The True Nature of Curcumin's Polypharmacology

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Abstract

Curcumin, a concentrated extract of the herb, turmeric, is a widely used medicinal agent purported to deliver significant anti-inflammatory and other pharmacological activities. As much as curcumin presents a narrower range of pharmacological activity over the whole herb, the extract is still comprised of multiple curcuminoid constituents that contribute to a polypharmacology. Curcumin has been administered successfully in clinical trials to treat depression; Alzheimer's and other neurological diseases; autoimmune and auto inflammatory disorders; and various types and stages of cancer with reasonable success but also with conflicting reports. Upon meta-analysis of the plethora of curcumin-related research it is evident that the pharmacology of this extract is not fully understood.

The naturally occurring, highly homologous curcuminoid analogues are assumed to partake in similar and additive pharmacological events due to their common structural features. However, a perspective shift is presented to feature their electrochemical and structural differences and highlight the potential for each curcuminoid to also exhibit unique pharmacology that is distinct from the others. This, in part, is shown to help explain curcumin's polypharmcology when administered to treat multiple diseases that manifest with pathological features and symptoms, nevertheless, that are quite diverse.

A full review explains how highly hydrophobic and extremely reactive curcuminoid chemistry can still be administered orally; is bioavailable despite conflicting reports that it is not; and delivers efficacious pharmacology systemically as a direct function of the parent curcuminoid molecules and in an additive manner through the accompanying auto-oxidative degradation by-products of the parent curcuminoids.

Keywords

Anti-inflammatory; Curcumin; Polypharmacology; Curcuminoid; Turmeric; Cancer; Alzheimer's disease

Introduction

Curcumin (diferuloylmethane) is a major active constituent of turmeric (Curcuma longa) [1] with an expansive pharmacology including anti-inflammatory [1], anti-carcinogenic [2], wound healing [3] and antibacterial [4] to name just a few features. Its safety is well established by centuries of use in food and traditional medicine [5-7]. Subcellular signalling proteins such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [8], c-Jun N-terminal kinase (JNK) [9], Protein Kinase C (PKC) [10], AKT and mechanistic target of rapamycin (mTOR) signalling [11,12], and mitogen-activated protein kinases (MAPKs) [13] have made a sizeable list of curcumin's pharmacological targets that continues to evolve. Additionally, these targets are central to the pathology of diseases that are prolific in society today such as neurological disease [14,15], autoimmunity [16,17], cardiovascular disease [18,19] and even cancer [20]. This all makes for a rather exciting story for curcumin as a potential medicinal agent.

The very fact that the list of targets and mechanisms of activity by curcumin continues to grow is, itself, demonstrative of our incomplete understanding of the fundamental underlying mechanism by which curcumin pharmacology modulates disease pathology. Studies have shown curcumin to inhibit growth factors and growth factor receptors as well as the downstream signals including PI3K and extracellular-signal activated kinase (Erk); and oncogenes such as c-jun and c-myc [21,22]. The extract is shown to inhibit expression of epidermal growth factor receptor (EGFR) and erythroblastosis oncogene B (ErbB2) [23]; inhibit enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX)[24-27]; facilitate transcription factors such as nuclear factor erythroid 2-related factor (Nrf2) [28] that can contribute to endogenous antioxidant status and protect cells from oxidation; while it inhibits activator protein – 1 (AP-1) and tumor necrosis factor α (TNFα)[29,30]. Curcumin is shown to inhibit cytokines such as interleukins 1, 2, 6 and 8 [25,30-32]. The extract is also shown to suppress Interleukin (IL)-12 in macrophages [33] while promoting the anti-inflammatory IL-10 [34]. How is all this possible and how can this be harnessed and controlled?

Curcumin comprises a subset of active constituents. The three main naturally occurring curcuminoid analogues found within

the curcumin extract are diferuloylmethane (curcumin I), desmethoxycurcumin (curcumin II) and bis-desmethoxycurcumin (curcumin III) [35,36] as seen in Figure 1. They typically exist naturally in proportions that range between 65-80% curcumin I, 10-25% curcumin II and 0.2-3.0% curcumin III [37]. Curcumin delivers a polypharmacology that exhibits a narrower range of activity than the whole herb [38,39]. However, the curcumin extract is certainly not maximally selective as it is still delivering multiple active constituents each potentially exhibiting a polypharmacology of their own.

Figure 1: Comparing curcuminoid structure with steroid hormone homology.
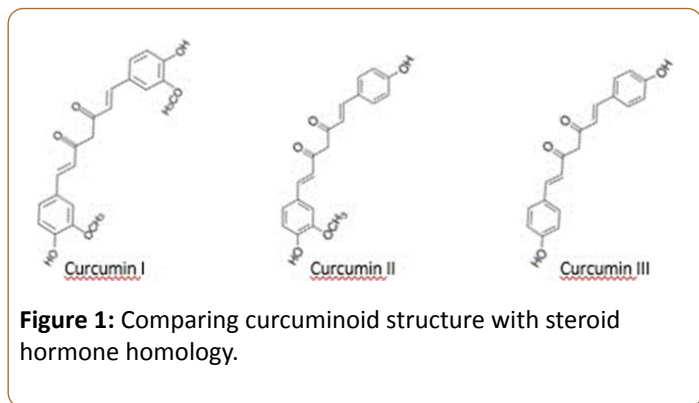
There is yet another component of the pharmacology that may be contributing to curcumin's polypharmacological nature. The sub-constituent curcuminoids readily give rise to auto-oxidative degradation products [40-42], some of which we know to exhibit pharmacological activity that we may have attributed to the curcuminoids in the past. Despite the conflicting findings on these curcuminoid by-products, they may be playing a monumental role in the pharmacology of this remarkable extract; a role that needs to be viewed with a more focussed lens.

Clinical Benefits of Curcumin

Since long ago, oral dosing of curcumin with as little as 20 mg three times daily has been shown to improve acute and chronic hepatitis [43]. Curcumin is a potent cholegogue inducing gall-bladder contraction and bile elimination [44] conducive to bladder stone management. However, the more recent understanding of curcumin's anti-inflammatory pharmacology and what this means in the context of disease management has elevated interest in the extract as a potential treatment for many modern epidemics. Curcumin is also shown clinically to enhance cytotoxicity of various drug-resistant strains of cancer [45].

In clinical trials patients with various cancer-related risks including bladder cancer, cervical cancer, intestinal metaplasia and oral leukoplakia were treated with systematically escalating doses up to 8000 mg daily of curcumin for three months [46]. Results were indicative of a significant anti-cancer effect by the curcumin treatment with relatively little to no toxicity. In murine models curcumin is also shown to ameliorate functional and structural abnormalities associated with cancer drug cisplatin-induced neuropathy [47].

In the treatment of orbital pseudotumors curcumin produces significant positive results. After following these patients for as long as two years at three month intervals, four patients recovered completely among five who stayed in the study to completion. One patient experienced complete regression but with some limited movement as a residual symptom [48]. The treatment of psoriasis by oral curcumin administration is shown to produce an excellent therapeutic outcome in two patients encouraging the need for larger controlled trials [49]. Topical application of curcumin preparation shows curcumin treatment to produce a more profound resolution than calcipotriol or non-treated (control) patients with various degrees of psoriasis [50].

A twenty-four week double blind placebo-controlled study resulted in an inconclusive position on curcumin's effects on Alzheimer's patients [51]. Curcumin use did show signs of β-Amyloid changes in serum indicative of β-Amyloid disaggregation and a tendency towards fewer adverse events for patients using curcumin. However no improvement in cognitive performance in the curcumin group over controls is established. However, since the control group did not shown cognitive decline during the period of the trial, the study design will need to be modified to be able to better evaluate these outcomes; better controls, larger groups and longer trials are expected requirements acknowledged by the authors.

However, researchers have not given up on the extract when it comes to amyloidogenic diseases. *In vivo* murine studies show that curcumin does cross the blood brain barrier [52,53] and binds to amyloid plaques when orally fed or directly injected into the carotid artery [54]. When coupled to the known *in vitro* results associated with Alzheimer's disease biomarkers these findings are suggestive of efficacy against Alzheimer's pathology [55]. Other studies show curcumin improves cognitive function in patients with Alzheimer's disease [53]. More research is required to further define curcumin's clinical efficacy and mechanisms involved in the framework of Alzheimer's pathology.

Curcumin is shown to deliver anti-depressant like activity similar to that of fluoxetine and imipramine [56] and the mechanism might involve increasing brain derived neurotrophic factor (BDNF) [57]. On the other hand curcumin's anti-depressant-like activity maybe a function of inhibitory activity on IL-6 and IL-1 [35,58] since dysregulation of these cytokines and the systemic inflammatory activity that can rise from this may contribute to depression pathology [59,60].

Curcumin is shown to inhibit p300-HAT to improve cardiac hypertrophy and heart failure in animal models [61,62]. Curcumin delivers better results than diciofenac sodium in a recent study of patients with active rheumatoid arthritis comparing these therapies [6,63]. Curcumin appears to correct cystic fibrosis transmembrane conductance (CTFR) defects associated with cystic fibrosis (CF) in murine models [64]. Curcumin administration stimulates muscle regeneration after traumatic injury [65]. Curcumin improves COPD-like airway inflammation [66].

All those in a small group of five ulcerative colitis patients improved using 550 mg curcumin twice daily as treatment for a month followed by a month of three daily 550 mg doses [7].

Curcumin pharmacology looks promising to say the least but these remarkable results are also in conflict with similar studies showing lack of success in clinical and preclinical models with curcumin treatment [67] such as in depression models where curcumin's effects are found to not be significant [68]; where in other independent studies of CTFR (CF) defects curcumin's benefits were not repeatable [69]; and in research using high curcumin doses to treat inflammatory conditions such as rheumatoid arthritis patients experienced improvements as much as but not more than those receiving phenylbutazone [7].

Curcumin pharmacokinetics

Curcumin bioavailability

Despite the abundance of experimental and anecdotal clinical evidence demonstrating the health benefits of orally routed curcumin, limited to no serum curcumin is found in test subjects even at extremely high dosing that exceeds 10,000 mg daily [70,71]. The reasons for the low tissue or serum availability appear to be due to multiple compounding factors including low bioavailability [72] and expeditious metabolic degradation [73] that causes rapid elimination of the curcuminoids [72]. The naturally occurring curcuminoid analogues are highly hydrophobic [74,75], a characteristic thought to play a major role in bioavailability [72]. Overcoming the hydrophobic characteristics of the curcuminoids resolves only one of the challenges, however. There are other curcuminoid issues related to pharmacokinetics that are outstanding and are likely far more central to the understanding and efficacy of curcuminoid pharmacology than the bioavailability limitation.

The low bioavailability of curcumin is assumed due to the lack of serum curcuminoids [70] and the common excessive efflux of some curcumin preparations in fecal matter upon oral administration [76]. In comparison with intraperitoneal administration of pure curcumin extract which excludes the tumerone fraction, 75% of orally administered curcumin extract was excreted in feces with more than 10% found in bile [76] in a mouse model. In human patients, Cheng et al report that even with 8000 mg of oral curcumin administered daily, serum concentrations were found to be 1.77 +/- 1.87 microM [46]. In colorectal patients taking up to 3600 mg of curcumin orally daily neither curcumin nor its metabolites were found at quantifiable levels in plasma, blood and urine [77]. In a human Phase I clinical trial, Sharma et al found curcumin and its metabolites in plasma in the 10 nM range after oral dosing as high as 3600 mg daily [70]. In the treatment of pancreatic cancer using orally administered curcumin plasma curcumin levels are found to range between 22-41 ng/ml [71].

Poor curcumin/curcuminoid bioavailability is thought to be caused by the highly hydrophobic property of the phenolic compounds [75]. Many strategies have been applied to overcome the hydrophobicity of curcuminoids in an attempt to improve bioavailability such as interacting them with beta-casein (micellar casein) to improve solubility in aqueous mediums [78];

encapsulation of curcuminoids in hydrophobically modified starch [79], and phosphatidylcholine interactions with curcuminoids to enhance bioavailability and delivery [80,81]. Administration of complexed curcuminoid-phosphatidylcholine is in fact shown to deliver a higher serum payload of curcumin over curcumin powder alone [82]. However, more detailed studies might be needed to determine if the incremental serum curcuminoids found with this reacted curcuminoid complex is a function of improved solubility and bioavailability. Could the improved survival of serum curcuminoids be a function of recipient-induced alteration in hepatic enzyme activity that may reduce the clearance rate of curcuminoids from blood? In addition, feed type [83], fiber content [84] and many other factors can also play into gastric emptying rate [85] gastrointestinal transition rate and macronutrient digestion and absorption [86]. This all influences drug transition rate and bioavailability as well and are not always fully accounted for in these studies.

The bioavailability limitation of curcumin, however, may be also overstated because studies also show that curcumin can efficiently find its way into serum at concentrations that are rather significant [51]. Thirty-four subjects of a six-month trial using powdered curcumin versus encapsulated curcumin presents a different bioavailability story. This study shows a mean plasma curcumin level of 490 nM amongst both curcumin groups but an interestingly higher (940 nM) level for the curcumin capsule group over the group fed curcumin powder at the daily dose of 1.0 gram daily. A group using 4.0 grams daily was also evaluated but serum curcumin results with this higher dose was not significantly higher.

However, it's interesting to note that while curcumin levels differed, levels of tetrahydrocurcumin, ferulic acid and vanillic acid did not differ between patients using powdered curcumin and those using capsules. The powder form could be performing less effectively due to the need to mix it in aqueous or other solutions that allow the auto-degradation process to start in on curcuminoid degradation long before it even enters the lumen. Interestingly, serum levels of curcumin could only be detected in the presence of glucuronidase inhibitor [51]. Here we have a clear indication that bioavailability of curcumin can be functional and maybe, the serum limitations are more attributable to shortfalls in curcumin formula design and post absorption modification and degradation that play a larger role in serum survival. Figure 2 presents a schematic that highlights multiple sources of curcumin/oid degradation that could affect curcumin "apparent" bioavailability. This degradation starts with the type of curcumin delivery form or formula and carries through to the final reagents and solvents used in analysis.

Curcumin metabolism

It is well understood that metabolic degradation of curcumin is rapid and efficient. In the preliminary study by Baum et al [51] it was determined that serum curcumin could be increased within 1.5 hours of oral administration with food to 250 nM and to 270 nM by four hours with water only. By twenty-four hours post-administration serum curcumin levels fell to 60 nM. No significant differences were found between the groups taking 1.0 gram curcumin daily versus the group taking 4.0 grams daily.

This study proves to be one that highlights the true potential of curcuminoid bioavailability; it can be viable for a properly formulated curcumin treatment. Degradation and metabolic modification, on the other hand, may be the more difficult challenge. In fact, in this same study, at 2.5 hours after oral curcumin administration serum ferulic acid is found to be 110 +/- 20 nM, vanillic acid is 50+/-20 nM, total curcuminoids found to be 1100+/-260 nM, tetrahydro curcumin is found to be 440+/-100 nM, and no vanillin is found.

Enzymatic metabolism of curcuminoids starts in the intestinal lumen and is quickly followed by hepatic enzyme activity [87, 88]. Although it is not clear whether Phase I metabolic enzymes such as the P450 CYPs are directly involved in curcuminoid metabolism, their influence may be indirect as explained further here. Once in the blood, for example, curcuminoid survival is prolonged or protected by serum albumin [89] which likely forms micellar systems with the systemic curcuminoid. Cationic micelles of curcuminoid [90], for instance, which can be achieved with beta casein are not only said to improve bioavailability but also protect the curcuminoids from premature degradation [78]. Binding of curcuminoids *in vitro* to bovine serum albumin (BSA), likely in the protein's hydrophobic pockets, results in a curcumin-BSA complex with improved curcumin stability [91]. In fact, curcumin solubility is increased as much as 10-fold in the presence of BSA [92].

In vivo, curcuminoids are quickly converted to dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. These metabolites are quickly further subjected to glucuronation and sulfation to form curcumin glucuronide, curcumin sulfate, dihdrocurcumin glucuroside, tetrahydrocurcumin glucuronoside, and hexahydrocurcumin glucuronoside [73,87,93,94].

This likely involves Phase II metabolic enzymes - UDP-glucuronosyltransferases (UGT) and Sulfotransferase enzymes (SULT) [95]. However, the literature is not black and white in this context. To throw another curve in the context of metabolic degradation it must be considered that curcumin metabolic degradation and elimination is shown in some studies to play out differently in the human versus rat model.

The human intestinal and hepatic cytosol is more likely to conjugate curcumin and produce the tetrahydrocurcumin metabolite in place of curcumin more abundantly than the rat model does [96]. What this means to total pharmacological potency is unexplored to date but what has been a problem up until now is the direct extrapolation from murine models to human models with lack of scientific support. More work needs to focus on unravelling this mystery.

There is no strong evidence to show that curcumin is subject to metabolism by P450. However, the Phase I P450 and the Phase II enzymes tend to aggregate at the membrane and influence each other. P450 (CYP), for instance, interacts intimately with UDP-glucuronosyltransferases (UGT) responsible for glucuronidation to form heteromers at the plasma membrane [97] that result in their competition for substrates and down- and up-regulation of activity [97]. It is possible that any substance or influence that affects P450 activity, such as

changes in membrane phospholipid constitution, may indirectly influence curcumin's metabolism [98]. Phosphatidylcholine in curcumin complexes that has been shown to improve solubility and bioavailability of curcumin [81] may also affect P450's since membrane phosphatidylcholine is thought to be the anchoring phospholipid for at least some P450 enzymes such as 2B4 [99].

Failure to detect functional levels of curcumin in the plasma after a steady oral loading period or administration by other route may also be attributed to instability and non-enzymatic degradation of the curcuminoids. Various human and rat studies demonstrate a short half-life for the curcuminoids [100,101]. Researches have shown that curcumin is more stable in solutions at pH<7.0 while it tends to be less stable in physiological pH of 7.8 or more [102] characteristic of the distal small intestine.

The curcumin non-enzymatic degradation products frequently reported are ferulic aldehyde, trans-6-(40-hydroxy-30-methoxyphenyl)-2, 4-dioxo-5-hexenal, feruloyl methane, ferulic acid and vanillin [102]. Ferulic acid and vanillin, are considered very small phenolic molecules with molecular weights of 151.15 g/mole [103] and 66.8 g/mole [104] respectively. They are soluble in aqueous solution and far more stable than the curcuminoids, themselves, in the biological medium [105-107].

The status of these non-enzymatic auto-oxidative degradation products is also in question and in conflict in the literature as the ones expected to be the major products in the past, vanillin and ferulic acid [42], are said to more recently be preceded by a bicyclopentadione product or other by-products that may not have yet been precisely identified [102,105,108,109]. Too much conflicting data has been presented in this context and although the multiple view-points are great to see for meta-analysis it must be considered that these conflicting positions on the status of the degradation by-products could also be a function of the variable conditions being used to study the curcuminoids.

Variable pH, temperature, serum protein and other conditions that, if even mildly varied, result in varying the stability, degradation dynamic and by-product yield.

These variables could factor into the equation at multiple levels when it comes to *in vitro* work; but even with *in vivo* work the feed types, curcumin specifications and animal condition all play a changeable role in the outcome.

Analysis of the blood work extracted including reagents used to treat final yields also influence the stability of the retained target curcuminoids; biochemicals we now know to be extremely vulnerable to degradation. All of these factors as shown in Figure 2 contribute to the variable results and inconsistencies we see in the literature. Somewhere in all this conflict, however, treatment with the right curcumin therapy successfully delivers relief to patients of many diseases.

Ultimately, we need to pin down the pharmacokinetics and isolated pharmacology of the curcuminoids and their downstream by-products in order to eliminate inconsistencies and produce a reliable curcumin-treatment.

Curcuminoids or their Degradation Product?

The enzymatic metabolism of curcumin is shown in some studies to reduce curcumin's pharmacological potency significantly [110,111]. However, other studies indicate that at least one of these metabolic by-products could be contributing to curcumin's polypharmacology in tissues [112]. Tetrahydrocurcumin is purported to deliver a significant anti-inflammatory pharmacology [110-113]. In fact, more recent studies are pointing to this reduced derivative of curcumin having antioxidant activity and antihyperlipidemic effects at least as potent as curcumin [114]. Tetrahydrocurcumin is shown in some studies to perform well as an inhibitor of NF-kappa-B and protector of oxidative damage after ischemic episodes [115]. While it is shown to deliver more anti-inflammatory activity than curcumin in a carrageenan-induced murine inflammatory model [116] it performs not nearly as well as curcumin in other studies [117]. Other studies again, show varied activity with curcumin performing better than tetrahydrocurcumin on targets like COX-2 inhibition [118].

Aside from metabolic degradation as a factor altering curcuminoid pharmacology, the curcuminoids can exist as different tautomers - the enol and keto tautomers, [119,120] as shown in Figure 3. The keto form predominates in a solution of pH 3-7 while at a pH above 7.8 the enol form predominates in solution [121]. The enol form (>pH 7.8) serves as an electron donor while the keto form (pH 3-7) serves as a hydrogen atom donor; although both forms can serve as antioxidant. Nevertheless, the environment in which the curcuminoid exists influences its electrochemical properties factoring, yet again, as another source of pharmacological variability.
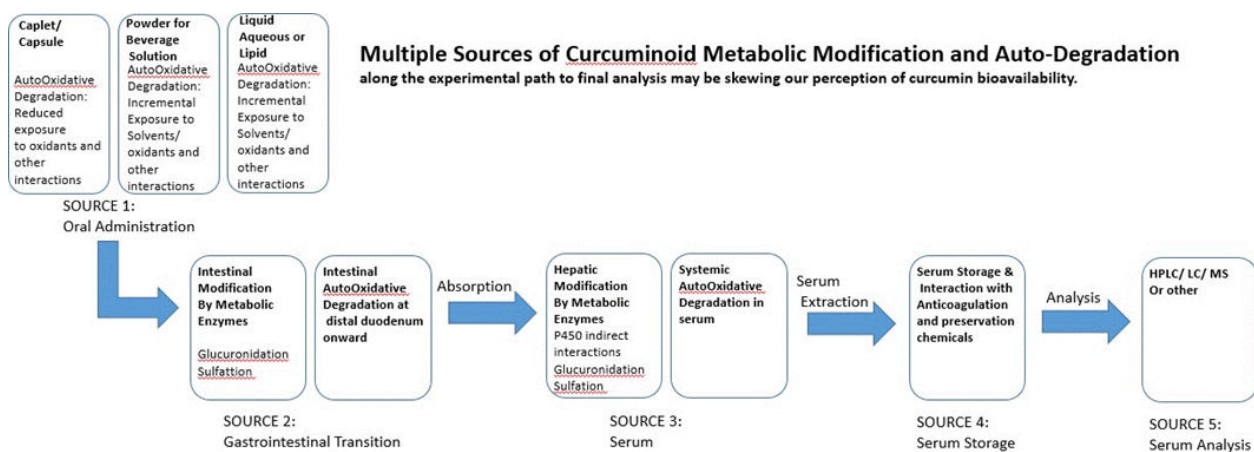

Figure 2: Curcuminoids are inherently vulnerable to degradation by various mechanisms including UV light (photo) degradation exposure [150]; in aqueous solution of higher pH [151], exposure to buffers, assay reagents and HPLC solvents and their distinct pH [152].
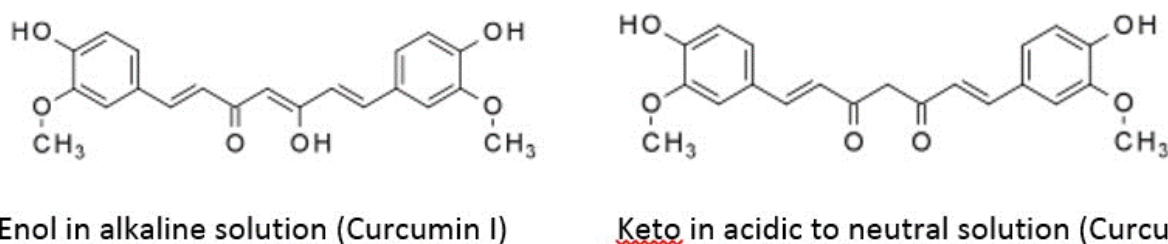

Figure 3: Curcumin can exist in different tautomers - the enol and keto tautomers.

The story with regards to the non-enzymatic auto-degradation products of curcumin is even more colourful and adds even more mystery. Curcuminoids also undergo non-enzymatic auto-oxidative degradation and as we've seen this is more likely to occur at pH>7.0 [102]. It was shown that as much as 90% of curcuminoids are degraded within 30 minutes in a serum-free medium at pH 7 at 37°C [122]. Even in the presence of serum, 50% of curcumin is degraded to its degradation by-products within eight hours [102]. The true nature of this degradation yield is still not conclusively understood.

Research by Martelli et al show that curcumin activates the transient receptor potential cation channel subfamily V member 1 (TRPV1) also known as the vanilliod receptor 1. This receptor is the target of vanillin, a degradation product of curcumin. By this mechanism vanillin and/or curcumin could be inducing symptomatic relief isf Dinitrobenzene sulfonic acid (DNBS) - induced colitis in mice [123]. Multiple studies point to NF-kappa-B inhibition by curcumin and this being the root activity that results in subsequent IL-1, IL-6 and IL-8 inhibition [124-126].

Similarly, vanillin can also inhibit NF-kappa-B and caspase-1 [127]. COX is inhibited by vanillin [127]. In fact, vanillin's effects are COX-2 specific delivering the beneficial pharmacology associated with nonsteroidal anti-inflammatory drugs. Interestingly, curcumin is shown to inhibit COX as well [128,129]. Kim et al also show that vanillin protects rat neurons from oxidative stress [130]. Curcumin does the same by inducing expression of antioxidant defensive genes through Nrf2 activation [28, 131].

Ferulic acid, another curcumin degradation product, displays pharmacological activity similar to curcumin's as well. Studies demonstrate that ferulic acid supplementation can facilitate hypotension through NO-mediated vasodilation [132]; a result also seen with curcumin administration [133]. Ferulic acid is shown to have significant antitumor activity [134] as does curcumin [135]. Ferulic acid is shown to inhibit NF-kappa -B [136]. Curcumin has been shown to destabilize preformed β-amyloid protein including inhibition of soluble oligomer and fibril aggregation to subsequently or also independently reduce associated neurotoxicity by these proteins [54,137-141]. Ferulic acid is shown to have similar activities *in vitro* [130,139,142,143].

Similar pharmacological activities of curcumin and its oxidative degradation products strongly suggest a contribution by curcumin's auto-oxidative degradation products to curcumin pharmacology *in vivo*. This may explain the therapeutic results with curcumin administration despite low bioavailability or more accurately low serum levels of the curcuminoid analogues. The fact that we experience efficacious results with oral curcumin administration with or without the identification of significant serum curcuminoid concentrations supports the notion that vanillin, ferulic acid and/or other degradation products of curcumin may be responsible at least partially for the clinical benefits of curcuminoids.

The variety of experimental models used to investigate curcumin includes *in vitro* and *in vivo* studies using various representations of turmeric and the common extract, curcumin. Curcumin's pleiotropic properties certainly make it a versatile molecule. The question is whether this pleiotropy is a function of one curcuminoid analogue on multiple targets, the naturally inherent three curcuminoid analogues, the degradation products, or all of these factors? A better understanding of the complex nature of this activity can help us decode and identify the active components contributing to the polypharmacology. With this mapping, improved selectivity by curcumin-based drugs can be established and improved indication-specific drug designs with improved reliability and repeatability can be created. As we have it today, too many variables are at play.

Conclusion

One of the challenges faced today with respect to curcumin acceptance in mainstream medicine is its polypharmacology or lack of clear cellular targeting. Drug target selectivity is central to allopathic drug design for reasons that are valid [144,145]. However, an emerging drug paradigm that centers on polypharmacology [145,146] to produce a synergistic therapeutic outcome is gaining some momentum for reasons that may also be valid. In essence, polypharmacology as a treatment model is already established in mainstream allopathic medicine and is in use to treat many complex disorders today including autoimmune disease [147,148] and especially cancers [146,149]. Interestingly, curcumin falls into this class of drug perfectly; however, in order to better understand the entire scope of this polypharmacology by curcumin much more work needs to be done.

It is evident that curcumin extracts are made up of multiple naturally occurring curcuminoid analogues that must be studied in isolation in order for the distinct pharmacological features for each to be better defined. This may help formulators produce condition-specific products using the curcuminoid analogues with greater precision. In addition, it must be made very clear whether we have an influence in the *in vivo* model by the auto-oxidative by- products of curcumin or any of the enzymatic degradation products such as tetrahydrocurcumin. The level of contribution not only as constituents to serum bioactives but more accurately the tissue distribution of these potentially active degradation products must be defined.

Serum curcumin levels appear in the literature to not correlate well with efficacy of curcumin-based treatment protocols. Despite low to no serum curcumin upon oral administration in some studies efficacy against various human diseases from cancer to neurological has been well documented [72]. However, as we've seen some studies show that serum curcumin levels can be increased significantly with properly designed curcumin therapies. In addition, as serum curcumin/oid levels rise, in just hours the curcumin auto-oxidative degradation by-products can accompany the parent molecules in systemic circulation to contribute synergistic and/or additive pharmacology. This cannot be discounted.

Other challenges seem to compound the curcuminoid mystery including the lack of curcumin extract standardization. Curcumin extracts are notoriously comprised of varying proportions of the naturally inherent curcuminoid analogues. This in itself produces another layer of inconsistency when testing one curcumin standard against others. Lastly, the reports of the curcuminoid pharmacokinetics in the literature are conflicting and this is expected to be a function of the varying conditions influencing degradation of the variable curcuminoid proportions in multiple additive ways starting with formulation design and delivery form of the curcumin-therapy. This variability continues based on transition time and oxidative status in the lumen to interactions of different biochemicals used in the analysis of blood work as portrayed in Figure 2. Our very attempts to isolate, extract and assay these compounds produces degradation vulnerability that impairs accurate evaluation of curcumin/oid pharmacokinetics.

Everything from formulation, delivery form, Intestinal transition rate, diet, serum extraction method and serum storage and analysis can play a role in altering perceived bioavailability and serum stability. These represent multiple sources of variance and conflict from researcher to researcher.

In fact, we believe the very *in vivo* pharmacologically active biochemicals have been grossly missed in the past but have not

been considered even in tissue distribution analysis – an endeavor that is so easily measured if one accepted the auto-degradation by-products as a plausible source for, at least, part of the curcumin/oid pharmacology. These by-products are relatively stable in aqueous solution where the parent curcuminoids are not. We believe this to more than just plausible; it is cautiously expected to be highly likely.

The future requires a completely different outlook; first off by accepting polypharmacology or Network Pharmacology as a viable drug model by which the accepted Systems Biology is addressed with a pharmacological model that fits it like a glove. Secondly, the possibility that the degradation by-products are playing a significant role in one way or another in the expansive curcumin polypharmacology should be seriously investigated. The role that tetrahydrocurcumin might be playing must also be considered. Tissue distribution analysis must be employed with this objective in mind; and with clear consideration of the degradation potential inherent in the analytical process, itself. After this dust settles we'll get to a starting line and determine what it is we are really studying and with this curcumin may get the credit it deserves even in mainstream medicine.

Conflict of Interest

One of the authors, Franco Cavaleri, is the owner of a corporation that funds and executes research on nutraceutical pharmacology and experimental medicine and has been involved in the research of curcuminoid pharmacology.

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