TETRAHYDROCURCUMINOIDS CG:

Bioactive Antioxidant Compounds From Curcuminoids

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

Protocols of studies on cosmeceutical products performed /sponsored by Sabinsa Corporation are based on **alternatives to animal testing**. Any references to animal tests appearing in product informational materials are related to information from published general scientific literature compiled therein.

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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 antioxidants[1].

Curcuminoids are reported to be potent antioxidant compounds by virtue of their molecular structure[1]. 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 vivo*[2]. The poor circulating bioavailability[4] 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 Tetrahydrocurcuminoids [5,6,7].

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 vivo*[2].

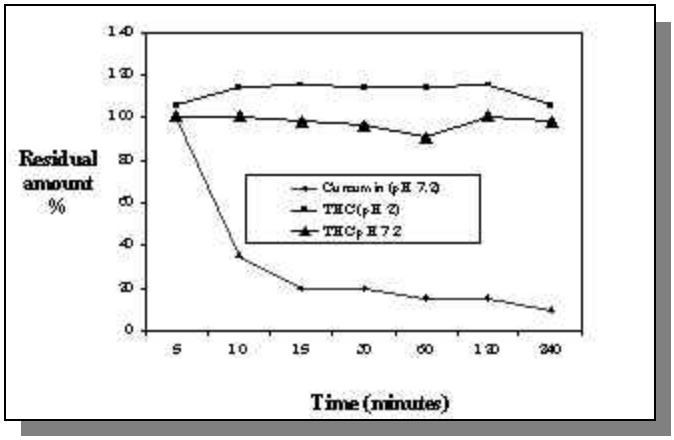

Figure 2: Stability of THC at physiological pH

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 rats[10,11]. 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).

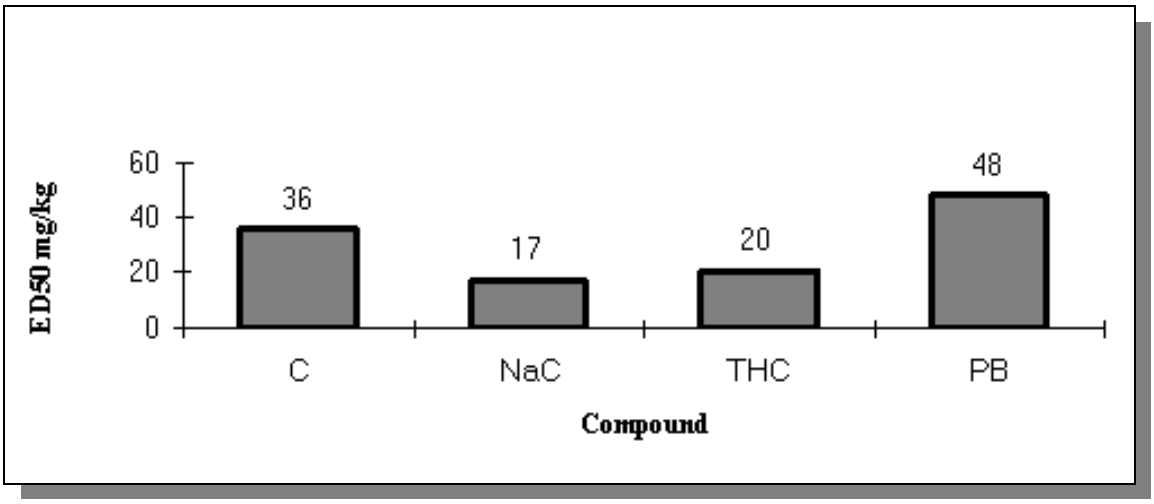

Figure 3: Effect of curcumin and its analogs on carrageenin-induced paw edema in rats[8]

C : Curcumin, NaC : sodium curcuminate,
THC : Tetrahydrocurcumin, PB : Phenylbutazone

Antioxidant Effects

In a series of studies conducted by Sabinsa Corporation[10], 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:

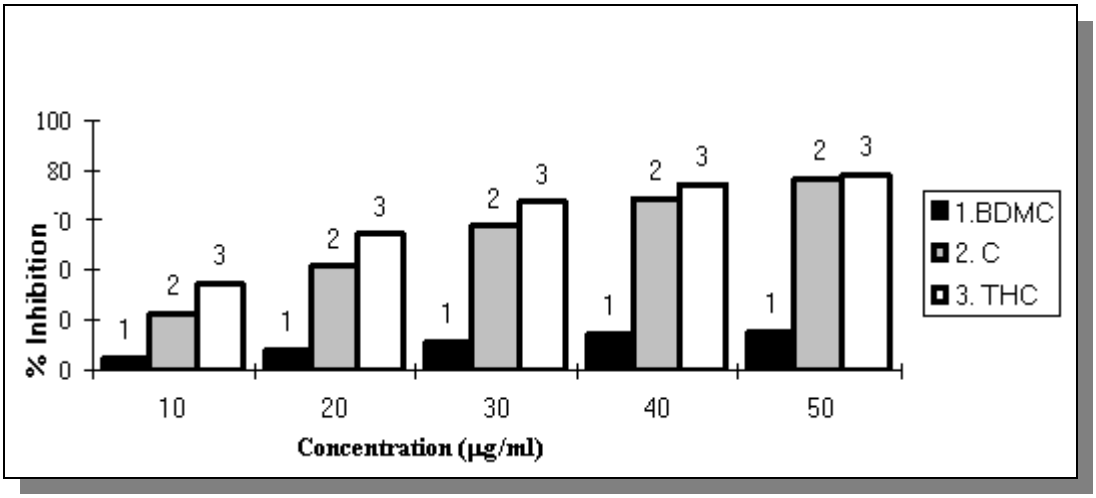

Figure 4: Free radical scavenging ability of curcuminoids

BDMC : Bisdemethoxycurcumin; C: Curcumin , THC: Tetrahydrocurcumin

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 (Figure 5)[5]. The authors concluded that these results suggest that Tetrahydrocurcumin must play an important role in the antioxidant mechanism of Curcumin *in vivo*[5].

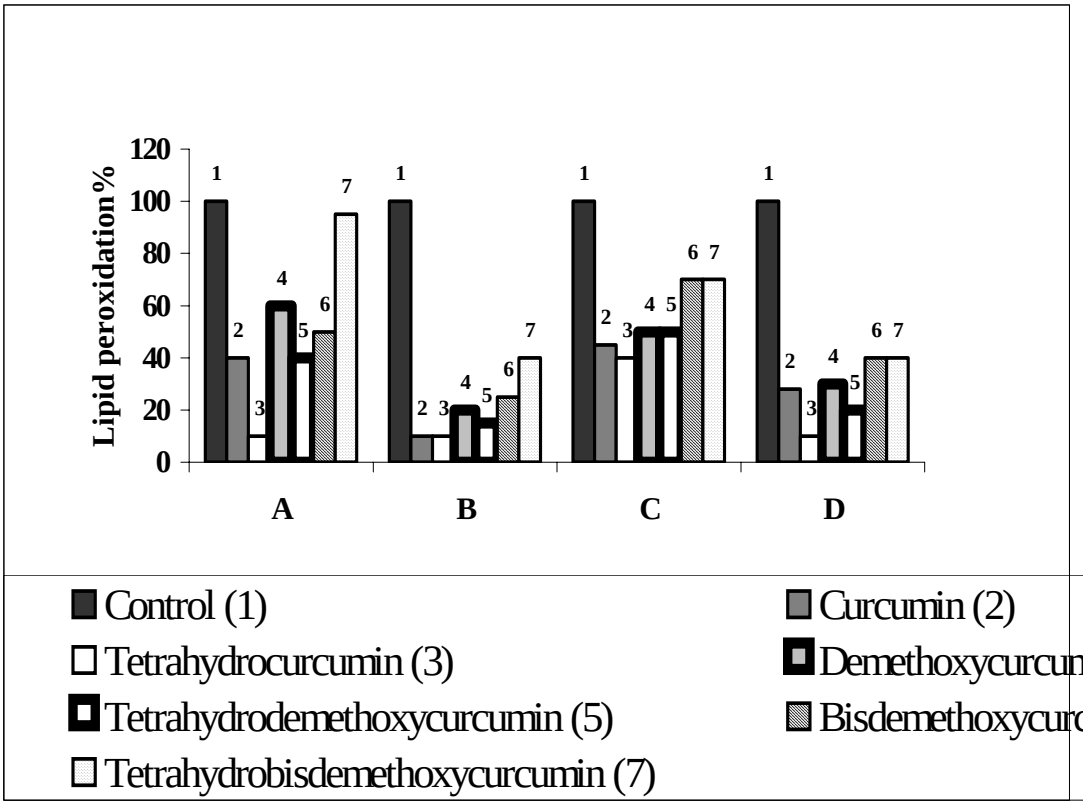

Figure 5: Comparative Antioxidant Activity of the Curcuminoids and Tetrahydrocurcuminoids in Laboratory Models

A recent study further validated the well-known superior antioxidant properties of THC and explained the mechanism of antioxidant action[6]. 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 peroxyl radical, efficiently. They attempted to explain the mechanism of antioxidant action of THC on the basis of the molecular structure (Figure 6). 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 6).

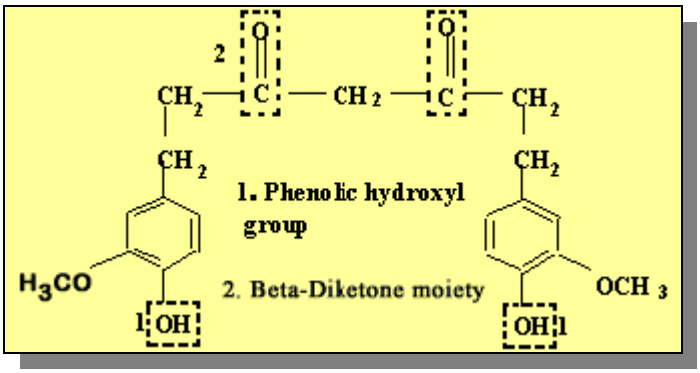

Figure 6: Structure of Tetrahydrocurcumin

As tetrahydrocurcumin 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 6).

A recent study investigated the inhibitory effects of curcumin and two tetrahydrocurcuminoids on oxidative stress induced by the tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in differentiated HL-60 cells. All compounds exhibited significant inhibition of active oxygen generation[6]. Thus the biotransformation of curcuminoids to THC and the stability of THC play important roles in the biological effects of curcuminoids in the body. THC therefore function as efficient antioxidants in biological systems.

USE OF THC IN COSMETIC FORMULATIONS

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 *in vitro* studies. This study suggests that curcuminoids and therefore THC offer protection to the skin and could be included in as functional antioxidants in topical preparations[11].

Free radical chain reactions are implicated in most degenerative biological reactions. Free radicals on the surface of the skin, generated through exposure to ultraviolet radiation, chemicals or other environmental stress factors catalyze aging of the skin. THC scavenge free radicals, thus preventing their formation. Additionally, these compounds also inhibit the propagation of free radicals. These antioxidants also help to improve the shelf life of fat-based topical formulations by inhibiting the autoxidation of fats. The anti-inflammatory effects of THC combined with their efficient antioxidant action render them useful as ingredients in anti-aging formulations and in topical formulations designed to maintain general skin health and integrity. The powerful antioxidant activity of THC could also slow down melanogenesis, thereby lightening the skin tone. THC was also shown to inhibit the action of tyrosinase that participates in melanin formation[13].

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GLOBAL CONTACT & PROFILE

USA:

Sabinsa Corporation – NJ
70 Ethel Rd West, #6
Piscataway, 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

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