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File: ■ Turmeric (*Curcuma longa*, Zingiberaceae)
■ Curcumin
■ Medicinal Chemistry
■ Drug Discovery

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RE: Assessment of the Medicinal Chemistry of Curcumin: When a Natural Product Is Not a Suitable Conventional Pharmaceutical Drug Lead

Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. *J Med Chem.* January 11, 2017. doi: 10.1021/acs.jmedchem.6b00975.

Turmeric (*Curcuma longa*, Zingiberaceae), the source of curcumin, has been used as a food, spice, and traditional medicine for thousands of years. The curcumin isolated from the rhizome has been researched as a therapeutic agent for many different conditions and diseases.

This review evaluated the medicinal chemistry of curcumin — a name used by the authors for both the individual curcuminoid compound and mixtures of curcuminoids (some of the biologically active compounds in turmeric root and its extracts) — to determine if it is a suitable lead for the development of conventional pharmaceutical drugs. Although the review focuses on curcumin, the paper may also serve as a general guide on how to assess natural products (or, more specifically, pure compounds derived from chemically complex plant material) as potential candidates for pharmaceutical drug development. According to the authors, ideal candidates are chemically stable and have high water solubility, potent and selective target activity, high bioavailability, broad tissue distribution, stable metabolism, and low toxicity. The review presents evidence that curcumin does not exhibit these properties.

After analyzing the relevant scientific literature, the authors reported high variability in curcumin purity, in addition to a "widespread lack of characterization of ‘curcumin’ materials." Despite most commercial "curcumin" ingredients and finished products’ containing multiple compounds (i.e., the curcuminoids curcumin, demethoxycurcumin, and bisdemethoxycurcumin), the specific composition was not always defined (presumably in the products’ labels and/or in the reviewed articles). Therefore, the review uses "curcumin" interchangeably with "curcuminoids," noting that variability in commercial curcumin preparations is an obstacle to interpreting and reproducing experimental results.

According to the authors, curcumin exhibits all behaviors of pan-assay interference compounds (PAINS),[1-9] which tend to give false positives in assay readouts. Assay interference may result from various properties or "behaviors" of PAINS, including covalent labeling of proteins, metal chelation, redox reactivity, aggregation, membrane disruption, fluorescence interference, or structural decomposition. Curcumin has been shown to do all of the above, which leads the authors to caution that "any report of [curcumin] activity in an assay that does not either exclude or account for these potential modes of assay interference should be treated with caution."

Researchers have reported that curcumin has a high rate of bioactivity.[10] Of particular concern is curcumin's stability, which reportedly decreases by 50% within 20 minutes at neutral pH, room temperature, and in an aqueous buffer solution. While curcumin is more stable in acidic environments (i.e., solutions with a pH of less than 7), curcumin shifts to a much less soluble form as the pH of its environment decreases.[12,13] The authors state that "Nearly all the manuscripts reviewed failed to consider the stability of [curcumin]," and that the "time frame for [assays] described in publications included in NAPRALERT allows for significant degradation of curcumin."

The authors stress the importance of the initial characterization of the curcumin material, but they note that it is also imperative to identify amounts of degradation products present at the end of an experiment.[14] "The polypharmacology of curcumin may in part, or even largely, be due to the sum of its degradation products. Instability of curcumin must be considered when interpreting bioassay results, if stability is not otherwise demonstrated. Curcumin stability can be improved with lipid encapsulation or nanoparticles, but these will have to be evaluated as new compounds with potential cytotoxicity."

"Curcumin also displays undesirable physicochemical properties relative to known drugs," the authors added. The main concern is that curcumin forms chemical aggregates (colloids) under many common bioassay conditions. Enzymes, which are often targeted in standard bioassays, can be inhibited by colloids.

Curcumin bioactivity was often observed at concentrations typically above the critical aggregation concentration threshold for curcumin. In addition, the authors found that "appropriate counterscreens for assay interference were frequently not performed, and target engagement was not confirmed nor was target selectivity." Identifying the locations of cellular targets is important, "as curcumin has been shown to perturb cell membranes," leading to "membrane perturbation mistaken for specific binding to membrane-associated proteins."[7]

The authors then discuss curcumin's pharmacokinetic properties, which are described as "generally accepted … as poor."[15,16] This review evaluated whether curcumin has suitable absorption, distribution, metabolism, excretion, and toxicology for a "drug lead." In all clinical studies reviewed, the authors found no detection of curcumin in the serum of the majority of subjects tested. While distribution of curcumin in humans has been "sparingly studied," rodent models suggest that curcurmin has a high variability in distribution.[16-18] The authors state that this variability could be due to differences in material, extraction, preparation, detection methods, or lack of specificity in detection assays used.

Extensive research has examined curcumin metabolism in human liver microsomes and has shown a high potential for modification by both first and second phase metabolism. Regarding excretion, rodent studies show that the majority of curcumin is excreted in the feces, while small amounts may be absorbed and excreted unchanged, or not absorbed at all and passed directly to feces. Metabolized curcumin is excreted in urine as glucuronide and sulfate conjugates.

Regarding its toxicology, curcumin has been shown to interact with human enzymes (e.g., cytochrome P450s and glutathione S-transferase) that have been implicated in the occurrence of adverse events or interactions with conventional pharmaceutical drugs. Curcumin has been reported as toxic against many cancer cells lines, but it has been reported as toxic against normal human cells in only a few studies.[19, 20]

The authors caution those who seek to improve the pharmacokinetics of curcumin, as they could increase these potential cytotoxic effects.[19] The hypothesis as to why there is such a high observed tolerance in humans and low rate of adverse events in the vast amount of curcumin literature is that it is all "likely due to … poor absorption and low bioavailability." However, the authors also mention it is possible that the benefits of curcumin on human health could be due to effects on the gut microbiome,[15] making absorption moot (although curcumin's lack of efficacy at high doses in clinical trials does not bode well for this hypothesis).

One common theme the authors found disturbing is that "published bioactivity data of curcumin are typically not evaluated critically before [they are] used to justify further research." This review intends to help ensure that researchers and readers are assessing the medicinal chemistry of bioactivity assays before moving forward with further research. The authors remain skeptical that oral curcumin (as a single compound) has any effect on human health, and their review of clinical trials does not support further investigation into curcumin as a conventional pharmaceutical therapeutic agent. The review concludes that curcumin does not possess the properties required for a reliable conventional drug candidate. While isolated curcumin may not be a viable conventional therapeutic, according to this review, natural products require a holistic approach be considered, as well. As the authors explain, "there is increasing evidence that [chemically complex traditional medicine] agents cannot be described with reductionist pharmacology models."[21]

This article was covered fairly extensively in the mainstream media in the US with the misleading message that turmeric and/or curcumin-standardized turmeric extracts have been found to be ineffective.

—Alexis Collins, MA, MS

ABC Comments

The different uses of curcumin as a conventional drug and as a dietary supplement must be distinguished. Caution must be taken when interpreting in vitro data using this pure compound or group of curcuminoids, and extrapolating the observed effects into activities in humans. Curcumin has produced positive results in many of these tests, and some of these results *are* likely due to assay interferences, as detailed by the authors,

rather than actual bioactivity of curcumin. Based on the available data, the usefulness of curcumin as a conventional drug (e.g., to treat cancer or Alzheimer's disease) is limited.

However, this does not mean that turmeric and products made from turmeric do not have beneficial bioactivities. The use of curcuminoids, turmeric extracts, or powdered turmeric as a dietary supplement, in particular to address inflammatory conditions, has merit and warrants further investigation. The limitations in bioavailability and stability of curcumin are well-known, and can be addressed to some extent by improving the formulations, as has been done with some commercial turmeric extracts. Clinical studies that have shown positive results with curcumin in the area of osteoarthritis, for example, have been published. Therefore, the authors' statement that "curcumin [which includes curcuminoid mixtures consisting of curcumin, demethoxycurcumin and bisdemethoxycurcumin at various concentrations according to the authors] has never been shown to be conclusively effective in a randomized, placebo-controlled clinical trial for any indication" is inaccurate.

In addition, the use of curcumin (or turmeric) preparations on a regular basis may have some disease-preventing effects. It takes substantial effort to prove a preventive effect scientifically, since extensive long-term investigations are necessary, but the available data suggest that curcumin might be beneficial for the prevention of certain inflammatory diseases, and possibly others.

Finally, the authors raise an interesting point, which is the potential that curcumin provides health benefits through interactions with the gut metabolome. As they note: "As an alternative approach, it may be possible for curcumin to have an effect on human health without being absorbed. Emerging research suggests that it could affect the gut microbiota, which has been linked to several chronic diseases."

—Stefan Gafner, PhD

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Referenced article can be accessed at
https://www.researchgate.net/publication/312232986_The_Essential_Medicinal_Chemistry_of_Curcumin.