Curcumin in Chronic Hepatitis

Subjects: Biochemistry & Molecular Biology
Contributor: Laura-Marinela AILIOAIE, Gerhard Litscher

Curcumin, as a natural product, is inexpensive, without side effects, and can stimulate very well certain areas of the human immune system. The cytotoxicity of curcumin as photosensitizer could be expanded by the intravenous blue laser blood irradiation (IVBLBI) or photobiomodulation in patients with chronic hepatitis B infection, Hepatitis B e-antigen (HBeAg)-positive, noncirrhotic, but nonresponsive to classical therapy.

Keywords: blue laser ; hepatitis B ; hepatocellular carcinoma ; laser blood irradiation ; photodynamic therapy ; ultrabioavailability

1. Chronic Hepatitis B Infection

Hepatitis B is a DNA virus that infects liver cells and can cause both acute and chronic disease. Hepatic infection is one of the main causes of cirrhosis, hepatic decompensation, and hepatocellular carcinoma and, even in this third millennium of modern medicine, there are no satisfactory therapies for chronic hepatitis B virus. All up-to-date treatments are limited. There is still a gap in the scientific knowledge and a sterilization cure may not yet be possible with the removal of both covalently closed circular DNA (cccDNA) and the embedded HBV DNA.

2. Antiviral Properties of Curcumin and Applications

Antibacterial, antiviral, and anti-inflammatory properties of curcumin as a highly polyphenolic molecule were discovered many years ago and, since then, its strong antioxidative, antiproliferative, and apoptosis-promoting effects have been studied in many different cells. Safe and well tolerated even at higher doses, curcumin has been used for treating hyperproliferative diseases [1]. There are studies that have demonstrated the valuable pharmacological impact of curcumin in hepatitis B [2], diabetic microangiopathy, immune-mediated inflammatory diseases, and even cancer [3].

Very recently, it has been shown that phytosomal curcumin with higher bioavailability blocks the formation of HCC, improves hepatic histopathology, reduces lipid accumulation and leukocyte infiltration, and diminishes total tumor volume in transgenic mice. Thus, there is a chance of HCC chemoprevention in chronic HBV infection [4]. With a maximum light absorption at 420 nm [5], the cytotoxicity of curcumin as photosensitizer could be expanded by the intravenous blue laser blood irradiation (IVBLBI) [6].

It is widely known that photobiomodulation is a highly effective method for treating patients with various diseases. Low-intensity (low-energy) laser light used today is safe and may even increase the effectiveness of biological agents in some unresponsive cases [7]. It does not have teratogenic, mutagenic, or carcinogenic properties [8] but, on the contrary, it ensures the protection of organisms against the most different pathogenic factors of biological, chemical, or physical nature, triggering the processes of repair and regeneration inside the living cells [6].

How to kill a virus with laser? Blue laser blood illumination should be preferably used for the correction of immune disorders of various etiologies and as an antimicrobial therapy. For example, in a recently published article by Zhu et al. it was proven by ex vivo and in vivo studies that antimicrobial blue light is a potential alternative or adjunctive therapeutic for infectious keratitis [9]. The mechanism of action of antimicrobial blue light is still not fully understood. A common hypothesis is that antimicrobial blue light excites the naturally occurring endogenous porphyrins or/and flavins in microbial cells and subsequently leads to the production of cytotoxic reactive oxygen species (ROS) [10]. Host–virus interactions in recent literature include the vital role played by host metabolism on viral replication and the proactive participation of mitochondria in this process. Different viruses use distinctive strategies to modulate mitochondrial bioenergetics and enhance viral replication. As a result, energy-yielding metabolic pathways are programmed to provide both energy and biosynthetic resources to drive viral protein synthesis and produce infectious particles. Therefore, metabolic antagonists may prove important not only to outline efficient therapy strategies but also to shed light on the pathogenesis of viral infections [11].

Low-level laser therapy allows the consideration of photobiomodulation as an active therapeutic factor, potentiating the curcumin effect [6]. Curcumin features many of the attributes of an ideal photosensitizer for photokilling of pathogens: It is small, can form singlet oxygen in an aprotic environment, and features excellent biocompatibility [12]. UltraCur, a curcumin–whey complex with a 15,000-fold bioavailability and patented in the USA, has a bioavailability equal to 240,000 mg standard curcumin and could be successfully used in connection with the blue laser for treating chronic infectious and age-related diseases [6].

4. Curcumin and the Preventive Role in Hepatocellular Carcinoma

Turmeric is the flowering plant *Curcuma longa* of the ginger family, Zingiberaceae. Curcumin (bis-α, β-unsaturated β-dietone) is a polyphenol extracted from the plant *Curcuma longa* that has proven its chemopreventive capacity in carcinogenesis by targeting signaling pathways, regulating the expression of cell adhesion and inhibition of cell proliferation, migration, invasion, angiogenesis, and tumor metastases [13][14][15][16][17].

Curcumin is known as a powerful oxidant, which can stabilize the systems of anti-oxidant enzymes of the liver, reduce the level of superoxide anions (O^{2-}), hydroxyl radicals (OH^{-}), and increase the level of antioxidants by activating superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione S-transferase (GST) [18][19].

Through its polyphenolic action, curcumin works competitively with an inhibitory role on the two isoforms of the enzyme inosine monophosphate dehydrogenase (IMPDH), which is a regulator of intracellular guanine nucleotides. It also plays a particularly important role in signal transduction, energy transfer, glycoprotein synthesis, DNA, RNA, and other multiple processes for cell vitality and proliferation [20][21].

Its properties as an anti-inflammatory agent, along with its strong antioxidant capacity, have increased interest in curcumin as a therapy for chronic liver disease. Several studies report that curcumin is a potent anti-inflammatory agent and can modulate nuclear factor kappa beta (NF-κB); inhibit phospholipases, cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX); and decrease the concentrations of TNF alpha, IL-1, IL-6, and agonist of peroxisome proliferator-activated receptor gamma (PPARγ), which has an important role in inhibiting pro-inflammatory pathways [22][23][24][25].

Phytosomal curcumin has been shown experimentally to have effects on peroxisome proliferator-activated receptor gamma (PPARγ) anti-inflammatory activation, pro-inflammatory NF-κB inhibition, suppression of mammalian target of rapamycin (mTOR) deactivation oncogene, improvement of hepatic histopathology (steatosis and necroinflammation), and reduction in volume HCC [26].

Another hypothesis is that curcumin inhibitory activity in HBV infection is achieved by inhibiting the function of histone acetyltransferase p300 (multifunctional transcriptional coactivator that interacts with numerous transcription factors and protein/histone acetyltransferase activity) that will lead to histone deacetylation related to cccDNA [27][28].

This hypothesis was the basis of an experimental study on a HepG2.2.15 cell line stably transfected with HBV and curcumin treated, after which the ELISA technique assessed the expression levels of HBV surface antigen HBsAg, and HBeAg antigen. Depending on the dose and time, curcumin decreased the expression of HBsAg and HBeAg and played a significant role in remarkably reducing the replication of the intracellular HBV DNA intermediates and HBV cccDNA. In the end, the study proved that curcumin would inhibit HBV gene replication by reducing cccDNA-bound histone acetylation processes and would have a cccDNA-targeted antiviral agent perspective in chronic HBV infection [29].

Curcumin, the polyphenolic compound [30] with antioxidant, anti-inflammatory, antiviral, and chemoprotective properties alone or in combination with other agents or even with the blue laser [31], could be an effective drug for therapy and cancer prevention [32].

5. Photodynamic Therapy with Blue Laser and Curcumin in Hepatic Viral Infections

Photodynamic therapy (PDT) is a modern treatment that uses light (phototherapy) together with a light-sensitive chemical that, in the presence of molecular oxygen, causes cell death in the target tissue by phototoxicity. The purpose of PDT is to induce various cellular responses, from the inactivation of bacteria and viruses to the necrosis or apoptosis of pathological cells, using the three absolutely necessary elements: Laser light, molecular oxygen, and a nontoxic, light-sensitive substance, named photosensitizer (PS). PDT has been extensively investigated and applied in the last decades, proving to be an effective method of treatment. As a two-step procedure, PDT begins with the administration of the photosensitizer, followed by exposure to light, in order to obliterate the pathogens or the malignant structures [33].

Due to the fact that curcumin is a potent inhibitor of NF-κB signaling and of the expression of viral oncogenes E6 and E7, in decreasing the integrase and viral protease of HIV-1, in the intracellular accumulation of p53, and, consequently, in decreasing the RNA level of intracellular HBV, several studies have been performed in an attempt to use it as a photosensitizer in photodynamic therapy [34]. PDT as a state-of-the-art medical technology, using blue light (400–470 nm), can effectively fight bacterial, fungal, and viral infections. Photoreceptors, which are specific cellular structures, can absorb only specific wavelengths of light. Light interaction with these photoreceptors will trigger a cascading cellular signal, which will affect the chemical behavior, the metabolism, the movement, and the expression of genes inside the cell. All associated enzymes and/or proteins will be affected [31].

Blue light releases nitric oxide (NO), known to be a growth, immune, and neuro-modulator, as well as a stimulator of stem cell proliferation, playing critical roles in pain reduction, vasodilation, and angiogenesis through c-GMP (cyclic guanosine monophosphate) pathway. The blue laser has a strong anti-inflammatory effect by reducing proinflammatory cytokines (for example, IL2, IL6, TNF-alpha) and acts on cellular signaling pathways (e.g., NF-kB) and other factors that contribute to a variety of diseases (CRP, leptin, chemokines, etc.). Blue light is effective in treating infections by producing ROS (especially in combination with photosensitive substances such as riboflavin or curcumin) [6][31]. Great efforts are currently being made to explore the clinical value of blue light in the fight against viral infections, an example being the current COVID-19 pandemic [35]. Another possible mechanism would be the action of blue light on the integrity of the cell membrane, with the decrease of the transmembrane potential and, consequently, the rapid disturbance of cellular functions [36].

References

1. Bruzell, E.M.; Morisbak, E.; Tonnesen, H.H. Studies on curcumin and curcuminoids. XXIX. Photoinduced cytotoxicity of curcumin in selected aqueous preparations. Photochem. Photobiol. Sci. 2005, 4, 523–530.
2. Rechtman, M.M.; Har-Noy, O.; Bar-Yishay, I.; Fishman, S.; Adamovich, Y.; Shaul, Y.; Halpern, Z.; Shlomai, A. Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1alpha. Febs. Lett. 2010, 584, 2485–2490.
3. Mirzaei, H.; Shakeri, A.; Rashidi, B.; Jalili, A.; Banikazemi, Z.; Sahebkar, A. Phytosomal curcumin: A Review of pharmacokinetic, experimental and clinical studies. Biomed. Pharmacother. 2017, 85, 102–112.
4. Teng, C.F.; Yu, C.H.; Chang, H.Y.; Hsieh, W.C.; Wu, T.H.; Lin, J.H.; Wu, H.C.; Jeng, L.B.; Su, I.J. Chemopreventive effect of phytosomal curcumin on hepatitis B virus-related hepatocellular carcinoma in a transgenic mouse model. Sci. Rep. 2019, 9, 10338.
5. Kunwar, A.; Barik, A.; Priyadarsini, K.I.; Pandey, R. Absorption and fluorescence studies of curcumin bound to liposome and living cells. Barc. Newsl. 2007, 285, 213.
6. Weber, M.; Weber, R.; Junggebauer, M. Photodynamic low-level-laser therapy. Chapter 6. In Medical Low-Level Laser Therapy-Foundations and Clinical Applications-Research Book, 2nd ed.; ISLA-International Society for Medical Laser Applications: Beverungen, Germany, 2015; pp. 431–465. ISBN 978-3-00-050017-6.
7. Chiran, D.A.; Litscher, G.; Weber, M.H.; Ailioaie, L.M.; Ailioaie, C.; Litscher, D. Intravenous laser blood irradiation increases efficacy of etanercept in selected subtypes of juvenile idiopathic arthritis: An innovative clinical research approach. Evid. Based Complement. Altern. Med. 2013.
8. Moskvin, S.V.; Kisselev, S.B. Laser Therapy for Joint and Muscle Pain; Triada: Sewickley, PA, USA, 2017; Volume 216, pp. 175–176. ISBN 978-5-94789-787-6.
9. Zhu, H.; Kochevar, I.E.; Behlau, I.; Zhao, J.; Wang, F.; Wang, Y.; Sun, X.; Hamblin, M.R.; Dai, T. Antimicrobial blue light therapy for infectious keratitis: Ex vivo and in vivo studies. Investig. Ophthalmol. Vis. Sci. 2017, 58.1, 586–593.
10. Dai, T.; Gupta, A.; Murray, C.K.; Vrahas, M.S.; Tegos, G.P.; Hamblin, M.R. Blue light for infectious diseases: Propionibacterium acnes, helicobacter pylori, and beyond? Drug Resist. Updat. 2012, 15, 223–236.
11. El-Bacha, T.; Da Poian, A.T. Virus-induced changes in mitochondrial bioenergetics as potential targets for therapy. Int. J. Biochem. Cell Biol. 2013, 45, 41–46.
12. Araújo, N.C.; Fontana, C.R.; Gerbi, M.E.M.; Bagnato, V.S. Overall-mouth disinfection by photodynamic therapy using curcumin. Photomed. Laser Surg. 2012, 30, 96–101.
13. Li, W.; Guo, Y.; Zhang, C.; Wu, R.; Yang, A.Y.; Gaspar, J.; Kong, A.N.T. Dietary phytochemicals and cancer chemoprevention: A perspective on oxidative stress, inflammation, and epigenetics. Chem. Res. Toxicol. 2016, 29, 2071–2095.

14. Kotecha, R.; Takami, A.; Espinoza, J.L. Dietary phytochemicals and cancer chemoprevention: A review of the clinical evidence. Oncotarget 2016, 7, 52517–52529.

15. Wang, D.; Veena, M.S.; Stevenson, K.; Tang, C.; Ho, B.; Suh, J.D.; Duarte, V.D.; Faull, K.F.; Mehta, K.; Srivatsan, E.S.; et al. Liposome-encapsulated curcumin suppresses growth of head and neck squamous cell carcinoma in vitro and in xenografts through the inhibition of nuclear factor κB by an AKT-independent pathway. Clin. Cancer Res. 2008, 14, 6228–6236.

16. Jobin, C.; Bradham, C.A.; Russo, M.P.; Juma, B.; Narula, A.S.; Brenner, D.A.; Sartor, R.B. Curcumin blocks cytokine-mediated NF-κB activation and proinflammatory gene expression by inhibiting inhibitory factor I-κB kinase activity. J. Immunol. 1999, 163, 3474–3483.

17. Plummer, S.M.; Holloway, K.A.; Manson, M.M.; Munks, R.J.L.; Kaptein, A.; Farrow, S.; Howells, L. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-κB activation via the NIK/IKK signalling complex. Oncogene 1999, 18, 6013–6020.

18. Maiti, P.; Dunbar, G.L. Use of curcumin, a natural polyphenol for targeting molecular pathways in treating age-related neurodegenerative diseases. Int. J. Mol. Sci. 2018, 19, 1637.

19. Biswas, S.K.; McClure, D.; Jimenez, L.A.; Megson, I.L.; Rahman, I. Curcumin induces glutathione biosynthesis and inhibits NF-kappaB activation and interleukin-8 release in alveolar epithelial cells: Mechanism of free radical scavenging activity. Antioxid. Redox Signal 2005, 7, 32–41.

20. Moghadamtousi, S.Z.; Kadir, H.A.; Hassandarvish, P.; Tajik, H.; Abubakar, S.; Zandi, K. A review on antibacterial, antiviral, and antifungal activity of curcumin. BioMed. Res. Int. 2014, 186864.

21. Shah, C.P.; Kharkar, P.S. Inosine 5′-monophosphate dehydrogenase inhibitors as antimicrobial agents: Recent progress and future perspectives. Future Med. Chem. 2015, 7, 1415–1429.

22. Menon, V.P.; Sudheer, A.R. Antioxidant and anti-inflammatory properties of curcumin. Adv. Exp. Med. Biol. 2007, 595, 105–125.

23. He, Y.; Yue, Y.; Zheng, X.; Zhang, K.; Chen, S.; Du, Z. Curcumin, inflammation, and chronic diseases: How are they linked? Molecules 2015, 20, 9183–9213.

24. Hong, J.; Bose, M.; Ju, J.; Ryu, J.H.; Chen, X.; Sang, S.; Lee, M.J.; Yang, C.S. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: Effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis 2004, 25, 1671–1679.

25. Mazidi, M.; Karimi, E.; Meydani, M.; Ghayour-Mobarhan, M.; Ferns, G.A. Potential effects of curcumin on peroxisome proliferator-activated receptor-gamma in vitro and in vivo. World J. Methodol. 2016, 6, 112–117.

26. Tan, A.; Yeh, S.H.; Liu, C.J.; Cheung, C.; Chen, P.J. Viral hepatocarcinogenesis: From infection to cancer. Liver Int. 2008, 28, 175–188.

27. Zhu, X.; Li, Q.; Chang, R.; Yang, D.; Song, Z.; Guo, Q.; Huang, C. Curcumin alleviates neuropathic pain by inhibiting p300/CBP histone acetyltransferase activity-regulated expression of BDNF and cox-2 in a rat model. PLoS ONE 2014, 9, e91303.

28. Balasubramanyam, K.; Varier, R.A.; Altaf, M.; Swaminathan, V.; Siddappa, N.B.; Ranga, U.; Kundu, T.K. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J. Biol. Chem. 2004, 279, 51163–51171.

29. Wei, Z.Q.; Zhang, Y.H.; Ke, C.Z.; Chen, H.X.; Ren, P.; He, Y.L.; Hu, P.; Ma, D.Q.; Luo, J.; Meng, Z.J. Curcumin inhibits hepatitis B virus infection by down-regulating cccDNA-bound histone acetylation. World J. Gastroenterol. 2017, 23, 6252–6260.

30. Mughal, M.H. Turmeric polyphenols: A comprehensive review. Integr. Food Nutr. Metab. 2019, 6.

31. Weber, M.; Weber, R.; Junggebauer, M. Intravenous laser blood irradiation—Introduction of a new therapy. Chapter 5. In Medical Low-Level Laser Therapy-Foundations and Clinical Applications-Research Book, 2nd ed.; ISLA-International Society for Medical Laser Applications: Beverungen, Germany, 2015; pp. 279–297. ISBN 978-3-00-050017-6.

32. Giordano, A.; Tommonaro, G. Curcumin and cancer. Nutrients 2019, 11, 2376.

33. Van Straten, D.; Mashayekhi, V.; De Bruijn, H.S.; Oliveira, S.; Robinson, D.J. Oncologic Photodynamic therapy: Basic principles, current clinical status and future directions. Cancers 2017, 9, 19.

34. Wiehe, A.; O'Brien, J.M.; Senge, M.O. Trends and targets in antiviral phototherapy. Photochem. Photobiol. Sci. 2019, 18, 2565–2612.

35. Enwemeka, C.S.; Bumah, V.V.; Masson-Meyers, D.S. Light as a potential treatment for pandemic coronavirus infections: A perspective. J. Photochem. Photobiol. B 2020, 207, 111891.
36. Biener, G.; Masson-Meyers, D.S.; Bumah, V.V.; Hussey, G.; Stoneman, M.R.; Enwemeka, C.S.; Raicu, V. Blue/violet laser inactivates methicillin-resistant Staphylococcus aureus by altering its transmembrane potential. J. Photochem. Photobiol. B 2017, 170, 118–124.

Retrieved from https://encyclopedia.pub/entry/history/show/23904