The Concept of a Green Drug, Curcumin and It's Derivatives as a Model System

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Abstract: Only 5-15% of the ~25000 existing species of plants have been examined for the presence of biologically active compounds. The ancient medical systems use a much larger palette of herbs for therapy. Systematic drug discovery involving using cues provided from traditional medical systems is bound to produce a new generation of green drugs. Curcumin the primary active ingredient in *Curcuma longa* is used as a model to enunciate the concept of green drug development. Synthetic and formulation based approaches to optimize the bioactivity of curcumin is presented.

Keywords: Green drug, curcumin, traditional medicine, GRAS, renewable resource, derivative.

INTRODUCTION TO "GREEN DRUGS"

A ***green drug*** is one which can be directly used after isolation from a plant / natural source after purification and formulation or one which can be produced with minimum chemical manipulation involving few efficient chemical reactions. The need for "green drugs" is not immediately evident, however if one looks at most pharmaceutical drugs in the light that they are products synthesized from petrochemical building blocks which are derived from non-renewable petroleum and coal/fossil fuel resources the importance for developing "green drugs' in future becomes clear. The fact that the fuel and energy users have been impacted adversely by the "oil crisis" is evident both from refereed publications [1] and from daily newspaper headlines. For United States, Europe, India, China, Pakistan and many other countries which are primarily importers [1] of crude oil and petrochemicals it would be wise to identify, develop and produce drug raw materials and drugs which are based on renewable resources. The immediate large scale switch over from drugs produced via multi-step organic synthesis based on petrochemical building blocks is impractical. However, the dedication of research activities, financial resources and energies towards the discovery, development and production of "green drugs" is vitally important; this proactive approach would ensure that in future if petrochemical building blocks become expensive and scarce due to natural depletion of petrochemical resources or due to unfavorable political relations between fossil fuel producing and importing nations a wholly new generation of drugs based on renewable resources will be available to treat diseases. The scarcity of petrochemical building blocks for the drug industry is not likely to occur in the immediate future; however given the fact that drug development is a long term effort (it takes almost 15 years between identifying a drug candidate and finally marketing it) the systematic development of green drugs should ideally commence immediately.

Plants are natural bioreactors which synthesize pharmacologically active compounds. Natural product based drug development is attractive: 61% of 877 small molecule chemical entities approved as drugs during the period 1981-2000 can be traced to or were inspired by natural products [2]. Many whole herbs and natural products contain combinatorial libraries of bioactive compounds, these have been exploited for over 5000 years in ancient medical systems such as Ayurveda origins ascribed to Charaka, Siddha founded by Agastya and Unani [3-6]. There have been several cases of past successes in the development of plant derived pharmaceutical drug products, it is however estimated that only 5-15% of the ~25000 existing species of higher plants have been systematically mined by western science for the presence of biologically active compounds [6]. The ancient medical systems use a much larger palette of herbs for therapy. The fact that a particular herb has been used by Ayuvedic/Unani/Siddha practitioners for curing a specific disease implies that the herb most probably contains bioactive compounds which cures that particular diseased state.

Systematic "green drug" development based on "cues" and collaborations between the "East and the West" (practitioners of the ancient medical systems and chemist, biologists and doctors) is bound to reap a rich harvest. It should be noted that many drugs produced via Biotechnology: protein drugs, monoclonal antibodies [7] and small molecule which are produced recombinantly [8] could be classified as green drugs, these are not discussed in detail in the current article. The widely prevalent practice in the drug industry is to identify a single molecule drug candidate which is then evaluated in preclinical experiments and in clinical trials. This approach may work in the case of some "green drug" candidates but not all of them because many Ayurvedic/ Siddha formulations use multiple herbs or natural products in various forms such as powder, Lehiam (herbal extracts in clarified butter), organometallic complex forms (Mezukus or Bhasmas), aqueous extracts or as oils for topical application. In many cases the natural products act in a synergistic fashion an example of synergy will be discussed in a later section. Liv 52 ™ is a rare example of an approved multiple herb based drug, it is a hepatoprotective product which is supplied in tablet form, it consists of capers (*Capparis spinosa*), chicory (*Chicorium intybus*), Black Nightshade (*Solanum nigrum*), Arjuna (T*erminalia arjuna*), *Cassia occidentalis* and Yarrow (*Achillea millefolium*). It has been approved by the "Intercantonal Office for the Control of Medicines" (the Swiss equivalent of the FDA); it would not be wrong to say that some form of "Biotechnology" has been around for over 5000 years. In 2006 FDA approved the first single herb derived drug, an extract of green tea.

The opinion that only single molecule entities should be used to treat a particular diseased state is a highly oversimplified reductionist hypothesis: nature provides all the sources of food for human consumption, the vegetables, fruits, whole grain, nuts, pulses, milk and other protein sources are a complete food for maintaining and running the human biochemical organism in excellent condition. Each of these sources such as vegetables for instance consists of a complex mixture of molecules, if we extend the single molecule hypothesis to foods one has to restrict one's consumption to amino acids, monosaccharides, vitamins, minerals and lipids in a tablet form; this idea is obviously absurd. Now given the fact that nature has provided all sources of food (complex arrays of compounds) for the healthy running and maintenance of the human biochemical organism, it is a perfectly reasonable hypothesis that in nature are provided the solutions for fixing the human biochemical organism when its biochemistry is thrown off gear [5]. The fact that a significant fraction of the drugs developed by the pharmaceutical industry so far has come from natural products strongly supports this hy-

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pothesis [9]. The idea of using multiple natural product formulations as foods is accepted without much ado by most of humanity including the scientific community, this is the input that is necessary for the healthy running and maintenance of the "human biochemistry lab". Many Siddha and Ayurvedic medicines are delicately crafted multiple natural product based formulations which have been used in fixing the "human biochemistry lab" when its chemistry is thrown off gear. It is incorrect to assume that all the formulations work, a majority of these formulations have not been tested scientifically in clinical trails and some are available in the United States through the largely unregulated food supplement industry.

A COLLABORATIVE APPROACH TOWARDS GREEN DRUGS

"But there is neither east nor west, Border, nor Breed, nor Birth,

When two strong men stand face to face, tho' they come from the ends of the earth."[10]

These words of Kipling are perfectly crafted for the two components discussed here, eastern medicine and western technology and a harmonious exchange between both partners. Siddha, Ayurvedic and Unani formulations that are employed to treat routine ailments rely on the use of herbs which are cultivated in herbal gardens or as cash crops such as Senna Angustifolia (a laxative). However a significant number of "traditional medicines" which are used to treat serious and rare ailments are based on herbs which are procured from the forests. Deforestation and the unscientific technique of collecting herbs without a systematic program to replant them have endangered many species. Plant biotechnologists can make an invaluable contribution by applying tissue culture and cloning methods to generate seedlings, the systematic farming of these would ensure that these herbs become a renewable resource. Each lead herb saved from extinction by systematic cultivation is potentially a new embryonic drug waiting to be nurtured and developed.

Most herbs used in traditional medical formulations are almost "sure hits" as a source for drug targets. An example is Resperine which was identified in the Indian Snake Root (*Rawolfia sepentina*). The approach of synthesizing massive random combinatorial libraries of compounds with the hope of developing a drug is like a three year old with a metal detector hunting for gold in his back yard. In 1996, Guida estimated that the size of the pool of drug candidates under a molecular weight of 500 Daltons to be 10^{63} [11], a random combinatorial library of 10^7 compounds is tiny compared to the estimated pool of drugs, even with large random combinatorial libraries the likelihood that one is searching in the wrong place is high. This mathematics has been painfully worked out on a multi billion dollar Big Pharma playing field: in the last 25 years only one de novo combinatorial compound has been approved as a drug [12]. In contrast examining Siddha and Auyurvedic formulations for globally marketable drug formulations and single molecule drug targets would be like mining for gold in the Coolgardie mines: over 74% of our plant-derived major medicines were discovered by following "folk lore leads" [6], digitalin from foxgloves (Digitalis purpurea) serves as an example. The following excerpt from an article in the Chemical and Engineering expressed by Dr.Samuel Danishefsky from Columbia University sheds light on this issue: "smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled", he says. "Thus the decision on the part of several pharma companies to get out of natural products business is gross foolishness. There are major teachings in these natural products that we would well consider. They may be reflecting eons of wisdom and refinement. In fact, one of the most promising approaches in diversity chemistry is to produce diversity-chemistry-derived collections that benefit from or partake of the "wisdom of the natural products" [13].

The same protocol and battery of tests that is adopted at the stage at which a drug is in a phase three human clinical trials has to be rigorously applied to promising herbal formulations. Every formulation ratified by this approach is a green drug ready for the global market. If one was to look at the big picture from a commercial viewpoint, all the steps in the conventional drug development approach starting from the *in vitro* assays and *in vivo* studies in animals, except for dose dependant toxicity studies may not be required in the green drug context because one is evaluating a formulation that has been consumed by/used to treat humans over centuries. One can envisage a green revolution in medical science [5]. The time required to ratify and introduce a multiple herb based green drug in the market would be much less than that which is needed to translate a conventional drug from the test tube to the market because many steps involved in the conventional protocol (such as cell cultures based assays etc.) may not be relevant. The Indian government is in the process of establishing a Traditional Knowledge Digital Library, a comprehensive encyclopedia which has 120,000 formulations, 20 million pages of translated information from 100 ancient texts [14]. This will serve as an immense resource for the development of "green drugs." To blindly suppose that all these formulations are nontoxic and effective just because they have been around for hundreds of years would be an absurd assumption, key formulations have to be tested in phase 3 style clinical trials in India / other countries and dose dependant toxicity in animals have to be performed. Many traditional medicine formulations have been patented for example AYUSH-64 - an antimalarial preparation (Indian Patent No. 152863), was patented by the Central Council for Research in Ayurveda and Siddha; these patents maybe licensed.

One of the reasons Big Pharma may not be interested in developing green drugs could be the fact that they cannot possibly patent multiple herb formulations or single molecule entities directly isolated from natural products which have already been used to treat humans for thousands of years, this should not be an overriding factor in not moving forward because there is significant money to be made in green drugs: One can anticipate the same profit margins which the generics markets enjoys, the public in general believes that herbal medicines do not have side effects and this impression would lead to a huge marketing advantage, it is not unreasonable to assume that consumers would prefer a herbal formulation over a standard pharmaceutical drug if both of them prove to be effective in the treatment of a particular medical condition. Multiple herb formulations have been patented by alternative medicine suppliers. Formulation patents can be licensed or jointly filed with "alternative medicine" practitioners or with governmental agencies. I have closely interacted with a Siddha Physician (Dr. Paul Nadar) based in India for over two years [5]. Some of his medicines such as Atakamani are plant extracts in vegetable oils to be consumed orally, most consumers would refuse to drink an oil. Joint development of such formulations in gelatin capsule form is necessary. There is a lot of scope for improvement and innovation in which industrial partners can participate; for instance one of Paul Nadar's constant complaints was that the herbal formulations that were produced by powdering roots using industrial pulverizers never matched up to the quality of his laboriously manually ground formulations. A possible explanation for his observation is that the heat generated by the use of crude industrial pulverizers degraded many of the thermally sensitive bioactive components in the herbs. Cryopulverization is a solution to the problem; in fact cryopulverized herbs will be more effective than manually powdered formulations. Single molecule drugs synthesized by novel chemical modification of natural products can be patented. The countries such as India, China or Pakistan have much to gain from joint ventures with academic researchers in the US and elsewhere in projects funded by

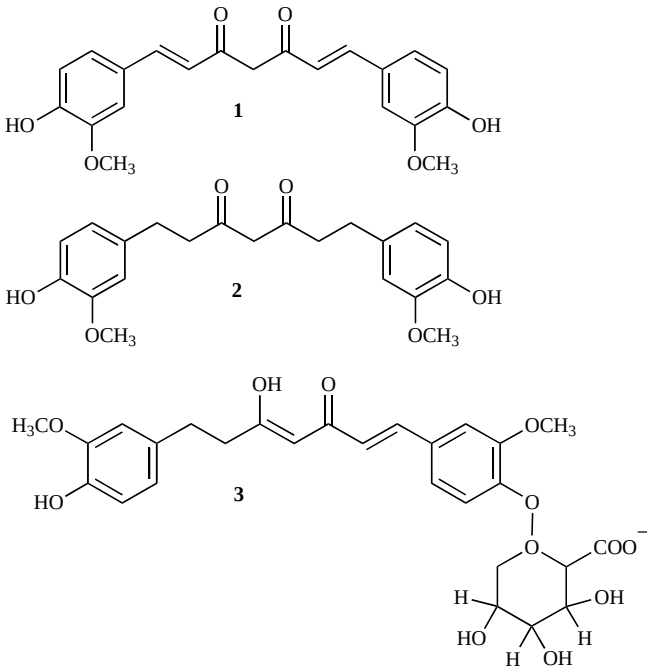
agencies such as the National Institute of Health and with multinational industrial partners. The systematic cultivation of herbs which is an essential part of producing herbal formulations is bound to boost agriculture and create several jobs; collaborative research projects and funding between chemists biologists and herbal medical practitioners is bound to yield a rich reward. Intellectual property development/licensing from government agencies or with individual practitioners in these areas will lead to economic prosperity. Only by being ready to share, jointly develop and expand on this traditional knowledge can countries such as India fully benefit from this tremendous resource. Judicious joint development with academic researchers from other countries such as the US and the pharmaceutical industries can create a 'green drug' industry which can lead to a beneficial economic impact which rivals the currently booming software industry in India. The countries on one hand and the Big Pharma on the other should look beyond narrow nationalistic considerations and myopic short term profits because if this traditional knowledge is wisely exploited and packaged for the global audience; it can fill the pharmaceutical pipelines with a new generation of drugs which are more affordable to patients.

TOWARDS A CURCUMIN BASED GREEN DRUG

Curcuma longa is used as a spice in South Asian cooking, as a cosmetic and in the ancient Ayurvedic system of medicine [15]. Turmeric or Haldi is the dried powdered rhizome derived from the plant. Curcuminoids constitute around 5% of most turmeric preparations and can be readily isolated from the plant [16]. Mahasudarshan is an example of Ayurvedic formulation (from Banyan Botanicals) it contains both Curcuma longa and Black pepper. There has recently been tremendous interest in curcumin, [(1*E*, 6*E*)-1, 7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene 3,5-dione] the primary active ingredient in turmeric, because it has been shown to have antioxidant [16, 17], anticancer [18, 19], anti-inflammatory [20], anti-Alzheimer's disease activity [21] and antibiotic activity [22]. Curcumin works on many biological pathways, it is a potent NF-κβ inhibitor via this key receptor many down stream targets are modulated including gene products involved in blocking apoptosis (Bcl-2, Bcl-xL, XIAP), angiogenesis (VEGF) and metastasis (adhesion molecules) [16, 23]. Curcumin has been shown to reduce pathology in AD mouse models overproducing Aβ [21]. Curcumin appears to have multiple neuroprotective mechanisms including inhibition of inflammation, suppression of Aβ production, reduction of reactive oxygen species by chelating metals, inhibition of stress pathways and induction of heat shock proteins [24]. Curcumin is an excellent candidate for developing a green drug because (a) Turmeric has been used in Ayurvedic formulations for centuries which implies that it is most probably non toxic and is generally regarded as safe by the FDA (b) It can be isolated from Curcuma *longa* in reasonable yields and is inexpensive. (c) It has a relatively simple chemical structure which lends itself to efficient chemical manipulation. For a simple spice which is consumed (~0.5g) on a daily basis by the south east asian population it is quite remarkable that there have been over 2600 peer reviewed articles published in English since 1966, ~19 review articles have been written in the last ten years and curcumin has been or is currently being used in over 17 clinical trials [16]. An ideal "green drug" candidate should lend itself to direct isolation and usage (from a natural source) with either no chemical manipulation or with minimum chemical manipulation to optimize pharmacokinetics and therapeutic efficacy. The fact that a particular "green drug source" such as turmeric has and is being consumed in significant quantities by a large human population for over 5000 years without any obvious side effects implies that the equivalent of "unofficial" phase three clinical trial and beyond has occurred for turmeric many centuries ago. Over 5000 years of consumption of turmeric in humans with no obvious side effects implies that all those cycles in which society declares drugs such as Vioxx (non steroidal anti-inflammatory drug manufactured Merck) as a wonder drug and later as poison (Vioxx was voluntarily withdrawn by Merck after it was found that it increases the risk of cardiovascular events including heart attack and stroke) have been successfully passed by curcumin a long time ago. It would be wise to introduce minimum or zero chemical alterations to a molecule such as curcumin in developing it as a single molecule drug candidate because the safety of the parent compound (GRAS) has already been established. Thus in the case of a green drug, the synthesis of a smart library of derivatives (ideally with other GRAS molecules) and not analogs (molecules having the same shape but those which are very different structurally) would be the way to proceed. In fact in the case of green drugs even if an analog (which is chemically very different) has slightly improved therapeutic potential compared to a simple derivative, it may be a wise choice to employ the derivative in clinical trails because the safety of the main pharmacophore has already been irrefutably established (e.g. curcumin). In the long term this conservative approach may pay off because unforeseen problems such as the Vioxx recall maybe less likely to occur. The above strategy is a broad guideline. The safety of curcumin has been established in recent clinical trials, in a trial conducted in Taiwan volunteers were fed 8 g of curcumin orally with no toxic side effects, only 1.77 μM concentration of curcumin was detected in the plasma; this is most probably because of the fact that curcumin is relatively hydrophobic with poor water solubility [25, 26]. In most culinary recipes turmeric is lightly heated in vegetable oils and then added to foods, this ensures that the curcuminoids which are lipid soluble dissolve in oil potentially increasing the bioavailability. It is not surprising that oral dosage of 8 g of practically water insoluble curcumin tablets in the clinical trial described above resulted in a very low plasma concentration of curcumin. It is possible that if scientists conducting the clinical trials had taken cues from either Ayurvedic formulations or from culinary traditions of the East by solubilizing turmeric (in their case curcumin) in a lipophilic environment before administering it to patients, the measured plasma concentrations may have been much higher; the general message is that one can potentially save considerable time, energy and money if one takes early cues from ancient medical systems or in this case culinary customs before embarking on experiments involving 'green drugs' which have previously been investigated and used by other cultures for centuries: there is no point in reinventing the wheel. It should be noted that recently this problem has been addressed by producing solid lipid nanoparticle, liposomal and other nanoparticulate formulations of curcumin, these will be discussed later.

The glucuronidation of curcumin *in vivo* is another possible reason for the observation of very low plasma levels of the compound (Scheme **1**) [27].

Commercial formulations such as Supercurcumin with Bioperine ® are a combination of curcumin and piperine from black pepper. It has been shown that the glucuridination of curcumin is suppressed by piperine: in a study it was shown that in humans a dose of 2 g curcumin alone resulted in serum levels of curcumin which were undetectable, concomitant administration of piperine 20 mg increased the bioavailability of curcumin by 2000% [28]. It should be noted that this synergy between black pepper and turmeric has been exploited in Ayurvedic formulations and in Indian cooking for centuries for example Mahasudarshan is an example of an Ayurvedic formulation which contains both turmeric and black pepper, Pav Bhaji Masala (a spice mix) manufactured by Everest Inc contains both turmeric and black pepper. The traditional medicine based approach is based on the hypothesis/foundation that in a formulation each natural product component has its role to play; in a poem, a piece of architecture or a painting each word, brick or brush stroke has its role in creating the whole, in an analogous fashion each herb in a herbal formulation has its role (many times synergistic) to play in the final product. There are thousands of such formulations each one crafted to address specific diseased states. Tur-



Scheme 1. Chemical structures of curcumin (**1**), tetrahydrocurcumin (**2**) and curcumin glucoronide (**3**).

meric and Curcumin is only the tip of the iceberg, western science has hardly begun to scratch the surface of traditional medicine.

SYNTHESIS OF WATER SOLUBLE CURCUMIN FORMULATIONS, ORGANOMETALLIC COMPLEXES AND CURCUMIN DERIVATIVES

Formulations

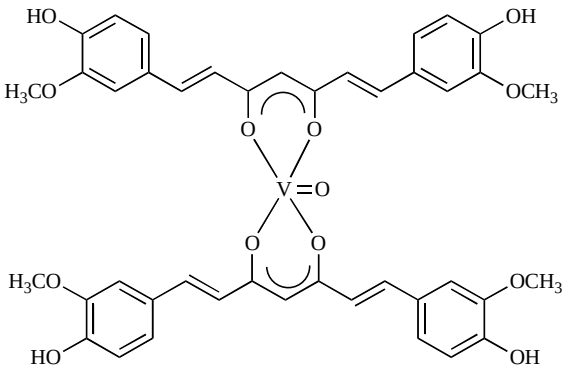
Nanoparticles formed by random copolymers of N-vinyl-2-pyrrolidone-N-isopropyl acryl amide poly(ethylene glycol) monoacrylate have been loaded with curcumin to produce a water soluble formulation " Nanocurcumin"[29]. Nanocurcumin particles were ~50 nm in size, bioefficacy of this construct was comparable to curcumin in *in vitro* assays using pancreatic cancer cell lines (NF-κβ inhibition, induction of apoptosis and down regulation of pro inflammatory cytokines); *in vivo* studies have not been reported by the authors yet. Solid lipid nanoparticles ~450 nm size incorporating up to 70% w/w curcumin have been prepared using a microemulsion technique [30]. Lyophilized solid lipid nanoparticles were stable over six months, they were employed in a topical cosmetic formulation which significantly reduced skin wrinkles, improved skin moisture and the firmness, elasticity, and viscoelasticity of the skin of the volunteers. It must be noted that turmeric is a widely used cosmetic, for example Vicco ®. A colorless hydrogenated derivative of curcumin, tetrahydrocurcumin (**2**) (Scheme **1**) is also used as a cosmeceutical for example Anew® manufactured by Avon.

Liposomal formulations of curcumin have been developed. DMPC (1,2-Dimyristoyl-sn-glycero-3-phosphocholine) and DMPG (1,2-dimyristoyl-sn-glycero-3-phospho-rac-1-glycerol) loaded curcumin liposomes have been evaluated both *in vitro* and *in vivo* in the mouse model [31]. The activity of liposomal curcumin was comparable to or better than that of free curcumin at equimolar concentrations, it down-regulated NF-κβ, suppressed cell proliferation, and induced apoptosis of human pancreatic cells in vitro. In vivo liposomal curcumin suppressed pancreatic carcinoma growth in murin xenograft models and inhibited tumor angiogenesis. There are other reports of liposomal curcumin formulations [32]. A curcumin-phospholipid complex has recently been reported, the complex has better hepatoprotective activity compared to free curcumin [33]. Bovine serum albumen and Chitosan have been employed to encapsulate curcumin to produce biodegradable microspheres [34]. Curcumin has been solubilized using polymeric micelles, the formulation has been evaluated in the mouse model: it was shown via an HPLC assay that the micellar formulation increased the half-life of curcumin 162-fold compared to unformulated curcumin and that it increased the volume of distribution by 70-fold [35].

Curcumin Derivatives

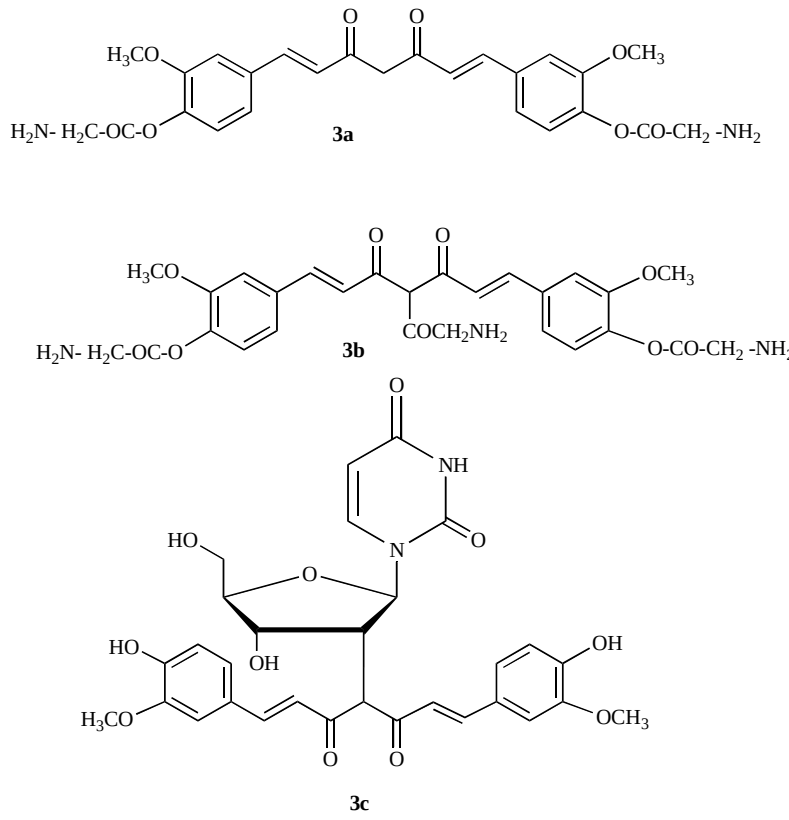
The chemical modification of 'green drug candidates' using few efficient reactions to produce derivatives with optimized bioefficacy and pharmacokinetics is another route to green drugs. Curcumin is an excellent model system to explore this concept because of its simple structure, therapeutic promise and ready availability from commercially grown Curcumin *longa*. It should be noted that representative examples from literature which describes the efficient synthesis of curcumin derivatives is discussed here, curcumin analogs [36] are not covered in this article.

Curcuminoids (1,7-diaryl-1,6-heptadiene-3,5-diones) bind several metal ions, through keto-enol tautomerization of the β-diketonate moiety to form metallocomplexes. Vanadyl curcumin (Scheme **2**.) was recently reported, it was several-fold more potent than curcumin as an inhibitor of synoviocyte proliferation which is a measure of anti-arthritic potential [37]. The Vanadyl complex was also more effective than curcumin in inhibiting mouse lymphoma cell growth. A five-coordinate curcumin–gold complex, $Au(cur)_2Cl$ has been synthesized [38]. The curcumin gold complex was shown to be more effective than curcumin in reducing "paw swelling" using a rat model for arthritis. Curcumin-copper complexes have also been prepared, $Cu(curcumin)_2$ complexes were more cytotoxic in cultured L929 cells than uncomplexed curcumin, a significant reduction in solid tumor volume was observed in tumor-bearing mice treated with this complex [39]. Curcumin copper complexes also serve as excellent superoxide dismutase mimics and are potent free radical scavengers [40]. It has been shown that the curcumin-manganese complex Mn(cur)(OAc) has protective effects in a transient ischemia mouse model of neuronal damage [41].

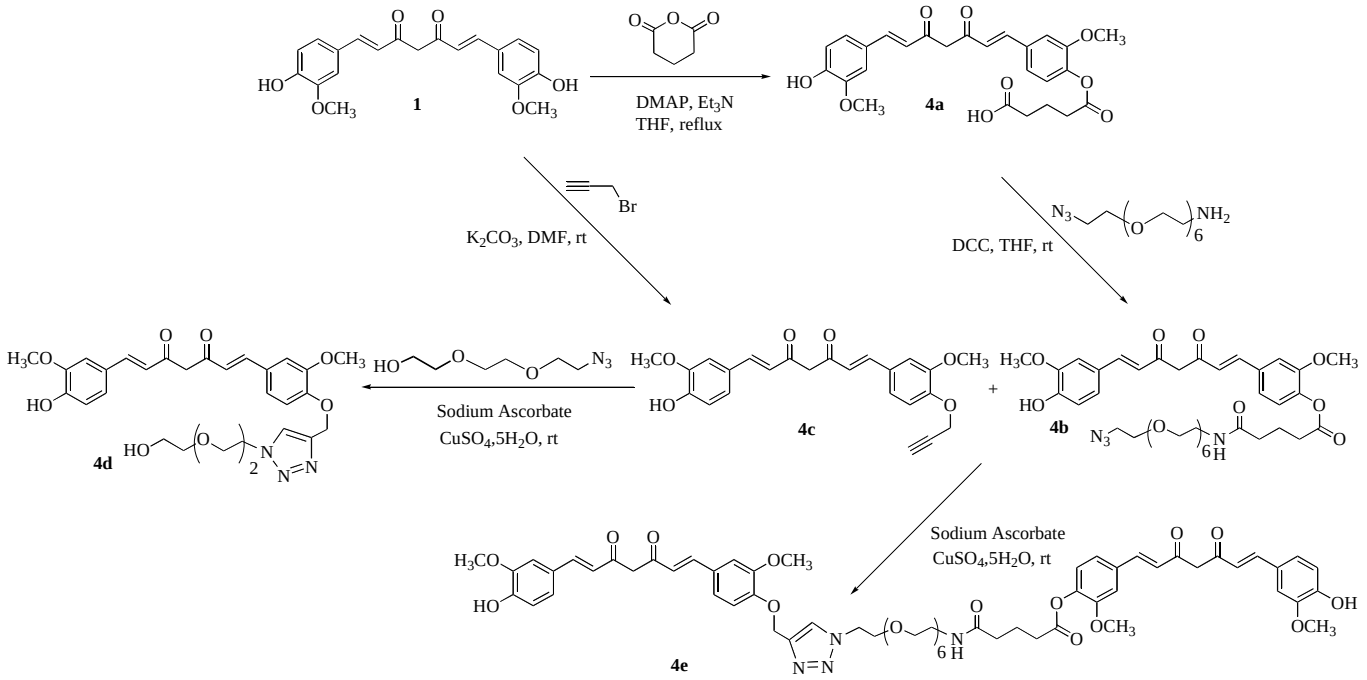


Scheme 2. Vanadyl Curcumin.

Curcumin derivatives with glycine and uridine have been synthesized (Scheme **3**) [22]. Uridine is part of the bacterial genome and glycine is part of bacterial cell walls, these derivatives were shown to be more effective than curcumin against several multi-resistant Gram positive and Gram negative bacteria. The minimum inhibitory concentration (MIC) of **3a** against *Streptococcus pyogenes* was impressive 1.88 μmol/mL, MIC of the commercial antibiotic Amoxyclav against this strain was 7 μmol/mL. These derivatives were effective against β-Lactamase producing microorganisms, they are promising drug candidates to combat the problem of antibiotic resistance.

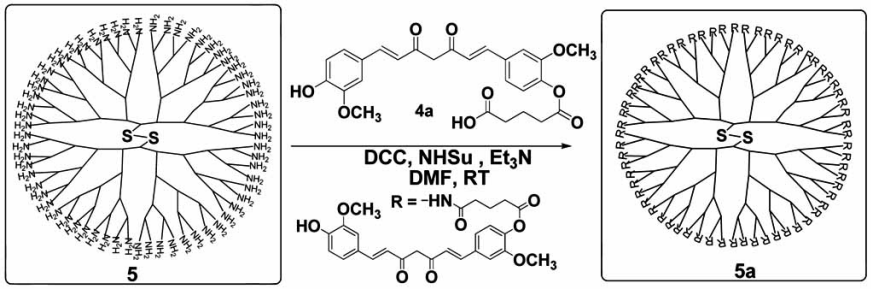


Scheme 3. Glycine and uridine derivatives of curcumin.



Scheme 4. Synthesis of mono-functional curcumin derivatives.

The development of a synthetic methodology to produce curcumin derivatives with water solublizing groups including synthetic polymers and targeting proteins can potentially enhance the therapeutic efficacy of curcumin. A general synthetic technology to produce monofunctional curcumin derivatives in which one of the phenolic groups of curcumin was chemically modified with reactive groups was recently developed (Scheme **4**) [19]. The approach involved direct one/two step covalent modification of curcumin to produce the mono-functional derivatives (with, azide, alkyne, carboxylic acid and PEG groups) in good yields. The synthesis of small molecule mono-functional curcumin derivatives afforded two advantages: (a) The presence of at least one free phenolic group is necessary for the biological activity of many antioxidants like curcumin. It must be noted that monofunctional derivatives of curcu-



Scheme 5. Synthesis of Dendrimer-Curcumin Conjugate.

min retain their ability to bind and dissociate amyloid fibrils *in vitro* [19, 42] (b) Conjugates produced by using monofunctional derivatives produce soluble products in high yields whereas bifunctional derivatives would result in insoluble cross-linked products. A curcumin dimer in which two curcumins were connected *via* a PEG spacer was synthesized by condensing curcumin azide and curcumin alkyne using the copper catalyzed azide-alkyne "click" reaction [43]. The curcumin dimer selectively destroyed human neurotumor cells *in vitro* [19].

Another route to curcumin-PEG derivatives has been reported recently in which the phenolic groups of curcumin is covalently modified with activated Polyethylene glycol [44]. A Generation 4 cystamine core poly(amidoamine) dendrimer, with amine surface groups was coupled to curcumin mono-carboxylic acid **4a** to produce a water soluble polyvalent biomimetic polyphenol (Scheme **5**). The synthetic methodology developed affords a general strategy for attaching curcumin to various macromolecular scaffolds. Curcumin mono-carboxylic acid, Curcumin mono-alkyne and Curcumin azide are currently being attached to amine/azide/alkyne derivatives of carbohydrates to screen a range of carbohydrate derivatives of curcumin to optimize brain uptake of the carbohydrate conjugates via the glucose transport mechanism [19, 45].

CONCLUSIONS AND FUTURE DIRECTIONS

Many whole herbs and natural products contain combinatorial libraries of bioactive compounds; these have been exploited for over 5000 years in ancient medical systems. Only 5-15% of the ~25000 existing species of plants have been systematically mined by western science for the presence of biologically active compounds. The ancient /traditional medical systems use a much larger palette of herbs for therapy. The systematic collaborative approach of interacting with traditional medical practitioners and using cues from traditional medical formulations to generate green drugs from renewable resources presented here is bound to reap a rich harvest. The research efforts to develop curcumin a model green drug via a formulation approach (nanoparticle, lipsomal and micellar) and efficient covalent derivatization strategies presented here is only the proverbial "tip of the iceberg" of a vast exciting, unexplored pharmaceutical gold mine.

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