

# Treating Chronic Wounds Using Photoactive Metabolites: Data Mining the Chinese Pharmacopoeia for Potential Lead Species<sup>#</sup>



## Authors

Francesca Scotti<sup>1</sup>, Linru Mou<sup>1</sup>, Chen Huang<sup>1</sup>, Anthony Booker<sup>1,2</sup>, Caroline Weckerle<sup>3</sup>, Caroline Maake<sup>4</sup>, Michael Heinrich<sup>1</sup>

## Affiliations

- 1 Research Group “Pharmacognosy and Phytotherapy”, UCL School of Pharmacy, London, UK
- 2 Research Centre for Optimal Health, School of Life Sciences, College of Liberal Arts and Sciences, University of Westminster, London, UK
- 3 Institute of Systematic and Evolutionary Botany, University of Zürich, Zürich, Switzerland
- 4 Institute of Anatomy, University of Zürich, Zürich, Switzerland

## Correspondence

Prof. Michael Heinrich  
Research Group “Pharmacognosy and Phytotherapy”,  
UCL School of Pharmacy, Univ. London  
29–39 Brunswick Sq., London WC1N 1AX, UK  
Phone: + 44 20 77 53 58 44  
m.heinrich@ucl.ac.uk

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Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

## Correspondence

Dr. Francesca Scotti  
Research Group “Pharmacognosy and Phytotherapy”,  
UCL School of Pharmacy, Univ. London  
29–39 Brunswick Sq., London WC1N 1AX, UK  
Phone: + 44 20 77 53 58 44  
francesca.scotti@ucl.ac.uk

## ABSTRACT

Efficient wound treatment that addresses associated infections and inflammation remains one of the big unmet needs, especially in low- and middle-income countries. One strategy for securing better healthcare can be using medicinal plants if sufficient evidence on their safety and therapeutic benefits can be ascertained. A unique novel opportunity could be photo-enhanced wound treatment with a combination of light-sensitive plant preparations and local exposure to daylight. Data mining strategies using existing resources offer an excellent basis for developing such an approach with many potential plant candidates. In the present analysis, we researched the 535 botanical drugs included in the Chinese pharmacopoeia and identified 183 medicinal plant species, 82 for treating open wounds caused by trauma and 101 for inflammatory skin conditions. After further screening for reports on the presence of known photoactive compounds, we determined a core group of 10 scientifically lesser-known botanical species that may potentially be developed into more widely used topical preparations for photodynamic treatment of infected wounds. Our predictive approach may contribute to developing a more evidence-based use of herbal medicines.

<sup>#</sup> Dedicated to Prof. Dr. Otto Sticher on the occasion of his 85th birthday.

## ABBREVIATIONS

|      |  |
|------|--|
| CNKI | China National Knowledge Infrastructure        |
| CP   | Pharmacopoeia of the Peoples Republic of China |
| TCM  | traditional Chinese medicine                   |

## Introduction

Diverse concepts and strategies have driven the search for novel treatment options based on medicinal plants. Natural product isolation, building libraries, and their subsequent screening have been one “classical” approach [1,2], as have been ethnopharmacological ones generally focusing on small collections of often lesser-known species [3] and subsequent screening. There have been continuous efforts to develop strategies for a more stringent and evidence-based preselection, based, for example, on specific chemical parameters and rules (in the case of natural product screening or the frequency of use in ethnopharmacology). Individual species, especially those already available as herbal medicinal products, continue to be developed, often with a vision for a more evidence-based practice [4]. However, little attention has been paid to the existing generally published information on the use of medicinal plants, based on the pre-existing evidence in larger datasets and its systematic exploration. Here we explore such a strategy focusing on potential new methods for treating infected wounds based on the information available in the Pharmacopoeia of the People’s Republic of China [5].

## Wound treatment

The effective treatment of chronic wounds is one of the major unmet medical needs in healthcare. There is a considerable body of literature available on applying Chinese medicinal plants for the treatment of wounds. With over 2000 years of documented use, TCM has formed a unique system of medicine for the diagnosis and treatment of disease [6]. It heavily relies on plant-based medicines, with nearly 1000 medicinal plants recorded in ancient books and documents as main therapeutic agents. TCM has vast and untapped potential for evidence-based therapy [7] and modern therapeutic agents, with the CP [5] being a resource well worth exploring in more detail.

Wound healing is the physiological process of restoring the integrity of the skin and/or mucosae after trauma [8] Both ancient documents and modern TCM literature report medicinal plants recommended for their wound treatment properties. Medicinal plants and their active metabolites may positively stimulate or support the wound-healing process using different mechanisms. They can strengthen the interaction between various cells and growth factors on the wound surface, enhance the oxidative metabolism of the activated immune cells at the wound site, improve local microcirculation, affect the pH of the wound, help keep the wound moist, influence trace elements on the wound surface, and improve the expression ratio of type III and type I collagen to promote wound healing [9]. In addition, antibacterial, antiviral and antifungal effects will provide support in wound treatment. Clearly, there are potential risks associated with such uses, an as-

pect that also calls for a detailed assessment of the potential and limitations of such interventions.

The CP, which is based on the theoretical concepts of TCM, distinguishes between 2 major types of wounds: wounds caused by physical trauma (like traumatic bleeding, insect and snake bites, burns, bruises, gouges, and frostbites) and inflammation-related wounds (including ulcerations, hemorrhoids, dermatitis, eczema, psoriasis, ringworm, and skin infections). Much of the previous research in this area has focused on the plants’ anti-inflammatory, antimicrobial, and circulatory properties, as reported in the CP. A recently proposed strategy for identifying lead extracts and metabolites for novel topical treatments is the search for light-absorbing metabolites in species used traditionally in wound treatment, as we had detailed recently [10]. Medicinal plants combining antimicrobial and photoactivity could be reasonable candidates for photo-enhanced wound treatment, further developing photodynamic therapy (PDT) [11,12]. The screening of the CP [5] for plants used in TCM for wound treatment and displaying both antimicrobial and photodynamic activity seems a suitable novel strategy to identify species for potential clinical application of PDT.

## Photoactivity

It is well known that certain medicinal species contain photosensitizers (PSs), light-sensitive molecules that may have evolutionary evolved as part of the plant’s defense system against pathogens and herbivores [13,14]. A very well-investigated example of a herbal PS is hypericin, a perylenequinone found in the flowers and leaves of Hypericaceae (the St. John’s Wort family), which may cause pronounced skin photosensitivity (e.g., in grazing animals) [15]. Other plant-derived PSs may belong to chemical classes of furanocoumarins, polyacetylenes, xanthenoids, anthraquinones, porphyrins, thiophenes, curcuminoids, or phenalones [16]. However, not all of these are likely to be suitable candidates due to well-known phototoxic effects and the potential absence of photosensitizing effects.

Generally, the effects of PSs after light-activation may be clinically exploited for PDT, which has shown very promising outcomes in the treatment of wounds in animals and humans, including chronic conditions such as ulcers as well as for keratosis [11,12].

PDT has been developed in Europe from the beginning of the twentieth century and is now clinically approved worldwide as a modality against different types of cancer [17]. By attacking vital cellular components like nucleic acids, proteins, and lipids, photosensitizers may damage cells to the extent that eventually induces cell death mechanisms and locally destroy the illuminated PS-bearing tissue [16].

## The role of PDT in wound treatment

It has been observed that with certain “mild” PDT conditions (e.g., low photosensitizer and/or low light doses), photodynamic actions may not cause cytotoxicity but rather result in repair processes. The exact mechanisms of action responsible for PDT-promoted wound healing are not completely clear yet. However, they have been reported to relate to the proliferation and activation of wound-associated fibroblasts and the induction of acute inflam-

mation with subsequent recruitment of immune cells and secretion of growth factors that remove damaged cells and promote the healing process, respectively [11, 12].

However, in cases of wounds infected with microbes, such as chronic wounds that are prone to difficult-to-treat infections, PDT may additionally exert beneficial activities since, with different natural and synthetic PSs, it had been shown to successfully kill microorganisms, including bacteria, viruses, fungi, and protozoa [18]. Especially given emerging clinical problems with multi-drug-resistant bacteria, approaches such as PDT that work on drug-resistant strains and do not seem to generate resistance themselves are urgently needed. While the underlying mechanisms of antimicrobial PDT are not fully resolved for all pathogenic species, it had been proposed that it may target bacterial cell walls and/or nucleic acids and may even be effective on bacterial biofilms that are often inaccessible for common drugs [19–21]. Many *in vivo* wound treatment studies have focused on *Staphylococcus aureus*, one of the major culprits of wound infections, as well as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [11, 12].

## Aims and Objectives

By researching the CP [5] with a data mining approach, this analysis aims to identify medicinal plant species with known wound healing, anti-inflammatory and antimicrobial effects that may be combined with photodynamic protocols. In order to identify novel light-sensitive leads, the focus is on scientifically lesser-known plant species that, if known, contain compounds with absorbance maxima in the range of 250–500 nm. Our analysis comprises the first step to develop new concepts for treating wounds, especially in low and middle-income countries.

## Methods

In general terms, the data-mining approach followed 3 steps, which sequentially helped narrow down the list of species that have promising potential. Monographs are included in this paper. The approach was not strictly systematic since some of the criteria used in steps 2 or 3 are based on evidence beyond purely phytochemical and pharmacological data. This includes assessing the potential of specific single compounds known from a species as a positive criterion and excluding endangered species or those whose published relevant data were considered of poor quality and low reliability.

### STEP 1: Identification of plants used in TCM to treat wounds

As the last available English edition of the CP (2015 ed.) constitutes the official modern TCM repository, it was screened for plants used to treat wounds (caused by external factors [e.g., cuts, ulcers]) and inflammatory skin conditions or infections (e.g., eczema, psoriasis). The inclusion criteria comprise ailments reported in the CP such as bites (often insect and snake bites), traumatic bleeding, bruises and gouges, ulcerations, burns, measles, hemorrhoids, eczema, dermatitis, ringworm, skin infections, skin rashes, psoriasis.

### STEP 2: Selection of plants that contain classes of metabolites known to have potential photoactivity

The literature was searched for the included species to collect information on their metabolites, using first the CP, then CNKI – 中国知网 (the official and most comprehensive scientific database in China, also covering studies that do not come from peer-reviewed sources including secondary sources [e.g., publications by Schools of TCM]), PubMed, and Science Direct.

Based on this information, the list was narrowed to species reported to contain classes of compounds considered of particular relevance for photoactivity, as listed by Siewert and Stuppner (2019), namely alkaloids, furanocoumarins, polyacetylenes, xanthenoids, anthraquinones, porphyrins, thiophenes, curcuminoids, and phenalenones [16].

### STEP 3: Level of evidence

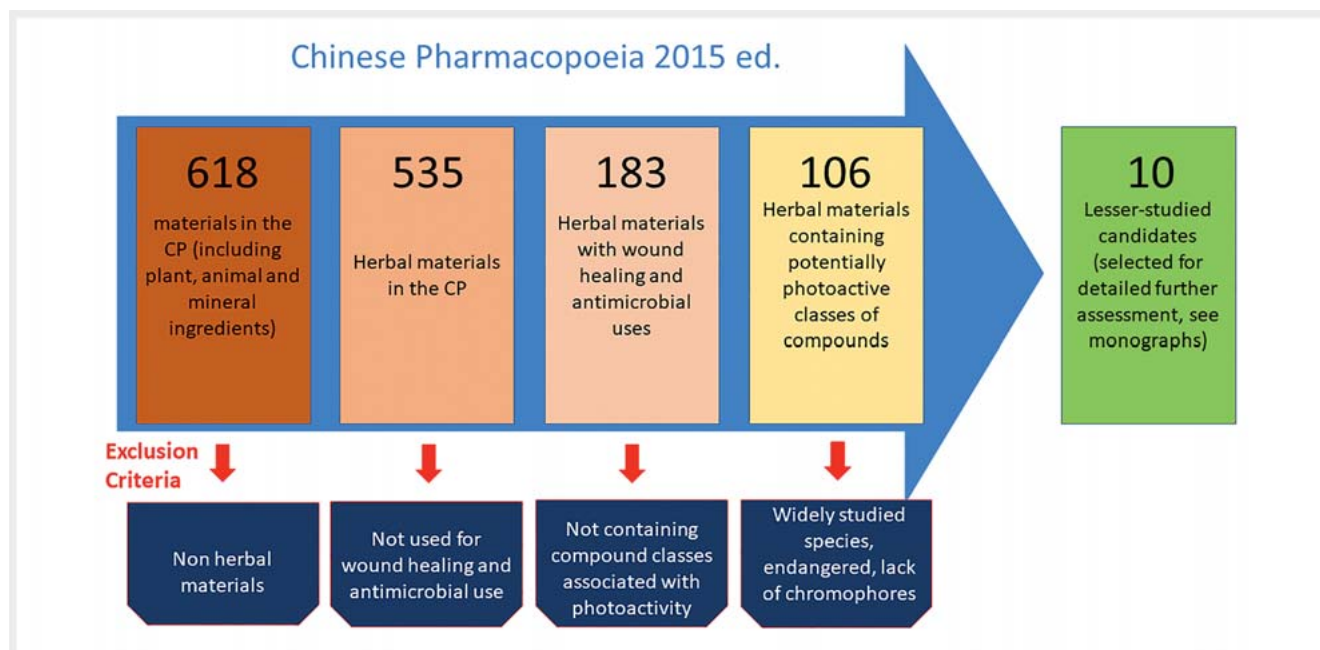
In this step, “well-studied” species were excluded based on the level of evidence available in the literature (more than 20 hits on PubMed and/or 500 hits on CNKI). At this stage, species identified as endangered were excluded and, in the case of herbal materials containing only alkaloids as compounds of interest (see step 2), based on the structural information published (when available), the lack of a chromophore was used as an exclusion criterion for the species.

Following these steps, information obtained from the literature on chemical composition, *in vivo* and *in vitro* pharmacology, clinical evidence, toxicity, and safety was critically evaluated for the selected species (see Results).

## Results and Discussion

Among the 618 medicinal materials/entries/ingredients recorded in the CP, 535 are botanical drugs from 624 medicinal plant species, 376 genera, and 132 plant families [5]. Of these, 183 medicinal plant species are indicated for wound treatment. Included are species used to treat open “traumatic wounds”. These may result from injuries where an external force has caused a trauma that led to a break in the skin tissue—from lacerations to bruises, burns, and abrasions. Also included are species indicated to treat inflammation-related wounds (including dermatitis, skin rash) and other related changes in physiological and biochemical conditions in the body.

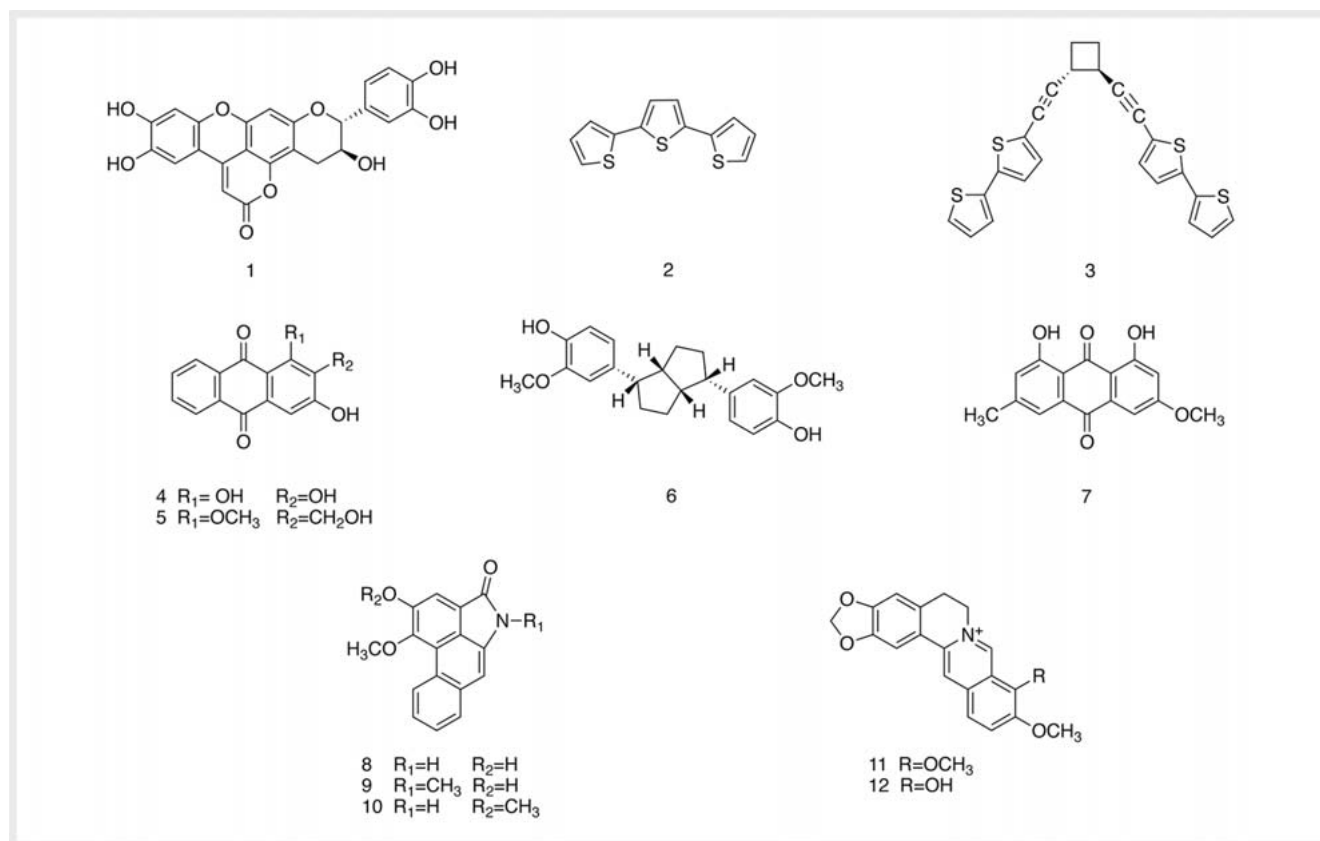
In the CP, among the 183 medicinal plant species used in wound treatment, there are 112 species that, based on the presence of some metabolites (see step 2 in Methods for the list of classes considered of interest), could show potential photoactivity (see supplementary Table 1S for the complete list). Among these species, those with the lowest number of literature hits (see step 3 in Methods) were further evaluated on a case-by-case basis. This led to the exclusion of endangered species (e.g., *Psammosilene tunicoides* W.C.Wu & C.Y.Wu), do not contain known chromophore-bearing structures, or showed problems relating to the evidence base available, including poorly conducted studies. After applying the exclusions, there was a list of 10 species of interest (see ► Fig. 1 and Table 1). The selected herbal candidates were then critically evaluated concerning their potential for wound treatment, based on the chemical, pharmacological, and toxico-



► **Fig. 1** Flow chart—the overarching strategy for the data mining approach.

► **Table 1** Species selected for this analysis for their applicability in the treatment of traumatic wounds and inflammatory skin conditions.

| Drug                            | Botanical source   | Family        | Plant part used        | Use                                       | Preparation  |
|---------------------------------|--|---------------|------------------------|---|--|
| Bistortae Rhizoma               | <i>Bistorta officinalis</i> Delarbre   | Polygonaceae  | Dried rhizome          | Insect or snake bites                     | Decoction, poultice                                  |
| Conyzae Herba                   | <i>Eschenbachia blinii</i> (H.Lév.) Brouillet  | Asteraceae    | Dried aerial part      | Traumatic bleeding                        | Decoction, poultice                                  |
| Echinopsis Radix                | <i>Echinops humilis</i> M.Bieb. <i>Echinops grijisii</i> Hance                         | Asteraceae    | Dried root             | Dermatitis, skin rashes                   | Decoction  |
| Knoxiae Radix                   | <i>Knoxia roxburghii</i> subsp. <i>brunonis</i> (Wall. ex G.Don) R.Bhattacharjee & Deb | Rubiaceae     | Dried tuberous root    | Dermatitis                                | External application, internally in pills and powder |
| Polygalae japonicae Herba       | <i>Polygala japonica</i> Houtt.  | Polygalaceae  | Aerial parts           | Insect or snake bites, bruises and gouges | Decoction, powder, poultice                          |
| Polygoni perfoliati Herba       | <i>Persicaria perfoliata</i> (L.) H.Gross  | Polygonaceae  | Aerial parts           | Insect or snake bites                     | Decoction, lotion poultice                           |
| Saururi Herba                   | <i>Saururus chinensis</i> (Lour.) Bail.  | Saururaceae   | Dried aerial parts     | Dermatitis, eczema                        | Poultice   |
| Semiaquilegiae Radix            | <i>Semiaquilegia adoxoides</i> (DC.) Makino  | Ranunculaceae | Dried root             | Insect or snake bites                     | Decoction  |
| Siphonostegiae Herba            | <i>Siphonostegia chinensis</i> Benth   | Orobanchaceae | Dried aerial parts     | Traumatic bleeding                        | Decoction, powder                                    |
| Trachelospermi Caulis et Folium | <i>Trachelospermum jasminoides</i> (Lindl.) Lem.                                       | Apocynaceae   | Dried stem with leaves | Bruises and gouges                        | Decoction  |



► Fig. 2 Sample metabolites, with potential relevance.

logical evidence available in published literature, and short monographs were produced for each of them.

### Bistortae Rhizoma

*Bistortae rhizoma* consists of the roots of *Persicaria bistorta* (L.) Samp. (syn: *Polygonum bistorta* L., Polygonaceae). In the CP, *B. rhizoma* is designated for clearing heat and detoxifying, reducing swelling, and stopping bleeding. It is indicated for diarrhea, fever, cough, scrofula, mouth and tongue sores, hemorrhoids, and snake and insect bites. *B. rhizoma* shows a prominent cardiovascular protective [22], antimicrobial [23–25], anti-inflammatory [26], antitumor [27], and analgesic effects [28].

According to Wang et al., a total of 158 metabolites have been identified from *B. rhizoma*, including 78 from its essential oil [29]. Other metabolites include organic acids, flavonoids, phenolic acids, and alkaloids. In the CP, gallic acid is used as a quality marker in TLC. The most typical metabolites are 5-glutinen-3-one and catechin with anti-oxidation and anti-inflammatory activities, respectively [29].

Liu et al. (2006) tested the antibacterial effects of ethanol extracts of *B. rhizoma* and bistortaside A (absorbance maxima at 214, 253, and 279 nm); gallic acid (absorbance maximum at 269 nm in an acidic environment); and **1** (► Fig. 2), mururin A, a flavonolignan with absorbance maxima between 220 and 393 nm [23,30]. Both total ethanolic extract and the individual compounds showed different degrees of inhibition on *S. aureus*,

*E. coli*, *Bacillus subtilis*, *Bacillus proteus*, *Enterobacter aerogenes*, *P. aeruginosa*, and *S. pneumoniae*, with gallic acid having the strongest bacteriostatic effect [23–25].

The plant has also shown anti-inflammatory activity that has been linked to the presence of 5-glutinen-3-one and friedelanol. In the carrageenan-induced rat paw edema model, 2 fractions obtained from the 70% ethanol extract showed a significant inhibitory effect on the rat paw edema. The effect was similar to that of positive control indomethacin [26]. After structural analysis, the 2 fractions consisted respectively of 5-glutinen-3-on and friedelanol [26].

Anthraquinones, a well-known class of photoactive compounds, have been isolated from different *Polygonum* species, including *Persicaria* (formerly *Polygonum*) *bistorta*. Included among them are the widely known emodin, chrysophanol, and aloe-emodin [31,32]. The latter has a photo yield [ $\Phi\Delta$ ] of 0.54 (MeCN, 355 nm) with an absorbance maximum of 430 nm [33].

No data on toxicity and clinical data on wound treatment activity is available for *B. rhizoma*.

### Conyzae Herba

*Conyzae herba* is the dried aerial part of *Conyza blinii* H.Lév (syn: *Conyza dunniana* H.Lév., Asteraceae). *C. Herba* is recorded in the CP to treat lung inflammation, cough, excessive phlegm, throat pain, dental ulcer, jaundice, and traumatic bleeding. *C. Herba* has anti-inflammatory effects on chronic bronchitis [34], anti-ulcer ef-



fects on gastric ulcers [35], and antitumor and bacteriostatic effects [36,37].

The main metabolites are diterpenoids and triterpenoids, including saponins, the latter accounting for 1.6% to 3% of the metabolites in *C. Herba* [36]. The diterpene blinin, isolated by Yang et al. in 1989, is a marker substance for *C. Herba* in the CP, with the content of blinin not being less than 0.3% [38]. Other metabolites include alkenynes, flavonoids, sterols, phenylpropanoyl esters, lactones, tannins, coumarins, essential oil, and organic acids [36].

The aqueous extract of *C. Herba* had a significant inhibitory effect on Gram-positive bacteria, including *S. aureus* and *B. subtilis*, with a minimum inhibitory concentration (MIC) of 12.5 mg/mL and 50 mg/mL, respectively [37]. However, no relevant effects on Gram-negative bacteria were recorded [37].

Some potentially relevant pharmacological effects of the drug if used internally have also been reported. Su et al. applied pyloric ligation-induced acute gastric ulcer in rats to test the anti-ulcer effect [39]. The results suggested that the ethanol extract of *C. Herba*, at the dose of 50 mg/kg, significantly reduced the size of the ulcer and the content of malondialdehyde (MDA) in the gastric mucosal tissue. Further studies by Ma and Liu indicated a protective effect against gastric ulceration [39,40]. *C. Herba* can be used to treat chronic bronchitis [34].

Qi et al. tested acute toxicity on mice, guinea pigs, and cats for *C. Herba*. For intragastric administration in mice, the value of LD<sub>50</sub> measured was 508 mg/kg, and the maximum tolerance was 315 mg/kg [41]. The LD<sub>50</sub> was 140 mg/kg for guinea pigs, and the maximum tolerance was 82 mg/kg. The drug was given to guinea pigs by intraperitoneal injection [41]. The maximum tolerance for cats was 25 mg/kg [41]. The LD<sub>50</sub> of the total saponins from *C. Herba* was 1.29 g/kg [42].

## Echinopsis Radix

*Echinopsis radix* is the dried root of *Echinops davuricus* Fisch. ex Hornem. (syn: *E. latifolius* Tausch., Asteraceae) or *Echinops grijsii* Hance, and both species are accepted as sources of the botanical drug. Importantly, before 1995, the CP did not distinguish between *E. radix* and *Rhapontici radix* (from *Leuzea uniflora* [L.] Holub., syn.: *Rhaponticum uniflorum* [L.] DC.), which were collectively recorded as *Rhapontici radix*.

According to the CP, *E. radix* can be used to clear heat, detoxify the body, promote lactation, reduce breast swelling and pain, and treat carbuncles, skin rash and treat tuberculosis. The photoactive thiophene  $\alpha$ -terthienyl is used as a chemical quality marker in the CP [43]. Thiophenes have absorption maxima in the 314–350 nm range [16].

*E. radix* contains thiophenes, flavonoids, terpenes (triterpenes and sesquiterpenes), alkaloids, steroids, and fatty acids, as well as lignans, lactones, amides, and coumarins [44,45], who have been reported for a variety of activities, including antiviral, antitumor, antifungal, anti-inflammatory hepatoprotective [46], and antibacterial [44].

The antiviral activity of  $\alpha$ -terthienyl (2; ► Fig. 2) specifically required 320–400 nm wavelength for activation [47], which is lower than the preferred wavelengths (around 600 nm) for therapeutic applications. A variety of thiophenes has been isolated from *E. radix*, including 5-(but-3-en-1-ynyl)-2,2'-bithiophene,  $\alpha$ -ter-

thienyl, cardopatine (3; ► Fig. 2), and 5-acetyl-2,2'-bithiophene [48], which when photoactivated have antiviral and cytotoxic effects [43]. Irradiation of  $\alpha$ -terthienyl and its 15 analogs with near-UV light showed antiviral and cytotoxic effects on murine mastocytoma cells and murine cytomegalovirus while in the dark, only 5 analogs were cytotoxic and 1 was antiviral [43]. A study reported that under irradiation at 320–400 nm,  $\alpha$ -terthienyl had antiviral activity against the human immunodeficiency virus, while in the dark or visible light, this activity was nonexistent or not apparent [47]. Under UVA radiation,  $\alpha$ -terthienyl inhibited the growth rate of *Microsporum cookei* [49], which can cause dermatophytosis such as tinea capitis. In addition, recently, 3 bithiophenes with interesting dimeric structures—echinbithiophene dimers A, B, and C, isolated from *E. davuricum*—showed significant activity against different phytopathogenic fungi and 1 nematode, especially echinbithiophene dimer A, which is comparable to the positive control, carbendazim [50].

Hong et al. studied the influence of the extraction method on the antibacterial effect of a total polysaccharide fraction isolated from the ethanol extract of *E. radix*. The fraction showed the strongest antibacterial effects on *P. aeruginosa* [51]. The decoction of *E. radix* inhibited *B. subtilis* with a MIC of 0.25 g/mL and *S. aureus* and *P. aeruginosa*, both with MIC of 0.5 g/mL [44]. In addition, Li et al. compared the antibacterial effect of different fractions of the ethanolic extract. The ethyl acetate fraction and *n*-butanol fraction had a bacteriostatic effect on *S. aureus*, *E. coli*, *S. enterica*, *B. subtilis*, and *P. aeruginosa* [52].

Li et al. assessed the anti-inflammatory effect of an ethanol extract of *E. Radix*. The total ethanol extract at the dose of 2.5 g/kg significantly affected xylene-induced ear swelling in mice, reducing the swelling by one-third [52]. The chloroform fraction had the strongest effect, with an inhibition of 64% at the dose of 0.023 g/kg, while the inhibition rate by aspirin was 40.8% [52]. The decoction of *E. radix* also has an anti-inflammatory effect, as shown by Shuo et al. using xylene-induced ear swelling in mice and formaldehyde-induced paw edema in mice [44]. Lin et al. suggested that the main anti-inflammatory fraction of the ethanolic extract of *E. radix* was the chloroform-soluble fraction, which had a significant effect on carrageenan-induced paw edema in mice [53]. The decoction (2.50 g/kg, 5.00 g/kg) inhibited xylene-induced ear swelling in mice and reduced the number of writhing times caused by acetic acid in mice ( $p < 0.05$ ). The decoction (2.50 g/kg) exerted an anti-inflammatory effect on mice foot swelling caused by formaldehyde ( $p < 0.05$ ) [54]. This suggests that *E. radix* has good anti-inflammatory and analgesic effects.

*E. radix* is a promising candidate in the context of PDT, considering the photoactive thiophenes as potential PSs. However, there is no clinical evidence regarding its topical application on wounds nor any studies assessing adverse events.

## Knoxiae Radix

*Knoxiae radix* is the dried root of *Knoxia roxburghii* subsp. *brunonis* (Wall. ex G. Don) R. Bhattacharjee & Deb (Rubiaceae). In the CP, it is listed under its synonym *Knoxia valerianoides* Thorel ex Pitard. with uses to treat carbuncles and sores, as a purgative and anti-ulcer agent, as well as to dislodge phlegm.

The main bioactive metabolites of *K. radix* include anthraquinones, triterpenoids, lignans, coumarins and sitosterones [55, 56]. Several anthraquinones, well-known photoactive compounds, have been isolated. Among them are rubiadin (4; ► Fig. 2) and damnacanthol (5; ► Fig. 2) [57], with  $[\Phi_{\Delta}] = 0.34$  ( $\text{CHCl}_3$ , 377 nm), absorbance maximum = 410 nm, and  $[\Phi_{\Delta}] = 0.31$  ( $\text{CHCl}_3$ , 377 nm), absorbance maximum = 350 nm, respectively [58]. In the CP, 3-hydroxymorindone and lucidin are TLC-based quality markers. Two fractions of the ethanolic extract of *K. radix* showed antiviral activity on Coxsackievirus B3, an enterovirus, with  $\text{IC}_{50}$  values of 19.24  $\mu\text{M}$  and 11.11  $\mu\text{M}$ , and one of them also inhibited influenza virus A/Hanfeng/359/95 with an  $\text{IC}_{50}$  value of 11.11  $\mu\text{M}$  [57]. It was reported that the 50% ethanol extract of *K. radix* has significant inhibitory effects on *E. coli* K88 and hemoclastic *E. coli* at a concentration of 0.5 g/mL, while water extracts did not exert any significant effect [59].

In assessing the acute toxicity of both the water and alcohol extract of *K. radix*, no mice died at any of the administered dosages (24.6 to 60.0 g/kg) [60]. Eyes and skin irritation tests were carried out in the same study. The water and alcohol extracts were applied into rabbits' eyes respectively and rinsed after 2 min. No sign of edema and hyperemia was observed in the eye areas [60]. A wound was cut in the shape of '#' on one side of the rabbit's spine, then 0.1 mL of the extract was applied to the wound for 4 hours. The wound did not worsen, and no edema occurred, which indicated that both extracts were nonirritating to rabbit eyes and skin [60]. It needs to be highlighted that such assessments are of ethical concern and, most likely, also of limited scientific value.

In the Chinese Compendium of Materia Medica (a monograph written by Li Shizhen in the Ming dynasty), it is reported that the combination of *Knoxia valerianoides* and *Glycyrrhiza radix* should be avoided, as it can be toxic. While some preliminary data point to potential toxicity [61], the CP suggests that *K. radix* has low toxicity, and no obvious acute and subacute toxicity have so far been reported [62].

### Polygalae japonicae Herba

*Polygalae japonicae herba* is the dried aerial part of *Polygala sibirica* L. (syn: *Polygala japonica* Hoult., Polygalaceae). Based on the CP, *P. japonica* is used to treat cough, excessive phlegm, throat pain and swelling, snake and insects bite, traumatic wounds, and sebaceous glands suppurate.

Saponins are the main metabolites of *P. japonica*, including hederagenin, tenuifolin and polygalasaponin F [63]. In the CP, polygalasaponin F is used as a quality marker, and its content should not be less than 0.6%. At present, about 54 saponins have been isolated from *P. japonica* [63]. Other metabolites include flavonoids [64], polysaccharides [65], anthraquinones (including emodin, aloe-emodin emodin-8-O- $\beta$ -D-glucopyranoside and trihydroxyanthraquinone), and xanthenes [66]. The plant has shown anti-inflammatory [67], analgesic [68], antitumor, cell-protective, anti-depressant [63], and anti-bacterial effects [69].

Li et al. tested the bacteriostatic effect of an oral decoction with *P. japonica* as its main ingredient. The experiment utilized 20 mice infected with *S. aureus*. Ten Mice were given the preparation by intragastric administration, and 10 were administered

water as a control. After 24 h, all the mice in the control group died, while the 6 mice in the drug treatment group survived (17.5 g/kg) [70]. This result suggests that the oral decoction may improve the ability of mice to resist *S. aureus* infection [70].

The anti-inflammatory effect of *P. japonica* has been widely reported. In one study, the total saponin fraction isolated from fermented *Polygalae japonicae herba*, which was administered intragastrically (6 g/kg) for 5 consecutive days, significantly inhibited xylene-induced ear swelling in mice with an inhibition rate of 42.5%, while that of the positive control indomethacin was 64.6% [68]. The total saponin (6 g/kg) also significantly inhibited the acetic acid-induced vascular permeability in mice with an inhibition rate of 44.7% [68]. In addition, Liu et al. investigated its analgesic effect. The total saponin fraction significantly reduced acetic acid-induced writhing numbers in mice at the dose of 6 g/kg [68]. Two sucrose esters, tenuifolioside B and  $\beta$ -D-[3-O-(3,4,5-trimethoxycinnamoyl)]-fructofuranosyl- $\alpha$ -D-[6-O-(4-methoxybenzoyl)]-glucopyranoside from the root of *P. japonica*, inhibited the nitrite and PGE2 production in LPS-stimulated BV2 microglia cells with  $\text{IC}_{50}$  ranging from 11.7 to 22.5  $\mu\text{M}$  [67]. This result suggests that these 2 metabolites may be of interest for further research on neuroinflammatory diseases.

Mashed fresh *Polygalae japonicae herba* was applied topically to the wounds of 6 patients with a snake bite, without including a control group. The wounds' redness and swelling disappeared after 4 days, and the patients recovered after 7 days [71].

Yuan et al. performed an acute toxicity test by intraperitoneal injection on mice with an  $\text{LD}_{50}$  of 32 g/kg [69]. Zhu et al. determined the acute oral toxicity of total saponins in *Polygalae japonicae herba* at the highest dose of 13.3 g/kg by intragastric administration in mice. The authors did not observe death in the mice after 7 days [72].

### Polygoni perfoliati Herba

*Polygoni perfoliati herba* is the aerial part of *Persicaria perfoliata* (L.) H. Gross. (Polygonaceae), and it is listed under its synonym *Polygonum perfoliatum* L. in the CP. *Polygoni perfoliati herba* is used as pectoral, and it is used in TCM, as described in the *Wanbing Huichun* (1615 A.D.), as a compress to treat snake and insect bites, as an aqueous decoction applied topically as a wash in cases of eczema, and as a water or wine decoction taken orally to alleviate the symptoms of other skin diseases.

More than 80 metabolites with anti-inflammatory, antibacterial, anti-hemorrhage and other activities have been isolated, including flavonoids, anthraquinones (including emodin, emodin methyl ether and aloe-emodin [73]) [74, 75] (for their photoactivity, see *B. rhizoma*), terpenoids, phenolic acid, and alkaloids [76, 77]. In the CP, quercetin is used as the quality marker using TLC. Some metabolites isolated from *Polygoni perfoliati herba* are useful to differentiate *P. perfoliata* from other plants in the Polygonaceae family. Homoisoflavanones have only been isolated from *P. perfoliata* and other 2 *Polygonum* species [78]. Two different sesquignans have been isolated from *P. perfoliata* and *P. orientale* L., respectively, one with a 2,6-di-(substituted aryl)-cis-3,7-dioxabicyclo[3.3.0] octane skeleton and one with a tetrahydrofuran-9,9'-monoepoxy lignan structure [78]. 8-Oxo-pinoresinol (6, ► Fig. 2; another 2,6-diaryl-cis-3,7-dioxabicyclo[3.3.0] octane

lignan) was isolated from *P. perfoliata*, and it has not been reported from other species of *Polygonum* yet [78].

As early as 1978, in China, some scholars recorded the therapeutic effect of *P. perfoliatum* on *Herpes zoster* [79]. The ethanolic extract of *P. perfoliatum* exhibited antiviral activity on *Herpes simplex virus-1* (HSV-1), with a viral inhibition rate of 78% [76]. This rate was close to that of the positive control, acyclovir, which was 82% [76].

The 75% ethanol extract of *Polygoni perfoliati herba* was shown to have a strong inhibitory effect on *S. aureus* (MIC =  $5 \times 10^{-2}$  mg/mL), *P. aeruginosa* (MIC =  $10 \times 10^{-2}$  mg/mL), *B. subtilis* (MIC =  $10 \times 10^{-2}$  mg/mL), and *Proteus* (MIC =  $5 \times 10^{-2}$  mg/mL) [80]. The ethyl acetate extract and *n*-butanol extract also had a strong inhibitory effect on *B. subtilis* and *P. aeruginosa* [80]. In addition, the ethyl acetate extract also inhibits the growth of fungi, such as *Candida albicans* with MBC = 0.49 g/mL [77].

In a recent study, a mouse skin wound model demonstrated the therapeutic effect of the water decoction of *P. perfoliatum* on wounds [81]. The mice were given the decoction by intragastric administration before cutting a wound on the soles of their paws. Both the decoction and the positive control dexamethasone had anti-inflammatory effects, but the former accelerated wound healing while the latter slowed it down. In this study, the percentage of wound area at different times was used as the standard to measure the degree of wound healing.

Several studies have shown the anti-inflammatory properties of *Polygoni perfoliati herba*. In a single cohort clinical study with no control group, by Ling, Fang, and Yang (2010), the decoction of *Polygoni perfoliati herba* was used topically to treat hemorrhoids with a healing rate of 92.5% [82]. The ethanol extract reduced the xylene-induced auricle swelling in mice by 82% compared to 62% for aspirin as the positive control [77]. The ethanol extract of *P. perfoliatum* could reduce the contents of prostaglandin E2 and interleukin 24 in the inflammatory tissue in the mice toe swelling model induced by carrageenan with a dose of 5 g/kg [83]. Additionally, quercetin-3-O- $\beta$ -D-glucuronide isolated from *P. perfoliatum* had a stronger anti-inflammatory effect on dimethyl benzene-induced mice ear edema than aspirin [84].

In an acute toxicity test in mice, *Polygoni perfoliati herba*, formulated as capsules, did not show any obvious acute toxicity ( $p > 0.05$ ), as no deaths were recorded and major physiological functions were not altered, except for a decrease of activity within 1 h from administration [85].

*Polygoni perfoliati herba* has shown antiviral, bacteriostatic, anti-inflammatory, and hepatoprotective effects [76]. It is often applied clinically in TCM to treat skin diseases of viral origin and inflammatory gynecological conditions [76]. The bacteriostatic, antiviral, and anti-inflammatory effects might support its use in wound treatment, as suggested by the recent results of Du et al. [81]. A preliminary clinical study points to a reduction of the wound area and a shortening of the wound treatment time in traumatic infected wounds [86], but more detailed pharmacodynamic and clinical research is needed.

## Saururi Herba

Saururi herba is the dried aerial part of *Saururus chinensis* (Lour.) Baill. (syn: *Saururopsis chinensis* [Baill.] Turca., Saururaceae). In

the CP, Saururi herba is recorded to treat edema in the body and dysuria; as a topical application, it is recommended for infected suppurative skin and eczema.

An essential oil and many metabolites have been isolated from Saururi herba, including lignans, flavonoids, polysaccharides, polyphenols, terpenes [87], anthraquinones (including emodin and physcion, 7, ► Fig. 2), and aristolactam alkaloids (8, 9, and 10 where the latter, cephalenone B, has an absorbance maximum in methanol at 384 nm; ► Fig. 2) [88]. The lignans, including saucarnetin and sauchinone, were the main bioactive metabolite [89]. Sauchinone is used as a quality marker in the CP, with a minimum content of 0.1%. Flavonoids are another abundant class consisting mainly of flavonols and their glycosides, including lutein, quercetin and hyperoside [90].

Saururi herba has hepatoprotective [91], central nervous inhibiting [92], anti-inflammatory [93], blood sugar-regulating [94], antitumor [95], antiviral [96], and antibacterial [97] effects. A 70% ethanol extract and a water extract of Saururi herba are bacteriostatic on *S. aureus* [97]. The water extract (8 g/kg) of Saururi herba significantly inhibited the xylene-induced ear swelling and cotton ball implantation-induced granuloma in mice by 36% and 22%, respectively [93]. The water extract (8 g/kg) also significantly inhibited acetic acid-induced writhing numbers in mice and raised the pain threshold of hot plated-induced pain in mice [93].

A formula with Saururi herba as the main ingredient had an inhibitory effect on skin itching caused by phosphoric histamine [98]. Wang and Zhou applied the formula lotion to the trimmed back of guinea pigs, and then 0.2% phosphoric histamine was injected subcutaneously. The inhibition rate of the lotion was 26%, compared to 34% for the positive control fluocinolone acetonide [98].

The water extract, essential oil, and 95% ethanol extracts of the aerial parts and roots were tested for acute toxicity in mice, with only the ethanol extracts showing toxicity [99]. The LD<sub>50</sub> of 95% ethanol aerial part extract and root extract were 3.15 g/kg and 17.15 g/kg, respectively [99].

## Semiaquilegiae radix

Semiaquilegiae radix is the dried root of *Semiaquilegia adoxoides* (DC.) Makino (Ranunculaceae), as listed in the CP.

In the clinical application of TCM, a decoction of *Semiaquilegiae radix* is used to treat carbuncles, scrofula, mastitis, snake bite, tumor, and nephropathy [100]. *Semiaquilegiae radix* can be combined with *Lonicerae Japonicae flos*, *Violae herba*, *Chrysanthemi indici flos*, and *Taraxaci herba* in a formula named Wu Wei Xiao Du Yin (toxin dispersing beverage) to treat acne [101, 102]. Lithospermoside and griffonilide are used, by the CP, as quality markers for the herbal material. *Semiaquilegiae radix* contains alkaloids, lactones, cyanogenic glycosides, phenolic acids, and at least one nitro compound [103].

Photoactive alkaloids are considered the main antibacterial active ingredients. Liu and Ji isolated berberine (11) and berberrubine (12) from *Semiaquilegiae radix* [104]. The 2 metabolites had bacteriostatic effects on some bacteria affecting plants, such as *Ralstonia solanacearum*, *Erwinia carotovora* pv. *Carotovora*, and *Pseudomonas syringae* pv. *actinidiae*. The 2 alkaloids inhibit various



bacteria and fungi; berberine has antifungal effects on *C. albicans*, *Cryptococcus*, and dermatophytes [105]. Berberrubine has a good inhibitory effect on *E. aerogenes*, *E. coli*, *Shigella castellani*, and methicillin-resistant *S. aureus* [106]. Wang et al. (2003) tested the bacteriostatic effects of water decoction of the “toxin dispersing beverage” formula and each plant in this formula. *Semiaquilegiae radix* showed the best effects on *P. aeruginosa* among the 5 herbal ingredients of the formula and was also active against *S. aureus* [102].

Lithospermoside and griffonilide serve as quality markers and have also shown anti-inflammatory activity. They inhibit xylene-induced ear swelling in mice with the dosage of 50 mg/kg, and griffonilide, in particular, can inhibit inflammation by up to 64% [107].

Berberine and berberrubine are known photoactive alkaloids. Berberine has previously been experimentally applied in PDT for cancer treatment [14], showing an absorbance maximum of 420 nm [108], and berberrubine has shown an absorbance between 300 and 516 nm depending on the choice of solvent and pH [109].

No toxicity data is available, but there is a single major adverse event report from 2002 (trance and trembling potentially ascribable to idiosyncrasy), using the previously mentioned quintaherbal formula “toxin dispersing beverage” [110].

## Siphonostegiae Herba

*Siphonostegiae herba* consists of the dried aerial part of *Siphonostegia chinensis* Benth. (Orobanchaceae). According to the CP, *Siphonostegiae herba* is mainly used to treat hemorrhage, bruise, abnormal menstruation, edema, and other diseases related to blood circulation. It is mostly used externally on wounds (including the juice obtained by crushing fresh plants), prepared as a decoction or soaked in yellow wine and taken orally to treat trauma.

It contains essential oil, flavonoids, alkaloids, and lignans [111]. In the CP, luteolin and acteoside are quality markers with minimal contents of 0.05% and 0.06%, respectively.

The pharmacological activities of *Siphonostegiae herba* include hepatoprotective effects, antiplatelet aggregation, choleragogue, removing blood stasis, and antimicrobial action [111].

A decoction of *Siphonostegiae herba* showed bacteriostatic effects on *S. aureus*, *Bacillus anthracis*, group B *Streptococcus*, *Corynebacterium diphtheriae*, *Salmonella typhi*, *P. aeruginosa*, and *Shigella dysenteriae* [111].

Mice were given a drug decoction (10 mL/kg) by intragastric administration to assess whether it promotes blood circulation using the clotting time via the angular vein method [112]. It prolonged the clotting time ( $250.3 \pm 94.4$  s) compared with the normal saline group ( $133.40 \pm 16.6$  s). In addition, its effect on thrombosis in rats was determined. Measurements of the length of the clot showed that the water decoction made it shorter than the normal saline group [112].

In the acute toxicity test, mice were given a single liquid injection at a dosage of 130 g/kg. The intervention resulted in mild diarrhea in a small number of mice, but none died; this compares to using 30 g in humans in clinical settings. Assuming 50 kg for an adult patient,

this suggests that *Siphonostegiae herba* is safe in the clinical application as the maximum tolerable dose is over 200 times higher than that used in humans [113].

## Trachelospermi Caulis et Folium

*Trachelospermi caulis et folium* are the dried leafy stems of *Trachelospermum jasminoides* (Lindl.) Lem. (Apocynaceae). In TCM, *Trachelospermi caulis et folium* is used to clear heat, remove edema, treat swelling and painful throat, and relieve muscle spasms and injuries [114]. In other TCM documents, like *Jiangxi Herbal Medicine* (Revolutionary Committee of Health Bureau of Jiangxi Province, 1970), *Trachelospermi caulis et folium* is used as a powder for external use and soaked in wine for oral use to treat skeletal-muscular pain, open wounds, and bleeding. It is classed as having compatibility with myrrh and licorice, among others, for treating sores.

Metabolites isolated from *Trachelospermum caulis et folium* mainly include flavonoids, lignans, triterpenes, alkaloids, anthraquinones (including emodin) [115, 116], and steroids [117]. One triterpene, tracheloside, is used as a quality marker in the CP, with a minimum amount of 0.45% [114]. Five indole alkaloids bearing chromophores with potential photoactivity were isolated from the leaves and stems, including coronaridine, voacangine, apparicine, conoflorine, and 19-epi-voacangarine [118].

Anti-fatigue, antioxidative, antitumor, anti-inflammatory, analgesic, sedative, and hypnotic effects have been reported [114, 119–121]. The hot plate method and acetic acid writhing method were used [122, 123] to determine the analgesic effect of *Trachelospermi caulis et folium* after intraperitoneal injection or intragastric administration in mice [122, 123]. The total flavonoids extracted from *Trachelospermi caulis et folium* water extract raised the pain threshold of hot plate reaction in mice and reduced writhing. The total flavonoids inhibited ear swelling and toe swelling in mice [123].

Apparicine has demonstrated potential in treating gout by inhibiting xanthine oxidase *in vitro* with an  $IC_{50}$  of 0.65  $\mu$ M, while the positive control allopurinol had an  $IC_{50}$  of 0.60  $\mu$ M [124]. It is worth noting that voacangine has shown antiangiogenic activity both *in vitro* and *in vivo*, which could be detrimental while treating wounds [125].

The existing literature focuses on its antifatigue, sedative, antitumor, antioxidative, and hypolipidemic effects. Studies on antibacterial activity are lacking. Overall research on *Trachelospermi caulis et folium* is very limited and lacks clinical data.

## Future Research on Plants Identified as Potential Leads for PDT Therapies

This data-mining study explored the CP to identify potential leads for developing PDT-based herbal medicinal products for wound treatment. Candidate species were selected based on their traditional use in TCM for diseases (as defined in the context of the CP) that could be linked to antimicrobial properties and the treatment of different types of wounds/skin inflammation. The candidates were then assessed ethnopharmacologically based on the existing chemical, pharmacological, and toxicological evidence, including

species that can be used based at least in part on photoactive metabolites. The species were identified using a combination of criteria as defined above. However, this approach requires integrating information from different categories of data—phytochemistry, photoactivity, pharmacology/microbiology—and, in many cases, very limited information is available on the photoactivity of the metabolites. When available, such information is for single compounds, while the specific aim of the wider project is to identify easy-to-use extracts as potential leads. Such leads can then be developed into preparations with a clearly defined profile of quantified marker compounds. Importantly, the activity may well be a combination of effects of different (classes of) compounds with or without photoactivity.

In this data mining step, we had to take a broad perspective, looking at classes of compounds that contain well-known photoactive compounds (as defined, for example, by Siewert and Stuppner (2019) [16]). We decided to focus on lesser-known species since these may offer the greatest chemobiological potential. In the next steps, a detailed chemical characterization combined with an assessment of the extracts' and compounds' photo and pharmacological activity will be required. Those with the most promising activity profile will be further assessed in more mechanistic *in vitro* and *in vivo* models.

## Conclusion

After a systematic assessment of the 618 medicinal materials (botanical ones and other drugs derived from natural sources) included in the CP, we identified 10 species that may be relevant for future studies on photodynamic treatments of infected wounds. In more general terms, the approach used here offers a novel strategy to base the primary selection of species on an empirical basis using existing large-scale datasets, such as the CP. This analysis does not consider the Chinese traditional medical concepts and is not in a strict sense based on TCM concepts.

Further steps of this research will assess target species to make easy-to-prepare extracts available as a low-cost first aid intervention in lower- and middle-income countries. In this context, the project is not about “drug discovery” in the sense of identifying “new” compounds but developing phytotherapeutic preparations with the extract being the active agent (i.e., a therapy based on the combined effects of different classes of natural products—a *planta medica*). In the later stages of the project, defined production processes and methods for quality control will be required. However, if found, new single photoactive compounds would not be excluded and may well be another outcome of the later stages of this project.

Data mining is proposed here as a strategy for systematically and rationally selecting species to be assessed pharmacologically. Existing datasets with albeit preliminary evidence are used as a basis for selecting species to be investigated experimentally on different targets and diseases. This approach offers a broader basis in terms of chemo-biodiversity, and thus, we expect that it would be much more likely to successfully enable the development of herbal medicinal interventions, which are efficient and safe to use, provided that the material can be sourced sustainably based on access and benefit agreements, as required.

## Supporting Information

A list of the botanical drugs from the CP that, based on some metabolites, could show potential photoactivity (Table 15) is provided as supporting information.

## Contributors' Statement

M.H. designed the study and supervised the project including an MSc dissertation by CH and an MRes dissertation by LM, who gathered the data and provided an analysis. F.S. contributed to the design and the supervision of LM and led in the analysis of the chemical data. A.B. contributed aspects esp. relating to plant sciences and ethnopharmacology, C.W. on the taxonomy and botany, C.M. on photodynamic aspects. All authors read the MS and approved the final version.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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