TETRAHYDROCURCUMINOIDs: PRODUCT WRITE-UP
Bioactive Antioxidant Compounds From Curcuminoids

Authors: Muhammed Majeed, Ph.D. & Lakshmi Prakash, Ph.D.
INTRODUCTION

Tetrahydrocurcuminoids (THC)*, a colorless hydrogenated product derived from the yellow curcuminoids, (the biologically active principles from the rhizomes of Curcuma longa), function as efficient antioxidant compounds. The superior antioxidant property of THC, combined with the lack of yellow color, render this product useful in achromatic food and cosmetic applications that currently employ conventional synthetic antioxidants¹.

Curcuminoids are reported to be potent antioxidant compounds by virtue of their molecular structure¹. THC have also shown significant antioxidant action in a number of in vitro and preclinical studies. Tetrahydrocurcuminoids are valued as the ultimate metabolites of the Curcuminoids in vivo². The poor circulating bioavailability³ of the parent curcuminoids, often attributed to their limited uptake due to poor water solubility, often impairs their biological effects in vivo. If supplied as their ultimate metabolites, this problem could be overcome. Substantial beneficial effects could be achieved with lower levels of these active metabolites as compared to the parent compounds. Several independent studies reported the significant antioxidant effects of the Tetrahydrocurcuminoids⁴,⁵,⁶.

METABOLISM OF CURCUMIN

In an early study which elucidated the metabolic disposition of curcumin in rats, Curcumin labeled with deuterium and tritium was prepared. Oral and intraperitoneal doses of [3H]curcumin led to the fecal excretion of most of the radioactivity. The major biliary metabolites were glucuronides of tetrahydrocurcumin and hexahydrocurcumin. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid. Metabolites were identified using chemical ionization mass spectrometry⁷.

A recent study² investigated the pharmacokinetic properties of curcumin in mice and further clarified the nature of the metabolites of curcumin. Curcumin (0.1 g/kg) was administered intra-peritoneally to mice and about 2.25 g/ml appeared in the plasma in the first 15 minutes. Treatment of the plasma with beta-glucuronidase resulted in a decrease in the concentrations of two putative conjugates and the concomitant appearance of tetrahydrocurcumin (THC) and curcumin, respectively. To investigate the nature of these glucuronide conjugates in vivo, the plasma was analyzed by electrospray technique.
The chemical structures of these metabolites, determined by mass spectrometry, suggested that curcumin was first biotransformed to dihydrocurcumin and THC and that these compounds subsequently were converted to monoglucuronide conjugates (Figure 1).

**STABILITY OF CURCUMIN AND THC AT PHYSIOLOGICAL pH**

The *in vivo* behavior of a biologically active compound depends much on its stability at physiological pH levels. In this context, the stability of curcumin and THC at different pH values was studied. THC was very stable in 0.1 M phosphate buffers of various pH values. Moreover, THC was more stable than
curcumin in 0.1 M phosphate buffer, pH 7.2 (37°C) (Figure 2). These results, together with previous findings, suggest that curcumin-glucuronoside, dihydrocurcumin-glucuronoside, THC-glucuronoside, and THC are major metabolites of curcumin in vivo².

Figure 2: Stability of THC at physiological pH

**PHARMACOLOGICAL EFFECTS OF THC**

**Anti-inflammatory Action**

Curcumin and four synthetic analogs were examined for antiinflammatory potential in carrageenin induced foot paw edema and cotton pellet granuloma models of inflammation in rats⁸⁻⁹. The antiinflammatory potency of tested curcumin, curcumin analogs and phenylbutazone were established in the following order:

1. sodium curcumin
2. tetrahydrocurcumin
3. curcumin
4. phenylbutazone
5. triethylcurcumin.

Sodium salt of curcumin was effective at half the dose of the parent compound, curcumin. Comparison of curcumin and its analogs in acute and subacute models of inflammation revealed that curcumin analogs are more active in alleviating acute inflammation (Figure 3).
Antioxidant Effects

In a series of studies conducted by Sabinsa Corporation, the free radical scavenging ability of various curcuminoids were evaluated by using the DPPH (1,1 diphenyl-2-picrylhydrazyl) -radical scavenging method. The results are shown in Figure 4:

These results indicate that addition of curcuminoids resulted in the significant neutralization of free radicals in a dose-dependent manner, Tetrahydrocurcumin being the most effective, followed by curcumin and Bisdemethoxycurcumin.
One study evaluated the comparative antioxidant activity of curcuminoids and tetrahydrocurcumin in vitro using linoleic acid as the substrate in an ethanol/water system as well as using rabbit erythrocyte membrane and rat liver. It was found that Tetrahydrocurcumin had the strongest antioxidant activity among all curcuminoids in each assay system (Figures 5-8). The authors concluded that these results suggest that Tetrahydrocurcumin must play an important role in the antioxidant mechanism of Curcumin *in vivo*.

**Figure 5: Comparative Antioxidant Activity of the Curcuminoids and Tetrahydrocurcuminoids in rabbit erythrocyte membrane system model (determined by TBA method)**

**Figure 6: Comparative Antioxidant Activity of the Curcuminoids and Tetrahydrocurcuminoids in rat liver microsomes model (determined by TBA method)**
The role of curcuminoids as topical antioxidants has been validated in laboratory experiments. Curcuminoids are reported to protect normal human keratinocytes from hypoxanthine/xanthine oxidase injury in \textit{in vitro} experiments. It was surmised in this study that since curcuminoids synergistically
inhibit nitroblue tetrazolium reduction, a decrease in superoxide radical formation leading to lower levels of hydrogen peroxide could be their probable mode of action. The authors of this study propose that lower levels of hydrogen peroxide, leading to decreased cytotoxic effects, may be responsible for the protective effects of curcuminoids\textsuperscript{11}. This study suggests that curcuminoids and THC offer protection to the skin and could be included in antioxidant topical preparations.

A recent study further validated the well-known superior antioxidant properties of THC and explained the mechanism of antioxidant action\textsuperscript{5}. The inhibitory effects of curcumin and tetrahydrocurcumin on the lipid peroxidation of erythrocyte membrane induced by tertbutylhydroperoxide was studied. The results demonstrated that THC showed a greater inhibitory effect than curcumin. The authors concluded that THC must scavenge free radicals such as tert-butoxyl radical and peroxy radical, efficiently. They attempted to explain the mechanism of antioxidant action of THC on the basis of the molecular structure (Figure 9). They concluded that the beta-diketone moiety of THC must exhibit antioxidant activity by cleavage of the C-C bond at the active methylene carbon between two carbonyls in the beta-diketone moiety. As THC is one of the major metabolites of curcumin, the authors propose that this compound may exhibit the observed physiological and pharmacological properties in vivo by means of the beta-diketone moiety as well as phenolic hydroxy groups (Figure 9).

![Figure 9: Structure of Tetrahydrocurcumin](image)

**Chemopreventive Effects:**

The chemopreventive effects of curcuminoids are well-documented\textsuperscript{1}. One 12-week study examined the chemopreventive effects of carotenoids such as fucoxanthin, lycopene and lutein as well as curcumin and THC on the development of putative preneoplastic aberrant crypt foci in colons of mice initiated with the tumor promoter 1,2-dimethylhydrazine dichloride (DMH). Of the compounds tested, dietary fucoxanthin (0.01\% in drinking water), lutein (0.05\% in the diet) and THC (0.5\% in the diet) significantly reduced the number of aberrant crypt foci, when administered from weeks 5 to12 of the
Significant inhibition of ACF (aberrant crypt foci) development in the colons of mice treated with fucoxanthin, lutein to THC when given in the post-initiation phase (tumors were initiated using DMH) (Figure 10(a),(b)) was observed. Influence of proliferation of colonic crypt epithelial cells was also assessed in terms of 5-bromo-2'-deoxyuridine (BrDU) incorporation. BrDU labeling indices (LI) in mice treated with lutein and 0.5% THC were significantly decreased in both upper and lower half compartments of colonic crypts as compared to the controls (Figure 11).

The dose dependent decreases of BrDU LI observed for lycopene and THC indicate that larger doses might be more effective for inhibition of ACF development. This study demonstrated that THC is more active than the parent compound, curcumin, in terms of inhibition of ACF development and cell proliferation. This observation combined with the fact that THC which has both phenolic and diketone moieties in the same molecule, is a stronger antioxidant \(^4,5\), suggests that THC might be particularly suitable for application as a chemopreventive agent against \textit{in vivo} carcinogenesis.

Figure 10(a): Comparative chemopreventive effects of carotenoids, curcumin and THC against colon cancer (formation of aberrant crypt foci (ACF) in mice
The findings from laboratory experiments that THC is more stable than curcumin in buffer solutions of physiological pH (pH 7.2) and basic pH, as well as in plasma are significant. The authors of this study concluded that this suggests that derivatives such as glucuronated curcumin and THC serve as bioavailable forms of curcumin in vivo. Thus the biotransformation of curcumin to THC and the stability of THC play important roles in the biological effects of curcumin in the body. THC therefore functions as an efficient antioxidant in biological systems.
REFERENCES


7. Holder GM et AL. (1978) The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. Xenobiotica, 8(12):761-8


GLOBAL CONTACT & PROFILE

USA:
Sabinsa Corporation – NJ
20 Lake Drive
East Windsor, NJ 08854
O: +1.732.777.1111
F: +1.732.777.1443
E: info@sabinsa.com

Sabinsa Corporation – UT
750 S. Innovation Circle
Payson, UT 84651
O: +1.801.465.8400
F: +1.801.465.8600
E: info.utah@sabinsa.com

Australia:
Sabinsa Australia Pty Ltd
O: +61 (02) 9356 2211
F: +61 (02) 9356 2308
E: australia@sabinsa.com

China:
Sabinsa China Office
O: +86 (25) 5238 9432/33
F: +86 (25) 5238 9436
E: marketing@sabinsa.com.cn

Europe:
Sabinsa Europe GmbH
O: +49 6103 270 1111
F: +49 6103 270 1127
E: sabinsa.europe@sabinsa.com

Japan:
Sabinsa Japan Corporation
O: +81 (42) 997-4620
F: +81 (42) 997-4621
E: info@sabinsa.co.jp

Malaysia:
Sabinsa Malaysia Sdn Bhd
O: +60-379-606-535
F: +60-379-607-535
E: malaysia@sabinsa.com

South Africa:
Sabinsa S.A. (Pty) Limited
O: +27-76-483-7758
F: +27-11883-4567
E: sa@sabinsa.com

"The vision of a research scientist takes on social and commercial expressions.” This in short explains the genesis and growth of the Sabinsa – Sami Labs Group of Companies.

Company Profile:
Sabinsa Corporation, founded in 1988, is a manufacturer and supplier of herbal extracts, cosmeceuticals, minerals and specialty fine chemicals. Sabinsa’s mission is to provide alternative and complementary natural products for human nutrition and well-being. Over the past ten years, Sabinsa has brought to market more than 50 standardized botanical extracts and privately funded several clinical studies in conjunction with prestigious institutions in support of these products. Its present operations have grown to employ 1000 people worldwide in ten manufacturing, R&D and/or distribution facilities. Additionally, botanical cultivation efforts undertaken by the organization now total nearly 40,000 acres to ensure sustainable supplies on its key products. All products intended for human consumption are certified Kosher.

Visit us: www.sabinsa.com