

# Research and future trends in the pharmaceutical development of medicinal herbs from Chinese medicine

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## Abstract

Issues concerning the past and future development of medicinal herbs from Chinese medicine (CM) are addressed in this paper. In the Western world, medicinal herbs are becoming increasingly popular and important in the public and scientific communities. In contrast to their regulated status in China and other countries, herbal medicines are regarded as dietary supplements in the US. Accordingly, research must continue worldwide to identify and improve the efficacy of the active principals of herbs both singly and in combination – from active ingredients, active fractions, and active herbal formulations. While Western medicine currently employs pure, single compounds, either natural or synthetic, CM has long used multiple combinations of compounds in the form of processed natural products, primarily medicinal herbs, to treat and relieve the symptoms of many different human diseases. CM may have fewer and less severe side effects than single pure drugs, making CM especially attractive to the consumer. In effect, CM's focus on combination therapy does serve both ancient and modern theories. However, research using modern analytical and chemical techniques is needed to ensure efficacy and safety, to provide qualitative and quantitative analyses for dietary supplements, and to develop new, effective and safe world-class drugs. Drug design is an iterative process. Bioactivity-directed fractionation and isolation identify active natural compounds from single herbs or formulations. These lead structures can be chemically modified and improved through knowledge of structure–activity relationship, mechanism of action, drug metabolism, molecular modelling and combinatorial chemistry studies. Finally, efficacy and toxicity determination as well as clinical trials can contribute to the generation of new drugs from CM. To continue the legacy of CM, as well as the worldwide uses of other medicinal herbs, continued investigation of active formulations, bioactive fractions, and isolated compounds is critical to drug development in the 21st century.

**Keywords**  
Medicinal herbs  
Chinese medicine  
Drug discovery  
Drug development

Medicinal herbs, including those used in Chinese Medicine (CM), are being accepted and used increasingly by the general population, studied rigorously by scientists in academia and industry, and manufactured internationally. The focus of herbal medicine on the patient rather than the disease is appealing to consumers. Chronic and age-related diseases (including antioxidant and anti-aging, blood pressure-lowering, hypolipidemic, blood sugar-lowering, anti-allergic, and anti-arthritis effects), disease prevention and health maintenance are particularly attractive targets. Examples of some of the medicinal herbs used widely in the US and Europe include comfrey (*Symphytum officinale*), echinacea (*Echinacea purpurea*), feverfew (*Tanacetum parthenium*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginseng (*Panax*

*ginseng*), saw palmetto (*Serena repens*) and St. John's wort (*Hypericum perforatum*)<sup>1</sup>.

With this increasing popularity also comes the need for competent monitoring and scientific research to maintain quality assurance (QA) or control (QC) of botanical, chemical, manufacturing, biological, and clinical aspects in order to guarantee value, safety, and efficacy of herbal products. In the US, herbal medicines are dietary supplements. Thus, to address the growing need for consumer information and protection and to promote good manufacturing practices (GMP) standards, independent testing programmes, such as the Natural Nutrition & Foods Association (NNFA) and the online (Consumer-Lab.com), have been established recently. Both programmes have registration or approval standards and use

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physical and analytical testing technologies to monitor herbal products<sup>†</sup>. In their independent tests, these organizations have found many marketed manufactured herbals, such as ginkgo and saw palmetto, to be insufficient in selected marker compounds. Clearly, QA/QC and monitoring must be improved diligently to promote the safe use of herbal products.

Herbs have been used as folk medicines from mankind's beginnings and also have been the source of many 'modern' single drugs. In the current practice of drug discovery, a herb or herbal prescription is targeted from folk or clinical experiences. Extraction of the target herbal medicine results in the most promising new active natural products or their synthetic analogues through verified pharmacological testing and bioactivity-directed fractionation and isolation (BDFI) of active portions. The ultimate drug candidates enter the next stage of drug design, which is drug development. At this step, efficacy and toxicity are determined and production, formulation, and toxicological studies are performed. Clinical trials are the ultimate logical goal of these preclinical steps.

However, the multi-component and synergistic nature of CM should not be ignored. In future drug discovery and development, research must continue worldwide to identify and improve the efficacy of herbal active principals both singly and in combination from active ingredients, active fractions, and active prescriptions of herbal formulations.

### Overview of Chinese medicine

Several reviews of Chinese medicinal plant-derived chemotherapeutic agents have been published<sup>2-8</sup>. CM is based on a long tradition of herbal medicine. Both single herbs, such as ginseng, ginkgo (Ying-Shin), ephedra (Ma-Huang), apricot seed (Xin-Jen), and licorice (Gan-Tsao), and more often, multi-component herbal formulations, such as Ma Xin Shi Gan Tang (Ma-Huang & Xin-Jen Combination) have been used medicinally since antiquity. All Chinese medicinals are derived from natural products, with more than 80% from plants. Folk drugs (Min Chien Yao) and about 500 commonly prescribed Chinese traditional drugs (Chung Yao)<sup>9</sup>, derived from about 5000 plant species with identified therapeutic value, are used according to a series of systemic and self-contained theories in order to relieve and cure many different human diseases and health conditions. CM has undergone thousands of years of accumulated human trials and remains today a unique, fundamental foundation for modern drug discovery and development.

Chinese and Western medicines have both contributed greatly to health and disease treatment, but each has formed its own fundamental rules. These rules make the

<sup>†</sup>This information is presented to indicate the need for standardization and QC of herbal products. These agencies have developed their own methodologies, which does not negate the need for further validation and research efforts.

two quite different, in practice and in theory, especially in the drugs they design and use. Western medicine uses pure natural or synthetic compounds aimed at a single target, while CM uses processed crude multi-component natural products – in various combinations and formulations aimed at multiple targets – to treat a totality of different symptoms. Specific CM treatments are chosen based on careful diagnostic observations and systematic principles. The three most common treatment principles are mobilization of blood circulation and treatment of stasis, promotion of vigour and stabilization of vitality, and treatment of fever and inflammation along with detoxification<sup>9</sup>. Terminologies such as bodily energy or qi, yin/yang, and coolness/heat are central to CM and establishing an optimum balance of such forces is considered important to promote health<sup>10</sup>.

Thousands of herbal formulations (consisting of four to 12 individual herbs, in general) have been recorded in Chinese medical literature from the earliest known 'Shen Nung Ben Tsao Jing' to the more contemporary Chinese *Materia Medica*<sup>9,10</sup>. Chinese herbal pharmacology studies the composition, actions, indications, dosages, and clinical uses of herbal formulations. The herbal components can be ranked into four types<sup>10</sup>. The effectiveness of the principal herb is aided by the supporting herbs:

- imperial herb – the chief herb (main ingredient) of a formula
- ministerial herb – ancillary to the imperial herb, it augments and promotes the action of the former
- assistant herb – reduces the side effects of the chief herb
- servant herb – harmonizes or coordinates the actions of the other herbs

In the four-herb combinations shown in Table 1, the change in composition (one different and three identical ingredients, different proportions and different imperial/ministerial herbs) induces different pharmacological actions<sup>11</sup>.

### Modernization of CM

Modern technologies being used or under development for the QC of CM include: microscopic analyses (morphological investigation and powder methods), chromatographic methods for fingerprint profiling [thin-layer chromatography, high-performance liquid chromatography, liquid chromatography and gas chromatography (TLC, HPLC, LC, GC), GC- and LC-mass spectrometry (GC-MS and LC-MS), LC/MS/MS and capillary electrophoresis (CE)], DNA polymorphism methods to analyse DNA sequences and establish relationships between genomic DNA fragment patterns and ratios of active components, and biological methods or bioassays. Modern instrumental quantification, identification, and comparison have been documented increasingly, for example, for licorice (by HPLC<sup>12</sup>), ginseng

**Table 1** Herbal formulations: comparison of composition and action

Herbal formula	Single herb (ratio)					Action
	Ma-Huang	Licorice	Apricot seed	Cinnamon	Gypsum	
Ma-Huang Combination	5	1.5	5	4	–	Induces sweating and suppresses coughing
Herb ranking	I	S	A	M		
Ma-Huang & Apricot Seed Combination	4	2	4	–	10	Suppresses sweating and coughing
Herb ranking	M	S	A		I	

I, imperial herb; M, ministerial herb; S, servant herb; A, assistant herb.

(by positive ion MS<sup>13</sup>) and Uncariae powder (Gou-Teng-San) (by 3D-HPLC<sup>14,15</sup>). The latter prescription is used in exceptionally nervous patients, who exhibit, among various symptoms, insomnia (Shu-Wei Hsu's 'Pen Shih Fang', Sung Dynasty) and vascular dementia<sup>14</sup>.

Such technical modernization of CM is crucial to promote standardization and establish QC through qualitative and quantitative analysis of active constituents and bioactivity. In addition, efforts should be made to guarantee safety by evaluation of toxicity and side effects and to ensure efficacy based on clinical scientific observation, including double-blind clinical trials, rather than anecdotal evidence only. Similarly, dietary supplements must meet all high quality assurance standards.

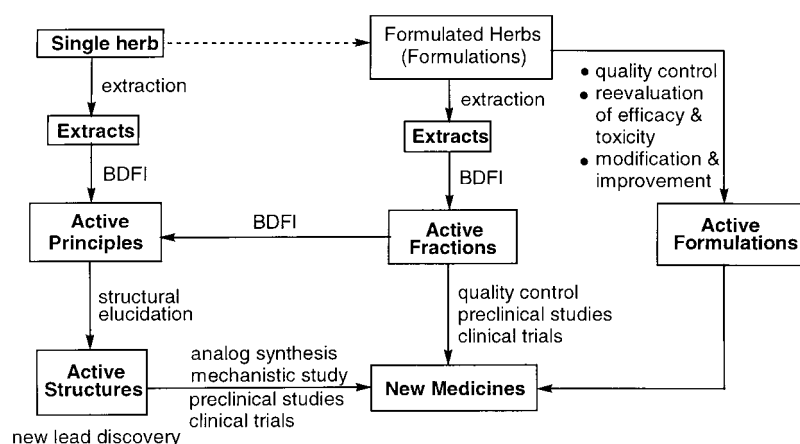
Modern analytical and pharmacological methods are being used to research and document the properties (not only the quantitative composition, but also the pharmacological action) of herbal formulations in comparison with their individual components. For example, over a 3-hour time course, the anti-tussive activity of the original four-component prescription of Ma-Huang & Xin-Jen Combination was reported to be greater than that of either Ma-Huang alone or of any two of the remaining ingredients<sup>9</sup>. The following three approaches for the development of new, effective and safe world-class drugs can be envisioned.

- Active principals (bioactive compounds) approach
- Active fractions approach
- Active formulations approach

Figure 1 illustrates graphically that, now and in the future, not only bioactive principals (lead compounds or leads), but also active fractions and active formulations, must be investigated to continue the legacy of CM, as well as the uses of other medicinal herbs, for drug development in the 21st century.

### Current drug development process based on CM research

Prior to clinical trials, the two main preclinical stages of drug design are drug discovery and drug development. The first stage is an iterative process of (1) lead discovery through bioactivity-directed fractionation and isolation (BDFI) of natural bioactive lead compounds from single herbs, extract fractions, or herbal prescriptions and (2) lead improvement through chemical modification and synthesis of improved analogues. The rational design of synthetic analogues uses (a) structure–activity relationship (SAR) studies to evaluate qualitative and quantitative SAR, (b) mechanism of action studies to study drug–receptor interactions and specific enzyme inhibition, (c) drug

**Fig. 1** Principal concepts of research on new medicinals

**Table 2** Chemotherapeutic agents from Chinese medicine

Disease/drug	Chinese formulation; natural source	Comments	Reference
<i>Chronic myelocytic leukemia</i> Indirubin and its methylated analogues	'Dang Gui Lu Hui'; <i>Indigo naturalis</i>		16,17
<i>Malaria</i> Artemisinin and its synthetic derivatives including artemether	'Qing Hao'; <i>Artemisia annua</i>	Latter compound is in clinical use in China and in Phase II clinical trials in the US	18–20
<i>Various cancers</i> Camptothecin	<i>Camptotheca acuminata</i> (Han Lien)	Natural alkaloid is a potent DNA topoisomerase I (topo I) inhibitor. Used to treat gastric, rectal, colon, and bladder cancers	21
9-Amino and 10-hydroxy camptothecin, topotecan, and irinotecan		Natural and synthetic derivatives of camptothecin	22–26
7-(Acylhydrozono)-formyl camptothecins		Water-soluble compounds synthesized to combat poor water solubility of camptothecin. Compound with a 7-(L-tyrosylhydrazono) group was more potent than camptothecin in causing protein-linked DNA breaks and in inhibiting DNA topo I; however, it was less toxic in several cancer cell lines	27
<i>Hepatitis</i> DDB, synthetic analogue of natural schizandrin C	<i>Schizandra</i> species	Used in China to treat a chronic and persistent form of hepatitis	28
<i>Nervous system disorders</i> Huperzine A	<i>Huperzia serrata</i>	Used in CM to treat mental disorders. Potent reversible cholinesterase inhibitor. Improves learning, facilitates memory retrieval. 99% effectiveness rate in treating 128 patients with myasthenia gravis	29
<i>Encephalomyelitis, toxic dysentery, and Meniere's disease</i> Anisodamine	<i>Anisodus tanguticus</i>	Used in China to treat pain and functions as a cholinergic blocking agent with low toxicity	30,31
<i>Glaucoma</i> Baogongteng A	'Ding Gong Teng'; <i>Erycibe obtusifolia</i>	Tropane alkaloid; strong myotic agent	32,33
<i>Fertility regulation</i> Yuanhuacin	'Yuan Hua'; <i>Daphne genkwa</i>	Augments uterine contractions. Used clinically with few side effects to induce abortion. Also has antileukemic properties	34–36
<i>Heart disease</i> Tanshinone IIA	<i>Salvia miltiorrhiza</i>		37

metabolism studies to determine bioactive metabolites or block metabolic deactivation, (d) molecular modelling studies to determine 3D pharmacophores, and (e) combinatorial chemistry studies to generate leads by the creation of chemical libraries. The goals are to improve pharmacological profiles by increasing activity, decreasing toxicity, or circumventing metabolic, pharmacokinetic, solubility, or drug-resistance problems. The examples in the next section illustrate the diversity, rationale, and power of these processes.

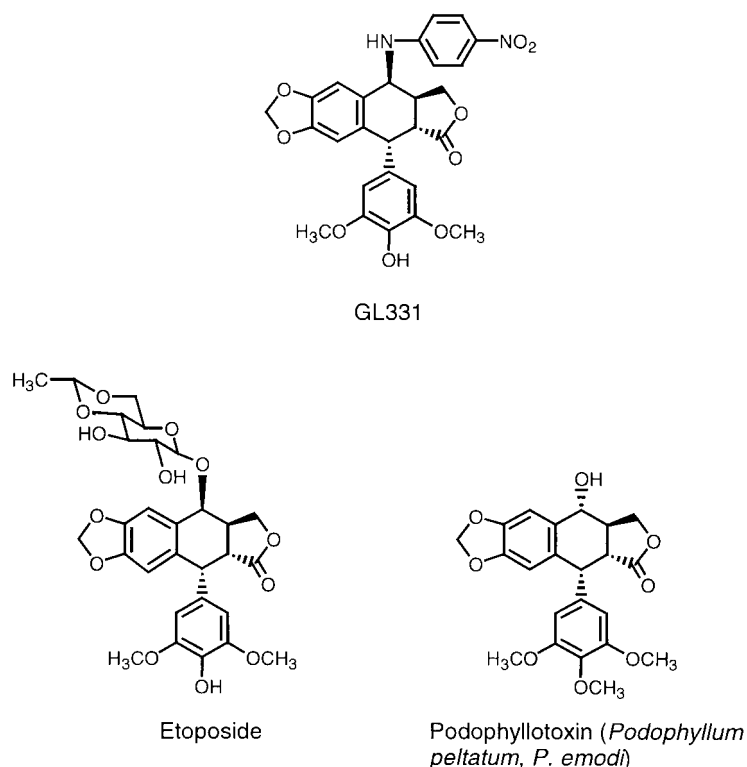
### Examples of known and developing drug agents from CM: including from the author's Natural Products Laboratory (NPL)

As early as 1882, investigation of CM led to the discovery of

ephedrine from *Ephedra sinica* (Ma-Huang). This compound and its numerous synthetic analogues are used today as effective anti-asthma agents. Table 2 shows other drugs generated by research on CM for other diseases and disorders<sup>16–37</sup>.

The preclinical development of bioactive natural products and their analogues as chemotherapeutic agents is a major objective of the NPL. Current research programmes at the NPL include the following.

1. Plant anti-tumour agents – novel plant-derived cytotoxic anti-tumour principals and analogues.
2. Novel anti-tumour etoposide analogues – design and synthesis of novel analogues related to the anti-cancer drug etoposide with better pharmacological profiles as described below for GL331 (Fig. 2).
3. Development of anti-AIDS agents – plant-derived anti-



**Fig. 2** GL33, an anti-cancer lead compound in development at the NPL, and its synthetic and natural lead compounds

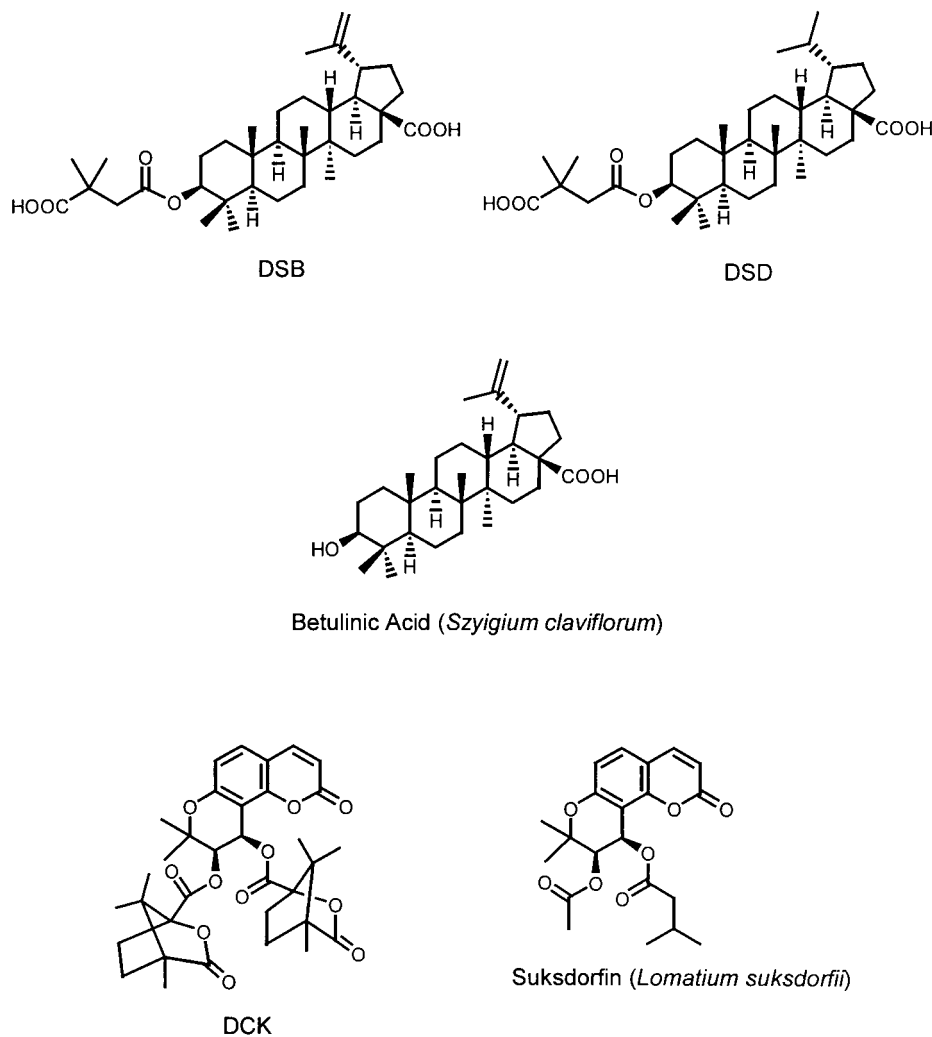
- HIV compounds. Two classes of modified natural products [triterpene derivatives DSB and DSD, developed from betulinic acid (*Szygium claviflorum*) and the coumarin derivative DCK, developed from suksdorfins [*Lomatium suksdorfii* or *Angelica morii* (Shan Du Huo)] are under development as clinical trials candidates (Fig. 3)<sup>38</sup>.
- Novel anti-malarial agents – anti-malarial analogues related to qinghaosu.
  - Anti-viral hepatitis drugs – design and synthesis of analogues related to DDB, a clinically useful anti-viral hepatitis drug (see Table 2) and other new leads.
  - New non-steroidal anti-inflammatory and anti-arthritis agents.
  - New anti-fungal agents.
  - Novel anti-viral agents – inhibitors of HSV I and II and HCMV.
  - Combinatorial chemistry – focused combinatorial libraries based on bioactive natural products models.
  - Chinese medicines – discovery and development of active principals, fractions, and formulations from traditional Chinese herbal medicines.

In the area of anti-cancer drug design, the NPL has discovered more than 1000 new cytotoxic anti-tumour principals and their derivatives or synthetic analogues from medicinal herbs in the past nearly three decades. Cytotoxic extracts, fractions and compounds are screened first in an initial in-house human tumour cell line (HTCL) panel and

then followed through BDFI, focusing on one or two of the most active bioassays systems. Promising samples are confirmed active by evaluation in National Cancer Institute (NCI) *in vitro* HTCL and *in vivo* xenograft assays<sup>39</sup>. In this manner, bioactivity- and mechanism-directed fractionation and isolation of Chinese medicinal herbs, coupled with rational structural modification and synthesis, have resulted in more than 100 new cytotoxic anti-tumour compounds and their analogues that are of current interest to NCI and have shown confirmed activity in NCI's *in vitro* primary human tumour cell lines bioassay<sup>40</sup>.

The success of this process is illustrated by the development of the epipodophyllotoxin derivative GL331 (Fig. 2) from a natural product model. Etoposide is a semi-synthetic derivative of the natural product podophyllotoxin, which is isolated from *Podophyllum peltatum* or *P. emodi* (Xi Zhang Guei Chiu) (Fig. 2). However, their differences include both structural changes at the 4- and 4'-position and their mechanism of action: podophyllotoxin targets tubulin, while etoposide targets the enzyme DNA topo II<sup>41</sup>. Etoposide and the related thiophene analogue teniposide are widely used to treat various cancers, including leukaemias and lymphomas; however, myelosuppression, drug resistance, and poor bioavailability remain problems associated with their use<sup>42–44</sup>.

Using cytotoxicity and enzyme inhibition assays coupled with computer modelling studies, the NPL developed



**Fig. 3** Structures of anti-HIV natural lead compounds and their synthetic analogues in development at the NPL

several series of active analogues, including 4-alkylamino and 4-arylamino epipodophyllotoxin analogues, such as GL331<sup>45</sup>. GL331, which contains a *p*-nitroanilino moiety at the 4 $\beta$  position of 4'-demethyl-epipodophyllotoxin, has emerged as an excellent drug candidate from the anti-cancer programme at the NPL. GL331 was patented by Genelabs Technologies, Inc., has completed successful Phase I clinical trials as an anti-cancer drug at the M.D. Anderson Cancer Center, and currently is in Phase II clinical trials against various cancers<sup>46</sup>. GL331 showed marked anti-tumour efficacy in four tumour types (non-small and small cell lung, colon, and head/neck cancers), minimal side effects, and an MTD of 300 mg m<sup>-2</sup>. Formulated GL331 shows desirable stability and biocompatibility and good pharmacokinetic profiles. GL331 and etoposide both function as topo II inhibitors; however, GL331 is more active both *in vitro* and *in vivo*, is synthesized and, therefore, potentially manufactured in fewer steps, and can overcome multi-drug resistance in

etoposide-resistant variant cancer cell lines. Overall, GL331 is an exciting new chemotherapeutic candidate. Much of this work on the development of GL331 and other topoisomerase inhibitors as anti-tumour agents has been reviewed<sup>47</sup>.

### New trends and technologies in CM research

Chinese medicinals are being studied increasingly as multi-component entities as well as through their individual active components. For example, the eight-herb formulation 'Hsiao Ching Long Tang' (Minor Blue Dragon Combination) was found to inhibit the Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA)<sup>48</sup>. Also, two lignans, asarinin and xanthoxylol, isolated from a single herbal component, inhibited carcinogenesis in mouse skin and pulmonary tumours<sup>49</sup>. Chinese formulations are also being viewed not only as sources of single drugs, but as therapeutic tools themselves.

Formulations and extracts<sup>50–52</sup> have been used to treat hepatitis (Ku Huang injection), brain disease (Deng Zhan Xi Xin injection), and cardiovascular disease (Di Ao Xin Xue Kang tablet and Su Xiao Chiu Xing pill). In addition, modern tissue culture methods can produce active CM principals such as ginseng and shikonin (used for burns, inflammation and wounds, and also in cosmetics)<sup>53–55</sup> in large quantities over a period of several months. Finally, controlled clinical trials of CM<sup>56,57</sup> have been documented in Western medical journals, as has the validity of synergy between components of a medicinal plant<sup>58</sup>.

## Conclusions

CM will continue to provide a broad base for the discovery of new drugs, not only from bioactive lead compounds, but also from active fractions and active formulations. Highly efficient bioactivity-directed fractionation and isolation, structure characterization, analogue synthesis and mechanistic studies will provide the process by which new single compounds and active fractions can be developed as clinical candidates.

The safety and efficacy of single herbs and of multi-component prescriptions must be verified and ensured by reliable pharmacological and toxicological methods and standards and by clinical trials.

Modern technology must be applied to establish quality controls and standardize herbal products using biological and chemical markers.

In summary, new drug discovery and development from CM should proceed through three approaches: pure active principals, active fractions, and validated or improved formulations.

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