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Letter to the Editor

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Curcumin May (Not) Defy Science

We wrote "The Essential Medicinal Chemistry of Curcumin" (TEMCC)[1] to raise awareness among medicinal chemists, natural product chemists, and other scientists to the challenges associated with working with a specific compound (curcumin; not identical with a plant or plant extract) that is an AIC (assay interference compound), a PAINS (pan-assay interference compound), and an IMP (invalid/improbable metabolic panacea). The overwhelming coverage of our article indicates the importance of the topic for the field of drug discovery and nature-based medicine. We also note, however, that some researchers may have missed a few of the finer and/or less familiar points of our manuscript. Such appears to be the case with the Letter to the Editor "Curcumin May Defy Medicinal Chemists" that was recently published in *ACS Medicinal Chemistry Letters*.

Based on a subset of comments in the scientific and popular literature, we believe we must review some basic facts. Curcumin is a single chemical entity. It degrades rapidly at neutral pH in water. Curcumin is the most prominent member of the diarylheptanoid family of compounds, termed curcuminoids, which are contained in (not: are) turmeric and, along with many other constituents, in extracts of turmeric. Curcuminoids, as typically sold (though there are notable exceptions), contain three primary components and ∼15% of oleoresins and essential oil that typically remain unidentified in commercial products.

One key question, we believe, is "what is/are the active component(s) of turmeric?" Others have rightly pointed out that turmeric contains hundreds of potentially bioactive compounds and that the hypothetical "curcumin-free" turmeric would still show bioactivity.[2] One of our many concerns was with the apparent reductionist approach to turmeric that placed all of the bioactivity on curcumin, a compound with numerous liabilities (instability, poor solubility, low bioavailability, poor selectivity, and multiple modes of assay interference) that also happens to be the major constituent of most turmeric extracts. This reductionist approach has led to the use of curcumin as a lead compound, a designation that is at best employed euphemistically as curcumin is severely out of balance as a true lead for further optimization.

As emphasized in our article,[1] it is important to point out that we cannot, nor pretend to, perform an exhaustive review of the vast literature on "curcumin", and that our study was especially not a meta-analysis of all "curcumin" clinical trials (we will use quotes when the intervention material is not completely characterized). The authors of "Curcumin May Defy Medicinal Chemists" state that "even if 1% of the papers published make sense, it would still be a sizable number to warrant against passing a negative verdict on the whole field." This seems to equate the number of manuscripts with scientific fact. If the fundamental foundation of curcumin bioactivity was based on 100 papers that did not take into account its AIC potentials (e.g., aggregation, fluorescence, and reactivity interference, etc.), or did not consider the difference between curcumin and *Curcuma*, the amount of confounding variables would make the following work inconclusive at best, regardless of the number of manuscripts.

In TEMCC,[1] we focused on the AIC, PAINS, and IMP features of curcumin. We decided to examine a select group of clinical trials of "curcumin" that we thought would best be illustrative of its potential utility. We chose colon cancer because curcumin is most likely to be active in the gut. We chose pancreatic cancer because of its lethality. We chose Alzheimer's disease because these studies are representative of other clinical trials in the central nervous system setting. We chose radiation dermatitis because we reasoned skin application could be an ideal test of "curcumin's" efficacy. It was only after we started to read the clinical trial reports that we realized the "curcumin" was dosed orally. In none of the studied cases was any consistent efficacy observed.

The authors of "Curcumin May Defy Medicinal Chemists" describe clinical studies examining treatment for rheumatoid arthritis (RA)[3] and chronic obstructive pulmonary disease (COPD).[4] There are a few initial points that exclude them from being used as a rebuttal to our analysis. First, neither use pure (95+%) curcumin. Both studies use a commercial curcuminoid mixture that contains other components. Second, only one of the two was double-blinded and placebo controlled. Finally, neither shows a statistically significant improvement in patient outcomes.

As medicinal and natural product chemists, molecular pharmacologists, and physician scientists, we must be comfortable critically analyzing a broad range of data, and this includes human trial data. We begin with the "curcumin" and RA trial published by Chandran et al.[3] This study was single-blinded and not placebo controlled. For dosing, it used BCM-95, which is a "reconstituted turmeric extract standarised [sic] with [sic] curcuminoids"[5] that is described as containing ar-turmerone to provide enhanced bioavailability. This intervention material is not simply curcumin, and saying or implying that it is falls into a fallacy of composition. Regarding the observed outcome, while the authors show a trend for "curcumin" causing improvement in RA patients, the difference vs diclofenac sodium is not statistically significant (neither better nor worse). Further, based on the study design, it would be incorrect to claim any effects seen in the treatment groups are directly linked to the therapeutic, as there is no placebo group for comparison. Finally, the statistical analysis done was inappropriate for the data presented. The baseline values contain data from individuals who did not complete the study. The data was analyzed by *t* tests and unspecified ANOVA, when clearly non-normally distributed data and discrete/categorical values were involved and should have been analyzed using nonparametric tests.[6] There was also no adjustment of *p*-values in pairwise comparisons to control for family wise error. In Table 1, we have taken the raw data from Tables 4 and 5 of

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Table 1. Comparison of Reported within-Group and between-Group Significance of "Curcumin"[a] and RA

parameter	group	baseline[b]	EOT[b]	within group p value[b]	between group EOT p value[c]	baseline to EOT change p value[c]
disease activity score	"curcumin"	6.40 ± 0.73	3.55 ± 0.73	<0.05	0.544[d]	1.000[d]
	"curcumin" + diclofenac sodium	6.44 ± 0.51	3.58 ± 0.71	<0.05	0.995[e]	1.092[e]
	diclofenac sodium	6.72 ± 0.87	3.89 ± 1.43	<0.05	0.695[f]	0.998[f]
visual analogue scale	"curcumin"	68.57 ± 17.14	27.5 ± 9.35	<0.05	0.135[d]	0.975[d]
	"curcumin" + diclofenac sodium	77.25 ± 9.65	34.29 ± 26.75	<0.05	0.496[e]	0.978[e]
	diclofenac sodium	78.25 ± 11.25	39.17 ± 20.1	<0.05	0.770[f]	0.916[f]

[a]See main text for comments on the intervention agent. [b]Reported in Chandran et al.[3] [c]Calculated between groups using ANOVA with Tukey's HSD posthoc test for single-step multiple comparison. [d]"Curcumin" vs diclofenac sodium groups. [e]"Curcumin" vs curcumin + diclofenac sodium groups. [f]"Curcumin" + diclofenac sodium vs diclofenac sodium groups.

Table 2. Determination of End of Treatment Values for Placebo and "Curcumin" Treatment[a] Groups from COPD Subjects

	baseline[b]		percent change, %[b]		end of treatment[c]	
parameter	placebo	treatment	placebo	treatment	placebo	treatment
BMI, kg/m^2	24.4	22.1	−0.7	0.9	24.2	22.3
SBP, mmHg	127.7	127.6	1.4	−1.3	129.5	125.9
DBP, mmHg	70.5	70.7	2.9	3.5	72.5	73.2
HbA1c, %	5.3	5.4	0.0	0.4	5.3	5.4
BS, mg/dL	98.6	102.8	14.5	5.8	112.9	108.8
TG, mg/dL	160.1	146.3	14.5	9.2	183.3	159.8
LDL-C, mg/dL	104.5	106.8	11.4	4.6	116.4	111.7
HDL-C, mg/dL	60.1	62.1	2.0	−2.8	61.3	60.4
UA, mg/dL	6.2	6.6	2.3	2.4	6.3	6.8
γ-GTP, IU/L	39.8	52.3	−1.2	−5.7	39.3	49.3
Cre, mg/dL	1.0	0.9	1.4	2.9	1.0	0.9
CRP, mg/dL	0.2	0.3	11.1	−12.5	0.2	0.3
SAA-LDL, μg/mL	8.9	14	10.8	−2.0	9.9	13.7
AT-LDL, μg/mL	1.2	1.4	14.8	−1.6	1.4	1.4
FEV_1, %	64.7	61.9	−3.6	−1.9	62.4	60.7

[a]See main text for comments on the intervention agent. [b]Reported in Funamoto et al.[4] [c]Calculated using the given baseline data and reported percent change for each value.

this study and done between-group ANOVA analyses on two different values using Tukey's HSD posthoc test for single-step multiple comparison. The difference between the end-of-treatment values of any of the groups was not statistically significant (see "between group EOT p value" column in Table 1). In addition, we determined there was no statistical significance in the observed change for each treatment group (see "baseline to EOT change p value" column in Table 1). However, the study authors rightly state that another larger trial would have to be done in order to determine if "curcumin" could actually be effective. Moreover, a recent meta-analysis of eight validated arthritis studies that employed "curcumin" highlighted the lack of significant efficacy in this and other studies.[7] Of additional interest is that this study appears to measure the levels of fetal bovine serum in healthy adults (see Table in the publication), a surprising component of human fluids.

The "curcumin" and COPD trial published by Funamoto et al. is a double-blinded, placebo-controlled study.[4] However, it employs Theracurmin, a "highly-bioavailable" form of turmeric extract, which contains approximately 30% curcumin and therefore cannot be simplified as being curcumin. This, again, severely decreases strength of an argument for curcumin as the therapeutic agent and is consistent with the TEMCC content.[1] Moreover, the prestudy parameters in the study arms showed significantly different values for patient BMI and AT-LDL levels, suggesting suboptimal cohort stratification. The final, post-treatment values are also presented as the percent change in each parameter, not clinical outcomes. Additionally, it appears that statistical analysis was done on the percent change instead of measured values, an uncommon, if not inappropriate, way to treat clinical data. Similar to the RA study, the baseline values contain data from individuals who did not complete the study. While the percent change in both BMI and AT-LDL levels is reported as statistically significant, closer inspection reveals this to be irrelevant. First, by using the reported percent change to calculate the final values for each parameter, we can determine the post-treatment values for each group (final column, Table 2). The AT-LDL levels were exactly the same for each group after 24-weeks of treatment. Second, after determining the absolute change between pre- and post-treatment, a t test reveals that none of the changes were statistically significant (Table 3). This suggests that the percent change observed is due to random variation and regression toward the mean. Finally, with 15 comparisons being made in this study, there is approximately a 50% chance that there will be at least one significant p value < 0.05.[6] With two values reported at <0.05, it is not an unreasonable expectation that at least one of them is simply significant by chance, especially when the above considerations are made. Moreover, AT-LDL is an experimental biomarker, has only been reported in a single cohort of 183 patients to our knowledge,[8] and has not been

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Table 3. Determination of Absolute Change and Statistical Significance between Pre- and Post-Treatment Values for Placebo and "Curcumin"[a] Groups from COPD Subjects (Within-Group Analysis)

	absolute change[b]		unpaired t test[c]	
parameter	placebo	treatment	placebo	treatment
BMI, kg/m^2	−0.17	0.2	0.872	0.724
SBP, mmHg	1.8	−1.7	0.805	0.768
DBP, mmHg	2.0	2.5	0.584	0.528
HbA1c, %	0.0	0.0	1.000	0.829
BS, mg/dL	14.3	6.0	0.216	0.456
TG, mg/dL	23.2	13.5	0.479	0.529
LDL-C, mg/dL	11.9	4.9	0.205	0.528
HDL-C, mg/dL	1.2	−1.7	0.723	0.668
UA, mg/dL	0.1	0.2	0.752	0.581
γ-GTP, IU/L	−0.5	−3.0	0.952	0.803
Cre, mg/dL	0.0	0.0	0.898	0.656
CRP, mg/dL	0.0	0.0	0.790	0.818
SAA-LDL, μg/mL	1.0	−0.3	0.676	0.973
AT-LDL, μg/mL	0.2	0.0	0.075	0.810
FEV_1, %	−2.3	−1.2	0.287	0.554

[a]See main text for comments on the intervention agent. [b]Calculated from the baseline data in Funamoto et al.[4] and the end of treatment values determined in Table 2 (*vide supra*). [c]Baseline to end of treatment for each value, within group.

widely validated for clinical significance in COPD patients. A recent meta-analysis of the inflammatory markers associated with the pathogenesis of COPD makes no mention of AT-LDL from the analysis of 24 observational studies reporting on 10,677 COPD patients and 28,660 control subjects.[9] Collectively, these observations are incompatible with claims of therapeutic efficacy of curcumin for treating COPD.

Regarding the preclinical studies described in the letter, we would suggest: (1) thorough characterization of the identity, quality, and content/purity of any "curcumin" product, including pure curcumin, as well as other relevant curcuminoids discussed in TEMCC;[1] (2) especially for biological studies, consideration of the concepts of static and dynamic residual complexity of both curcumin and *Curcuma* derived materials, which cover purity, (in)stability, as well as metabolic and chemical conversions *in vitro* and *in vivo*;[10,11] this requires (3) verification of curcumin levels at various stages of the experiment given its instability in aqueous solutions; and (4) use of additional control compounds including interference controls, inactive analogues, other relevant curcuminoids, and possibly unrelated compounds.[12]

Interestingly, by stating that curcumin can only be observed transiently in the plasma of animals, the authors of the letter confirm that curcumin itself can be excluded as the pharmacologically active agent. Even an immune memory effect, which is measurable,[13] requires circulatory exposure of an infectious or vaccination agent. Without measurable outcomes, either analytical or clinical, there is no evidence that curcumin itself acts through any therapeutic mechanism at all, medicinal chemistry known or otherwise.

Finally, we continue to emphasize that our article was a review of published data concerned with the curcumin portion of *Curcuma* research. We made several cautionary recommendations and suggestions for alternative research approaches based on a comprehensive collection of facts, but we did not summarily dismiss research into *Curcuma longa*, its extracts and preparations, or any other (isolated) chemical constituents. We strive to aid our community in effective research toward new therapeutics from any and all sources through medicinal and natural product chemistry best practices, and critical review of the science upon which we all base our work.

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ABBREVIATIONS

AIC, assay interference compound; ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; EOT, end-of-treatment; HSD, honest significant difference; IMP, invalid/improbable metabolic panacea; PAINS, pan-assay interference compounds; RA, rheumatoid arthritis; TEMCC, The Essential Medicinal Chemistry of Curcumin

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EDITOR'S NOTE

The views expressed in this letter are those of the authors and not necessarily the views of the ACS.

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