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Effects of carbonization processing on quality control, chemical compositions, and pharmacological mechanism of Ganjiang (Zingiberis Rhizoma)

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Ganjiang (Zingiberis Rhizoma, ZR) and Jiangtan (Carbonized Zingiberis Rhizoma, CZR) have long been used in traditional Chinese medicine (TCM) with a rich history in the treatment of various ailments. While ZR and CZR obviously stem from the same botanical source, their attributes, chemical compositions, pharmacological behaviors, and clinical applications are different owing to variations in the extent of drying and processing they undergo. In this paper, data pertaining to ZR and CZR were retrieved from databases including China National Knowledge Infrastructure (CNKI), PubMed, Web of Science, and Google Scholar. These sources were scrutinized to elucidate the distinctions between ZR and CZR arising from carbonization processing in terms of their ethnopharmacology, quality control, chemical compositions, biological activities, pharmacological mechanisms, and clinical uses. In this study, a total of 56 chemical constituents were identified and isolated from ZR and CZR, which primarily encompassed volatile oils, gingerols, and diphenylheptane compounds. CZR's pharmacological effects include hemostatic, anti-oxidant, analgesic, antibacterial, anti-cancer, and other biological activities. ZR has pungent and warm properties. It is a Yang-supplementing herbal medicine for ailments exacerbated by cold or damp climatic influences. CZR is a product of ZR after undergoing high temperature, with diminished intensity of its pungent and warm attributes. This change leads to a more gradual treatment efficacy, renowned hemostatic effects and its ability to gently invigorate the spleen and effectively alleviate diarrhea. Currently, research on the pharmacological mechanism of CZR is mainly focused on the effects of CZR on coagulation and fibrinolysis. Although the healing effect of CZR has long been known, and some correlation has been found between the changing composition and the changing color of the decoctions, people still lack relatively clear processing mechanisms to reflect the characteristics and specific quality standards of the ingredients of CZR's hemostatic effect. This review provides a systematic summary on quality control, chemical composition, ethnopharmacology, and pharmacology of CZR, offering novel perspectives for advancing the exploration of additional carbonized herbal medicine and fostering their application in clinical settings.

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1 Introduction

One single traditional Chinese medicine (TCM) herb often possesses multiple effects owing to its complex compositions. In clinical treatment, it's unnecessary to utilize all roles that TCM herbs play. Instead, it is important to tailor the treatment to the patient's specific conditions and realize therapeutic outcomes through focused use of TCM herbs. The processing of TCM herbs is a crucial step to reduce their toxicity or side effects and strengthen their efficacy for clinical uses, which is in accordance with the syndrome differentiation and treatment principle in TCM. In the work *Enlightenment on Materia Medica* (*Ben Cao Meng Quan*, 《本草蒙筌》), CHEN Jiamo of the Ming Dynasty emphasized that the utmost significance in the production of TCM lay in the art of moderate processing. Insufficient manufacturing and processing could impede the desired effects, while excessive processing could lead to the loss of intended outcomes. The intention here wasn't to foster mystique; rather, it's to highlight that different processing methods held distinct significance.

Ganjiang (Zingiberis Rhizoma, ZR) and Jiangtan (Carbonized Zingiberis Rhizoma, CZR) originate from the rhizomes of Zingiberaceae plants. However, their properties and pharmacological effects are different du[e](#page-12-0) [t](#page-12-1)o variations in the degree of drying and processing $[1, 2]$ $[1, 2]$ $[1, 2]$ $[1, 2]$ $[1, 2]$. This is very common in the production and clinical application of medicinal herbs. However, diverse processing techniques or procedures (such as heating methods, temperatures, and duration) can yield CZR with similar outward appearances. So, relying merely on traditional methods to classify carbonized products and assess their quality through visual attributes like color and texture can lead to inaccurate conclusions. Such approaches are challenging to guarantee the safety and consistency of carbonized TCM products for their clinical application, which is an urgent issue to be addressed in the TCM world.

In this paper, data pertaining to ZR and CZR were retrieved from databases including China National Knowledge Infrastructure (CNKI), PubMed, Web of Science, and Google Scholar. These sources were scrutinized to elucidate the distinctions between ZR and CZR arising from carbonization processing in terms of their ethnopharmacology, quality control, chemical compositions, biological activities, pharmacological mechanisms, and clinical uses. This review provides a comprehensive overview and analysis of the quality control measures for CZR, the influences of the carbonization process on its chemical compositions, biological activities as well as its clinical uses. It is hoped that this manuscript will generate novel insights into future exploration of chemical constituents, pharmacological mechanisms of CZR, and its clinical application.

2 TCM theory and clinical application

2.1 The origin and history of ZR and CZR

ZR, denoting the desiccated rhizome of *Zingiber officinale* Roscoe (*Z. officinale*)([Figure 1](#page-2-0)), holds the name of "Ganjiang (Rhizoma Zingiberis)" in China. Its origin traces back to *Shennong's Classic of Materia Medica* (*Shen Nong Ben Cao Jing*, 《神农本草经》)*,* in which it was introduced over 2 000 years ago as an integral component of Chinese herbal medicine. The history of ZR carbonization processing can be retraced to *Inner Canon of Huangdi · Su Wen*(*Huang Di Nei Jing · Su Wen,*《黄帝内经·素问》), while the stir-frying technique of ZR was initially documented in *Synopsis Golden Chamber* (*Jin Kui Yao Lue*, 《金匮要略》). Throughout different dynasties, a multitude of TCM works have documented various processing techniques and prerequisites for ZR, which encompass procedures such as cleansing, cutting, stir-frying (including with or without adjuncts like millet wine, salt, and sand), as well as the infusion of herbal juices through gentle simmering $[1, 2]$ $[1, 2]$ $[1, 2]$. CZR represents carbonized ZR through stir-frying processing. It is known as "Jiangtan (Carbonized Ganjiang)" in China and was initially documented in the *Tai Ping Sacred Remedies* (*Tai Ping Sheng Hui Fang,* 《太平圣惠方》). In [Figure 1](#page-2-0), visual depictions encompass decoction pieces, powder forms, and transmission electron microscope (TEM) structural scans of ZR and CZR.

Fresh ginger has been used to treat various symptoms and conditions, which include combating early pregnan-cy-related nausea and vomiting [\[3](#page-12-2)], countering chemotherapy-induced side effects $^{[4]}$ $^{[4]}$ $^{[4]}$, addressing metabolic issues like obesity $^{\left[5\text{-}7 \right]}$ $^{\left[5\text{-}7 \right]}$ $^{\left[5\text{-}7 \right]}$, and diabetes $^{\left[8 \right]}$, as well as mitigating coldinduced discomforts such as coughs, muscular pains, and asthma $[9, 10]$ $[9, 10]$ $[9, 10]$. According to TCM theories, ZR is classified as a Yang-supplementing remedy for ailments triggered by cold and damp climatic influences $^{[11]}$ $^{[11]}$ $^{[11]}$. It has been attributed with various benefits, including its potential for anti-diabetic $[12]$ $[12]$, anti-cancer $[13]$ $[13]$, anti-inflammatory $[14]$ $[14]$, anti-oxidant and immunomodulatory effects [\[15](#page-12-13), [16](#page-12-14)]. CZR is considered a warming medicine, with effects of invigorating the spleen and alleviating diarrhea, as well as to stimulate meridian and halt bleeding $[17]$ $[17]$. It is often used to treat uterine bleeding, cold deficiency syndrome, and spleen-yang deficiency syndrome accompanied by hematemesis, hematochezia, or diarrhea [\[18](#page-12-16)[-20](#page-13-0)] .

2.2 The hemostatic theory within carbonized medicinal herbs

Carbonized medicinal herbs represent a distinctive category of Chinese medicine endowed with a multitude of pharmacological attributes. Such herbs are produced by being subjected to carbonization process under high

Figure 1 The decoction pieces, powder forms, and TEM structural scans of ZR and CZR A, ZR decoction pieces. B, ZR powder. C, TEM structural scan of ZR (5 mm). D, TEM structural scan of ZR (200 μm). E, CZR decoction pieces. F, CZR powder. G, TEM structural scan of CZR (5 mm). H, TEM structural scan of CZR (200 μm).

temperature. They hold significant roles in the clinical practice of Chinese physicians across various dynasties, gradually giving rise to the formation of carbonized medicinal herbs centering on the treatment of hemorrhagic disorder.

In the Yuan Dynasty, GE Kejiu emphasized in the *Miraculous Book of Ten Prescription* (*Shi Yao Shen Shu,* 《十药神书》) that, "warm blood fosters circulation, cold blood stagnation, and bleeding ceases when red encounters black". In the Ming Dynasty, LI Shizhen proposed that all carbonized medicinal herbs have effects on halting bleeding. For example, *Compendium of Materia Medica* (*Ben Cao Gang Mu,* 《本草纲目》) encompasses over 200 varieties of carbonized medicinal herbs, which are extensively used in addressing conditions such as bloodrelated disorders, sores, soup fire injuries, menstrual ailments, anorectal diseases and so on. In ancient times, Chinese physicians observed that a significant portion of hemostatic remedies had undergone carbonization processing, leading to the emergence of the notion "black can triumph over red". This concept, grounded in the principles of the five elements TCM theory, indicates that carbonized medicinal her[bs posse](#page-2-1)ss the ability to arrest bleeding $^{[21]}$ $^{[21]}$ $^{[21]}$, as depicted in [Figure 2](#page-2-1).

Figure 2 The law of promotion and restraint in the five elements TCM theory

The five circles represent five elements, wood, fire, earth, gold, and water, which align with five distinct colors, cyan, red, yellow, white, and black in the figure. The circular arrangement in the figure illustrates a sequence of mutual promotion through the indicated arrows, progressing as follows: "fire generates earth, earth generates gold, gold generates water, water generates wood, and wood generates fire". According to the directional arrows displayed in the five-pointed star cycle in the figure, the elements also exhibit a successive pattern of restraint: fire restrains gold, gold restrains wood, wood restrains earth, earth restrains water, and water in return restrains fire. Just as water can extinguish fire, an analogous principle that black can conquer red applies. Hence, carbonized medicinal herbs (black) could halt bleeding (red). Throughout history, numerous Chinese medical practitioners have employed carbonized medicinal herbs to address bleeding symptoms, with favorable outcomes yielded. The traditional hemostatic theory within carbonized medicinal herbs encapsulates the culmination of ancient TCM physician's extensive medicinal experiences, showcasing distinctive TCM thoughts and bearing the hallmark TCM characteristics.

2.3 Clinical application

Different from chemical hemostatic drugs, known for their clinical tolerability but associated with potential severe side effects such as thrombosis, carbonized medicinal herbs often exhibit a synergistic interaction with numerous targets. Their hemostatic impact is moderate, rendering the[m](#page-13-2) extensively applicable in diverse bleeding disorders [\[22](#page-13-2)] , including metrorrhagia, uterine bleeding, hemoptysis, epistaxis, blood in stool, hem[atu](#page-13-3)ria, purpura, etc., as well as gastrointestinal diseases $^{[23]}$ $^{[23]}$ $^{[23]}$, such as abdominal pain and diarrhea.

ZR and CZR are two ginger products that undergo different processing, with the former crafts through lowtemperature drying (not surpassing 60 °C), while the latter undergoes high-temperature frying until its color turns to black (typically exceeding 200 °C). Their taste, efficacy, and clinical applications are completely different after carbonization processing. [Table 1](#page-3-0) and [Table 2](#page-4-0) list the classic practical prescriptions commonly used in TCM clinics which are containing ZR and CZR.

In both ancient and contemporary TCM clinical practices, ZR exerts a robust influence in igniting the body's internal warmth, making it a crucial remedy for condi-tions caused by cold and damp climatic influences [\[10](#page-12-8)], such as cough, asthma, bronchitis, abdominal pain, diarrhea, gastroenteritis, and osteoarthritis. As reported on China Central Television Channel 4, "Chinese Medicine Fights the Epidemic" program on March 5, 2020, all healthcare professionals at Tongxu County People's Hospital in Henan Province, a facility that played a crucial role in treating patients afflicted by Corona Virus Disease 2019 (COVID-19), administered Gancao Ganjiang Decoction, after which not a single case of COVID-19 infection

Table 1 Clinical applications of ZR

was reported among the professionals $^{\text{\tiny{[33]}}}$ $^{\text{\tiny{[33]}}}$ $^{\text{\tiny{[33]}}}$. While direct experimental evidence supporting Gancao Ganjiang Decoction's impact on COVID-19 was short, it was worth noting that this formulation was believed to have fortified the chest and Yang, strengthened the spleen and stomach, and enhanced immunity in people. This is also a valuable experience and a noteworthy TCM strategy in fighting epidemics.

The effect of CZR on kindling internal warmth within the body diminishes as a result of carbonization processing, leading to a comparatively mild pharmacological impact. CZR is effective in hemostasis, and is employed to treat uterine bleeding, cold-deficiency syndrome, and spleen-Yang deficiency syndrome accompanied by hematemesis, hematochezia, or diarrhea. For example, the renowned prescription, Shenghua Decoction, normally used in the treatment of postpartum conditions, employed CZR to exert a hemostatic influence, effectively preventing postpartum uterine bleeding. If the ZR in this

Table 2 Clinical applications of CZR

prescription is not charred, it may cause adverse symp-toms such as uterine fever or bleeding [\[31](#page-13-10)].

3 The preparation of CZR

The quality of carbonized medicinal herbs is primarily influenced by the temperature, heating duration, and methods. Hence, a substantial number of TCM practitioners are currently engaged in researching the most favorable parameters for carbonization processing. For ex-ample, MENG et al. [\[34](#page-13-11)] utilized the central composite design-response surface methodology by identifying heating temperature, duration, and drug concentrations as screening variables, and in combination with its absorption capacity through the assessment of tannin, 6-gingerol and 6-shogaol for optimization. Ultimately, they determined the ideal carbonization processing method for CZR, which was slicing ZR into 0.55 cm segments and then subjecting them to frying at 310 °C for 15.5 min $^{[34]}.$ $^{[34]}.$ $^{[34]}.$

Simultaneously, some researchers used the sand scalding technique during carbonized medicinal herb preparation to ensure stable heating. For example, SHEN et al. ^{[\[35](#page-13-12)]} conducted a comparative study on the absorption capacity, primary chemical constituents, fingerprints, and pharmacological effects of CZR prepared with and without the use of the sand scalding technique. The

with-sand-scalding technique involved sand frying ZR at 240 ± 5 °C for 8 min, while the without-technique encompassed direct frying of ZR at 270 ± 10 °C for 30 min to prepare CZR. The findings indicated that the sand-fried carbonization process out performed direct frying $^{\left[35\right] }$.

In addition, during the heating process of TCM herbs, intricate chemical reactions such as the Maillard and caramelization reactions occur, leading to shifts and intensification in the color of the herbs [\[36](#page-13-13), [37\]](#page-13-14) . Therefore, employing color analysis emerges as a valuable tool for selecting optimal carbonization processing techniques. LIN et al. [\[38](#page-13-15)] used SPSS 24.0 software to analyze the correlations between the concentrations of 6 components (gingerone, 6-gingerol, 8-gingerol, 6-shogaol, diacetoxy-6 gingerdiol, and 10-gingerol) in ZR and CZR, and their respective color L^{*} (representing lightness value), a^* (indicating red and green component value), *b* * (signifying yellow and blue component value). The outcomes revealed that L^* and b^* exhibited a highly significant negative correlation with zingerone content, while manifesting a markedly positive correlation with the remaining five constituents. On the other hand, *a* * demonstrated a distinctly positive correlation with zingerone, yet displayed no discernibl[e](#page-13-15) correlation with the remaining five con-stituents ^{[[38\]](#page-13-15)}. This discernment underscored a distinct

connection between the alterations in compositional elements and shifts in colors. And it was noteworthy that the empirical intuition of experienced processing practitioners in evaluating the quality of carbonized medicinal herbs based on color bears certain scientific evidences.

Given that the frying pans or ovens used in laboratory research markedly differ from the massive machinery production in factories, the parameters optimized in the laboratory are not perfectly suitable for industrial production. Therefore, most of the current carbonization processing techniques of TCM herbs are still conventional, with the extend of carbonization heavily reliant on experiential judgement. This reliance inherently introduces notable subjectivity, thereby impeding the robust regulation of process variables crucial for the carbonized medicinal herb preparation. The solution to this problem needs to rely on the development and application of highlevel intelligent carbonization processing equipment.

4 Quality control

The assessment of ZR is systematically governed by five distinct aspects containing its characterization, morphology identification, microstructure analysis, Thin Layer Chromatography (TLC) identification, and the comprehensive evaluation of volatile oil and 6-gingerol concentrations. Conversely, the *Pharmacopoeia of People's Republic of China* (*Chinese Pharmacopoeia*, 2020 edition) lacks a comprehensive quality standards for CZR, including only morphology identification and the quantification of 6-gingerol content. As a result, CZR continues to adhere to the traditional "burning ash without ash formation" criterion for rough quality control. The quality control parameters for both ZR [and CZR](#page-5-0) in the *Chinese Pharmacopoeia* are outlined in [Table 3](#page-5-0). Consequently, the quality of CZR depends on the quality of ZR as well as the specific stir-frying methodology employed.

Raw ZR and CZR are commonly presented as agricultural and sideline products in the medicinal material trading sectors. In most cases, their quality is measured based on qualitative characteristics such as color, taste, and smell. Regrettably, these evaluations often entail a substantial degree of inaccuracy. Therefore, the imperative arises to establish streamlined and expeditious methodologies capable of distinguishing between the raw ZR and CZR obtained through varying degrees of processing in the trading sectors. We used a new technology to explore the microscopic changes in ZR and CZR through the utilization of scanning electron microscopy (SEM)([Figure 1](#page-2-0)). It was found that subsequent to heating, the surface of ZR exhibited a notably heightened roughness, accompanied by a subtle reduction in the network texture, a decrease in the size of tissue particles, and an augmentation in the abundance of carbonized particles.

Similar to CZR, the quality standards of existing carbonized medicinal herbs primarily revolve around description of visual attributes. This reliance on experiential assessments by processing personnel to ascertain the adherence of carbonized medicinal herbs to quality control through traditional methods such as visual inspection, olfactory examination, taste evaluation, and tactile assessment, has posed challenges in ensuring the safety and stability of their clinical use. Although certain standards do encompass aspects like identification and content quantification, the parameters are largely reflective of those found in the quality standards of the original raw TCM herbs. What's conspicuously lacking is well-defined quality standards for carbonized medicinal herbs that are not only rooted in a comprehensible processing mechanism, but also capture the hemostatic components inherent in the carbonized herbs. These standards should align with contemporary quality control of TCM herbs with distinct characteristics and specificity.

Consequently, various researchers have assessed and analyzed the chemical compositions of ZR and CZR. For instance, LI et al. [\[39](#page-13-19)] used ultra-performance liquid chromatography coupled with quadrupole-time-of-flight mass spectrometry (UPLC/QTOF-MS) to distinguish fresh, dried, stir-fried, and carbonized ginger extracts. In the study, a total of 27 compounds were identified from four samples. XUE et al. [[40\]](#page-13-20) performed non-targeted metabolomics-based profiling of ZR and CZR by UPLC/ QTOF-MS combined with multivariate analysis and compounds identification, with a total of 33 gingerols selected among 59 gingerols as novel markers for materials authentication in ZR and CZR. SAMRAT et al. [[41\]](#page-13-21) used hyperspectral imaging combined with chemometric modelling to identify the real-time determination of the ratio of 6-gingerol and 6-shogaol in ZR powder. Their findings underscored the potential viability of this method as a rapid and non-destructive approach for predicting the quality of ZR.

Table 3 The quality control measurements of ZR and CZR in *Chinese Pharmacopoeia* (2020 edition)

Name	Color description	Water detection	Ash detection (Total ash)	Volatile oil content	Extract content	Determination of content	
						Marker component	Content requirement
ZR	The surface is gray-yellow or light gray-brown, and the interior is yellow-white or gray-white	$\leq 19.0\%$	$\leq 6.0\%$	$\geqslant 0.8\%$	$\leq 22.0\%$	6-Gingerol	$\geq 0.60\%$
CZR	The surface is black, and interior is brown				$\leq 26.0\%$	6-Gingerol	$\geq 0.05\%$

—: it is not required in the *Chinese Pharmacopoeia* (2020 edition).

To sum up, existing quality investigations of ZR and CZR predominately focus on discerning the basic alterations in visual attributes and key components before and after carbonization processing. A notable gap persists in terms of tracking and elucidating the evolving dynamic of visual characteristics and constituents, as well as the intricate interplay between components and pharmacological activities, pharmacological activities, and clinical efficacy during the stir-frying carbonization process. This underscores the pressing need for the development of quality assessment methodologies for ZR and CZR, signifying a critical avenue for future research endeavors.

5 Chemical constituents

The chemical constituents of ginger are vast and divergent, contingent upon whether it exists in its raw or

Table 4 Chemical compounds in ZR and CZR

processed form. In this review, our objective is not to comprehensively list all documented ginger compounds, but rather to summarize the main components with pharmacological implications in ZR and CZR. The primary chemical constituents present in ZR and CZR predominantly encompass volatile oils, gingerols, and diphenylheptane $^{[42, 43]}$ $^{[42, 43]}$ $^{[42, 43]}$ $^{[42, 43]}$ $^{[42, 43]}$.

5.1 Volatile oils

The pungent smells of ZR and CZR primarily originate from volatile oil, the concentration of which diminishes during the transformation of ZR into CZR, thereby bestowing a milder medicinal nature. The core constituents of these essential oils include sesquiterpene carbohydrates and sesquiterpenoids. [Table 4](#page-6-0) lists the main volatile oil components (listed as No. 1 to No. 30). Their structures are presented in [Figure 3](#page-8-0).

Table 4 Continued

+ : detected in samples. ND: can't be found in samples. NR: no researches were carried out.

Figure 3 The chemical structures of volatile oils

5.2 Gingerols

Gingerols, the principal spicy constituents found in ginger, serve as the primary functional elements within the Zingiber species. These gingerol-related compounds are believed to demonstrate notable anti-inflammatory and anti-nausea effects $^{[49, 50]}$ $^{[49, 50]}$ $^{[49, 50]}$ $^{[49, 50]}$ $^{[49, 50]}$. It is a mixture composed of a variety of substances. The molecular structure of each component substance contains a 3-methoxy-4-hydroxyphenyl functional group. Based on variations in the hydrocarbon chain linked to the functional group, gingerol can be classified into shogaol, para-zingerone, zingerone, gingerdione, etc. $^{[46]}$ $^{[46]}$ $^{[46]}$. There are more than a dozen of clear gingerols, including 6-, 8-, 10-, and 12-gingerol. These components share similarities in both properties and structures, characterized by molecular arrangements featuring C₃-Carbonyl and C₅-hydroxyl (i.e., *β*-hydroxyketone structure), which makes gingerol chemically unstable. Contemporary understanding suggests that fresh ginger contains minimal amount of gingerol and zingerone, with their presence becoming more prominent due to the dehydration of gingerol during the storage and processing of ginger [\[51](#page-14-1)] . The primary gingerol constituents of ZR and CZR (No. 31 - No. 48) are enumerated in [Table 4](#page-6-0), and their corresponding structures are presented in [Figure 4](#page-8-1).

Figure 4 The chemical structures of gingerols

5.3 Diphenylheptanes

Diphenylheptanes constitute a group of compounds characterized by a core 1,7-diphenylheptane structures, which can be categorized as linear and cyclic based on their structural arrangements ^{[\[52](#page-14-2)]}. Over the past few years, numerous researchers have conducted investigations into the diphenylheptanes in Zingiberaceae, revealing significant pharmacological potentials encompassing antiinflammatory, anti-oxidant, antibacterial, antiviral, and antitumor effects ^{[\[53](#page-14-3), [54](#page-14-4)]}. Its representative compound, curcumin, showcased remarkable biological efficacy and held promising avenues for development. However, its clinical application was hindered by suboptimal pharma-cokinetic attributes [\[55](#page-14-5)]. [Table 4](#page-6-0) lists the main diphenylheptane constituents in ZR and CZR (No. 49 - No. 56), [while th](#page-9-0)eir corresponding structures are illustrated in [Figure 5](#page-9-0).

Obviously, the carbonization process undeniably influences the chemical compositions of ZR. Varying degrees of heating and preparation lead to significant shifts in the quantity and quality of the volatile oil's chemical composition. For instance, ZR contained as much as 40.48% *α*-citral, while the content of *β*-sesquiterpene experienced marginal reduction. Comparatively, CZR exhibited elevated levels of gingerene and *β*-sesquiterpene, and intriguingly gave rise to novel constituents such as

Figure 5 The chemical structures of diphenylheptanes

α-caryophyllene, decalin, and *γ*-elemene ^{[[44\]](#page-13-24)}. Numerous experimental investigations have consistently demonstrated that the stir-frying carbonization process would diminish the volatile oil concentration and increase the content of gingerol and polysaccharides. The intricate interplay between the shifts in these component concentrations and the corresponding alterations in pharmacological effects warrants further comprehensive explorations. Consequently, CZR and ZR manifest distinct pharmacological profiles, underscoring the need to judiciously select appropriate carbonized herbal medication and processing degrees in accordance with specific ailments.

6 Pharmacological effects

Adhering to the principle of "burning to ash without becoming ash" helps preserve certain inherent properties and TCM attributes even after carbonization processing. Aligned with the nature and therapeutic potential of ZR, the pharmacological effects of CZR predominantly manifests in hemostatic and antioxidative effects.

6.1 Hemostatic effects

Hemostasis involves a complex series of coagulation and fibrinolysis processes $[56, 57]$ $[56, 57]$ $[56, 57]$ $[56, 57]$ $[56, 57]$. It facilitates blood clotting,

reduces vascular permeability, induces vasoconstriction, suppresses fibrinolysis processes, and stimulates platelet aggregation. As a result, the current focus of the pharmacological mechanism of carbonized TCM herbs for the treatment of hemostasis is predominantly through assessing platelet count, hemorheology changes and the evaluation of four clotting items [\[58](#page-14-8), [59\]](#page-14-9): prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB). These investigations aim to elucidate the influences of CZR on the coagulation system, fibrinolysis system, platelet function, hemorheology and so on.

The emulsion of ZR's volatile oil was observed to extend the blood coagulation duration in mice. It was reported that CZR notably reduced clotting time in mice, suggesting the presence of volatile oil and water-soluble procoagulant elements in ZR's impact on the coagulation system. Moreover, higher temperature was [fo](#page-14-10)und to promote the effects of the latter constituents [[60\]](#page-14-10) . CZR might hinder the activation of plasminogen and elevate the [FIB](#page-13-0) levels to [ex](#page-14-11)ert its hemostatic and coagulation effects [[20\]](#page-13-0). SU et al. $^{[61]}$ $^{[61]}$ $^{[61]}$ showed that CZR might affect the coagulation system of rats and regulate the thromboxane B_2 and 6-keta-prostaglandin F_{1α} lev[el](#page-13-30)s to achieve hemostasis and coagulation. SU et al. $[19]$ $[19]$ employed metabolomics to investigate changes in serum metabolites among rats with deficiency-cold and hemorrhagic syndrome. This study aimed to elucidate CZR's hemostatic potential, with the findings revealing that CZR was capable of restoring biomarkers in deficiency-cold hemorrhagic syndrome rats to physiologically normal level, and glycine, tryptophan, and lactic acid emerged as biomarkers reflecting CZR's warm meridian hemostatic effects [\[19](#page-13-30)]. Drawing upon neural network analysis of *in vivo* constituents and pharmacodynamics, ZHOU et al. $^{[62]}$ $^{[62]}$ $^{[62]}$ identified 6-gingerol, zingerone, and diacetyl-6-gingerol as the primary active compounds within CZR for hemostasis, collectively accounting for a substantial 73% contribution. Gingerols such as 6-gingerol and 10-gingerol had thermoregulatory effects through the activation of transient receptor potential channels, specifically transient receptor potential vanilloid 1 and transient receptor potential channel protein A1. This activation led to heightened intracellular $Ca²⁺$ concentration, subsequently elevating body temper-ature [[63,](#page-14-13) [64](#page-14-14)]. Thus, the anti-bleeding effect of CZR is closely related to the intrinsic anticoagulant activity and the activation of the FIB system.

6.2 Anti-oxidant effects

MASUDA et al. $^{[65]}$ $^{[65]}$ $^{[65]}$ revealed that the side chain groups within curcumin and diphenylheptane compounds demonstrated anti-oxidant effects. This was achieved through the inhibition of free radical activity, as confirmed by free radical scavenging assays and *in vitro* antioxidant tests. Through a comparative analysis of the antioxidant activities of ginger and its various processed products, LI et al. [[66\]](#page-14-16) discovered that CZR exhibited the most potent anti-oxidant effect due to the substantial generation of 6-gingerenol and gingerone during processing, enabling the regulation of free radical activity. Over the last two decades, a multitude of studies have delved into the anti-oxidant prowess of curcumin and the intricate mechanisms underlying its free radical scavenging capabilities. These investigations have unveiled that both free and encapsulated curcumin possess the capacity to indirectly enhance anti-oxidant enzymes like superoxide dismutase, catalase, and glutathione. Despite these advancements, a debate persists regarding the specific element that truly governs curcumin's anti-oxidant activity, that is whether it's the central methylene hydrogen, aldehyde hydrogen or phenolic hydrogen within the heptadiene, as indicated by conflicting findings $[67, 68]$ $[67, 68]$ $[67, 68]$ $[67, 68]$.

6.3 Other effects

Analysis of neurotransmitter levels in mice demonstrated that the CZR nanocomponent effectively elevated enkephalin, endorphin, and 5-hydroxytryptamine concentrations in the brain tissue of mice. This substantiated the CZR nanocomponent's capacity for a central analgesic effect ^{[\[69](#page-14-19)]}. Within human monocytic leukemia cells (THP-1), 10-gingerol, 6-shogaol, and 8-shogaol inhibited the ability to impede the direct binding of serum levels of intercellular adhesion molecule-1 (sICAM-1) to lymphocyte function-associated antigen-1 (LFA-1), a lymphocyte function-related antigen $^{[70]}$ $^{[70]}$ $^{[70]}$. By interacting with deoxyribonucleic acid (DNA), 6-gingerol showed the potential to initiate cell death through autophagy as well as apoptosis mediated by caspase-3^{[\[49](#page-13-29)]}. The 6-gingerol showed robust antibacterial effect against Helicobacter pylori, with the conformational correlation underscoring the essential role of the ginerols' shorter alkyl side chains in effectively inhibiting these microorganisms $^{[71]}$ $^{[71]}$ $^{[71]}$. The incorporation of double bonds and linear chains within 6 shogaol might amplify the neuroprotective potential inherent in this compound category $^{[72]}$ $^{[72]}$ $^{[72]}$. Emerging from the heating of gingerols, shogaols exhibited heightened efficacy in curbing the generation of inflammatory mediators and reactive oxygen species (ROS), coupled with superior thermal stability relative to gingerols. A non-irritating derivative of 6-paradol, namely 6-shogaol, circumvented adverse effects like gastric irritation [\[73](#page-14-23)] .

7 Discussion

7.1 Chemical composition and quality control of CZR

CZR encompasses a wide range of compounds including gingerols (6-gingerol, 8-gingerol, 10-gingerol, and diacetyl-6-gingerol), 6-gingerenol, 6-gingerenone, and gingerone. In a study by ZHOU et al. $^{[62]}$ $^{[62]}$ $^{[62]}$, employed a neural network to analyze *in vivo* composition and pharmacodynamics, it was revealed that 6-gingerenol, gingerone, and diacetyl-6-gingerol stood out as the primary pharmacological contributors to CZR's capability for promoting menstrual warmth and halting bleeding. These key components collectively accounted for a substantial 73% of the effect ^{[\[62](#page-14-12)]}. CHEN et al. ^{[[45\]](#page-13-25)} employed ultra high performance liquid chromatography-orbitrap high-resolution accurate mass spectrometry (UHPLC-Orbitrap HRMS) in conjunction with metabolomics multivariate analysis to analyze changes in non-volatile components within ZR after being processed. The results showed notable discrepancies in the relative contents of 11 compounds, including 6-shogaol, 8-shogaol, and methylacetoxy-6-gingerdiol, after concoction. Notably, the relative proportions of gingerenols within ZR exhibited substantial en-hancement in response to the carbonized processing [[45\]](#page-13-25). But the transformation of ZR into CZR led to the reduction in the concentrations of 17 compounds including 4-gingerenol, 6-gingerenol, 6-gingerol, 8-gingerol, and 1,7-bis(3,4-di-hydroxyphenyl)-3-heptanone, with the exceptio[n o](#page-12-16)f gingerone, which showed a substantial increase [[18\]](#page-12-16) . Therefore, it is advisable for the *Chinese Pharmacopoeia* to institute distinct quality standards and

content specifications for CZR as opposed to ZR. This approach would facilitate precise differentiation between prepared decoction pieces and ensure effectively quality management.

7.2 Discussion on clinical applications of ZR and CZR

Despite both ZR and CZR originating from the same source, their clinical applications exhibit distinct variations. ZR is characterized by its pungent and warm properties, rendering it crucial for detoxification, antiemetic, and tonic purposes. Apart from its association with spleen and lung meridians, ZR also corresponds to the heart and kidney meridians, making it particularly suitable for addressing conditions exacerbated by cold or damp climatic influences. For example, Gancao Ganjiang Decoction finds application in treating severe cough and pulmonary infections in COVID-19 patients. However, caution must be exercised due to ZR's potent warming properties, potentially leading to heightened effects that could impact the body's Qi and blood. Therefore, its administration often requires combination with adjunctive remedies like licorice to mitigate potential side effects [\[24](#page-13-5), [74](#page-14-24)] . However, CZR undergoes high-temperature processing, which diminishes its pungent and warm attributes, resulting in a gentler efficacy that preserves the body's natural immunity. Furthermore, this processing augments its astringent properties, notably enhancing its effects in hemostasis and alleviating diarrhea. Therefore, CZR holds clinical utility when administered in tandem with other medications to address diverse condition stemming from bleeding or blood deficiency co-occurring with a cold constitution $^{[30, \, 75]}$ $^{[30, \, 75]}$ $^{[30, \, 75]}$ $^{[30, \, 75]}$ $^{[30, \, 75]}$. For example, Shenghua Decoction is used for postpartum lochia and cold abdominal pain; Liqi Sanyu Decoction is used for bleeding and dizziness after abortion; Yanghe Decoction is employed for countering cold-related issues attributed to blood deficiency; and Buqi Jieyun Decoction is applied to the treatment of postpartum hemorrhage and dizziness.

7.3 Pharmacological mechanisms for the treatment on hemostasis with CZR

From the perspective of TCM theory, bleeding signifies a pathological state wherein blood escapes the confines of blood vessels. Factors that can cause bleeding including external Yang heat forcing blood to flow recklessly, excessive Yang Qi in the organs leading to Qi and blood rushing back, lack of blood absorption by Qi or internal obstruction of blood stasis leading to blood not following the meridians, and various traumatic damage to the meridians and collaterals. This complex interplay, including traumatic injuries or disruptions to blood vessels and meridians, collectively contributes to incidence of bleeding. Modern medicine believes that the human blood

system comprises two interdependent yet opposing dynamic equilibrium system: coagulation and anticoagula-tion, along with fibrinolysis and antifibrinolysis <a>[\[76](#page-14-26)]. Disruption of this delicate equilibrium can result in the emergence of either bleeding or thrombotic disorders. Deviations from these mechanism, whether due to inherent or acquired issues concerning vessels walls, platelets, coagulation, and fibrinolysis, collectively underlie the development of bleeding disorders. The hemostatic efficacy of TCM involves a series of complex coagulation and fibrinolytic processes, mainly including the enhancement of blood coagulation, the mitigation of vascular permeability, facilitation of vasoconstruction, suppression of fibrinolytic activities, and stimulation platelet aggregation $^{\scriptscriptstyle [58]}$ $^{\scriptscriptstyle [58]}$ $^{\scriptscriptstyle [58]}$.

Therefore, the current research on the pharmacological mechanisms underlying the hemostatic properties of carbonized TCM herbs predominantly delve into its impact on the coagulation system, fibrinolytic system, platelet function, and blood rheology. These investigations involve assessments of platelet count, changes in blood rheology and measurement of key coagulation parameters including PT, APTT, TT, and FIB. The process of [CZR's w](#page-11-0)arming and hemostatic mechanisms is shown in [Figure 6](#page-11-0).

CZR, administeres via gavage to rats with deficiencycold and hemorrhagic syndrome, demonstrates a capacity to significantly shorten the coagulation time, including TT, PT, and APTT, in rats displaying evidence of clod-induced bleeding. Additionally, it exhibits the ability to elevate plasma viscosity, extend euglobulin lysis time, and augment FIB content. *In vitro* cellular assays, gingerone, diacetyl-6-gingerol, and 6-gingerol exhibit the potential to enhance the expression of procoagulant factors such as TF, FXII, FXa, FIIa, VWF, and ITGB3, which are secreted by human vascular endothelial cells. Simultaneously, they demonstrate inhibitory effects on the expression of tissue plasminogen activator/plasminogen activator inhibitor-1 (t-PA/PAI-1), leading to a reduction in fibrinolytic system activity and consequent suppression of fibrinolysis, thus contributing to pro-coagulant outcomes.

Figure 6 The process of CZR's warming and hemostatic mechanisms

8 Conclusion

In this review, we have systematically compiled a overview encompassing the realms of quality control, chemical composition, ethnopharmacology, and pharmacological behaviors of CZR. Our focus rested upon discerning the principal chemical distinctions existing between ZR and CZR, with particular emphasis placed on volatile oils, gingerols, and diphenylheptane compounds. However, the bioactivities attributed to gingerols and shogaols, two primary constituents found in ZR and CZR, respectively, demonstrate distinct and diverse characteristics. The comparative analysis of their biological activities remains largely uncharted. Furthermore, constituents like diphenylheptanes have yet to receive adequate research. Given the potential influence of various factors on chemical composition, it becomes imperative to elucidate the evolving patterns in order to provide enhanced direction for clinical applications. Subsequent studies could delve deeper into unraveling the underlying material foundation of CZR's hemostatic effects. This could be achieved through an exhaustive multi-omics exploration, including aspects such as pharmacodynamics, pharmacokinetics, pharmacokinetic-pharmacodynamic correlation, metabolomics, proteomics, and correlation analysis of network pharmacology and its mechanism of action. We anticipate that the insights gleaned from this discourse will not only foster a better understanding of other carbonized medicinal herbs, but also facilitate their secure and effective clinical application.

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Competing interests

The authors declare no conflict of interest.

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炒炭炮制对干姜质量控制、化学成分和药理作用的影响

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【摘要】干姜和姜炭作为中药被广泛用于治疗各种疾病,悠久历史。两者均来源于姜科植物的根茎,由于干燥 和炮制加工程度的不同,其中药药性、化学成分、药理活性和临床应用均有所不同。本文从中国知网 (CNKI)、 PubMed、Web of Science 和 Google Scholar 数据库收集了干姜炒炭前后的信息,通过系统地回顾有关姜炭的 民族药理学、质量控制、化学成分、生物活性和临床应用的文献,总结讨论了干姜和姜炭的区别。在化学成分分 析中,我们从干姜和姜炭中共分离鉴定出 56 种化学成分,主要是挥发油、姜辣素和二苯庚烷;在药理作用中,姜 炭主要表现出止血、抗氧化、镇痛、抗菌和抗癌等一系列生物活性;在临床应用中,干姜辛热,被认为是一种补阳 药,通常用于治疗寒冷或潮湿天气引发的疾病,姜炭是一种由干姜在高温下炮制加工的产品,其辛热之性减弱, 因此药效变温和,以其止血和温脾止泻作用而闻名。目前对姜炭止血的药理机制的研究主要是探讨姜炭对凝血 系统和纤溶系统的影响。尽管姜炭的疗效早已得到认可,且饮片成分的变化和颜色的变化之间存在一定的相关 性,但仍然缺乏相对清晰的炮制机理指导下的反映炭药止血功效成分的特征性和专属性质量标准。本文综述了 姜炭的质量控制、化学成分、民族药理学和药理作用机制,也为其他炭药的进一步研究提供了新的见解,促进其 临床的安全应用。

【关键词】干姜;炮制;炒炭;化学成分;质量控制;止血活性