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Exploring wine-processing: a distinctive classic technique in TCM

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Wine-processing represents a distinctive technique in Traditional Chinese medicine (TCM) preparation. Refined through millennia of practice, it embodies ancient wisdom in modulating medicinal properties. This method utilizes interactions between wine and herbs to enhance targeted delivery, moderate cold/bitter properties, amplify therapeutic effects, and reduce toxicity. Its clinical significance remains paramount. We systematically analyzed literature from scientific databases (Baidu Scholar, CNKI, Google Scholar, PubMed, ScienceDirect, Web of Science, SciFinder), historical texts, and the 2025 Chinese Pharmacopoeia. Graphical abstracts were generated using the Generic Diagramming Platform (GDP, https://www.BioGDP.com) to identify research gaps and future priorities. Evidence confirmed wine-processing improves channel tropism, enhances kidney/liver tonification, and increases bioactive compound solubility. Nevertheless, significant challenges hinder its modernization. Future research should prioritize process parameter optimization, quality-marker discovery, and multi-omics studies to scientifically elucidate efficacy-toxicity modulation mechanisms and advance clinical translation of this traditional technique.

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1 Introduction

Traditional Chinese Medicine (TCM) processing refers to the processing of raw herbs through physical or chemical methods to change their properties and flavors, enhance their clinical efficacy, or reduce their toxicity.[1] Wine-processing alters the chemical composition and biological activity of herbs by wine-mediated dissolution and transformation.[2] The core of wine-processing lies in leveraging wine's solubility. Through treatments like soaking and decoction, it promotes active ingredient dissolution/transformation and adjusts the meridian-tropism characteristics of medicinal materials, thereby enhancing clinical efficacy.

In the theoretical system of TCM, wine holds dual attributes as "both food and medicine". TCM recognizes three main clinical values of wine: (1) as a standalone drug, the "*Huangdi Neijing* (黄帝内经)" recorded that "When people drink alcohol, the defensive qi first reaches the skin and fills the collateral vessels. The collateral vessels are filled first. Therefore, when the defensive qi is balanced, the nutritive qi is full, and the meridians are greatly filled". It can be seen that TCM believes that wine can dredge the meridians, warm yang and dispel cold, and guide the efficacy of drugs;[3] (2) combined with herbs to make medicinal wines, for example, Compendium of Materia Medica listed 30 health-preserving wines;[4] (3) in the processing of medicinal materials, wine can not only dissolve the active ingredients of drugs but also enhance their efficacy through its volatile nature. Thus, the unique theory of "wine-processing to elevate efficacy" was developed. Ancient medical practitioners took advantage of these characteristics of wine and summarized a systematic method for processing medicinal materials, known as wine-processing of TCM. This involves using yellow rice wine or white wine as a medium and applying techniques such as wine frying, wine steaming, and wine stewing to activate the properties of the herbs.

Wine-processing has been used for thousands of years. However, its modern use has greatly declined. The 2025 Chinese Pharmacopoeia listed only 19 wine-processed products. This was a sharp drop of 92.8% from the 267 types recorded in the Qing Dynasty. Based on bibliometric analysis, research on Chinese medicinal wine-processing in Chinese literature primarily centered on the varieties of wine-processing, techniques, processed products, quality standards, and mechanisms. In contrast, studies in English literature predominantly focused on chemical constituents, pharmacokinetics and tissue distribution, as well as the mechanisms underlying pharmacological effects. This article reviewed recent advancements in wine-processing by examining adjuvant types, methodologies, objectives, optimization of processing techniques, and the impact of wine-processing on the chemical composition,

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pharmacodynamics, and pharmacokinetics of Chinese medicinal materials. Furthermore, it critically analyzed and discussed existing gaps in current research.

Existing reviews often focus narrowly on individual steps of wine-processing, failing to connect chemical changes with biological effects. This review systematically linked processing parameters to compositional shifts, efficacy modulation, and pharmacokinetics. We elucidated transformation mechanisms to establish the chemical basis for bioactivity, constructing a comprehensive "Process-Constituent-Effect" framework. By identifying research gaps, this work provided a theoretical foundation for quality control and clinical translation, addressing the lack of systematic and mechanistic insights in the current literature.

2. Types of wine

2.1 Wine-mediated processing

The types of wine used for rituals have been recorded as "the fragrant sacrificial wine (鬯其酒)" since the Oracle Bone Script era. "A Sacrificial Wine (鬯酒)" refers to the fragrant wine made from mugwort.[5] In the Zhou Dynasty, "*Rites of Zhou* (周礼)" recorded the practice of using wine for preserving corpses, at which point wine already had multiple functions such as being a beverage, a seasoning, and a preservative.[6] During the Spring and Autumn and Warring States periods, the medical book "*Prescriptions for Fifty-two Diseases* (五十二病方)" unearthed from the Ma Wang Diu Han Tomb included over 40 kinds of medicinal wine, pioneering the precedent of combining wine and medicine for treatment, and the theory of "Medical Wine Origin" and "Medicinal Wine Origin" began to sprout.[7] In the Ming Dynasty, Li Shizhen in "*Compendium of Materia Medica* (本草纲目)" classified wines into three major systems: wine, distilled wine, and grape wine, laying the foundation for the classification of medicinal wine in later generation.[8]

Yellow rice wine, also known as clear wine or rice wine in ancient times, is a fermented wine made from glutinous rice, japonica rice, millet and other grains as the main raw materials, with the addition of fermentation agents such as koji and yeast.[9] The Han Dynasty text, "*Treatise on Cold Pathogenic and Miscellaneous Diseases* (伤寒杂病论)" by Zhang Zhongjing was a milestone for yellow rice wine. He first used "clear wine" as the base for decoctions, such as in the *Zhi Gancao* Decoction, where the warming and unblocking properties of clear wine were utilized to enhance the efficacy of the medicine, greatly expanding the clinical application scope of medicinal wine.[10] During the Tang and Song Dynasties, wine-making was very popular. The "*Newly Revised Materia Medica* (新修本草)" mentioned a variety of raw materials for wine-making, but only "rice wine" was used in medicine.[11] Baijiu, historically referred to as distilled liquor, is a spirit produced from grains, primarily utilizing fermentation agents like Daqu, Xiaoqu, or Fuquand yeast.[4] It is produced through processes such as steaming, saccharification, fermentation and distillation. Before the Yuan Dynasty, medicinal wines mostly used low-wine grain-based fermented wines as the base. Traditional brewing used simple equipment. It had short cycles. Because of this, the wine spoiled easily. Distilled liquor with stronger preservative properties gradually became popular. Although there have been technical changes in the selection of alcoholic beverages for medicinal purposes throughout history, the consensus that grain-fermented "rice wine" is superior has persisted, which is the yellow rice wine as defined in the 2025 edition of the Chinese Pharmacopoeia.[12,13] Currently, most Chinese herbal slice processing enterprises mainly follow the national standard GB/T 13662-2018 for yellow rice wine as the quality control criterion. The physical and chemical requirements mainly include sugar content, wine content, pH, and total acid, *etc*.[14]

However, there are no clear guidelines on the variety selection, ethanol concentration, and proportion of yellow rice wine for medicinal use, leading to significant differences in the quality stability and clinical efficacy of wine-processing Chinese medicines. Therefore, it is still necessary to establish scientific guidelines through modern analytical techniques and pharmacological evaluation methods.

2.2 Health wine

For medicinal soaking, Baijiu is often used, while yellow rice wine is preferred for steaming.[15] While wine was used therapeutically, its primary role was often that of a solvent. The general concept of medicinal wine involves steeping herbs in a distilled spirit to produce a clear, liquid preparation.[16] The prototype of modern Chinese health wines is, in fact, this traditional medicinal wine.[17] During the Yuan, Ming, and Qing dynasties, medical practitioners placed greater emphasis on herbal combinations and the principle of "medicinal food homology". This shifted the application of wine from treating diseases toward reinforcing vitality and preserving health. For instance, the *Compendium of Materia Medica* (本草纲目) documents wines such as those made with Lycii fructus and Ginseng radix et rhizoma, which were primarily valued for their ability to "nourish essence and strengthen tendons and bones".[6]

The functional organic compounds in health wines determine their efficacy. These wines target deficiencies in Yin, Yang, Qi, and Blood, promoting organ function and holistic health. Benefits include enhanced immunity, reduced fatigue, delayed aging, and longevity.[18] For example, a wine made from dried lychee and Lycii fructus is documented to boost antioxidant enzymes like SOD and CAT, and modulate immune cytokines such as IL-10, thereby aiding Qi and Blood metabolism.[19]

Despite their popularity, China's medicinal wine industry faces significant challenges:some formulas ignore TCM principles or use excessive ingredients, while many older OTC products lack updated safety and efficacy data. Advancing the industry requires multidisciplinary studies to clarify these mechanisms, establish chemical fingerprints, and link specific components to health benefits. Strengthened quality control and regulation are also crucial to prevent counterfeit products and misleading claims. This comprehensive approach is essential for the industry's sustainable development and the preservation of this traditional practice.

3. Historical development of wine-processing methods

The earliest records of wine-based processing methods dated to the Spring and Autumn and Warring States periods. The Western Han medical text "Prescriptions for Fifty-two Diseases" described wine-based techniques, such as making pills and cooking with wine. One instruction was to "Boil with half a dou of pure wine," demonstrating that the versatile use of wine in drug processing was recognized early on.[13] In the late Eastern Han Dynasty, Zhang Zhongjing's texts, "*Treatise on Febrile Diseases* (伤寒论)" and "*Synopsis of the Golden Chamber* (金匮要略)" detailed multiple wine-based methods like wine decoction and mixed wine-water decoction, significantly expanding their application.[20] During the Northern and Southern Dynasties, Lei Xiao's "Leigong *Treatise on the Preparation* (雷公炮炙论)" systematically categorized wine-processing into methods like wine steaming, wine soaking, wine calcination and quenching, and wine boiling, providing important theoretical basis and practical guidance for the subsequent research on drug processing.[21,22] By the Ming and Qing dynasties, the variety of wine-processed drugs reached its peak; the "*Compendium of Materia Medica*" documented over 95% of entries utilizing wine. This era not only continued earlier techniques but also developed more than ten new methods, including steaming and stir-frying, while establishing strict standards for auxiliary materials, procedures, and quality.[6] Through systematic research, we have summarized the methods of making medicinal wine in various historical periods. The detailed information can be found in SI Table S1.

The wine-processing method has evolved through generations, with diverse techniques arising from varied medical interpretations. In ancient prescriptions, medicinal materials were moistened with wine and then dried. Different drying methods gave rise to methods such as washing with wine, soaking in wine, and stir-frying with wine. In fact, these are all the sources of the wine frying method or wine steaming method described in the 2025 edition of the Pharmacopoeia. The current Chinese Pharmacopoeia recognizes several wine-processing methods, including wine soaking, wine moistening, wine frying, wine steaming, wine stewing, SI Table S2 detailed their specific processes and distinct technological characteristics.

However, modern medical research shows that when wine is metabolized in conjunction with some TCMs, it can easily lead to liver and kidney damage. Moreover, wine consumption can affect the absorption, distribution, and metabolism of drugs.[4] Many traditional applications of wine in Chinese medicine, such as its use in topical dressings or as a vehicle for oral medications, have been significantly simplified or abandoned in modern practice. Further research into processing techniques and their integration with modern medicine is therefore critically important. This direction is vital not only for preserving traditional knowledge but also for driving innovation within contemporary healthcare systems.

4. Salt processing TCM

The development of wine-processed products is similar to the methods of wine-processing. From the Song Dynasty to the Ming Dynasty was a prosperous period for the development of wine-processed products, and a large number of such products emerged. In the Qing Dynasty, there were 267 kinds of TCM processed with wine. People's understanding of TCM has gradually deepened. The specific situations of newly added and continued use of wine-processed TCM were shown in SI Tables S3 and S4.

5. Wine-processing technology

The processing of traditional Chinese medicine adheres to the ancient maxim of "In the preparation of medicines, moderation is of utmost importance" and emphasizes precise control. Modern research optimizes process parameters by establishing correlation models between chromaticity, components, and pharmacological effects, combined with orthogonal experiments and the response surface method. The development of traditional Chinese medicine processing has shown a significant transformation. It is moving away from a single judgment based on traditional experience. Instead, it is now adopting a comprehensive evaluation system. This new system combines multiple indicators. These indicators include physical properties, chemical components, and biological activities. For example, Fan used near-infrared spectroscopy to detect the active components of *Cornus* officinalis processed with wine to different degrees. It was found that the hydroxyl groups and C–O bonds remained stable during the processing of *Cornus* officinalis, and the carboxylic acid content in the processed products reached its peak after 8-12 hours of processing, which could be regarded as the optimal processing duration;[23] Zhou *et al.* used the activity of earthworm fibrinolytic enzyme as the evaluation index, and the processing temperature, processing time, amount of added wine, and moistening time as the influencing factors, and optimized the wine frying parameters of *Pheretima* through the orthogonal experiment method;[24] He *et al.* determined the optimal production process conditions for *Ligustri lucidi* fructus by comparing the content of specnuezhenide and the appearance characteristics of the wine-steamed products;[25] Zhang *et al.* designed an orthogonal experiment to optimize the wine steaming process of *Curculiginis* rhizome (CU), with the contents of curculigoside, orcinol gentiobioside, orcinol glucoside, and wine soluble extracts as the evaluation indicators, and the amount of added wine, moistening time, and steaming time as the influencing factors;[26] Zhao *et al.* comprehensively scored the appearance characteristics, 5-hydroxymethylfurfural content, polysaccharide content, and antioxidant capacity of wine *Polygonati* rhizoma (PR) as the evaluation indicators, and optimized the wine steaming process of PR using the orthogonal experiment method.[27]

However, there are still unsolved problems in the process optimization of wine-processing and wine production: the scientific mechanism is weak, and the interaction mechanism between excipients and decoction pieces has not been clarified;

the quality control system is lagging behind, the key parameters of some medicinal materials still rely on empirical operation, and the quality evaluation of decoction pieces lacks a multi-dimensional comprehensive standard covering physical and chemical properties and biological activity; technology transformation is disjointed, the connecting mechanism from laboratory research to pilot production is not yet perfect, and industrial production still uses extensive mode. To solve the above problems, it is necessary to take the multi-dimensional interaction of "excipient-medicinal materials-decoction system" as the entry point, and combine the theory of supramolecular self-assembly to systematically analyze the co-solubility and dynamic assembly law of excipents such as yellow rice wine and honey and active substances of medicinal materials in the processing process;[28] the application of modern research methods such as mass spectrometry imaging,[29] response surface method and AHP-CRITIC mixed weighting method can optimize the processing technology, develop quantifiable quality markers (Q-markers), and finally realize the scientific transformation of laboratory technology to standardized pilot production, and promote the upgrading of traditional wine technology to a data-driven modern pharmaceutical model.

6. Wine-processing purpose

Practice has shown that processing medicinal materials with wine can change or moderate the medicinal properties, guide the medicinal effects upwards, enhance the efficacy of drugs, facilitate the pulverization of medicinal materials, and mask unpleasant odors and tastes. It is of great significance in clinical medication.[30] The effects of processing with wine can be divided into the following two aspects:

(1) Enhancing Therapeutic Efficacy: wine-processing enhances the efficacy of herbal medicines through several mechanisms. (1) Directing Therapeutic Action Upward and Modulating Potency: the concept of "directing upward" has two implications. First, it directs the therapeutic action to the upper parts of the body and enhances bioavailability. For instance, wine *Chuanxiong* rhizoma exhibited higher plasma concentrations and area under the curve for ligustilide and ferulic acid compared to the raw herb, suggesting improved circulation and metabolic exchange.[31] Similar pharmacokinetic changes were observed for *Ligustri lucidi* fructus (LLF).[32] Second, it moderates overly potent or drastic drug actions. For example, wine-processing significantly reduced the content of combined anthraquinones in Rhei radix et rhizoma (RR), thereby mitigating its purgative effect.[33] (2) Moderating cold drug properties: wine-processing can temper the "cold" nature of certain herbs. Research confirmed that processing *Anemarrhenae* rhizoma with wine alleviated its cold property, as evidenced by increased plasma Ca^{2+}–Mg^{2+}-ATPase activity, which enhances bodily heat production.[34] (3) Strengthening specific actions: wine-processing can intensify actions like promoting blood circulation, removing meridian obstructions, and tonifying the liver and kidneys. For example, wine frying *Achyranthis bidentatae* radix was shown to intervene in chemically-induced liver failure in rats by reducing oxidative stress, suppressing inflammation, and inhibiting hepatocyte apoptosis.[35]

(2) Wine-processing can change the physical state of drug tissues. Research showed that wine-processing can significantly increase the porosity and surface area of medicinal materials. The ethanol and organic acid components in yellow rice wine may act as penetrants, accelerating the release of components and enhancing specific medicinal effects, making them easier to apply: (1) it makes certain drugs easier to pulverize and increases the extraction of active ingredients; promotes the transdermal absorption of certain drugs, enhances the wettability of drugs and the permeability of skin capillaries, a model developed by Wang *et al.* using multivariate statistics confirmed that administering herbs with yellow wine promotes the dissolution of active components;[36] (2) reducing toxicity: pretreatment with wine can reduce the toxicity of certain herbs. For instance, wine soaking and water rinsing of *Psoraleae* fructus reduced the dissolution of psoralidin and isopsoralen, thereby lowering its potential hepatotoxicity;[37] (3) it masks unpleasant odors and tastes. The mellow substances such as esters in wine can mask unpleasant odors and tastes. The fishy and muttony odors of animals, which are caused by substances like trimethylamine and aminovaleraldehyde, can volatilize with the wine, such as *Pheretima*, Gecko, *Zaocys*, Ziheche (Dried Human Placenta) and Agkistrodon *etc.*[38]

7. Effect of wine-processing on chemical composition

The core of the wine-processing technology lies in utilizing the polarity and thermodynamic properties of ethanol. Through the dual effects of physical penetration and chemical reactions, it regulates the physical and chemical properties of drug components. These heating-induced transformations, including glycoside hydrolysis and the Maillard reaction, exert a comprehensive influence on the chemical composition of herbs. Investigating these changes is fundamental to understanding the mechanisms behind enhanced efficacy, reduced toxicity, and the emergence of novel therapeutic effects. This knowledge forms a critical foundation for deciphering the scientific principles of wine-processing and guides future research in the field.

7.1 Rhei radix et rhizoma (RR)

Analytical studies using UHPLC, HPLC, and UV spectroscopy have identified consistent patterns in the chemical composition [31]of RR before and after processing, although discrepancies exist due to variations in processing conditions, botanical origin, and study design. A well-established transformation involves anthraquinones. During the wine-processing of *Rheum palmatum* L., the content of bound anthraquinones decreased significantly, with a concurrent increase in free anthraquinones.[39] This conversion is positively correlated with processing intensity, as quantitative analysis of different processed forms of *Rheum tanguticum* Maxim. ex Balf. demonstrated a smaller reduction of bound anthraquinones in wine RR compared to

intensely steamed RR.[40] The observed reduction in anthraquinone glycosides and increase in aglycones were likely attributable to the thermal cleavage of glycosidic bonds during the steaming process. Tannins undergo a similarly significant transformation, characterized by a marked decrease in total content and a rise in gallic acid levels. For instance, the tannin content in steam RR was reported to drop from 3.59% to 0.33%. The specific reduction in condensed tannins further supported the role of high-temperature processing in degrading tannin structures.[41] Literature indicated that the heat-cleaning and detoxifying effects of RR are primarily attributed to its tannins and free anthraquinones. It was hypothesized that the changes in these components formed the material basis for the enhanced efficacy and upward-direction of the therapeutic action after wine-processing.[42] Supporting this, Zeng Chao *et al.* found that steam RR with wine reduced the content of combined anthraquinones, increases the level of free anthraquinones, and degraded the structure of sennosides. These chemical transformations were likely the primary reason for the moderated purgative effect and the strengthened blood-activating function of steam RR.[43]

However, significant discrepancies exist among different studies. For instance, Zhang *et al.* reported elevated catechin levels in both wine and steam RR compared to the raw RR.[40] In contrast, Wang *et al.* detected no catechin in steam RR, a discrepancy potentially attributable to differences in steaming duration; the former process may have been insufficient to cause complete degradation, while the latter's prolonged heating likely led to its breakdown.[44] Another example is the analysis of emodin and chrysophanol. While Zhao *et al.* observed a marked increase in these compounds after processing in *R. palmatum* and *Rheum officinale* Baill., the results for *Rheum tanguticum* Maxim. ex Balf. were inconsistent, potentially influenced by a small sample size ($n = 1$) and its associated specificity bias.[45]

7.2 *Polygonati* rhizome (PR)

Studies on the wine-processing of *Polygonati* Rhizoma (PR) reveal that the primary changes in saccharides involve oligosaccharide hydrolysis and polysaccharide modification. This process prompts the hydrolysis of oligosaccharides, significantly increasing the content of small-molecule sugars such as fructose and glucose, with fructose levels rising by 4 to 27 times compared to the raw PR.[46–48] The mechanism of oligosaccharide hydrolysis is illustrated in Fig. 1. Further research by Xu Rujing *et al.* on *Polygonatum cyrtonema* Hua from Jiuhua Mountain demonstrated that its polysaccharide fraction undergoes a pattern of "content decrease accompanied by structural modification" after wine steaming.[49]

Specifically, the total polysaccharide content decreases, while the molecules undergo structural remodeling, evidenced by a significant increase in molecular weight and the appearance of esterification on β-glycosidic bonds. Furthermore, during the wine steaming of PR, steroidal saponins undergo concurrent transformation and loss, characterized by divergent response trends among molecular weight classes due to

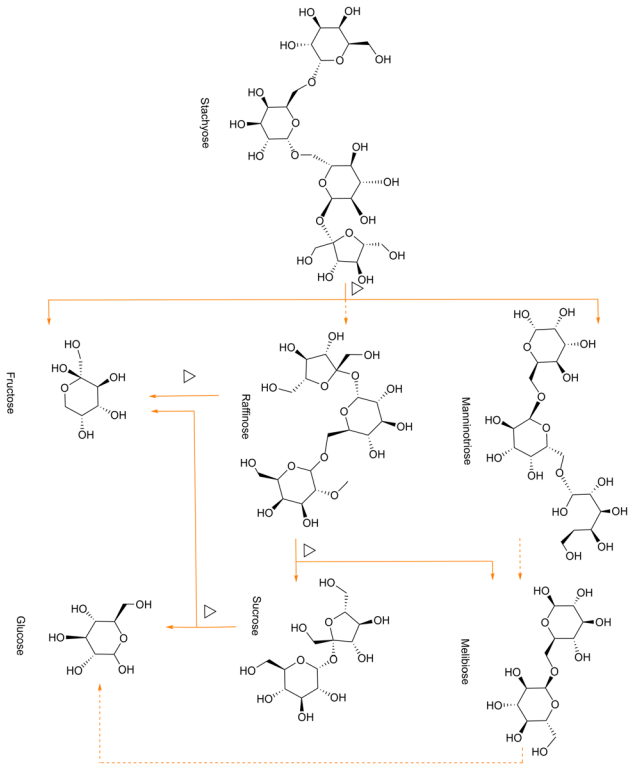

Fig. 1 Schematic diagram of oligosaccharide hydrolysis mechanism.

saponin interconversion, aglycone volatilization, and polarity-driven solubility changes post-hydrolysis.[50] For example, dioscin can be converted into trillin and diosgenin through a hydration reaction, while narcissin undergoes thermal hydrolysis into secondary aglycones accompanied by a decrease in rutinose content.[51] Additionally, protodioscin undergoes deglycosylation to form pseudoprotodioscin, which is subsequently deglycosylated to form secondary saponins, leading to a decreasing trend in the former and a rise-then-fall trend in the latter.[52] The dynamic process of glycosidic bond cleavage is exemplified by the thermal degradation of dioscin (Fig. 2), which illustrates the generation of its aglycone and monosaccharides.

It is also important to note that the Maillard reaction between sugars and amino acids is a key driver of compositional changes during PR processing.[53] As shown in Fig. 3, glucose first condenses with an amino compound (–NH–R) to form *N*-glucosylamine, which then undergoes rearrangements to generate Schiff base, 1,2-enaminol, and finally ARPs (Amadori rearrangement products). Under the condition of pH $\leq$ 7, ARPs convert into 1,2-enaminol, which further undergoes a series of reactions to produce 5-HMF. Specifically, 25 new components, including furans, aldehydes, alcohols, and alkanes, were identified in the processed samples, while 9 original alkanes and fatty acids disappeared. This shift in composition is closely associated with the formation of characteristic Maillard reaction products, such as furans and 5-hydroxymethylfurfural (5-HMF).[54] Further research has confirmed that the 5-HMF content in the ethyl acetate fraction of processed *Polygonatum cyrtonema* Hua increased significantly.[55] Moreover, the generation of both

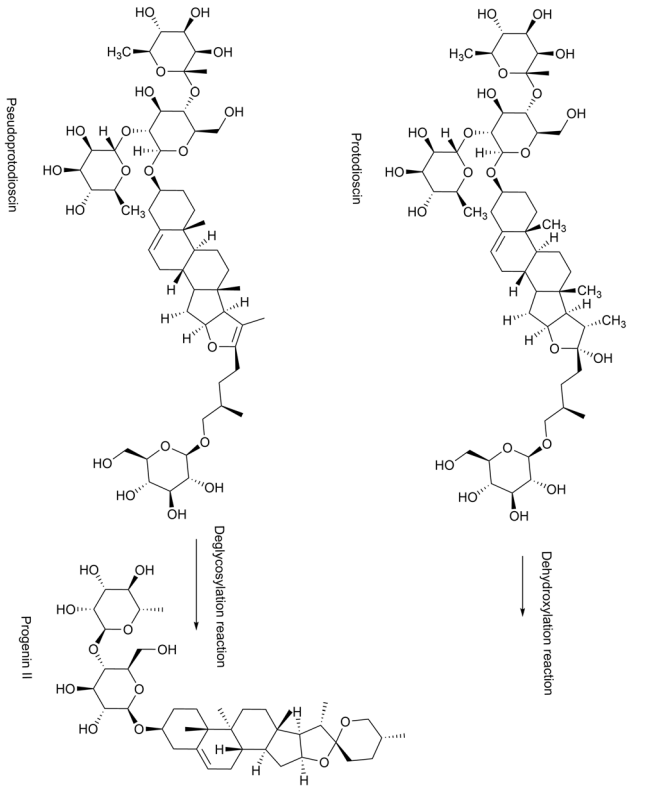

Fig. 2 Hydrolysis of dioscin.

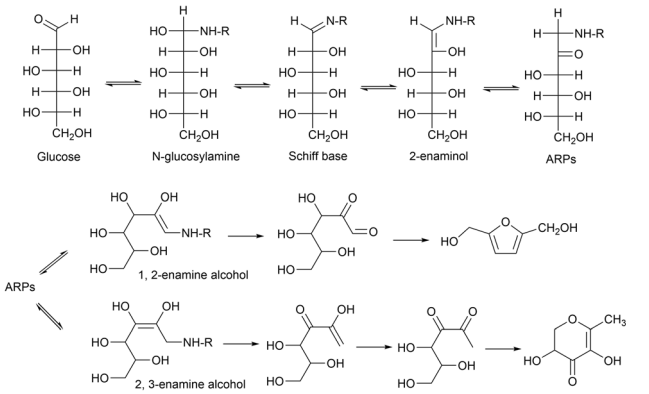

Fig. 3 Maillard reaction process.

5-HMF and 5-hydroxymaltol (DDMP) was detected in three different *Polygonatum* species following wine-processing, providing additional evidence for the crucial role of the Maillard reaction in the processing mechanism.

Substantial variation exists among different studies, primarily regarding species-specific differences and the dynamics of compositional changes during processing. For instance, Zeng *et al.* reported significant interspecies differences in the content of 5-HMF and DDMP among three *Polygonatum* species. In *Polygonatum cyrtonema* Hua, the DDMP content peaked after 24 hours of processing and subsequently declined, whereas 5-HMF accumulated continuously.[56] This pattern highlights distinct kinetics in the underlying Maillard reaction pathways. Amino acid metabolism also exhibits unique characteristics during processing. In a separate study, Wu *et al.* used pre-column derivatization HPLC to analyze hydrolyzed amino acid content in three *Polygonatum* species before and after processing. They found a significant increase in total amino acid content after wine-processing, but a specific decrease in histidine.[57] The authors postulated that the overall increase may be related to the generation of protein-like components from the Maillard reaction, while the decline in histidine likely involves its selective consumption as a specific reactant.

7.3 *Corni* fructus (CF)

The processing of *Corni* fructus (CF) with wine induces three primary types of chemical transformations. First, the thermal degradation of iridoid glycosides is a prominent change. Heat-labile compounds such as geniposide and morroniside undergo hydrolysis or glycosidic bond cleavage, converting into smaller molecules like loganin and gallic acid. This leads to a marked decrease in their original concentrations.[58] Quantitative analyses confirmed this trend, showing a reduction of over 40% in total iridoid glycoside content after processing, which substantiates the pervasiveness of hydrolytic degradation.[59] Second, CF components are converted into furan derivatives *via* deglycosylation, a key metabolic pathway. Polysaccharides, oligosaccharides, and glycosides undergo sequential deglycosylation and dehydration, yielding 5-HMF and its glycosides.[60,61] Supporting this, Shilin Sun *et al.* used isotope labeling to demonstrate that the Maillard reaction is the dominant pathway for saccharide degradation. Furthermore, they found that high-pressure steam processing with wine significantly enhanced 5-HMF yield, indicating that reaction conditions critically influence conversion efficiency. Finally, the esterification of specific glycosides offers a novel perspective on how processing enhances efficacy. For example, 7-*O*-methylmorroniside is converted into 7-*O*-ethylmorroniside in the ethanol medium. This alteration in molecular polarity may improve the bioavailability of the active compounds, providing a molecular-level explanation for the traditional processing method's scientific basis.[59]

It is worth noting that the processing method has a crucial impact on the yield of 5-hydroxymethylfurfural. Long Qiong *et al.* reported that wine-processing increases 5-HMF.[62] Conversely, Niu Minjie *et al.* found only high-pressure wine-steaming is effective, not conventional methods. They propose high pressure accelerates the sugar dehydration step required for 5-HMF formation. Furthermore, the increase in 5-HMF and gallic acid may explain the herb's anti-osteoporosis effect. 5-HMF inhibits osteoclasts, while gallic acid promotes osteoblast growth, linking the chemical changes directly to the pharmacology.[60,61]

7.4 *Ligustri lucidi* fructus (LLF)

The wine-processing of LLF induces three characteristic and co-occurring chemical transformations. First, the targeted hydrolysis of glycosides is a central process. Specifically, speciosenin

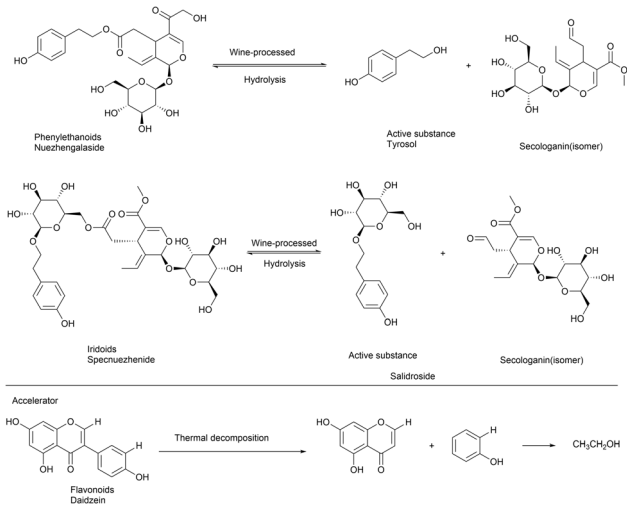

Fig. 4 Transformation pathways of key chemical components during the processing of *Glossy Privet* Fruit.

undergoes ester bond hydrolysis to form salidroside under high temperature and humidity. Concurrently, iridoid and phenylethanoid glycosides experience glycosidic bond cleavage, facilitated by the combined effects of the acidic wine medium and heat. This reaction significantly increased the content of small molecules such as hydroxytyrosol.[63–67] Second, sugar degradation and the Maillard reaction form a synergistic pathway. Consequently, polysaccharide content decreased by 5.54–49.88%, while the level of 5-HMF increased by 21 to 70-fold.[65,68] Furthermore, Zhang *et al.* demonstrated that the wine-processing of LLF involves a series of synergistic chemical reactions, with oxidation being central. These reactions, which include hydrolysis under high temperature and acidity, thermal protein denaturation, flavonoid decomposition, and ethanol-mediated transformation, collectively enhance the activity of phenethyl alcohol glycosides. This is accompanied by characteristic changes: a decrease in iridoid glycosides, total protein, and flavonoids, and an increase in total sugars. Fig. 4 provides a clear schematic of the key transformation pathways, such as the hydrolysis of glycosides and thermal decomposition of flavonoids, visually explaining the mechanism behind the generation of active materials.[67,68]

However, the change in speciosenin content during the wine-processing of LLF exhibits a directional discrepancy. In conventional wine-steaming, its content decreased significantly due to hydrolysis.[63–65] In contrast, under milder, shorter processing conditions, the decomposition rate of its precursor, oleonuezhenide, may exceed the hydrolysis rate of speciosenin itself, leading to a net increase in speciosenin. This phenomenon indicates that processing parameters can be tuned to direct the outcome by manipulating the dynamic balance between hydrolysis and generation reactions.[69]

7.5 *Schisandrae chinensis* fructus (SCF)

The wine-processing of SCF revolves around the differential hydrolysis of ester bonds in its lignan components. Studies indicated that ester-containing lignans (*e.g.*, schisantherin D) undergo hydrolytic degradation under the combined effect of heat and acidic conditions, while the content of non-ester lignans (*e.g.*, gomisin D) increased significantly. This divergence was quantitatively characterized by the increase of seven lignans and the decrease of five others.[70–72] Discrepancies in reported lignan changes stem from the structural sensitivity of the analytes. Lignans with ester bonds are prone to hydrolysis, whereas stable structures like schisandrin A and B remain largely unaffected by processing parameters. An apparent content increase may occur if the temperature or duration is insufficient to reach the reaction threshold, resulting in a hydrolysis rate slower than the decomposition rate of precursor compounds. Furthermore, these compositional changes are linked to traditional efficacy and activity regulation. The elevated level of protocatechuic acid provided a material basis for the traditional use of "processed SCF for tonification".[73] Concurrently, the accumulation of 5-HMF, which correlates with processing intensity, underscored the universal mechanisms of sugar degradation and the Maillard reaction.[74] Volatile oils follow a unique "thermal degradation-dissolution regulation" pattern, where high temperature degrades thermosensitive components, but ethanol facilitates the release of lipophilic ones, establishing a new dynamic equilibrium with reduced total content but the emergence of new constituents.[75]

This model elucidates the "Process-Component-Efficacy" relationship and directs optimization strategies: by fine-tuning parameters such as temperature and duration, one can strategically enrich desired compounds like protocatechuic acid while preserving thermolabile volatiles, ultimately achieving a precise balance of bioactive constituents.

7.6 *Scutellariae* radix (SR)

The study of SR processing reveals a significant dependence on the specific techniques used, which differentially regulate its flavonoid and polysaccharide content. Drying, boiling, and steaming effectively preserve baicalin. This is attributed to the inactivation of enzymes during heating, which prevents the premature hydrolysis of glycosidic bonds. For instance, Shan Chongchong's study found that slices processed under atmospheric pressure for 30 minutes retained a high level of baicalin. In contrast, conventional stir-frying with wine can lead to thermal degradation if temperature is not carefully controlled, causing baicalin to break down into its aglycones, baicalein and wogonin.[76–78] However, an optimized wine-stirring process, which precisely controls temperature and includes a sealing and moistening step, can minimize baicalin loss. This process results in only a slight decrease in baicalin content, coupled with a moderate increase in aglycone levels. This aligns with the chemical principle of "moderate heating promotes conversion" and corresponds to the traditional objective of wine-stirring—to moderate the herb's bitter-cold properties and enhance its anti-inflammatory effects.[79] Research by Xiong You *et al.* provided direct evidence for this, showing that baicalin content and anti-inflammatory activity increased in parallel during the optimal wine-stirring period (before 18 minutes), thereby validating the traditional experience of "moderate wine-stirring for efficacy

enhancement".[80] Conversely, polysaccharides follow an inverse pattern. Wine-stirring promotes polysaccharide dissolution, while wine-steaming causes their degradation. This highlights how the differences between moist-heat and dry–heat treatments directly impact the stability of these macromolecules.[81]

Current research contradictions focus on wine-stir-frying's effect on baicalin. Yang Xinwen *et al.* reported significant baicalin loss,[76,77] while another study found higher content compared to steaming.[82] This discrepancy likely stems from varying process parameters. The former may use excessive temperature or omit a moistening step, accelerating decomposition. The latter likely employs optimized temperature with moistening, reducing degradation and potentially improving dissolution. Thus, specific procedural differences require further validation.

7.7 *Coptidis* rhizome (CR)

Research indicated that key parameters, such as temperature and wine quantity, significantly influence the content and transformation of the primary active alkaloids in CR. Studies by Zhong Lingyun *et al.* reported a significant increase in alkaloid content post-processing, suggesting ethanol may enhance dissolution.[83] Conversely, Jiang Xue *et al.* observed that five characteristic alkaloids initially increased and then decreased with rising temperature (120–160 °C), peaking at 160 °C, accompanied by the formation of berberrubine.[84] Further work by Shen Xiaoqing *et al.* demonstrated that optimal alkaloid retention occurred at specific temperature-wine combinations, confirming that an appropriate amount of wine exerts a protective effect.[85]

A notable discrepancy exists in the reported magnitude of alkaloid changes, with increases ranging from 23–45% in one study[83] to within ±8% in another.[86] This variation is likely attributable to heterogeneity in critical processing parameters. Future research should establish a standardized parameter control system and utilize techniques like LC-MS to trace alkaloid transformation pathways.

7.8 Other

Pei *et al.* used UHPLC-Q-Orbitrap HRMS to identify 71 chemical components in *Chuanxiong* Rhizoma (CH) before and after wine-processing. They pinpointed 34 components with altered concentrations: 19 increased and 15 decreased. The increases may be due to enhanced solubility in the wine, while the decreases likely result from the structural degradation of compounds during processing.[87] In a study on *Achyranthis Bidentatae* Radix (ABR), Ying Wang *et al.* found that wine-processing significantly increased the total polysaccharide content, although the levels followed a pattern of initial increase followed by a decrease. This trend was attributed to the initial leaching of components from the rice wine and the breakdown of cell walls by heat; however, prolonged heating may lead to the carbonization and degradation of polysaccharides.[88] Further illustrating the impact of wine-processing, Yu Hui *et al.* detected seven active components—morroniside, loganin, sweroside, paeoniflorin, gallic acid, 5-HMF, and paeonol—in both the raw and wine-processed versions of *Cornus* officinalis when prepared in Liuwei Dihuang Decoction (LWDD). However, the wine-processed LWDD formulation contained higher levels of gallic acid and 5-HMF but lower levels of morroniside compared to the decoction made with the raw herb.[89] Zhang Jiani *et al.* further reported that the contents of morroniside, sweroside, and paeoniflorin in the complete LWDD were slightly higher than in a drug pair containing only raw Moutan Cortex, while loganin content was similar.[90] These specific compounds are considered the key material basis for the anti-osteoporosis effects of both raw and processed forms. The processed product, however, demonstrated superior efficacy by more significantly modulating bone metabolism markers and increasing bone mineral density, with the wine-processed *Cornus* officinalis showing a particularly strong effect on enhancing bone density.[91] The complexity of herbal processing and formulation is further highlighted by Hu Jingli *et al.*, who compared the chemical profiles of raw and wine-processed ABR. They identified 113 compounds in wine-processed ABR, 16 of which were unique to it, while 97 were common to both forms. In a subsequent analysis of Danggui Buxue Decoction and its individual herbs (wine-processed *Angelica* and honey-fried *Astragalus*), 13 compounds were found exclusively in the complete decoction, and 53 were identified only in the individual herbs.[92]

Collectively, these studies demonstrated that the chemical composition of a traditional Chinese medicine formula is not merely the sum of its individual herbs. Instead, the decoction process induces a series of physical and chemical interactions. These reactions can alter the profile of chemical constituents, leading to the disappearance of some compounds and the formation of new ones.

7.9 Summary

While current research on the impact of wine-processing on chemical compounds has made progress, several limitations persist.

(1) Narrow focus on official monographs: existing studies predominantly focus on the qualitative and quantitative analysis of components specified in pharmacopoeias and the primary constituents of herbal pieces. This has led to a insufficient understanding of the transformation patterns and potential bioactivities of non-pharmacopoeial components, hindering the development of a robust system for identifying and evaluating quality markers (Q-Markers). To address this gap, we have systematically compiled data on other compounds (including non-pharmacopoeial components) and their changes reported in the literature. These findings, detailed in Table 1, provide a foundational resource for future research into non-pharmacopoeial components.

(2) Lack of systematic research: this issue manifests in two key areas. First, there is high repetition in studies but poor consistency in findings. For example, reports on the change in curculigoside content—a core active component in wine-processed *Curculiginis* rhizoma—are highly contradictory. Some studies found no significant change after processing,[93]

Table 1 Chemical composition changes of TCMs after wine-processed[a]

TCM	Species	Medicina parts	Processing method	Composition change	References
RR	*Rheum palmatum* L. *Rheum tanguticum* Maxim.ex Balf. *Rheum officinale* Baill	Dried root and rhizome	Wine steamiest and wine frying	Cianidanol↑ Gallic acid↑ Polydatin↑ Sennoside B↓ Sennoside A↓ Chrysophanol-8-*O*-β-D-glucoside↓ Physcion-8-β-D-glucoside↓ Chrysophanic acid↓	40 and 44
			Wine frying	Aloe emodin↑ Rhein↑ Emodin↑ Physcion↑	40
			Wine steaming	Aloe emodin↑ Rhein↓ Emodin↓ Physcion↓	40
			Wine steaming	Aloe-eModin-8-*O*-β-D-glucoside↓ Rhein-8-*O*-β-D-glucoside↓ Emodin-8-*O*-β-D-glucoside↓ Aloe-emodin-3-(hydroxymethyl)-*O*-β-D-glucoside↓ Chrysophanic acid↓ Rhein↑ 4′-Hydroxyphenyl-2-butanone-4′-*O*-β-D-(2″-*O*-galloyl-6″-*O*-(4′-hydroxy) cinnamoyl)-glucoside↓ 4′-Hydroxyphenyl-2-butanone 4′-*O*-β-D-(6″-*O*-cinnamoyl)-glucoside↓ 4′-Hydroxyphenyl-2-butanone 4′-*O*-β-D-(6″-*O*-galloyl)-glucoside↓ *trans*-3,5,4′-Trihydroxystilbene 4′-*O*-β-D-(6″-*O*-galloyl)-glucoside↓ *trans*-3,5,4′-Trihydroxystilbene 4′-*O*-β-D-glucoside↓ Physcion↑ Aloe emodin↑	41
			Wine steaming	Emodin↑ Chrysophanic acid↓	45
SR	*Scutellaria baicalensis* Georgi	Dried root	Wine frying	baicalin↓ Baicalein↑	98 and 99
			Wine frying	Scutellarin↓ baicalin↓ Wogonoside↓ Baicalein↑ Wogonin↑	77 and 79
			Wine frying	Berberine chloride↑	83
CR	*Coptis chinensis* Franch. *Coptis deltoidea* C.Y.Cheng et Hsiao *Coptis teeta* wall	Dried rhizome	Wine frying	Jatrorrhizine chloride↑	83 and 86
			Wine frying	Palmatine hydrochloride↑ epiberberine↓	
			Wine frying stewing	Coptisine chloride↓ Palmatine hydrochloride↓ Huangjinoside A↓	86 and 46
PR	*Polygonatum kingianum* Coll.et Hemsl. *Polygonatum sibiricum* Red. *Polygonatum cyrtonema* Hua	Dried rhizome	Stewing wine steaming stewing	Huangjinoside B↓ 7,2′-Dihydroxy-3′,4′-dimethoxyisoflavanone↓ Ginsenoside Rc↓ manninotriose↓ Melibiose↓ Stachyose tetrahydrate↓ Galactose↑ Huangjinoside I↑ 5-Hydroxymethylmaltol↑ D-Sucrose↓	46 and 47
				Raffinose↓ Melibiose↓	47 and 54

Table 1 (*Contd.*)

TCM	Species	Medicina parts	Processing method	Composition change	References
			Wine steaming stewing wine steaming<	D-Fructose↑ D-Glucose↑ D-Xylose↑ Toluene↑	
			Wine steaming wine steaming	Isobutyl acetate↓ 2-Ethyl-4-methyl-1,3-dioxolane↑ 2-Hexanone↑ Ethyl butyrate↑ Butyl acetate↓ 2-methyloctane↑ Ethylbenzene↓ 3-Methyloctane↑ *m*-Xylene↓ Styrene↓ *o*-Xylene↓ Propylbenzene↓ 3-Ethyltoluene↓ 2-Ethyltoluene↑ 2,2,4,6,6-Pentamethylheptane↓ Decane↓ 1,2,3-Trimethylbenzene↓ Indan↓ 2-Ethyl-p-xylene↓ 4-Ethyl-o-xylene↓ 3-Ethyl-o-xylene↑ 1-Nonanal↑ 2,3-Dihydro-3,5-dihydroxy-6-methyl-4(H)-pyran-4-one↑ Decyl aldehyde↑ 4,6-Dimethyl dodecane↑ 2,6,11-Trimethyl dodecane↑ 1-Dodecanol↑ Tetradecane↓ *n*-Hexadecane↑ Heptadecene↑ *n*-Nonadecane↓ *n*-Heptadecane↓ *n*-Octadecane↓ Phytane↓ Diisobutyl phthalate↓ Methyl palmitate↓ Palmitic acid↓ Dibutyl phthalate↓ Palmitic acid ethyl ester↑ Methyl linoleate↓ Methyl linolenate↓ Linoleic acid↓ Ethyl linoleate↓ *n*-Heneicosane↑ Bis(2-ethylhexyl) adipate↓ *n*-Eicosane↑ Bis(2-ethylhexyl) phthalate↑ *n*-Nonacosane↓ γ-Sitosterol↑ 2-Methyloctacosane↑ *trans*-Squalene↓ Tetratetracontane↑ cycloartenol↓ *n*-Hexatriacontane↓ Neosibiricoside A↑	54 and 100
			Wine steaming wine steaming	Diosgenin↑ Madecassic acid↓ geniposide↓	58, 61, 100 and 101

Table 1 (*Contd.*)

TCM	Species	Medicina parts	Processing method	Composition change	References
CF	*Cornus officinalis* Sieb. et Zucc	Dried ripe sarcocarp	Wine steaming wine steaming	morroniside↓ Rutin↓ Verbenalin↓ loganin↑ Gallic acid↑ Quercetin↑ Kaempferol↑ 5-HMF↑ Cornuside↓	58, 59, 61 and 101
			Wine steaming wine steaming	7-*O*-Methyl-morroniside↓ sugiol↓ 7-*O*-ethyl-Morroniside↑ Triethyl Chebulate↑	59 and 102
			Wine steaming wine steaming	Triethyl Gallate↑ theogallin↑ (−)-Epigallocatechin↑ Theogallin↑ Swertiamarine↓ 1,2,3-tri-*O*-galloyl-β-D-glucose↓ Sweroside↑	102 and 101
			Wine steaming wine steaming	Verbenalin↑ 7-β-*O*-Methylmorroniside↑ 7-α-*O*-Ethylmorroniside↑ 7-β-*O*-ethyl-Morroniside↑ specnuezhenide↓	101 and 63
LLF	*Ligustrum lucidum* Ait	Dried ripe fruit	Wine steaming wine steaming	Echinacoside↓ Verbascoside↓ salidroside↑ tyrosol↑ loganetin↑	63 and 66
			Wine steaming wine steaming	hydroxytyrosol↑ Echinacoside↓ Rutin↓ Hyperoside↓ Cynaroside↓ Quercitrin↓ Eriodictyol-7-*O*-glucoside↓ Eriodictyol↓ Eriocitrin↓ Homoplantaginin↓ Naringenin-7-*O*-glucoside↓ Naringenin↓ luteolin↓ Apigenin↓ Polysaccharide↓	66 and 68
			Wine steaming wine steaming	5-Hydroxymethylfurfural↑ Gomisin D↑	68, 70 and 73
SCF	*Schisandra chinensis* (Turcz.) Baill	Dried ripe fruit	Wine steaming wine steaming	Protocatechuic acid↓↑ Citric acid↓ 6-Methylcitric Acid↓ 6-*O*-Benzoylgomisin O↑	70, 72, 73 and 103
			Wine steaming wine steaming	Gomisin D↑ Schisandrin A↑ Gomisin T↑ Schizandrin B↑ Schisandrin C↑ Schisantherin A↓ Schisantherin B↓ Schisantherin C↓ Schisantherin D↓ Neokadsuranic acid B↓ 3-Carene↑	72, 75 and 103
				2-Isopropyl-5-methylanisole↑	75 and 104

Table 1 (*Contd.*)

TCM	Species	Medicina parts	Processing method	Composition change	References
			Wine steaming wine frying	α-Terpinene↑ β-bourbonene↑ Alloaeromadendrene↑ Neolongifolene↑ Acoradiene↑ chamigrene↑ sesquiphellandrene↑ Nerolidol↑ α-Pinene↓ Camphene↓ (+)-4-carene↓ D-limonene↓ Thujopsene↓ Nonanal↑	
CU	*Curculigo orchioides* Gaertn	Dried rhizome	Wine frying	Phenol↑ (+)-Dipentene↓ Terpinene↓ α-Ylangene↓	104

[a] ↑ denotes a rise; ↓ denotes a fall.

others reported a significant increase,[94] while some concluded a decrease.[95] These discrepancies may stem from small sample sizes and insufficient experimental replication in some studies, which amplifies the role of chance. Furthermore, variations in the preparation of the processed herbs and whether content calculations are based on dried weight could also influence the results. Second, the research scope is narrow. Current efforts are concentrated on only a few herbs, such as RR and PR, failing to cover the entire system of wine-processed materials. Consequently, the general principles deduced regarding the impact of processing techniques on chemical composition remain limited and fragmented, impeding the development of a systematic and structured research framework.

(3) Weak mechanistic studies: there is a notable lack of systematic research that connects chemical transformations to the basis of pharmacological efficacy, leaving the mechanisms of action for processed herbal pieces poorly understood.

To overcome these limitations, a multi-faceted approach is recommended. Future work should establish disease-specific efficacy evaluation models and adopt a "Processing-Transformation-Activity" framework. Advanced techniques like UPLC-Q-TOF/MS should be employed to track the dynamic changes in chemical components during processing. These chemical profiles should then be correlated with changes in herbal properties and endogenous metabolism *in vivo* to identify potential active compounds. Activity should be further validated using a combination of *in vitro* and *in vivo* models. To enhance methodological rigor, a "Minimum Data Set" standard should be implemented. This would define core parameters for auxiliary materials and processing conditions, as well as experimental design requirements including sample size justification and number of replicates. Finally, research efforts must be expanded. A classification matrix based on "Herb Category-Component Type" should be constructed, and the resulting data should be integrated into a centralized database for wine-processed materials. This database will be instrumental in deciphering the common mechanisms by which wine-processing modifies herbal medicines.

8. Effect of wine-processing on pharmaco loy

Yellow rice wine possesses sweet-pungent properties and intense thermal nature. Its aromatic profile enhances therapeutic delivery by promoting dispersion and activation of medicinal compounds. Wine-processed herbs are primarily employed to treat rheumatic pain, meridian obstruction, blood stasis, and inflammatory swelling. These preparations demonstrate three core therapeutic actions: dispelling cold through meridian warming, facilitating joint mobility, and enhancing blood circulation. This review systematically summarized recent advances in understanding how wine-processing modifies pharmacological activities and clinical applications of traditional herbs.

8.1 Enhance the effect of warming and tonifying the liver and kidneys

Sun *et al.* integrated renal metabolomics and proteomics to investigate the therapeutic mechanism of wine CF in chronic renal failure. They identified inhibition of LPS/IL-1-mediated retinol X receptor function as a key pathway, with FMO3 and CYP2E1 as core targets;[96] Lin examined Wnt pathway modulation by differently processed PR in lung-yin-deficient mice. Processed PR suppressed Wnt4 *m*RNA/protein but upregulated Gsk-3β, ultimately inhibiting β-catenin. Its yin-nourishing effect

correlated with suppressed Wnt activation, with efficacy ranking: nine-cycle-steamed PR > single-steamed PR > raw PR. Wine-processed PR showed better yin-nourishing effects than steamed-only preparations.[97] Bi investigated compositional changes in LLF processing for kidney-yin deficiency therapy. Specnuezhenide was found unstable and hydrolyzed at high temperatures, indicating its non-essential role post-processing. Instead, hydrolytic conversion of specific iridoid glycosides correlated with efficacy. Wine-steamed LLF regulated cAMP, cGMP, ACTH, Cor, and Na^+/K^+-ATPase levels while suppressing renal AQP1/AQP2 protein expression;[105] long demonstrated superior therapeutic outcomes of wine-processed CF over crude CF in chronic renal failure models. 5-HMF potentially mediated these effects through antioxidant activity and bone metabolism regulation. Reduced levels of certain components may concurrently diminish adverse effects, collectively enhancing therapeutic efficacy.[62]

8.2 Clear heat and detoxify, inhibit inflammatory response

Wine exhibits pungent-heat properties with an upward-directing characteristic. In herbal processing, wine-treatment modifies the therapeutic orientation of selected herbs, directing their effects upward to enhance efficacy in upper body regions. RR primarily promotes purgation and clears heat-fire. Wine RR demonstrates moderated purgative effects while showing enhanced efficacy against heat-toxins at the blood level in the upper jiao;[106] SR is characteristically bitter-cold. Wine frying moderates its cold nature while enhancing its capacity to clear lung heat from the upper jiao,[99] These effects are mechanistically linked to wine frying's dual actions: upward direction of therapeutic properties and efficacy potentiation.

Modern pharmacological research indicated that heat-clearing and detoxifying effects correlate with anti-inflammatory and antimicrobial activities. SUN Ting–ting *et al.* investigated wine-processed PR using stepwise ethanol precipitation. PSPW-3 exhibited enhanced immunomodulatory activity, potentially due to its unique structural features facilitating immune cell receptor binding and activation. All fractions contained high galactose proportions, with PSPW-3 comprising 79.3% galactose and 15.33% mannose. These monosaccharides likely participate in cellular signaling and immune cell activation pathways;[107] Shi *et al.* demonstrated that wine-processed PR reduced irritancy while enhancing immunomodulation and hypoglycemic effects. Maillard reactions during processing generated compounds like 5-HMF, which collectively contributed to efficacy potentiation. This processed material enhanced immunity by modulating immune responses, activating immune cells, and promoting cytokine secretion;[108] Jiang *et al.* demonstrated that *Clematidis* radix et rhizome (CL) exerted multi-target therapeutic effects against rheumatoid arthriti. This efficacy enhancement was potentially mediated through glycolytic inhibition, gut microbiota modulation, and PI3K-AKT/HIF-1α pathway regulation. Investigation of wine-processed CL revealed that thermal processing and rice wine synergistically generated complex porous structures, significantly increasing dissolution of triterpenoid saponins and enhancing bioactivity. In adjuvant-induced arthritis rat models, wine-processed CL suppressed secretion of inflammatory factors (TNF-α, IL-6), reduced synovial hyperplasia and cartilage erosion, and alleviated weight loss and joint swelling. These findings indicated that pore structure complexity is a key mechanism enhancing bioactive compound dissolution and pharmacological efficacy;[109,110] Using CCl_4-induced liver fibrosis models, Niu demonstrated that high-pressure wine steamed CF significantly attenuated hepatic inflammation and fibrosis, outperforming unprocessed materials. The processed form modulated 10 metabolic pathways (including glycerophospholipid and retinol metabolism) and normalized 10 fibrosis-related biomarkers, thereby ameliorating hepatic inflammation and fibrosis.[60]

8.3 Exerts analgesic effects, enhancing blood circulation and collateral activation

Clinically, wine-processing is frequently applied to herbs with blood-activating, stasis-resolving, collateral-dredging, and analgesic properties. This serves dual purposes: facilitating synergistic actions between wine and herbal compounds, and enhancing the dissolution of bioactive constituents to improve therapeutic efficacy;[111] Liu *et al.* established a model of dysmenorrhea in mice by using estradiol benzoate combined with oxytocin. They found that ethanol EF could reduce the number of writhing, prolong the latency period, increase the levels of serum PGE_2 and NO, and decrease the level of endothelin-1. Its analgesic effect was superior to that of the raw product. UPLC-Q-TOF-MS analysis showed that the contents of five analgesic components such as rutin significantly increased after being processed by wine, and there were 7 different compounds between raw EF and wine EF. Among them, 7-hydroxy coumarin and the other two compounds might improve uterine smooth muscle contraction by regulating endocrine factors and the P2X3-Ca^{2+} pathway to achieve analgesia.[112,113]

The enhanced blood-activating effects of wine-processed RR, *Salviae miltiorrhizae* radix et rhizome (SM), and *Paeoniae* radix alba (PRA) are likely attributed to: Increased pinelloside and rhein content in processed RR, Elevated tanshinone IIA and tanshinone I levels in wine-processed SM, with improved bioavailability of modified components, reduced paeoniflorin and increased albiflorin concentrations in wine-processed PRA,These compositional changes constitute the primary material basis for enhanced hematinic efficacy post wine-processing;[114] Research by Ying Wang *et al.* revealed that wine-processing time critically influenced the anticoagulant activity of *Angelica* sinensis polysaccharides. The activity was maximized at 22 minutes, a effect attributed to the optimized molecular profile and chemical makeup achieved through processing.[88]

8.4 Optimizes drug safety profile

Wine-processing reduces toxicity in certain herbs through multiple mechanisms: Wang *et al.* demonstrated crud RR tannins induce hepatotoxicity in zebrafish larvae. Processed RR significantly decreased tannin content, acute toxicity, and liver

damage;[115] Ying established structure-toxicity relationships for BV components, revealing how temperature, light, and ethanol during processing alter chemistry and toxicity. Ethanol dissolution and thermal effects denature proteins (reducing irritation) while transforming bufadienolides. This reduced toxic bufogenins content, achieving toxicity reductio;[116] The effect of wine-processing on the spleen index of mice was reduced in *Euphorbiae* ebracteolatae radix. Additionally, wine-processing of *Psoraleae* fructus, CU, *Dichroae* radix, and *Polygoni* multiflori radix can also reduce their toxicity. Furthermore, wine-processing reduces herbal irritancy and modifies odors of zoological materials, enhancing patient compliance, PR exhibits irritancy. Lin demonstrated that nine-cycle-steamed *Polygonatum kingianum* Coll.et Hemsl. reduced hemolytic activity and irritancy;[97] wine fried Zaocys processed at 80 °C for 2.5 hours effectively reduced pungent aldehydes/sulfides while generating aromatic esters and heterocyclic compounds, achieving significant deodorization.[116]

8.5 Other

Modern research revealed synergistic cardiocerebrovascular protective mechanisms in wine-processed herbs: in the field of myocardial protection, Dan *et al.* demonstrated that after SCF was steamed with wine, it significantly increased the content of lignans, regulated the balance of neurotransmitters, inhibited the excessive activation of the HPA axis, and enhanced the melatonin signal, thereby achieving a synergistic improvement in insomnia and cardiovascular function;[117] Bai *et al.* compared crude and wine-processed *Siegesbeckiae* herba (SH) protection in hypoxic H9c2 cardiomyocytes: both exhibited cytoprotection *via* antioxidative stress and apoptosis inhibition, with crude SH superior in enhancing antioxidant capacity and cell viability, while wine-processed SH showed greater efficacy in preserving membrane integrity. Comprehensive evaluation indicated marginally superior marginally superior cardioprotection by crude SH against hypoxic injury;[118] Pei *et al.* found wine fried CH elevated anti-inflammatory/antioxidant constituents, inhibited inflammatory responses and apoptosis *via* TNF signaling, and enhanced neuroprotection by regulating STAT3/MMP9 target networks, thereby exerting protective effects against cerebral ischemia.[87]

Wine-processing demonstrates significant advantages in metabolic regulation: beyond cardiovascular protection, wine SCF modulated gut microbiota composition, reduced intestinal and plasma lactate levels, suppressed hepatic GPR81 expression while activating cAMP signaling. This mechanism ameliorated anxiety behaviors and hippocampal neuroinflammation induced by chronic unpredictable stress, with enhanced efficacy post-processing;[103] Regarding bone metabolism, Wen *et al.* demonstrated that prescriptions containing wine-processed or crude CF (LWDD formula) intervened in early postmenopausal osteoporosis progression. The wine CF group showed superior anti-osteoporotic effects, potentially due to higher total bioactive content. These constituents balanced osteoblast/osteoclast differentiation, enhanced bone mineral density, and mitigated pathological processes in Postmenopausal Osteoporosis;[119] Liu *et al.* observed that both crude and wine fried CU prevented retinoic acid-induced osteoporosis in mice, with wine CU exhibiting superior efficacy. This effect correlated with upregulated osteoprotegerin expression and downregulated RANKL protein levels.[120]

Wine fried *Anemarrhenae* rhizome (AR) exhibits moderated bitter-cold properties, attenuating growth suppression and energy metabolism inhibition in rats. Plasma concentrations of lactate, pyruvate, and triglycerides were significantly reduced, indicating enhanced hypoglycemic and hypolipidemic effects post-processing. Newly formed constituents like 20(R)-ginsenoside Rh2 correlate with enhanced therapeutic efficacy;[121] Liu *et al.* compared crude/wine *Sophorae flavescentis* radix and their Xiangshen Pill (香参丸) formulations in ulcerative colitis mice: both crude and processed materials effectively alleviated ulcerative colitis symptoms, with wine containing pills demonstrating optimal efficacy. Xiangshen Pills should preferentially incorporate wine-processed material, potentially through enhanced antioxidant capacity, NF-κB signaling inhibition, and reduced pro-inflammatory cytokine release.

While research has explored the pharmacological effects of wine-processing on TCM, key mechanisms remain unclear. For instance, most studies lack dedicated control groups for the excipient (wine), making it difficult to determine whether observed benefits—such as reduced toxicity and enhanced efficacy—stem from the wine itself or the processed herb; current evaluation systems are often inadequate. Relying on a single pharmacological model or limited efficacy indicators fails to capture the multi-component, multi-target nature of TCM. Furthermore, clinical research is scarce. Current evidence relies heavily on animal and *in vitro* studies, limiting robust validation of human efficacy and safety and hindering clinical adoption. To address these gaps, future research should: (1) incorporate rigorous controls: include excipient-only control groups (*e.g.*, pure wine-processed under simulated conditions) to isolate wine's contribution; (2) track chemical dynamics: employ techniques like Fourier-transform infrared spectroscopy to monitor real-time chemical changes during processing; (3) adopt holistic mechanistic studies: utilize bioinformatics approaches (*e.g.*, network pharmacology, metabolomics) to investigate multi-component, multi-target, and multi-level pharmacological mechanisms, elucidating interactions between chemical profiles and biological effects; (4) prioritize clinical validation: conduct multi-center clinical trials using real-world data to definitively establish the efficacy and safety profiles of wine-processed TCM for clinical translation.

9. Effect of wine-processing on *in vivo* behavior

Our systematic analysis of TCM processing mechanisms reveals that current research primarily focuses on chemical transformations during processing and associated changes in pharmacological effects. However, critical gaps remain in understanding the pharmacokinetic profiles of active constituents—including absorption, tissue distribution, and

metabolism—before and after processing. This hampers comprehensive elucidation of the material basis for efficacy and underlying mechanisms of action. Emerging methodologies, such as molecular imaging and bioinformatics, now offer novel pathways to uncover the scientific rationale underpinning processing techniques. This study synthesizes recent animal pharmacokinetic investigations (within the past five years) on wine-processed TCMs. We specifically examine how processing enhances enterohepatic cycling of active constituents and alters blood–brain barrier permeability. These findings provide crucial evidence for clarifying the material basis of efficacy and mechanisms of action.

A pharmacokinetic study by Pei *et al.* demonstrated the superiority of wine-processed Chuanxiong, which yielded higher plasma levels (C_{max}) and systemic exposure (AUC_{0-t}) of active compounds, along with a longer half-life for ligustilide A, compared to the crude herb. These findings confirm the bioavailability-enhancing effect of wine-processing.[15] By demonstrating increased distribution of gentiopicrosin to the heart, liver, and lungs (upper-jiao organs), research by Jian-Zhi Sun *et al.* on wine-processed *Gentianae* Radix offers a scientific explanation for the traditional principle of "wine-processing for upward-direction and meridian-guiding".;[122] Wu *et al.* demonstrated that wine-processing of CF prolonged mean residence time (MRT_{0-t}) of active markers while accelerating absorption (reduced T_{max}). Tissue redistribution showed decreased gastric/colonic deposition but increased intestinal, hepatic, renal, and pulmonary distribution-aligning with CF's traditional tonifying effects. Multi-target analysis revealed 46 processing-induced targets, predominantly modulating liver (38), heart (37), and lung (34). This multi-organ targeting network provides a mechanistic foundation for wine-processed CF's actions in liver-kidney tonification, immunomodulation, and anti-aging;[123] A multi-omics study revealed the superior efficacy of wine-processed *Rehmanniae* radix in intracerebral hemorrhage models. Unlike the crude form, wine RR specifically regulated Acp6 and amino acid pathways, influenced 58 key metabolites, and enhanced glycine/serine metabolism. A critical finding was its ability to restore cerebral energy metabolism *via* elevated phosphoserine, demonstrating neuroprotection through coordinated proteomic and metabolomic reprogramming.[124] Chen *et al.* characterized the pharmacokinetics of six propolis constituents following wine-processing using UPLC-Q-Exactive Orbitrap MS. Most compounds exhibited biphasic absorption profiles. Fifteen phase I/II metabolites were identified, predominantly glucuronide and sulfate conjugates, indicating systemic exposure occurs *via* both parent compounds and metabolically activated derivatives-expanding the mechanistic basis for processed propolis efficacy.[125]

Current studies revealed significantly enhanced distribution of active constituents to target organs (*e.g.*, heart and brain) following wine-processing, potentially explaining the pharmacokinetic basis for its cardioprotective and neuroprotective effects. However, notable limitations persist: (1) most investigations lack comprehensive assessment of wine-processing on complete ADME profiles (absorption, distribution, metabolism, excretion); (2) critical knowledge gaps exist regarding intestinal distribution patterns and interactions with gut microbiota. Therefore, future research can conduct comprehensive evaluations of the processes of *in vitro* absorption, metabolism, and excretion through methods such as liver microsome assays, intestinal perfusion models, biliary cannulation and urinary excretion analysis to fully characterize *in vitro* ADME processes. Combining these with gut metabolomics will elucidate intestinal distribution dynamics and interaction mechanisms between active constituents and gut microbiota.

10 Conclusions

Processing represents a core discipline within TCM, with wine-processing holding distinct theoretical and practical significance among traditional techniques. Wine exhibits sweet-pungent properties with intense warming characteristics. Its aromatic nature enhances drug potency by promoting upward movement and dispersion, facilitating blood circulation, and serving as an effective organic solvent for active constituents. Modern wine-processing primarily employs rice wine or baijiu as media, utilizing techniques including wine frying, wine steaming, wine soaking, and wine moistening. These methods modulate herb properties to better align with patient constitutions and conditions. Crucially, wine-processing reduces toxicity of certain materials, enhancing safety while potentiating therapeutic efficacy. Contemporary integration with novel technologies—including chromaticity-component-efficacy correlation modeling and orthogonal testing—has enabled standardized quality control. This evolution significantly enhances processing efficiency and bioactivity. Such innovations revitalize traditional practices while bridging TCM with modern science, accelerating the modernization of herbal medicine. Systematic experimental and clinical studies continue to elucidate the unique therapeutic advantages of wine-processing across various diseases, driving clinical adoption. Standardization and quality control now constitute critical research priorities to ensure clinical safety and efficacy. Deepening research continues to refine theoretical frameworks, establishing comprehensive processing principles that advance scientific standardization of TCM. Furthermore, standardized processing enhances patient trust and acceptance, facilitating global dissemination of TCM. Integration with modern medicine revitalizes traditional herbs while unlocking broad research horizons for TCM's future development.

Modern pharmacological research confirmed that wine-processing profoundly alters herbal chemical profiles, modifying constituent composition and concentration while significantly regulating pharmacokinetic behavior—including absorption, distribution, and metabolism. These transformations collectively enhance therapeutic efficacy, reduce toxicity, and enable tissue-targeted delivery. Despite advances in elucidating processing mechanisms, critical limitations persist: (1) insufficient understanding of excipient-active constituent interactions; (2) absence of integrated quality standards combining physicochemical properties and bioactivity; (3) overreliance on single pharmacological models that fail to correlate compositional changes with multi-target mechanisms.

Existing reviews often focus on isolated aspects of the process, lacking a comprehensive analysis that links chemical changes to biological effects. This review addressed these gaps by systematically integrating the entire wine-processing framework—including excipients, methodology, chemical composition, efficacy, and pharmacokinetics—to elucidate the chemical transformations and their direct biological consequences. By critically mapping the research landscape and identifying key knowledge gaps, this work provided a theoretical foundation for optimizing processing techniques and guiding clinical translation, thereby offering a systematic and mechanistically-informed perspective that is currently absent from the literature.

To advance this field, future research must adopt a multi-faceted strategy to overcome existing bottlenecks. The following roadmap outlines a path from fundamental research to clinical application: (1) elucidate fundamental mechanisms: introduce supramolecular self-assembly theory to investigate the co-dissolution and assembly patterns between wine excipients and herbal constituents. This will provide a theoretical foundation for optimizing processing parameters; (2) optimize processes with advanced analytics: systematically optimize processing techniques by employing a suite of advanced methods. This includes spectrum-effect analysis, response surface methodology,[126] AHP-CRITIC mixed weighting, machine learning, and modern instrumentation (*e.g.*, colorimeters, electronic tongues[127]) to ensure scientific rigor and reliability; (3) establish comprehensive evaluation systems: develop a holistic quality assessment framework based on component structure theory and overall quality-efficacy relationships. This approach will provide a deeper and more systematic understanding of the chemical transformations and pharmacological mechanisms underlying wine-processing; (4) validate with clinical evidence: conduct multi-center clinical trials to systematically evaluate the safety and efficacy of wine-processed herbs. This critical step will bridge traditional knowledge with modern scientific validation. This synergistic integration of traditional knowledge and modern science will standardize and modernize wine-processing technologies.

Author contributions

HJ, LY and HK conceived of and designed the review; LQ and CS searched the literature and downloaded the documents and made classification; JL wrote the paper; AH and HJ checking the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Abbreviations

ABR	*Achyranthis bidentatae* radix
AR	*Anemarrhenae* rhizome
ASR	*Angelicae sinensis* radix
CF	*Corni* fructus
CH	*Chuanxiong* rhizoma
CR	*Coptidis* rhizome
CL	*Clematidis* radix et rhizome
CU	*Curculiginis* rhizome
DDMP	5-Hydroxymethylmaltol
GC-MS	Gas chromatography-mass spectrometry
HPLC	High performance liquid chromatography
LLF	*Ligustri lucidi* fructus
LWDD	Liuwei dihuang decoction
PL	*Platycodonis* radix
PR	*Polygonati* rhizoma
RR	Rhei radix et rhizoma
SCF	*Schisandrae chinensis* fructus
SM	*Salviae miltiorrhizae* radix et rhizome
SR	*Scutellariae* radix
TCM	Traditional chinese medicine
UPLC	Ultra-high performance liquid chromatography
UPLC-Q-Orbitrap-MS	Ultra-performance liquid chromatography quadrupole orbitrap mass spectrometry
UPLC-Q-TOF-MS/MS	Ultra-performance liquid chromatography-quadrupole-time-of-flight tandem mass spectrometry
PRA	*Paeoniae* radix alba
SH	*Siegesbeckiae* herba
5-HMF	5-hydroxymethylfurfural

Data availability

No data was used for the research described in the article.

Supplementary information: wine-processing techniques in successive dynasties, operational specifications for modern wine-processing of traditional Chinese medicines, newly added wine-processed varieties in successive dynasties, and the inclusion of wine-processed medicinal materials in modern pharmacopoeias. See DOI: **https://doi.org/10.1039/d5ra05383h**.

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