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Review

Plant Pharmacophylogeny: Review and Future Directions*

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ABSTRACT Medicinal plants have provided numerous medicinal active ingredients for thousands of years and these ingredients have been used in Chinese medicine (CM) and traditional pharmacologies worldwide. Recently, the exploitation and utilisation of medicinal plant resources has increased significantly. The results of the studies have led to the identification of many active components, such as steroidal alkaloids, saponins, terpenoids, and glycosides, in various medicinal plants with different evolutionary levels. Moreover, research on the chemical classification, molecular phylogeny, and pharmacological activity of medicinal plants is increasing in popularity. Pharmacophylogeny is an interdisciplinary topic that studies the correlation between plant phylogeny, chemical composition, and curative effects (pharmacological activity and the traditional curative effect) of medicinal plants. In addition, it provides the basic tools to enable research and development of CM resources. This literature review, based on the genetic relationship between phytogroup and species, highlights the formation process, research content, applications, and future directions of pharmacophylogeny.
KEYWORDS pharmacophylogeny, phytogroup, molecular phylogeny, chemical composition, curative effect

For many centuries, medicinal plants have been an important source of medicines. Moreover, most Chinese herbal medicines originate from plants, hundreds of thousands of plants in the world have gradually evolved over a long historical period. During this process, the morphological, physiological, and biochemical characteristics, chemical components, and corresponding traditional curative effects of medicinal plants form a close or distant phylogenetic relationship[(1)] e.g., *Ranunculaceae* (Appendix 1). Based on this foundation, academician XIAO Pei-gen theorised that pharmacophylogeny is a new, interdisciplinary, and engaging subject that extensively studies the relationship between chemical composition and efficacy (traditional curative effect and pharmacological activity) of medicinal plants.[(2)] The core of the theory is to connect the chemical or bioactive components and the curative effect of medicinal plants. Moreover, it is emphasised that genetically close medicinal plants contain similar chemical or bioactive composition and have similar curative effects. This concept has attracted wide attention of the medical field. In addition, it has emerged as a more important part for the exploration of the distribution of chemical components in medicinal plants.[(3)] Pharmacophylogeny involves many interdisciplinary subjects, such as plant phylogenetics, plant taxonomy, phytochemistry, pharmacology, molecular systematics, genomics, and informatics. The establishment of the discipline has promoted the discovery of new medicinal plant resources, enriched the impact of basic research on the modernisation of Chinese medicine (CM), and provided new theories and methods for the development of new drugs. This discipline has provided direction and theoretical guidance for the study of the internal relationship of medicinal plants and has an important significance for the development of CM resources. Based on the genetic relationships between the phytogroup and species, this paper has systematically summarised the formation process and research content, applications, developments, and future directions of pharmacophylogeny.

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Formation Process and Research Content

Traditional taxonomy is based on the external morphology and characteristics of plants; thus, there are many limitations on the accurate analysis of the problems for the classification of medicinal plants. As a result of developments in science, chromosome classification, DNA hybridisation, and microscopic classification have been added to the traditional taxonomy methods, which has enriched the morphological comparison methods used for medicinal plants.(2)

In the 1960s, as many of the chemical components of the plants have been clarified, there was understanding gradually deepen between the plant's relationship and the chemical components. Plant chemotaxonomy developed into a new science based on the chemical constituents and the traditional morphological taxonomy, in which the genetic relationship among various groups was studied, and the evolution of plants was explored. Plant chemotaxonomy has an important role in the exploration of the distribution of chemical constituents in medicinal plants, and revealed the rules of phylogenetic development in plants at the chemical level. However, it focused mainly on certain types of chemical components, and the phytogroups were not systematically studied. Secondly, there was no comprehensive combination of pharmacological and traditional curative effects.(4)

XIAO Pei-gen(2) combined plant systematics, phytochemistry, pharmacology, molecular systematics and computer technology to comprehensively study the medicinal phytogroups of *Hyoscyamus niger* L., *Berberis amurensis* Rupr., *Rheum palmatum* L., *Aconitum carmichaelii* Debeaux, *Paeonia lactiflora* Pall., *Coptis chinensis* Franch., *Thalictrum aquilegifolium* Linn. var. *sibiricum Regel et* Tiling,(5,6) *Lithospermum erythrorhizon Sieb. et* Zucc., Typha angustifolia L.(7) and *Rhododendron simsii* Planch. at the end of 1970s.(8-10) It revealed the relationships between phytogenetic, chemical components, and therapeutic effects of various phytogroups, which was called pharmacophylogeny. Continued research on *Ranunculaceae*,(11) *Berberidaceae*,(12) *Magnoliaceae*, *Solanaceae*, *Labiatae*, and *Liliaceae* using pharmacophylogeny has yielded great achievements.(13-15) With the emergence of new technologies and concepts, Xiao's team proposed pharmacophylogenomics in 2014, based on rapidly developing molecular biology and omics.(16) Combing the traditional pharmacological accumulation and pharmacological studies, they explored phylogenetic and evolutionary relationships of *Ranunculaceae* and important genera at the level of genome, transcriptome and metabolome. It is revealed that the internal relationship between genetic and chemical diversity of medicinal plant and metabolic phenotypes.(17)

The research scope of pharmacophylogeny is multidisciplinary infiltration cooperation. The correlation between chemical constituents, pharmacological effects, and the traditional therapeutic effects of medicinal plants has been clarified by various research methods used in different disciplines, and the intrinsic relationship of medicinal plants has been summarised. The information described the distribution law and the screening method of medicinal plant active substances. Morphology and molecular systematics provided substantial and accurate evidence of phylogenetic relationships. Information about the chemistry and biosynthesis of medicinal plants has improved the basic research into pharmacodynamics and enriched the phytochemical taxonomy.(17) The combination of traditional curative effects with chemical composition and systematics has stimulated ideas for the development of new drugs. *Mentha haplocalyx* Briq., *Perilla frutescens* (L.) Britt., and *Mosla chinensis* Maxim are medicinal plants of *Labiaceae* family. The smell of these plants is aromatic, containing rich volatile oil, and has therapeutic effects in dispelling wind to relieve exogenous syndrome. However, in the *Labiaceae* family, there are plants of the genus *Rabdosia* (Bl.) Hassk, such as *R. rubescens*, *R. serra* (Maxim.) Hara and *R.a nervosa* (Hemsl.) C. Y. Wu et H. W. Li. The smell of these plants is not aromatic, often with a clear bitter taste, and almost no volatile oil. Most of these plants contain diterpenoid bitter lactone compounds, exerting the effect of anti-cancer, anti-bacterial, heat-clearing and detoxification. A number of plant groups worthy of further study were summarized through the preliminary comprehensive arrangement of pharmacophylogeny, combined with the chemical composition and pharmacological action (Appendix 2).(17)

Meanwhile, the applications of pharmacophylogeny are conducive to the discovery of new resources of rare and endangered medicinal plants. The established theory has also contributed to the prediction of active ingredients and confirmed the structural identification and component determination in medicinal plants, which has enriched the impact of basic research on modernisation of CM. At present, the phylogenetic relationships of more than 24 phytogroups have been studied, including *Iris* L., Atractylodes DC., *Angelica* L., *Rheum* L., *Aconitum* L., *Curcuma* L., *Paeonia* L., *Salvia* L., *Physalis* L., *Pyrus* L., *Ephedra* Tourn ex L., *Flemingia* Roxb. ex W.T. Ait., Dendrobium Sw., Thalictrum L., Lycoris Herb., *Dipsacus* L., *Glycyrrhiza* L., *Coptis* Salisb., *Sedum* L., *Rosa* L., *Dioscorea* L., *Fritillaria* L., and *Swertia* L. (Appendix 3).[18] Among these groups, the genera of *Fritillaria*, *Aconitum*, *Iris*, and *Salvia* are the focus of study, and the research has focused mainly on the chemical constituents, pharmacological activities, traditional therapeutic effects, and molecular phylogenetic analysis.

Applications of Pharmacophylogeny

Aconitum L.

Aconitum L. is a large genus in the family *Ranunculaceae*. Many species in this genus have been used as poisons and medicinal plants with analgesic, anti-inflammatory, antiarrhythmic, and cardiac effects. Studies on phytotoxic and therapeutic effects, the connections between genetic relationships, and the chemical composition of *Aconitum* in China proved that *Aconitum* L. consisted of 3 well-described subgenera, subgen. *Aconitum*, subgen. *Lycoctonum* (DC.) Peterm., and subgen. *Gymnaconitum* (Stapf) Rapaics.[19] Among them, the species are in *Aconitum* subgen. *Lycoctonum* is mainly composed of C18-diterpenoid alkaloids and lycoctonine-type C19-diterpenoid alkaloids. Owing to their relatively lower toxicity, this subgenus is potential to development into new medicines for the treatment of conditions such as rheumatism, pain, and irregular menstruation. *Aconitum* subgen. *Aconitum* is the largest subgenus, and is usually divided into 2 sections, including sect. *Sinaconitum* and sect. *Aconitum*. The latter section of species in China is usually divided into 9 series. The series *Inflata* includes 2 most widely medicinally used *Aconitum* species, *A. carmichaeli* and *A. kusnezoffii*, which are now listed by the Chinese Pharmacopoeia Commission. They contain diester C19-diterpenoid alkaloids or aconitine-type 15-hydroxyl monoesters, which are highly complex chemical constituents in the genus *Aconitum* with strong toxicity; thus, they should be used with caution. The plants in series *Tangutica* and series *Rotundifolia* have been traditionally used in the Tibetan, Mongolian, and Uygur regions of China for treatment of high fever. They mostly contain lactone-type C19-diterpenoid alkaloids and sporadically include C20-diterpenoid alkaloids with relatively lower toxicity and are important species for the development of new medicines. It is very difficult to the taxonomy of *Aconitum*, and there is no perfect classification system. The phytochemical and pharmacophylogenetic research into *Aconitum* requires continued study.[19,20]

Salvia L.

Salvia L., a large genus belonging to the family of *Lamiaceae* includes many important medicinal plants with significant pharmacological effects. There are approximately 1,000 species of *Salvia* L. in the world. There are 84 species of *Salvia* in China, 43 of which have medicinal value (not including varieties), and 23 of them are considered *S. miltiorrhiza*.[21] According to the study, 43 medicinal plants of the genus were divided into 3 groups, comprising species from Sect. *Eurysphace Stib*. or *Drymophace* (group 1), Subg. *Allagospadonopsis Briq*., Sect. *Plethiosphace*, or Sect. *Notiosphace* (group 2), and Subg. *Jungia* and Sect. *Eusphace* (group 3). From the perspective of pharmacophylogeny, there are similar compounds and curative effects among individuals in the broad group 1. Among them, the plants in group 1 are used as "Danshen" in folk medicine for promoting blood circulation, regulating menstruation, and activating meridian and collateral, owing to the abundance of abietane diterpenes and caffeic acid derivatives in these plants.[22] Medicinal plants with the same curative effect contain similar active components and exhibit close kinship. Therefore, the medicinal plants of *Salvia* L. can be further developed and utilised as alternative sources of "Danshen". The medicinal plants in group 2 (*S. plebeia* R. Br., *S. deserta* Schang, and *S. chinensis* Benth.) have the functions of clearing heat, detoxification, and diuresis, and are rich in triterpenoids and royleanone-type diterpenoids. The plants in group 3 are from South America and Europe. Many studies showed that the plants of group 3 contain clerodane-type diterpenoids.[23] In a word, *Salvia* L. is a group with high medicinal value. Although individual species are grouped into the same group according to their morphological characteristics, their chemical composition and efficacy are distinct from those of other plants in the same group. Therefore, it is suggested that some similarities in the morphology of these species may result from convergence and evolution.[1]

Iris L.

The *Iris* species, belonging to the family Iridaceae, consists of approximately 300 species worldwide. Approximately 60 species, 13 varieties and 5 forms are distributed in the south west, north west, and north east of China. There are more than 30 species used in CM. *Iris tectorum* and *I. dichotoma* Pall. along with some other *Iris* plants are extensively utilised as Shegan medicine in areas of China. The rhizome of *Iris tectorum* was recorded as a medicine in the first Chinese monograph on herbal medicines "Shen Nong's Herbal Classic (*Shen Nong*

Ben Cao Jing)", which was completed in approximately 200 AD. It is a widely growing plant species in China and has been recorded to treat sore throat, disperse phlegm, and heat-clearing and detoxifying. *I. dichotoma* Pall., known as Bai Shegan, is often used as a substitute for Shegan for the treatment of swelling of throat, gum sore, stomach ache, hepatitis, and mastitis.[24] As Shegan medicines, *I. dichotoma* Pall. and the main *Iris* plants have been utilised for a long time, but little is known about their phytochemical and pharmacological properties. The pharmacological activities of *Radix Pulsatilla* have focused mainly on the constituent isoflavones, which have been screened for anti-tumor, anti-bacterial, and anti-inflammatory activity, and effects on cardiovascular disease, liver inflammation and other diseases. The study on the activity of *Radix Leucaria* chinensis has not been reported in the literature so far. Phenolic glycosides are precursors of flavonoids and isoflavones, and different distributions of isoflavones and phenolic glycosides are observed in different groups of *Iris*. According to the relevant literature, the plants of the genus *Echinocephala*, the subgenus of *Euphorbia*, *Chicken Corolla* and hairy appendages contain isoflavones. Simultaneously, higher levels of phenolic glycosides in *Belamcanda chinensis* (L.) Redouté, Subgen. *Iris*, *Subgen Pardanthopsis*, and *Subgen*. *Crossiris* Spach, but no related compounds were found in plants without appendages. *Iris tenuifolia* and *Iris tianshanensis* also contain isoflavones.[25] The chloroplast rbcL gene sequences of 5 medicinal plants, *Belamcanda chinensis* (L.) DC, *Iris tectorum* Maxim., *Iris dichotoma* Pall., *Iris japonica* Thunb., and *Iris germanica* L., were analysed by Huang, et al.[26] The results showed that *B. chinensis* (L.) DC and *I. tectorum* Maxim. were closely related to each other, and *Iris* species and *I. japonica*, belonging to the *Subgenus Crossiris*, were also closely related to each other, which was consistent with the traditional plant taxonomy. Zhang, et al[25] used the inter-simple sequence repeat (ISSR) molecular marker technique to analyse the polymorphism of 37 *Iris* materials. In total, 328 bands were amplified, of which were 327 polymorphic bands. The proportion of polymorphism was 99.7%, which indicated that there was abundant genetic diversity among species of *Iris*. Based on the molecular systematic cluster analysis of 328 markers produced by 15 effective primers, *I. dichotoma* Pall. was divided into a single subgenus, which showed that the relationship between the *Subgen*. *Pardanthopsis* and the other 5 subgenera of *Iris* was relatively distant. However, it did not support the juxtaposition of *I. dichotoma* Pall. and the genus *Iris*.

Fritillaria L.

Fritillaria L. is a genus in the family *Liliaceae*. Many new species and varieties of the genus *Fritillaria* have been described in China in recent years, with the number of taxa reaching 80 species. According to traditional descriptions, *Fritillaria* is used for clearing heat and moistening Fei (Lung) dryness, relieving cough, dispersing knot, and eliminating stagnation. A study of the history, geographical distribution, plant classification, chemical composition, and application of the Chinese materia medica *Bulbus Fritilariae Cirrhosae* revealed that it can be divided into 6 types: Zhe Beimu (*F. thunbergii* of cultivated), Yi Beimu (*F. walujewii* and *F. pallidiflora*), Ping Beimu (*F. ussuriensis* of cultivated), Chuan Beimu (*F. cirrhosa* D. Don, *F. przewalskii*, and *F. unibracteata*), Hubei Beimu (*F. hupehensis* of cultivated), and Anhui Beimu (*F. anhuiensis*).[27] All types, except Anhui Beimu, were recorded in the latest edition of the Chinese Pharmacopoeia Commission. The main active component of the Chinese materia medica Beimu is steroidal alkaloids; these are its characteristic components and are of taxonomic significance. Through a comparison of the chemical composition and morphology of *Fritillaria*, it was found that although some species had similar chemical compositions, the morphological changes were large, displaying the complexity of the group of *Fritillaria*. In contrast, when some chemical constituents were quite different, the morphological changes were not obvious, such as *F. hupehensis* and *F. puqiensis*. What's more, study had used a random amplified polymorphic DNA technique to study the molecular biological and pharmacophylogenetic classification of the complex group of *Fritillaria*, which, to some extent, explained the current classification.[28]

Rheum L.

Rheum L. is a genus in the family *Polygonaceae*. Through the multivariate analysis of the botanical, phytochemical, and pharmacological properties of the genus, *Rheum* was divided to sect. *Rheum*, sect. *Palmata*, sect. *Spiciformia*, and sect. *Nobilia*, with a close genetic relationship observed between these sections. Of the species in the sect. *Acuminata*, sect. *Deserticola*, and sect. *Globulosa*, some are crossed and mixed. In addition to the individual species of *R. lhasaense* A. J. Li et P. K. Hsiao, the plant of this genus commonly contains anthraquinone derivatives, with a total anthraquinone content of 1%–8%. As a medicinal material in the current edition of the national pharmacopoeia, the plants in *Rhubarb* have obvious catharsis effect and only exist in sect. *Palmata*. In the application of *Rheum*, *R. palmatum* L., *R. tanguticum* Maxim. ex Balf., and *R. officinale* Baill., included in the sect.

Palmata, are used in CM. They have obvious differences from other species in other sections of *Rhubarb* in terms of their active components and pharmacological effects. Although the medicinal materials of *R. hotaoense* C.Y. Cheng et T.C. Kao, *R. australe* D. Don, *R. franzenbachii* Münter, and *R. wittrockii* C.E. Lundstr. in the sect. *Rheum* of *Rheum* are used as *Rumex madaio* and folk rhubarb in some areas and are similar to *Rheum* in their phylogenetic arrangement, their comprehensive characteristics are not closely related to the essential difference between the 2 groups and they cannot be mixed with each other.[29,30] Studies on the seed morphological indices, ISSR molecular markers, and sequence-related amplified polymorphism (SRAP) molecular markers of *Rheum* different varieties showed that the 3 kinds of *R. tanguticum* Maxim. ex Regel were grouped together, and that the relationship between *R. palmatum* L. and *R. offcihale* L. was close to 1 group. The results were consistent with the previous AFLP analysis.[31,32]

Trib. Cimicifugeae

Trib. *Cimicifugeae* belongs to the family *Ranunculaceae*, and include 5 genera: *Beesia*, *Souliea Franch*., *Cimicifuga, Actaea*, and *Anemonopsis*. Centinaria is mainly distributes in North America, Asia, and the northern temperate zone of Europe. There are 4 genera in China, with 1 genus endemic to China. Constantine plants have a long history of use as medicine, with *Cimicifuga foetida* L., *C. dahurica* (Turcz.) Maxim., and *C. heracleifolia* Kom. included in the Chinese Pharmacopoeia. In terms of plant morphology and cytology, some scholars believe that the genus *Trib*. *Cimicifugeae* is clearly different from other genera. However, J.A. Compton, a British botanist, determined the DNA ITS sequence of the genus *Cimicifuga* L. and *Actaea* L., and it is thought that that they have similar taxonomic status and should be merged into 1 genus.[33] In terms of chemical studies, Gao, et al[34] studied the chemical constituents of the genus *Actaea* L., and found that, similar to other plants of the family, they mainly contained 9,19-cycloartane glycosides and cinnamic acid derivatives. *Ranunculaceae* plants generally contain ranunculine or magnoline. However, there are some special compounds in *Ranunculaceae* plants, such as cycloartane glycosides, cimifugin, and visnagin, which makes *Trib*. *Cimicifugeae* special among *Ranunculaceae*. The compounds were selectively distributed in the *Trib*. *Cimicifugeae*, and their distribution was related to the phylogenetic relationships of the family. Among them, 9,19-cycloartane glycosides are the characteristic chemical constituents of *Trib*. *Cimicifugeae* plants. The specific furan oxygen ring structure can be considered the quintessential component of the chemical taxonomy. The study has shown that indole alkaloids can be isolated from *Cimicifuga* L. and *Souliea* Franch..[35] Therefore, indole alkaloids can also be used as a characteristic chemotaxonomic substance. In addition, the pentacyclic triterpenoid compounds contained in the genus *Beesia* and *Souliea Franch*., but not reported in the genus *Cimicifuga* L. The genus *Beesia* could become an independent branch because of its special saponins. This is similar to other plants in the *Ranunculaceae* family, but the heat-clearing and detoxifying effects of the *Trib*. *Cimicifugeae* plants are relatively rare in *Ranunculaceae*. Thus, this effect can be identified as a separate population from other *Ranunculaceae* plants. In the *Trib*. Cimicifugeae, both *Actaea* L. and *Cimicifuga* L. exert the effect of curing rash, and in some places, *Actaea* L. can be used as substitutes for *Cimicifuga* L., thus there is a certain similarity in the curative effect (curing various kinds of inflammation) of these 2 groups. Moreover, the effect of activating blood circulation from *Beesia* is unique to these 2 genera, however, there is no record in other genera of *Cimicifuga* L. Therefore, the relatedness was analysed from the perspective of the curative effect, and the close genetic relationship between *Actaea* L. and *Cimicifuga* L. and their similar efficacy were identified. Through the consideration of the difference in their morphology and cytology, it has proposed that the genera *Actaea* L. and *Cimicifuga* L. may be a small branch of the family of *Trib*. Cimicifugeae, in which *Actaea* L. was more evolved.[35]

Schisandraceae

The *Schisandra* plants are often grouped in the *Magnoliaceae* family and are divided into 3 tribes: the tribe *Illicieae*, tribe *Magnolieae*, and tribe *Schisandreae*. In 1830, blume formally described *Schisandraceae*, and proposed that it was related to Magnoliaceae. In Cronquist classification, it is classified as a separate family and is divided into *Schisandra* and *Kadsura Kaempf*. According to the results of chemical studies, lignans and triterpenes are the chemical components of *Schisandraceae* plants, and dibenzocyclooctadiene lignans are mainly found in *Schisandraceae* plants, which is of taxonomic significance.[36] At present, no alkaloids have been found in the *Schisandraceae* and *Octagonaceae*, while 2 types of cyclojackfruit triterpenes (A-ring closed ring and A-ring open ring) have been isolated from both *Schisandraceae* and *Octagonaceae*, suggesting a common origin. Therefore, the *Schisandraceae* is a separate family from the traditional *Magnoliaceae* and is closely related to the Illicieae family, as supported by morphology, pathology, embryology, cytology, and chemical classification.[36] Forty-two spirobenzofuranoid dibenzocyclooctadiene lignins isolated from *Schisandraceae* can distinguish *Schisandrae* from *Kadsura Kaempf*. With the exception of *S. arisanensis* and *S. rubriflora* in the genus *Schisandra*, this type of composition is only distributed in the vines and stem of the genus *Kadsura Kaempf*, and characterized by the effects of calcium antagonism, anticoagulant and platelet aggregation inhibition, which shows that the medicinal plants of the *Schisandra* genus have a strong active material basis for activating blood and removing blood stasis. Meanwhile, *Schisandraceae* plants have a protective effect on the liver. This is related to the lignins contained in *Schisandraceae* plants. Lignans with liver-protecting effects are often found to have unesterified substituting groups at the C6 and C9 of the octahedron ring, and such components are widely distributed in the fruit of *Schisandra* and the vines and stem of *Kadsura Kaempf*. The lignans C6 and C9 contained in this family often have better anti-human immunodeficiency virus and antitumor activities with hydroxyl or esterified substituent groups.[36] In summary, we found that the compounds with the traditional curative effects in *Schisandraceae* plants tend to be those that are more primitive, whereas the novel activities are often found in the compounds with a higher degree of evolution.

Berberidaceae

Berberidaceae contains 14 genera and 650 species, of which 10 genera and 320 species are found in China, mainly in the northern temperate zone and subtropical high mountain areas.[37] This family is an important group of medicinal plants; almost all genera and most species are of medicinal value. The rigorous study of berberines revealed a correlation between the pharmacophylogeny, the chemical composition, and therapeutic effect. According to Airy Shaw's classification system, *Berberidaceae* is broadly divided into 4 related families: *Nandinaceae*, *Berberidaceae*, *Leonticaceae*, and *Podophyllaceae*.[38] The most controversial issues in this system are to upgrade the single genus *Nandina* Thunb. and classify the woody genera *Berberis* L. and *Mahonia* N., as well as the herbaceous genera *Epimedium* L. and *Vancouveria* C. into the narrow *Berberidaceae*, since the herbaceous and woody genera are closely related. *Berberidaceae* plants are rich in chemical components, and most of related compounds have great similarities. It mainly includes components such as benzyl isobenzylquinoline, podophyllotoxin lignan, quinolizidine alkaloid, icariin flavonoid, coumarins, and other flavonoids. *Berberis* L. and *Mahonia* N. plants in *Berberidaceae* are important raw material sources of berberine, and both contain dibenzylisoquinoline alkaloids. In addition, the curative effects of them are very similar. Modern pharmacological studies have shown that the alkaloids often have antibacterial, antiphlogistic, cholagogic, antihypertensive, immune-promoting, and antiarrhythmic effects.[39] In terms of the traditional curative effect, *Berberis* L. has the effects of heat-clearing and detoxifying, removing dampness, and is mainly used for the treatment of dysentery, gastroenteritis, conjunctival congestion, swelling, and pain.[40] *Mahonia* N. has the functions of heat-clearing and detoxifying, and is also used for treatment of the same conditions.[41] Li, et al[42] used polyacrylamide gel electrophoresis and polymerase chain reaction (PCR)-direct sequencing to analyse the peroxidase isozyme and internal transcribed spacer sequence of ribosomal DNA in 7 populations of 3 species of *Berberis* L. The experimental results showed that there were 11 peroxidaseisozyme bands, of which 3–6 were from 3 populations of *Berberis tsienii* T.S. Ying, 3–4 from 3 populations of *Berberis weiningensis* T.S Ying, and 2–3 from 1 population of *Berberis wilsonae* Hemsl. Different species have unique band characteristics, which can be used as an auxiliary basis for species identification. Cluster analysis of the isozyme level and ITS sequence showed that *Berberis weiningensis* T.S. Ying. and *Berberis wilsonae* Hemsl. were closely related. In addition, plants of the same family and different genera have the same curative effect, for example, *Dysosma* and *Diphylleia* (anti-viral effect), *Peoniaceae* and *Cynanchum* (anti-inflammatory effect), *Epimedium* and *Vancouver* (anti-aging effect), have very similar chemical compositions and close relationships.

Developments and Future Directions

In summary, the discipline of pharmacophylogeny has emerged in response to the general trend for subject integration. It is expected that under the guidance of CM theory, multidisciplinary comprehensive research will be conducted using new concepts, new methods, and innovative technologies to promote the theoretical construction and practical application of CM resources and better support the modernisation of CM. For example, although the active ingredients of some medicinal plants have been elucidated, the content is insufficient. Thus, new resources with high content can be sought in plants that are close pharmaphylogenetic relatives. *Maytenus hookeri* Loes. of *Phyllostachidaceae* has a good anticancer effect, but with a low content of the active ingredient maytansine. Some scholars have also isolated maytansine from the congeneric plant *M. buchananii* and *Putterlickia verrucose* from the same family.[17] In addition, as an important part of CM, ethnic medicines, including Mongolian, Tibetan, Uigur, and Zhuang medicines, can yield unique effects on many common diseases and intractable diseases (cardiovascular disease, nervous system diseases, liver disease, hemopathy and dermatosis).[43,44] However, the complexities of ethnic medicine materials have restricted its modernisation. The optimum starting point is the application of pharmacophylogeny to the various systematisation of ethnic medicine materials.[45,46] In addition, pharmacophylogeny also plays an important role in the conservation of medicinal plants. It provides theoretical and methodological support for the determination of conservation objects, the composition and analysis of medicinal components of medicinal plants, and the search for new medicinal plants. Furthermore, pharmacophylogeny can be combined with biogeography to study the origins of medicinal plants, thus providing a solid foundation for the conservation of medicinal plants.

Pharmacophylogeny is a multi-dimensional interdisciplinary subject focused on the related plants and pharmacophylogenomics, rather than a closed single discipline.[47] This study is expanding and the knowledge pedigree is rapidly and continuously increasing. Therefore, new interdisciplinary knowledge and techniques need to be integrated in the proposed study to promote the development of pharmacophylogeny.[16] To produce innovative research in pharmacophylogeny, the following future perspectives should be developed. Firstly, the organic combination of experimental taxonomy, molecular taxonomy, quantitative taxonomy, and modern computer technology to objectively reflect the relationship between taxonomic groups.[48] At the same time, a suitable mathematical model should be selected to establish a CM network that reflects the pharmacophylogenetic relationships.[49] Secondly, modern analytical methods, gas chromatography, high performance liquid chromatography, gas chromatography-mass spectrometer, and liquid chromatography-mass spectrometer, should be combined with cluster analysis to establish the chemical and biological fingerprints of CM to explore the similarity of phytochemical components in various groups and the distribution law of chemical components.[50] Modern drug screening technology, high-throughput screening system, ultra-high-throughput screening system, gene chip technology, combinatorial chemistry, genomics, biological information, and computer drug screening technology are used to screen medicinal plants on a large scale. We should summarize the relationship between the traditional curative effect and the modern pharmacological effect, to establish the relationship between plant system and curative effects, big data of active ingredients, biological activities and curative effect.[51] Finally, multidisciplinary information on plant physiology and biochemistry, genomics, proteomics, and metabolomics may be integrated through the network to analyse the plant kinship relationship indicated by the huge amount of information in the intelligent database.[52] All these technologies and efforts, particularly pharmacophylogeny, are crucial to unlock the full medical potential of CM.

In conclusion, there should be a relatively uniform standard for the definition of kinship, the selection of research materials, and experimental design. In addition to clarifying the morphology of the coexistence of different biological species and phenotypic traits, the plant physiology, the biochemical, molecular systematics, genomic, proteomic and metabolomic comprehensive analysis of pharmacophylogeny recognition mechanisms will be the next phase of the research. This research will help to reveal the main methods of kin recognition, material selection, and plant discovery to enable the study of the mechanisms, development and contents of traditional medicines.

Conflict of Interest

There are no conflicts of interest.

Author Contributions

Xiao PG and Li MH conceived the structure of article. Gong X, Yang M, He CN, Bi YQ, and Zhang CH searched the literature. Gong X, Yang M and Bi YQ wrote the paper. He CN and Zhang CH reviewed and edited the manuscript. All authors read and approved the manuscript for publication.

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