Adverse events related to ligustrazine-containing drugs for cardiovascular and cerebrovascular diseases

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Abstract

Introduction: To characterize adverse-event (AE) reporting patterns and disproportionality signals for three ligustrazine-containing injectable formulations used for cardiovascular and cerebrovascular diseases: ligustrazine, Ginkgo biloba with ligustrazine, and Salvia miltiorrhiza with ligustrazine.
Material and methods: Publicly available WHO-VigiAccess data were searched on November 24, 2024. Reports were summarized by formulation, sex, age group, continent, year, MedDRA System Organ Class (SOC), and Preferred Term (PT). Disproportionality was assessed using the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network/Information Component (BCPNN/IC), and Empirical Bayes Geometric Mean (EBGM). For each formulation, the comparator consisted of all other medicinal-product reports available through the VigiAccess/VigiBase aggregate counts. Because spontaneous-report data lack exposure denominators, results are interpreted as reporting signals rather than incidence, absolute risk, comparative clinical safety, or causal evidence.
Results: A total of 32,017 reports were retrieved: 12,640 for ligustrazine, 246 for Ginkgo biloba with ligustrazine, and 19,131 for Salvia miltiorrhiza with ligustrazine. Reports were overwhelmingly Asia-based. The 45–64-year age group accounted for the largest reporting proportion across formulations, and adult reports represented more than 99% of reports in each group. General disorders/administration-site conditions, skin and subcutaneous tissue disorders, gastrointestinal disorders, nervous system disorders, and vascular disorders were frequent SOC categories. Ginkgo biloba with ligustrazine showed a relatively stronger skin-disorder signal at the SOC level (ROR = 3.36; PRR = 2.78; IC = 1.48; EBGM = 2.78), but interpretation is limited by the small report volume. Salvia miltiorrhiza with ligustrazine showed prominent phlebitis-related PT signals, including superficial phlebitis (EBGM = 191.09), phlebitis (EBGM = 155.82), and infusion-site phlebitis (EBGM = 125.62). Ligustrazine reports frequently included pruritus, chest pain, nausea, dizziness, and rash. Age and sex patterns were interpreted only as reporting distributions, not as incidence peaks or susceptibility signals.
Conclusions: The three ligustrazine-containing injectable formulations showed different AE reporting patterns in VigiAccess. These findings should be considered hypothesis-generating pharmacovigilance signals and require validation in denominator-based, clinically annotated, and preferably prospective data sources. Clinical interpretation should account for geography,

product utilization, indication, infusion practice, reporting bias, duplicate reporting, and the highly unbalanced number of reports across formulations.

Key words: ligustrazine, cardiovascular and cerebrovascular diseases, adverse event, WHO-VigiAccess, traditional Chinese medicine.

Introduction

Cardiovascular and cerebrovascular diseases (CCVDs) remain major causes of morbidity, mortality, disability, and health-system burden worldwide. They include coronary artery disease, hypertension-related vascular injury, heart failure, arrhythmias, ischemic stroke, transient ischemic attack, peripheral vascular disease, and other hemodynamic disorders that affect cardiac, cerebral, and systemic blood flow [1–5]. Standard care usually includes risk-factor control, antiplatelet or anticoagulant therapy when indicated, lipid-lowering treatment, blood-pressure management, reperfusion or revascularization procedures, rehabilitation, and long-term secondary prevention.

Traditional Chinese medicine (TCM) injections are used in parts of China and Asia as adjunctive therapies for ischemic cardiovascular and cerebrovascular conditions. Ligustrazine, also known as tetramethylpyrazine (TMP), is an alkaloid originally isolated from Ligusticum chuanxiong and is used in several injectable formulations. In clinical practice, ligustrazine may be used as a monomer formulation or in compound injections that combine TMP-related components with Ginkgo biloba extract or Salvia miltiorrhiza-derived constituents [6–10]. These products are used mainly as prescription injectable medicines in inpatient or institution-based settings rather than as over-the-counter supplements.

Despite extensive clinical use in China, the international clinical positioning of ligustrazine-containing injections remains limited. We did not identify routine recommendations for these exact formulations in major international stroke or cardiology guidelines. Their use should therefore be interpreted as largely China/Asia-centered and often adjunctive. Chinese and integrated Chinese-Western medicine guidance documents and clinical studies discuss some related TCM injections for ischemic stroke or coronary syndromes, but the level of evidence, indications, patient selection, and setting of use differ across products [11, 12].

Post-marketing pharmacovigilance is essential for products with broad real-world use, particularly injectable formulations in which adverse-event reports may be influenced not only by pharmacology but also by indication, disease severity, infusion concentration, vehicle, venous access, catheter care, infusion duration, and manufacturer-specific formulation features. Spontaneous reporting systems can identify potential safety signals and changes in reporting patterns but cannot estimate incidence or establish causality because they lack exposure denominators and are vulnerable to underreporting, stimulated reporting, duplicate reports, coding variability, and confounding [13–17].

The novelty of the present study is the comparative description of three ligustrazine-containing injectable formulations in a global spontaneous-report database, with concurrent SOC-level and PT-level signal detection and explicit attention to limitations in interpretation. The aim was to characterize AE reporting patterns and disproportionality signals for ligustrazine, Ginkgo biloba with ligustrazine, and Salvia miltiorrhiza with ligustrazine, and to identify safety topics that merit targeted clinical monitoring and denominator-based validation.

Material and methods

Study design and reporting framework

This was a retrospective pharmacovigilance signal-detection study using public, aggregated, spontaneous AE reports from WHO-VigiAccess. No drug samples were purchased, no patients were enrolled, and no animal experiments were performed. The study was planned as a descriptive and disproportionality analysis and was revised with reference to recent recommendations for reporting disproportionality analyses of spontaneous-report pharmacovigilance data, including the READUS-PV framework [15, 16].

Drug formulations and clinical/regulatory context

The target formulations were ligustrazine, Ginkgo biloba with ligustrazine, and Salvia miltiorrhiza with ligustrazine. Table I summarizes the formulation context, principal constituents, clinical positioning, and regulatory context. These products are injectable medicinal products used mainly in China/Asia. They should not be interpreted as dietary supplements. In China, injectable medicines are regulated by the National Medical Products Administration (NMPA), and manufacturers/marketing authorization holders are subject to requirements including Good Manufacturing Prac-

Table I. Formulation and clinical/regulatory context of ligustrazine-containing drugs

Formulation	Principal constituents/ chemical features	Clinical positioning	Regulatory and quality context
Ligustrazine (tetramethylpyrazine, TMP)	TMP; molecular formula C8H12N2; commonly described as a vasoactive alkaloid with antioxidant, anti-inflammatory, microcirculatory, and calcium-antagonist-related experimental properties.	Used in China mainly as an adjunctive injectable therapy for ischemic cardiovascular/ cerebrovascular and peripheral vascular conditions. Not routinely recommended in major international stroke/ cardiology guidelines.	Prescription injectable medicine in China; regulated under NMPA medicine and pharmacovigilance frameworks rather than as an OTC dietary supplement.
Ginkgo biloba with ligustrazine injection	TMP-related component combined with Ginkgo biloba extract constituents such as flavonoids and terpenoid lactones.	Used mainly in China/Asia for ischemic cerebrovascular disease, vertigo/tinnitus, and peripheral circulatory disorders. Evidence and guidance are mainly regional.	Prescription injectable medicine; potential variation may relate to extract standardization, manufacturer process, excipients, and batch quality.
Salvia miltiorrhiza with ligustrazine injection	TMP-related component combined with Salvia miltiorrhiza constituents such as salvianolic acids and tanshinones.	Used mainly in China/ Asia as an adjunctive therapy for ischemic stroke, coronary artery disease, myocardial ischemia, and microcirculatory disorders. Some Chinese/integrated-medicine guidance discusses related products for ischemic stroke.	Prescription injectable medicine; production and PV are supervised under NMPA/ GMP/GVP expectations, but multiple manufacturers and formulation variability may affect reporting patterns.

tice (GMP) and Good Pharmacovigilance Practice (GVP). Because multiple manufacturers and formulation processes may exist, marker-compound standardization, purity, potency, contaminants, excipients, and batch consistency may affect safety reporting and generalizability [18, 19].

Data source and extraction

WHO-VigiAccess (https://www.vigiaccess.org) was searched on November 24, 2024 for AE reports associated with the three target formulations. VigiAccess provides public access to aggregate information from VigiBase, the WHO global database of individual case safety reports. Reports were summarized by formulation, sex, age group, continent, year, MedDRA SOC, and MedDRA PT. Because the public interface returns aggregated report counts, patient-level information on indication, dose, infusion method, comorbidity, concomitant medicines, manufacturer, batch, rechallenge/ dechallenge, and outcome was not available.

All SOC categories returned by VigiAccess with non-zero/publicly available counts for the target formulations were summarized. We no longer selected SOCs subjectively as "most relevant." At the PT level, frequent events were ranked by reporting proportion, and disproportionality signals were interpreted only as potential over-reporting signals. A single spontaneous report may contain multiple SOCs and PTs; therefore, SOC and PT totals can exceed the number of unique reports.

Disproportionality analysis and comparator definition

For each target formulation and AE term, *a* 2×2 contingency table was constructed as follows: a = reports containing both the target formulation and the target AE; *b* = reports containing the target formulation and other AEs; *c* = reports containing the target AE and other medicinal products; and *d* = reports containing other medicinal products and other AEs (Supplementary Table SI). The comparator for the primary analysis was therefore "all other drugs" in the VigiAccess/VigiBase aggregate background. This comparator is transparent and reproducible from public VigiAccess counts but is imperfect because it can be confounded by geography, indication, administration route, reporting culture, and product utilization. The public VigiAccess interface did not permit restricted comparator analyses by TCM-injection class, disease indication, infusion route, country, manufacturer, or calendar period. This limitation is emphasized in the interpretation.

Signal detection used four commonly applied disproportionality approaches. The criteria for detecting a significant signal are detailed in Supplementary Table SII. ROR was calculated as $(a/c)/(b/d)$, equivalently ad/bc. PRR was calculated as $[a/(a + b)]/[c/(c + d)]$. BCPNN was summarized by the Information Component (IC) and its lower 95% credibility boundary (IC025). EBGM was summarized by EBGM and the lower 90% con-

fidence bound (EB05). Signals were considered positive when the lower 95% confidence interval of ROR exceeded 1 with at least three reports, PRR was at least 2 with χ^2 at least 4 and at least three reports, IC025 exceeded 0, or EB05 exceeded 2, depending on the method [17, 20–23].

Statistical analysis and sensitivity rules

Descriptive statistics were reported as counts and percentages. Percentages for sex, age, continent, and report year were calculated within each formulation. SOC percentages were calculated within the SOC-term total for each formulation because each report can contain multiple coded terms. Frequent PTs were ranked by reporting proportion within formulation. No incidence rate, risk ratio, odds of clinical occurrence, or comparative safety rate was calculated because VigiAccess does not provide the number of exposed patients, administered units, treatment duration, prescriptions, procurement volume, or market share.

Because the Ginkgo biloba with ligustrazine dataset contained only 246 reports, Ginkgo-related PT signals were interpreted cautiously. Events with small counts were considered unstable even when disproportionality metrics were numerically high. An adult-only descriptive sensitivity analysis was also performed by restricting the age distribution to reports in the 18–44 years, 45–64 years, 65–74 years, and 75 years categories. For descriptive display, Ginkgo biloba with ligustrazine PTs with fewer than 10 reports were retained for transparency but marked as unstable and in the relevant figure captions.

Table II. Demographic and temporal characteristics of AE reports for three ligustrazine-containing formulations

Characteristics	Ligustrazine	Ginkgo biloba with ligustrazine	Salvia miltiorrhiza with ligustrazine
Number of AE reports	12640	246	19131
Sex			
Female	7000 (55.38%)	135 (54.88%)	10240 (53.53%)
Male	5626 (44.51%)	110 (44.72%)	8863 (46.33%)
Unknown	14 (0.11%)	1 (0.41%)	28 (0.15%)
Age			
0–27 days	12 (0.09%)	0	11 (0.06%)
28 days to 23 months	8 (0.06%)	0	13 (0.07%)
2–11 years	26 (0.21%)	0	21 (0.11%)
12–17 years	29 (0.23%)	1 (0.41%)	78 (0.41%)
18–44 years	1007 (7.97%)	24 (9.76%)	2405 (12.57%)
45–64 years	5115 (40.47%)	108 (43.90%)	7901 (41.30%)
65–74 years	3703 (29.30%)	69 (28.05%)	4617 (24.13%)
75 years	2718 (21.50%)	43 (17.48%)	4066 (21.25%)
Unknown age	22 (0.17%)	1 (0.41%)	19 (0.10%)
Continent			
Asia	12639 (99.99%)	246 (100%)	19131 (100%)
Europe	1 (0.01%)	0	0
Report year			
2014	842 (6.66%)	0	2823 (14.76%)
2015	732 (5.79%)	0	2415 (12.62%)
2016	890 (7.04%)	7 (2.85%)	2378 (12.43%)
2017	849 (6.72%)	14 (5.69%)	2265 (11.84%)
2018	542 (4.29%)	6 (2.44%)	1425 (7.45%)
2019	1759 (13.92%)	19 (7.72%)	2710 (14.17%)
2020	4630 (36.63%)	99 (40.24%)	4462 (23.32%)
2021	1450 (11.47%)	83 (33.74%)	510 (2.67%)
2022	368 (2.91%)	12 (4.88%)	99 (0.52%)
2023	362 (2.86%)	6 (2.44%)	30 (0.16%)
2024	216 (1.71%)	0	14 (0.07%)

Results

Report characteristics

As of the VigiAccess search date, 32,017 reports were retrieved: 12,640 for ligustrazine, 246 for Ginkgo biloba with ligustrazine, and 19,131 for Salvia miltiorrhiza with ligustrazine. Women accounted for slightly more reports than men for each formulation, but this should be interpreted as a reporting distribution rather than sex-related susceptibility or clinical risk. Reports were overwhelmingly Asia-based: 99.99% of ligustrazine reports, 100% of Ginkgo biloba with ligustrazine reports, and 100% of Salvia miltiorrhiza with ligustrazine reports originated from Asia. Only one ligustrazine report originated from Europe. Therefore, the dataset should be viewed as Asia-centric rather than globally representative.

The 45–64-year group accounted for the largest reporting proportion for all three formulations. Adult reports dominated the dataset. In the adult-only sensitivity analysis, adult reports accounted for 12,543 of 12,640 ligustrazine reports (99.23%), 244 of 246 Ginkgo biloba with ligustrazine reports (99.19%), and 18,989 of 19,131 Salvia miltiorrhiza with ligustrazine reports (99.26%). The 2020 peak in reporting was observed across the three formulations and may reflect reporting policies, pharmacovigilance awareness, utilization changes, or stimulated reporting rather than a change in incidence (Table II).

SOC distribution

At the SOC level, the most frequent categories across formulations were general disorders and administration-site conditions, skin and subcutaneous tissue disorders, gastrointestinal disorders, nervous system disorders, and vascular disorders. SOC totals exceeded the number of unique AE reports because one report can contain multiple SOC/PT terms (Table III).

Disproportionality analysis for general disorders and skin disorders

General disorders/administration-site conditions showed weak or non-specific signals across the three formulations. Skin and subcutaneous

Table III. SOC distribution of AE terms for three ligustrazine-containing formulations

System Organ Class	Ligustrazine	Ginkgo biloba with ligustrazine	Salvia miltiorrhiza with ligustrazine
General disorders and administration site conditions	4,824 (22.35%)	100 (20.62%)	7,239 (22.32%)
Skin and subcutaneous tissue disorders	4,343 (20.12%)	119 (24.54%)	5,964 (18.39%)
Gastrointestinal disorders	3,748 (17.36%)	57 (11.75%)	4,509 (13.90%)
Nervous system disorders	3,121 (14.46%)	57 (11.75%)	4,280 (13.19%)
Cardiac disorders	1,740 (8.06%)	29 (5.98%)	2,588 (7.98%)
Respiratory, thoracic and mediastinal disorders	1,243 (5.76%)	45 (9.28%)	2,211 (6.82%)
Vascular disorders	882 (4.09%)	26 (5.36%)	3,298 (10.17%)
Immune system disorders	668 (3.09%)	11 (2.27%)	879 (2.71%)
Psychiatric disorders	239 (1.11%)	3 (0.62%)	288 (0.89%)
Investigations	238 (1.10%)	11 (2.27%)	346 (1.07%)
Eye disorders	152 (0.70%)	12 (2.47%)	260 (0.80%)
Musculoskeletal and connective tissue disorders	135 (0.63%)	7 (1.44%)	217 (0.67%)
Ear and labyrinth disorders	95 (0.44%)	N/A	97 (0.30%)
Injury, poisoning and procedural complications	53 (0.25%)	2 (0.41%)	77 (0.24%)
Renal and urinary disorders	40 (0.19%)	2 (0.41%)	41 (0.13%)
Hepatobiliary disorders	29 (0.13%)	2 (0.41%)	40 (0.12%)
Metabolism and nutrition disorders	15 (0.07%)	N/A	22 (0.07%)
Infections and infestations	8 (0.04%)	1 (0.21%)	15 (0.05%)
Congenital, familial and genetic disorders	6 (0.03%)	1 (0.21%)	42 (0.13%)
Reproductive system and breast disorders	3 (0.01%)	N/A	8 (0.02%)
Blood and lymphatic system disorders	3 (0.01%)	N/A	15 (0.05%)
Product issues	2 (0.01%)	N/A	2 (0.01%)
Total SOC terms	21,587 (100%)	485 (100%)	32,438 (100%)

Percentages are calculated using the SOC-term total for each formulation. A single report can contain multiple SOCs/PTs; therefore, totals exceed the number of unique reports.

Table IV. Disproportionality signals for selected SOC categories

Formulation	SOC	Case count	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EB05)
Ligustrazine	General disorders	4824	1.13 (1.10, 1.17)	1.10 (1.07, 1.13)	0.14 (0.09)	1.10 (1.07)
Ligustrazine	Skin disorders	4343	2.60 (2.52, 2.69)	2.28 (2.22, 2.34)	1.19 (1.14)	2.28 (2.21)
Ginkgo biloba with ligustrazine	General disorders	100	1.02 (0.82, 1.27)	1.02 (0.85, 1.21)	0.02 (-0.29)	1.02 (0.82)
Ginkgo biloba with ligustrazine	Skin disorders	119	3.36 (2.73, 4.13)	2.78 (2.38, 3.25)	1.48 (1.16)	2.78 (2.26)
Salvia miltiorrhiza with ligustrazine	General disorders	7239	1.13 (1.10, 1.16)	1.10 (1.08, 1.12)	0.14 (0.10)	1.10 (1.07)
Salvia miltiorrhiza with ligustrazine	Skin disorders	5964	2.33 (2.26, 2.39)	2.08 (2.04, 2.13)	1.06 (1.02)	2.08 (2.03)

Table V. Top 20 PT signals ranked by EBGM for the three formulations

Ligustrazine PT	EBGM (EB05)	Ginkgo biloba with ligustrazine PT	EBGM (EB05)	Salvia miltiorrhiza with ligustrazine PT	EBGM (EB05)
Cardiac flutter	49.15 (45.76)	Suffocation feeling†	40.40 (12.98)	Phlebitis superficial	191.09 (156.65)
Merycism	35.80 (19.78)	Cardiac flutter†	27.87 (14.90)	Phlebitis	155.82 (147.74)
Rubella	32.14 (12.03)	Rash papular†	18.86 (8.43)	Infusion-site phlebitis	125.62 (97.68)
Infusion-site phlebitis	29.96 (16.09)	Hyperpyrexia†	17.08 (7.08)	Vascular malformation	100.76 (74.13)
Suffocation feeling	27.84 (22.67)	Tachypnea†	15.86 (5.10)	Vein discoloration	63.19 (40.14)
Vascular pain	26.35 (18.80)	Eyelid edema†	14.98 (5.60)	Cardiac flutter	34.88 (32.55)
Phlebitis	25.72 (22.04)	Chest pain	13.63 (9.79)	Laryngeal discomfort	34.95 (27.04)
Dysphoria	23.67 (19.12)	Flushing	12.82 (7.79)	Suffocation feeling	24.77 (20.73)
Phlebitis superficial	22.30 (11.14)	Blood pressure decreased†	8.46 (3.16)	Infusion-site reaction	24.08 (16.81)
Laryngeal discomfort	18.69 (12.18)	Pruritus	6.92 (5.20)	Vascular pain	22.69 (16.87)
Convulsions local	18.66 (10.59)	Anaphylactic shock†	7.53 (3.12)	Head discomfort	21.60 (19.19)
Hyperpyrexia	17.96 (15.79)	Dysphonia†	7.27 (2.34)	Larynx irritation	21.65 (14.36)
Cardiac discomfort	18.12 (12.94)	Palpitations	7.08 (4.08)	Anesthesia oral	21.32 (16.88)
Vascular malformation	18.03 (7.49)	Arrhythmia†	6.56 (2.11)	Conjunctival disorder	20.93 (9.38)
Dry mouth	16.88 (15.64)	Chills	5.71 (3.82)	Angiopathy	20.13 (15.29)
Head discomfort	16.52 (14.00)	Blood pressure increased†	5.76 (2.57)	Merycism	19.49 (10.12)
Tachypnea	15.91 (13.42)	Rash	4.85 (3.52)	Cardiac discomfort	18.80 (14.35)
Gastric dilatation	15.92 (9.23)	Anaphylactic/ anaphylactoid responses†	4.42 (1.65)	Tachypnea	18.18 (15.96)
Chest pain	12.99 (12.35)	Dizziness	4.02 (1.80)	Convulsions local	15.52 (9.35)
Infusion-site rash	13.82 (6.20)	Dyspnea	3.65 (2.33)	Tongue paralysis	15.35 (9.53)

†*Ginkgo biloba with ligustrazine PTs based on fewer than 10 reports; these low-count signals are retained for transparency but should be regarded as unstable and hypothesis-generating only.*

tissue disorders showed a stronger SOC-level signal for Ginkgo biloba with ligustrazine than for the other two formulations, but the Ginkgo estimate was based on only 119 skin-disorder reports among 246 total formulation reports and should be considered unstable (Table IV).

Frequently reported PTs

The most frequently reported PTs differed by formulation. For ligustrazine, frequent PTs included pruritus, chest pain, nausea, dizziness, and rash. For Ginkgo biloba with ligustrazine, pruritus, rash, chest pain, dizziness, and nausea were among the most frequent PTs, and the small total report number should be considered when interpreting rankings. For Salvia miltiorrhiza with ligustrazine, chest pain, pruritus, nausea, dizziness, rash, phlebitis, and flushing were among the frequently reported PTs. These frequencies describe report content only; they are not event rates per treated patient.

EBGM-ranked PT signals

EBGM ranking identified several formulation-specific PT signals. For ligustrazine, high EBGM values were observed for cardiac flutter, merycism, rubella, infusion-site phlebitis, suffocation feeling, vascular pain, and phlebitis. For Ginkgo biloba with ligustrazine, high EBGM values were observed for suffocation feeling, cardiac flutter, rash papular, hyperpyrexia, tachypnea, and eyelid edema; however, the small report volume limits stability. For Salvia miltiorrhiza with ligustrazine, the strongest EBGM-ranked PTs were phlebitis-related or vascular terms, including superficial phlebitis, phlebitis, infusion-site phlebitis, vascular malformation, and vein discoloration. These signals warrant targeted clinical review and denominator-based validation. For the Ginkgo biloba with ligustrazine column, PTs based on fewer than 10 reports are flagged as unstable and should not be interpreted as robust formulation-specific signals (Table V; Figures 1–3).

Discussion

This revised analysis describes AE reporting patterns for three ligustrazine-containing injectable formulations in VigiAccess. The strongest messages are methodological as well as clinical. First, the dataset is large overall but highly unbalanced across formulations. Second, the reports are essentially Asia-centric, limiting international generalizability. Third, general/administration-site and skin-related reports were common across formulations, while the Salvia miltiorrhiza combination showed particularly strong phlebitis-related PT signals. Fourth, the Ginkgo biloba combination showed a stronger skin-disorder SOC signal, but this finding is unstable because only 246 reports were available for that formulation.

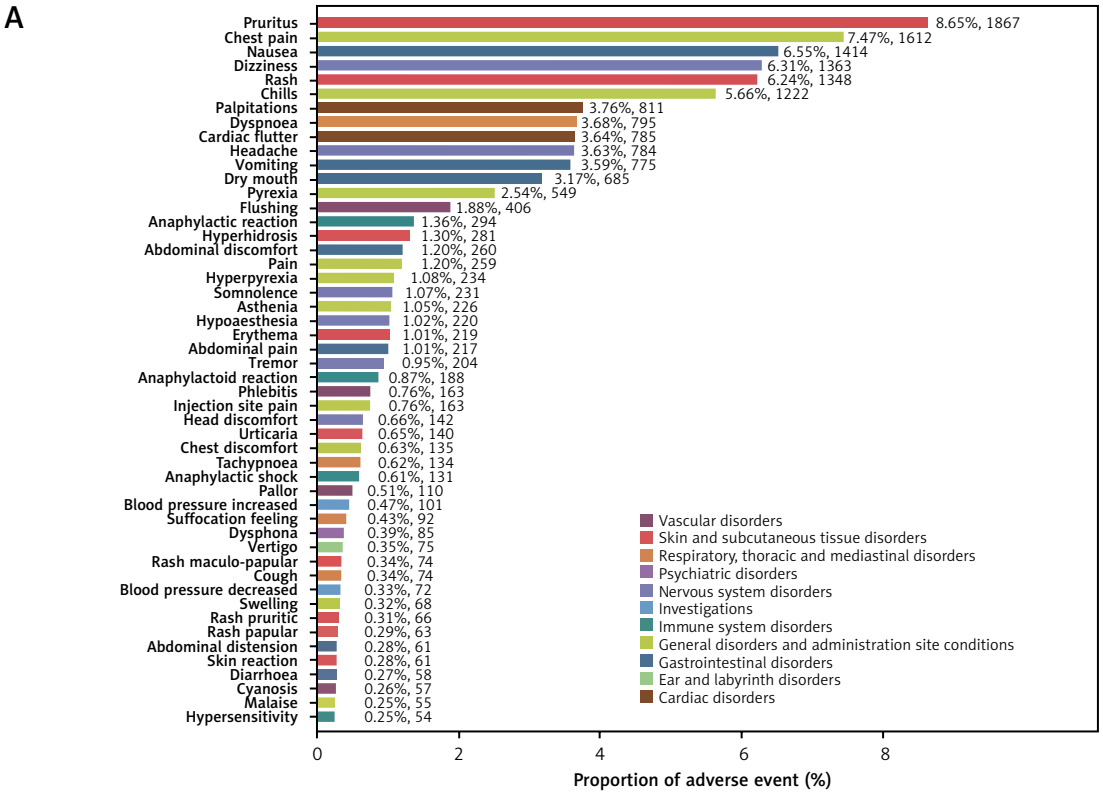
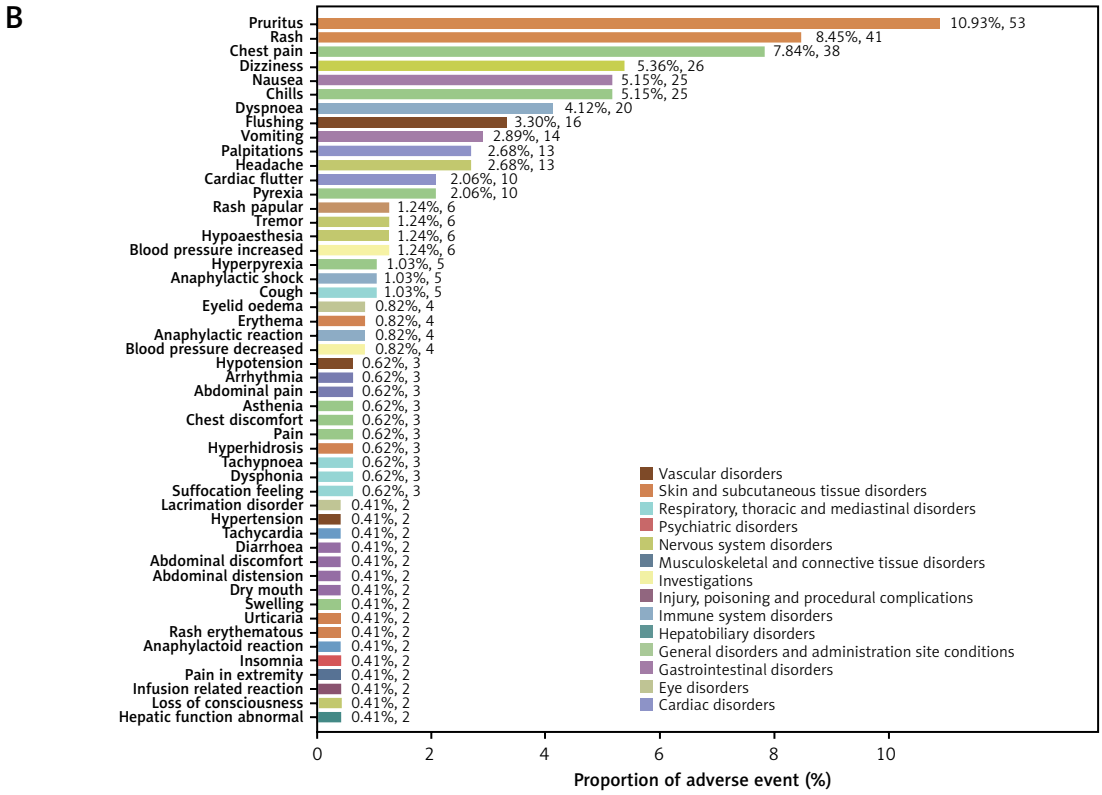


Figure 1. Top 50 adverse reactions ranked by reporting proportion for ligustrazine (**A**)



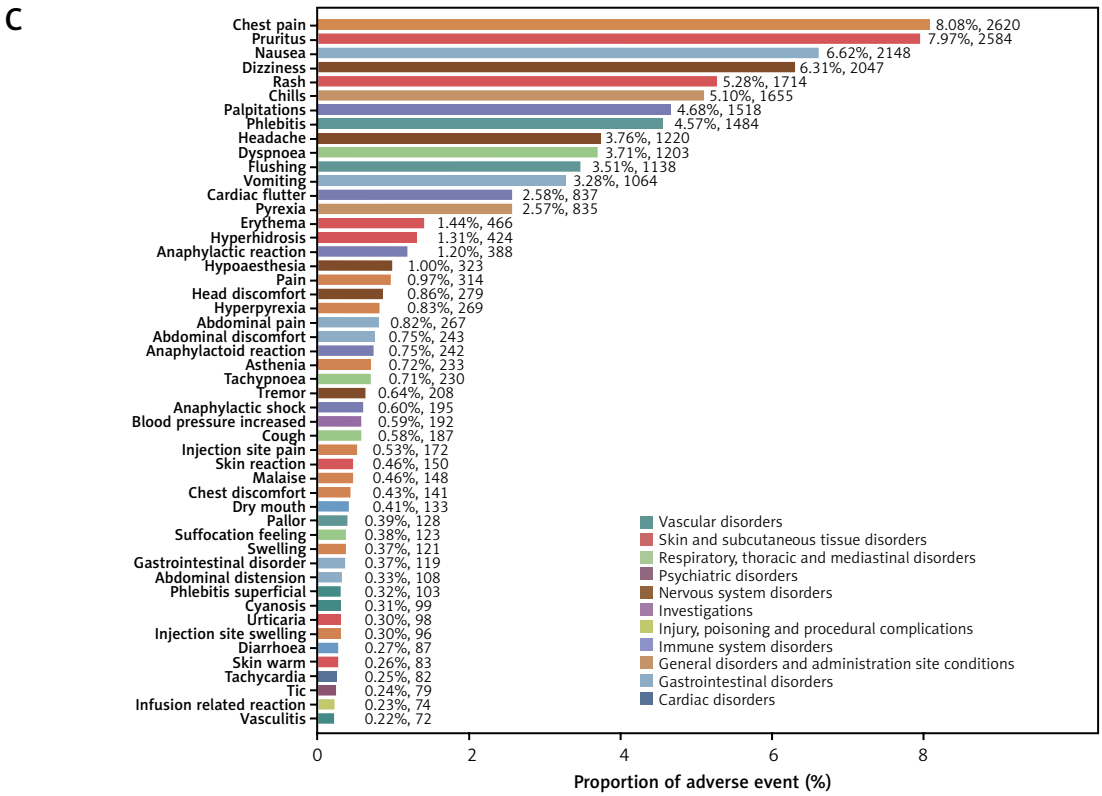


Figure 1. Cont. Ginkgo biloba with ligustrazine (**B**) and Salvia miltiorrhiza with ligustrazine (**C**). Numerical labels show both reporting percentages and case counts

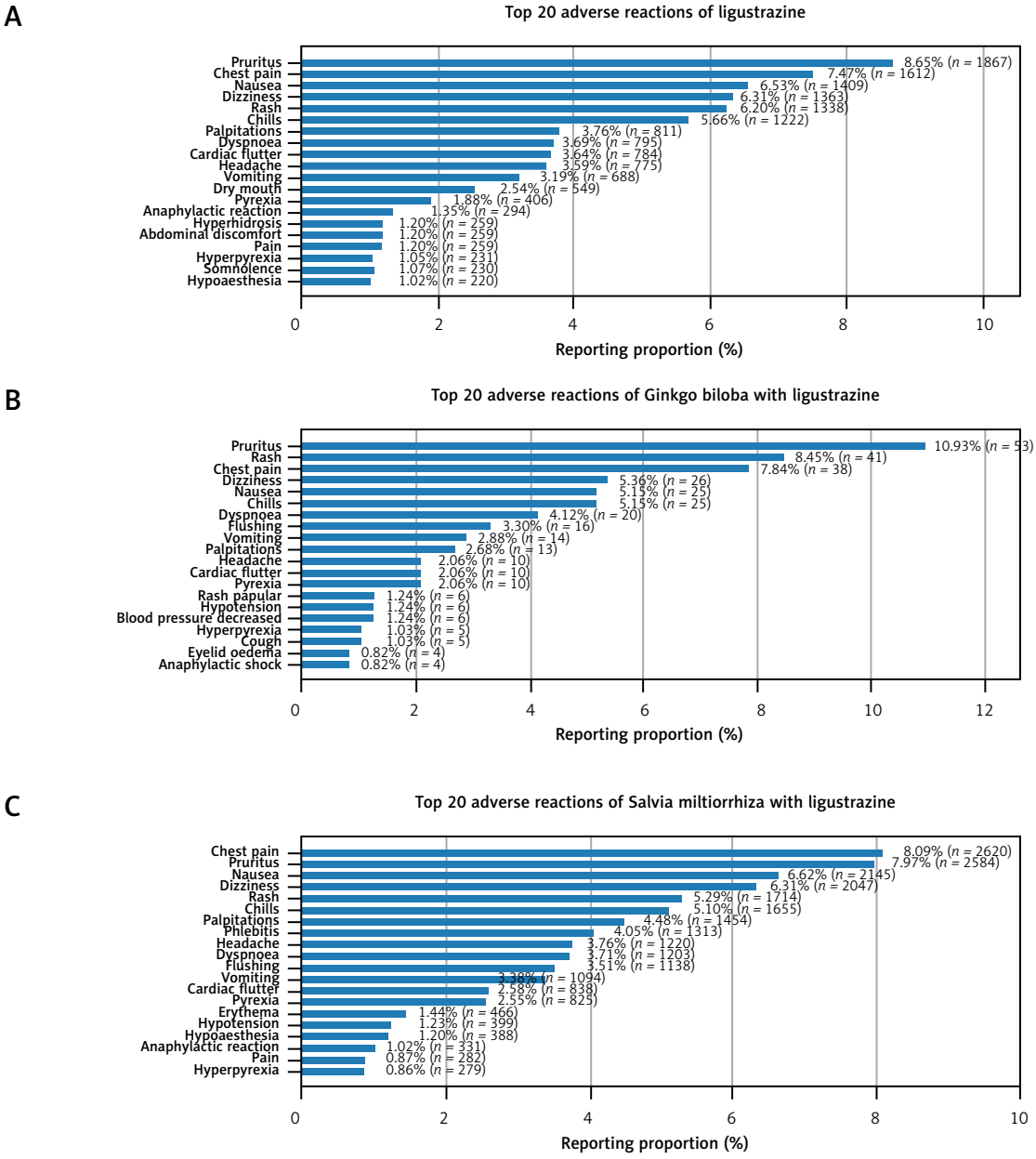


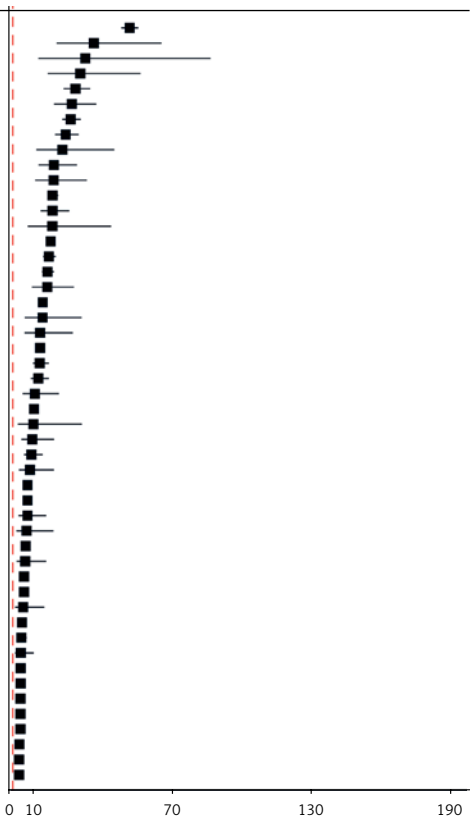
Figure 2. Top 20 reported adverse reactions ranked by reporting proportion for ligustrazine (**A**), Ginkgo biloba with ligustrazine (**B**), and Salvia miltiorrhiza with ligustrazine (**C**)

These findings are consistent with the use pattern of TCM injections in China and with previous literature suggesting that dermatologic, cardiovascular, respiratory, and administration-site reactions are important safety topics for injectable herbal or herb-derived formulations [6–10, 24–27]. However, the present data cannot indicate whether the clinical probability of a given AE is higher for one formulation than another. Differences in report counts may reflect utilization, hospital procurement, reporting intensity, manufacturer availability, indication, disease severity, or calendar-year changes rather than pharmacologic toxicity alone.

The clinical interpretation of these signals requires context. Ligustrazine-containing injections are used mainly in China/Asia, often as adjunctive inpatient or institution-based therapies for ischemic cardiovascular/cerebrovascular disorders. We did not identify routine endorsement of these exact formulations in major international stroke or cardiology guidelines. Chinese or integrated-medicine guidance and regional studies discuss selected TCM injections or related products, particularly in ischemic stroke, but their recommendations should not be extrapolated to global practice without considering evidence grade, patient selection, indication, and healthcare setting [11, 12].

A

Case System Organ Class (SOC)	Preferred Term (PT)	Case reports	ROR (95% CI)
Cardiac disorders	Cardiac flutter	785	51.43 (47.87, 55.24)
Psychiatric disorders	Merycism	11	36.04 (19.92, 65.22)
Infections and infestations	Rubella	4	32.33 (12.10, 86.40)
General disorders and administration site conditions	Infusion site phlebitis	10	30.14 (16.19, 56.12)
Respiratory, thoracic and mediastinal disorders	Suffocation feeling	92	28.09 (22.88, 34.49)
Vascular disorders	Vascular pain	34	26.51 (18.92, 37.14)
Vascular disorders	Phlebitis	163	26.02 (22.30, 30.37)
Psychiatric disorders	Dysphoria	85	23.86 (19.28, 29.54)
Vascular disorders	Phlebitis superficial	8	22.40 (11.18, 44.86)
Respiratory, thoracic and mediastinal disorders	Laryngeal discomfort	21	18.77 (12.23, 28.82)
Nervous system disorders	Convulsions local	12	18.73 (10.63, 33.02)
General disorders and administration site conditions	Hyperpyrexia	234	18.21 (16.00, 20.71)
Cardiac disorders	Cardiac discomfort	34	18.20 (13.00, 25.50)
Congenital, familial and genetic disorders	Vascular malformation	5	18.09 (7.52, 43.52)
Gastrointestinal disorders	Dry mouth	685	17.45 (16.17, 18.83)
Nervous system disorders	Head discomfort	142	16.67 (14.13, 19.66)
Respiratory, thoracic and mediastinal disorders	Tachypnoea	134	16.05 (13.54, 19.03)
Gastrointestinal disorders	Gastric dilatation	13	15.97 (9.26, 27.53)
General disorders and administration site conditions	Chest pain	1612	13.99 (13.30, 14.72)
General disorders and administration site conditions	Infusion site rash	6	13.86 (6.22, 30.88)
Gastrointestinal disorders	Lip discolouration	7	12.81 (6.10, 26.90)
Immune system disorders	Anaphylactoid reaction	188	12.76 (11.05, 14.74)
Psychiatric disorders	Tic	53	12.66 (9.66, 16.58)
General disorders and administration site conditions	Infusion site pain	40	12.16 (8.91, 16.58)
General disorders and administration site conditions	Infusion site pruritus	8	10.53 (5.26, 21.06)
Cardiac disorders	Palpitations	811	10.29 (9.59, 11.04)
Vascular disorders	Shock symptom	3	9.98 (3.22, 30.99)
Nervous system disorders	Quadriplegia	8	9.47 (4.73, 18.95)
Gastrointestinal disorders	Anaesthesia oral	20	9.04 (5.83, 14.03)
Respiratory, thoracic and mediastinal disorders	Larynx irritation	6	8.50 (3.82, 18.93)
Vascular disorders	Flushing	406	7.44 (6.74, 8.20)
Immune system disorders	Anaphylactic reaction	294	7.40 (6.59, 8.30)
Eye disorders	Lacrimation disorder	7	7.38 (3.52, 15.50)
Gastrointestinal disorders	Gastrointestinal tract irritation	4	6.97 (2.61, 18.59)
General disorders and administration site conditions	Chills	1222	6.60 (6.23, 6.99)
Musculoskeletal and connective tissue disorders	Muscle discomfort	5	6.45 (2.68, 15.51)
Skin and subcutaneous tissue disorders	Skin reaction	61	5.91 (4.59, 7.60)
Skin and subcutaneous tissue disorders	Pruritus	1867	5.91 (5.63, 6.19)
General disorders and administration site conditions	Foaming at mouth	4	5.50 (2.06, 14.67)
Gastrointestinal disorders	Abdominal discomfort	260	5.03 (4.45, 5.68)
Gastrointestinal disorders	Epigastric discomfort	24	4.77 (3.20, 7.12)
Skin and subcutaneous tissue disorders	Macule	6	4.56 (2.05, 10.16)
Skin and subcutaneous tissue disorders	Rash popular	63	4.46 (3.48, 5.72)
Immune system disorders	Anaphylactic shock	131	4.46 (3.75, 5.29)
Injury, poisoning and procedural complications	Infusion related reaction	53	4.42 (3.37, 5.78)
Vascular disorders	Pallor	110	4.34 (3.60, 5.23)
Nervous system disorders	Dizziness	1363	4.33 (4.10, 4.58)
Vascular disorders	Cyanosis	57	3.86 (2.98, 5.01)
Skin and subcutaneous tissue disorders	Hyperhidrosis	281	3.78 (3.36, 4.25)
Skin and subcutaneous tissue disorders	Rash	1348	3.76 (3.56, 3.97)



B

Case System Organ Class (SOC)	Preferred Term (PT)	Case reports	ROR (95% CI)
Respiratory, thoracic and mediastinal disorders	Suffocation feeling	3	40.65 (13.06, 126.50)
Cardiac disorders	Cardiac flutter	10	28.44 (15.20, 53.20)
Skin and subcutaneous tissue disorders	Rash papular	6	19.09 (8.53, 42.71)
General disorders and administration site conditions	Hyperpyrexia	5	17.25 (7.15, 41.64)
Respiratory, thoracic and mediastinal disorders	Tachypnoea	3	15.95 (5.13, 49.63)
Eye disorders	Eyelid oedema	4	15.10 (5.64, 40.39)
General disorders and administration site conditions	Chest pain	38	14.71 (10.56, 20.48)
Vascular disorders	Flushing	16	13.22 (8.03, 21.76)
Investigations	Blood pressure decreased	4	8.52 (3.19, 22.80)
Skin and subcutaneous tissue disorders	Pruritus	53	7.65 (5.75, 10.17)
Immune system disorders	Anaphylactic shock	5	7.60 (3.15, 18.34)
Respiratory, thoracic and mediastinal disorders	Dysphonia	3	7.31 (2.35, 22.74)
Cardiac disorders	Palpitations	13	7.25 (4.18, 11.57)
Cardiac disorders	Arrhythmia	3	6.60 (2.12, 20.53)
General disorders and administration site conditions	Chills	25	5.97 (3.99, 8.93)
Investigations	Blood pressure increased	6	5.82 (2.60, 13.01)
Skin and subcutaneous tissue disorders	Rash	41	5.21 (3.78, 7.17)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	20	3.76 (2.41, 5.89)
Nervous system disorders	Dizziness	26	3.64 (2.45, 5.40)

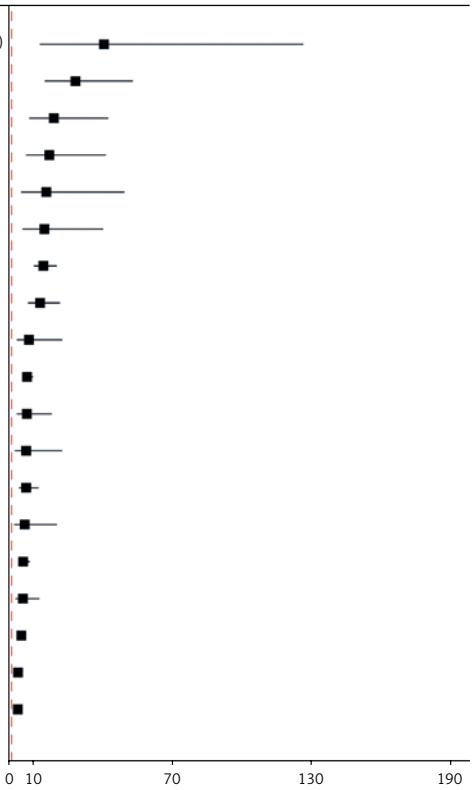


Figure 3. ROR-based disproportionality signal profiles for ligustrazine (**A**), Ginkgo biloba with ligustrazine (**B**), and Salvia miltiorrhiza with ligustrazine (**C**)

C

Case System Organ Class (SOC)	Preferred Term (PT)	Case reports	ROR (95% CI)
Vascular disorders	Phlebitis superficial	103	202.31 (165.85, 246.78)
Vascular disorders	Phlebitis	1484	170.52 (161.69, 179.84)
General disorders and administration site conditions	Infusion site phlebitis	63	130.35 (101.36, 167.63)
Congenital, familial and genetic disorders	Vascular malformation	42	103.75 (76.33, 141.02)
Vascular disorders	Vein discolouration	19	64.33 (40.87, 101.27)
Cardiac disorders	Cardiac flutter	837	36.11 (33.71, 38.69)
Respiratory, thoracic and mediastinal disorders	Laryngeal discomfort	59	35.35 (27.35, 45.69)
Respiratory, thoracic and mediastinal disorders	Suffocation feeling	123	25.02 (20.95, 29.89)
General disorders and administration site conditions	Infusion site reaction	30	24.26 (16.94, 34.74)
Vascular disorders	Vascular pain	44	22.86 (16.99, 30.75)
Nervous system disorders	Head discomfort	279	21.90 (19.46, 24.65)
Respiratory, thoracic and mediastinal disorders	Larynx irritation	23	21.78 (14.46, 32.83)
Gastrointestinal disorders	Anaesthesia oral	71	21.48 (17.01, 27.13)
Eye disorders	Conjunctival disorder	6	21.05 (9.44, 46.98)
Vascular disorders	Angiopathy	51	20.27 (15.39, 26.70)
Psychiatric disorders	Merycism	9	19.60 (10.18, 37.73)
Cardiac disorders	Cardiac discomfort	53	18.92 (14.44, 24.79)
Respiratory, thoracic and mediastinal disorders	Tachypnoea	230	18.39 (16.15, 20.94)
Nervous system disorders	Convulsions local	15	15.59 (9.39, 25.89)
Nervous system disorders	Tongue paralysis	17	15.42 (9.57, 24.83)
General disorders and administration site conditions	Chest pain	2620	15.25 (14.66, 15.88)
Eye disorders	Amaurosis	3	14.92 (4.80, 46.36)
Respiratory, thoracic and mediastinal disorders	Pharyngeal disorder	21	14.89 (9.70, 22.86)
Vascular disorders	Flushing	1138	14.14 (13.33, 15.00)
General disorders and administration site conditions	Hyperpyrexia	269	13.90 (12.32, 15.67)
Psychiatric disorders	Dysphoria	72	13.42 (10.64, 16.92)
Cardiac disorders	Palpitations	1518	12.96 (12.31, 13.64)
Psychiatric disorders	Encopresis	4	12.80 (4.79, 34.16)
Psychiatric disorders	Tic	79	12.57 (10.08, 15.68)
Eye disorders	Conjunctival oedema	9	11.48 (5.97, 22.10)
Gastrointestinal disorders	Gastric dilatation	14	11.44 (6.77, 19.34)
Immune system disorders	Anaphylactoid reaction	242	10.93 (9.63, 12.40)
Vascular disorders	Vasculitis	72	10.53 (8.35, 13.28)
Skin and subcutaneous tissue disorders	Skin reaction	150	9.70 (8.26, 11.39)
General disorders and administration site conditions	Infusion site pruritus	9	7.88 (4.10, 15.16)
General disorders and administration site conditions	Infusion site pain	37	7.48 (5.41, 10.32)
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema	52	7.34 (5.59, 9.63)
Nervous system disorders	Quadriplegia	9	7.09 (3.69, 13.64)
Gastrointestinal disorders	Lip disorder	8	6.70 (3.35, 13.40)
Immune system disorders	Anaphylactic reaction	388	6.49 (5.87, 7.17)
Eye disorders	Lacrimation disorder	9	6.32 (3.29, 12.16)
General disorders and administration site conditions	Chills	1655	5.91 (5.63, 6.21)
Skin and subcutaneous tissue disorders	Skin warm	83	5.71 (4.60, 7.08)
Skin and subcutaneous tissue disorders	Pruritus	2584	5.40 (5.19, 5.62)
Vascular disorders	Cyanosis	99	4.47 (3.67, 5.44)
Immune system disorders	Anaphylactic shock	195	4.42 (3.84, 5.08)
Nervous system disorders	Dizziness	2047	4.33 (4.14, 4.53)
Skin and subcutaneous tissue disorders	Cold sweat	71	4.18 (3.31, 5.28)
Injury, poisoning and procedural complications	Infusion related reaction	74	4.10 (3.27, 5.16)
Gastrointestinal disorders	Epigastric discomfort	31	4.10 (2.88, 5.83)

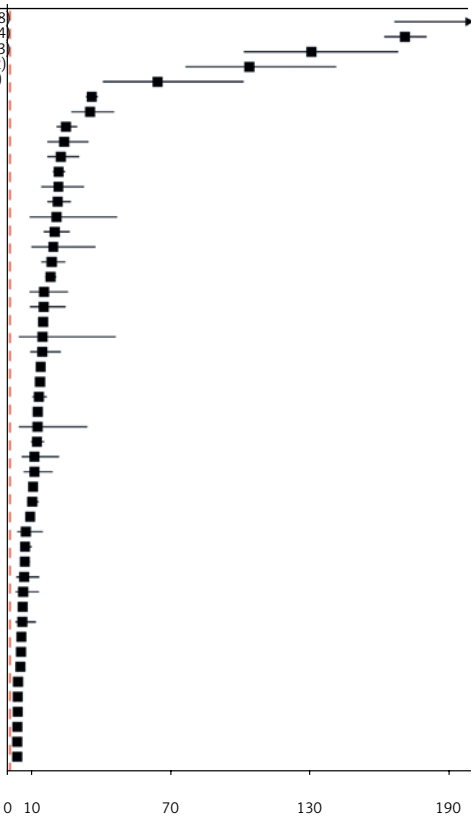


Figure 3. Cont. Salvia miltiorrhiza with ligustrazine (**C**)

Exposure scale remains unknown. We sought publicly accessible formulation-specific exposure and market-utilization data, including treated-patient denominators, prescription or administration volumes, procurement data, and market-share information, but did not identify data that could be linked reliably to the VigiAccess report counts. VigiAccess does not provide the number of treated patients, administered doses, prescriptions, treatment duration, procurement volume, annual units sold, or market share. Therefore, the imbalance in reports – 246 for Ginkgo biloba with ligustrazine versus 19,131 for Salvia miltiorrhiza with ligustrazine – may simply reflect product utilization or reporting environment. This is a major limitation for public-health interpretation and prioritization.

These products should be discussed as injectable medicines, not as dietary supplements. In China, medicine production and post-marketing surveillance are overseen within the NMPA framework. The Good Pharmacovigilance Practice framework requires marketing authorization holders and applicants to establish pharmacovigilance systems, and ADR reporting is supported by national and provincial monitoring networks [18, 19]. Nonetheless, spontaneous reporting remains vulnerable to underreporting, duplicate reporting, coding heterogeneity, and variations in reporting practices between institutions and regions.

Manufacturing and quality context also matters. Compound TCM injections may contain multiple active compounds and excipients, and multiple manufacturers may exist. Standardization of identity, purity, potency, marker compounds, contaminants, and batch consistency is therefore relevant for interpreting safety signals. VigiAccess does not provide manufacturer- or batch-level details, so this study cannot separate pharmacologic effects from formulation or quality-related contributors.

The phlebitis-related signals for Salvia miltiorrhiza with ligustrazine may be clinically important because phlebitis can be influenced by venous irritation, infusion concentration, infusion vehicle, osmolarity/pH, infusion speed, catheter dwell time, catheter site care, and patient vascular status. Salvia-derived constituents and ligustrazine have experimental vascular and antiplatelet activities, but VigiAccess data cannot determine whether these mechanisms caused the reported events. Therefore, vascular inflammation, endothelial irritation, and administration-related factors should be treated as hypotheses for follow-up studies rather than conclusions from the present analysis.

Similarly, the skin-related signal for Ginkgo biloba with ligustrazine may be compatible with hypersensitivity or allergic-type reporting, but causal immunologic mechanisms cannot be inferred from aggregate spontaneous reports. The finding should prompt attention to rash, pruritus, anaphylaxis-related terms, and prior allergy history in clinical monitoring, especially because combination herbal injections may include multiple constituents that complicate attribution.

Based on these hypothesis-generating signals, clinicians using ligustrazine-containing injections should apply standardized infusion procedures, document infusion concentration/vehicle and rate, monitor for vascular irritation and skin reactions, and consider patient-level factors such as age, vascular access, allergy history, comorbid cardiovascular/cerebrovascular disease, and concomitant antiplatelet or anticoagulant therapy. Hospitals and pharmacovigilance units should strengthen complete AE documentation, including manufacturer, batch number, indication, dose, infusion practice, timing, seriousness, dechallenge/rechallenge, and outcome.

Future research should validate these signals using denominator-based data sources, such as hospital electronic health records, procurement-linked exposure data, prescription/administration records, active surveillance networks, or full case-level pharmacovigilance databases. Restricted comparator analyses involving similar injectable cardiovascular/cerebrovascular agents or TCM injections would be particularly useful.

This study has important limitations. First, VigiAccess is based on spontaneous reports and lacks exposure denominators, so the analysis cannot estimate incidence, prevalence, absolute risk, relative risk, or comparative safety. Second, reporting is influenced by underreporting, stimulated reporting, publicity, regulatory changes, local reporting culture, seriousness of events, and product utilization. Third, reports may be duplicated or incompletely coded, and MedDRA coding can vary. Fourth, patient-level factors such as indication, disease severity, comorbidities, concomitant medicines, dose, infusion route, infusion concentration, catheter care, manufacturer, batch, and outcomes were unavailable. Fifth, nearly all reports originated from Asia, so findings should not be generalized internationally. Sixth, the small Ginkgo biloba with ligustrazine dataset makes PT-level signal estimates unstable. Finally, the all-other-drugs comparator can introduce confounding by geography, indication, administration route, and reporting environment.

In conclusion, this pharmacovigilance analysis identified different AE reporting patterns and disproportionality signals for ligustrazine, Ginkgo biloba with ligustrazine, and Salvia miltiorrhiza with ligustrazine. The Salvia miltiorrhiza combination showed prominent phlebitis-related reporting signals, whereas the Ginkgo biloba combination showed relatively stronger skin-disorder signals but with substantial small-sample uncertainty. These results are hypothesis-generating and should not be interpreted as incidence, absolute risk, comparative clinical safety, or causality. Denominator-based active surveillance and clinically annotated studies are needed to validate the signals and guide risk minimization.

Data availability statement

The datasets analyzed in this study are available through WHO-VigiAccess (https://www.vigiaccess.org). The information comes from VigiBase, the WHO global database of reported potential side effects of medicinal products, developed and maintained by the Uppsala Monitoring Centre. The information does not represent the opinion of UMC or WHO, and it cannot by itself establish that a medicinal product caused an event.

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Ethical approval

Ethics approval and informed consent were not required because the study used public, aggregated, anonymized pharmacovigilance data and involved no human intervention, identifiable participant data, animal experiment, pathological examination, or biological sample.

Conflict of interest

The authors declare no conflict of interest.

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