2022

Whitepaper

SABINSA®

INTEGRATING CURCUMIN C3 REDUCT®

IN NEW PRODUCT DEVELOPMENT

www.sabinsa.eu

Executive Summary

Sabinsa has developed Curcumin C3 Reduct®, the only reductive metabolites of curcuminoids on the market to have been approved as a Novel Food by the European Food Safety Authority (EFSA). Easy to integrate into existing production processes and with the concentrated benefits of curcumin, C3 Reduct® has been shown to boost organ health and deliver a range of other targeted functionalities.

This makes it ideal to help product developers meet consumer health and wellness expectations – and open up new market opportunities.

Curcumin, the principal curcuminoid sourced from the spice turmeric, has gained increasing global recognition for its multiple health benefits, in particular its antioxidant and anti-inflammatory properties. As a result, the ingredient is used as a means of supporting healthy living and longevity, and in managing inflammation and joint soreness.

A principal advantage of C3 Reduct® is that these health benefits are concentrated and enhanced. C3 Reduct®, wherein curcuminoids are already converted to Tetrahydrocurcuminoids (THCs), means that the product is directly assimilated in the body as beneficial metabolites. This is important as the metabolites are more bioavailable than the parent curcuminoids.

In fact, C3 Reduct® is the only EFSA-approved product of its kind on the market. Other curcumin-based products have to deliver curcumin in large doses to offer functionality. With C3 Reduct® however, manufacturers can avoid the need to up dosages or mix curcumin with other artificial additives to increase bioavailability. This is because C3 Reduct® delivers active metabolites directly to the body.

Curcumin is also yellow in colour, which can lead to staining issues along the production line. C3 Reduct® can also help product developers to overcome this issue, because THCs are colourless. Manufacturers therefore do not have to worry about staining or off-colours.

Post-Covid, consumers are more than ever looking for effective, preventive health solutions that are supported by science. The purpose of this White Paper is to help product developers better understand the functional benefits of C3 Reduct®, to identify formulation opportunities and to bring to market health and wellness products that meet consumer demands.

The wonders of curcumin

Curcumin, a natural compound present in the spice turmeric, has been the focus of clinical investigations for centuries. Ancient Ayurvedic texts wrote about the health benefits of turmeric almost 2500 years ago, identifying its usefulness in treating rheumatism, asthma, liver disorders and various allergies[1]. Recent studies have shown that curcumin can improve systemic markers of oxidative stress[2] – a catalyst for vital organ complications.[3] Today, turmeric is extensively used in Indian cuisine, as well as a preservative, colouring agent and flavouring in drinks. Curcumin is often available in several forms including capsules, tablets, ointments, energy drinks, soaps, and cosmetics.[4]

The exact mechanisms and potential of its bioactive components however have only recently been investigated. A key milestone in this journey was the successful isolation and identification of turmeric's active principles, curcuminoids. These were found to be responsible for not only the yellow colour of turmeric roots, but also for health benefits to which turmeric has been associated with.[5] Sabinsa's C3 Reduct® represents an important new milestone in fully exploiting the potential health benefits of curcumin.

1. Priyadarsini K.I. The chemistry of curcumin: From extraction to therapeutic agent. Molecules. 2014;19:20091–20112. doi: 10.3390/molecules191220091.
2. Sahebkar A., Serbanc M.C., Ursoniuc S., Banach M. Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. J. Funct. Foods. 2015;18:898–909. doi: 10.1016/j.jff.2015.01.005.
3. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763. doi: 10.1155/2017/8416763. Epub 2017 Jul 27. PMID: 28819546; PMCID: PMC5551541.
4. Gupta S.C., Patchva S., Aggarwal B.B. Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials. AAPS J. 2013;15:195–218. doi: 10.1208/s12248-012-9432-8
5. Aggarwal B.B., Kumar A., Bharti A.C. Anticancer potential of curcumin: Preclinical and clinical studies. Anticancer Res. 2003;23:363–398.

What makes C3 Reduct® different?

— THCs – the most potent substance among curcuminoids

Tetrahydrocurcuminoids (THCs) are a colourless or white metabolite of curcumin, first identified in 1978.[6] These are the major active metabolites of curcumin formed in the body, and have the key advantage of having higher bioavailability than - while retaining all the beneficial properties of - parent curcuminoids.

As a reductive metabolite, THCs also show higher stability over a large pH range as compared to the major turmeric components, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Unlike other biologically inactive curcumin metabolites, such as curcumin glucuronide and curcumin sulphate, THCs have also been shown to be relatively active in its pharmacological activities, especially its antioxidative properties.

The knowledge that gut resident bacteria metabolise curcuminoids to THCs – a highly powerful and stable reductive metabolite, conferring similar yet stronger benefits than the parent curcuminoids – inspired Sabinsa to explore reductive metabolites in greater depth. The objective was to develop a product that delivers more functionality at lower doses than other conventional curcumin-based products on the market.

— Direct assimilation as a metabolite

C3 Reduct® has been designed to fully harness the benefits of THCs. The product is the hydrogenated derivative of the curcuminoids from Curcumin C3 Complex®, and contains a minimum of 95 % Tetrahydrocurcuminoids (THCs). Critically, curcumin C3 Reduct® is more readily absorbed through the gastrointestinal tract than curcumin, and can be thus directly assimilated more efficiently.[7]

What usually happens is that curcuminoids, once ingested, reach to intestine. Curcuminoids are converted to Dihydrocurcuminoids and then to Tetrahydrocurcuminoids (THCs) by the enzyme curcumin/dihydrocurcumin reductase (CurA), produced by intestinal microorganisms[8].

Other reductive enzymes in the gut also metabolise curcumin to THC. This then enables the molecules to pass through the absorption barrier to enter the biological system. The reductase system at the cellular level then converts the curcumin to THC.

In C3 Reduct®, Curcuminoids are already converted to Tetrahydrocurcuminoids (THCs). In addition to THC, Tetrahydrodemethoxycurcumin (THDMC), and Tetrahydro bisdemethoxycurcumin (THBDMC) are the other two major reductive metabolites of curcuminoids present in Curcumin C3 Reduct®.

As we shall see, several studies have demonstrated better pharmacological activity for C3 Reduct® than curcumin. Furthermore, C3 Reduct® exhibits better superoxide-scavenging activity, and decreases the deterioration of various lipid components by inhibiting lipid oxidation, making it suitable for various formulations.

The pharmacological activities of Curcumin C3 Reduct®, combined with the lack of staining yellow colour, provide possibilities for use as a natural antioxidant and anti-inflammatory across a wide range of products, from organ and oral care to sports performance products.

6. Holder G.M., Plummer J.L., Ryan A.J. Metabolism and Excretion of Curcumin (1,7-Bis-(4-Hydroxy-3-Methoxyphenyl)-1,6-Heptadiene-3,5-Dione) in the Rat. Xenobiotica. 1978;8:761–768. doi: 10.3109/00498257809069589

7. Saradhi UV, Ling Y, Wang J, Chiu M, Schwartz EB, Fuchs JR, Chan KK, Liu Z. 2010. A liquid chromatography–tandem mass spectrometric method for quantification of curcuminoids in cell medium and mouse plasma. Journal of Chromatography B. 878(30): 3045-3051.

8. Hassaninasab A, Hashimoto Y, Tomita-Yokotani K, Kobayashi M. 2011. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. Proceedings of the National Academy of Sciences. 108 (16): 6615-6620.

Functional possibilities of C3 Reduct®

— Healthy Living through supporting organ health

C3 Reduct® can help developers to formulate products - approved by EFSA and backed by science - that more effectively target organ health. Numerous studies have shown that C3 Reduct® can support the health of organs such as the liver, the lungs, the brain, the kidneys and the gut, among others. An increasingly health-conscious consumer base – as well as an ageing population – is actively looking for products that target and help prevent specific ailments, and which have scientific support.

For example, fibrosis in various organs - such as in the lungs and the liver – can occur for a variety of reasons, and is a common condition. A key issue is the fact that current pharmaceuticals have difficulty in treating this condition. This is where the effective, targeted antioxidant and anti-inflammatory properties of C3 Reduct® could be useful to product formulators, and appeal to consumers looking for science-backed products.

● C3 Reduct® and lung health

Diseases of the respiratory system accounted for 7.9 % of all deaths in the EU in 2017[9]. Since the Covid pandemic, consumers are increasingly looking for preventive products that can boost lung health. C3 Reduct® has been shown to help mitigate fibrosis of the lungs.

In unpublished trials, C3 Reduct® was shown to significantly reduce the expression of inflammatory markers such as IL-6 and IFNγ in lung tissues of rats with bleomycin-induced pulmonary fibrosis. C3 Reduct® effectively reduced the collagen deposition in alveolar epithelial cells (A549 cells) induced with $CoCl_2$. Treatment with C3 Reduct® also altered the relative gene expression of EMT markers (E-cadherin and vimentin) in the A549 cells in comparison to $CoCl_2$ treated cells.

● C3 Reduct® and brain health

Europe's ageing population has also seen a growing focus placed on brain health and mitigating against age-related neurological disorders such as Alzheimer's Disease. Indeed, nutraceutical products that help consumers to maintain brain health is a category that is only set to grow.

Neuroinflammation is implicated in many neurological disorders. C3 Reduct® possesses excellent antioxidant and anti-inflammatory properties, which could be useful in protecting the brain against such conditions. In trials, THC has been shown to reduce inflammation and thus neurodegeneration, because it possesses anti-amyloid activity. THC has also been shown to help reduce glutathione in the brains of diabetic rats, suggesting efficacy in protecting against lipid peroxidation-induced membrane damage.[10]

9. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Respiratory_diseases_statistics&oldid=576401

10. Aynun N. et. al. 2008. Curcumin Structure-Function, Bioavailability, and Efficacyin Models of Neuroinflammation and Alzheimer's Disease. The Journal of pharmacology and Experimental Therapeutics. 326:196–208

- **Curcumin C3 Reduct® for healthy liver**

The global prevalence of liver diseases has increased in the past few decades, and these remain a leading cause of mortality and morbidity worldwide. C3 Reduct® has been shown to be effective in reducing inflammation and cell infiltration into the liver, which could enable developers to better target the market for liver health products.

C3 Reduct® has been shown to help prevent the occurrence of erythromycin estolate-induced liver damage. Levels of lipid peroxidation products such as TBARS and hydroperoxides were significantly decreased in rat studies, while the antioxidant glutathione (GSH) increased in vivo, indicating the protective effect of C3 Reduct® against oxidative stress[11]. In trials, THC treatments also resulted in a reduced activity of β-hydroxy-β-methylglutamyl coenzyme A (HMGCoA) reductase in rats, an enzyme that catalyses the rate-limiting step in tissue cholesterol synthesis.[12]

- **Curcumin C3 Reduct® for gut health**

Research has revealed that gut health is directly or indirectly linked to various organs and glands in our body. Several human chronic diseases like inflammatory bowel disease (IBD), obesity, colon cancer, diabetes, and neurological disorders are found to be associated with gastrointestinal (GI) health. What's more consumers are increasingly aware of this link, and looking for products that support gut health in a preventive manner.

Curcumin C3 Reduct® has been shown to attenuate inflammatory responses and maintain colon health, by selectively inhibiting the enzymes of inflammatory pathways such as cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS) and downregulating ERK1/2 activation. Long-term (23 weeks) consumption of Curcumin C3 Reduct® was shown to result in a significant reduction in the colon polyp multiplicity without any noticeable side effects in mice with azoxymethane (AOM)-induced colon cancer.[13]

Supplementation of Curcumin C3 Reduct® has also been shown to reduce the relative abundances of pro-inflammatory bacteria and barrier function in the gut of ovalbumin (OVA)-induced asthmatic mice, indicating its beneficial effects on gut microbiome modulation and colon health.[14]

C3 Reduct® and diabetes

Diabetes is the fastest growing metabolic disorder in the world and a major cause of morbidity. Several in vivo studies have demonstrated the beneficial effects of Curcumin C3 Reduct® on the management of healthy sugar levels.

Oral administration of Curcumin C3 Reduct® for example showed a significant decrease in the level of blood glucose with a significant increase in the level of plasma insulin in STZ-nicotinamide diabetic rats.[15] C3 Reduct® has also been shown to effectively reduce the crosslinking of collagen by non-enzymatic advanced glycated end product (AGE) formation or by the enzymatic glucose incorporation in diabetic rats. Collagen is an important protein constituent of connective tissues that gives skin, bone, and tendons strength and flexibility. Administration of Curcumin C3 Reduct® for 45 days to diabetic rats reduced the elevated accumulation of collagen as well as its degree of glycation and crosslinking.[16]

11. Pari L, Murugan P. 2005. Effect of tetrahydrocurcumin on blood glucose, plasma insulin and hepatic key enzymes in streptozotocin induced diabetic rats. Journal of Basic and Clinical Physiology and Pharmacology. 16(4): 257-274
12. Pari L, Murugan P. 2007. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. Renal Failure. 29(7): 881-889
13. Lai CS, Wu JC, Yu SF, Badmaev V, Nagabhushanam K, Ho CT, Pan MH. 2011. Tetrahydrocurcumin is more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis. Molecular Nutrition and Food Research. 55(12): 1819-1828
14. Wu Y, Chen Y, Li Q, Ye X, Guo X, Sun L, Zou J, Shen Y, Mao Y, Li C. 2021. Tetrahydrocurcumin alleviates allergic airway inflammation in asthmatic mice by modulating the gut microbiota. Food and Function. 12(15): 6830-6840
15. Pari L, Murugan P. 2007. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. Renal Failure. 29(7): 881-889
16. Pari L, Murugan P. 2007. Influence of tetrahydrocurcumin on tail tendon collagen contents and its properties in rats with streptozotocin–nicotinamide-induced type 2 diabetes. Fundamental and Clinical Pharmacology. 21(6): 665-671

— Curcumin C3 Reduct® for Oral Health

Oral diseases are widely prevalent around the globe. Conditions such as gingivitis and canker sore affect millions of consumers with oral cancer being one of the ten most common cancers in the world.[17] C3 Reduct® has been shown to offer gingivitis and canker sore patients significant relief.

For example, a recent clinical study was conducted on 31 canker sore and 29 gingivitis patients for 21 days.[18] Patients were instructed to consume one chewable tablet of C3 Reduct®, containing 100 mg of THCs, twice a day. Clinical symptoms improved within 14 and 21 days of treatment, with a significant reduction in reddening, burning sensation, and throat numbness in canker sore patients.

Throat pain, difficulty in chewing/swallowing, and VAS pain score were also relieved in these patients, with the disappearance of both single and multiple lesions. In gingivitis patients, gingival appearance, bleeding and inflammation were significantly reduced by the C3 Reduct® treatment.

Another study demonstrated the efficacy and safety of THC applied in gel form in the treatment of oral leukoplakia.[19] All patients reported a reduction of burning sensation within three weeks of starting treatment and were completely asymptomatic by the end of the study.

— Sports nutrition

- **Anti-Inflammatory activities**

Exertion during sport or physical activity can lead to inflammation in the body. While inflammation is an important biological process, helping to eliminate the initial cause of cell injury in the host defence system, chronic inflammatory reactions can cause tissue injuries, leading to various disorders. The anti-inflammatory properties of C3 Reduct® hold significant promise in the development of effective sports nutrition products.

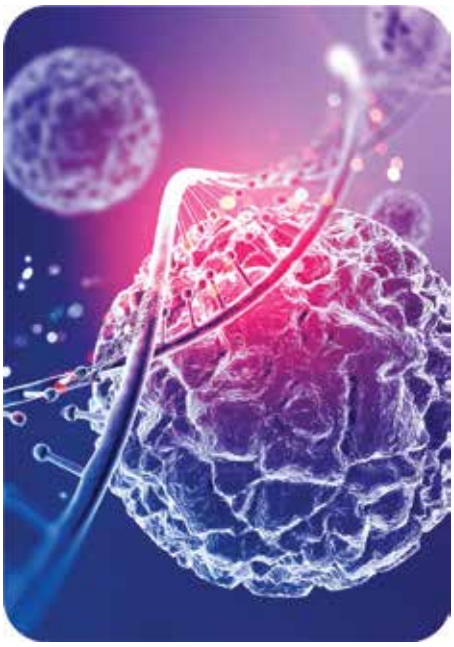
In unpublished studies, C3 Reduct® has been shown to reduce the expression of inflammatory markers such as IL-6 and IFNγ in lung tissues of rats with bleomycin-induced pulmonary fibrosis. Reduced accumulation of inflammatory cells in lung broncho-alveolar lavage (BAL) fluids was also observed in C3 Reduct® treated animals compared to bleomycin treated group.

Agents that downregulate NF-κB and NF-κB–regulated gene products have potential efficacy against several of these diseases. Curcumin and THC has been shown to block NF-κB activation increased by several different inflammatory stimuli[20].

THC can also be used to target good joint health. One disease associated with inflammation, both chronic and acute, is osteoarthritis (OA), a chronic joint condition, affecting over 250 million people worldwide[21]. Several studies have shown the anti-arthritic effects of THC in humans with OA and rheumatoid arthritis (RA). In particular, THC - but not curcumin - was shown to prevent glucose intolerance, which might be involved in exacerbating osteoarthritis.[22]

17. https://www.healthdata.org/gbd/2019
18. Majeed M, Majeed S, Nagabhushanam K. 2020. Efficacy and safety of tetrahydrocurcuminoids for the treatment of canker sore and gingivitis. Evidence-Based Complementary and Alternative Medicine. 2020.
19. Chhaparwal Y. et al. Efficacy and Safety of Tetrahydrocurcuminoid in the treatment of Oral Leukoplakia: a Pilot Study Asian Journal of Pharmaceutical and Clinical Research Vol 11, Issue 12, 2018
20. Z.-B. Zhang, D.-D. Luo, J.-H. Xie, et al. "Curcumin's Metabolites, Tetrahydrocurcumin and Octahydrocurcumin, Possess Superior Anti-inflammatory Effects in vivo Through Suppression of TAK1-NF-κB Pathway," Frontiers in Pharmacology, vol. 9.
21. Hunter D.J., Schofield D., Callander E. The individual and socioeconomic impact of osteoarthritis. Lancet Nat. Rev. Rheumatol. 2014;10:437–441. doi: 10.1038/nrrheum.2014.44.
22. Park S. et. al. 2016. Curcumin and tetrahydrocurcumin both prevent osteoarthritis symptoms and decrease the expressions of pro-inflammatory cytokines in estrogen-deficient rats. Genes & Nutrition. 11:2

- **Activating AMP Kinase for maximum energy**



In addition to its anti-inflammation properties, THC has demonstrated significant functionality in maintaining energy balance within the body. This - together with its colourless nature – opens up new possibilities in the sports nutrition sector.

Central to this is AMP-activated protein kinase (AMPK). APMK is a central regulator of energy homeostasis, which coordinates metabolic pathways and thus balances nutrient supply with energy demand. AMPK inhibits ATP-consumption and stimulates ATP-production under energy depleted conditions. The activation of AMPK is also known to suppress the gene expression of G6Pase and PEPCK, and inhibit hepatic glucose production.

In studies, THCs have been shown to increase the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC) in H4IIE and Hep3B cells. In fact, a study found that while curcumin delivers 400 times the potency of metformin, THC delivers an impressive 100 000 times the potency. Studies also demonstrated that THC was more effective in inhibiting G6Pase gene expression compared to curcumin.[23]

Production benefits of C3 Reduct®

While there is a great deal of scientific support when it comes to the functional benefits of C3 Reduct®, the colourless nature of THC can also bring cost savings to manufacturers. For contract manufacturers working in small batches for example, using curcumin typically requires dedicated equipment and extensive cleaning between shifts, because of the yellow colour.

Because C3 Reduct® is colourless, this means no staining, either during processing or in the final consumer product. If a manufacturer wishes to change the colour of the product with a natural ingredient, this will not alter the product's or clean label properties.

Authorisations and approvals

Sabinsa has obtained Novel Food approval from the European Food Safety Authority (EFSA) for C3 Reduct® - the only curcuminoid to be awarded EFSA Novel Food status (Regulation 2015/2283)[24].
This means that product developers can use C3 Reduct® safe in the knowledge that it meets and surpasses the most stringent thresholds for safety. The THCs from turmeric are well characterised, and compliant with European Regulations. The novel food is safe and devoid of allergic potential.

This Novel Food is intended to be used as food supplement (as defined in Directive 2002/46/EC) at a maximum daily dose of 140 mg intended for the adult population and excluding children. The product is approved as per Implementing Regulation EC 2022/96 amending Implementing Regulation (EU) 2017/2470.[25] As this White Paper has outlined, numerous trials and studies have supported the safety and efficacy of C3 Reduct®.

23. Teayoun K., Curcumin activates AMPK and suppresses gluconeoenic gene expression in hepatoma cells Biochemical and Biophysical Research Communications 388 (2009) 377–382

24. https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32015R2283

25. https://eur-lex.europa.eu/eli/reg_impl/2017/2470/oj

SABINSA®

CURCUMIN C3 REDUCT®

ABOUT SABINSA

Sabinsa Corporation, founded in 1988 by Dr. Muhammed Majeed, is a manufacturer and supplier of herbal extracts, cosmeceuticals, minerals and specialty fine chemicals. Sabinsa's mission is to provide evidence-based natural products for human functional nutrition and well-being.

Its present operations have grown to employ 1000 people worldwide in ten manufacturing, R&D and distribution facilities. Additionally, botanical cultivation efforts undertaken by the organisation now total nearly 40 000 acres to ensure sustainable supplies on its key products.

With more than 120 scientists working full time conducting ongoing research in Europe, India and the United States, Sabinsa continues to develop and patent beneficial nutrients for the world market.

Contact Us

+49 6103 270 11 11

info@sabinsa.eu

www.sabinsa.eu
www.c3reduct.com

Monzastrasse 4,
63225 Langen,
Germany