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Letter to the Editor

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A Realistic View on "The Essential Medicinal Chemistry of Curcumin"

The review paper entitled "The Essential Medicinal Chemistry of Curcumin", published in the *Journal of Medicinal Chemistry*, by Nelson et al.[1] is a well-designed paper, presenting a new (and negative) approach to the well-known biologically active compound; curcumin. Although some arguments throughout this paper are completely true, the approach of the authors is unfortunately far from impartial, and many of the conclusions the authors draw from some of their referred papers are especially hard to accept.

On page 1621, line 11, the authors mention that the in vivo stability of curcumin is $T_{1/2} < 5$ min and $F < 1\%$ by referring to the research papers of Wang et al.[2] and Yang et al.[3] (refs 27 and 28 of the original paper). Interestingly, neither Wang nor Yang et al. directly report these values as the half-life of curcumin, which makes this a very biased supposition of the authors. The paper, published by Wang et al., reports the stability of curcumin in buffer solvents at laboratory conditions and in rat blood circulation. Since it is impossible to directly dissolve curcumin in water, curcumin was dissolved in methanol and then diluted with a buffer, and the amount of curcumin was measured in HPLC at different intervals. It is obvious that curcumin will start precipitating upon dilution with a buffer. Thus, it is doubtful that the sample injected in HPLC or administered to rats includes the supposed amount of curcumin.

Yang et al. also do not report the half-life of curcumin below 5 min. This paper reports the elimination period as 28.1 ± 5.6 and 44.5 ± 7.5 min for 500 mg/kg, p.o. and 10 mg/kg, i.v. of curcumin, respectively. It is noteworthy that the half-life results are reported by the studies made in rats, not human studies. A rat weighing 400 g has a total blood volume of approximately 25.6 mL,[4] and the human blood volume is approximately 5.5 L. The half-life measurements of the compound during blood circulation were made without considering the insolubility of curcumin in buffer solutions or the stability measurements in rat blood circulation and therefore do not accurately illustrate the fate of curcumin upon circulation within human blood. More interestingly, the authors acknowledge that the half-life of curcumin with pH 7.4 and 37 °C in human blood is 360−480 min in Supplemental Table 2 of ref 1. However, they report its stability as $T_{1/2} < 5$ min on page 1621, left column line 11.

IS THE "ALLURE OF THE GOLDEN SPICE" FAKE?

On page 1623, left column, line 17, the authors refer to the paper published by Burgos-Morón et al. entitled "The Dark Side of Curcumin"[5] (also ref 5 of the original paper). The authors did not take into consideration the article published by Kurien et al., which actually is a response paper to Morón et al.[6] The paper criticizes Morón et al.'s article not only by referring to related research but also by conducting new investigations to refute their theory. So, we will not further discuss the ideas about "the dark side of curcumin"; however, since the authors have used this expression a lot throughout the paper, we would like to stress that the paper by Burgos-Morón et al. is not a research paper, but is just a Letter to the Editor[5] and should not be referred to as a credible source.

IS CURCUMIN A PAINS, IMPS, AND POOR LEAD COMPOUND?

The authors claim that curcumin is a pan assay interference (PAINS) compound by referring to the papers by Baell et al.[7,8] (refs 6 and 40 of the original paper). Although this is a very important warning to all scientists who work on the bioactivities of curcumin, this is an insignificant point unless some real experiments conducted showed that the biological activities of curcumin are not raised from its unique structure, but from its assay interference property. These are considerations that must be taken into account when determining selection criteria for high-throughput screening experiments. However, real results obtained from human trials and case reports[9−12] are more valid than all theoretical warnings.

In addition, the authors enumerate the properties of PAINS one by one, declaring that curcumin has all of those properties by giving references for each of them. It is interesting to note that they call curcumin a "fluorescence interferer" by referring to the paper of K. I. Priyadarsini[13] (ref 48 of the original paper). This paper does not report a fluorescence interfering property for curcumin but rather suggests that curcumin is a "bimolecular sensitive fluorescent probe". Not all compounds with fluorescence property are interferers. Numerous activities of curcumin, which have been listed here as the causes of PAINS, are caused by its unique structure and have been discussed in various structure−activity relationship (SAR) papers.[14,15]

Here, we would like to add another point. One of the authors of this review, Guido F. Pauli, has previously authored two papers on the isolation of compounds similar to curcumin and bioactivity of curcumin. In the first manuscript, the authors searched for diarylheptanoid compounds, reporting that the first diarylheptanoid to be discovered was curcumin. The compounds possess a 1,7-diphenylheptane skeleton and exhibit prominent pharmacological activities such as estrogenic, anticancer, antibacterial, antioxidative, anti-inflammation, and antiosteoporotic properties.[16] In this study, the authors conducted very important NMR studies on diarylheptanoids. It is obvious that the instability of a compound would show up in NMR studies due to the occurrence of degradation compounds or the derivatives of the parent compound, but the authors fail to mention any problems regarding the instability of curcumin or similar compounds during the assay. In the second study, the same author reports the chemopreventative property of curcumin related to quinone oxidoreductase 1.[17] This paper by Pauli et al. is the best evidence to show the generalization of behaviors of curcumin as PAINS and IMPS in vitro and in vivo is a wrong approach. The

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caution by the authors of this Review regarding false results, which could stem from curcumin activities, is very relevant. However, the authors take it further and imply that this compound has no efficacy.

However, various effects of curcumin, which could be due to its metabolites, must not be counted as disadvantages, but rather an advantage of curcumin. Since diseases like cancer and Alzheimer's have multiple causes, "Multi Target Natural Compounds" like curcumin, which can inhibit the progression of disease in several different ways, are important for treating those diseases.[18] Curcumin should be designated as a poor lead compound because of poor ADMET. The expression on page 1625, left column, line 8, regarding unsuccessful attempts in improving ADMET of curcumin is completely wrong information. There are bioavailable curcumin formulations on the market for which the benefits have been scientifically proven including using curcumin in combination with Bioperin,[19,20] Longvida,[21] Theracurmin,[22−24] Curcumin Phytosome Meriva,[25,26] and BCM-95.[27,28]

Furthermore, meta-analyses have been made of various clinical trials of curcumin, which should not be ignored. All of these analyses confirm the results obtained from these trials with curcumin.[29−31]

IS CURCUMIN UNSTABLE?

The claims of the authors in this part and related references are in contradiction. In the NMR study made by Payton et al.[32] (ref 63 of the original paper), there is no evidence of instability, probably because in NMR curcumin is completely soluble in the solvents used, so no precipitation occurs. However, in the paper by Griesser et al.[33] (ref 66 of the original paper) curcumin is dissolved in ethanol at 5 mM, followed by 500-fold dilution with water. It is obvious that curcumin will start to precipitate in water. This little comparison shows how studies made by Payton et al. and Griesser et al. contradict each other. Regarding the stability of curcumin in blood circulation, some papers report its existence in blood as curcumin glucuronide and curcumin sulfate after 24 h.[34] It seems that the stability of curcumin depends on the solvents used under laboratory conditions and its bioavailability in the body.

THE MOST IMPORTANT IGNORED TRUTH ABOUT CURCUMIN; NF-KAPPA B INHIBITION

Nuclear Factor-Kappa B (NF-κB) is a key inflammatory transcription factor expressed frequently in tumors. Therewithal, NF-kB has an important role in various cellular processes such as proliferation, apoptosis, inflammation, and immune response. Several recent preclinical and clinical studies, including meta-analysis made by Wu et al.[35] have shown that significant NF-κB expression is associated with chemotherapy and radiation resistance and poor outcome in several human cancers. Moreover, NF-κB expression was shown to be a TNM stage-independent poor prognostic factor.[35] Since apoptosis induction is the major mechanism of action in radiotherapy and mostly in chemotherapy, it is no wonder that preclinical and clinical observations indicate that NF-κB plays an important role in inhibition of apoptosis resulting in chemo- and radioresistance. Thus, inhibition of NF-κB could be a new approach in cancer treatment.[36,37] Curcumin inhibits NF-κB activation through suppression of inhibitor kappa B alfa (IκBα) kinase and Akt activation.[38,39] Preclinical in vivo and in vitro trials that combine curcumin with chemotherapeutics and tyrosine kinase inhibitors have shown that this combination shows better results than each treatment alone.[36,37,40] Sun et al. have shown that curcumin dually inhibits mTOR (Mammalian Target of Rapamycin) and NF-κB pathway through a crossed Phosphatidylinositol 3-Kinase/Akt/Inhibitor κB complex signaling axis in adenoid cystic carcinoma (ACC)[41] in vivo. Recently, our group has successfully treated a c-kit and NF-κB overexpressed adenoid cystic carcinoma patient.[10] This success was a reflection of the in vivo studies published by Sun et al. The patient is being followed and has shown complete response for four years. To illustrate the chemical stability of curcumin, we report here the stability results of an i.v. formulation of curcumin. This formulation is a compounding pharmacy product, which was prepared by dissolving curcumin in alcohol and Kolliphor ELP. As it is clarified in supporting data, there is not any significant change in the ratio of curcuminoids, even after 12 months of storage.

CONCLUSION

We agree that the most important issue associated with studies on curcumin is its solubility. However, Nelson et al. pessimistically attribute the research failures as inefficacy of curcumin. We would like to emphasize the importance of a logical approach of scientists studying natural products such as curcumin, which could be a very important adjunctive treatment agent for multiple diseases, especially cancer. Scientists must appreciate the genius designs coming from nature considering the lives that could be saved by using them.

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ASSOCIATED CONTENT

Supporting Information

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Ratio of curcuminoids in an injectable formulation, prepared using ethanol and Kolliphor ELP, is measured at the zero point (Figure 1) and after 12 months (Figure 2) by HPLC. Percentages of dissolved curcumin in this formulation at the initial point and after 3, 6, and 12 months in two different climate zones (Tables 1 and 2) to affirm the stability of curcumin (PDF)

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