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Where is the hope for drug discovery? Let history tell the future

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For drug discovery, historical experience is always of significance. Through examining the history of traditional medicines, we find that these medicines have more implications for drug discovery than just providing new chemical entities. The history of traditional medicines indicates that they depended more on the combination of natural agents than on screening new agents to find new remedies. This phenomenon suggests that shifting the current drug discovery paradigm from 'finding new-entity drugs' to 'combining existing agents' may be helpful for overcoming the 'more investment, fewer drugs' challenge. We show that clues to finding antidementia combinatorial drugs can be derived from traditional medicine formulae. It seems that to create a brighter future of drug discovery, we would better go back to history.

The past decade has witnessed an unprecedented predicament in drug discovery and development: more funds were invested, but fewer new drugs were generated [1,2]. Thus, every drug designer is wondering: where is the hope for drug discovery? In China, there is a famous saying 'lessons learned from the past can guide one in the future'. Thus, we speculate that the future of drug discovery may reside in history.

For drug discovery, historical experience is always significant. Formerly, Nobel laureate Sir James Black stated that the most fruitful basis for the discovery of a new drug is to start with an old drug [3]. Now, the pharmaceutical industry turns to historical experience again, with an attempt to find novel drugs from traditional medicines [4,5]. Indeed, some traditional-medicine-derived drugs or candidates, such as artemisinin, camptothecin, capsaicin, celastrol, curcumin, huperzine A and triptolide, have attracted much attention from mainstream medicine [5–9].

Considering the fact that traditional medicines have developed over thousands of years and have made great contributions to maintaining the health of the Chinese people (amongst others), we think that the evolutionary experience of traditional medicines may have more implications for modern drug discovery (which began to blossom only a century ago) rather than just providing new chemical entities.

Paradigm shift in traditional medicines

Through examining the phylogeny of traditional medicines, we noticed that there existed a paradigm shift during their long-time development, namely, from finding single agents (herbs, minerals and animals) to combining them to generate new remedies. This is best reflected in the evolution of traditional Chinese medicine (TCM).

TCM has a history of more than 4000 years and is still popular in China and becoming more and more accepted by Western countries [10]. The initial TCM prescription consisted of only a single agent [11]. With the accumulation of therapeutic experience, the ancient Chinese realized that combining diverse natural medicines to constitute a formula (Box 1) could efficiently enhance the therapeutic effects (according to the legend, it was Yi Yin (a prime minister of Shang Dynasty, lived around 3500 years ago) who created the TCM formula) [12]. From then on, TCM depended more and more on the combinatorial use of natural agents than on screening new agents to find new remedies.

As shown in Table 1, the most ancient TCM book *Prescriptions for Fifty-two Diseases*, compiled around ~300 BC, recorded 247 agents and ~150 formulae [12]. Two thousand years later, the number of TCM agents was raised merely sevenfold (from 247 to 1892), while the quantity of formulae increased more than 400 times (from 150 to 61,739) [11,12]. This trend in TCM

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BOX 1

TCM formula: traditional principle and modern elucidation

During the thousands of years' development, various practical theories have been developed by ancient Chinese doctors to direct the constitution of TCM formulae [53]. One of the major principles of these theories is that the multiple agents contained in one formula must work synergistically. To help understand the principle, the TCM agents were usually endued with different roles, such as 'Master (*jun*)', 'Adviser (*chen*)', 'Soldier (*zuo*)' and 'Guide (*shi*)' [54–56]. The mission of a 'Master' agent is to treat the principal symptom of the disease. The role of 'Adviser' agent(s) is to potentiate the effect of 'Master' or treat the accompanying symptoms. The task of 'Soldier' agent(s) is to enhance the therapeutic effects and modulate the adverse effects of 'Master' and/or 'Adviser' agents. The duty of 'Guide' agent(s) is to guide the active ingredients of other agents to reach the specific target organs and to harmonize the actions of these agents. Although these terms do not sound very scientific (especially from the viewpoint of modern science), they have been justified, at least for a formula (*Fu Fang Qing Dai Pian*), consisting of *Realgar* (tetraarsenic tetrasulfide) ('Master'), *Radix Salviae Miltiorrhizae* ('Adviser' and 'Guide'), *Indigo Naturalis* ('Soldier' and 'Guide') and *Radix Pseudostellariae* (also an 'Adviser', but not essential for this formula). This formula was created by Dr. Huang Shi-Lin 20 years ago and has proved clinically effective in the treatment of human acute promyelocytic leukemia (APL) [57]. Recently, through revealing the functions of the principle active ingredients of *Realgar*, *Indigo Naturalis* and *Radix Salviae Miltiorrhizae*, the synergistic mechanism of this formula was preliminarily elucidated [58]. First, tetraarsenic tetrasulfide directly attacks the promyelocytic leukemia (PML)-retinoic acid receptor α (RARα) oncoprotein and promotes APL cell differentiation, therefore it behaves like a 'Master'. Second, the principal components of *Radix Salviae Miltiorrhizae* and *Indigo Naturalis*, that is, tanshinone IIA and indirubin, respectively, potentiate tetraarsenic tetrasulfide-induced ubiquitination and degradation of PML-RARα, thus they serve as 'Adviser' and 'Soldier'. Finally, indirubin and tanshinone IIA also work as 'Guide' to enhance the expression of Aquaglyceroporin 9, which helps transport tetraarsenic tetrasulfide into APL cells and thus augments its efficacy [59].

evolution continued until the spread of modern Western medicine in China one century ago, when TCM began to combine with modern Western drugs further to enhance its diversity [13]. For instance, 80 years ago, the outstanding TCM doctor, Zhang Xi-Chun, creatively incorporated *Gypsum fibrosum*, a TCM agent that has been used for more than 2000 years, with aspirin, a typical Western drug, to create an unprecedented Chinese-Western combined formula to treat febrile arthritis [13]. Nowadays, to tackle all kinds of diseases, TCM doctors rely on the combination of about 500 agents [14].

Besides TCM, the combinatorial strategy was also popular in other traditional medicinal systems. For example, formula rudiments can be found in the very ancient Egyptian medicinal book *Ebers papyrus*, written in 1552 BC [15].

TABLE 1

Evolution of traditional Chinese medicine (TCM) [11,12]

Time	Number of TCM agents	Number of TCM formulae
~300 BC	247[a]	~150[a]
221 BC–220 AD	365[b]	~260[c]
581–960 AD	850[d]	~6,000[e]
960–1368 AD	1558[f]	~20,000[g]
1368–1643 AD	1892[h]	61,739[i]

[a] From *Prescriptions for Fifty-two Diseases* (~300 BC), Anonymous.
[b] From *Shen Nong Ben Cao Jing* (25 –220 AD), Anonymous.
[c] From *Shang Han Za Bing Lun* (210 AD), written by Zhang Zhong-Jing.
[d] From *Xin Xiu Ben Cao* (659 AD), written by Li Ji and Su Jing *et al.*
[e] From *Wai Tai Mi Yao* (752 AD), written by Wang Tao.
[f] From *Zheng Lei Ben Cao* (1082 AD), written by Tang Shen-Wei.
[g] From *Sheng Ji Zong Lu* (1111–1117 AD), compiled by Zhao Ji.
[h] From *Ben Cao Gang Mu* (1578 AD), written by Li Shi-Zhen.
[i] From *Pu Ji Fang* (1406 AD), written by Zhu Di.

Implications for the paradigm shift in modern drug discovery

Most modern drug discovery is based on the lock-and-key theory, which attempts to use one single compound to hit one target to combat the related disease [16,17]. However, as the pathogenesis of many diseases involves multiple factors, a selective single-target compound usually fails in the fight against these multigenic diseases [18,19]. In addition, as the human body is an extremely complex network, inhibiting a single target usually has little therapeutic effect (because of redundancy within systems) [20–22], and can exert unexpected side effects (because of the breaking of the balance of the network) [23]. Thus, it seems that the 'one-disease–one-drug' paradigm is responsible, at least in part, for the current predicament in the pharmaceutical industry [17,24,25]. Inspired by the developmental history of traditional medicines, especially TCM, we suggest that to overcome the challenge of 'more investment, fewer drugs', maybe we should shift the drug discovery paradigm from 'finding new-entity drugs' to 'combining existing agents', which is corroborated by the following analyses.

The past 100 years of effort from medicinal chemists have accumulated a large number of drugs and candidates (around 170,000) [26,27], a number in the region of 100 times greater than the potential drug targets (around 1500) [28]. Therefore, existing drugs and candidates may have covered a significant number of potential drug targets, if one considers the fact that the ligand-binding sites are much less diverse than protein architectures [29–31] and one drug indeed can bind to several receptors [32,33]. In addition, the structures of the existing drugs and candidates are highly diversified, even compared with natural products or the components derived from natural medicines (as illustrated by the chemical spaces in Fig. 1). Therefore, it seems that to cover a wider biological space, combining the existing agents is more efficient than exploring the untouched chemical space. In fact, the multicomponent therapeutic strategy has been given much attention in recent years, which has the following advantages over single-component strategy: (i) it may exert synergistic effects to explore a wider biological space with less expense; (ii) it modulates the biological networks modestly and thus may be efficient in controlling complex disease systems; (iii) it exerts effects at low concentration, thus is safer than single-component drugs and (iv) it can deal with

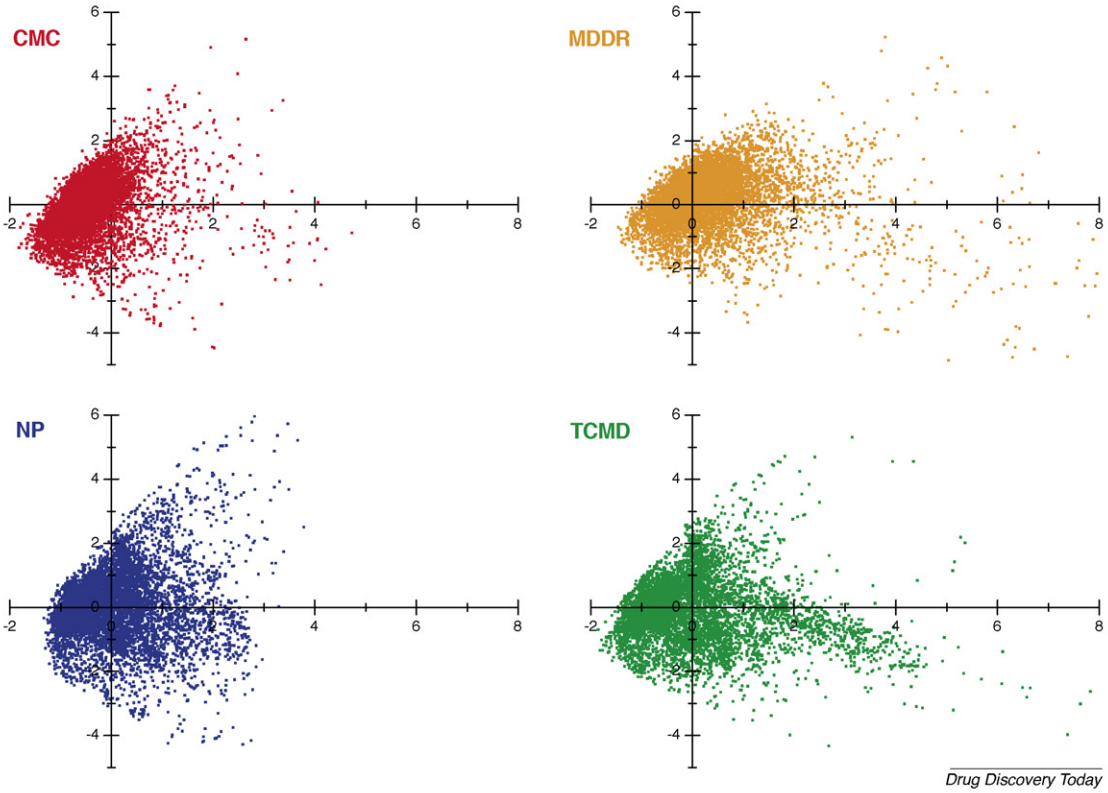

FIGURE 1

Chemical space of clinically used drugs (~8000 molecules randomly selected from comprehensive medicinal chemistry (CMC) database) (in red), drug candidates (~8000 molecules randomly selected from MDL Drug Data Report (MDDR) database) (in orange), natural products (~8000 molecules randomly selected from the CRC dictionary of natural products) (in blue) and traditional medicine components (~8000 molecules randomly selected from traditional Chinese medicine database (TCMD)) (in green). The chemical space is defined with the first two principal factors of 15 molecular descriptors calculated by Cerius 2 software.

drug resistance that becomes more and more severe for antibiotics, antimalarial and anticancer drugs [18,19,22,34–37].

Implications for the combination of modern drugs or candidates

To implement this new drug discovery strategy, however, we still have to cope with some challenges, such as the explosive increase of drug combination quantities, the unpredictable pharmacokinetic properties of multiple components and the potential risks of drug–drug interactions. In spite of the rapid technical progress in high-throughput screening [38], high-content screening [39], systems biology [34,40] and -omic technologies [41], it is still likely to take a long time to perfect the related techniques [42].

Because traditional medicines, in particular TCM, have accumulated rich experience in the combinatorial use of natural medicines (for instance, more than 100,000 formulae have been documented in TCM [43]). We speculate that we may be able to start with traditional medicines to find modern drug combinations [44]. This tactic is preliminarily supported by the finding that a certain part of TCM components have counterparts in modern Western drugs or candidates and the synergistic effects of some TCM formulae can be understood in terms of the Western-medicine-justified activities [45–47]. In addition, starting with traditional medicines will have the advantage of controlling the pharmacokinetics and drug–drug interactions of multiple components, because most combinatorial modes of TCM combinations have been used clinically for hundreds of years and by thousands (if not millions) of patients.

To evaluate further the potential of this tactic, we will focus on antidementia TCM formulae to examine whether some clues could be derived from these prescriptions to help find antidementia combinatorial drugs.

Dementia, which mainly includes Alzheimer's disease and vascular dementia, is becoming one of the most threatening diseases to humankind. However, owing to the extremely complex pathogenesis of dementia, there is, as yet, no efficient therapeutic approach to treatment. There is some accumulated evidence of the value of TCM in the treatment of dementia. Recently, a statistical analysis of 1232 antidementia TCM formulae revealed that the herbal combination of *Rhizoma Chuanxiong*, *Radix Salviae Miltiorrhizae*, *Radix Polygalae Tenuifoliae* and *Rhizoma Acori Tatarinowii* was most popular in these formulae [48]. Hundreds of components can be identified from these herbs through searching traditional Chinese medicine database (TCMD) (containing ~10,000 components derived from more than 4000 herbs, animals and minerals) [49]. By comparing the structures of these components with those recorded in the MDL Drug Data Report (MDDR) database [27], we found that some components have been recognized by modern medicine. For instance, tetramethylpyrazine and 3-*n*-butylphthalide (from *Rhizoma Chuanxiong*) are neuronal injury inhibitors; miltirone (from *Radix Salviae Miltiorrhizae*) is an anxiolytic; 9-*cis*,12-*cis*-linoleic acid (from *Rhizoma Chuanxiong*) is a healer for cognition disorders; baicalin (from *Radix Salviae Miltiorrhizae*) holds anti-inflammatory and antioxidant potentials (Fig. 2). All of these

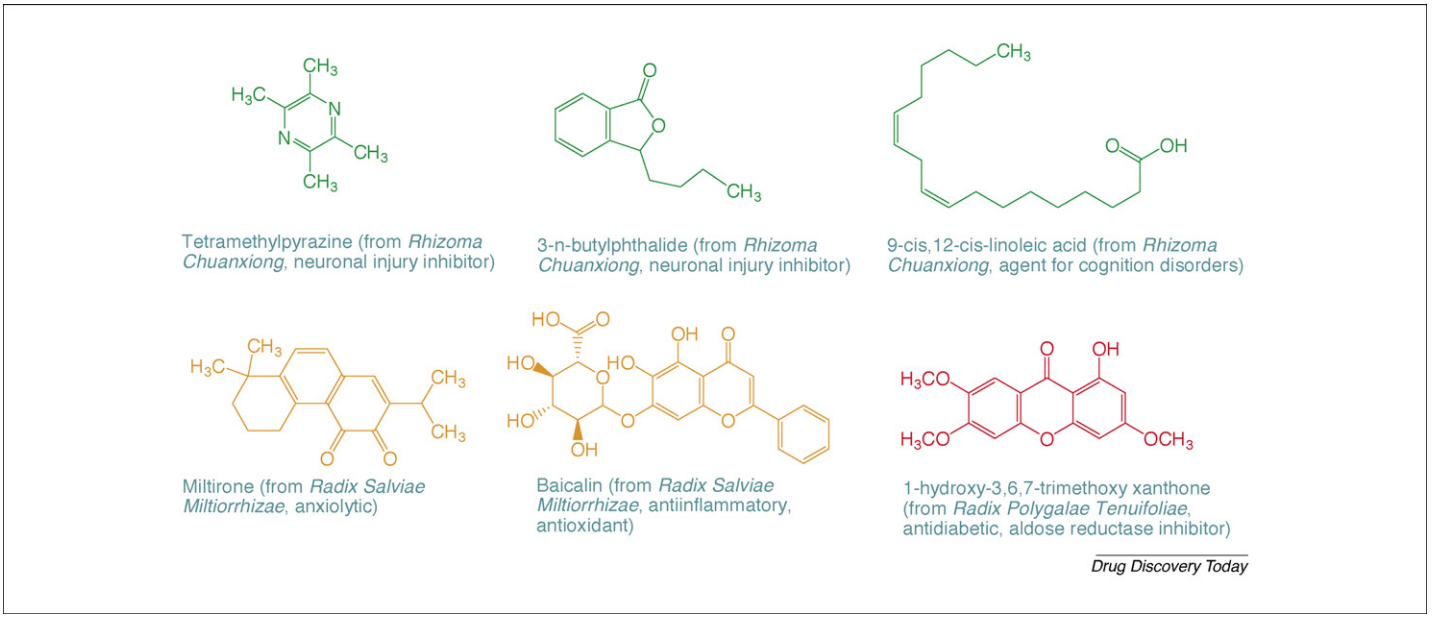

FIGURE 2

Components derived from the most popular antidementia TCM herbal combination.

activities may be helpful in ameliorating dementia. In addition, *Radix Polygalae Tenuifoliae* contains 1-hydroxy-3,6,7-trimethoxy xanthone (Fig. 2), which is annotated as an antidiabetic and an aldose reductase inhibitor in MDDR database and thus probably beneficial to the treatment of diabetes-related cognitive decrements [50]. More interestingly, recent studies revealed that xanthones are promising multipotent anti-AD agents, with potentials of inhibiting monoamine oxidases (A and B), acetylcholinesterase, scavenging free radicals and chelating transition metal ions [51]. Taken together, antidementia TCM formulae indeed contain various Western-medicine-justified antidementia components, which are likely to act synergistically in the fight against dementia. Thus, combining these Western drugs (or candidates) according to the combinatorial modes in TCM formulae may exhibit better antidementia effects than the single compounds; this concept provides a good starting point for further research.

Conclusion

The historical experiences embedded in traditional medicines not only provide valuable clues for finding new-entity drugs, but also may help to shift the drug discovery paradigm from 'finding new-entity drugs' to 'combining existing agents', and might even direct the agent combination. The latter potential of traditional medicines is expected to become more important with the development of natural medicine chemistry, especially the progression of the Herbalome Project [52]. Thus, it seems that to create a brighter future of drug discovery, we would better go back to history.

Competing interests statement

The authors declare no competing financial interests.

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