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REVIEW

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# Topical and transdermal botanical formulations of the Chinese pharmacopoeia—A review

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## Abstract

In pharmaceutics, ingredients are classified as active ingredients and excipients. In topical/transdermal phytomedicines, an ingredient may serve both functions. Published information on these dual-purpose ingredients and their pharmacological relevance is limited. An intriguing scenario arises in traditional Chinese medicine (TCM) formulations, where active ingredients and excipients are undifferentiated. This study analyzes ingredients in TCM topical/transdermal formulations, aiming at harmonization of understanding of TCMs. The most commonly recorded ingredients from such formulations in the Chinese pharmacopoeia 2020 (ChP 2020) are reviewed, aiming at developing innovative topical/transdermal phytomedicines. Current editions of Chinese historical documents were reviewed to explore the principles underlying the use of these ingredients. TCM formulations containing botanical drugs for topical/transdermal application were selected from the ChP 2020. The use of botanical materials in TCM formulations is guided by the "Jun-Chen-Zuo-Shi" principle rooted in Yin-Yang and the five elements' theories. In the ChP 2020, 155 botanical drugs, along with 40 excipients (from the "procedure" section, focusing on processing and technical parameters), were identified from 34 botanical formulations intended for topical/transdermal application. Pungent and aromatic botanical materials were the most frequently recorded. Adhesive plasters were the most commonly recorded TCM dosage form, employing specific matrix blends. This new perspective of study reveals the prevalence of pungent and aromatic botanical materials, the common use of adhesive plasters, multifunctional properties of botanical oils, and formulation adaptability in TCM topical/transdermal products. These insights should inform novel formulation designs for both pharmaceutical and phytopharmacological research.

**KEYWORDS**
botanical formulation, Chinese pharmacopoeia, ingredient, topical, transdermal

## 1 | INTRODUCTION

The focus of medicinal plant research has mostly been on the pharmacological and medical properties of botanical extracts and their metabolites, including their uses in traditional medicine and often as a part of drug discovery programs (Atanasov et al., 2021; Dias et al., 2012). Topical and transdermal routes offer numerous advantages over delivery via the conventional systemic approaches, including localized drug administration, higher drug concentration at target sites, avoidance of degradation in the gastrointestinal tract, prevention of first-pass metabolism in the liver, attainment of constant plasma levels, and noninvasiveness with easy application (Leppert et al., 2018; Marwah et al., 2016; Punjataewakupt et al., 2019). Consequently, topical application of medicinal plant preparations has become a research strategy, that is receiving increasing attention. A number of topical botanical formulations, such as Atrogel® Arnica Gel and Rowiren® cream, have been granted traditional herbal registration (THR) as herbal medicines and have been available on the UK market for some years.

However, simply investigating the pharmacological and medical properties of the active ingredient is insufficient for developing appropriate topical formulations. Understanding the optimal selection of excipients and the interactions among ingredients is also critical for designing topical formulations. Given the lack of detailed reviews on such excipients and ingredients, this work aims to provide a comprehensive overview offering new insights from both the perspectives of phytotherapy research and pharmaceutics.

In traditional Chinese medicine (TCM), medicinal plants have a long history of external use. Presently, the Chinese pharmacopoeia (ChP) provides extensive records of botanical formulations. The ingredients utilized in topical and transdermal botanical TCM formulations present a vast database for such a review. However, the ChP shows conceptual and ultimately philosophical differences compared with pharmacopoeias in other countries (Leong et al., 2020). Thus, this review also requires a careful assessment of the terminologies employed in the ChP. To achieve this, a better understanding of the framework of TCM is necessary by delineating the historical background of TCM. Therefore, this review also represents a first step toward attempting to harmonize the different pharmacopoeial approaches.

### 1.1 | Aim of the review

The differences between botanical formulations in China and European countries should not be overlooked in research. Consistency and coherence are necessary for regulating the quality, safety, and efficacy of pharmaceutical products. This review aims to disentangle the underlying reasons contributing to such differences. The overarching objective is to reach a harmonized understanding of the topical and transdermal botanical formulations in China, with a TCM background.

Focusing on the historical and culture background of TCM, this review aims to gain an understanding of the principles guiding the use of botanical ingredients in TCM's topical/transdermal formulations.

This paper focuses on topical/transdermal formulations sourced from plants. It aims to provide a broad overview of ingredient usage of such formulations in the ChP 2020. Hence, this review explores both the pharmacologically active constituents and excipients utilized in topical/transdermal botanical TCM formulations.

### 1.2 | Definition of the terms "botanical drug(s)" and "ingredients"

The term "botanical drug(s)" refers to raw or processed botanical materials originating from plants, including plant parts, plant exudates, botanical extracts, and enriched fractions derived from these drugs, which contain both pharmacologically active and inactive metabolites. Since the classification into medicines versus cosmetics/supplements/medical devices depends on national and regional regulations, here we use the term "botanical drug" irrespective of any accepted uses as a medicine or as it relates to pharmacological activities reported. The description "Natural product(s)" is not used in this review, because of the ambiguous use of the term and the inclusion of other materials such as animals and minerals.

The term "ingredients," used in formulations from a botanical source, covers botanical drugs and excipients. They can be identified from both the "Ingredients" and "procedure" section of the ChP 2020. The "ingredients" section lists the botanical drugs used in the formulation, including raw or processed botanical materials, botanical extracts, and metabolites derived from them. The combination of botanical materials listed in this section is called the TCM formula. The processing of botanical materials in the TCM formula, including steaming, fermenting, and boiling in specific extraction solvents prior to formulation, is typical for Chinese medicine but not reported in European, American, and other pharmacopoeias. The "procedure" section describes the main processing steps and necessary technical parameters, and generally defines the name of the extraction solvent, steps for extraction, separation, concentration, and drying as well as necessary conditions. The ingredients used in the "procedure" section are considered inactive and contribute solely to the product formulation.

### 1.3 | Definition of the terms "topical delivery" and "transdermal delivery"

Given that the ChP and the European Pharmacopoeia (Ph. Eur.) do not explicitly define "topical delivery" and "transdermal delivery," the United States Pharmacopoeia (USP) is referred to here. According to the USP-NF <1151> (2021) and <3> (2023), topical delivery is defined as drug products applied to the external surface of the body with the intent to achieve a local effect of the drug, where local action can occur at or on the surface of the application site (e.g., stratum corneum), in the underlying tissues (e.g., epidermis and/or dermis), and in subcutaneous tissues (e.g., muscle or joint). Transdermal delivery is defined as the application of formulations to the external surface of the body where the drug substance passes through the dermal layer into the bloodstream to achieve a systemic effect.

## 1.4 | Drug regulation in China today

The National Medical Products Administration (NMPA) is the drug regulatory authority in China, and is also responsible for regulating cosmetics. The NMPA Drug Search (National Medical Products Administration, 2023) and Pharmacopoeia of the People's Republic of China (ChP) are two databases under the control of the NMPA for pharmaceutical products available in the Chinese market.

The NMPA Drug Search (National Medical Products Administration, 2023) provides information on registered drugs in China, including botanical formulations. This database is regularly updated and provides comprehensive information on registered drugs in China, including their indications, dosages, routes of administration, and manufacturers. Thus, the NMPA drug search database allows users to search for information on drugs that have been approved for marketing in China, which includes botanical formulations. Details of the botanical source, indications, dosage forms, and manufacturers of these botanical formulations are provided. However, the NMPA drug search database does not provide a product list. Obviously, all drugs, including botanical formulations, that are approved for marketing in China are required to meet certain quality and safety standards set by the NMPA. However, it is still possible that some products on the market may not meet these standards. The NMPA has established a system of post-market surveillance and monitoring to ensure the safety and efficacy of drugs on the market (Liang et al., 2021).

By comparison, the ChP is the official compendium of standards for crude/processed drugs, botanical extracts, and formulations used in TCM, including botanical formulations. It provides detailed information on their quality, purity, as well as therapeutic uses and effects. The ChP is used as a reference for regulatory purposes in China. The ChP does not provide a comprehensive list of all approved botanical formulations that are currently on the pharmaceutical market in China. However, to be included in the ChP, a botanical formulation must meet certain criteria, such as having a long history of reported safe and effective use in TCM and having been subjected to extensive testing and research to demonstrate its safety and efficacy (Scotti et al., 2021). Thus, the inclusion of a botanical formulation in the ChP is based on a thorough evaluation of the scientific evidence available concerning its safety and efficacy.

## 1.5 | A comparison between the ChP and the Ph. Eur.

A comparison between the ChP and the Ph. Eur. with reference to the information recorded in the monographs is detailed in Figures 1.1 and 1.2.

Botanical formulations, such as the Daiwenjiu plaster from the ChP and Arnica tincture from the Ph. Eur., are selected as examples for comparative purposes. The Daiwenjiu plaster is used to warm meridians, dissipate cold, and relieve pain. Arnica tincture is used to relieve bruises, sprains, and strains. Both monographs have similar information for identification and tests, as well as character/description. Compared with the Ph. Eur., the monograph in the ChP additionally includes information on actions, indications, administration, dosages, and storage. Clear differences can be found between the information recorded in the "ingredients" section of the ChP and the "content" (under the "definition") section of the Ph. Eur. The ChP places more emphasis on the botanical materials used, while the Ph. Eur. highlights the active (or marker) compound of the formulation. The ChP also gives a detailed description of processing botanical materials into a formulation in the "procedure" section, while the Ph. Eur. shows a rather simplified description in this "production" section.

**Daiwenjiu Gao**
**(代温灸膏)**
Daiwenjiu Plaster

**Ingredients** Capsici Fructus; Cinnamomi Cortex; Zingiberis Rhizoma Recens; Cinnamomi Oleum.

**Procedure** Pulverize Capsici Fructus, Cinnamomi Cortex and Zingiberis Rhizoma Recens to coarse powders. Macerate with ethanol three times, 24 hours for the first time, 72 hours for the second time and 48 hours for the third time, filter. Combine the filtrates and concentrate to a thick extract with relative density of 1.30-1.35 (70℃), add the plaster base made from rubber, zinc oxide, rosin etc, mix well with Cinnamomi Oleum to produce adhesive matter. Spread the adhesive matter on the tape, cut into sections, cover with liner, and cut into small pieces.

**Description** Orange yellow pieces of rubber plaster; odour, aromatic.

**Identification** (1) Macerate overnight 6 pieces, removed from the coating and cut into strips with width of 1 cm, in 50 ml of ethanol in a stopper conical flask, and filter. Evaporate the filtrate at 60-70℃ on a water bath to dryness, and dissolve the residue in 2 ml of ethanol as the test solution. Dissolve cinnamic aldehyde CRS in ethanol to prepare a solution containing 1 μl per ml as the reference solution. Carry out the method of thin layer chromatography 〈0502〉, using silica gel G as the coating substance and a mixture of petroleum ether (60-90℃) and ethyl acetate (17 : 3) as the mobile phase. Apply separately 2 μl each of the above two solutions to the plate. After developing and removal of the plate, dry in air. Spray with dinitrophenylhydrazine TS. The spot in the chromatogram obtained with the test solution corresponds in position and colour to the spot in the chromatogram obtained with the reference solution.

(2) To 6 pieces, removed from the coating, add 20 ml of chloroform, dissolve the ointment base by stirring, add 30 ml dehydrated ethanol, solidify the ointment base by stirring, allow to stand for 10 minutes, filter. Repeat the above operation with chloroform and dehydrated ethanol, combine the filtrate and evaporate to dryness. Dissolve the residue in 2 ml of dehydrated ethanol, centrifuge. Apply the supernatant to the column of C18 SPE (300 mg). Elute with 5 ml water and 5 ml 30% methanol in turn, discard the eluates. Then Elute with 5 ml 70% methanol, collect the eluates as the test solution. Dissolve capsaicin CRS in methanol to produce a solution containing 30 μg per ml as the reference solution. Carry out the method for high performance liquid chromatography 〈0512〉, use octadecylsilane bonded silica gel as the stationary phase and a mixture of acetonitrile and 0.1% phosphoric acid (45 : 55) as the mobile phase. Maintain the temperature of the column at 35℃. As detector a spectrophotometer set at 270 nm. The number of theoretical plates of the column is not less than 3000, calculated with reference to the peak of capsaicin. Inject accurately 10 μl of each of the two above solutions into the column. The retention time of the peak in the chromatograph obtained with the test solution corresponds to that in the obtained with the reference solution.

**Plaster content** Not less than 1.7 g per 100 $cm^2$. 〈0122, *method 1*〉, using ether as the solvent.

**Other requirements** Comply with the general requirements for adhesive plasters of cataplasms 〈0122〉.

**Determination of ethanol-soluble extractives** Measure the area of two pieces, removed from the cover liner, cut into pieces, to a stopper conical flask, add 50 ml of dehydrated ethanol, stopper tightly, and macerate for 16 hours, filter, wash the container and residue with three 10-ml of dehydrated ethanol, combine the washings with the filtrate in a evaporating dish, dried to constant weight, evaporate to dryness on a water bath at 60-70℃, dry the residue in a desiccator for 3 hours, weigh accurately, and calculate. It contains not less than 0.20 g per 100 square centimeter.

**Actions** To warm the meridians, dissipate cold and relieve pain.

**Indications** *Bi* disorders due to wind-cold stagnation, manifested as cold pain in the waist, back, joints and limbs; Coldness and pain in the epigastrium and abdomen, deficiency cold and diarrhea due to cold damaging the stomach and spleen; Chronic rheumatoid arthritis and gastroenteritis with the symptoms described above.

**Administration and Dosage** For topical administration. Apply a plaster on the acupoints according to the symptoms.

**Storage** preserve in tightly closed containers, stored in a cool place.

**FIGURE 1.1** Sections in the monograph of a botanical formulation in the ChP (Chinese Pharmacopoeia Commission. (2015). Pharmacopoeia of the People's Republic of China (English version). China Medical Science Press, Beijing, China [in Chinese].). * The copyright for the content in this figure is held by the publisher of the monograph.

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## ARNICA TINCTURE

### Arnicae tinctura

DEFINITION

Tincture produced from *Arnica flower (1391).*

*Content*: minimum 0.04 per cent of total sesquiterpene lactones, expressed as dihydrohelenalin tiglate ($C_{20}H_{26}O_5$; $M_r$ 346.4).

PRODUCTION

The tincture is produced from the herbal drug by a suitable procedure using 10 parts of ethanol (60-70 per cent *V/V*) for 1 part of drug.

CHARACTERS

*Appearance*: yellowish-brown liquid.

IDENTIFICATION

Examine the chromatograms obtained in the test for *Arnica chamissonis* Less. - *Calendula officinalis* L. - *Heterotheca inuloides* Cass.

*Results*: see below the sequence of fluorescent zones present in the chromatograms obtained with reference solution (a) and the test solution. Furthermore, in the chromatogram obtained with the test solution, other fluorescent zones may be present, especially in the upper third of the chromatogram.

| Top of the plate | |
|---|---|
| Caffeic acid: a blue zone | |
| | 2-4 blue zones, very faint to intense |
| ——— | ——— |
| | A blue zone, faint to equivalent |
| | A yellowish-green zone, faint |
| ——— | ——— |
| | A yellow or orange zone, faint to equivalent |
| | A blue zone, equivalent to intense |
| | A yellow or orange zone, faint |
| Rutoside: a yellow or orange zone | |
| **Reference solution (a)** | **Test solution** |

TESTS

***Arnica chamissonis* Less. – *Calendula officinalis* L. – *Heterotheca inuloides* Cass.** High-performance thin-layer chromatography (*2.8.25*).

*Test solution.* The tincture to be examined.

*Reference solution (a).* Dissolve 2.0 mg of *caffeic acid R* and 2.5 mg of *rutoside trihydrate R* in *methanol R* and dilute to 10.0 mL with the same solvent.

*Reference solution (b).* Dilute 2.5 mL of reference solution (a) to 10.0 mL with *methanol R*.

*Reference solution (c).* Dissolve 1 mg of *chlorogenic acid R* and 2.5 mg of *hyperoside R* in *methanol R* and dilute to 10 mL with the same solvent.

*Intensity markers*: caffeic acid for the blue or greenish-blue fluorescent zones and rutoside for the yellow and orange fluorescent zones.

*Plate*: *TLC silica gel $F_{254}$ plate R* (2-10 µm).

*Mobile phase*: *formic acid R, water R, ethyl acetate R* (6:9:90 *V/V/V*).

*Application*: 2 µL, as bands of 8 mm.

*Development*: 70 mm from the lower edge of the plate.

*Drying*: in a current of air at room temperature for 5 min.

*Detection*: heat at 100-105 °C for 5 min; spray the warm plate with a 10 g/L solution of *diphenylboric acid aminoethyl ester R* in *methanol R*, then with a 50 g/L solution of *macrogol 400 R* in *methanol R*; allow to dry in air for 5 min and examine in ultraviolet light at 366 nm.

*System suitability*: reference solution (c):

- the chromatogram shows in the lower third 2 distinct zones which may be partially overlapping; the lower zone (chlorogenic acid) shows a light blue fluorescence and the upper zone (hyperoside) shows a yellow or orange fluorescence.

*Results*: the chromatogram obtained with the test solution does not show an orange-yellow fluorescent zone corresponding to the blue fluorescent zone due to caffeic acid in the chromatogram obtained with reference solution (a), nor does it show an orange-yellow fluorescent zone corresponding to the zone due to rutoside in the chromatogram obtained with reference solution (a).

**Ethanol** (*2.9.10*): the final ethanol concentration is not less than 90 per cent of that of the initial extraction solvent.

**Methanol and 2-propanol** (*2.9.11*): maximum 0.05 per cent *V/V* of methanol and maximum 0.05 per cent *V/V* of 2-propanol.

**Dry residue** (*2.8.16*): minimum 1.7 per cent.

ASSAY

Liquid chromatography (*2.2.29*).

*Internal standard solution.* Dissolve immediately before use 10.0 mg of *santonin CRS* and 20 mg of *butyl parahydroxybenzoate R* in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

*Test solution.* To 5.00 g of the tincture to be examined add 5 mL of *water R* and 2.00 mL of the internal standard solution. Transfer the solution obtained to a 50 mL centrifuge tube containing 3 g of *neutral aluminium oxide R*. Rinse the flask with 2 mL of water and transfer the rinsings to the centrifuge tube. Shake for 120 s and centrifuge at 2500 *g* for 10 min. Transfer the supernatant into a 50 mL round-bottomed flask and evaporate to dryness under reduced pressure in a water-bath at a temperature not exceeding 50 °C. Dissolve the residue in 3.0 mL of *ethanol (96 per cent) R* and filter through a membrane filter (nominal pore size 0.45 µm).

*Reference solution.* Dissolve 20 mg of *ethyl parahydroxybenzoate R* and 20 mg of *methyl parahydroxybenzoate R* in *methanol R* and dilute to 10 mL with the same solvent.

*Column*:

- *size*: *l* = 0.12 m, Ø = 4 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm);
- *temperature*: 20 °C.

*Mobile phase*:

- *mobile phase A*: *water for chromatography R*;
- *mobile phase B*: *methanol R1*;

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - 3 | 62 | 38 |
| 3 - 20 | 62 → 55 | 38 → 45 |
| 20 - 30 | 55 | 45 |
| 30 - 55 | 55 → 45 | 45 → 55 |

*Flow rate*: 1.2 mL/min.

*Detector*: spectrophotometer at 225 nm and at 350 nm.

*Injection*: 10 µL of the test solution and the reference solution.

*Relative retention* with reference to santonin (retention time = about 8.2 min): methyl parahydroxybenzoate = about 0.6; ethyl parahydroxybenzoate = about 1.2; butyl parahydroxybenzoate = about 4.5.

*The assay is not valid unless*:

$$\frac{A_1}{A_2} \leq 0.05$$

$A_1$ = total area of peaks eluting between the peaks due to santonin and butyl parahydroxybenzoate in the chromatogram obtained with the test solution at 350 nm; disregard any peaks with an area less than 0.1 times the area of the peak due to santonin;

$A_2$ = total area of peaks eluting between the peaks due to santonin and butyl parahydroxybenzoate in the chromatogram obtained with the test solution at 225 nm.

*System suitability*:

- *resolution*: minimum 5.0 between the peaks due to methyl parahydroxybenzoate and ethyl parahydroxybenzoate in the chromatogram obtained with the reference solution at 225 nm.

Calculate the percentage content of total sesquiterpene lactones, expressed as dihydrohelenalin tiglate, using the following expression:

$$\frac{A_2 \times m_2 \times p \times 1.187}{A_3 \times m_1 \times 5}$$

$A_2$ = total area of peaks eluting between the peaks due to santonin and butyl parahydroxybenzoate in the chromatogram obtained with the test solution at 225 nm;

$A_3$ = area of the peak due to santonin in the chromatogram obtained with the test solution at 225 nm;

$m_1$ = mass of the tincture to be examined used to prepare the test solution, in grams;

$m_2$ = mass of *santonin CRS* used to prepare the internal standard solution, in grams;

$p$ = percentage content of santonin in *santonin CRS*;

1.187 = peak correlation factor between dihydrohelenalin tiglate and santonin.

**FIGURE 1.2** Sections in the monograph of a botanical formulation in the Ph. Eur (Council of Europe. (2022). European Pharmacopoeia 11.0. Council of Europe, Strasbourg, France.). * The copyright for the content in this figure is held by the publisher of the monograph.

Generally, the ChP records more information on the botanical origin and processing methods, but does not identify the pharmacologically active compounds as clearly as the Ph. Eur.

## 2 | METHODS

### 2.1 | Historical and cultural background of TCM

To understand the principles for ingredient selection in TCM formulas, a brief review of the history and culture of China was conducted. This was conducted by reference to a review article on TCM by Catic et al. (2018), a book chapter on Yin Yang and Wu Xing by Chen (2022), a webinar on TCM and Chinese culture by Peng (2023), and modern editions of ancient Chinese documents, including Shang Shu (尚书, Fu, 2022; Qian & Qin, 2019), Shen Nong Ben Cao Jing (神农本草经, Sun & Sun, 2018), and Huang Di Nei Jing (黄帝内经, Zhou & Fan, 2017).

Therefore, the origins and evolution of TCM theories were clarified within the context of Chinese history and philosophical culture. The establishment of guidelines for ingredient selection in TCM is discussed, along with a detailed examination of ingredient categorization in TCM formulas.

## 2.2 | Review of ingredients recorded in the ChP—Data inclusion/exclusion criteria

Topical/transdermal formulations with a botanical source were identified in the ChP (Figure 2.1). The concept of "sovereign (Jun, 君), minister (Chen, 臣), adjunct (Zuo, 佐), and envoy (Shi, 使)" in medical prescriptions suggests that in TCM there is no direct equivalent to active ingredient and excipient. A drug acting as 使 (Shi) can still have pharmacological effects but will not be as "strong" and "targeted" as a "sovereign." Cinnamomi Oleum used in DaiWenJiu Plaster, is an example. Cinnamomi Oleum is listed in the "ingredient" section as a pharmacologically active ingredient. However, it also comprises the oil phase in the formulation. Many topical/transdermal formulations used in biomedicine include substances or extracts which function both as excipients and pharmacologically active ingredients.

Therefore, the focus of this analysis needs to be on defining which ingredients in a formulation have the function of an "excipient," that is, the ingredients that only contribute to the formulation of topical/transdermal products. The "procedure" section in the ChP 2020 describes the main processing steps and necessary technical parameters, and generally defines the name of extracting solvent, steps for extraction, separation, concentration, and drying as well as necessary conditions. These procedures of producing formulations are modified based on traditional processing methods. Hence, the ingredients listed in the "procedure" sections solely contribute to the formulation of topical/transdermal products and are regarded as excipients. The detailed chemical description

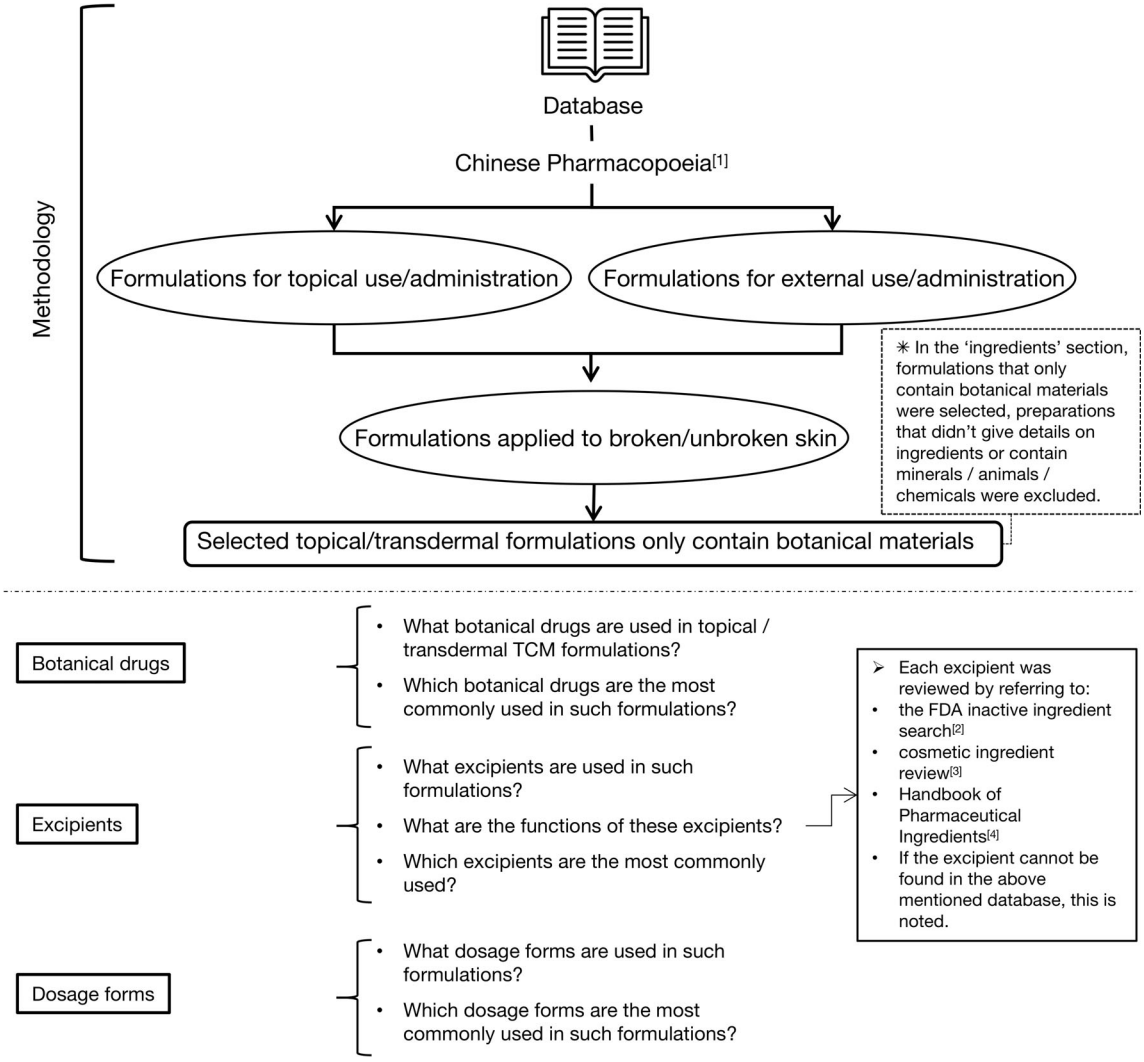


**FIGURE 2.1** Schematic diagram of methodology and criteria used for data collection. [1] Chinese Pharmacopoeia Commission. (2020). *Pharmacopoeia of the People's Republic of China*. Beijing, China: China Medical Science Press [in Chinese]. [2] [database] U.S. Food and Drug Administration. Inactive ingredient search for approved drug products. Available at: https://www.accessdata.fda.gov/scripts/cder/iig/index.cfM [Accessed 25 Oct 2023]. [3] [database] Personal Care Products Council. (2023). Cosmetic ingredient review. Available at: httPs://online.personalcarecouncil.org/jsp/IngredInfoSearchResultPage.jsp [Accessed 10 Nov 2023]. [4] Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ. (2020). *Handbook of Pharmaceutical Excipients*. 9th ed. New York, USA: American Pharmacists Association.

and cosmetic functions of excipients are also discussed, with reference to the Handbook of Pharmaceutical Excipients, Cosmetic Ingredient Review Database (CIR), and FDA inactive ingredient database.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Framework of traditional Chinese medicine

TCM has a long history of using botanical materials for medicinal purposes through various administration routes, including topical and transdermal administration (Cheng et al., 2020; Leung et al., 2016; Li et al., 2022).

Research on TCM formulations contributes to pharmacology studies, particularly in the context of development and innovation in TCM. With current science and technology, interdisciplinary studies on TCM are becoming more and more important (Li et al., 2023; Yagüe et al., 2022). Promising botanical metabolites have been found, and novel drugs are being developed (Atanasov et al., 2021; Kim et al., 2022; Nasim et al., 2022). Biomedical[1] approaches and TCM both draw conclusions from observing nature and aim to improve healthcare and specific treatments. While TCM has historically, been more focused on observational approaches and on a complex theoretical framework, in recent decades, biomedical methods have been incorporated, focusing on developing an experimental evidence-based medicine approach (Fung & Linn, 2015; Pritzker & Hui, 2012). Few current studies examine the history, culture, and philosophical principles behind TCM. Thus, this review includes a discussion of the history and culture of China, along with their connection to the principles underlying TCM. This context is important for understanding how ingredients are used in TCM formulations.

TCM theories are influenced by the four main ancient philosophical traditions/culture, Yi (易), Confucianism (儒), Taoism (道), and Buddhism (佛). The modern TCM practice is additionally driven by the socioeconomic developments in the People's Republic of China. The four main theories that contribute to the medical practice of TCM are the Yin Yang theory (阴阳理论), Wu Xing/five elements theory (五行理论), Zang Fu Jing Luo/Organs and meridian theory (脏腑经络理论), and Yao Xing/drug character theory (药性理论). These theories evolved under the influence of various ancient Chinese philosophical cultures, prevailing at different times in history. The influence of Yi (易), Confucianism (儒), and Taoism (道) to Yin Yang (阴阳) and Wu Xing (五行) theory is discussed in more detail. This provides context for the use of topical/transdermal TCM formulations and their specific ingredients. These philosophical traditions and core TCM theories originated in China, serving as the foundation for understanding TCM.

[1]Biomedicine as used in this paper refers to the science-based approaches which use a mechanistic concept of pharmacological targets and compounds acting on them in combination with the use of clinical studies, as developed over the last 50 years.

#### 3.1.1 | The origin of Yin Yang and Wu Xing TCM theories

Since Xi Zhou (around 1046 BCE–770 BCE), people follow the guidelines in "Yi Jing" (易经, written around 1046 BCE–770 BCE) to understand the world and make predictions of the future. With regards to medical practice, the guidelines in "Yi Jing" helped to understand the cause of disease, and thus guided people to find methods for treatment. "Yi Jing" started the Yi culture; it generally explains the origin, development, and relationship between Yin and Yang. This led to the Yin Yang theory in TCM. "Yi Jing" was interpreted by scholars over time from various cultural backgrounds. The current version of "Yi Jing" is considered as a historical compilation of scholars' work. This compilation demonstrates the increasing interpretation, development, and use of Yin and Yang theory in numerous aspects of daily life. The Wu Xing/five elements theory originated later than the Yin Yang theory. The concept of Wu Xing is firstly recorded in "Shang Shu" (尚书, around 1046 BCE–551 BCE):

> '水火者，百姓之所饮食也；金木者，百姓之所兴作也；土者，万物之所资生也，是为人用。..... 五行，一曰水，二曰火，三曰木，四曰金，五曰土。水曰潤下，火曰炎上，木曰曲直，金曰從革，土曰稼穡。'
> (Fu, 2022; Qian & Qin, 2019).

> Water and fire are what people drink and eat. Metal and wood are what people use to make things. Earth is where everything grows. These five materials are of vital use to human... Wu Xing/five materials are water, fire, wood, metal and earth. Water has the character of moisturizing and flowing downward. Fire has the character of hot, warm and going upwards. Wood possesses the characteristics of growth, flexibility, and the ability to bend and stretch. Metal has the character of withstanding severe conditions and can be refined and shaped into a sharp weapon with various forms. Humans cultivate and harvest grains on the earth. Earth possesses properties of birth, transformation and capacity. (translated by author: Gu)

Water, fire, wood, metal, and earth were regarded as the five most important materials for the existence of life. Through the accumulation of observations on nature throughout history, people gradually gained an understanding of the characteristics of the five elements. The five materials began to be treated as five elements for categorization, thus forming the five elements theory in TCM. Like "Yi Jing," "Shang Shu" was also interpreted by various scholars along the history. The concept of five elements was expanded and connected to the categorization of items in both the in vitro and in vivo scenarios. The relationship between the five elements was also explained. However, scholars later questioned the reliability of the current content in "Shang Shu," noting that the version of Shang Shu available today is different from its original edition.

### 3.1.2 | The influence of ancient Chinese philosophical traditions to the development of TCM theories

The emergence of academic philosophical schools such as Confucianism (儒家, proposed by 孔子—Confucius active around 500 BCE) and Taoism (道家, founded by 老子-Lao Zi, lived in 571 BCE–471 BCE) happened during the great intellectual emancipation between Dong Zhou (770 BCE–221 BCE) to the Qin Han dynasties (221 BCE–220 CE). Various academic thoughts encouraged the formation of TCM theories and guidelines. Confucius (孔子, lived in 551 BCE–479 BCE), a scholar who founded Confucianism, interpreted "Yi Jing," re-edited "Shang Shu" and proposed "the doctrine of the mean (中庸)." He emphasized the importance of taking the mean and reaching a balance. Therefore, the balance between Yin and Yang, as well as among the five elements is still considered important to maintain health. People believe that Yin and Yang are in a dynamic balance; the skew of dynamic balance between Yin and Yang is regarded as the cause of disease. The five elements have an inter-promotional and inter-restraining relationship. The over-strength or over-weakness of certain elements will break the balance among the five, also considered as the cause of disease. On the other hand, Taoism indicated that "human is an integral part of the nature, rules follow the nature, countries and people should be governed by non-interference (天人合一，道法自然，无为而治)." This indication not only advises how to govern a country and its people, but also shows the importance of treating humans and nature as an integral part. Thus, the five elements were expanded, linking to in vivo and in vitro factors as shown in Figure 3.1.

### 3.1.3 | Development of guidelines for ingredient use in TCM formulas

Under the influence of Confucianism and Taoism, the Yin-Yang and Five elements theory were interpreted and expanded. The theory of medical practice was gradually evolving; the guidelines for using ingredients in TCM formulae were also developed. Physicians, drawing from these theories, combined drugs with complementary effects to achieve desired clinical outcomes. This approach aimed to avoid adverse side effects linked to single-drug consumption, promoting balance between Yin and Yang, as well as among the Five Elements. To optimize efficacy and moderate side effects, principles were established. For allowing strategic combinations in formulae, guidelines on categorizing drugs were performed. An important guideline, structured around four hierarchical ranks—Monarch (Jun 君), Minister (Chen 臣), Assistant (Zuo 佐), and Envoy (Shi 使)—reflected the Imperial Court's hierarchy. To understand the role of ingredients used in TCM formulae, it is necessary to refer to classical Chinese medicine documents. Notably, during the Dong Zhou (770 BCE–221 BCE) to the Qin Han (221 BCE–220 CE) period, the earliest written records on TCM theory, "Huang Di Nei Jing" (黄帝内经, written between 475 BCE and 220 CE), and TCMs, "Shen Nong Ben Cao Jing" (神农本草经, written between 221 BCE and 220 CE), emerged. Ma et al., 2022 worked on verifying the relationship between the ingredients used in a TCM formula. These authors attempted to explain the relationship between Monarch (Jun 君), Minister (Chen 臣), Assistant (Zuo 佐), and Envoy (Shi 使) ingredients, based on "Shen Nong Ben Cao Jing" (神农本草经):

| Five Elements (五行) | In vivo | | | | | | |
|---|---|---|---|---|---|---|---|
| | Five Zangs (五脏) | Five Fu (五腑) | Five sense (五官) | Five body structure (五体) | Five emotion (五志) | Five body fluid (五液) | Five pulse (五脉) |
| Wood (木) | Gan/Liver (肝) | Dan/Gallbladder (胆) | Eye (目) | Jin (筋) | Anger (怒) | Tear (泪) | Xuan (弦) |
| Fire (火) | Xin/Heart (心) | XiaoChang/Intestinum tenue (小肠) | Tongue (舌) | Mai (脉) | Happy (喜) | Sweat (汗) | Hong (洪) |
| Earth (土) | Pi/Spleen (脾) | Wei/Stomach (胃) | Mouth (口) | Meat (肉) | Thoughtful (思) | Thin saliva (涎) | Huan (缓) |
| Metal (金) | Fei/Lung (肺) | DaChang/Intestinum crassum (大肠) | Nose (鼻) | Skin and hair (皮毛) | Sadness (悲) | Snivel (涕) | Fu (浮) |
| Water (水) | Shen/Kidney (肾) | PangGuang/bladder (膀胱) | Ear & Two lower orifices (耳及二阴) | Bone (骨) | Afraid (恐) | Thick saliva (唾) | Chen (沉) |

| Five Elements (五行) | In vitro | | | | | | |
|---|---|---|---|---|---|---|---|
| | Five sounds (五声) | Five flavors (五味) | Five colors (五色) | Five change (五化) | Five qi (五气) | Five direction (五方) | Five seasons (五季) |
| Wood (木) | Jue (角) | Sour (酸) | Blue (青) | Birth (生) | Wind (风) | East (东) | Spring (春) |
| Fire (火) | Zhi (徵) | Bitter (苦) | Red (赤) | Grow (长) | Heat (暑) | South (南) | Summer (夏) |
| Earth (土) | Gong (宫) | Sweet (甘) | Yellow (黄) | Transform (化) | Wet (湿) | Center (中) | Long summer (长夏) |
| Metal (金) | Shang (商) | Pungent (辛) | White (白) | Harvest (收) | Dry (燥) | West (西) | Autum (秋) |
| Water (水) | Yu (羽) | Salty (咸) | Black (黑) | Store (藏) | Cold (寒) | North (北) | Winter (冬) |

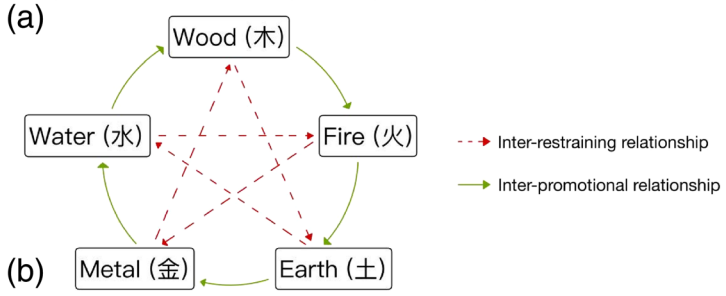


**FIGURE 3.1** (a) Five elements in the TCM theory and how they are expanded to the in vivo and in vitro factors. (b) Five elements and their inter-promotional and inter-restraining relationship. TCM, traditional Chinese medicine.

上药一百二十种，为君，主养命以应天，无毒，多服，久服不伤人。欲轻身益气，不老延年者，本上经。中药一百二十种为臣，主养性以应人，无毒，有毒，斟酌其宜，欲遏病补虚羸者，本中经。下药一百二十五种为佐使，主治病，以应地。多毒，不可久服。欲除寒热邪气、破积聚、愈疾者，本下经。...药有君臣佐使，以相宣摄合和... (Sun & Sun, 2018).

There are 120 upper-class drugs, acting as Monarch (Jun 君). They nourish life in accordance with nature, are non-toxic, and can be consumed in abundance without harming people over long periods. Those who wish to lighten the body, boost vitality, and extend their years should primarily consult this category. There are also 120 middle-class drugs, serving as Minister (Chen 臣). They nourish one's nature in accordance with human needs, and some are non-toxic while others are toxic. Their use should be carefully considered. Those aiming to counter diseases and reinforce weaknesses should refer to this category. Additionally, there are 125 lower-class drugs, acting as Assistant (Zuo 佐) and Envoy (Shi 使). They mainly address illnesses and correspond to the earth element. These drugs often possess strong toxicity and should not be used for extended periods. Those seeking to dispel pathogenic influences, eliminate accumulated blockages, and hasten recovery should refer to this category. Drugs can be classified as Jun, Chen, Zuo and Shi, working together to harmonize and balance the body. (translated by author: Gu)

On the other hand, 'Huang Di Nei Jing' (黄帝内经) states another definition for Jun, Chen, Zuo and Shi ingredients:

...方制君臣何谓也?...主病之谓君，佐君之谓臣，应臣之谓使，非上下三品之谓也。...三品何谓?...所以明善恶之殊贯也。 (Zhou & Fan, 2017).

What is the relationship among Monarch (Jun 君), Minister (Chen 臣), Assistant (Zuo 佐), and Envoy (Shi 使) in medical prescriptions?... The Jun ingredients are responsible for treating diseases. The Chen ingredients assist Jun ingredients in their pharmacological activities, just like ministers assist monarchs in politics. The Zuo and Shi ingredients follow the pharmacological activities exerted by Jun and Chen ingredients. It does not just refer to concept of Jun, Chen, Zuo, Shi in the classification of drugs into upper, middle and lower classes (as stated in 'Shen Nong Ben Cao Jing')... Why drugs need to be classified into three classes?... This is to distinguish drugs based on their level of side effects and toxicity, so as to understand the quantity of specific drugs used in medical practice. (translated by author: Gu)

These two books identify two original definitions of the Jun, Chen, Zuo, Shi ingredients. Both books laid the groundwork for ingredient selection based on the guideline: the sovereign TCM (Jun, 君) provides the therapeutic thrust; the minister TCMs (Chen, 臣) assist with the therapy; the adjunct TCMs (Zuo, 佐) moderate harshness, along with a range of other functions; the envoy TCMs (Shi, 使) either guide the sovereign TCM to the appropriate organ or have a harmonizing effect (Butler, 2022).

### 3.1.4 | Development of external treatments in TCM

The Qin and Han dynasties (221 BCE–220 CE) laid the foundation for TCM external treatments. Classic works like the "Huang Di Nei Jing" and the "Shen Nong Ben Cao Jing" initially revealed the theoretical basis of external treatments (Yin-Yang and Five Elements theory) and ingredient selection method (following the principles of Jun, Chen, Zuo, Shi compatibility). "Jin Gui Yao Lue" (金匮要略, written in around 150 CE–219 CE) further enriched external treatment methods by introducing therapies such as washing and fumigation. In later developmental stages, especially during the Song, Jin, and Yuan periods (from 960 CE to 1368 CE), works like the "Tai Ping Sheng Hui Fang" (太平圣惠方, written in 978 CE–992 CE) proposed new approaches to external treatments, and the proliferation of *materia medica* expanded the scope of external treatments. By the Ming and Qing periods (from 1368 CE–1912 CE), works such as the "Zheng Ti Lei Yao" (正体类要, written in around 1529 CE) and "Li Yue Pian Wen" (理瀹骈文, written in around 1865 CE) systematically expounded the theoretical foundation of traumatology treatments and external treatment methods. The "Ben Cao Gang Mu" (本草纲目, written in 1552 CE–1578 CE) summarized previous experiences, enriching external treatment prescriptions and methods. Generally, the theory of Yin-Yang and Five Elements played a crucial role throughout this extensive development. It not only influenced the establishment of the theoretical framework in TCM, but also guided the compatibility and application of ingredients. Consequently, the concept of Yin-Yang and Five Elements helped Chinese medical practitioners comprehend the mechanisms behind diseases, fostering further advancements in external treatments and providing significant support for the clinical application of TCM.

### 3.1.5 | Current debates on TCM

Overall TCM theories are intertwined with Chinese history and culture, as shown in Figure 3.2 and are a crucial element to understand the concepts used in the ChP, as well as in the way medicines are perceived and classified. In biomedicine, materials are considered to be based on atoms and molecules, while TCM considers materials that are based on Yin and Yang. The Yin-Yang and Five Elements theory were interpreted throughout the history, consequently propelling the development of ingredients selection for topical and transdermal TCM formulations.

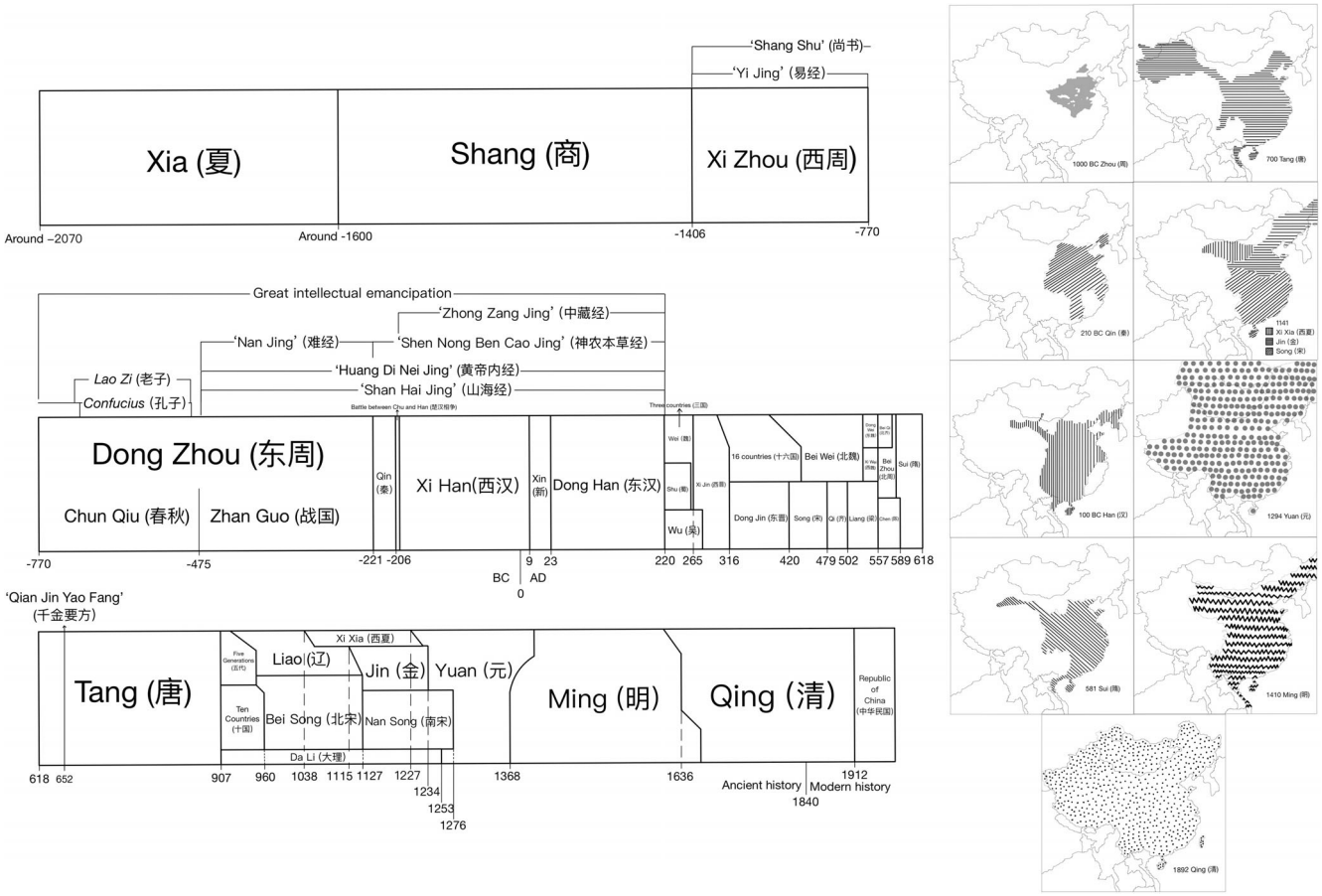


**FIGURE 3.2** History, culture, and change of China from Xia Chao (created by author: Gu).

While the philosophical framework has often been seen as an essential basis of TCM, a number of scholars, including Paul Unschuld and Rhonda Chang, indicated that contemporary Chinese medicine is not TCM (Unschuld, 2013 [2018]), but instead represents "theoretical principles for new Chinese medicine." This is based on an anatomical understanding of the body and disease. Contemporary Chinese medicine results in different healing outcomes from TCM (Chang, 2014). The debate on current TCM development is ongoing. However, the principles of Yi (易) have became integrated into the daily lives of people in Asian countries, underscoring the impact of ancient Chinese wisdom.

## 3.2 | ChP 2020—A general review of topical and transdermal TCM formulations with a botanical origin

### 3.2.1 | General overview

The ChP 2020 consists of four volumes, and is updated every 5 years:

I. Monographs of medicinal materials and the prepared slices of Chinese crude drugs, oils, fats and extracts, single-item preparations, etc.
II. Monographs of chemical drugs, antibiotics, biochemical drugs, and radioactive drugs.
III. Biologics.
IV. Pharmaceutical inactive ingredients and general chapters of preparations, testing methods, standard substances, reagents, and guidelines.

With records of modified TCM formulations currently available on the market, Volume I forms the basis for this review. The ingredient selection principle for TCM formulations in the ChP are still mainly under the guidance of "Jun Chen Zuo Shi" to reach a balance in Yin-Yang and five elements. However, the ChP modified the processing method of formulae for improved quality control (Luo et al., 2021).

ChP 2020 Vol. I comprises three parts: Part I. Chinese *Materia Medica* and Prepared Slices of Chinese Crude Drugs (药材和饮片). Part II. Oil, Fats and Extractives (植物油脂和提取物). Part III. Traditional Chinese Patent Medicines (成方制剂) and (和) Single Herb Preparations (单味制剂) (Figure 3.3a). Both single herb preparations (单味制剂) and traditional Chinese patent medicines (成方制剂) are called "中成药" (Pinyin: "Zhong-Cheng-Yao," various English translations can be found for this term, including: patent medicines, traditional Chinese patent medicines, Chinese patent drugs/medicines, Chinese medicines

and prepared prescriptions). The concept of Zhong-Cheng-Yao (中成药) may be divided into two categories (NMPA, 2017):

> 中成药有两种概念:一种是狭义的中成药，它主要是指用一定的配方将中药加工或提取后制成具有一定规格，可以直接用于防病治病的一类药品 … 另一种是广义的中成药，它除包括狭义中成药的概念外，还包括一切经过炮制加工而成的中药材。 (NMPA, 2017).

> One is looking at a narrow scope. This mainly refers to the type of medicine formulated with specific formulae using processed TCM or TCM extracts, meeting certain specifications, and can be directly used for preventing and treating diseases. … The other is looking at a broad scope, which includes not only the concept of Zhong-ChengYao in the narrow scope, but also encompasses all TCM materials that have undergone processing. (translated by author: Gu)

Since Zhong-Cheng-Yao (中成药) refers to phytopharmaceuticals produced industrially and sold on the Chinese market, a more suitable English term for it may be "*commercial TCM formulations*." Based on the above, here we suggest the term "commercial TCM formulations" for Zhong-Cheng-Yao (中成药) rather than other English translations (mostly labeled as "Chinese Patent Medicines"). This is because the term "patent medicine" is both misleading (since these products mostly do not have patent protection) and not well-understood outside the Chinese language region. These commercial TCM formulations (Zhong-Cheng-Yao, 中成药) can be found directly on the market. Chinese crude drugs, prepared Chinese crude drugs, oil, fats, and extracts mainly work as pharmacologically active ingredients in commercial TCM formulations (Zhong-Cheng-Yao, 中成药). Occasionally, these commercial TCM formulations (Zhong-Cheng-Yao, 中成药) use botanical materials individually in applications (single herb preparation, 单味制剂). However, the prevailing practice involves using a blend of two or more botanical materials, with or without the presence of excipients, in botanical formulations (Traditional Chinese Patent Medicines, 成方制剂, which could be more clearly termed as "poly-TCM formulations"). Thus, compared with single herb preparations (单味制剂), traditional Chinese patent medicines (成方制剂) contain multiple TCMs in their formulas.

### 3.2.2 | Topical and transdermal TCM formulations with a botanical origin

Among 2048 commercial TCM formulations (Zhong-Cheng-Yao, 中成药) recorded in the ChP 2020 Vol. I, approximately 120 are clearly stated for external use, which includes administration to different topical areas, such as the skin, nasal, ocular, buccal, anal and vaginal application. Among these topically administered formulations, 78 formulations are recorded as suitable for topical administration to the skin area. Thirty nine contain animal and mineral materials, 3 (Yunnan Baiyao, Yunnan Baiyao Jiaonang, Xiaotong Tiegao) do not have clear records of the TCM ingredients, 2 are modified with chemical ingredients while 34 only contain botanical materials (Figure 3.3b). Thus these 34 TCM formulations were selected for further examination.

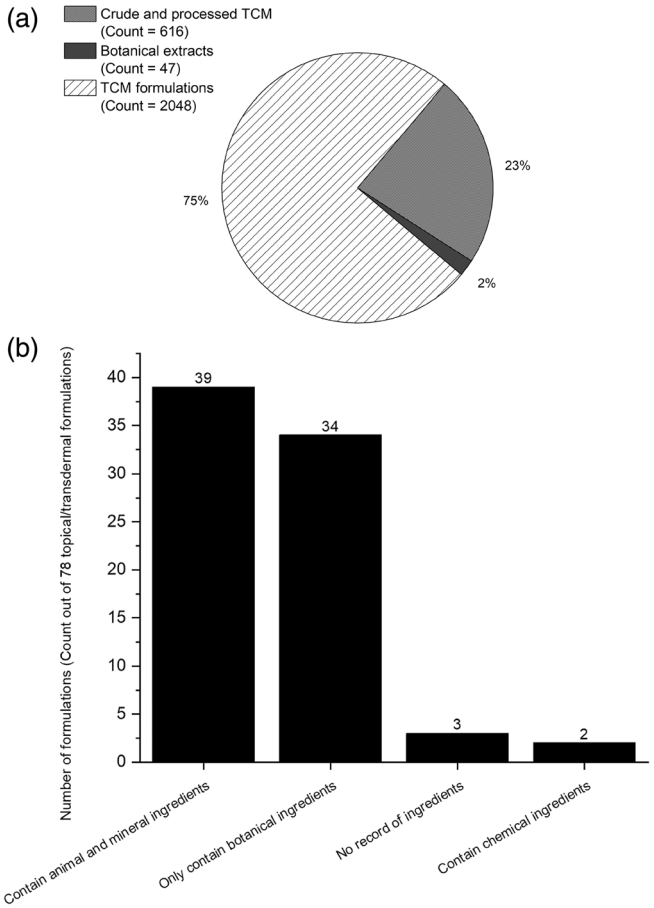


**FIGURE 3.3** Recordings in the ChP 2020—classification of TCMs and TCM formulations. (a) General classification of TCMs in the ChP 2020 and ratios of different classes of TCMs. (b) Different types of topical/transdermal TCM formulations. TCM, traditional Chinese medicine.

The ChP not only covers aspects relevant to the composition and quality of the *materia medica* but includes a range of other aspects. With a focus on topically used formulations of botanical origin, the preparation procedure, actions, indications, administration method, and ingredients of the selected 34 TCM formulations are listed in Appendix 1 in Data S1 (Topical/transdermal TCM formulations with botanical source only—English version) and Appendix 2 in Data S1 (Topical/transdermal TCM formulations with botanical source only—Chinese version). Clearly, many of the uses and preparations, including the way botanical drugs are combined, are strongly influenced by the philosophical framework outlined above. The information listed in Appendices 1 and 2 in Data S1 was used for further analysis.

In the ChP the concept of active ingredient and excipients is not clearly stated. As stated in Section 3.1, based on the traditional TCM theory, it is inappropriate to simply classify the ingredients in TCM formulations as active ingredients or excipients. However, TCM formulations recorded in the ChP 2020 are modified traditional Chinese formulations with an influence of biomedical approaches. The "Ingredient" section mostly follows the TCM theory, providing the traditional Chinese formula. The ingredients listed in this section are considered as "botanical drugs." On the other hand, the ChP aims at standardizing TCM formulations. The "procedure" section describes a modified processing method of botanical drugs listed in the "ingredients" based on the traditional processing method, with a separate section describing biomedical concepts. Compared with the traditional processing method, the modified method defines specific conditions for extraction and formulation, such as extraction temperature and time, density of extract and viscosity of final formulation. Additionally, some chemicals, such as preservatives (ethyl para-hydroxybenzoate), surfactants (polysorbate 80), and pH adjusters (triethanolamine), are used to enhance stability of TCM formulations to improve safety and quality control. These ingredients are considered excipients as used in current TCM formulations. Appendices 3 and 4 in Data S1 list all botanical drugs and excipients used in the 34 TCM formulations reviewed separately.

### 3.3 | Botanical drugs used in modified topical and transdermal TCM formulations with a botanical origin—Based on the ChP

A total of 155 botanical drugs are identified from the above 34 TCM formulations (Appendix 3 in Data S1, including the 155 botanical drugs, with information on their plant sources, recording status on the ChP, and active/inactive metabolites[2]). The ChP was referred to when collecting "active/inactive metabolites" for each botanical drug. Thus, the active/inactive metabolites are not listed for botanical drugs that have no record in the ChP.

The most used botanical drugs in topical and transdermal botanical formulations were assessed in detail based on Appendix 3 in Data S1. Figure 3.4 shows the most commonly used botanical materials in topical/transdermal TCM formulations with a botanical source. From which camphor (樟脑), borneolum syntheticum (冰片), and l-menthol (薄荷脑) are metabolites that can be extracted from plants. Olibanum (乳香) and myrrha (没药) are both plant exudates. Angelicae dahuricae radix (白芷), Angelicae sinensis radix (当归), Chuanxiong rhizoma (川芎), Rhei radix et rhizoma (大黄), and Saposhnikoviae radix (防风) are dried roots or rhizomes. Four out of the top 10 most commonly used botanical drugs are species of the *Apiaceae* Lindl., including Angelicae Dahuricae Radix, Angelicae Sinensis Radix, Chuanxiong Rhizoma, and Saposhnikoviae Radix. Two out of the top 10 are species of the *Lauraceae* Juss., including Borneolum Syntheticum and camphor. Another 2 out of the top 10 are species of the *Burseraceae* Kunth, including Myrrh and olibanum. l-Menthol from the *Lamiaceae* Martinov accounts for 1 out of the top 10. And Rhei Radix et Rhizoma from the *Polygonaceae* Juss. accounts for the last 1 out of the top 10 (Figure 3.5).

Most of the top 10 botanical materials contain aromatic metabolites. For example, *Angelica* spp. (Apiaceae), *Cinnamomum* spp. (Lauraceae), and *Mentha* spp. (Lamiaceae) are all aromatic botanical drugs and are frequently used in selected formulations of the ChP. Menthol is an aromatic metabolite from *Mentha* spp., known for its antipruritic, antiseptic, analgesic, and cooling effects (Patel et al., 2007). Additionally, various studies have reported the use of menthol, one of the most abundant active metabolites in *Mentha canadensis* L., as a penetration enhancer for some pharmacologically active compounds. Huang et al. (2019) used atomistic simulation to show that menthol can potentially enhance the permeation of quercetin through skin. It is hypothesized that menthol may enhance the transmembrane transport of quercetin via interactions with both lipids and quercetin itself. Olivella et al. (2007) and Dai et al. (2018) also provide experimental evidence for the possible permeation enhancement ability of menthol. Olivella et al. (2007) chose the hairless part of porcine skin. In this permeation study using Franz diffusion cells (dose: 0.246 g of gel formulation containing 0.02225 g of quercetin through a permeation area of 1.767 $cm^2$) and by incorporating 1.42% of menthol in the formulation. The cumulative amount of quercetin permeated was at least doubled, compared to the formulation without enhancer. Dai et al. (2018) examined the permeation behavior of ligustrazine with or without menthol in a rat abdominal skin permeation study using Franz diffusion cells (dose: 1 mL of 0.2% ligustrazine solution through a permeation area of 0.785 $cm^2$), showing promising permeation-enhancing effects of menthol. However, different experimental conditions, such as animal species and dose amount, may affect the permeation behavior of drugs (Neupane et al., 2020). Generally, menthol, as a common metabolite from *Mentha* spp., is reported to have pharmacological effects and also has been shown to contribute to penetration enhancement for topical and transdermal formulations. In the specific cases of *Angelica* spp. and *Cinnamomum* spp., no systematic assessment of metabolites was conducted for topical and transdermal botanical formulation design. Hence, further research on genus *Mentha*, as well as the other most commonly used genera, such as *Angelica* and *Cinnamomum*, are still needed.

Another common characteristic among these 10 botanical drugs is their "pungent" (味辛) flavor. The five flavors of TCMs (sour—酸, bitter—苦, sweet—甘, pungent—辛, salty—咸) represent specific pharmacological characteristics expected from a medicine in the Chinese culture. These five "flavors" are classified based on the five elements theory (Figure 3.1). The pungent flavor corresponds to "metal" (金) in five elements. Several studies have investigated the pharmacological characteristics and underlying mechanisms of TCMs with different "flavors" (Cabout et al., 2017; Ouellette et al., 2019; Wang et al., 2023; Zhou & Zhu, 2013).

[2]The term ingredient is used to define not only a botanical drug, extract, and an excipient, but also an individual metabolite. In order to avoid confusion, we use the term metabolite(s) for individual compounds isolated from a plant or fungus. These may be active metabolites or inactive markers of an extract/botanical drug.

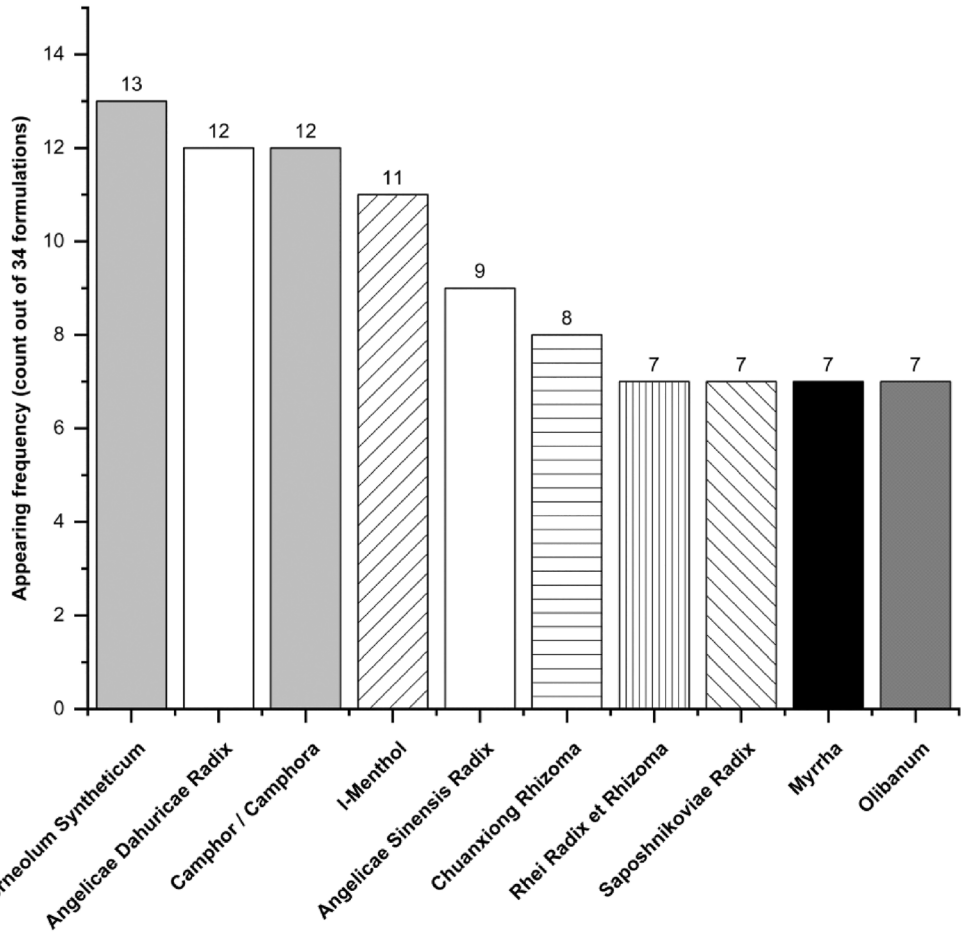


**FIGURE 3.4** Most commonly used botanical drugs in topical TCM formulations with a botanical source, for 34 selected formulations (e.g., 13 out of 34 for Borneolum Syntheticum); botanical drugs from the same family are shown in the same pattern.

Wang et al. (2023) carried out a metabolomics study on rats. These authors analyzed the blood samples of rats after treatment with TCM extracts of a specific "flavor." Niacinamide, PC(32:1), sphingomyelin, and PC(38:4) are characteristic metabolites from blood samples after treatment with "pungent flavored" TCMs. PC(32:1) is a phosphocholine, an intermediate in the synthesis of phosphatidylcholine in tissues. PC(38:4) is a phosphatidylcholine, which can regulate the physical properties of cell membranes. Wang et al. (2023) also pointed out that "pungent" flavored TCMs can regulate linoleic acid and α-linoleic acid metabolism. These two metabolic pathways and their metabolites can regulate glucose and lipid metabolism (Cabout et al., 2017; Ouellette et al., 2019). The pharmacological effects of "pungent flavored" TCMs primarily involve facilitating sweating, exhibiting anti-inflammatory, antiviral, and antibacterial properties, bidirectional modulation of the digestive system, promotion of blood circulation, and regulation of the nervous system (Zhou & Zhu, 2013). As Ramadon et al. (2022) stated, the vasodilatation of skin capillaries, blood flow, and higher quantity of capillary blood vessels can contribute to improved transdermal drug delivery. The increase of blood circulation, especially on the surface of skin, helps to create "sink" conditions at the application site, resulting in an enhancement of permeation of drugs. This may explain why pungent flavored TCMs are commonly used in topical and transdermal formulations. However, the underlying mechanism still needs to be explored and confirmed.

## 3.4 | Dosage forms and excipients used in modified topical and transdermal TCM formulations with a botanical origin—Based on ChP

The "ingredients" recorded in the "procedure" section of the ChP can be considered as excipients. The Ph. Eur. indicates, "the intended function of an excipient is to act as the carrier (vehicles or basis) or as a component of the carrier of the active substance(s) and, in so doing, to contribute to the product attributes such as stability, biopharmaceutical profile, appearance and patient acceptability and to ease with which the product can be manufactured. Usually, more than one excipient is used in the formulation of a medicinal product." It can be seen that excipients and dosage forms are closely related. It is meaningless to discuss excipients apart from dosage forms of medical products. Thus, the use of these excipients based on each dosage form are reviewed and discussed in this section.

A total of 40 excipients can be identified from the 34 reviewed formulations (Appendix 4 in Data S1). Some TCM formulations may be used for both oral and topical administration. When being used topically, some excipients have to be removed or added to the original formulations before being applied to the skin. Excipients that will not directly contact the skin or active ingredients are excluded in list (b) of Appendix 4 in Data S1, including a detailed chemical description and cosmetic functions of excipients. If the excipients are not found in the

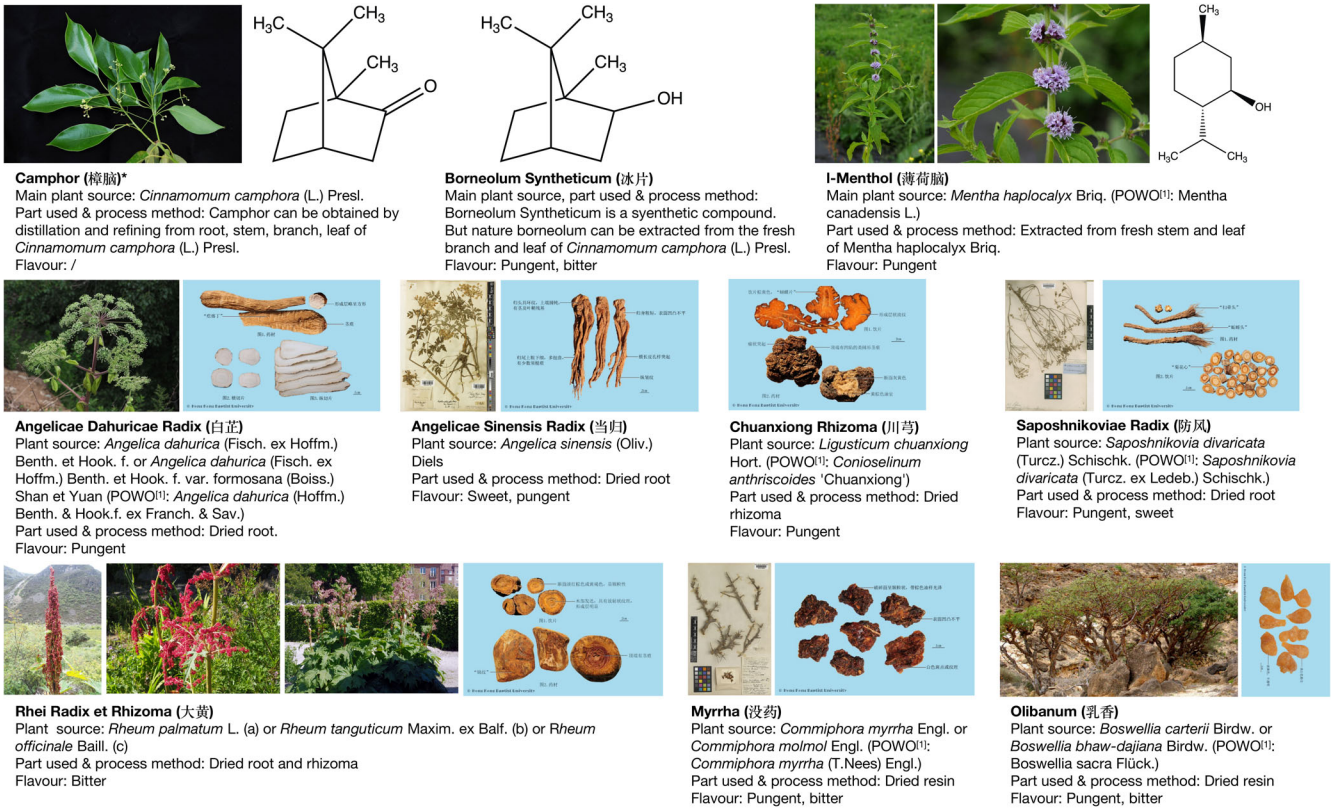


**FIGURE 3.5** Top 10 frequently used botanical drugs in topical TCM formulations with a botanical source, with information on their plant source and/or process method and flavor. TCM, traditional Chinese medicine.

Handbook of Pharmaceutical Excipients, Cosmetic Ingredient Review Database (CIR), and FDA inactive ingredient database, their chemical description and cosmetic functions are left blank in Appendix 4 in Data S1.

The 34 formulations can be grouped into nine dosage forms: TCM adhesive plasters, ointments, tinctures, powders, liniments, capsules, smeared films, oils, and pilulae (pills). Figure 3.6 shows the breakdown of each dosage form. In the ChP 2020 General Chapters, there is no clear definition for the dosage form described as a smeared film or botanical oil. However, the smeared film and botanical oil dosage forms are not formulations consistent with the other seven dosage forms, thus being treated as two individual dosage forms. The excipients used in each product are listed in Table 3.1. The excipients are arranged from the most to least recorded out of 34 formulations (top to bottom), and the formulations are arranged by dosage form. There is a total of 30 excipients that can be identified from 34 reviewed TCM formulations in the "procedure" section, which are directly applied to the skin. Since the detailed composition of the mixture of the plaster matrix is not fully disclosed, this mixture is treated as one excipient (Table 3.1). Inconsistencies between English and Chinese versions of some terminology can also be observed. Thus the same English term can be found in Table 3.1 for different Chinese terms. This includes "食用麻油" and "食用植物油" which in the ChP

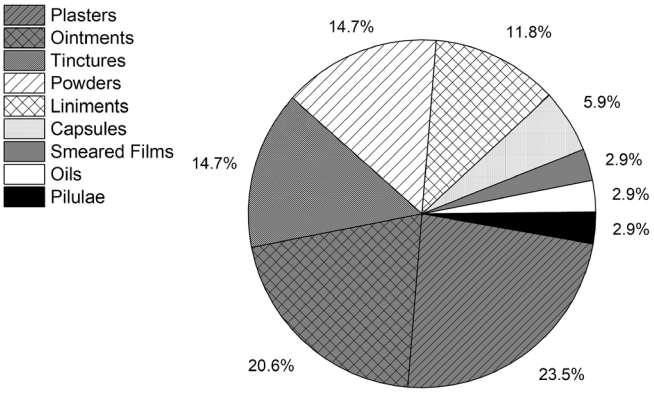


**FIGURE 3.6** Breakdown of each recorded dosage form (out of 34 selected formulations, e.g., 23.5% of the 34 selected formulations are plasters)—9 dosage forms can be recognized from topically applied TCM formulations with a botanical source in the Chinese Pharmacopoeia. TCM, traditional Chinese medicine.

are both translated as "edible vegetable oil." To be more specific, since "麻油" has been translated as "sesame oil," "食用麻油" may be translated as "edible sesame oil." If sesame oil is used as an excipient, the product label must state clearly whether it is edible or not. Additionally, "凡士林" and "黄凡士林" are both translated as "Vaseline."

**TABLE 3.1** List of excipients used in topically applied TCM formulations.

| Excipient English | Excipient Chinese | Dosage form | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Plaster | | | | | | | | Ointment | | | | | | | Tincture | | | | | | Powder | | | | | | Liniment | | | | Capsules | | | Smeared films | Oil | Pilula |
| | | TCM formulations | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | AYJZ | DWJ | GP | HXZT | SJ | SSZT | SK | TLQT | AM | RZJ | LGC | WSRY | ZJY | ZC | ZHSS | GTL | QSXZ | SSL | XZZT | YXQFZT | JF | KLC | RYJH | WH | YZ | KST | QWXC | SF | XN | SQXSN | ZS | STA | TS | QWKTZ |
| Ethanol | 乙醇 | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | |
| Water | 水 | ✓ | | | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ | | | | ✓ | | ✓ |
| Matrix with rubber and rosin… | 橡胶、松香等制成的基质 | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Beeswax | 蜂蜡 | | | | | | | | | | | | | ✓ | ✓ | ✓ | | | | | | | | | | | | | | | | | | ✓ | |
| Ethylparaben | 羟苯乙酯 | | | | | | | | | | | ✓ | ✓ | | | | | | | | | | | | | | | | ✓ | | | | | | |
| Ceresin wax; Ceresin | 地蜡 | | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | |
| Paraffin wax; Paraffin | 石蜡 | | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | |
| Glyceryl monosterate | 单硬脂酸甘油酯 | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Polysorbate 80 | 聚山梨酯80 | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | ✓ | | | | | | | |
| Stearic acid | 硬脂酸 | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Sesame oil | 麻油 | | | | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | ✓ | |
| Lanolin | 羊毛脂 | | | | | | | | | | | ✓ | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Triethanolamine | 三乙醇胺 | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Glycerin; Glycerine | 甘油 | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | ✓ | | |
| Vaseline | 凡士林 | | | | | | | | | | | ✓ | | ✓ | | | | | | | | | | | | | | | | | | | | | |
| Octadecanol | 十八醇 | | | | | | | | | ✓ | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Propanediol | 丙二醇 | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Sodium lauryl sulfate | 十二烷基硫酸钠 | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | |
| Refined honey | 炼蜜 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ |
| Edible vegetable oil | 食用麻油 | | | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | |
| Edible vegetable oil | 食用植物油 | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Potassium sorbate | 山梨酸钾 | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | |
| Concentrated ammonia | 浓氨溶液 | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | |
| Polyvinyl alcohol | 聚乙烯醇(药膜树脂04) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | | |

**TABLE 3.1** (Continued)

| Excipient English | Excipient Chinese | Dosage form | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Plaster | | | | | | | | Ointment | | | | | | | Tincture | | | | | | Powder | | | | | | Liniment | | | | | Capsules | | Smeared films | Oil | Pilula | | | | | |
| | | TCM formulations | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | AYJZ | DWJ | GP | HXZT | SJ | SSZT | SK | TLQT | AM | RZJ | LGC | WSRY | ZJY | ZC | ZHSS | GTL | QSXZ | SSL | XZZT | YXQFZT | JF | KLC | RYJH | WH | YZ | KST | QWXC | SF | XN | SQXSN | ZS | STA | TS | QWKTZ | | | | | | | |
| Vaseline | 黄凡士林 | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Liquid paraffin | 液状石蜡 | | | | | | | | | | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Plumbi Oxydum Flavum | 红丹 | | | ✓ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Acidic ethanol | 酸性乙醇 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | | | | | | | | | | | | |
| Phenol | 苯酚 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | | | | | | | |
| Acetate acid | 稀醋酸 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ✓ | | | | | | | | | |
| **Abbreviations** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **TCM formulations—full English name** | | | | | | | | |
| AM | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Anmo Ointment | | | | | | | | |
| AYJZ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Anyang Jingzhi Plaster | | | | | | | | |
| DWJ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Daiwenjiu Plaster | | | | | | | | |
| GP | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Goupi Plaster | | | | | | | | |
| GTL | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Gutongling Liquid | | | | | | | | |
| HXZT | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Huoxue Zhitong Extract | | | | | | | | |
| JF | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Jiufen Powder | | | | | | | | |
| KLC | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Kanli Coarse Powder | | | | | | | | |
| KST | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Keshangtong Liniment | | | | | | | | |
| LGC | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Laoguancao Ointment | | | | | | | | |
| QSXZ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Qushang Xiaozhong Tincture | | | | | | | | |
| QWKTZ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Qiwei Ketengzi Pills | | | | | | | | |
| QWXC | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Qiwei Xiaocuo Liniment | | | | | | | | |
| RYJH | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Ruyi Jinhuang Powder | | | | | | | | |
| RZJ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Red Zhengjin Ointment | | | | | | | | |
| SF | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shangfa Liniment | | | | | | | | |
| SJ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shangjie Plaster | | | | | | | | |
| SK | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shukang Plaster | | | | | | | | |
| SQXSN | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Sanqi Xueshangning Capsules | | | | | | | | |
| SSL | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shaoshangling Tincture | | | | | | | | |
| SSZT | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shangshi Zhitong Plaster | | | | | | | | |
| STA | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Shutong'an Smeared Films | | | | | | | | |
| TLQT | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Tongluo Qutong Plaster | | | | | | | | |
| TS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Tangshang Oil | | | | | | | | |
| WH | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Wuhu Powder | | | | | | | | |
| WSRY | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Waishang Ruyi Ointment | | | | | | | | |

(Continues)

TABLE 3.1 (Continued)

| Abbreviations | TCM formulations—full English name |
|---|---|
| XN | Xuanning Liniment |
| XZZT | Xiaozhong Zhitong Tincture |
| YXQFZT | Yunxiang Qufeng Zhitong Tincture |
| YZ | Yuzhen Powder |
| ZC | Zicao Ointment |
| ZHSS | Zihua Shaoshang Ointments |
| ZJY | Zhengjinyou Ointment |
| ZS | Zhishang Capsules |

To be more precise, since "Vaseline®" is a trade mark, "凡士林" should refer to "petroleum jelly" and "黄凡士林" should refer to "yellow petroleum jelly."

Generally, and as expected, the use of excipients is specific to certain dosage forms. As expected, ethanol and water are the most frequently used excipients (19/34, 56% and 18/34, 53%) since they mostly function as extraction solvents. Ethanol may also function as a permeation enhancer (Haq & Michniak-Kohn, 2018). Notably, the plaster is the most commonly recorded dosage form for topical and transdermal TCM formulations with a botanical origin. Consequently, the TCM adhesive plaster, comprised of a mixture of rubber, rosin, and some other ingredients, is also frequently recorded (7/34, 21%). The detailed composition of this matrix for the adhesive plaster has not been fully disclosed in the ChP. Records for this matrix vary depending on the TCM formulation. Rubber and rosin are repeatedly recorded as ingredients in this matrix, but other ingredients, including zinc oxide, petroleum jelly (recorded as: Vaseline), wool fat/lanolin, and gasoline, may also be used. The inconsistency noted for recordings of different formulations in English version, may also be due to use of synonyms such as wool fat and lanolin.

The detailed discussion of excipients employed in each type of dosage form is reported in the following sections.

### 3.4.1 | TCM adhesive plasters

(*Refer to Appendix 1 in Data S1 and* Table 3.1 *for detailed information for specific formulations and dosage forms*)

As shown in Figure 3.6, the TCM adhesive plaster is the most commonly recorded TCM dosage form among 34 selected formulations used for topical administration. This dosage form is applied to the skin for a prolonged period of time. The application time for the TCM adhesive plaster can vary based on the severity of symptoms, normally less than 24 h. The TCM adhesive plaster is normally used for relieving pain and bruises. The part of skin in contact with the plaster should be intact. Commonly, a mixture of rubber, rosin, and some other ingredients is used as the matrix of this dosage form. Most of these plasters, use ethanol and/or water as the extraction solvent for botanical materials. Then the extract will be incorporated into the plaster matrix.

The adhesive black plaster is another widely used type of plaster in traditional topical and transdermal formulations (ChP Commission, 2020) with a specific preparation method. Most adhesive black plasters are excluded from this review because they require animal/mineral materials. To prepare an adhesive black plaster, pulverized or sliced TCM material should be fried in a sufficient amount of edible vegetable oil at a high temperature until the materials all turn carbonized on the surface. When the oil can form semisolid droplets when dropped into water, the fried oil can be filtered, and a specific amount of lead tetraoxide ($Pb_3O_4$) is mixed with the filtered oil at a high temperature (~360°C), until the whole oily mixture turns black. Afterwards the oily mixture is immersed in water to prepare a semisolid to solid paste. The semisolid to solid paste will then be warmed

up and softened to be applied on fabric or animal skin, and the black plaster is made. In this review, only the Goupi plaster is a black plaster using botanical ingredients solely. This may be an interesting formulation to explore.

The adhesive property of plasters helps to achieve sustained drug delivery to the application site (Wong et al., 2023). Since this is the dosage form that is most commonly recorded in topical and transdermal TCM formulations with a botanical origin, the composition of the plaster matrix should be studied in more detail.

### 3.4.2 | Dosage forms for topical administration only

(*Refer to Appendix 1 in Data S1 and* Table 3.1 *for detailed information for specific formulations and dosage forms*)

Ointments, liniments, botanical oils, and smeared films are only for topical use. Sometimes it is clearly stated to avoid broken skin during application of these preparations for various purposes, such as relieving bruises, pain, anti-arthritis, and reducing headache. For example, the liniment dosage form is only intended for application to unbroken skin. However, some formulations in the dosage forms of oils, smeared films, and ointments may be applied to broken skin for wound healing.

*Ointments*

Ointments have the most complicated excipient list among the nine dosage forms. Based on the General Chapters in the ChP 2020 Vol. IV, ointments are uniform semisolid formulations comprising drug substances with oleaginous or water-soluble bases and are intended for external application to the skin. They may be classified as oil-in-water and water-in-oil types, depending on the different bases.

In the ChP 2020, three formulations, Anmo ointment, Laoguancao ointment, and Waishang ruyi ointment, ethanol and water are extraction solvents where water also acts as the aqueous phase. Waxes, petroleum jelly, liquid paraffin, and octadecanol are commonly used as oil phases. To prepare an ointment, the aqueous phase and oil phase should be mixed with surfactants, such as glyceryl monostearate, polysorbate 80, stearic acid, and sodium lauryl sulfate (SLS). Additionally, preservatives and pH adjusters can also be added. For other oleaginous-based ointments, Zicao ointment and Zihua shaoshang ointment are both a mixture of vegetable oil with beeswax as a stiffener, where vegetable oil acts as both the oil base and extraction solvent. The Red zhengjin ointment and Zhengjinyou ointment are similar in terms of active ingredients; the difference is only that Red zhengjin ointment additionally contains cinnamon oil as a botanical drug, while Zhengjinyou ointment does not. It is noteworthy to look at the botanical drugs of these two oleaginous-based ointments, because these botanical drugs are essential oils. In this case, these botanical drugs also act as the oil base of these two formulations. Thus stiffeners (beeswax, ceresin wax, or paraffin) are directly added to the botanical drugs. In terms of minor differences in excipients between these two ointments, different kinds of petroleum jelly are used. Concentrated ammonia (pH adjuster) is added only to Red zhengjin ointment and beeswax is only added to Zhengjinyou ointment.

*Liniments*

According to the General Chapters in the ChP 2020 Vol. IV, liniments are liquid formulations made of drug substances and suitable solvents such as ethanol and oil, intended for external use to rub on unbroken skin. It is very characteristic for liniments to have simple excipients, mostly containing ethanol and/or water as solvents, and some contain other ingredients such as surfactants and preservatives.

*Oils*

In Tangshang oil, sesame oil is the main excipient and is used as the extraction solvent for some of the active ingredients. According to the CIR, sesame oil and other botanical oils have skin conditioning, occlusive, emollient, moisturizing, and other properties. It is worthwhile for future studies to look into the use of botanical oils in cosmetics, in terms of their multi-functions. Phenol has been widely studied for its antimicrobial activity and has been used as a preservative in many pharmaceutical products, such as peptide and protein products (Meyer et al., 2007). Beeswax is used to solidify the oil phase.

*Smeared films*

For Shutong'an smeared films, water and ethanol are used as extraction solvents. Specially, polyvinyl alcohol is used here as a film-forming agent (as well as a viscosity-increasing agent) and glycerin is used to adjust viscosity (viscosity-decreasing agent).

Generally, the multifunctional use of botanical oils as both pharmacologically active botanical drugs and excipients for formulation show their promising use in topical and transdermal botanical formulations. Further studies on their physicochemical properties and potential functions would be useful to guide their proper use in formulation design.

### 3.4.3 | Dosage forms can be adapted to topical administration from oral delivery

(*Refer to Appendix 1 in Data S1 and* Table 3.1 *for detailed information for specific formulations and dosage forms*)

Traditional Chinese poly-botanical formulations with dosage forms of powders, capsules, pilulae, and tinctures for oral administration can be adapted for topical and transdermal application. The adapted powders, capsules, and pilulae formulations are mostly applied to the intact skin only. This can be deduced through their medicinal uses and administration route, or it is clearly stated that the product should not be used on broken skin, such as Sanqi Xueshangning Jiaonang. However, for Ruyi Jinhuang San (dosage form: powder) it is not specified if broken skin should be avoided.

*Powders, capsules, and pilulae*

Some formulations, originally with dosage forms of powder, capsules, and pilulae, are primarily used orally for various effects. These formulations can also be adapted for application to unbroken skin, mostly for relieving bruises, numbness, or pain. When utilized topically or transdermally, the initial step involves removing powders from capsules. Similarly, pilulae must be ground into powders as well.

Subsequently, additional components, such as alcohol, vinegar, green tea, honey, or sesame oil, will be incorporated into the powders before application to the skin. For certain applications requiring long-term administration, it may be necessary to cover the application area with a support like cotton or cloth.

The excipients used in the processing method of these formulations are added for oral use. For example, for Qiwei ketengzi pills, water is used as the extraction solvent for some active ingredients. Refined honey serves as a binding agent, bringing together the concentrated water extract and the remaining pulverized botanical materials to create pills. In these dosage forms, the refined honey does not act as a humectant, skin-conditioning agent, or solvent, as reported in the CIR. In comparison, to be adapted for application to the skin, the additional ingredients added to the original formulations assist topical application. The instructions for using these ingredients are recorded in the "Administration and Dosage" section of the monographs in ChP.

*Tinctures*

Unlike powders, capsules, and pilulae, tinctures may be used topically, without the addition of other excipients during application. Like liniments, tinctures also contain water and ethanol as solvents. Tinctures are clear liquid formulations of drug substances macerated or dissolved in ethanol at a specified concentration or made by diluting the fluid extracts. Tinctures are intended for oral administration and external application. The main difference between liniments and tinctures is that tinctures can be used both orally and externally, while liniments are only intended for external use.

## 4 | CONCLUSIONS

This review examines a neglected aspect both in pharmaceutics and phytopharmacology—the use of ingredients (botanical drugs and excipients) in topical and transdermal botanical formulations. To understand the principle of ingredient selection for TCM formulas, the historical and culture background of TCM theories and guidelines has been explored. Topical and transdermal formulations derived from botanical drugs recorded in the ChP 2020 were also reviewed. Based on the concepts of TCM, the ingredients of these TCM formulations were identified and discussed.

Confucianism and Taoism are two philosophical cultures originating in ancient China. Scholars of Confucianism and Taoism pointed out the importance of reaching a balance between Yin Yang and maintaining harmonization among the five elements. The ingredient selection guideline in TCM, the "Jun, Chen, Zuo, Shi" guideline, was developed to achieve balance among TCMs in a formula. This ingredient selection guideline provides instructions for studying traditional formulas, including the formulae of traditional topical and transdermal formulations. Based on this guideline, ingredients in traditional Chinese formula are separated into four categories. Therefore, the concept in modern pharmaceutical science of categorizing ingredients into active ingredients and excipients cannot be applied to TCM formulations. This is exemplified in the differences between the monographs on Daiwenjiu plaster and Arnica tincture in the ChP and Ph. Eur, respectively. Since ingredients are not categorized as active ingredients and excipients in TCM formulations, the ChP places more emphasis on listing the botanical materials used in the TCM formula. This provides information on what botanical materials are selected and how they are combined to achieve desired therapeutic effects. In comparison, the Ph. Eur. clearly states the amounts of active compounds in the formulation for specific pharmacological activities.

The ChP 2020 supports the standardization of TCM formulations for better safety and quality control for the current pharmaceutical market. Thus, modified TCM formulations are recorded in the ChP 2020, incorporating traditional Chinese formulae with biomedical approaches. The ingredients used under the guidance of the traditional guideline are termed as "botanical drugs," corresponding to the "ingredients" section of a ChP monograph. The ChP modified the traditional TCM formulations through a biomedical approach to ensure better safety and quality control of the final product. The ingredients introduced to the modified traditional Chinese formulations are termed as "excipients," corresponding to the "procedure" section of a ChP monograph.

The most commonly recorded "botanical drugs" in the formulations reviewed were found to be aromatic botanical materials, containing low molecular weight aromatic metabolites such as menthol. Several studies show a potential permeation enhancement effect of menthol. Thus, further studies on aromatic metabolites from genera like *Angelica* spp., *Cinnamomum* spp., and *Mentha* spp., are very promising for exploring multifunctional ingredients that can be used in topical and transdermal formulations. "Botanical drugs" recorded in topical and transdermal TCM formulations are also mostly "pungent" in "flavor." There are several studies working on understanding the molecular mechanism for "pungent" and "flavor" in TCM. "Pungent flavored" TCMs are reported to have the effect of increasing blood circulation, which can enhance skin permeation. But more studies are still needed to confirm whether "pungent flavored" botanical drugs have penetration enhancement functions. Additionally, it is also worthwhile to study other potential uses of "pungent flavored" botanical drugs in topical and transdermal delivery and their underlying mechanisms. Aromatic botanical materials and the concept of pungency in TCM provide an expanded concept of excipients and point to a different approach in ingredient selection for topical and transdermal formulation design.

The plaster is the most commonly recorded dosage form for topical and transdermal TCM formulations with a botanical origin. Although the composition of the plaster matrix is not fully disclosed in the ChP, the plaster remains a valuable dosage form. Developing plasters in phytomedicine with reference to TCM practices and improving these formulations with modern pharmaceutical technologies worth further research. Botanical oils are multifunctional, serving dual roles as both pharmacologically active botanical drugs and excipients. They could be employed in formulating dosage forms, such as ointments and oils. Further studies on botanical oils could provide a better basis for using these ingredients in such formulations. Last but not least, some tinctures and traditional Chinese formulations, with original dosage forms of powders, capsules, and pilulae, can be used both orally and topically. This broaden the selection of botanical ingredients for

novel formulation design on both oral and topical/transdermal formulations, from the perspective of TCM.

Most importantly, this assessment provides a basis for understanding how the ingredients are selected for topical/transdermal botanical TCM formulations in the ChP. Therefore, different approaches of the ChP and the Ph. Eur. in interpreting these preparations can be compared. Cross-cultural communication is necessary for phytomedicine (Heinrich et al., 2021). The paper offers an understanding of these different approaches and, therefore, is a basis for a more harmonized approach in pharmaceutical and medical practice.

## AUTHOR CONTRIBUTIONS

**Jingyi Gu:** Conceptualization; data curation; formal analysis; methodology; project administration; writing – original draft; writing – review and editing. **Majella E. Lane:** Conceptualization; supervision; writing – review and editing. **Bruno Da Silva Sil Dos Santos:** Supervision; writing – review and editing. **Michael Heinrich:** Conceptualization; methodology; supervision; writing – review and editing.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. All co-authors have reviewed and approved the manuscript's content, and there are no financial interests to disclose. We certify that this submission is original work and is not being considered for publication elsewhere.

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this review article are available in the public domain. Specifically, the data analyzed are derived from the Chinese Pharmacopoeia 2020 & 2015, and a monograph from the European Pharmacopoeia 11.0. (EDQM).

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## SUPPORTING INFORMATION

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