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A DISCUSSION ON THE FUNDAMENTAL ASPECTS OF THE MEDICINAL CHEMISTRY OF CURCUMIN

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Abstract:

The ancient herbal remedy known as turmeric contains a small amount (less than 5 percent) of the compound known as curcumin. The widespread research into curcuminoids may be attributed to both the potential medicinal applications of turmeric and the simplicity with which curcuminoids can be isolated. Recent research has shown that curcumin is a candidate for both the PAINS (panassay interference chemicals) and the IMPS (invalid metabolic panaceas) categories. Because of the probable misleading activity of curcumin in vitro and in vivo, over 120 clinical studies of curcuminoids have been conducted in an effort to treat a variety of ailments. No clinical study of curcumin that was controlled by placebo and conducted with double blinding has ever been successful. This publication examines the fundamental medicinal chemistry of curcumin and gives data that demonstrates curcumin is an unstable, reactive, and nonbioavailable chemical. As a result, the author concludes that curcumin is a very implausible lead. On the basis of this comprehensive analysis, a discussion of prospective new areas for research on curcuminoids is presented.

Keywords: *Clinical Trial, Curcumin, Traditional Medicine, Turmeric*

Introduction:

Many pharmaceuticals on the market today start off as natural compounds, often known as NPs. This value was recently acknowledged on a broader scale, as the discoverers of the anthelmintic avermectin family of NPs shared the Nobel Prize in Physiology or Medicine in 2015 with the discoverers of artemisinin. Plasmodium falciparum malaria was successfully treated with artemisinin, a natural product that was identified after it was extracted from an Artemisia annua plant used in traditional Chinese medicine (TCM). This prize was seen as a confirmation of the general usefulness of traditional Chinese medicines by a few researchers. 1,2 Recent reports have labelledcurcumin, a component of the spice turmeric and part of the mixture of compounds known as curcuminoids, as both a PAINS (pan assay interference compounds)3 and an IMPS (invalid metabolic panaceas) compound. This stands in stark contrast to the assertion that the role of certain ethnic and

traditional medicines (TxMs) in medical practise has been vindicated. 4 In addition, several studies have discussed the possible "dark side of curcumin," which includes the following: 5–9 disadvantages have been identified for curcumin, some of which include its poor pharmacokinetic and pharmacodynamic (PK/PD) features, its limited effectiveness in a number of illness models, and its hazardous effects under particular testing settings. 5 These warning findings seem to have been washed away in the deluge of articles, reviews, patents, and websites advocating the use of curcumin (and its principal commercial source, turmeric) as an anticancer agent. Turmeric is the primary source of curcumin for commercial usage. 10,11,12 a therapy for Alzheimer's disease,13,14 erectile dysfunction treatment,15,16 baldness treatment,17,18 hirsutism treatment,19 a fertility-boosting extract,20 and contraceptive21 extract, together proving the features anticipated of a panacea.

Scientific articles that are based simply on the basic concept of the reported activity and therapeutic value of curcumin continue to be published on a regular basis. This abundance of data served as the impetus for the creation of a Curcumin Resource Database (CRDB) in the year 2015. This database aims to facilitate the preclinical development of curcuminoidsby putting more than 1000 analogues and their alleged molecular target24 within easy reach of researchers through the use of a Web interface. The fact that the CRDB covers over 9000 publications and 500 patents is evidence of the magnitude of both the scientific interest and the vast amount of dormant information that is waiting for a more global, medicinal chemistry interpretation. Specifically, the information is waiting for an answer to the question, "What does this all mean?" Curcumin (1; Figure 1) and related curcuminoids are the species that are extracted from turmeric, and they are generally what is marketed or examined in clinical studies. The primary objective of this publication is to conduct a review of curcumin (1; Figure 1) and related curcuminoids. Let's begin by laying the groundwork for this Miniperspective with the use of a straightforward example. It has been shown that artemisinin (2) functions like an effective long-range and targeted missile that zeroes in on heme-loving parasites and eliminates them in a stunning burst of nonselective reactivity. Figure 1 illustrates this phenomenon. 25 Artemisinin has a structure that includes peroxide, which leads one to believe that it would be very unstable in a living environment. On the other hand, the fact that it is stable in vivo (T1/2 = 2.5 hours, and F = 30 percent) gives evidence that,

from a pharmacokinetic point of view, it is sufficiently stable to be an effective treatment. Curcumin, on the other hand, is more analogous to a missile that has shown excellent promise in early testing (in vitro), despite the fact that these tests may have been bedevilled by design problems that led to several misfires. In other words, curcumin has the potential to be an effective treatment for a variety of diseases. Both its in vitro and in vivo stabilities are appalling (T1/2 5 min; F 1 percent)27,28 compared to those of commercial medications. The structure of 1 predicts that it would be unstable in a biological milieu, and it really is.

Curcumin Is A Pains, IMPS, And Poor Lead Compound:

Curcumin Is a PAINS. Compounds that have been seen to demonstrate activity in various kinds of assays by interfering with the assay readout rather than via particular compound/target interactions are referred to as pan-assay interference compounds (PAINS). PAINS stands for "pan-assay interference substances." There have been a lot of compound classes defined, and a lot of them have been recognised as PAINS or prospective PAINS. The PAINS-type characteristics covalently tagging of proteins, metal chelation, redox reactivity, aggregation, membrane rupture, fluorescence interference, and structural disintegration are all shown by Compound 1. This means that any claim of its activity in an assay should be taken with care if it does not either exclude or account for these possible forms of assay influence. Reviewers of government proposals in the United States that depend on published evidence about the bioactivity of curcumin should give this factor a lot of thought since it is a very significant aspect. The most current standards for the examination of proposals submitted to the United States National Institutes of Health (NIH) demand four additional factors to show reproducibility. These considerations include the premise, the design, the variables, and the authentication. Therefore, any proposal that is based on the apparent bioactivity of curcumin should ensure that the "scientific premise forming the basis of the proposed research" is sound (that is, published activity is not simply a result of assay interference) and that the "chemical resources" are "authenticated." This means that analytical and target engagement methods should be employed in order to provide convincing evidence that curcumin is the causative agent of activity.

Curcumin Is an IMP. When seen from a holistic perspective, IMPS are ineffective metabolic panaceas that are situated in the epicentre of the natural

product "black hole" and have a tendency to deplete the available resources for research. IMPS, when considered as individual components, are prototypes of unlikely metabolic panaceas that display poor efficacy when used as pharmacological leads. The purported bioactive qualities of IMPS are very difficult to pin down due to the presence of a number of confounding elements, some of which may be in addition to PAINS features but are often distinct from them. 4 After conducting an analysis of the bioactivity profiles of curcumin that were published in the scientific literature from throughout the world, two general findings should serve as a warning: (2) the relatively high ratio of positive activities observed in relation to the overall number of different bioactivities recorded: little over 300 as measured using the NAPRALERT database. (1) the high rate at which this molecule, or combination, is reported as being bioactive. 4 Since 1975, the Program for Collaborative Research in the Pharmaceutical Sciences at the College of Pharmacy at the University of Illinois at Chicago has been the repository for the relational database known as NAPRALERT (www.napralert.org). This database contains information on the chemistry, biological activity, and folkloric use of natural products. NAPRALERT was established by the late Professor Norman R. Farnsworth. Since its inception, the organisation has accumulated data from more than 190 000 literature references and has records of more than 200 000 different chemical compounds from more than 60 000 kinds of life. As a consequence of this, NAPRALERT provides coverage for hundreds of thousands of reports of biological activity testing (including in vitro, in vivo, and clinical outcomes) for both natural product extracts (more than 400 000) and chemical isolates (more than 300 000).

The compound curcumin is not very good at leading. When the PK and PD characteristics of compound 1 are weighed against one another, the result is a lead compound that is fully unbalanced. A prototypical lead compound for therapeutic discovery and development typically possesses less than 1 M potency at its desired target(s), evidence of selectivity and tractable mechanism(s) of action, good bioavailability, chemical stability, and ADMET (absorption, distribution, metabolism, excretion, and toxicology) qualities that can be optimised in a reasonable number of synthetic cycles. However, there are exceptions to this rule and some discrepancies regarding what constitutes a "good" lead. None of these characteristics can be found in compound 1. In addition, efforts to enhance its

ADMET attributes, which are often the features of a molecule that are the most difficult to optimise, and to raise its specificity via chemical optimization and diverse formulations have, up to this point, been fruitless. Given the many structural properties that are apparently responsible for 1's "desirable" action, it may be hard to optimise its pharmacokinetics and pharmacodynamics. For instance, indiscriminate thiol reactivity is a trait that is often marked for optimization. This is because it is thought to be a primary reason for most of its polypharmacology; yet, this is one of the properties that is typically marked for optimization. There is no question that the utilisation of covalent reactivity in the creation of medicines may be beneficial. 55−62 On the other hand, this mechanism of action is either purposely built into the medicine as part of the discovery process or installed after the potency and ADMET qualities have been optimised. For instance,,-unsaturated reactive groups are often purposely added into compounds that have been refined and stabilised in order to boost the potency and selectivity of the compounds. It is quite probable that optimization to enhance the poor PK of one will simultaneously lead to a dulling of the PD fury of the substance.

Critical Analysis of Some Reported Activities of Curcumin (Real and Virtual):

It has been shown that compound 1 is active against a variety of biological targets. What is usually overlooked in these narrowly focused research is the fact that it does not discriminate between targets that are "good" and those that may be labelled "evil" (vide supra). There has been published an in-depth analysis of the structure-activity relationship (as well as the reactivity) of 1. In conclusion, it is quite likely that each functional group in 1 contributes to the reactivity and apparent activity of the molecule. For instance, it should not come as a surprise that compound 1 is able to covalently modify a variety of biological proteins due to the fact that it has two, unsaturated systems that are strong Michael acceptors for SH groups and have low pKa values. In addition, the two phenolic groups are sensitive to redox transformations, and the 1,3-dicarbonyl is a good chelator of metal ions. Both of these properties are found in the compound. In addition to the features described above, it is essential to take into account the activities that have been reported for compound 1 in light of the reactive functional groups that have been described above. The following case studies provide illustrative examples of

this essential factor to take into account (see also Supporting Information Table 1). One of the recurring ideas presented in these studies is especially unsettling: the published bioactivity data of 1 are often not subjected to rigorous evaluation before being utilised to support additional study in a given area. This is particularly concerning in light of the fact that the first activity reports have been withdrawn. 1

Critical Evaluation of Clinical Trials:

There have been reports that Compound 1 is active at several biological targets. What is not often stated in these targeted research is that it is not selective for targets that might be deemed "good" as opposed to those that may be considered "evil" (vide supra). There is a publication that has a thorough analysis of the structure-activity relationship of 1 as well as its reactivity. 106 To summarise, it is likely that each and every functional group in 1 contributes to the apparent activity and reactivity of the molecule. For instance, given that compound 1 has two, unsaturated systems that are strong Michael acceptors for SH groups and have low pKa values, the fact that it can covalently modify a variety of biological proteins should not come as a surprise. In addition to this, the two phenolic groups are able to undergo redox changes, and the 1,3-dicarbonyl is an efficient chelator of metal ions. In addition to the features discussed before, it is essential to take into account the reported activities of 1 in light of the reactive functional groups listed above. Case examples illustrating this crucial topic are provided down below for your perusal (see also Supporting Information Table 1). One of the recurring ideas presented in these studies is especially unsettling: the published bioactivity data of 1 are often not subjected to rigorous analysis before being utilised to support additional study in a given area. When the initial activity reports have been rescinded, this is a very worrying development.

Figures and Tables:

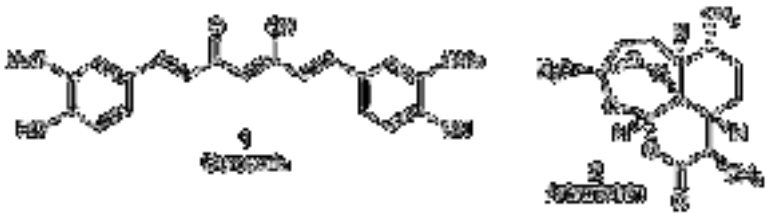

Figure 1.Structural comparison of curcumin and artemisinin.Curcumin has been the focus of heavy research for new drug development. Artemisinin is an FDA approved antimalarial

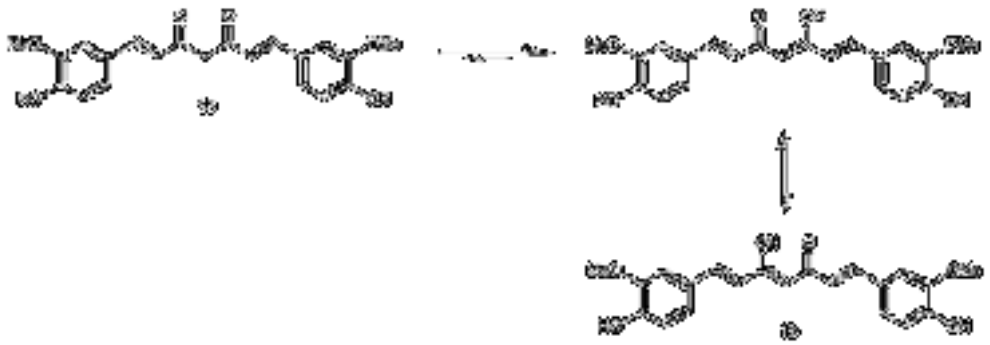

Figure 2.Tautomerization of compound 1. NMR studies show that compound 1 is not present in solution as the diketone (1a) but only as a mixture of the equally present (due to symmetry) enol structure

Table 1. Data Relating Cognitive Function of Nondemented Elderly Subjects and Their Self-Reported Curry Consumption

		unadjusted (MMSE)[b]		adjusted (MMSE)[c]	
curry consumption	no. subjects	mean	95% CI	mean	95% CI
never or rarely	163	24.9	24.2, 25.7	23.3	21.2, 25.4
occasionally	411	26.2	25.8, 26.6	24.8	22.9, 26.7
often	436	25.0	25.6, 26.4	24.8	22.9, 26.6
ANOVA		$p = 0.004$		$p = 0.023$	

[a]Cognitive function was evaluated using various ethnic versions of the MMSE scores for each group. [b]Unweighted sample estimates. [c]Weighted least-squares regression estimates adjusted for age, education, gender, ethnicity, etc. (20 variables total).

Conclusion:

Researchers find it almost hard to keep up with the most recent developments in their area because of the large number of articles that have been published on the topic of the biological activity of curcumin. In this article, an effort has been made to offer an overview of the research that has been done in medicinal chemistry, which will be beneficial for reviewers and researchers to think about while doing their respective jobs. At first glance, curcumin seemed to have a significant amount of promise for the creation of a medicinal product derived from an NP (turmeric) that is recognised as a GRAS substance. Regarding curcumin, curcuminoids, in vivo investigations, and clinical trials, we are of the opinion that there is "much ado about nothing." There is little doubt that the modest levels of systemic exposure that were documented in clinical studies do not justify further exploration into its potential use as a treatment. Curcumin may be beneficial without the need for it to be circulating throughout the body since it may exert its effects on the microbiota in the gut. As at

this moment, there is little evidence to support this notion, which will, in turn, restrict the usefulness of this particular delivery technique. It is possible that delivery technologies such as lipid vesicles, nanoparticles, and nanofibers might increase the bioavailability of 1, but doing so would potentially reduce the drug's therapeutic window and cause off-target toxicity due to the mechanisms described above. No of how it is delivered, the curcumin will eventually deteriorate once it is released into physiologic media, according to the research that is currently available. Analogues of 1 may be able to solve some of the delivery problems, but since they are novel chemical entities, they would need to go through a lot of costly preclinical testing before they could be used in clinical studies. Analogues of curcumin, in our view, are built on top of a foundation that is somewhat shaky.

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