of rheumatic patients, 1200 mg/d of curcumin was found to be well tolerated with no side effects, and exerted comparable antirheumatic activity to 300 mg phenylbutazone, an NSAID commonly prescribed to RA patients.[24]

This condition is characterized by hyperplasia of the synovial fibroblasts due in part to decreased apoptosis,[23] and synovial inflammation which is mediated through the cyclooxygenase (COX) catalyzation of arachidonic acid into prostaglandins (PG).[23] Additionally, COX-2 has been shown to downregulate cell apoptosis, exacerbating synovial thickening.[23] Exposure of synovial fibroblasts to curcumin in vitro resulted in decreased fibroblast growth via induction of fibroblast apoptosis, as well as reduced levels of COX-2 and PGE2,[23] suggesting a possible mechanism for the role of curcumin in treating patients with RA.

IMMUNOMODULATORY AND CHEMOPREVENTIVE ACTIVITY OF CURCUMIN

Curcumin has demonstrated its chemopreventive potential by inhibiting development and progression, targeting several steps in the pathway to malignancy[25]. Cancer-specific studies have demonstrated the chemopreventive effects of curcumin in leukemia[25] and colorectal,[11, 12, 13] prostate,[26, 27] bladder,[28] ovarian,[29] cervical,[30] and malignant glioma[31] cancers.

PROSTATE HEALTH

Prostate cancer is the most commonly diagnosed cancer in men and is the second leading cause of cancer-related deaths in North America.[26] Conventional medical treatment options — including surgery, chemotherapy, and radiation therapy — have demonstrated limited efficacy, particularly in the advanced stages of the disease, and metastatic disease remains incurable.[26] Hormone-sensitive tumours respond well to androgen reduction therapy, but hormone-refractory clones are often generated after treatment.[26] Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is a new treatment option for advanced prostate cancer that works by inducing apoptosis in various cancer cell types in vitro with little or no cytotoxicity to normal cells and exhibits antitumour activity in vivo without systemic toxicity.[26, 27] Concomitant supplementation with curcumin increases the sensitivity of hormone-refractory prostate cancer cells to TRAIL, leading to enhanced apoptosis.[26, 27]

CURCUMIN IS NEUROPROTECTIVE

Strokes are the 3rd leading cause of death in Canada, accounting for 7% of all deaths, and afflicting women more than men.[32] Ischemic stroke accounts for 80% of all strokes and occurs in two stages: in the first hour of reperfusion following 2 h of occlusion of the middle cerebral artery, the tissue is extensively restored, but secondary deterioration is observed at 4 h after recovery and onwards.[33] To study the neuroprotective effects of curcumin, cerebral ischemia was induced in rats via thromboembolic occlusion of the middle cerebral artery, and curcumin was administered after 4 h. Intraperitoneal curcumin injections resulted in dose-dependent reductions in cerebral infarct, edema volume, brain neutrophil infiltration, and neuronal reactive oxygen species levels, and aided in the maintenance of glutathione status.[33] Curcumin supplementation also significantly reduced sensory motor function deficits as evaluated 24h poststroke.[33] In another study exploring curcumin's neuroprotective effects, neuronal cells cultured with microglial cells were exposed to dopamine, LPS, and Aβ, three stimuli known to activate microglial cells, causing them to produce inflammatory mediators that induce neuronal cell death.[34] Dopamine also directly induces apoptosis of neuronal cells, by generating toxic metabolites such as hydrogen peroxide.[34] It was found that while curcumin failed to protect against dopamine-directed neuronal cell death, it exhibited dose-dependent blockade of the production of inflammation and cytotoxic mediators such as NO, TNF-α, IL1a, and IL6 produced from Aβ and LPS-stimulated microglia, suggesting that curcumin-mediated neuroprotective effects may be mostly due to its anti-inflammatory activity.[34]

REFERENCES

1. Pari, L., D. Tewas, and J. Eckel. "Role of curcumin in health and disease." Archives of Physiology and Biochemistry Vol. 114, No. 2 (2008): 127–149.
2. Hatcher, H., et al. "Curcumin: from ancient medicine to current clinical trials." Cellular and Molecular Life Sciences Vol. 65, No. 11 (2008): 1631–1652.
3. Anand, P., et al. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007 Nov-Dec;4(6):807-18. Epub 2007 Nov 14.
4. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res. 2014 May;28(5):633-42
5. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Planta Med. 1998, 64 (4), 353-6.
6. Singh J, Dubey RK, Atal CK. J. Pharmacol. Exp. Ther. 1986, 236 (2), 488-93.
7. Holt, P.R.; Katz, S.; Kirshoff, R. Curcumin therapy in inflammatory bowel disease: A pilot study. *Dig. Dis. Sci.* 2005, *50*, 2191–2193.
8. Hanai, H., et al. Curcumin maintenance therapy for ulcerative colitis: Randomized, multicenter, double-blind, placebo-controlled trial. *Clin. Gastroenterol. Hepatol.* 2006, 4, 1502–1506.
9. Colorectal Cancer Association of Canada
10. American Cancer Society
11. Villegas, I., S. Sánchez-Fidalgo, and C. Alarcón de la Lastra. "New mechanisms and therapeutic potential of curcumin for colorectal cancer." Molecular Nutrition & Food Research Vol. 52, No. 9 (2008): 1040–1061.
12. Watson, J.L., et al. "Curcumin induces apoptosis in HCT-116 human colon cancer cells in a p21-independent manner." Experimental and Molecular Pathology Vol. 84, No. 3 (2008): 230–233.
13. Ryu, M., et al. "Natural derivatives of curcumin attenuate the Wnt/β-catenin pathway through downregulation of the transcriptional coactivator p300." Biochemical and Biophysical Research Communications.
14. Milacic, V., et al. "Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo." Cancer Research Vol. 68, No. 18 (2008): 7283–7292.
15. Dulbecco, P., & Savarino, V. Therapeutic potential of curcumin in digestive diseases. World J Gastroenterol. 2013 Dec 28; 19(48): 9256–9270.
16. Sharma, R.A., et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 2004; 10: 6847-6854.
17. Garcea, G., et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev 2005; 14: 120-125.
18. Cruz-Correa, M., et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol 2006; 4: 1035-1038.
19. Carroll, R.E., et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res (Phila) 2011; 4: 354-364.
20. Naick H., et al. GADD45α modulates curcumin sensitivity through c-Abl- and JNK-dependent signaling pathways in a mismatch repair-dependent manner. Mol Cell Biochem. 2016 Mar;414(1-2):13-22.
21. Sahin, K., et al. Curcumin prevents muscle damage by regulating NF-κB and Nrf2 pathways and improves performance: an in vivo model. J Inflamm Res. 2016; 9: 147–154.
22. Aziz, MT., et al. Effect of novel water soluble curcumin derivative on experimental type- 1 diabetes mellitus (short term study). Diabetology & Metabolic Syndrome20124:30
23. Park, C., et al. "Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis." International Journal of Molecular Medicine Vol. 20, No. 3 (2007): 365–372.
24. Goel, A., A. Kunnumakkara, and B. Aggarwal. "Curcumin as 'Curecumin': from kitchen to clinic." Biochemical Pharmacology Vol. 75, No. 4 (2008): 787–809.
25. Su, C., et al. "Curcumin inhibits WEHI-3 leukemia cells in BALB/c mice in vivo." In Vivo Vol. 22, No. 1 (2008): 63–68. Vol. 377, No. 4 (2008): 1304–1308.
26. Deeb, D., et al. "Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-κB through suppression of IκB phosphorylation." Molecular Cancer Therapeutics Vol. 3, No. 7 (2004): 803–812.
27. Deeb, D., et al. "Chemosensitization of hormone-refractory prostate cancer cells by curcumin to TRAIL-induced apoptosis." Journal of Experimental Therapeutics & Oncology Vol. 5, No. 2 (2005): 81–91.
28. Tian, B., et al. "Effects of curcumin on bladder cancer cells and development of urothelial tumors in a rat bladder carcinogenesis model." Cancer Letters Vol. 264, No. 2 (2008): 299–308.
29. Javvadi, P., et al. "The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway." Molecular Pharmacology Vol. 73, No. 5 (2008): 1491–1501.
30. Wahl, H., et al. "Curcumin enhances Apo2L/TRAIL-induced apoptosis in chemoresistant ovarian cancer cells." Gynecologic Oncology Vol. 105, No. 1 (2007): 104–112.
31. Gao, X., et al. "Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome C from mitochondria." Journal of Experimental Therapeutics & Oncology Vol. 5, No. 1 (2005): 39–48.
32. Heart and Stroke Foundation of Canada
33. Dohare, P., et al. "Dose dependence and therapeutic window for the neuroprotective effects of curcumin in thromboembolic model of rat." Behavioural Brain Research Vol. 193, No. 2 (2008): 289–297.
34. Lee, H., et al. "Neuroprotective effect of curcumin is mainly mediated by blockade of microglial cell activation." Die Pharmazie Vol. 62, No. 12 (2007): 937–942.

For healthcare professional use only.