

Convergent Evolution of Medicines

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Convergent evolution is a central concept in evolutionary biology,^[1] and characterizes an interesting phenomenon: different species may use similar strategies to meet the similar needs of environmental acclimation. As evolution is not limited to biological systems, we speculate that this phenomenon may appear in other realms of nature and human society. By analyzing the phylogenies and chemical spaces of Chinese, Western, and other medicinal systems, we found that convergent evolution indeed exists for medicines.

Firstly, this phenomenon can be observed at the level of herbal medicines.

It is commonly known that, historically, people depended largely on herbs to combat diseases. By comparing the use of herbs in ancient medicinal systems of various nations, we noticed that some similar herbs have been independently discovered and used to treat similar diseases by different cultures. For instance, *Plantago sp.* has been used as a laxative in Europe, North Africa, and Asia for thousands of years.^[2] The antitussive effect of *Tussilago farfara* was documented in both the *Shen Nong Ben Cao Jing* and *De Materia Medica*. The former is a Chinese medicinal book that was compiled about 2000 years ago,^[3] while the

herbal medications identified in ancient China and elsewhere are presented in Table 1.

Secondly, the convergent evolution of medicines can be observed at the molecular level. That is to say, although different cultures used distinct herbs to treat the same conditions, similar active components are responsible, at least in part, for these herbal effects. For instance, *Rheum officinale* is a herb with laxative properties recorded in the *Shen Nong Ben Cao Jing*.^[3] In comparison, ancient Egyptians used *Aloe vera* and *Cassia angustifolia* as laxatives (according to *Ebers papyrus*, written in 1552 BC).^[8] It is inter-

Table 1. Similar herbs used in Chinese and other traditional medicines to treat the same conditions.

Effects	Chinese traditional herbs	Other traditional herbs
Analgesic	Bunge Prickly Ash Peel/ <i>Zanthoxylum bungeanum</i> ^[a]	Prickly Ash/ <i>Zanthoxylum americanum</i> (used by natives in North America) ^[b]
Analgesic/ Antipyretic	Weeping Willow/ <i>Salix Babylonica</i> ^[a,c]	White Willow/ <i>Salix alba</i> (used in Rome for ~2000 years) ^[c]
Anthelmintic	Szechwan Chinaberry Fruit/ <i>Melia toosendan</i> ^[a]	India Azedarach/ <i>Melia azedarach</i> (used in India for ~2000 years) ^[d]
	Sweet Wormwood Herb/ <i>Artemisia annua</i> ^[a]	Wormseed/ <i>Artemisia maritima</i> (used in Greece for ~3000 years) ^[b]
Antipyretic	Fineleaf Schizonepeta Herb/ <i>Nepeta tenuifolia</i> ^[a]	Catnip/ <i>Nepeta cataria</i> (used in Europe for ~2000 years) ^[b]
Antitussive	Coltsfoot/ <i>Tussilago farfara</i> ^[a]	Coltsfoot/ <i>Tussilago farfara</i> (used in Greece for ~2000 years) ^[b]
Diuretic	Common Knotgrass Herb/ <i>Polygonum aviculare</i> ^[b]	Common Knotgrass Herb/ <i>Polygonum aviculare</i> (used in Europe for ~2000 years) ^[b]
Emetic	Falsehellebore Root and Rhizome/ <i>Veratrum nigrum</i> ^[e]	Veratrum/ <i>Veratrum album</i> (used in Greece for ~2500 years) ^[f]
Hemostatic	Garden Burnet/ <i>Sanguisorba officinalis</i> ^[b]	Garden Burnet/ <i>Sanguisorba officinalis</i> (used in Europe for ~2000 years) ^[b]
Laxative	Plantain Seed/ <i>Plantago asiatica</i> ^[a]	Psyllium/ <i>Plantago psyllium</i> (used in Europe, North Africa, and Asia for thousands of years) ^[b]

[a] Recorded in the ancient Chinese medicinal book *Shen Nong Ben Cao Jing* (compiled about 2000 years ago).^[3] [b] From *Euro-American Botanical Medicines*.^[2] [c] From ref. [6]. [d] From *AYUR-VEDA Traditional Indian Medicine*.^[7] [e] From ref. [5]. [f] From *A History of Medicine*.^[4]

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latter was written by the famous Greek physician Dioscorides (40 AD–90 AD).^[2] *Veratrum album* was used as an emetic by Hippocrates (460 BC–377 BC).^[4] In China, the emetic potential of *Veratrum nigrum* was noticed as early as the late Neolithic age.^[5] More examples of similar

estimating to note that aloe-emodin (a laxative agent) is present in *Rheum officinale* and *Aloe vera*, and sennosides A and B (laxative agents) are also found in both *Rheum officinale* and *Cassia angustifolia*. Traditionally, Chinese and Indian medicinal systems used *Coptis chinensis* and

Berberis vulgaris, respectively, to treat diarrhoea,^[2,3] in which berberine (an antidiarrhoeal agent) is involved. In Table 2, more common components contained in different herbs used in ancient China and elsewhere to treat the same conditions are presented.

Considering that the herbs shown in Table 1 and Table 2 are widespread in the world and that there was little medicinal communication between China and other countries 2000 years ago, (the North American indigenous cultures being even more isolated), the traditional use of these herbal medicines concurrently by different cultures over thousands of years, can be best explained as the convergent evolution of these medicinal systems.

The convergent evolution of medicines implies that some modern natural product-derived drugs or candidates may have counterparts in traditional medicines, although these agents were not initially extracted from the traditional remedies. This speculation is preliminarily supported by a recent structural comparison between ~10 000 traditional Chinese medicine (TCM) components (recorded in the Traditional Chinese Medicine Database (TCMD)^[11]) and ~8000 modern drugs or candidates (recorded in

the Comprehensive Medicinal Chemistry (CMC) database^[12]), which revealed that 908 agent pairs are structurally similar (with similarity ≥ 0.85). Among them, 327 agent pairs are identical in structure.^[13] Furthermore, a comparison between ~10 000 TCM components and ~145 000 drug candidates (recorded in the MDL Drug Data Report (MDDR) database^[14]) identified 1054 structurally similar agent pairs (with similarity ≥ 0.85). It is interesting to note that some of the CMC counterparts identified were originally derived from foreign plants rather than TCM herbs.^[15] Considering the fact that the identified traditional medicine components only represent a small portion of the potentially vast chemical space, the development of natural medicine chemistry, especially the progression of the Herbalome Project,^[16] will lead to the discovery of more agents from traditional medicines and Western drugs or candidates that are similar.

The presence of structurally similar agents in traditional medicines and modern drugs not only provides further evidence to support the theory of convergent evolution of medicines, but also has significant implications in the design of combination drug therapies, which is a new direction in drug discovery. To cir-

cumvent the predicament of "more investments, fewer drugs" in current pharmaceutical industry,^[17] drug designers have begun to resort to multicomponent therapeutics.^[18] This new drug discovery paradigm attempts to incorporate two or more active ingredients (usually clinically used drugs or candidates) in one capsule to hit the multiple targets implicated in complex diseases.^[18] However, it is a huge challenge to appropriately select and combine the various agents.^[13] Considering the fact that practitioners of traditional medicines (especially TCM) have accumulated rich experience in the combined use of herbs and other natural materials,^[19] we speculate that traditional medicinal formulae can provide some clues to combining modern drugs or candidates.^[13] A precondition of this strategy is that at least some modern drugs or candidates, should have counterparts in traditional medicines. As described above, thanks to the convergent evolution of medicines, this precondition is preliminarily justified.

A proof-of-concept example to validate this drug discovery strategy is the herbal couple *Coptis chinensis* and *Evodia rutaecarpa* (also known as *Zuo Jin Wan*), which has been used in China for

Table 2. Common components partially responsible for the same therapeutic effects of different herbs used in Chinese and other traditional medicines.

Agents	Effects	Chinese traditional herbs	Other traditional herbs
Aloe-emodin	Laxative	Rhubarb/ <i>Rheum officinale</i> ^[a]	Aloe/ <i>Aloe vera</i> (used in Egypt for ~3500 years) ^[c]
Berberine	Antidiarrhoeal	Golden Thread/ <i>Coptis chinensis</i> ^[a]	Barberry/ <i>Berberis Vulgaris</i> (used in India for ~2000 years) ^[d]
Caffeine	Diuretic	Tea Leaves/ <i>Camellia sinensis</i> ^[b]	Cacao/ <i>Theobroma cacao</i> (used by native Central and South American cultures) ^[e]
Citral	Anthelmintic	Zingiber/ <i>Zingiber officinale</i> ^[a]	Garlic/ <i>Allium sativum</i> (used in Central Asia for ~2000 years) ^[e]
Eugenol	Analgesic	Bond Magnolia Flower/ <i>Magnolia liliflora</i> ^[a]	Clove/ <i>Eugenia caryophyllata</i> (used in India for ~2000 years) ^[f]
Hyoscyamine	Sedative	Henbane Seed/ <i>Hyoscyamus niger</i> ^[a]	Thornapple/ <i>Datura stramonium</i> (used in North Africa for ~3000 years) ^[e]
5-Methoxypsoralen	Dermatologic	Green Prickly Ash/ <i>Zanthoxylum schinifolium</i> ^[a]	False Bishop's Weed/ <i>Ammi majus</i> (used in Egypt for ~3000 years) ^[g]
Podophyllotoxin	Anthelmintic	Common Dysosma Rhizome/ <i>Dysosma versipellis</i> ^[a]	American Mandrake/ <i>Podophyllum peltatum</i> (used by North American autochthon) ^[d]
Sennosides A and B	Laxative	Rhubarb/ <i>Rheum officinale</i> ^[a]	Tinnevely Senna/ <i>Cassia angustifolia</i> (used in Egypt for ~3500 years) ^[c]

[a] Recorded in the ancient Chinese medicinal book *Shen Nong Ben Cao Jing* (compiled about 2000 years ago).^[3] [b] Recorded in the ancient Chinese medicinal book *Shen Nong Shi Jing* (compiled about 2000 years ago).^[3] [c] From ref. [8]. [d] From *Euro-American Botanical Medicines*.^[2] [e] From the *Encyclopedia of Medicinal Plants*.^[9] [f] From *AYUR-VEDA Traditional Indian Medicine*.^[7] [g] From ref. [10].

~700 years to treat gastric conditions^[13,19] and has been shown to reverse changes in metabolism in rats with colon cancers.^[20] From this herbal combination, some CMC agents were identified, such as berberine, calystigine (palmatine in TCMD) (antibiotics and potential inhibitors of *Helicobacter pylori*), limonene (an antineoplastic agent), and inhibitors of cancer cell multidrug resistance (MDR), such as obacunone and rutecarpine.^[21] Therefore, we suggest that combinations of these CMC agents and MDR inhibitors may be starting points for finding novel combinatorial remedies to combat gastric conditions and even tumors. It is interesting to note that the synergistic effects of anticancer agents and MDR inhibitors have also been observed in Western medicine for many years,^[22] independent of any TCM treatments, which suggests that the convergent evolution of medicines continues even at present and goes beyond single-component medicines.

In conclusion, over the long-term development of human cultures, different civilizations may independently find similar herbal medicines and/or components to combat the same diseases, and this can be regarded as a convergent evolution in medicinal systems. Nevertheless, it should be pointed out that this phenomenon does not mean that various societies must use similar remedies to treat the same conditions, which is akin to the phenomenon in biological evolution in which different species do not necessarily rely on similar strategies to acclimate to similar environments. The convergent evolution of medicines is of significance not only to the study of the history of medical sciences, but also to drug discovery, because it implies that

some modern drugs and candidates have counterparts in traditional medicines, which may be helpful to the discovery of novel combination drug therapies according to the traditional medicinal formulae.

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