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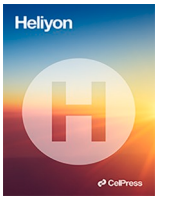

Research article

Safety and efficacy evaluation of Simo decoction and *Arecae semen* in herbal medicine practice

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ABSTRACT

Objective: The traditional Chinese patent medicine (TCPM), Simo decoction (Simo decoction oral solution), with its primary ingredient *Arecae semen* (Binglang, *Areca catechu* L.), known for its potential carcinogenic effects, is the subject of this study. The research aims to analyze the effectiveness and potential risks of Simo decoction, particularly as a carcinogen, and to suggest a framework for evaluating the risks and benefits of other herbal medicines.

Methods: The study is based on post-marketing research of Simo decoction and *Arecae semen*. It utilized a wide range of sources, including ancient and modern literature, focusing on the efficacy and safety of Simo decoction. The research includes retrospective data on the sources, varieties, and toxicological studies of *Arecae semen* from databases such as Pubmed, Clinical Trials, Chinese Clinical Trial Registry, China National Knowledge Infrastructure, WHO-UMC Vigibase, and China National Center for ADR Monitoring.

Results: Common adverse drug reactions (ADRs) associated with Simo decoction include skin rash, nausea, vomiting, abdominal pain, and diarrhea. However, no studies exist reporting the severe ADRs, such as carcinogenic effects. *Arecae semen* is distributed across approximately 60 varieties in tropical Asia and Australia. According to the WHO-UMC Vigibase and the National Adverse Drug Reaction Monitoring System databases, there are currently no reports of toxicity related to *Arecae semen* in the International System for Classification of ADRs (ISCR) or clinical studies.

Conclusion: Risk-benefit analysis in TCPM presents more challenges compared to conventional drugs. The development of a practical pharmacovigilance system and risk-benefit analysis framework is crucial for marketing authorization holders, researchers, and regulatory bodies. This approach is vital for scientific supervision and ensuring the safety and efficacy of drug applications, thus protecting public health.

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1. Introduction

Traditional Chinese herbal medicine, a vital aspect of traditional Chinese medicine (TCM), has a long-standing history and is extensively used worldwide. Its distinctive herbal components and therapeutic strategies are crucial in treating diverse health issues, garnering significant interest and prompting extensive research [1–4]. Despite its global application, the systematic scientific analysis of the risks and benefits associated with TCM poses a significant challenge [5,6]. This challenge arises due to the complex nature of TCM, which often includes a variety of herbal elements, each with unique effects on the human body [7–9]. Additionally, factors such as individual patient differences, dosages, and methods of preparation can impact the efficacy and safety of TCM. These complexities add difficulty to the scientific scrutiny of TCM [10–12].

In April 2013, multiple Chinese news sources disclosed a disturbing finding: Simo decoction, produced by Hansen Pharmaceutical Co., Ltd. (Yiyang, Hunan, China), contained Areca, a substance classified as a Group 1 carcinogen. This product was predominantly used by infants and young children. The primary source of concern regarding *Arecae semen* stems from its categorization as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). The widespread use of "Hansen Simo decoction" among infants and children has raised significant public alarm, resulting in widespread distress and even widespread panic [13–15].

In the field of traditional Chinese patent medicine (TCPM), Simo decoction (Simo decoction oral solution) is distinguished by its effectiveness in treating various symptoms, including vomiting, abdominal bloating, abdominal pain, constipation, and feeding intolerance in premature infants, as well as constipation and functional dyspepsia in older adults [16–19]. A key component of this decoction is *Arecae semen*, traditionally used for its properties in eliminating intestinal parasites, alleviating food stagnation, stimulating qi, promoting diuresis, and preventing malaria [20]. However, the growing public concern about *Arecae semen* arises particularly from its notable link to carcinogenic risks, highlighting the complexities and critical importance of analyzing TCM [21–23].

The primary aim of this research is to delve deeply into the efficacy and toxicity of Simo decoction, as well as the diversity and toxicity of *Arecae semen*, to provide data support for establishing a risk-benefit analysis system. This study involves a comprehensive review of both ancient and modern literature, analyzing the effectiveness and safety of the Simo decoction formulation, with a specific focus on the origin, variety, literature research, and retrospective toxicity data of *Arecae semen*. Additionally, we have referenced information from various databases to gain a comprehensive understanding of the potential risks associated with *Arecae semen*. Through this study, we aim to contribute a new perspective to the risk-benefit analysis of TCM and highlight the collaborative efforts among researchers, regulatory bodies, and pharmaceutical companies to ensure the safety and efficacy of TCM, thereby protecting public health. The insights gained from this work are expected to be significant in guiding the establishment of risk-benefit analysis systems for other TCMs in the future.

2. Materials and methods

This study was conducted as a post-marketing research investigation of Simo decoction and its main ingredient, *Arecae semen*. The efficacy and safety of Simo decoction were evaluated by analyzing data from ancient and modern literature. Special attention was given to retrospective data regarding the source, variety, authentication, and toxicity of *Arecae semen*. Various databases were used to source this data, including PubMed, Clinical Trials, Chinese Clinical Trial Registry, China National Knowledge Infrastructure, WHO-UMC Vigibase, and the China National Center for ADR Monitoring. Furthermore, the regulatory status of *Arecae semen* in multiple

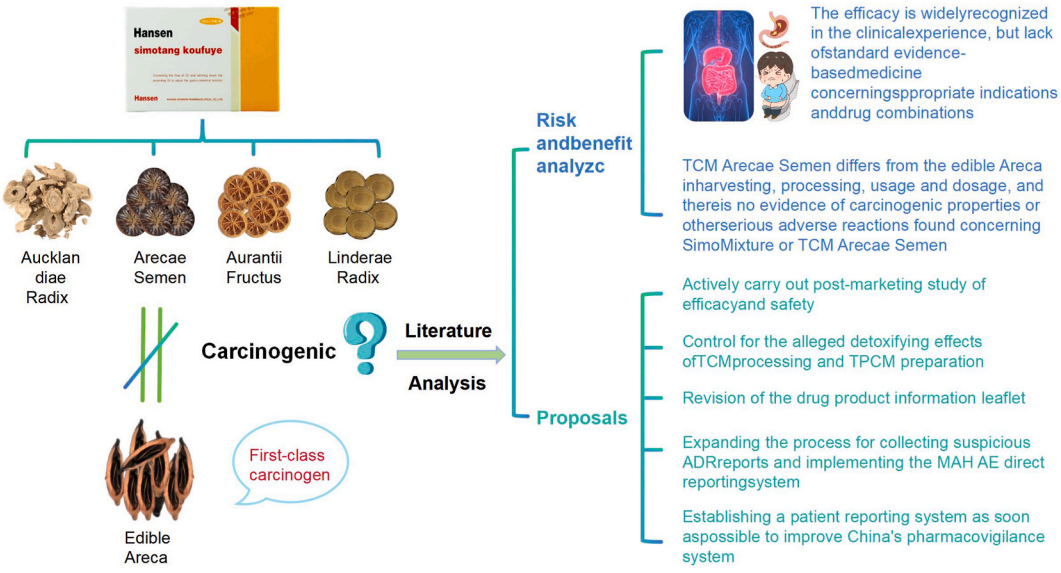

Fig. 1. Flowchart depicting the analysis of efficacy and safety of Simo decoction oral solution and its ingredient *Arecae semen*.

countries, such as China, Japan, Korea, Malaysia, the Philippines, Singapore, Thailand, India, Europe, and the United States, was considered in the study. The research also refers to authoritative texts, including the "Chinese Pharmacopoeia 2020."

The keywords used for our search were "Areca catechu L.," "Areca," "Areca nut," "*Arecae semen*," "Betel quid," "Betel nut," "Binglang," "Simo," "Simo decoction," "Toxicity," "Efficacy," "Safety," "Adverse drug reaction (ADR)," and "Carcinogenic.". The search, conducted in August 2023, yielded 289 articles. After excluding review articles, duplicate case reports, and irrelevant literature, 12 clinical reports and case studies specifically using *Arecae semen* and its preparations were included. Notably, no literature reporting adverse reaction events related to *Arecae semen* and Simo decoction was identified in the search results. The methodology and analysis process of this study are illustrated in Fig. 1.

3. Results

3.1. Sources and market research of Simo decoction

The origins of Simo decoction can be traced back to the Song Dynasty's medical text "*Jisheng Recipe*." Simo decoction is a traditional Chinese herbal formula that first appeared in the classic "*Treatise on Febrile Diseases*." Traditionally, Simo decoction is a herbal formula that requires sourcing raw materials from Chinese herbal medicine pharmacies or herbal stores and then brewing them into a medicinal soup according to specific proportions. The oral liquid form of Simo decoction represents a modern formulation, typically involving the extraction of its herbal components into a liquid form for convenient patient consumption. In TCM, this formula is considered a health-promoting and gastrointestinal-regulating herbal remedy. However, in modern China, Simo decoction is also used as a TCPM. It was first mentioned in the book "*The Revised Yanshi Formula*" during the Southern Song dynasty. Since then, it has been recorded in medical books of every subsequent dynasty, undergoing modifications and innovations to the original formula. TCM texts document different variations of Simo decoction, such as "*Yanshi Zaizao*" in the Southern Song dynasty, "*Zheng Yin Mai Zhi*" and "*Shuanglong*" in the Ming dynasty. The currently available version of TCPM, Simo decoction, is derived from the formula described in the "*Compilation of National Standards for Traditional Chinese Medicine*" (CNS TCPM) (2002 edition), which originates from the "*Shuanglong* Jiangche Version." The national drug standards for Simo decoction, as recorded in the CNS TCPMs are presented in Table 1 [24,25].

This product was launched in 1996 and is currently regulated by the NMPA as an over-the-counter (OTC) drug. The marketing authorization holder (MAH) for this product is Hunan Hansen Pharmaceutical Co., Ltd. In total, there are 206 registered products containing *Arecae semen*, including preparations such as Weiding tablets, Shenqi tea (Liuqu tea), Chaihu Shugen pills, Children's Qinshen pills, Haixian Qi pills, and Muxiang Shunqi pills.

3.2. Chemical components and carcinogenic risks of Arecae semen

Arecae Semen, the fruit of the areca nut, contains 50–60 % carbohydrates, 15 % lipids, proteins, crude fiber, minerals, flavon-3-ols, condensed tannins, and 0.2–0.5 % piperidine alkaloids. This includes constituents, such as arecoline, arecaidine, guvacoline, and guvacine (Fig. 2). Arecoline, the primary alkaloid, acts as a parasympathomimetic agent, functioning as a muscarinic receptor agonist and, in high doses, as a nicotinic receptor agonist. It exhibits various effects, including acetylcholine-like actions, vasodilation, blood pressure reduction, reflex tachycardia induction, intestinal tension and motility stimulation, secretion stimulation, myopathy, and bladder contraction [26]. *Arecae Semen* is often mixed with alkalizing agents like lime or ash, as well as cashews, spices, and flavorings. Sometimes, they are rolled in areca leaves, in what is known as "*Arecae Semen* chewing," a practice widely prevalent globally with an estimated 600 million consumers [27]. Regular chewing of *Arecae Semen* is associated with oral, pharyngeal, and esophageal cancers

Table 1
National drug standard for Simo mixture.

Drug composition	37.5 g of Aucklandiae Radix (Muxiang, *Aucklandia lappa* Decne.[1]), 37.5 g of Aurantii Fructus (Zhiqiao, *Citrus x aurantium* L.), 37.5 g of Unprocessed Arecae Semen, and 37.5 g of Linderae Radix (Wuyao, *Lindera aggregata* (sims) Kosterm.)
Procedure	The four ingredients are mixed and treated by steam distillation until 600 mL of aromatic water is extracted and preserved in a separate container. The residue is macerated in water 3 times, for 30 min each time and filtered. The filtrates are combined and concentrated until the extract reaches a relative density of 1.10 (60–70 °C). Ethanol is added to adjust the alcohol content to 75 % and the solution is incubated at 4 °C for 12 h. The ethanol is distilled from the filtrate until a non-alcoholic taste is achieved. After addition of water and stirring, the filtrate is incubated at 4 °C for another 12 h and filtered. The aromatic water, prepared above, is added with 240 g of high fructose corn syrup and 1.5 g of potassium sorbate, and mixed with the extract until a total volume of 1000 mL; this mixture is well stirred, stored at 4 °C for 36 h, and filtered to obtain the final product *("Elixir")*.
Actions	To direct Qi downwards and down bear counter flow, eliminate accumulation and relieve pain.
Indications	Infantile abdominal pain resulting from consumption of spoiled milk or food, a distended abdomen, other abdominal pain, crying, poor appetite, diarrhea or constipation. Qi stagnation and food accumulation in middle-aged and old people, a distended abdomen, abdominal pain and constipation, and recovery of gastrointestinal function after abdominal surgery.
Administration and dosage	For oral administration, • 10 mL per dose, three times a day, one-week course for adults. •3–5 mL per dose, three times a day, two-days course for newborn. •10 mL per dose, three times a day, 3–5 days course for infants.
Strength	10 ml per vial
Contraindication	Prohibited for pregnant women, and the people with intestinal obstruction, intestinal tumors, and gastrointestinal disability.

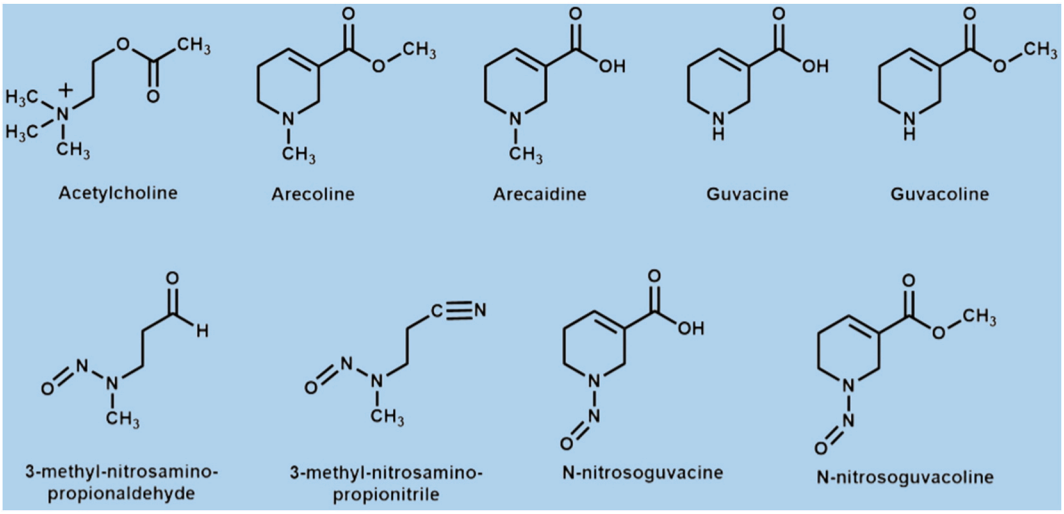

Fig. 2. Diagram depicting acetylcholine, piperidine alkaloids originating from *Arecae semen*, and prominent metabolites detected in saliva.

[26,27], and this association shows a dose-response relationship [27]. The carcinogenicity of *Arecae Semen* has been proven to be independent of tobacco (although tobacco significantly increases the risk) and is primarily attributed to the alkaline substances in chewing preparations, condensed tannins or nitrosamines formed in saliva with *Arecae Semen* alkaloids, particularly 3-methylnitroso-propionaldehyde, 3-methylnitrosopropionitrile (a rodenticide carcinogen), N-nitrosoguvacoline (NGC), and N-nitrosoguvacoline (NGL), associated with chronic inflammation, oxidative stress (reactive oxygen species and glutathione depletion), and cytokine production [28–30]. *Arecae Semen* also contains styrene, particularly safrole, which is also related to the carcinogenicity observed in *Arecae Semen* chewers [31]. In studies comparing *Arecae Semen* chewers and non-chewers, enormous risks were reported for chewing *Arecae Semen*, and it has been assessed as a Group 1 carcinogen by the IARC [32]. Oral leukoplakia and submucous fibrosis are two major oral potentially malignant disorders caused by *Arecae Semen* chewing [33]. Additionally, studies have confirmed that the frequency of *Arecae Semen* chewing correlates positively with the risk of cardiovascular diseases and all-cause mortality [34]. The carcinogenicity of *Arecae Semen* is associated with the production of reactive oxygen species during the chewing process, which can lead to DNA oxidative damage and the activation of oncogenes. Components in *Arecae Semen* can induce apoptosis in various cell types, including oral fibroblasts, keratinocytes, and endothelial cells. Epidemiological, animal, and in vitro study evidence suggests that *Arecae Semen* nuts are carcinogenic to humans [27], and theoretically, they could lead to genomic instability through DNA damage. The question of whether a threshold exists and whether an acceptable level of genotoxic compound exposure can be defined remains a matter of debate [35]. However, to date, no foundational or clinical research evidence has been found related to the carcinogenicity of *Arecae Semen* in TCM.

4. Risk-benefit analysis of Simo decoction

4.1. Clinical applications of Simo decoction

Simo decoction is utilized for a wide range of medical conditions, including the treatment of symptoms such as vomiting, bloating, abdominal pain, constipation, and feeding intolerance in premature infants [36,37]. It is also effective in addressing constipation and functional dyspepsia in older adults [38,39]. Furthermore, Simo decoction has shown efficacy in treating anorexia, as well as nausea and vomiting related to cardiopulmonary diseases. It plays a significant role in restoring gastrointestinal function after abdominal or cesarean surgeries and in promoting lactation in postpartum cesarean patients ([40–45].

Three clinical trials involving Simo decoction have been registered with the Chinese Clinical Trial Registry, the International Clinical Trials Registry Platform, and various clinical trial databases in China. Two of these studies focused on assessing the impact of a combined treatment of Simo decoction and acupuncture on the incidence of postoperative ileus (POI) in patients who had undergone colorectal cancer resection and liver resection. The findings indicated that this integrative approach, involving Simo mixture and acupuncture, effectively reduced the incidence of POI and decreased the length of hospital stays under experimental conditions. The first of these studies enrolled 565 patients aged 18 and above, all of whom had undergone primary resection for colorectal cancer. These patients were randomly divided into three groups: the first group received Simo decoction (10 mL/dose, from Hansen Pharmaceutical Co., Ltd.) along with intracavitary administration of vitamin B1 (50 mg × 2); the second group was given sugar-free chewing gum; and the third group received no treatment, with this regimen continuing for five consecutive days.

Relative to other patient cohorts, the group receiving Simo decoction combined with acupuncture demonstrated notably shorter durations of hospitalization, earlier occurrences of first flatus and bowel movements, and reduced rates of grade I and II complications [46]. The second investigation employed a randomized, double-blind, placebo-controlled methodology. This study included 162

patients, all aged 18 or older, who underwent open liver resection surgery. They were divided into three groups: 1) receiving Simo mixture (10 mL) along with thrice daily acupuncture point injections of vitamin B1 (50 mg × 2) for a total of 15 administrations (n = 55); 2) given sugar-free chewing gum three times a day (n = 53); 3) no intervention (n = 54), for 6 days or until gas discharge. The results indicated that the group treated with Simo decoction and acupuncture had significantly lower incidences of initial movement, excretion, grade I and II complications, and shorter hospital stays compared to the non-intervention group [47]. The third study is a current multicenter, prospective, randomized controlled trial focusing on enhancing the success rate of nasogastric tube placement post-pyloric stenting in patients with severe illnesses. The initial two clinical trials involving the combination of Simo decoction and acupuncture did not result in notable adverse reactions. However, the participants did not undergo long-term follow-up. It is important to note that the experiments conducted on cancer patients do not provide conclusive evidence regarding carcinogenicity.

4.2. Adverse effects associated with Simo decoction and Arecae semen

Our comprehensive analysis of case reports indicates that the safety concerns associated with Simo decoction are mainly due to allergic and gastrointestinal reactions. The clinical presentations include: 1) Skin and subcutaneous tissue disorders, characterized by widespread erythematous rashes across the body; 2) Gastrointestinal diseases, manifesting symptoms such as nausea, vomiting, abdominal pain, and diarrhea; 3) Neurological disorders, presenting as headache, flushing, palpitations, dry mouth, and irritability; 4) Blood and lymphatic system disorders, where the combination of Simo decoction and warfarin can lead to an increased international normalized ratio (INR). According to the evaluation criteria established by the NMPA, the causality of these side effects is determined by the relationship between the treatment and the occurrence of adverse reactions. In terms of other TCPMs containing *Arecae semen*, Muxiang Shunqi Pian has been found to induce toxic muscarine effects, whereas no correlation was found between Haixiang Shunqi tablets, Chinese yam, Feier tablets, and the case reports reviewed in the literature [48].

Based on current studies and clinical reports, no toxicological studies have been found post-use of Simo mixture containing *Arecae Semen* seeds. Moreover, there are no clinical reports linking oral consumption of Simo mixture containing *Arecae Semen* seeds to carcinogenic effects.

4.3. Key factors for risk-benefit analysis

In TCM, "*Arecae Semen*" typically refers to the raw, unprocessed form, often extracted in larger pieces. In contrast, the pharmaceutical product "Zhizhi Pian" incorporates these materials in a form that is either ready for direct clinical use or can be further processed for manufacturing [49]. Medical practitioners often adapt the processing techniques (such as cleaning, cutting, frying, boiling, and calcining) and preparation methods of *Arecae semen*, along with its clinical applications, in alignment with TCM principles and based on medicinal properties. To conduct a comprehensive risk-benefit analysis, it is crucial to thoroughly evaluate both the preparation characteristics and the clinical uses of *Arecae semen*. This detailed assessment is vital for understanding the full spectrum of potential risks and benefits associated with its use in various medical contexts.

4.4. Characteristics of prepared slices of Chinese crude drugs

TCM places great importance on the utilization of "authentic medicinal materials," a term reserved for high-quality, pure herbal substances. The term refers to medicinal materials with a long historical background, native to regions with the optimal conditions for growth, boasting outstanding varieties, high production, intricate processing, remarkable effects, and distinct regional characteristics [50,51]. *Arecae Semen*, listed in the "2020 Pharmacopoeia of the People's Republic of China," is the dry, mature seed of the palm plant *Arecae Semen*. The *Arecae Semen* produced in Hainan and southern Yunnan is recognized as a genuine regional medicinal substance. The pharmacopoeia describes three processed forms of *Arecae Semen*: unprocessed *Arecae Semen* (Binglang), stir-baked *Arecae Semen* (Chaobinglang), and charred *Arecae Semen* (*Arecae Semen* Tostum, Jiaobinglang), with processing involving stir-baking until it reaches a slightly yellow color (Stir-baked *Arecae Semen*) or a charred yellow (*Arecae Semen* Tostum). The method of roasting and optimal heat level significantly influence the efficacy of the medicine. *Arecae Semen* is known for its strong action against parasites and edema, commonly used for intestinal parasites, leg and foot swelling, chest tightness, varicose veins, cold damp syndrome, and other swelling syndromes [52]. Compared to the raw form, stir-baked and charred *Arecae Semen* are milder, with fewer side effects like nausea, diarrhea, and abdominal pain. Charred *Arecae Semen* is the mildest in effect, followed by stir-baked *Arecae Semen*, likely due to their varying degrees of reducing the content of *Arecae Semen* alkaloids [53]. Promoting the contraction of the ciliary muscle can be utilized in treating digestive system diseases [54]. Hence, physicians should prescribe the appropriate *Arecae semen* based on the patient's physical condition and acceptable risks.

4.5. Toxicological profile and safety data of Arecae semen

Arecae semen, a TCM, was initially documented in the "*Pharmaceutical Record* (*Yao Lu*)" by Li Dang in the Three Kingdoms era. The ancient Chinese medical treatise "*Ben Cao Bian Du*" explicitly notes the "mild toxicity" of *Arecae semen* [55]. Ancient texts also suggest that prolonged use of *Arecae semen* may negatively impact vital energy, essential for human health, by obstructing its flow. Therefore, its usage is generally discouraged for individuals with frail physical constitutions. *Arecae semen* is known for its spicy, bitter, and hot properties, which may deplete the body's fluids, elevate internal heat, and stimulate patients with Yin deficiency [56].

The Chinese Pharmacopoeia 2020 edition lists 83 types of toxic TCMs, categorizing 10 as highly toxic, 42 as toxic, and 21 as mildly

toxic. However, *Arecae semen* does not fall within these toxic classifications. Presently, there are no documented reports in the field of Chinese medicine indicating the carcinogenic potential of *Arecae semen*. Data from the National Adverse Drug Reaction Center and literature from CNKI and Wanfang databases revealed no individual safety reports (ICSRs) concerning Chinese herbal semen or over 200 samples containing Chinese herbal semen in TCPM. *Arecae semen* and its preparations have not been prohibited by any relevant authorities. Prior research has identified only one adverse reaction report of the Chinese medicinal herb *Arecae semen* [57]. This case suggests that *Arecae semen* may activate muscarinic acetylcholine receptors, leading to symptoms like nausea, vomiting, salivation, sweating, increased blood pressure, irritability, and dyspnea, potentially due to the cholinergic effects of its alkaloids. The causality of this adverse reaction, based on the criteria for determining adverse reaction causality, appears plausible, though the specific treatment details involving *Arecae semen*, in this case, were not documented.

Arecae semen was introduced to China from Malaysia more than 1600 years ago and continues to be widely used across tropical Asian regions, notably in Japan, South Korea, and India. Nonetheless, no reports linking *Arecae semen* to carcinogenicity have been found on the websites of the food and drug regulatory authorities of these countries. Additionally, the WHO-UMC database and the Chinese National Adverse Drug Reaction Monitoring Center database contain no individual case safety reports (ICSRs) indicating cancer caused by *Arecae semen* or related compound preparations of TCM.

4.6. Considerations for risk analysis of Arecae semen

In the risk analysis of *Arecae semen*, various factors should be considered, including its cultivation, processing, usage, and dosage. Approximately 60 species of *Arecae semen* are primarily found in tropical Asia and Australia, with two species, Areca catechu L. and Areca triandra Roxb. ex Buch.-Ham, mainly distributed across several Chinese provinces [58]. The Chinese Pharmacopoeia 2020 confirms that only *Arecae semen* is acceptable for use. The processed slices are either used as raw materials in TCM prescriptions or sold for producing TCM preparations. The risk assessment should differentiate between *Arecae semen* used in TCM and the edible variety, considering these various factors, such as cultivation, processing, usage, and dosage (Table 2).

5. Reflection and inspiration of Simo decoction

5.1. Overall risk-benefit analysis of Simo decoction

The risk-benefit analysis of Simo decoction, a formulation with over two decades of clinical use, reveals complex considerations. The brochure for Simo decoction specifies two indications aligned with "Chinese Medicine Syndrome," a concept challenging to parallel in contemporary medical terms. Research indicates moderate effectiveness of Simo decoction in treating conditions like functional dyspepsia, enterocutaneous fistula, gastroesophageal reflux disease, and postoperative constipation. However, evidence for other claimed benefits remains weak, primarily constituting low-level evidence or anecdotal case reports. A significant gap is noted in pinpointing precise indications and optimal drug combinations based on extensive exposure across a substantial patient population.

Simo decoction is prescribed to diverse demographic groups, including infants and the elderly, with the latter often receiving it as part of combination therapy with chemical drugs. To date, there is no substantial evidence indicating carcinogenic effects or severe

Table 2
The differences between TCM Arecae Semen and edible Areca.

	TCM Arecae Semen	Edible Areca
Medicinal parts	The dry and mature seed is called "Arecae Semen", which functions to expel worms, remove accumulation, move Qi, drain water, and disrupt malaria.	Dry Areca nut pieces
Processing methods	The plant can be processed before being used as medicine. It is reported that the various ingredients of TCM Arecae Semen will change to some extent after being processed. The longer the heating time and the higher the temperature, the greater the loss of arecoline and the larger the reduction in tannic acid content (Peng et al., 2017). Arecoline and tannins are considered to be the major toxic components of TCM Arecae Semen.	The plant is chewed directly or in complex mitures, notably with lime and sometimes with tobacco, cashew nut, spices and flavoring agents, or betel inflorescence or stems. Strong alkali treatment will increase the bioavailability of alkaloids and the formation of carcinogens such as nitrosamines.
Method of use	TCM Arecae Semen is commonly used in combination, rather than alone, according to the TCM theories of combinations (theories of the *"seven relations concerted application"*, of the *"eighteen clashes"* and *"nineteen-incompatibilities"*). Combinations are supposed to promote mutual reinforcement and assistance to increase efficiency and mutual detoxication.	Chewed in mouth for long time, with strong and long-lasting serious mechanical and chemical damage to the oral mucosa, resulting in probable precancerous lesions to sub-mucosal fibrosis, leukoplakia, lichen planus; shown to be carcinogenic.
Duration of use	The TCM Arecae Semen is only used for the short period of illness.	Chewing edible Areca can make people feel euphoric and comfortable. In Southeast Asia and parts of Southern China, people use Areca for recreational chewing, which may be one of the factors that cause high incidence of oral cancer in these areas.
Dose	Limited and small dosage. ChP 2015 stipulates that the daily dosage of TCM Arecae Semen is 3–10 g. When the product is used to expel parasites such as tape worm and fasciolopsis, the dosage is 30–60 g per day.	No stated/limited dosage. Moreover, addiction may result in large consumption.

adverse reactions directly attributable to Simo decoction. The safety concerns raised, such as skin and subcutaneous tissue disorders and gastrointestinal issues, have been primarily confined to individual case reports. Nonetheless, considering the long-term implications, it is plausible that a link between exposure to specific *Arecae semen* preparations and the subsequent development of carcinogenic effects may have been overlooked or inadequately investigated. This highlights the need for ongoing vigilance and comprehensive long-term studies to thoroughly understand the implications of using Simo decoction, especially among vulnerable patient groups.

6. Risk-benefit assessment of TCM preparations containing *Arecae semen*

TCM encompasses medicinal products and their preparations that are utilized in accordance with the principles of TCM theory [59, 60]. A comprehensive evaluation of the characteristics and clinical applications of TCM is essential for an accurate risk-benefit analysis. TCM includes Chinese Medicinal Materials (CMMs), prepared slices of Chinese crude drugs, and TCPMs, all regulated under national drug specification standards. There is a global tendency to assess the safety of TCM by conflating toxicity evaluations without adequately distinguishing between different formulations of distinct medications. An objective assessment of the risks associated with TCM [55] requires understanding the chemical composition of the drug, its interactions within complex formulations, and implementing vigilant drug monitoring. A prior study [61] has revealed that unprocessed *Arecae semen* seeds and their alkaloid content can induce hepatic injury, accelerate liver cell apoptosis in mice, and inhibit splenic cell metabolism. These substances also display immunotoxicity, cytotoxicity, and genotoxicity, potentially causing damage to hair follicle cells and reproductive dysfunction. Additionally, alkaloids in *Arecae semen* are known to cause nephrotoxicity. It is noteworthy that databases such as the World Health Organization-Uppsala Monitoring Centre vaccine database and national Adverse Drug Reaction Monitoring Systems have not reported toxicity for *Arecae semen* in the ISCR or in clinical research reports. This absence of reported toxicity underlines the complexity of evaluating the safety of *Arecae semen* in TCM preparations, necessitating a nuanced approach that considers both the potential therapeutic benefits and the risks associated with its use.

6.1. Active post-marketing efficacy and safety studies

Post-marketing research forms a critical component in reassessing the safety and efficacy of pharmaceutical products after their market release [62]. This responsibility predominantly lies with the MAH. Post-marketing studies are crucial for supplementing the limited scope of pre-market clinical trials, aiming to gather comprehensive information regarding the real-world application of the medication. These studies include gathering data on primary disease categories, stages of diseases, concurrent drug therapies, and any adverse reactions encountered. Through continuous review of safety literature worldwide and data from national centers monitoring ADRs, the MAHs are capable of performing thorough analyses of specific data subsets. This practice holds particular significance in detecting signals within distinct population cohorts, such as infants, the elderly, and other vulnerable groups that may be utilizing the medication. The development of risk management plans becomes imperative in order to effectively address clinical risks, cater to the requirements of special populations, and mitigate potential risks, including drug interactions. These post-marketing studies not only incorporate laboratory data but also provide robust evidence to support safety-related research endeavors. They play a pivotal role in identifying and mitigating potential risk factors guiding the safe and rational clinical use of pharmaceuticals. The findings from these studies are instrumental in reassuring the public about drug safety and in guiding healthcare professionals in making informed decisions about drug prescriptions and management [63].

6.2. Detoxification effects of TCM processing and TPCM formulations

The MAHs undertake comprehensive safety studies to examine the variability in Chinese medicines, with a special focus on *Arecae semen*. TCM theory outlines several objectives for processing crude drugs: 1) achieving uniform quality and size for enhanced repeatability and storage stability; 2) mitigating the toxicity or adverse effects of toxic crude drugs; 3) modifying the medicinal effects; 4) altering extractability; 5) improving stability and eliminating unpleasant flavors; 6) developing new, enhanced medications through processes like fermentation (European Council). In the case of *Arecae semen*, processing techniques such as blending, roasting, or calcination have been shown to reduce the alkaloid content [64], potentially impacting the levels of all alkaloids. The production process of Simo decoction, which includes boiling with water and three other plants during steam distillation and precipitation steps (Table 1), may also contribute to a decrease in both alkaloid and tannin content. Given that the alkaloids in *Arecae semen* are deemed primary carcinogens in this medicine (IARC, 2004), both processing and production should incorporate detoxification measures, which necessitate stringent control. The same considerations apply to *Arecae semen* tannins, which are sometimes viewed as genotoxic. While traditional processing is an art with no definitive endpoint, pharmaceutical practice requires clear-cut detoxification processes. Particularly with *Arecae semen*, a rationale akin to the management of pyrrolizidine alkaloid genotoxicity [65] should be adopted. If the presence of alkaloid is confirmed, maximum limits should be established for both the processed medicine and the final Traditional Patent Chinese Medicine (TPCM) formulation. Although the alkaloids of *Arecae semen* are often cited as the main active constituents due to their toxic muscarinic actions [64], this aspect complicates the risk assessment. A thorough investigation into the final Simo decoction product used in clinical research is necessary to determine 1) the actual content of alkaloids, tannins, and styrene; and 2) its genotoxicity as defined by herbal product guidelines [66]. This approach is crucial for reaching accurate conclusions on the safety and efficacy of *Arecae semen* in TPCM formulations.

6.3. Revisions and recommendations for Simo decoction drug information leaflet

Based on recent research findings, revisions are required for the indications listed in the Simo decoction information leaflet, as they currently do not align with the appropriate criteria. The term "Milk and food stagnation" fails to conform to the naming conventions outlined in the "Principles for Writing Instructions of Chinese Medicine and Natural Medicines" set by the NMPA in 2006. Therefore, the MAHs must submit revised materials and updated brochures to the NMPA, incorporating descriptions and names of TCM, TCM syndromes, and Western medical diseases. Moreover, the MAH must conduct standardized clinical trials based on the indications outlined in the drug registration criteria. Guidance on the clinical usage of Simo decoction should be precise, and overly broad indications should be eliminated to prevent confusion among clinicians.

The existing list of adverse reactions in the Simo decoction instructions lacks clarity. In light of our comprehensive evaluation and post-marketing research findings, we recommend the MAHs to include the following warnings in the leaflet:

1. Adverse Reactions: Potential skin and subcutaneous tissue disorders (such as rashes); gastrointestinal disorders (including nausea, vomiting, abdominal pain, and diarrhea); neurological disorders (like headache, palpitations, dry mouth, and irritability).
2. Precautions: Evidence suggests that the concurrent use of Simo decoction with warfarin may increase the International Normalized Ratio (INR) and the risk of bleeding. Therefore, caution is advised when considering alternative anticoagulant medications. Additionally, the inclusion of *Arecae semen* extract in Simo decoction, especially when combined with Artemisia annua, has been associated with increased toxicity [67]. Close monitoring is advisable during the administration of this medication.

Moreover, it is crucial to establish and periodically revise evidence-based guidelines for rational drug utilization, taking into account the most recent research discoveries regarding dynamic signal detection, special population considerations, and potential drug interactions.

7. Advancements in ADR reporting and MAH-adverse event (AE) system implementation

The drug monitoring system in China has evolved substantially over the past 30 years [68]. With the NMPA becoming a member of the International Research Institute in May 2017, China's pharmaceutical regulatory framework has seamlessly integrated into the global system, marking a new era of rapid advancement. The introduction of the MAH-AE direct reporting system, which commenced on January 1st, represents a significant step forward. Given the diverse patient demographics for Simo decoction, including infants, the elderly, and post-abdominal surgery patients, the MAH is tasked with refining its AE data collection and reporting processes. Active monitoring, especially in real-world studies, becomes crucial for these special patient groups. The effective implementation of a direct reporting system necessitates the establishment of a robust internal drug vigilance system, tailored to accommodate the unique aspects of OTC TCMs. To augment AE data collection, the MAH should broaden its reporting channels. This broadening should encompass the use of the official website for reporting and the analysis of social media data through text-mining technologies to capture patient reports. Additionally, developing a mobile application dedicated to facilitating spontaneous reporting of adverse reactions by patients can be a transformative step. This app should provide easy-to-use electronic medical tools to assist patients in accurately reporting adverse reactions. The integration of these advanced technological approaches will significantly enhance the efficiency and scope of ADR reporting, ensuring a more comprehensive understanding and management of potential risks associated with Simo decoction and other TCMs.

7.1. Development of a patient reporting system for drug safety enhancement

The establishment of a patient reporting system is of paramount importance to bolster the drug safety monitoring framework within our nation. The regulation of OTC drugs often lacks stringency in many countries, including China. A patient reporting system facilitates immediate access and submission of data concerning suspected ADRs, an approach particularly effective for monitoring OTC medications [26]. Several countries in Europe and North America have successfully adopted direct patient reporting systems, considerably expanding the literature range of collected reports on suspected acute adverse reactions [69]. The introduction of such a system in our country is expected to significantly encourage patient participation in drug vigilance activities. This initiative would not only enhance the scope of drug vigilance but also contribute significantly to the overall safety of pharmaceutical products. By enabling patients to report adverse reactions directly, the system can capture a wider array of data, thereby providing a more comprehensive and accurate picture of the safety profile of medications.

8. Discussion

This study undertook a detailed examination of the use of Simo decoction in specific demographic groups, namely premature infants, middle-aged adults, and the elderly. The results of our investigation highlighted the decoction's considerable effectiveness in mitigating symptoms like vomiting, bloating, abdominal pain, constipation, feeding intolerance, and functional dyspepsia. However, our research also identified common ADRs associated with Simo decoction, such as rashes, nausea, vomiting, abdominal pain, and diarrhea. These findings illuminate the complex nature of TCM and the critical necessity for ongoing research. The objective is to establish an equilibrium between the therapeutic benefits and safety concerns of such treatments. This balance is essential to maximize the positive outcomes while minimizing the risks, thereby enhancing the overall efficacy and safety profile of TCM like Simo decoction

in diverse patient populations.

The consumption and medicinal use of *Arecae Semen* exhibit distinct levels of toxicity. Studies have demonstrated that the habitual chewing of edible *Arecae Semen* increases the risk of heart failure, ventricular premature beats, and oral cancer [32,70]. In contrast, the use of *Arecae Semen* in TCM often involves its combination with other herbal ingredients, as seen in Simo Mixture, where *Arecae Semen* is mixed with Muxiang, Zhike, Wuyao, and others, undergoing specific processing techniques. Currently, there are no definitive reports on the carcinogenic risk of *Arecae Semen* as part of the Simo Mixture [21,22]. Although some studies have linked *Arecae Semen* to carcinogenic effects, conclusive evidence supporting this claim remains insufficient [20,23,71]. Existing research and literature primarily focus on the consumption of *Arecae Semen*, especially its association with oral cancer. There is a lack of substantial evidence directly linking the use of *Arecae Semen* in Simo Mixture with cardiovascular diseases. It is noteworthy that *Arecae Semen* used in TCM undergoes specialized processing and preparation, differing from the risks associated with direct chewing. Moreover, according to online reports, Hansen Pharmaceuticals conducted toxicological tests on Simo Mixture, indicating that it is safe and does not pose a carcinogenic risk. Similarly, search results from the Adverse Reaction Monitoring Center of NMPA from 1997 to 2011 show no carcinogenic adverse reactions associated with Simo Mixture. However, it must be noted that these findings require validation through large-scale clinical trials and in-vitro studies. Additionally, a more in-depth investigation is warranted to comprehensively evaluate the potential hazards of *Arecae Semen*, particularly its carcinogenicity. A key aspect of this study is the diversity and global distribution of *Arecae Semen*. We identified approximately 60 species of *Arecae Semen*, primarily located in tropical regions of Asia and Australia. This finding suggests the potential use of various *Arecae Semen* species in TCM preparations, which may influence their toxicity. Future research could explore the pharmacological differences among these various species of *Arecae Semen*.

This study highlights the complex dynamics involved in conducting risk-benefit analysis within the realm of traditional Chinese herbal medicine. This complexity is attributed to a multitude of factors, such as dose-response relationships, individual physiological variations, and the diversity in preparation methodologies. These elements add layers of intricacy to the assessment of risks associated with TCM, presenting significant challenges. Consequently, there is an imperative need for continuous refinement and standardization of methodologies used in risk-benefit analysis. Such advancements are crucial for precisely evaluating the safety and efficacy of TCM. This approach is essential not only for ensuring patient safety but also for maintaining the integrity and reliability of traditional Chinese medicinal practices.

The regulation of TCM is a crucial and intricate field that aims to guarantee the legality, quality, and clinical efficacy of TCM, with the ultimate objective of protecting patients' well-being [72–74]. Despite some advancements in the regulation of TCM, there continue to be challenges and unresolved issues [75,76]. Many nations have implemented regulations and standards to govern the practice of TCM, ensuring its quality and safety. These measures define guidelines for the production, quality control, sales, and clinical application of TCM, thus promoting standardization in the TCM market [77–79]. Clinical trials and research have been conducted to evaluate the effectiveness and safety of TCM, providing scientific evidence to support its rational clinical use and identify potential risks [1,2,5]. However, the complex nature of TCM, which typically consists of a combination of various natural herbal components, each with unique pharmacological effects and toxicities, complicates its evaluation and makes it challenging to determine its precise efficacy and associated risks [80–82]. Quality control is a critical concern in TCM due to its vulnerability to factors such as the quality of raw materials, processing techniques, and standardization levels. Ensuring consistency and high quality is indispensable in accurately assessing the effectiveness of TCM [83,84].

In addition, the enforcement of regulations poses a significant challenge in the expansive TCM market, raising concerns about the potential sale of non-compliant TCMs and endangering patients' well-being [77,85–87]. We suggest the implementation of a feasible drug surveillance system and the establishment of a risk-benefit analysis framework to regulate TCM in a scientifically sound manner. Regulatory agencies have a crucial role in ensuring the safety and effectiveness of TCM. Therefore, it is imperative to enhance cooperation, establish more stringent regulatory standards, and protect public health.

Based on our examination and consolidation of ancient and contemporary texts, we have deduced the following findings: (1) *Arecae semen*, a TCM, does not possess carcinogenic properties; (2) The consumption of *Arecae semen*, classified as a 'Group 1 carcinogen' by the IARC, differs significantly from the utilization of TCM containing *Arecae semen*; (3) It is crucial to evaluate the levels of pyridine alkaloids, tannins, and styrene in commercial products containing *Arecae semen*. Based on these grounds, we propose conducting a comprehensive risk-benefit analysis of herbal and traditional medicine. It is worth mentioning that, currently, safety case reports are the only available resources pertaining to the safety studies of Simo decoction and *Arecae semen*. Consequently, definitive results of comprehensive risk-benefit analysis are still pending, necessitating further rigorous randomized controlled trials and analysis of real-world data. This issue pervades the literature on these drugs. There is a dearth of clinical research investigating the safety and efficacy of these substances. Moreover, the prevalence of low-quality anecdotal evidence persists, suggesting a potential association between TCM and TPCM concerning AEs.

In summary, risk and benefit analysis poses greater challenges than conventional medications. It is imperative to develop a viable drug alert system and risk-benefit analysis framework tailored to the specific characteristics of each drug. The responsibility of ensuring the safety and effectiveness of drug usage extends beyond the MAHs, researchers, and regulatory agencies, necessitating the implementation of scientific oversight to safeguard public health.

The study concludes that a comprehensive understanding of the effectiveness of Simo decoction and the diverse properties of *Arecae semen* has been attained, providing essential data as support for analyzing the risks and benefits associated with TCM. This research offers novel perspectives on the complexity of TCM and its risk assessment from a scientific standpoint. Consequentially, it can aid healthcare practitioners in conducting more comprehensive evaluations of TCM in clinical practice. Nevertheless, this study has limitations regarding data availability and research design. Therefore, further research is necessary to address these gaps and acquire a more thorough comprehension of the safety and effectiveness of TCM. Future studies should explore extensive Chinese medicine

databases and devise innovative evaluation methods to further enhance the scientific assessment of Chinese medicine.

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Ethical statement

Ethical approval was not required for this study as it did not involve human or animal trials.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Jukai Huang: Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Yalu Wen:** Writing – original draft, Investigation, Funding acquisition, Data curation, Conceptualization. **Tianyi Yang:** Validation, Supervision, Methodology, Investigation. **Haibo Song:** Writing – review & editing, Writing – original draft, Visualization, Resources. **Ronald Meyboom:** Writing – original draft, Validation, Methodology, Investigation, Data curation. **Xiaohui Yang:** Writing – original draft, Visualization, Supervision, Investigation. **Lida Teng:** Writing – original draft, Resources, Methodology, Conceptualization. **Pierre Duez:** Writing – original draft, Methodology, Data curation. **Li Zhang:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

TCPM	traditional Chinese Patent medicine,
TCM	traditional Chinese medicine,
ADRs	adverse drug reactions
ICSRs	individual safety reports
MAHs	marketing authorization holders
ICSRs	Individual Case Safety Reports
AE	Adverse events
IARC	International Agency for Research on Cancer
OTC	over-the-counter
POI	postoperative ileus
NMPA	National Medical Products Administration

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