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The Modern Scientific Enigma of Processing in Traditional Chinese Medicine: Illustrated with Common Examples

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ABSTRACT

The processing of traditional Chinese medicine (TCM) represents a distinctive pharmaceutical practice in China and serves as a defining feature that sets Chinese medicine apart from natural or plant-based remedies. Documented as early as in the Huangdi Neijing (Inner Canon of the Yellow Emperor), TCM processing has evolved over more than 2,000 years through continuous inheritance, innovation, and development, combining TCM theory with clinical practice and holding a critical role within the field. In recent years, Chinese herbal pieces, as a form of TCM prescription, have demonstrated a notable impact in the prevention and management of COVID-19, highlighting their unique therapeutic value and contributing to China's clinical treatment strategies while offering international insights and expertise in epidemic control. This paper summarizes recent research progress on the processing of representative TCMs, examines the mechanisms by which processing modifies medicinal properties and reduces toxicity, and discusses the integration and application of various modern technologies and methods, thereby uncovering the contemporary scientific intricacies of TCM processing techniques.

Keywords: Modern analysis technique, Chemical component, Synergism and attenuation, Processing of traditional Chinese medicine (TCM)

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Introduction

Chinese medicinal materials require processing before clinical use, and this step represents the most distinctive feature that separates traditional Chinese medicine (TCM) from natural and plant-based medicines. TCM processing is a pharmaceutical technique grounded in TCM theory, guided by syndrome differentiation, the inherent properties of the medicinal material, and the specific requirements of dispensing and preparation [1]. During the COVID-19 pandemic, TCM played a unique role, with formulations such as the "three formulas and three medicines" contributing significantly. Statistics indicate that over 50% of the Chinese medicinal materials recommended in national COVID-19 prevention and treatment guidelines require processing methods including frying, honey-frying, and stir-frying with wine [2, 3].

According to TCM processing theory, these techniques can enhance therapeutic effects, reduce toxicity, modify drug properties, and facilitate dispensing [4]. With the advancement of modern science and the integration of new technologies, the mechanisms underlying the processing of certain TCMs have been elucidated through chemical, pharmacological, and pharmacodynamic studies, reaffirming the importance of TCM processing.

However, due to the complexity of TCM ingredients and their multifaceted therapeutic effects, the scientific basis of processing remains incompletely understood. This study reviews recent research on TCM processing, using common examples to summarize current knowledge, clarify chemical composition changes and underlying mechanisms, and provide guidance for optimizing processing techniques and developing quality standards.

Transformation of TCM ingredients and changes in drug efficacy induced by processing

Mechanism of ginseng processing

Ginseng, the dried root of Panax ginseng C. A. Mey, contains ginsenosides as its primary active compounds and has been used for millennia in China. Traditional processing methods include sun-drying and steaming. White ginseng is produced by drying fresh ginseng under the sun (moisture ≤12%), whereas red ginseng is obtained by steaming fresh ginseng at high temperatures followed by drying [5]. Studies indicate that red ginseng exhibits stronger pharmacological effects than fresh ginseng, including antioxidant, antidiabetic, antitumor, and antistress activities [6, 7].

Compared with fresh ginseng, white ginseng shows reduced levels of total saponins and malonyl ginsenosides but increased levels of ginsenosides Rb1 and Rg1 [8]. In red ginseng, ginsenosides Rg2, Rg3, Rh2, and Rh1 are higher than in fresh ginseng, along with rare ginsenosides such as Rk1, Rs3, and Rg5 [9]. These differences in pharmacological activity among processed ginseng products are primarily due to structural transformations of ginsenosides [10].

During processing, ginsenosides undergo multiple transformation pathways **(Figure 1)**. Unstable malonyl ginsenosides degrade into neutral ginsenosides under high temperature; some ginsenosides undergo acetylation or lose sugar moieties at the C-3, C-6, or C-20 positions to form rare ginsenosides. For instance, Rb1, Rb2, and Rc can convert into Rg3 and Rh2. Dehydration at the C-20 position can produce double bonds, yielding additional ginsenoside variants, such as the conversion of Rg3 into Rk1 and Rg5 [11]. Additionally, ginsenoside content rises when fresh ginseng is steamed at 98 °C but decreases at 120 °C, highlighting the importance of carefully controlling steaming time and temperature to prevent structural damage [12].

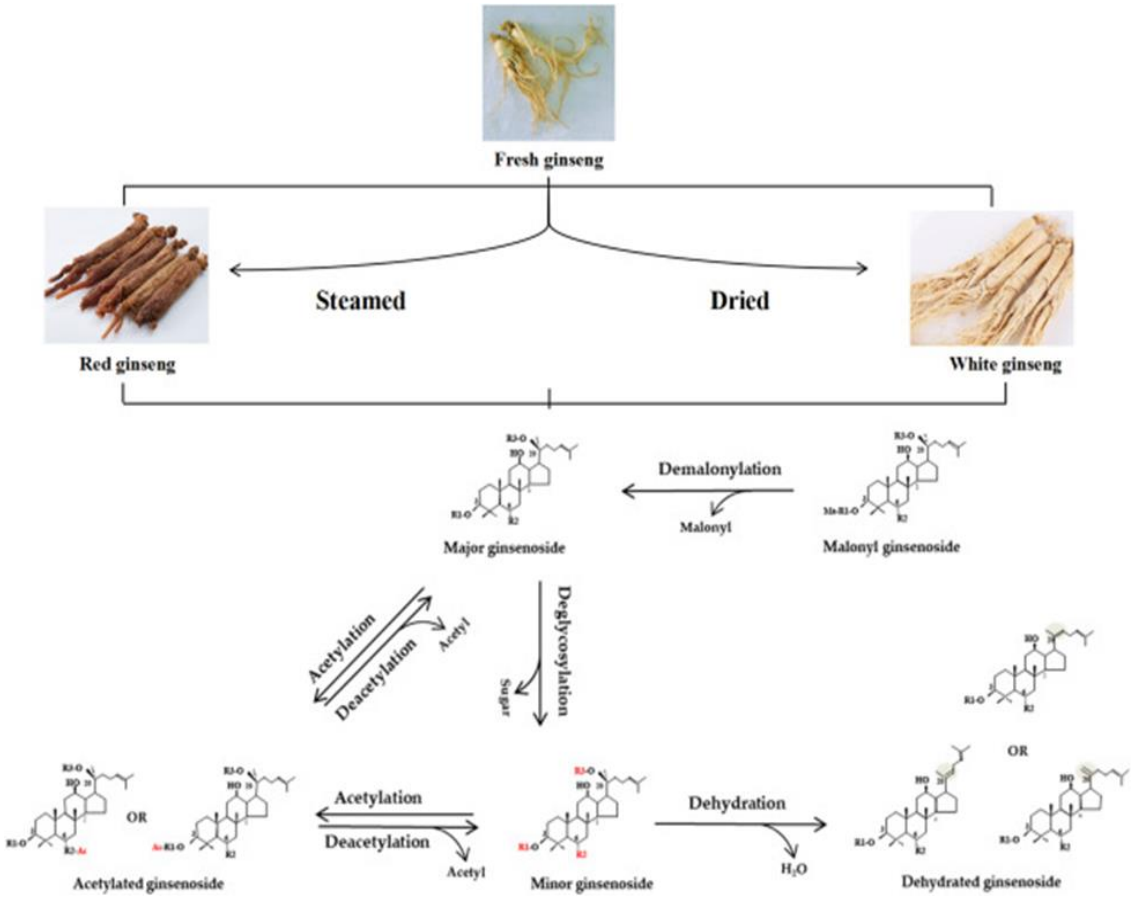


Figure 1. Transformation Pathways of Ginsenosides during Processing [8].

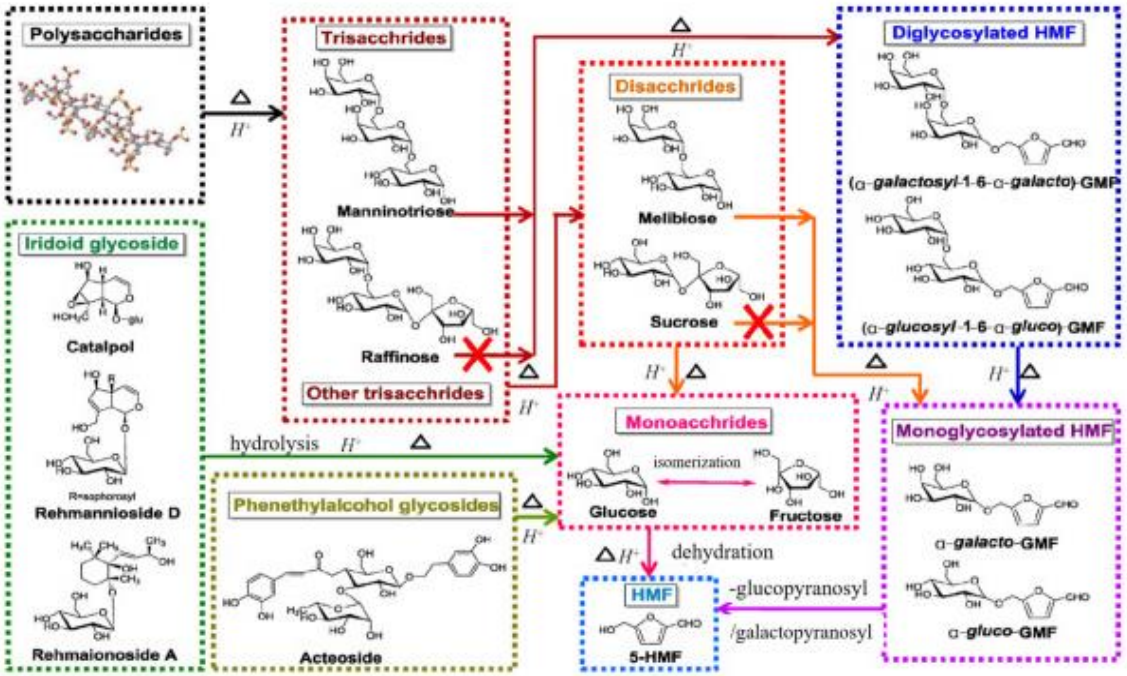
Mechanism of rehmanniae radix processing

Rehmanniae Radix is a widely used TCM in clinical practice and serves as the principal component of Liuwei Dihuang Pills, a well-known Chinese patent medicine. Research indicates that various processing methods can alter its chemical composition [13, 14]. The processed form, known as Rehmanniae Radix Praeparata, is typically produced by braising or steaming the raw herb with wine and is commonly applied in the treatment of "blood deficiency syndrome" [15]. Polysaccharides and iridoids have been identified as the primary active constituents

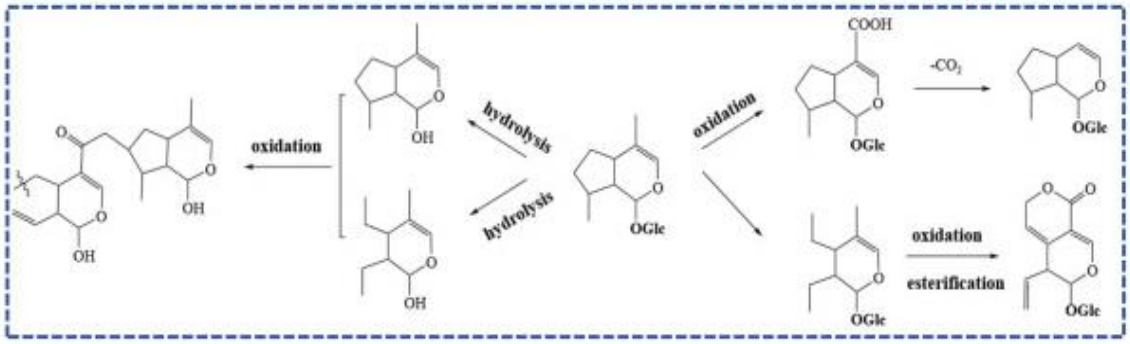
of Rehmanniae Radix. Li *et al*. [16] elucidated the transformation of these compounds during processing using marker discovery and simulated processing techniques grounded in chemomics.

During processing, sugars—including polysaccharides, oligosaccharides, and monosaccharides—and glycosides, such as iridoid and phenylethanol glycosides, gradually convert into furfural derivatives (glycosylated or non-glycosylated hydroxymethylfurfural, HMF) through desugarization and dehydration reactions. The glycosidic bond between the terminal furanose of raffinose and glucose is readily hydrolyzed to produce melibiose and fructose, which subsequently dehydrate to form 5-hydroxymethylfurfural (5-HMF) and HMF. Simulated processing studies revealed that mannotriose and melibiose not only produced hydrolyzed furfural but also yielded glycosylated HMF, confirming the stepwise conversion of sugars during processing. Chemical analyses showed that HMF and its glycosylated analogs are the main characteristic components of Rehmanniae Radix Praeparata **(Figure 2a)**. Notably, 5-HMF can bind to sickle hemoglobin, inhibiting red blood cell sickling, suggesting its potential for treating sickle cell anemia [17]. These findings indicate that 5-HMF-related compounds formed during processing are likely responsible for the enhanced efficacy of Rehmanniae Radix Praeparata in "tonifying blood and nourishing yin."

Processing also affects the iridoid constituents of Rehmanniae Radix [18]. Using HPLC/Q-TOF-MS to compare chemical profiles before and after processing revealed a decrease in iridoid glycosides and an increase in furfural derivatives, which may underpin changes in pharmacological activity **(Figure 2b)**. Catalpol is the major iridoid in Rehmanniae Radix. Experimental evidence indicates that heat treatment can decompose the enene ether structure and acetal groups in catalpol, leading to sugar loss, molecular rearrangement, or nucleophilic reactions that produce dark-colored compounds. These chemical changes alter the color, properties, and therapeutic effects of the herb, impacting its antithrombotic and hematopoietic activities [19]. In a mouse model of cyclophosphamide-induced myelosuppression, processed Rehmanniae Radix demonstrated superior hematopoietic effects compared with the raw herb [20].



a)



b)

Figure 2. Primary Mechanisms Underlying Changes in Polysaccharide and Iridoid Composition During the Processing of Rehmannia glutinosa [16].

Mechanism of polygoni multiflori radix processing

Raw Polygoni Multiflori Radix exhibits functions such as bowel relaxation and detoxification, whereas the processed form provides additional effects, including hair darkening, liver and kidney nourishment, blood essence tonification, muscle and bone strengthening, dampness elimination, and lipid reduction, exemplifying the typical TCM principle of different uses for raw and processed products [21]. Since the Song Dynasty, Polygoni Multiflori Radix has undergone diverse processing methods, including steaming, treatment with black bean juice, wine, and fermentation. Historical records, such as the Compendium of Materia Medica from the Ming Dynasty, note that its therapeutic efficacy is enhanced after "nine-time repeated steaming and drying."

The primary chemical constituents of Polygoni Multiflori Radix include stilbene glycosides, anthraquinones, and phospholipids, all of which are significantly altered by different processing techniques [22]. Stilbene glycosides, particularly 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (TSG), are present in high amounts and possess anti-inflammatory and antioxidant properties [23]. However, excessive or prolonged intake of TSG can lead to certain toxic effects [24]. Dong *et al*. [25] observed that stilbene glycoside content decreases following the nine-time steaming and drying process, likely due to hydrolysis into corresponding aglycones under heating, which explains the degradation mechanism of TSG during processing.

Anthraquinone derivatives in Polygoni Multiflori Radix are classified as free or conjugated anthraquinones and contribute to purgative, diuretic, anti-inflammatory, and hemostatic effects [26]. Studies indicate that processing reduces the herb's toxicity, possibly by hydrolyzing anthraquinone glycosides into aglycones, which lowers total anthraquinone content and thereby enhances safety while maintaining efficacy [27].

Sugars are another key component of Polygoni Multiflori Radix. According to the Chinese Pharmacopoeia and local processing guidelines, processed Polygoni Multiflori Radix (Polygonum Multiflorum Radix Preparata) exhibits a characteristic brown color inside and out, which serves as a visual index distinguishing it from the raw herb. Research suggests that this color change results from the Maillard reaction, wherein carbohydrate components react with proteins or amino acids under acidic, high-temperature conditions, progressively darkening the herb from yellow to brown and altering its properties [28].

Reduction of toxicity and retention of efficacy in TCM through processing

Mechanism of detoxification in aconitum processing

Raw Aconitum is highly toxic, with the potential to induce cardiotoxicity [29], and thus it is generally used only after processing, typically by boiling. Building on traditional processing knowledge, properly boiled and compatibly combined Aconitum can be safely and effectively used to treat various rheumatic pain conditions [30]. Alkaloids are both the primary pharmacologically active constituents and the main toxic components of Aconitum. During processing, these alkaloid components undergo chemical transformations that reduce toxicity while maintaining therapeutic effects [31]. Consequently, understanding the mechanisms and methods of Aconitum processing is crucial for providing a scientific foundation for its safe clinical application.

Research indicates that detoxification occurs because diester diterpene alkaloids (DDAs), such as aconitine and hypaconitine, are hydrolyzed into monoester diterpene alkaloids (MDAs) and non-esterified diterpene alkaloids (NDAs). Based on their substituents, aconitine alkaloids can be classified into highly toxic DDAs, low-toxic MDAs, and non-toxic NDAs. DDAs are chemically unstable: the acetyl group at the C8 position and the benzoyl

group at C14 are prone to hydrolysis or decomposition under heat or in the presence of water. Initially, DDAs lose the acetyl group at C8 to form MDAs, reducing toxicity by 200–500 times. Subsequently, the C14 benzoyl group is removed to produce NDAs **(Figure 3)**. Thus, heat treatment reduces Aconitum's toxicity primarily by promoting the hydrolysis of DDAs into the less toxic MDAs and NDAs [32].

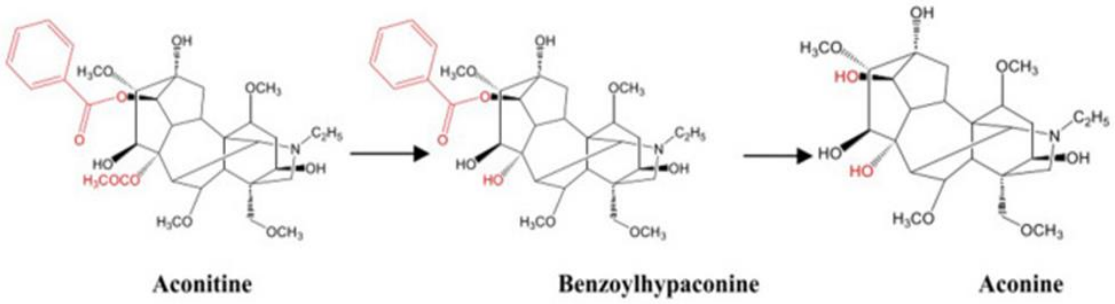
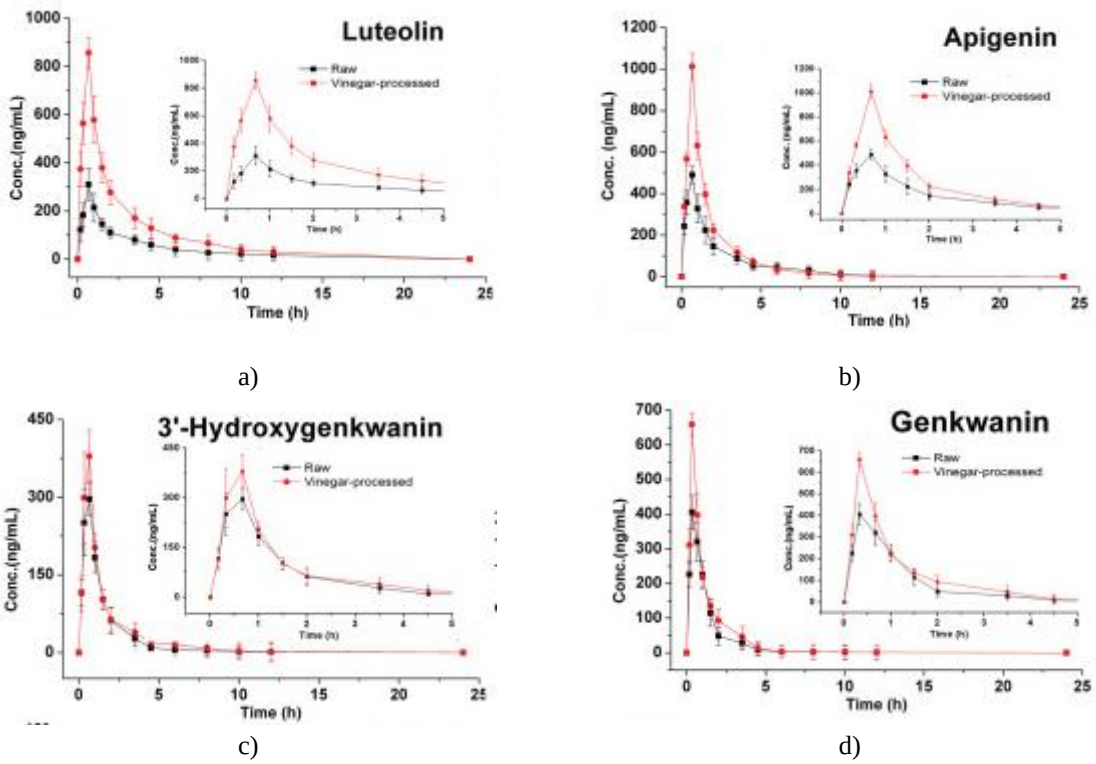


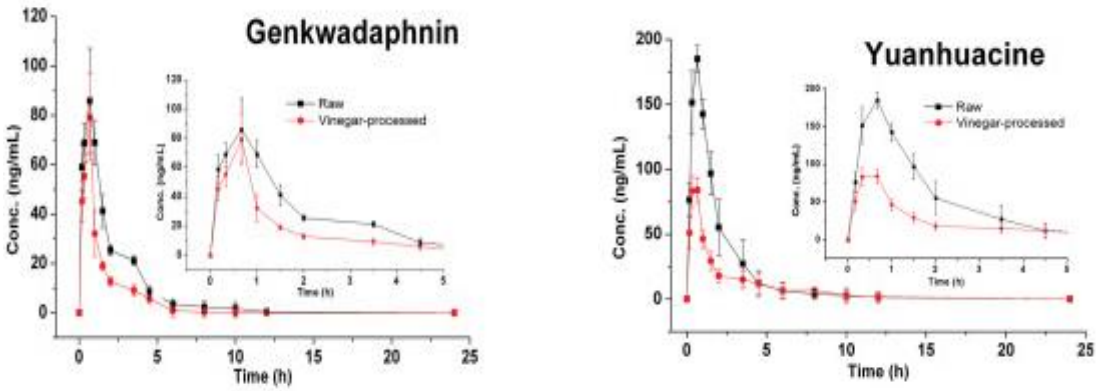
Figure 3. Hydrolysis of Alkaloids during Aconitum Processing.

Mechanism of detoxification in genkwa flos processing

Genkwa Flos, the dried flower buds of Daphne genkwa Sieb. et Zucc., exhibits sedative, analgesic, antiviral, anticancer, and anti-inflammatory properties [33]. However, modern studies indicate that excessive or prolonged use can damage the heart, liver, kidneys, and gastrointestinal tract [34]. Processing the herb by stir-baking with vinegar significantly alters its volatile components and chemical composition, leading to reduced toxicity and enhanced therapeutic effects [35].

Compounds such as genkwakine and genkwain may contribute to the hepatotoxicity of Genkwa Flos [36]. Tao *et al*. [37] applied UHPLC-MS/MS to compare the pharmacokinetics of raw versus vinegar-fried Genkwa Flos **(Figures 4a–4f)**. After oral administration of vinegar-fried Genkwa Flos, Cmax and AUC_{0-t} values for genkwain, 3′-hydroxygenkwain, apigenin, and luteolin were significantly increased ($p < 0.05$), while genkwakine levels in raw Genkwa Flos decreased markedly ($p < 0.05$). These results suggest that vinegar-frying improves the bioavailability of key active compounds while reducing toxic components, thereby producing synergistic therapeutic and detoxifying effects.





e) f)

Figure 4. Pharmacokinetic Curves of Six Components in Daphne genkwa before and after Stir-Baking with Vinegar [37].

Mechanism of detoxification of kansui radix stir-baked with vinegar

Kansui Radix, the dried root tuber of Euphorbia kansui T.N. Liou ex T.P. Wang, was first documented in Shen Nong's Herbal Lection. Due to its strong irritant effects on the skin, gastrointestinal tract, and mucous membranes, the traditional "stir-baking with vinegar" method has long been employed to mitigate the purgative effects and reduce toxicity of raw Kansui Radix both in vivo and in vitro. Recent studies have explored the chemical changes induced by vinegar processing and the mechanisms underlying its toxicity reduction [38].

Diterpenoids, the primary toxic constituents of Kansui Radix, are believed to be central to its toxicity. For example, the content of the main diterpenoid 3-O-(2′E, 4′Z-decadienoyl)-20-O-acetylingenol (3-O-EZ) significantly decreases after vinegar processing, with the ester bond cleaved and transformed into the less toxic compound ingenol. Simulation experiments verified this conversion pathway **(Figure 5)** [39]. Notably, 3-O-EZ cannot convert into ingenol without vinegar treatment, indicating that the vinegar plays a crucial role in modifying the terpenoid structure [40].

Metabolomic studies further demonstrate that vinegar-processed Kansui Radix alters metabolites in the liver and kidney of rats, normalizes glycolysis and amino acid metabolism disorders, and significantly reduces toxicity [41]. Additional research shows that vinegar-processed Kansui Radix can inhibit the intrinsic pathway of hepatocyte apoptosis by preventing mitochondrial cytochrome C release and blocking Caspase-3 and Caspase-9 activation, thereby mitigating liver toxicity [42]. These findings provide a mechanistic basis for understanding the detoxification effect of stir-baking Kansui Radix with vinegar.

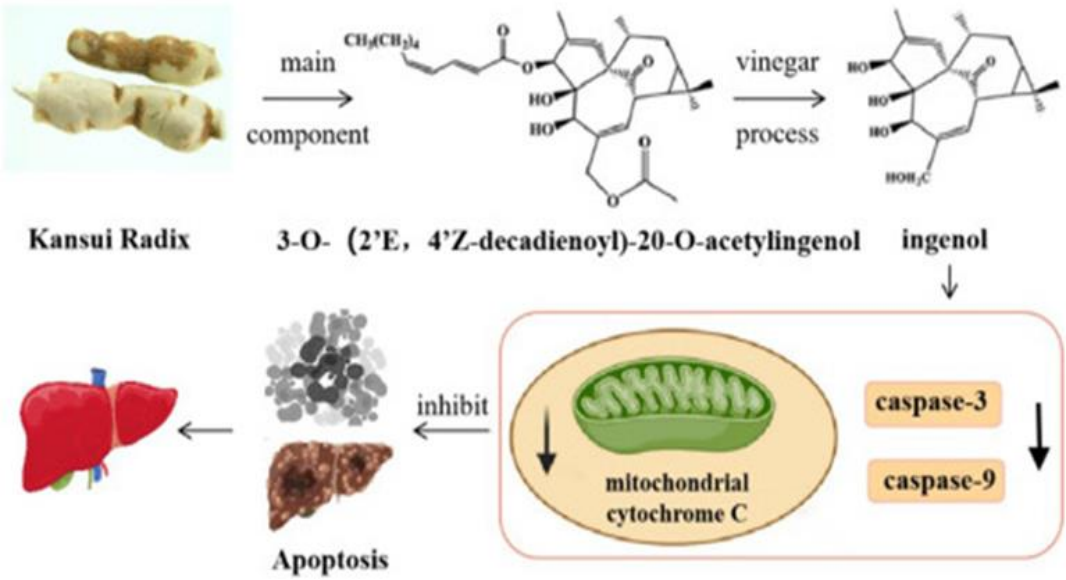


Figure 5. Conversion of Diterpenoid 3-O-EZ in Euphorbia kansui [39].

Changes in internal processes of TCM and efficacy enhancement induced by processing

In vivo pharmacokinetic study of rhei radix et rhizoma

Rhei Radix et Rhizoma, the dried root and rhizome of Rheum palmatum (Polygonaceae), has a bitter taste and cold nature, and is documented in the Shennong Classic of Materia Medica. It exhibits multiple therapeutic effects, including purgation, heat and fire clearing, blood cooling and detoxification, blood stasis removal, menstrual flow restoration, dampness elimination, and jaundice relief [43]. To mitigate its strong laxative effect, rhubarb is often processed with yellow rice wine through prolonged cooking [44]. Historical records, such as Zhang Zhongjing's Jin Kui Yu Han Jing from the Han Dynasty, describe processed rhubarb preparation as removing black skin, washing with wine, and soaking in wine. The 2020 edition of the Chinese Pharmacopoeia specifies "cooked rhubarb" as rhubarb steamed or stewed with wine.

Sennosides and anthraquinone glycosides are the main purgative constituents of Rhei Radix et Rhizoma [45]. Comparative in vivo studies have been conducted to assess differences between raw and wine-processed rhubarb. Plasma concentrations of six key components were measured in rats following oral administration. The results demonstrated that wine-processing altered rhubarb's pharmacokinetics: the parameters for representative free anthraquinones (emodin and aloe-emodin) changed significantly, with maximum plasma concentrations (Cmax) notably increased **(Figure 6)** [46]. Studies indicate that raw rhubarb contains higher levels of bound anthraquinones, which are converted to free anthraquinones during heat treatment [47]. Therefore, investigating how processing affects chemical composition, metabolism, and biological activity is essential for broadening rhubarb's applications, enhancing its efficacy, and improving safety.

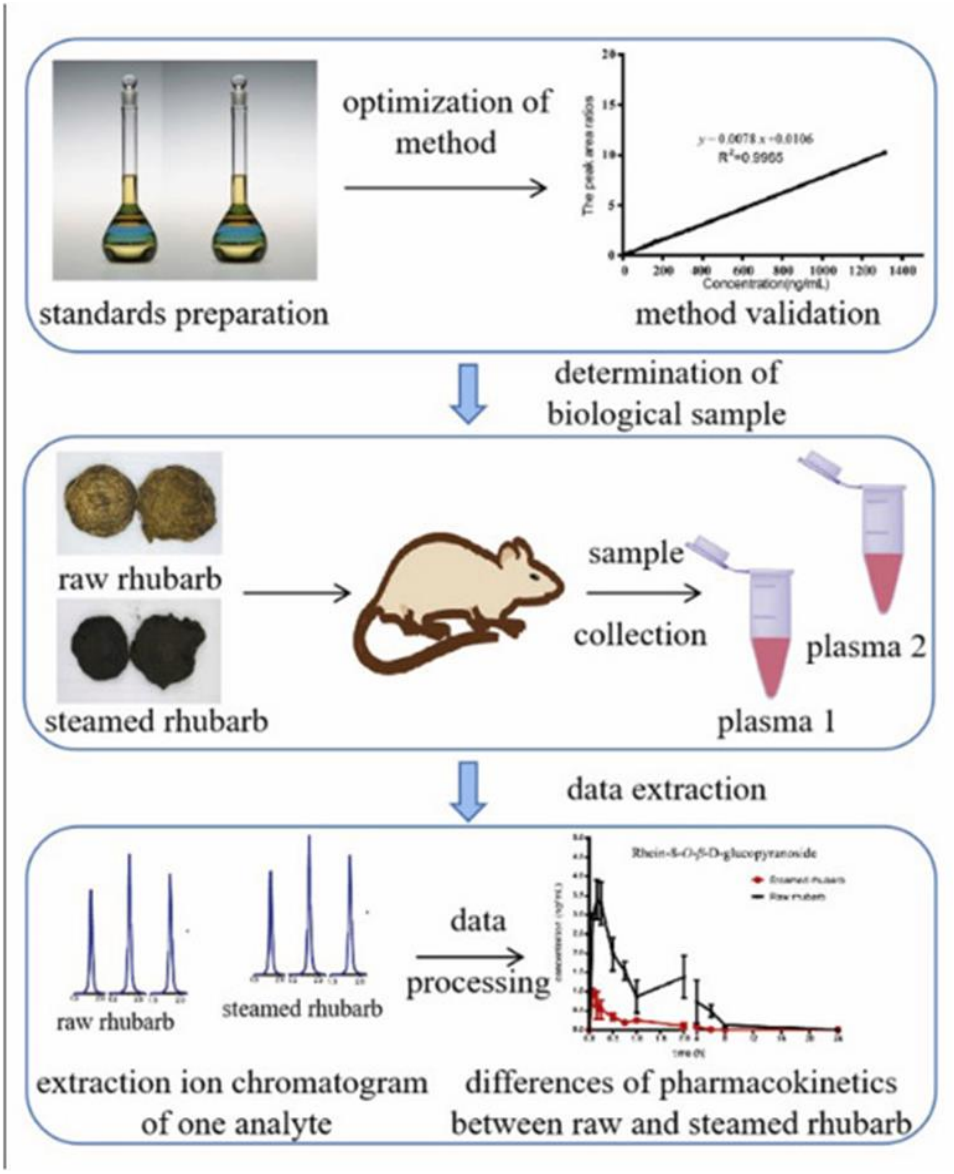


Figure 6. Pharmacokinetic Comparison between Raw and Wine-Stirred Rhubarb [46].

In vivo pharmacokinetics of bupleuri radix

Bupleuri Radix, obtained from the dried roots of Bupleurum chinense DC. or Bupleurum scorzonerifolium Willd. (Umbelliferae), is known for its antipyretic, analgesic, and antidepressant properties. According to the Chinese Pharmacopoeia, it is available in two forms: raw and vinegar-stir-fried, with evidence suggesting that vinegar-processed Bupleuri Radix exhibits stronger antidepressant effects [48]. The herb's pharmacological activity is largely attributed to saikosaponins [49].

Lu *et al*. [50] employed UPLC-MS/MS to quantify eight saikosaponins (SSa, SSb1, SSb2, SSb3, SSb4, SSc, SSd, and SSf) in rat plasma and compared their pharmacokinetic behavior in a depression model following administration of raw versus vinegar-fried Bupleuri Radix. Significant differences were observed in both AUC_{0-t} and Cmax values for the measured components, as illustrated in **Figure 7** [51]. These variations are likely due to the differing concentrations of active compounds between the two preparations.

Vinegar-stir-frying induces chemical transformations in saikosaponins: SSa and SSd are hydrolyzed into secondary saikosaponins SSb1 and SSb2, which enhance anti-inflammatory activity, modulate immunity, inhibit lipolysis, and stimulate PGE2 production [52]. Heat and acidic conditions during processing also promote cleavage of allyl oxygen bonds at C13 and C28, converting type I saikosaponins into type II heterocyclic diene structures [53] **(Figure 7)**. These changes improve the herb's therapeutic potency for liver-related disorders and depression, providing a mechanistic explanation for the efficacy enhancement observed with vinegar-stir-fried Bupleuri Radix.

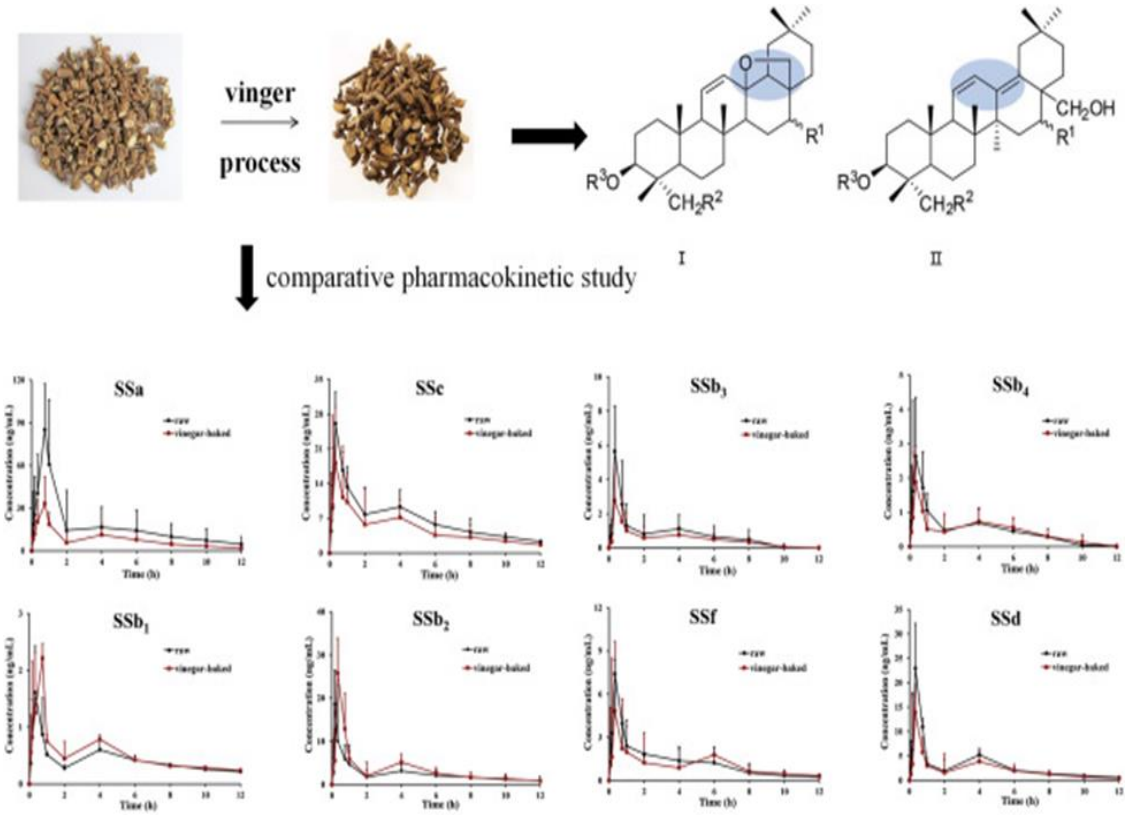


Figure 7. Structural Transformation and Pharmacokinetic Curves of Saikosaponins in Radix Bupleuri Before and After Vinegar Stir-Frying [51].

Conclusion

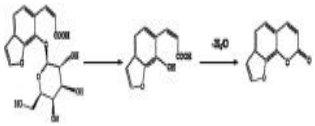
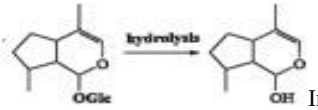
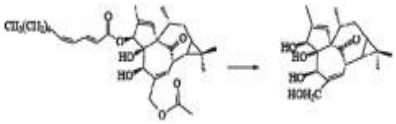
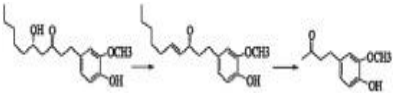
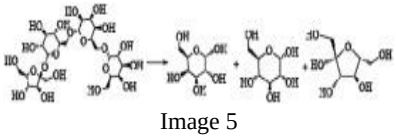
The processing of TCM plays a crucial role in determining the efficacy, safety, and quality of herbal medicines, making it essential to investigate how chemical components change during processing to establish reliable quality control standards. As the chemical constituents are the primary basis for TCM's therapeutic effects, alterations in these compounds underlie the changes in efficacy observed before and after processing. To better understand the

influence of different processing methods, numerous studies have employed modern analytical techniques to examine how processing affects TCM's chemical composition [54–56].

In recent years, innovative technologies and methodologies have emerged for this purpose, as summarized in **Table 1**. Among them, metabolomics has been widely applied to study TCM processing mechanisms, optimize decoction piece production, and improve quality standards [57–59]. For instance, Song *et al*. combined metabolomics with pseudo-targeted spectrum–effect analysis to identify potential hepatotoxic components in Polygoni Multiflori Radix, demonstrating that integrating metabolomics and chemometrics allows rapid identification of chemical markers before and after processing and provides insights into herb-induced hepatotoxicity [60].

Overall, TCM processing can modify the structure and concentration of active ingredients, enhance therapeutic effects, and reduce or mitigate toxicity, making it a critical step in TCM production and application. The integration of traditional processing methods with modern scientific techniques enables a clearer, more visual understanding of processing mechanisms. Research in this area not only minimizes risks associated with TCM use but also guides rational clinical application and supports the sustainable development of the TCM industry.

Table 1. Techniques applied in the study of the processing of TCM.

Technologies and methods	Type of reaction	Example	Reactive component	Chemical reaction	References
Pharmacokinetic and Toxicokinetic Study	dehydration reaction	*Psoraleae Fructus*	psoralen and isopsoralen	 Image 1	[61]
Metabolomic strategies and biochemical analysis	hydrolysis reaction	*Rehmanni -ae Radix*	iridoids	 Image 2	[19]
Simulation processing	hydrolysis reaction	*Kansui Radix*	diterpenoid	 Image 3	[39]
Non-targeted metabonomics combining with SIBDV method	decompositi on reaction	*Zingiberis Rhizoma*	6-gingerol	 Image 4	[62]
Spectrum-effect relationship analysis	hydrolysis reaction	*Rehmanni ae Radix*	polysacchar ide	 Image 5	[1]

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Conflict of Interest: None

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Ethics Statement: None

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