1 Dix Street
Worcester, MA 01609
508.752.1099
508.752.0993
www.bioactives.com

BioActives LLC.

Demethoxycurcumin and Bis-demethoxycurcumin From Turmeric

The culinary spice turmeric (*Curcuma longa)* is a well-recognized and highly-recommended herb in the Ayurvedic system of medicine. Many recent studies support the use of turmeric extracts, and its active component, curcumin, for its anti-inflammatory activity, inhibitory effect on tumor prorogation and neuroprotective effect. Turmeric extracts are usually standardized to 95% total curcuminoids. Curcumin is the principal curcuminoid found in commercially-available turmeric extracts. However, the curcuminoid mixtures also include two minor demethylated curcuminoids which are coextracted with curcumin -- demethoxycurcumin and bisdemethoxycurcumin. The commonly observed ratio of curcumin:demethoxycurcumin:bisemethoxycurcumin in commercially-available turmeric extracts is 66:23:11.[i] Animal studies report that coexisting curcuminoids improve the bioavailability of curcumin.[ii]

Like curcumin, these individual demethylated curcuminoids have demonstrated numerous biological properties such having antioxidant, anticarcinogenic, and hypocholesterolemic activities,[iii] as well as shielding progressive neuronal degeneration from increased oxidative attack.[iv] Curcuminoids also have a particular neuroprotective effect for Alzheimer's patients. Accumulation of amyloid-beta (Aβ) is one of the hallmarks of Alzheimer's disease (AD), and efficient clearance of Aβ by cells by phagocytosis of peripheral blood mononuclear cells (PBMCs) may be an important mechanism for controlling or preventing disease onset. PBMCs of most AD patients are defective in the phagocytosis of soluble Aβ. Natural curcuminoids were shown to restore Aβ phagocytosis by AD PBMCs and to up-regulate the expression of key genes.[v] In fact, each component of the curcuminoid mixture distinctly affects apoptotic gene expression in AD animal models, thus highlighting the therapeutic potential of each individual curcuminoid in AD.[vi]

In addition to studies on individual curcuminoids, research on novel mixtures of demethylated curcuminoids have shown to these compounds to be safe[vii] and to exhibit higher neuroprotective and anti-inflammatory efficacy *in vitro* than standard 95% curcuminoid extracts of turmeric.[viii]

In many cases, these minor constituents have been shown have higher potency compared to curcumin and unique activity. Bisdemethoxycurcumin (BDC) has been shown to:

- Have the greatest potency for stimulating Alzheimer Disease peripheral blood mononuclear cells compared to all other natural curcuminoids.[1,5,ix]
- Have higher antimetastasis potency than curcumin.[x]
- Accelerate gastric ulcer healing with potency equal to curcumin.[xi]

- Act as an inhibitor to inactivate human pancreatic α-amylase, a therapeutic target for oral hypoglycemic agents in type-2 diabetes.[xii]
- Have superior endothelial barrier protective activity than that of curcumin[xiii]
- Exhibit the strongest demethylation potency and therefore potential anti-cancer action compared to other curcuminoids.[xiv]
- Exhibit a significant inhibition of MMP-3 expression in breast cancer cells, whereas curcumin had no effect.[xv]

Demethoxycurcumin has been shown to:

- Have a higher antimetastasis potency than curcumin[10]
- Induce Phase II enzyme expression.[3]
- Have higher cytotoxic effects on prostate cancer PC3 cells compared with curcumin.[xvi]
- Exhibit a significant inhibition of MMP-3 expression in breast cancer cells, whereas curcumin had no effect.[14]
- Have the highest effect on spatial memory in AD animal model compared to other curcuminoids.[xvii]
- Exhibit the highest suppressive effect compared to other curcuminoids on anti-inflammatory markers,[xviii] particularly nitric oxide, [xix] TNF-alpha,[19] (NF-kappaB)[xx] and MAPKs[20] activation.
- Have significant protective potential (equal to curcumin) on the prevention of diabetic nephropathy *in vivo*.[xxi]
- Have higher stability than curcumin and significantly inhibit proliferation, migration and invasion of cultured prostate cancer cells[xxii] and breast cancer cells.[xxiii]
- Have higher potency than curcumin in the ability to induce apoptosis.[xxiv]

---

[i] Cashman JR., et al. Immune defects in Alzheimer's disease: new medications development. BMC Neuroscience 2008, 9(Suppl 2):S13.1-8.
[ii] Li R., et al. Metabolic and pharmacokinetic studies of curcumin, demethoxycurcumin and bisdemethoxycurcumin in mice tumor after intragastric administration of nanoparticle formulations by liquid chromatography coupled with tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2011;879(26):2751-8.
[iii] Kou MC., et al. Curcuminoids distinctly exhibit antioxidant activities and regulate expression of scavenger receptors and heme oxygenase-1. Mol Nutr Food Res. 2013. Feb 5. Epub ahead of print.

[iv] Agrawal SS., et al. Neurodegenerative Shielding by Curcumin and Its Derivatives on Brain Lesions Induced by 6-OHDA Model of Parkinson's Disease in Albino Wistar Rats. Cardiovasc Psychiatry Neurol. 2012;942981.
[v]Gagliardi S, et al. Evaluation in vitro of synthetic curcumins as agents promoting monocytic gene expression related to β-amyloid clearance. Chem Res Toxicol. 2012;25(1):101-12.

[vi]Ahmed T., et al. A comparative study of curcuminoids to measure their effect on inflammatory and apoptotic gene expression in an Aβ plus ibotenic acid-infused rat model of Alzheimer's disease. Brain Res. 2011;1400:1-18.
[vii]Krishnaraju AV. Safety and toxicological evaluation of demethylatedcurcuminoids; a novel standardized curcumin product. Toxicol Mech Methods. 2009;19(6-7):447-60.
[viii]Khanna S., et al. Neuroprotective and Antiinflammatory Properties of a Novel Demethylated Curcuminoid. Antioxidants and Redox Signalling. 2009;11(3):449-468.
[ix] Fiala M., et al. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. Proc Natl Acad Sci U S A. 2007;104(31):12849-54.
[x] Yodkeeree S., et al. Curcumin, demethoxycurcumin and bisdemethoxycurcumin differentially inhibit cancer cell invasion through the down-regulation of MMPs and uPA. J Nutr Biochem. 2009; 20(2):87-95.
[xi] Mahattanadul S., et al. Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric ulcer model system. Phytomedicine. 2009;16(4):342-51.
[xii] Ponnusamy S., et al. Discovering Bisdemethoxycurcumin from Curcuma longa rhizome as a potent small molecule inhibitor of human pancreatic α-amylase, a target for type-2 diabetes. Food Chem. 2012;135(4):2638-42.
[xiii]Kim DC, et al. Barrier protective activities of curcumin and its derivative. Inflamm Res. 2012;61(5):437-44.
[xiv] Liu YL, et al. The hypomethylation agent bisdemethoxycurcumin acts on the WIF-1 promoter, inhibits the canonical Wnt pathway and induces apoptosis in human non-small-cell lung cancer. Curr Cancer Drug Targets. 2011;11(9):1098-110.
[xv]Boonrao M. et al. The inhibitory effect of turmeric curcuminoids on matrix metalloproteinase-3 secretion in human invasive breast carcinoma cells. Arch Pharm Res. 2010;33(7):989-98.
[xvi] Hung CM., et al. Demethoxycurcumin Modulates Prostate Cancer Cell Proliferation via AMPK-Induced Down-regulation of HSP70 and EGFR. J Agric Food Chem. 2012 Aug 16. [Epub ahead of print]
[xvii]Ahmed T., et al. Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease. Neuroscience. 2010;169(3):1296-306.
[xviii]Guo LY., et al. Comparison of suppressive effects of demethoxycurcumin and bisdemethoxycurcumin on expressions of inflammatory mediators in vitro and in vivo Arch Pharm Res. 2008;31(4):490-6.
[xix] Zhang LJ., et al. Comparison of inhibitory potency of three different curcuminoid pigments on nitric oxide and tumor necrosis factor production of rat primary microglia induced by lipopolysaccharide. Neurosci Lett. ;447(1):48-53.
[xx] Zhang L., et al. Demethoxycurcumin, a natural derivative of curcumin attenuates LPS-induced pro-inflammatory responses through down-regulation of intracellular ROS-related MAPK/NF-kappaB signaling pathways in N9 microglia induced by lipopolysaccharide. Int Immunopharmacol. 2010;10(3):331-8.
[xxi] Liu JP., et al. The in vitro protective effects of curcumin and demethoxycurcumin in Curcuma longa extract on advanced glycation end products-induced mesangial cell apoptosis and oxidative stress. Planta Med. 2012;78(16):1757-60.
[xxii]Ni X., et al. Demethoxycurcumin inhibits cell proliferation, migration and invasion in prostate cancer cells.
Oncol Rep. 2012;28(1):85-90.
[xxiii]Yodkeeree S., et al. Demethoxycurcumin suppresses migration and invasion of MDA-MB-231 human breast cancer cell line. Eur J Pharmacol. 2010;627(1-3):8-15.
[xxiv] Lee JW., Dimethoxycurcumin, a structural analogue of curcumin, induces apoptosis in human renal carcinoma caki cells through the production of reactive oxygen species, the release of cytochrome C, and the activation of caspase-3.Korean J Urol. 2010;51(12):870-8.