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TCM-based new drug discovery and development in China

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[ABSTRACT] Over the past 30 years, China has significantly improved the drug development environment by establishing a series of policies for the regulation of new drug approval. The regulatory system for new drug evaluation and registration in China was gradually developed in accordance with international standards. The approval and registration of TCM in China became as strict as those of chemical drugs and biological products. In this review, TCM-based new drug discovery and development are introduced according to the TCM classification of nine categories.

[KEY WORDS] China; China Food and Drug Administration (CFDA); Traditional Chinese Medicine; Regulatory classification; Drug discovery; Drug development

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Introduction

In spite of the outstanding achievements of allopathic medicine, traditional medicines, including traditional Chinese medicine (TCM), continue to offer a predominant healing approach. It is estimated that 80% of the population of the developing world rely on traditional medicines for their primary health care needs [1]. TCM-based innovations are gaining more and more attention in China, and a series of reforms in the regulations of the China Food and Drug Administration (CFDA) are vigorously promoted.

Scientific and theoretical values of TCM are increasingly gaining international recognition and acceptance. TCM plays a significant role in the drug discovery and development process by generating a number of valuable drugs [2]. China enacted its first comprehensive Drug Administration Law in 1984 [3]. Around the same time, a new regulation describing the provisions for New Drug Approval was ratified [4]. Since the enactment of this tion, China has significantly improved its regulatory review system of new drugs [5]. In 1999, the State Drug stration (SDA), a new bureau respon-sible for new drug review was established and bestowed with the elaboration of the provisions for New Drug Approval [6]. The Drug Administration Law of 2001 is the fundamental law governing drug administration and ensuring drug quality and safety [7]. In 2002, the provisions for Drug Registration were issued, and the concept of drug registration was introduced for the first time, drawing on the experience of advanced drug registration from abroad, the basic rules of the World Trade Organization (WTO), and the regulations in China at that time. This signaled the beginning of a unified and improved stage in Chinese policy for drug registration. In 2005, the SFDA was established, which signaled a desire to conform to the general international practices. Another revision for Drug Registration (SFDA order 28) was issued in July 2007 and enacted on October 1, 2007 [8]. According to SFDA order 28, drugs shall be assessed for their safety, efficacy, and quality.

The enforcement of TCM registration in China became as strict as that of chemical drugs and biological products. Registration of TCM new drugs is subject to strict technical evaluation and clinical trial. Safety data are also required，however, TCM materials that demonstrate a long history of use may be exempted from submission of part of the requirements.

The following analysis is based on the number of new drugs approved by the Center for Drug Evaluation (CDE) as recorded in the annual reports of the SFDA from 2009 to 2013. In these reports, TCM and natural medicinal products

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are grouped into nine categories, with four of these categories representing the majority of new drugs, preparation with altered dosage form of marketed Chinese medicines and natural medicinal products, generics, and imported medicines. Over the past years, the number of new drugs approved has shown a yearly decrease, the quality is improving, and the number of generics is decreasing (Fig. 1).

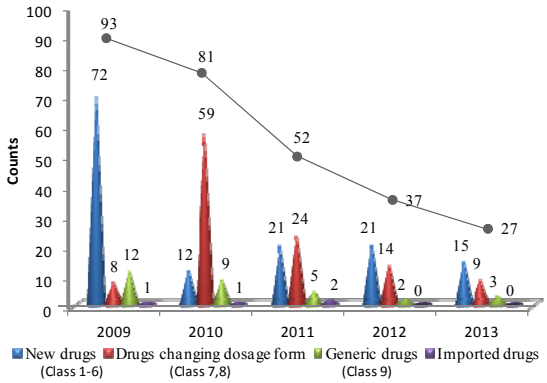

Fig. 1 SFDA-approved TCM drugs during 2009-2013

TCM-based new drug discovery

The current drug registration and administration in China follows the provisions enacted in 2007, in which TCM and natural medicinal products are classified into nine categories. Data adopted in this review were based on the information available at http://app1.sfda.gov.cn/datasearch/face3/dir.html.

Active ingredients and their preparations extracted from plants, animals, minerals, or other substances which have not been on the market in China

TCM-based novel drug discovery can be traced back to the isolation of ephedrine from the Chinese medicinal plant *Ephedra sinica* by Japanese and German scientists. The rapidly developing chemical, analytical, pharmacological and biological technologies and methods allow the discovery of numerous active compounds every year, some of which will be further developed into drugs. Newly developed single- compound drugs are listed in Table 1, some of which have been widely used in clinical practice. Despite the fact that some of the pure chemical entities derived from TCM resources may not registered under the TCM or natural drug category, but as chemical drugs, they can still be accounted for the great contribution of TCM to the medical world .

Table 1. The registration categories of TCMs and natural drugs—Class 1

	English name	Source	Indication
New single-compound medicine approved			
	20(*R*)-Ginsenoside Rg3	*Panax ginseng* C. A. Mey.	Anticancer
New single-compound medicine under development			
1	Andrographolide	*Andrographis paniculata* (Burm. f.) Nees	Antibiosis or anti-inflammation
2	Asiaticoside	*Centella asiatica* (L.) Urb.	Vulnerary
3	Astragaloside IV	*Astragalus membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) P. K. Hsiao, *Astragalus membranaceus* (Fisch.) Bunge	Antianginal
4	Baicalein	*Scutellaria baicalensis* Georgi, *Scutellaria linarioides* C. Y. Wu	Antivirus
5	Calebassine	*Cucumis melo* L.	Antihepatitis
6	Erianin	*Dendrobium chrysotoxum* Lindl.	Anticancer
7	Forsythiaside	*Forsythia suspensa* (Thunb.)Vahl	Antiviral
8	Gambogic acid	*Hypericum perforatum* L.	Anticancer
9	Hydroxysafflor yellow A	*Carthamus tinctorius* L.	Anticoagulant
10	Ligustilide	*Angelica sinensis* (Oliv.) Diels	Respiratory distress syndrome
11	Limonin	*Citrus limon* (L.) Osbeck	Anticancer, Antivirus
12	Nobiletin	*Citrus reticulata* Blanco	Anticancer
13	Norcantharidin	*Mylabris phalerata* Pallas *Mylabris cichorii* L.	Anticancer
14	Oridonin/Rubescensine A	*Rabdosia rubescens* (Hemsl.) H. Hara	Anticancer
15	Paeonol	*Paeonia suffruticosa* Andrews	Analgesic
16	Picroside II	*Picrorhiza scrophulariiflora* Pennell	Anti-cerebral ischemia
17	Polydatin	*Polygonum cuspidatum* Siebold & Zucc.	Anti-cerebral ischemia
18	Rheinic acid	*Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf., *Rheum officinale* Baill.	Antinephrosis
19	Salidroside	*Rhodiola crenulata* (Hook.f. et Thomson) H.Ohba	Immuno stimulant
20	Scutellarin	*Scutellaria baicalensis* Georgi, *Scutellaria barbata* D. Don, *Erigeron breviscapus* (Vaniot) Hand.-Mazz.	Anti-cardio-cerebral ischemia
21	Silymarin	*Silybum marianum* (L.) Gaertn.	Antihepatitis
22	Sophocarpine	*Sophora alopecuroides* L. *Sophora flavescens* Ait.	Anticarditis
23	Sophoricoside	*Sophora japonica* L.	Contraception
24	Tectorigenin sodium sulfonite	*Iris tectorum* Maxim.	Anti-infectious

Artemisinin is the most significant achievement in TCM-based drug discovery and development in history [9], and was isolated from the Chinese medicinal plant *Artemisia annua* [10]. Treatment of malaria with *Artemisia annua* could be traced back to "Zhouhou Beiji Fang" written by Hong Ge in the Eastern Jin Dynasty. Artemisinin is an anti-malaria medicine with high efficacy, quick action, and low toxicity [11]. For the past 100 years, quinine and its synthetic analog chloroquine were the drugs of choice to cure malaria; nevertheless, there were great difficulties due to drug resistance and toxic side effects. Artemisinin became a preferred alternative, and is now registered in more than 20 countries. With the increasing clinical use of artemisinin, its downside appeared gradually. Therefore, Chinese scientists have later developed, through structure modification of artemisinin, the second-generation artemisinin products: artemether [12], sodium artemether [13], and mixed artemether [14], which have gained wide international acceptance, and are of great assistance to countries with a high incidence of malaria in Africa.

Arsenic trioxide (As_2O_3) is the major component of TCM-white arsenic, its earliest record dates back to "Ri-Hua-Zi Bencao" during the Five Dynasty period, where it was used externally, due to its severe toxicity, to cure syphilis and scrofula. Forty-one years ago, ZHANG Ting-Dong from Harbin Medical University discovered that arsenic trioxide appeared to achieve a complete remission, for varying lengths of time, in more than 70% of acute promyelocytic leukemia (APL) patients. This finding was first reported in 1992 [15] and in the world-famous academic journals *Blood* [16] and *Science* [17]. In the opinion of *Blood* editors, the work of ZHANG Ting-Dong is very creative, and is an interesting discovery that apoptosis of leukemia cells can be induced by arsenic trioxide. Owing to the advantages of high treatment efficacy, long life cycle, low recurrence rate, and fewer side effects, arsenic trioxide was officially approved for the treatment of APL in 1999.

Schisandrae Chinensis Fructus (Wuweizi) is a well-known traditional Chinese medicine with a long history of clinical use to treat various diseases. Since the 1960s, Chinese scientists have carried out extensive research on Schisandrae Chinensis Fructus with respect to its clinical efficacy, active components, and pharmacological activities. Bifendate and its derivative bicyclol are the new Class 1 drugs discovered during the research on Schisandrae Chinensis Fructus in the 1970s by LIU Geng-Tao's team at the Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College [18]. Bifendate and its derivative are also used as intermediates in the synthesis of Schisandrin C. Bifendate showed protective activity against chemical-related liver-injury in animal models. Clinical trials confirmed its effect in decreasing alanine aminotransferase (ALT) and improving the main symptoms in viral hepatitis patients. Later it became a pioneering drug in China for curing hepatitis.

20(*R*)-Ginsenoside Rg_3 (Rg_3) isolated from red *Panax ginseng* showed a remarkable anti-tumor effect. Being a minor component in red ginseng (about 0.003%), Rg_3 was later synthesized by the Japanese researcher Xun Bei-Chuan [19] who confirmed its molecular formula in 1980, and proposed that Rg_3 could selectively restrain the invasion and metastasis of tumor cells. Further research on Rg_3 was later reported by scientists from Japan, China, Korea, Germany, and the USA. In 1995, the two Chinese scientists Li Fu and Qi Lu reported a breakthrough in the synthesis of Rg_3, which made possible its large-scale production and further research on the mechanism of its anti-tumor action. Rg_3 is also the principal active component of Shenyi capsules, and is the first approved Class 1 TCM new drug developed in China for clinical use against metastasis and recurrence of tumor. Beside its use in the treatment of non-small cell lung cancer, Shenyi capsule is also used for the treatment of lung cancer, gastric cancer, colorectal cancer, and liver cancer [20-21].

Among the above examples, only Shenyi capsule was approved as new TCM drug under the new drug registration regulations. Yet, it is beyond the question that all of these medicines were derived from TCM as a result of innovations based on TCM knowledge. Thus, with history as a guide, it appears that the successful application of TCM to drug discovery will benefit greatly from the knowledge of TCM traditional use and practice. It is worth noting that the chemical compositions of TCM are extremely complex, which requires the adoption of a series of approaches to discover new medicines with related knowledge such as ethnopharmacology, ethnobotany, functional genomics, and chemical information systems [22].

Newly discovered crude drugs and their preparations

"Newly discovered crude drugs and their preparations" (category 2) are crude drugs and preparations that have not been recognized as medicines in the regulations of the state, provinces, autonomous regions, or municipalities (collectively called "statutory standards"). Generally, there is a small number of "Newly discovered crude drugs and their preparations" that were registered as Class 2 new TCM drugs. From 1985 to 1999, only Testudinis Carapacis et Plastri, *Dracaena cochinchinensis*, *Fritillaria anhuiensis*, Panacis Quinquefolii Radix, Osteon Myospalacem Baileyi and a few others were approved. None has been fully approved for registration since 1999. A few were approved for clinical use, including *Epimeredi indica* [23], which is included by statutory standards but used as a Chinese traditional herb until now; *Cordyceps kyushuensis* [24], which is a new class for the native record; Sweet Potato Simon No.1 [25] imported from Brazil; *Garcinia mangostana* [26], which is not new, and was generally served as food instead of medicine; *Paecilomyces cicadae* [27], which is not included by statutory standards, but is modified and processed based on the classes included by statutory standards. It is difficult to register Class 2 new TCM drugs. Other than the systemic study of new preparations required by the laws and regulations for new drugs, the crude drugs used in the preparation should be registered following the standards for review and approval of "new drugs". Information about the effect of the environment, propagation, morphological description, cultivation techniques, postharvest handling, processing methods,

quality standards, safety, and efficacy of these crude drugs should be studied and assessed. This inevitably results in a lengthy development period of this kind of crude drug along with higher capital investment and greater risk. In the meantime, it is worth noting that the "new crude drugs" can constitute a new avenue for new drug innovation, especially if coupled with modem biotechnology tools, such as the fermentation of traditional Chinese medicines.

Table 2 TCM-based, new single-compound medicines

No.	English name	Source	Indication
1	Acebrophylline	*Camellia sinensis* (L.) Kuntze	Respiratory distress syndrome
2	Acetylaconitine	*Aconitum flavum* Hand.-Mazz.	Analgesic
3	Acetylsalicylic acid	*Cimicifuga heracleifolia* Kom., *Curcuma wenyujin* Y. H. Chen et C. Ling	Analgesic
4	Aescine sodium	*Aesculus wilsonii* Rehder	Anti-encephaledema
5	Anisodine hydrobromide	*Anisodus tanguticus* (Maxim.) Pascher	Anti-cephalagic
6	Armillarisin A	*Ligulariopsis shichuana* Y. L. Chen	Anti-infectious
7	Arsenic trioxide	Arsenic trioxide	Anticancer
8	Artemether	*Artemisia annua* L.	Antimalaria
9	Artemisinin	*Artemisia annua* L.	Antimalaria
10	Artesunate	*Artemisia annua* L.	Antimalaria
11	Atropine sulfate	*Atropa belladonna* L.	Spasmolytic
12	Baicalin	*Scutellaria baicalensis* Georgi	Antihepatitis
13	Berberine hydrochloride	*Coptis chinensis* Franch. *Mahonia bealei* (Fortune) Pynaert	Antidiarrhea
14	Bergeninum	*Bergenia purpurascens* (Hook.f. et Thomson) Engl.	Pectoral
15	Bifendate	*Schisandra sphenanthera* Rehder & E. H. Wilson	Antihepatitis
16	Bilobalide B	*Ginkgo biloba* L.	Platelet aggregation inhibitor
17	Bulleyaconitine A	*Aconitum kusnezoffii* Rchb.	Analgesic
18	Caffeic acid	*Solidago canadensis* L.	Antivirus
19	Caffeine	*Camellia sinensis* (L.) Kuntze	Central stimulant
20	Camphor	*Cinnamomum camphora* (L.) J.Presl	Epispastic
21	Cepharanthine	*Stephania japonica* (Thunb.) Miers	Antipulmonary fibrosis
22	Chlorogenic acid	*Eucommia ulmoides* Oliv. *Lonicera japonica* Thunb. *Lonicera hypoglauca* Miq. *Lonicera confusa* DC. *Lonicera dasystyla* Rehder	Antivirus
23	Cinchocaine hydroxychloride	*Papaver somniferum* L.	Pectoral
24	Codeine phosphate	*Papaver somniferum* L.	Pectoral
25	Colchicine	*Colchicum autumnale* L.	Anticancer
26	Curcumin	*Curcuma longa* L.	Antisepsis
27	Deslanoside	*Digitalis lanata* Ehrh.	Cardiotonic
28	Dicoumarol	*Medicago sativa* L.	Antithrombosis
29	Digoxin	*Digitalis lanata* Ehrh.	Cardiotonic
30	Dihydroartemisinin	*Artemisia annua* L.	Antimalaria
31	Dihydrocodeine tartrate	*Papaver somniferum* L.	Analgesic
32	Dihydroergotoxine mesylate	*Claviceps purpurea* (Fr.) Tul.	Anti-spirit degradation
33	Dioscin	*Dioscorea zingiberensis* C. H. Wright	Antitracheitis
34	B-elemene	*Curcuma wenyujin* Y. H. Chen et C. Ling	Anticancer
35	Dobutamine hydrochloride	*Mucuna sempervirens* Hemsl.	Anti-Heart failure
36	Ephedrine hydrochloride	*Ephedra sinica* Stapf	Anesthetic, Anti-hypotension
37	Eugenol	*Syzygium aromaticum* (L.) Merr. & L. M. Perry	Analgesic
38	Ferulic acid	*Ferula sinkiangensis* K.M.Shen *Ferula fukanensis* K.M.Shen, *Ligusticum striatum* DC.	Anti-erosclerotic
39	Galantamine hydrobromide	*Lycoris aurea* (L'Hér.) Herb.	Anti-poliomyelitis
40	Gallic acid	*Melaphis chinensis* (Bell) Baker	Antivirus
41	Gastrodin	*Gastrodia elata* Blume	Neurasthenic syndrome

continued

No.	English name	Source	Indication
42	Ginsenoside Re	*Panax ginseng* C. A. Mey.	Central depressant
43	20(*S*)-ginsenoside Rg3	*Panax ginseng* C. A. Mey.	Anticancer
44	Ginsenoside Rh2	*Panax ginseng* C. A. Mey.	Immunostimulant
45	Ginsenoside Rh3	*Panax ginseng* C. A. Mey.	Immunostimulant
46	Glycyrrhetinic acid	*Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Batalin, *Glycyrrhiza glabra* L.	Anti-inflammatory
47	Glycyrrhizic acid/ glycyrrchizin	*Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Batalin, *Glycyrrhiza glabra* L.	Antihepatitis
48	Homoharringtonine	*Cephalotaxus fortunei* Hook.	Anticancer
49	Houttuynin	*Houttuynia cordata* Thunb.	Anti-inflammatory
50	Hydroxycamptothecin	*Camptotheca acuminata* Decne.	Anticancer
51	(5*R*)-5-hydroxy triptolide	*Tripterygium wilfordii* Hook. f.	Antiarthritic
52	Indirubin	*Indigofera tinctoria* L. *Isatis indigotica* Fortune ex. Lindl.	Antileukemia
53	Ligustrazine hydrochloride	*Ligusticum striatum* DC. *Curcuma wenyujin* Y.H.Chen et C. Ling	Antithrombotic
54	Mannitol	*Veronica linariifolia* var. *dilatata* Nikai & Kitag.	Diuretic
55	Matrine	*Sophora alopecuroides* L. *Sophora flavescens* Aiton	Antihepatitis
56	Menthol crystal	*Mentha haplocalyx* Briq.	Anti-inflammatory
57	Methylergonovine maleate	*Claviceps purpurea* (Fr.)Tul.	Anti-urerine bleeding
58	Morphine sulfate	*Papaver somniferum* L.	Analgesic
59	9-nitrocamptothecin	*Camptotheca acuminata* Decne.	Anticancer
60	Noscapine	*Papaver somniferum* L.	Pectoral
61	Oleanolic acid	*Ligustrum lucidum* Aiton	Antihepatitis
62	Oxymatrine	*Sophora alopecuroides* L. *Sophora flavescens* Aiton	Antihepatitis
63	Papaverine hydrochloride	*Papaver somniferum* L.	Anti-cardio-cerebral ischemia
64	Pentoxifylline	*Theobroma cacao* L.	Cerebral circulation improver
65	Picroside ii	*Picrorhiza scrophulariiflora* Pennell	Anti-cerebral ischemia
66	Pilocarpine nitrate	*Cantleya corniculata* (Becc.) R. A. Howard	Antiglaucoma
67	Podophyllotoxin	*Sinopodophyllum emodi* (Wall. ex Hook.f. Thomson) T.S.Ying	Anticancer
68	Pseudoephedrine	*Ephedra sinica* Stapf	Anti-nasal congestion
69	Puerarin	*Pueraria lobata* (Willd.) Ohwi	Anti-meocardial ischemia
70	Quinine hydrochloride	*Cinchona ledgeriana* (Howard) Bern. Moens. ex Trimen	Antimalaria
71	Raceanisodamine hydrochloride	*Anisodus tanguticus* (Maxim.) Pascher	Analgesic
72	Reserpine	*Rauvolfia verticillata* (Lour.) Baill.	Antihypertensive
73	Santonin	*Compositae Artemisia* cina *Artemisia scoparia* Waldst. & Kitam.	Antiparasitic
74	Scopolamine butylbromide	*Scopolia japonica* Maxim.	Anesthetic
75	Securinine	*Securinega suffruticosa* (Pal1.) Rehder	Anti-poliomyelitis
76	Silibinin	*Silybum marianum* (L.) Gaertn.	Antihepatitis
77	Sodium alginate	*Laminaria japonica* Aresch	Anticancer
78	Sorbitol	*Pyrus lindleyi* Rehder	Diuretic
79	Sulfotanshinone sodium	*Salvia miltiorrhiza* Bunge	Antiatherosis
80	Taurine	*Calculus bovis*	Antipyretic
81	Taxol	Chinese yew	Anticancer
82	Tetrahydropalmatine sulfate	*Corydalis yanhusuo* (Y. H. Chou & Chun C. Hsu) W. T. Wang ex Z. Y. Su & C. Y. Wu	Neuroleptic
83	Thymol crystals	*Thymus serpyllum* L.	Antibiosis
84	Troxerutin	*Sophora japonica* L. *Ruta graveolens* L.	Platelet aggregation inhibitor
85.	Ursodeoxycholic acid	Bear Gall	Anti-gall-stone
86.	Vincristine sulphate	*Catharanthus roseus* (L.) G. Don	Anticancer
87.	Wogonin	*Scutellaria baicalensis* Georgi	Antitumor, Antihepatitis

New substitutes of existing Chinese crude drugs

"New substitutes of existing Chinese crude drugs" (Class 3) involves the replacement of crude drugs in TCM preparations which are toxic or in imminent danger of extinction. In general, the number of Class 3 registration is quite small, so far there are only three cases: *Calculus bovis*, bear gall powder and artificial musk were approved before 1999. From 1999 to now, only one drug, artificial tiger bone powder was registered. The "Review and Approval of New Medicine" regulations implemented on May 1st 1999 categorized "artifacts of crude drug" into Class 1 registration. The "artifacts of crude drug" is an artificial imitation product of a crude TCM drug, which maintains the characteristics and major components of the crude drug. The "Administrative regulations for medicine registration" implemented on May 1st 2005, and the subsequent revision of October 1st 2007 defined "artifacts of crude drugs" as "New substitutes of existing Chinese crude drugs" and categorized them into registration Class 3. So far, there are substitutes available for some of the crude drugs that are in imminent danger of extinction, but there are no examples of substitution of toxic crude drug.

New medicinal parts of existing crude drugs or their preparations

"New medicinal parts of existing crude drugs or their preparations" refers to the registration of using different parts of TCM materials, together with those that were traditionally used to make full use of TCM resources. This practice requires comparative studies of the chemistry, pharmacology, and clinical observation of different parts of the crude drugs. A typical example was to use the rhizomes and rootlets of *Panax notoginseng*, along with the traditionally used roots. In general, the number of "new medicinal parts of existing crude drugs or their preparations" registered as Class 4 is rather small, and there are none fully approved for registration from 1999 to now. At present, the following materials were submitted for registration: Miwu oil soft capsules, derived from Chuan- Xiong leaves of seedlings [28]; Yang-Shen-Guo-Guanxin tablets, with the pulp of American ginseng as a crude material [29]; and Hai-Sheng-Su pill, a type of glycopeptide extracted from *Tegillarca* body, which served as a crude material [30].

Active fractions and their preparations extracted from plants, animals, minerals, or other substances that have not been marketed in China

New TCM drugs of Class 5 refer to "active fractions and their preparations extracted from TCM articles that are plants, animals, minerals or other substances". It is required that the content of the components related to the pharmacological activity shall account for more than 50% of these extracts.

Since the review and approval of new drugs in 1985, at least 25 new drugs of this category have been approved (see Table 3), most of which are angiocardiopathy drugs approved after 2002. According to a statistical analysis of the registration of new TCM fraction drugs from 2004 to 2007 by CDE reviewer ZHOU Yue-Hua [31], the most common preparation technique of active fractions is macroporous adsorption resin technique, followed by solvent processing，supercritical fluid extraction, acid/base processing, acid precipitation after water extraction, and a polyamide resin. The most common active fractions are total flavonoids, total saponins, total polysaccharides, total lactones, and total alkaloids.

A typical example of a Class 5 new drug is Di'ao Xin Xue Kang capsules (dry extract of rhizomes of *Dioscorea nipponica*), which was approved in the 1980s as a new drug by the Ministry of Health, China. In March 2012, it was approved by the Dutch Medicines Evaluation Board (MEB) for marketing in the Netherlands as a traditional medicine [32].

In spite of the fact that the composition of Class 5 drugs is simpler than complex TCM preparations, they are still mixtures of chemical components, which require multi- component quality control methods, and, in some cases, pharmacokinetic studies are even requested. Development of a new drug based on an active fraction led to the development of a number of new analytical methods using advanced technologies, such as fingerprinting, LC/MS-based rapid qualitative analysis, pharmacokinetic studies of multi-component mixtures, and chemometrics-based multivariate analysis. These new techniques afforded tools to better understand the chemistry of traditional medicines and their mechanism of actions.

Preparations of traditional Chinese medicine formulas and natural medicine formulas that have not been marketed in China

These types of drugs are regulated as Class 6 new drugs, which were further divided on the basis of the nature of the materials into: 6.1 TCM combination preparations, 6.2 natural medicinal combination preparations, and 6.3 combination preparations consisting of TCM, natural medicinal compounds, and chemical medicines.

The TCM combination preparations of Class 6.1 are the major part of Class 6, and are considered to be safe and efficacious because of their long history of use. These preparations could skip Phase I or Phase II clinical study in some cases [33]. Natural medicinal combination preparations of Class 6.2 are based on traditional Chinese medical knowledge, and the composition and ratios of components of these preparations are defined depending on modern pharmacological screening. Their preclinical and clinical tests involve animal models and patients, based on their clinical indications. Class 6.2 preparations may contain extracts or active fractions. Class 6.3 is for combination preparations consisting of a TCM, natural medicinal compounds, and chemical medicines. The number of applications of Class 6.3 is quite small. Demonstration of the necessity, efficacy, and safety of the chemical medicines in the preparation is required, which greatly increases the difficulty for the development of these drugs. This illustrates the cautious attitude of Chinese medicine review department towards the addition of chemical medicines into TCM.

Table 3 TCM-based active fractions—Class 5

No.	Compound type	Source	Indication
1	Gypenoside	*Gynostemma pentaphyllum* (Thunb.) Mak.	Cardiovascular
2	Saponin	*Dioscorea nipponica* Makino *Dioscorea panthaica* Prain et Burk	Cardiovascular
3	Triglyceride	*Coix lacryma-jobi* L. var. *ma-yuen* (Roman.) Stapf	Tumor auxiliary
4	Flavonoids and diterpene lactones	*Ginkgo biloba* L.	Cardiovascular
5	Triterpene	*Ligustrum lucidum* Ait.	Hyperlipidaemia
6	Tannins	*Fagopyrum dibotrys* (D. Don) Hara	Anti-tumor
7	Carotenoid	*Crocus sativus* L.	Cardiovascular
8	Unsaturated fatty acids	*Ribes nigrum* L.	Hyperlipidaemia
9	Dihydroflavonol glycosides	*Drynaria fortunei* (Kunze) J. Sm.	Osteoporosis
10	Sulfated polysaccharides	*Laminaria japonica* Aresch.	Chronic renal failure
11	Glycosides	*Panax quinquefolium* L.	Cardiovascular
12	Chlorophylls	*Faeces Bombyx*	Hematogenesis
13	Secoiridiod glycosides	*Gentiana macrophylla* Pall.	Gastrointestinal motility
14	Protoparaxotriol saponins	*Panax notoginseng* (Burk) F. H. Chen	Cardiovascular
15	Curcumin	*Curcuma longa* L.	Hypolipidemic
16	Polysaccharide	*Astragalus membranaceus* (Fisch.) Bge.	Tumor auxiliary
17	Glycosides	*Cistanche deserticola* Y. C. Ma	Vascular dementia
18	Salvianolate	*Salvia miltiorrhiza* Bge.	Cardiovascular
19	Alkalis	*Leonurus japonicus* Houtt.	Metrorrhagia
20	Flavonoids	*Pueraria lobata* (Willd.) Ohwi	Cardiovascular
21	Glycosides	*Rehmannia glutinosa* Libosch.	Chronic glomerulonephritis light disorder
22	Fatty acids	*Perilla frutescens* (L.) Britt.	Hypolipidemic
23	Glycosides	*Dipsacus asper* Wall. ex Henry	Primary osteoporosis
24	Flavonoids	*Scutellaria baicalensis* Georgi	Acute pharyngitis
25	Diterpene lactones	*Ginkgo biloba* L.	Cerebral infarction

The best selling TCMs of Class 6 are listed in Table 4. The typical drug of this type is Compound Danshen Dripping pill (T89, also known as Dantonic® pill) which was approved in 1993, and is the most representative TCM combination preparation for Class 6.1. It was widely used in China to treat coronary artery disease and angina. It contains the water extracts of two herbs named *Salvia miltiorrhiza* and *Panax notoginseng*, plus borneol as transport enhancer. Dripping pill is a newer dosage form of Compound Danshen Tablets which was approved in the early 1970s. The dripping pill provides the advantages of rapid action, small dosage, and easy administration. Dantonic® pill overcame the drawbacks of conventional dosage form of TCM combination preparations, which allowed its export to 25 countries including Russia, Netherlands, South Africa, India, Canada, and the USA [7]. TCM combination preparations such as Dantonic® pill have a complex composition, which is quite different from those of modern chemical drugs, therefore it has still not been accepted as medicine in the main stream medical system. For instance, in USA and Canada, Dantonic® pill was introduced only as a dietary supplement or functional food product. This led to their use without proper medical supervision, and to higher rate of adverse reactions. In January 2010, the Phase II clinical RCT study of Dantonic® (Clinical trial No.: NCT00797953) was completed [34]. The purpose of this study was to determine the anti-angina effect and dose response of Dantonic® in patients with chronic stable angina pectoris in the United States [34]. In August 2012, the phase III trial of Dantonic® pill was initiated to test for its prevention and treatment of stable angina [34]. If the Phase III investigation is

Table 4 The best selling compound preparations of Chinese medicines in 2012—Class 6*

No.	Drug Name	No.	Drug Name
I. Cardiovascular and cerebrovascular diseases		VI. Musculoskeletal system diseases	
1	Compound Danshen Dripping Pills (复方丹参)	46	Jintiange Capsules
2	Naoxintong Capsules	47	Xiaotong Empladstrum
3	Suxiao Jiuxin Pills	48	Xianling Gubao Capsules
4	Shexiang Baoxin Pills	49	Tongzhi Surunjiang Capsules
5	Angong Niuhuang Pills	50	Qianggu Capsules
6	Tongxinluo Capsules	51	Fengshi Qutong Capsules
7	Wenxin Granules	52	Panlongqi Tablets
II. Oncology disease		53	Huoxue Zhitong Empladstrum
8	Jinshuibao Capsules	54	Hulisan Capsules
9	Huai'er Granules	55	Zhongtong'an Capsules
III. Respiratory system diseases		VII. Digestive system diseases	
10	Bailing Capsules	56	Maizhiling Tablets
11	Pudilan Xiaoyan Oral Solution	57	Compound Biejia Ruangan Tablets
12	Compound Xianzhuli Oral Solution (复方鲜竹沥)	58	Zhizhu Kuanzhong Capsules
13	Yiqing Capsules	59	Biantong Capsules
14	Shuanghuanglian Oral Solution	60	Wuzhi Tablets
15	Kangbingdu Oral Solution	61	Shenqi Jiangtang Granules
16	Milian Chuanbei Pipa Oral Thick Paste (蜜炼川贝枇杷)	62	Jianwei Xiaoshi Tablets
17	Xiao'er Feire Kechuan Oral Solution (小儿肺热咳喘)	63	Huoxiang Zhengqi Oral Solution
18	Jizhi Syrup	64	999 Weitai Granules
19	Qiangli Pipa Syrup		
20	Fielike Mixture		
21	Xiao'er Xiaoji Zhike Oral Solution		
IV. Gynecology Diseases		VIII. Urinary system diseases	
22	Guizhi Fuling Capsules	65	Niaoduqing Granules
23	Baofukang Suppository	66	Haikun Shenxi Capsules
24	Honghe Fujie Lotion	67	Huangkui Capsules
25	Danhuang Quyu Capsules	68	Congrong Yishen Granules
26	Sanjie Zhentong Capsules	69	Relinqing Granules
27	Hongjin Xiaojie Capsules	70	Compound Xuanju Capsules
28	Rupi Sanjie Capsules	71	Longqing Tablets
29	Xianyimucao Capsules	72	Liuwei Dihuang Pills
30	Baogong Zhixue Granules	73	Shenyan Kangfu Tablets
31	Fuke Qianjin Tablets / Capsules		
32	Jingxin Zhumian Oral Solution		
V. ENT（Ear Nose Throat）diseases		IX. Nervous system diseases	
33	Lanqin Oral Solution	74	Bailemian Capsule
34	Fuming Tablets	75	Yangxue Qingnao Granules
35	Biyuan Tongqiao Granules	76	Zhenbao Pills
36	Xianlubei Drops	77	Shugan Jieju Capsule
37	Kouyanqing Granules	78	Qingnao Fushen Oral Solution
38	Biyuanshu Oral Solution	79	Xinshenning Tablets
39	Qingyan Dripping Pills	80	Shumian Capsules
40	Jinsangzi Throat Lozenge	X. Dermatology diseases	
41	Manyan Shuning Granules	81	Pifukang Lotion
42	Compound Caoshanhu Lozenge	82	Bai Xuan Xia Ta Re Tablet
43	Xiguanshuang Spray	83	Runzao Zhiyang Capsules
44	Huangshi Xiangsheng Pills	84	Chushi Zhiyang Lotion
45	Yanlishuang Dripping Pills	85	Piminxiao Capsules
		86	Yinxieling Granules
		87	Qu Bai Ba Bu Qi Tablets
		88	Shiduqing Capsules

*The data are quoted from the Blue Book of Development about Chinese Medical Market in 2012, written by the China SFDA Southern Medical Economy Institute. Injections were not included.

successfully completed, Dantonic® pill would be submitted as a new drug application (NDA) to the FDA, and would hopefully be the first TCM drug approved in the USA. Several other TCM combination preparations are in the process of clinical trials developement for registration in FDA, such as Fuzheng Huayu Tablets (indication: hepatitis C), Kanglaite Injection (non-small cell lung cancer), Xuezhikang (hyperlipaemia), Kanion Capsules (primary dysmenorrhea), Xingling Granules (coronary artery disease), and Weimaining (lung cancer).

Three additional TCM categories

There are three additional categories to register Chinese medicines and natural medicines, including Class 7, Preparations with altered mode of drug delivery of marketed Chinese medicines and natural medicinal products; Class 8, Preparations with altered dosage form of marketed Chinese medicines and natural medicinal products; and Class 9, Generics. These three classes do not belong to the new drug category, and the number of applications and approval of generic drugs and those drugs with a simple change of dosage form is gradually declining.

Future prospects

At present, the quality control and the efficacy of preclinical and clinical evaluation are the key problems to restrict the development of TCM-based new drugs, especially for TCM formulas.

Because of the complex matrices of the TCM formulas, the analytical determination of the known active ingredients cannot meet the minimum requirement for drug quality control. The quality control system of TCM, including "source control", "process control", and "index control" should reflect the comprehensive characteristics of the TCM. The standard-setting should be away from the qualitative and quantitative model of single component of pharmaceutical products and embody the design ideas of the integrated control of the complex system. The quality evaluation system should be established based on the concept of "chemicals-efficacy-toxicity" that conforms to the characteristics of TCM.

The methodology and guiding principle of TCM efficacy evaluation which are currently used do not reflect the characteristics of TCM formulas. Almost all of the pharmacological experimental methods of TCM-based new drug have adopted the modern biomedical test models and methods which are similar or related to "syndromes" or "disease" of Chinese medicine. The lack of understanding of the mechanisms underlying TCM is undoubtedly a major reason for the widespread misconception and reluctant acceptance of TCM formulas. However, research progress may be restricted by the available methodology and technology. Further work is needed to develop the pharmacological methodology based on the theories of TCM, and establish the scientific model of TCM syndromes.

In the development and evaluation of TCM-based new drugs, the situation of over-emphasis on preclinical research (pharmacy, pharmacology, and toxicology) and ignorance of clinical research should be changed. Clinical trials are not taken seriously enough. The approval of TCM-based new drug in China is "strict entry and tolerant exit" so that applying for Drug Clinical Trial Approval is difficult, once the approval is achieved, the majority of New Drug Certificates can be approved. Instead, the United States FDA adopt a policy of "tolerant entry and strict exit", so that an Investigational New Drug (IND) application is much easier, whereas a New Drug Application (NDA) is very difficult. This approach has manifested a truly efficacy-centered purpose for the new drug development. Therefore, in the process of the implementation of GCP in China, attention should be paid to consistency with international GCP practice, which is based on the actual change of the disease state to evaluate the effect of drugs. Under the guidance of TCM theory, large-scale standardized clinical trials and the internationally recognized clinical evaluation are essential for the promotion and improvement of TCM-based new drugs.

Conclusion

More work is needed for new drugs based on TCM. On the one hand, there is a need to look for novel chemical entities that can be developed into single compound drugs; on the other hand, it is important to continue the research and development of classical TCM preparations. The majority of research projects are currently designed on the principles of modern medicine and chemistry. Approaches to drug discovery based on TCM should be consider more how to establish and include different screening models. During the development of TCM, greater attention needs to be paid to the integrated evaluation of the effectiveness based on TCM theory and clinical research. Particularly, promoting the attrition rate in the clinical trials process should be emphasized. Clinical safety and effectiveness is the fundamental starting point for new drug research.

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