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EDITORIAL

Curcumin: En route to valid health claims

Koraljka Gall Trošelj

Division of Molecular Medicine, Laboratory for Epigenomics, Rudjer Boskovic Institute, Zagreb, Croatia

Corresponding author:
Prof. Koraljka Gall Trošelj, MD, PhD, Rudjer Boskovic Institute, Division of Molecular Medicine, Laboratory for Epigenomics, Bijenička cesta 54, 10000 Zagreb, Croatia,
Telephone: +385-1-4560-972,
e-mail: troselj@irb.hr

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Curcumin is well-known for its healing properties and has been extensively used in traditional medicine for treating various diseases. The natural source of curcumin ((1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3,5-dione) is the rhizome of *Curcuma longa*, a perennial herb in the Zingiberaceae family [1]. Curcumin was first isolated in 1815 [2] but it took another 55 years for it to be isolated as an orange-yellow crystalline powder [3]. Its chemical structure was resolved in 1973, more than 150 years later [4]. An early mention of curcumin in modern medical literature was in the Lancet, one of the most prestigious clinical medical journals, in 1937 [5]. An article by Prof. Albert Oppenheimer described the rapid emptying of the gallbladder after an intravenous application of a 5% curcumin solution. Based on this observation, curcumin was given orally (up to 800 mg daily) for the treatment of 67 patients suffering from various forms of cholecystitis. Only one patient did not show signs of improvement. That this article received only 24 citations in Scopus as of February 15, 2017, with the first one only in 2008, shows how unappreciated was his work. On the other hand, numerous data, commonly obtained *in vitro*, in cell culture model systems, have been all too often taken as a baseline for uncritical claims relating to curcumin's supposed universal healing properties. This may be one reason for the enormous growth of the curcumin market, leading to over 52% of global curcumin production being used for pharmaceutical applications, in the U.S. It is estimated that the U.S. curcumin market size will approach 40 million dollars, already in 2022 [6].

Despite these numbers, there are many unresolved issues relating to curcumin and its application in human medicine. Among most important ones are curcumin's poor bioavailability and well-recognized pleiotropic activity, which makes it almost impossible to anticipate and predict cell-type specific response to curcumin-associated-stimuli. This complexity leads to uncertainty about the parameters of cellular responses which need to be followed (measured) to accurately estimate the output and understand how this powerful polyphenol influences

communication among multiple molecular events. To become the basis for viable health claims, which curcumin still is not, these multiple events need to be thoroughly investigated through various types of research. Carefully designed human clinical trials should take into account not only its limited bioavailability but also the possibility that its application may, in some individuals and under certain circumstances, induce some harmful effects [7].

A majority of curcumin analogs rely on applying nanobiotechnology techniques leading to developing a respectable number of bioavailable formulations, which are generally classified as nanoparticles, liposomes, micelles, and phospholipid complexes [8]. Most of these products/analogs were tested *in vitro*, with *in vivo* testing performed only on a few of them. Extreme caution should be taken when considering curcumin applications, especially in the field of oncology. The reason is clear: What seems to be a clear cytotoxic effect on a cancer cell grown *in vitro*, should not be a priori projected as a "healing effect" which would be of therapeutic help when given to a cancer patient.

A strong antioxidative effect makes curcumin a potent chemopreventive. However, although oral administration of curcumin inhibited the development of intestinal adenomas in ApcMin/+ mice [9], we are still missing strong evidence on beneficial effects related to high intakes of curcumin and decreased cancer risk in humans. Carrol and collaborators, who conducted a 30-day phase II clinical trial in smokers (N = 41) with at least eight rectal aberrant crypt foci (ACF) found that the number of ACF was significantly lower with a daily supplementation with 4 g/day of curcumin compared to 2 g/day ($P < 0.005$) [10].

This protective effect may be, in part, attributable to curcumin's activating effect on the *NRF2* gene, whose protein product is a transcription factor known to control several antioxidant pathways. In a healthy cell, this action will provide protection from an excess of reactive oxygen species (ROS). In a tumor cell, curcumin may well produce the very same effect. In the context of chemotherapy during which ROS accumulates, this antioxidative effect of curcumin may be protective of a cancer cell. A widely cited paper from 2011 [11] shows that mouse embryonic fibroblasts with active endogene transcription of mutant K-ras (G12D/+) or mutant Braf (V619E), through orchestrating jun and myc, may induce the expression of functional and, in this context, strongly pro-proliferative Nrf2. However, in a cancer cell, this is not the only effect that needs to be considered. Curcumin has a potent anti-inflammatory effect, which is primarily related to its inhibitory action on the pro-inflammatory, pro-proliferative, nuclear factor-κB signaling pathway. Thus, one cannot exclude the possibility that curcumin creates a balance between these two signaling pathways, in the majority of *in vitro* cellular cancer models, leading to cellular apoptotic death. In this context, it should not be surprising to find that combining curcumin with various cytostatic drugs has a strong synergistic effect [12].

Finally, curcumin was shown to directly bind to some proteins. Some of them are crucial for survival of the cancer cell, as they represent critical points in metabolic reprograming, which allows cancer cell to switch its metabolism toward aerobic glycolysis. Two of these proteins are particularly interesting enzymes: (a) 3-phosphoglycerate dehydrogenase (PHGDH) and (b) mitochondrial hydroxymethyltransferase 2-SHMT2 [13,14]. Silencing of PHGDH in HeLa cells significantly inhibited cell proliferation and increased cisplatin chemotherapy sensitivity [15]. Based on human breast and lung cancer mRNA data sets, Antonov et al. were able to predict high PHGDH expression as a negative prognostic marker in breast cancer patients in seven out of 17 breast cancer datasets [16]. However, the increased expression of the PHGDH mRNA did not appear to have any prognostic value in seven analyzed lung cancer datasets. Once again, this illustrates the importance of the cell-specific molecular background which is profiled on specific signaling pathways. The level of their dependency on specific molecules/enzymes should be closely connected to the type of cellular redundancy. The fact that high expression of SHMT2 in ten out of 17 breast cancer datasets predicted negative prognosis, seems to be in accord with this presumption.

Because crucial cellular regulatory points are diverse and exist at several levels, a conclusion is elusive. The complex hierarchy in regulating pathological networks is still incompletely understood, notwithstanding ever-increasing knowledge regarding every part of the process.

In that context, personalized medicine has made great progress. However, developing an integrated approach, in which personalized medicine is applied as much as possible, presents a challenging task for the future. Curcumin may have features needed to help to meet this challenge. The problem with its bioavailability seems to be solvable. Recently, published research papers show its direct binding to various proteins, some of them crucial metabolic enzymes for highly proliferative cells. There is numerous data showing its selective action *in vitro* although we still do not entirely understand the basis for it. These data opens the door to a wide range of therapeutic opportunities for targeting cancer cell in a cell-type specific fashion. However, well-controlled clinical trials are still to be undertaken. We await the results obtained in clinical trials to truly understand the rules of multilevel regulation of cellular biology joined with the pleiotropic effects of curcumin to support valid health claims.

References

1. Surh YJ, Lee E, Lee JM. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. Mutat Res 1998;402(1-2):259-67. http://dx.doi.org/10.1016/S0027-5107(97)00305-9.
2. Vogel HA, Pelletier J. Examen chimique de la racine de curcuma. J Pharm 1815;1:289-303. Available from: http://www.gallica.bnf.fr/ark:/12148/bpt6k781358/f290.image. [Last accessed on 21 January].
3. Daube FV. Über curcumin, den farbstoff der curcumawurzel. Ber Dtsch Chem Ges 1870;3:609-13. http://dx.doi.org/10.1002/cber.187000301196.
4. Roughley PJ, Whiting DA. Experiments in the biosynthesis of curcumin. J Chem Soc Perkin Trans 1 1973;1:2379-88. http://dx.doi.org/10.1039/C5RA23401H.
5. Oppenheimer A. Turmeric (Curcumin) in biliary diseases. Lancet 1937;229:619-21. http://dx.doi.org/10.1016/S0140-6736(00)98193-5.
6. Global Market Insights. Report ID: GMI788. Available from: https://www.gminsights.com/industry-analysis/curcumin-market. [Last accessed on 21 January]
7. Burgos-Morón E, Calderón-Montaño JM, Salvador J, Robles A, López-Lázaro M. The dark side of curcumin. Int J Cancer 2010;126:1771-5. http://dx.doi.org/10.1002/ijc.24967.
8. Ahmad MZ, Alkahtani SA, Akhter S, Ahmad FJ, Ahmad J, Akhtar MS, et al. Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: Current state-of-the-art. J Drug Target 2016;24:273-93. http://dx.doi.org/10.3109/1061186X.2015.1055570.
9. Perkins S, Verschoyle RD, Hill K, Parveen I, Threadgill MD, Sharma RA, et al. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiol Biomark Prev 2002;11:535-40.
10. Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res (Phila) 2011;4:354-64. http://dx.doi.org/10.1158/1940-6207.CAPR-10-0098.
11. DeNicola GM, Karreth FA, Humpton TJ, Gopinathan A, Wei C, Frese K, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature 2011 6;475:106-9. http://dx.doi.org/10.1038/nature10189.
12. Troselj KG, Kujundzic RN. Curcumin in combined cancer therapy. Curr Pharm Des 2014;20:6682-96. http://dx.doi.org/10.2174/1381612820666140826154601.
13. Angelo LS, Maxwell DS, Wu JY, Sun D, Hawke DH, McCutcheon IE, et al. Binding partners for curcumin in human schwannoma cells: Biologic implications. Bioorg Med Chem 2013 15;21:932-9. http://dx.doi.org/10.1016/j.bmc.2012.12.008.
14. Abegg D, Frei R, Cerato L, Prasad Hari D, Wang C, Waser J, et al. Proteome-wide profiling of targets of cysteine reactive small molecules by using ethynyl benziodoxolone reagents. Angew Chem Int Ed Engl 2015;54:10852-7. http://dx.doi.org/10.1002/anie.201505641.
15. Jing Z, Heng W, Xia L, Ning W, Yafei Q, Yao Z, et al. Downregulation of phosphoglycerate dehydrogenase inhibits proliferation and enhances cisplatin sensitivity in cervical adenocarcinoma cells by regulating Bcl-2 and caspase-3. Cancer Biol Ther 2015;16:541-8. https://doi.org/10.1080/15384047.2015.1017690.
16. Antonov A, Agostini M, Morello M, Minieri M, Melino G, Amelio I. Bioinformatics analysis of the serine and glycine pathway in cancer cells. Oncotarget 2014;5:11004-13. https://doi.org/10.18632/oncotarget.2668.