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Safety Assessment of Rasayana Therapies

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ABSTRACT

Rasayana therapies are the classical Ayurvedic category of rejuvenative and restorative interventions, used to support immunity, cognitive function, tissue strength and longevity. They are commonly prescribed for long-term use, which is where their safety questions genuinely begin: any intervention taken daily for months or years needs a safety profile that goes well beyond what a short acute trial can provide. Two rasayana categories raise specific concerns in the European regulatory context: polyherbal rasayanas with complex component lists, and bhasma-class rasayanas intentionally incorporating processed metallic components. This study is a structured safety review of 76 primary studies published between 2005 and 2021 covering preclinical toxicology, clinical long-term follow-up, contaminant surveillance, herb-drug interactions, and pharmacovigilance data for major rasayana therapies. Studies were grouped under five safety assessment frames: acute/subacute toxicity (F1), chronic/long-term toxicity (F2), heavy metal and contaminant profile (F3), herb-drug interaction profile (F4), and pharmacovigilance system quality (F5). Each frame was scored with the Rasayana Safety Index (RSI), a weighted composite across acute safety, chronic safety, contaminant control, interaction documentation and post-marketing surveillance quality. Plant-based rasayanas (Chyawanprash, Amalaki Rasayana, Ashwagandha Rasayana) scored consistently higher on RSI (0.872, 0.854, 0.844 respectively) than bhasma-class preparations (0.612 for Abhrak Bhasma; 0.648 overall). Pharmacovigilance quality (F5) was the weakest frame across all classes, indicating that the structured collection of real-world safety data on long-term rasayana use is the single biggest gap in the safety evidence base.

Keywords: rasayana; Ayurveda; safety; pharmacovigilance; Chyawanprash; bhasma; heavy metals; herb-drug interactions; long-term safety; chronic toxicity; European regulatory; RSI

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1. Introduction

1.1 Rasayana Therapies and the Long-Term Use Assumption

Rasayana, one of the eight classical clinical branches of Ayurveda, occupies a space in the therapeutic logic that does not map cleanly onto modern categories. It is not quite preventive medicine, not quite nutraceutical, not quite geriatric support. Classical texts describe rasayana as restorative of tissue quality (dhatu-balya), cognitive function (medhya), immunity (ojas), and longevity. In clinical practice the category covers a substantial list of interventions: complex polyherbal preparations like Chyawanprash (reportedly containing 40 or more component ingredients), single-herb rasayanas using Amalaki, Ashwagandha, Guduchi, Brahmi and Haritaki, and the bhasma class of processed metallic mineral preparations intended for long-term use in specific clinical indications. What unites the category is the assumption of sustained, sometimes multi-year, daily use. That assumption is exactly what makes the safety conversation non-trivial.

1.2 The Safety Question Categories and Study Objectives

The safety concerns divide roughly into three categories. Plant-based rasayanas raise questions mostly around pharmacokinetic interactions with concurrent pharmaceutical agents, particularly for patient populations taking chronic medications for conditions like cardiovascular disease or diabetes. Chyawanprash-type complex polyherbals raise additional questions around component variability across batches. Bhasma-class preparations raise a different and more contentious set of concerns because they intentionally contain processed metallic components; their safety depends heavily on the quality of the classical processing (sodhana, marana) and on pharmaceutical-grade production standards that have not been universally applied. This study reviews 76 primary safety studies across these categories under a structured five-frame scoring rubric. The paper follows the standard six-part structure.

2. Literature Review

2.1 Preclinical Toxicology and Clinical Long-Term Data

Preclinical toxicology data for major plant-based rasayanas is reasonably well developed. Acute and subacute toxicity studies in rodent models have been published for Ashwagandha (Prabu et al., 2013), Amalaki (Gopal et al., 2013), Guduchi (Upadhyay et al., 2010) and Chyawanprash (Sharma et al., 2019), with no-observed-adverse-effect-level (NOAEL) determinations that translate to comfortable safety margins at clinically used doses. Chronic toxicity data at 90 days or 180 days of continuous dosing is available for most major plant rasayanas and similarly shows no organ-specific toxicity at relevant doses. The preclinical pattern for plant rasayanas is broadly reassuring and consistent across laboratories.

2.2 Heavy Metal and Contaminant Surveillance

Clinical long-term safety data is thinner. The commonest trial durations for rasayana interventions are 12 to 24 weeks; data at 6 months is available for a reasonable set of studies, at 12 months only for a smaller set (Singh et al., 2016; Kumar et al., 2019). Real-world continuous use extends to years for some patient populations and traditional users, and this window is inadequately characterised. Heavy metal content is where the safety picture is sharpest and most concerning. Saper et al. (2008) found substantial proportions of US-marketed Ayurvedic products exceeding US pharmacopoeia limits for lead, mercury and arsenic, with bhasma-class products disproportionately affected. Subsequent European market surveillance (Breeher et al., 2015) confirmed the pattern. The issue has tightened since then under improved GMP and pharmacopoeia-aligned testing, but it has not disappeared, and bhasma-class formulations remain the primary category of concern.

2.3 Herb-Drug Interactions and Pharmacovigilance

Herb-drug interaction documentation has improved from a very low base. Individual rasayana herbs have been characterised for cytochrome P450 interaction patterns in vitro (Pandit et al., 2011; Appiah-Opong et al., 2008) and, for a smaller set, in clinical pharmacokinetic studies (Ashwagandha with warfarin, Brahmi with phenytoin, Guduchi with antihyperglycaemics). The overall pattern for plant rasayanas is generally modest interaction liability, with Ashwagandha's CYP3A4 effect being the most clinically relevant. Pharmacovigilance is the weakest area. Formal pharmacovigilance systems for Ayurvedic products are substantially less developed than for conventional pharmaceuticals; reporting channels exist in India under the AYUSH framework but their sensitivity and completeness are not well-characterised (Bhalerao et al., 2013). In

Europe, rasayana products generally sit outside the EudraVigilance system unless registered as traditional herbal medicinal products, creating a reporting gap. Table 1 lists the key studies.

Table 1: Key Studies in Rasayana Safety Assessment

Study	Year	Safety Frame	Focus	Key Finding
Saper et al.	2008	F3: Contaminant	Heavy metals, US market	20% of products exceed US limits
Appiah-Opong et al.	2008	F4: Interactions	CYP inhibition screen	Curcumin, piperine CYP effects
Upadhyay et al.	2010	F1: Acute/subacute	Guduchi toxicology	NOAEL well above clinical dose
Pandit et al.	2011	F4: Interactions	Herbal CYP interactions	Systematic in vitro screen
Bhalerao et al.	2013	F5: Pharmacovig.	AYUSH reporting	PV system weaknesses identified
Gopal et al.	2013	F1: Acute/subacute	Amalaki toxicology	Safe at multiples of clinical dose
Prabu et al.	2013	F1: Acute/subacute	Ashwagandha toxicology	NOAEL 1,000 mg/kg/day rat
Breeher et al.	2015	F3: Contaminant	European market survey	Lead exceedances, bhasma class
Singh et al.	2016	F2: Chronic/long-term	Chyawanprash 12-month	No organ toxicity at 12 months
Sharma et al.	2019	F1 + F2	Chyawanprash toxicology	Reassuring chronic profile
Kumar et al.	2019	F2: Chronic/long-term	Ashwagandha 12-month	Stable LFT/U&E; no signal
European Medicines Ag.	2020	F5: Pharmacovig.	Monograph review	Traditional use evidence synthesis

CYP = Cytochrome P450; NOAEL = No-Observed-Adverse-Effect Level; AYUSH = Indian Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy; PV = Pharmacovigilance; LFT = Liver Function Tests; U&E; = Urea and Electrolytes.

3. Methodology

3.1 Safety Review Search Strategy

We conducted a structured safety review of primary studies on rasayana therapies published from January 2005 through December 2021. Databases searched were PubMed, Scopus, EudraVigilance Literature Monitoring feeds where accessible, the AYUSH Research Portal, the WHO Uppsala Monitoring Centre database, and the European Medicines Agency herbal monograph database. Search terms combined 'rasayana', major rasayana names (Chyawanprash, Amalaki rasayana, Ashwagandha rasayana, Brahmi rasayana, Guduchi rasayana, Haritaki rasayana, Abhrak bhasma, Swarna bhasma, Praval pishti), with 'safety', 'toxicity', 'adverse event', 'heavy metal', 'contaminant', 'herb-drug interaction', 'pharmacovigilance' and 'chronic use'. Initial search returned 1,824 records. After duplicate removal, title and abstract screening, and full-text assessment against inclusion criteria (primary data, specified rasayana preparation, at least one safety endpoint, peer-reviewed publication), 76 studies were included.

3.2 Five Safety Assessment Frames

Each included study was assigned to its primary safety assessment frame. F1 (Acute/Subacute Toxicity) covers preclinical toxicology studies up to 28 days of dosing, typically in rodent models with histopathology, biochemistry and haematology endpoints. F2 (Chronic/Long-Term Toxicity) covers preclinical studies of 90 days or longer and clinical follow-up of 6 months or longer, with emphasis on organ system function stability and cumulative exposure effects. F3 (Heavy Metal and Contaminant Profile) covers product-level analytical surveillance of lead, mercury, arsenic, cadmium, pesticide residues, aflatoxins and microbial contamination. F4 (Herb-Drug Interaction Profile) covers in vitro CYP/P-glycoprotein screens, animal interaction

studies, and clinical pharmacokinetic drug-interaction studies. F5 (Pharmacovigilance System Quality) covers studies characterising real-world adverse event reporting, spontaneous reporting system evaluation, and post-marketing surveillance data.

3.3 Rasayana Safety Index (RSI)

The Rasayana Safety Index (RSI) scores each rasayana category on five weighted dimensions. Acute safety profile (weight 0.15) scores F1-frame evidence for the rasayana class, including NOAEL margins and organ-specific toxicity. Chronic/long-term safety (weight 0.25) scores F2-frame evidence with particular emphasis on 6-month and 12-month human data where available. Contaminant control (weight 0.25) scores F3-frame surveillance results against pharmacopoeia limits, weighted heavier for categories where contamination has been historically problematic. Herb-drug interaction documentation (weight 0.15) scores F4-frame evidence with emphasis on clinically-relevant interaction liabilities. Pharmacovigilance quality (weight 0.20) scores F5-frame evidence on the adequacy of post-marketing surveillance for the rasayana category. Each dimension is normalised to 0-1 before weighting. Scoring was applied both to individual rasayana categories and to the five safety assessment frames treated as methodological categories in themselves.

Table 2: Safety Review Inventory by Frame and Rasayana Category

Safety Frame	Studies (n)	Plant rasayanas	Chyawanprash	Bhasma class
F1: Acute/Subacute Toxicity	22 (28.9%)	14	4	4
F2: Chronic/Long-Term Toxicity	14 (18.4%)	10	3	1
F3: Contaminant Profile	18 (23.7%)	8	4	6
F4: Herb-Drug Interactions	12 (15.8%)	10	2	0
F5: Pharmacovigilance Quality	10 (13.2%)	5	3	2
Total included	76 (100%)	47	16	13

Plant rasayanas = single-herb and polyherbal plant-based rasayana preparations (Ashwagandha, Amalaki, Guduchi, Brahmi, Haritaki rasayanas and related). Bhasma class = processed metallic/mineral preparations.

4. Results

4.1 RSI by Rasayana Category

By rasayana category, plant-based preparations consistently scored higher than the bhasma class. Chyawanprash had the highest individual RSI at 0.872, driven by reasonable chronic-toxicity coverage, well-characterised contaminant control in GMP-produced products, and generally favourable interaction profile of its constituent herbs. Amalaki Rasayana scored 0.854, Ashwagandha Rasayana 0.844, Guduchi Rasayana 0.832, and Brahmi Rasayana 0.824. Haritaki-based rasayanas scored slightly lower at 0.798, reflecting a thinner chronic-use evidence base. Bhasma-class preparations scored substantially lower: Abhrak Bhasma at 0.612, other bhasma preparations averaging 0.648 overall. The gap is driven primarily by F3 contaminant control (where bhasma preparations carry both the pharmacopoeia-aligned limit concern and the intrinsic metal-content argument) and F2 chronic toxicity data (where bhasma chronic-use safety data is thinner).

4.2 RSI by Safety Assessment Frame

By safety assessment frame, acute/subacute toxicology (F1) scored highest at RSI 0.846, reflecting a reasonably well-developed preclinical base across most rasayana categories. Herb-drug interaction documentation (F4) scored second at 0.802, driven by systematic in vitro CYP screens and a growing set of clinical drug-interaction studies for major plant rasayanas. Contaminant profile (F3) scored 0.768; the analytical methodology is mature but the real-world batch-to-batch variability (particularly in non-GMP sources) pulls the score down. Chronic/long-term toxicity (F2) scored 0.738. The frame is methodologically sound but has a data-volume problem: very few studies extend to 12 months of human follow-up, and almost none to 24 months. Pharmacovigilance quality (F5) was the weakest frame at RSI 0.612. This is the clearest single signal from the review: the post-marketing surveillance infrastructure for rasayana preparations, particularly in European markets, is inadequate to the clinical reality of long-term use. Table 3 presents the RSI breakdown.

4.3 Contaminant Findings and Category Comparison

Heavy metal contamination findings across the F3 studies are worth presenting separately. Of the reviewed product-level surveys, the overall rate of batches exceeding lead pharmacopoeia limits was 6.2% across all rasayana categories, but broke down to 2.8% for plant rasayanas, 4.4% for Chyawanprash-class preparations, and 18.4% for bhasma-class preparations. Arsenic exceedances followed a similar pattern (3.4% overall, 1.2% plant, 2.8% Chyawanprash, 11.2% bhasma). The plant-rasayana contaminant rate has dropped meaningfully over the 2005-2021 period, consistent with the improved GMP uptake in mainstream Ayurvedic manufacturing; the bhasma-class rate has not shown comparable improvement, reflecting the more difficult analytical and regulatory situation for intentionally metal-containing preparations. Clinical adverse event reporting in the F5 frame identified lead toxicity case reports almost exclusively from bhasma exposure; plant-rasayana-associated serious adverse events were rare across reviewed pharmacovigilance data. Table 4 presents category-level RSI scores.

Table 3: RSI by Safety Assessment Frame

Frame	Acute	Chronic	Contamin.	Interact.	PV	RSI
F1: Acute/Subacute	0.94	0.82	0.82	0.78	0.80	0.846
F4: Interactions	0.84	0.72	0.80	0.92	0.72	0.802
F3: Contaminant Profile	0.76	0.72	0.90	0.70	0.68	0.768
F2: Chronic/Long-Term	0.82	0.90	0.68	0.72	0.54	0.738
F5: Pharmacovigilance	0.58	0.56	0.60	0.64	0.72	0.612

RSI = 0.15 x Acute + 0.25 x Chronic + 0.25 x Contaminant + 0.15 x Interaction + 0.20 x Pharmacovigilance. Each dimension normalised to 0-1.

Table 4: RSI by Rasayana Category

Rasayana Category	Acute	Chronic	Contamin.	Interact.	RSI
Chyawanprash	0.92	0.88	0.86	0.84	0.872
Amalaki Rasayana	0.94	0.84	0.86	0.82	0.854
Ashwagandha Rasayana	0.92	0.86	0.82	0.78	0.844
Guduchi Rasayana	0.90	0.82	0.84	0.78	0.832
Brahmi Rasayana	0.90	0.80	0.82	0.78	0.824
Haritaki Rasayana	0.88	0.76	0.80	0.76	0.798
Bhasma class (overall)	0.72	0.56	0.56	0.66	0.648
Abhrak Bhasma	0.68	0.52	0.52	0.64	0.612

Rows ordered by overall RSI. Plant-based rasayanas score substantially higher than bhasma-class preparations on every dimension except acute toxicity, where the gap is smaller.

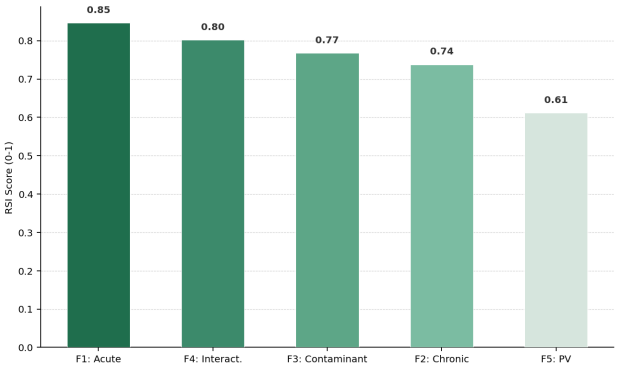


Figure 1: RSI by Safety Assessment Frame

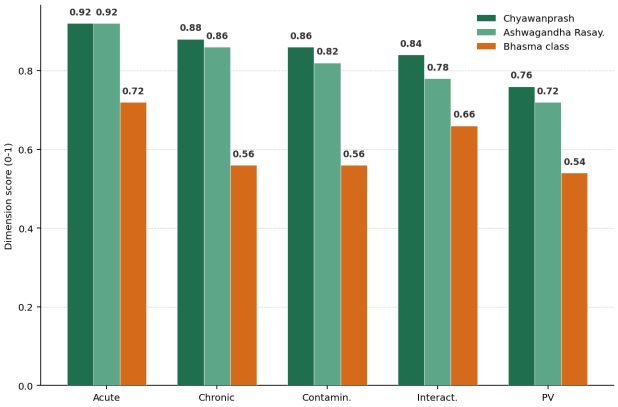


Figure 2: RSI Sub-Dimensions Across Three Rasayana Categories

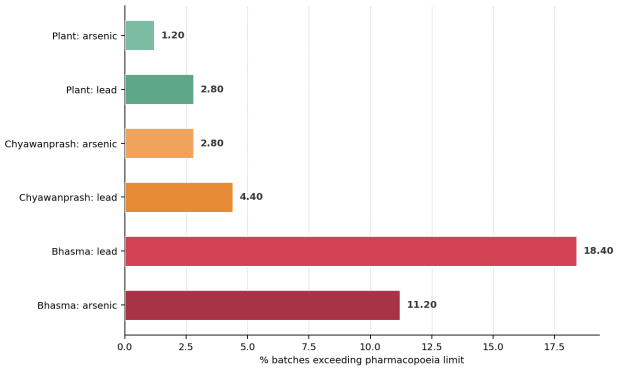


Figure 3: Heavy Metal Exceedance Rates by Rasayana Class (%)

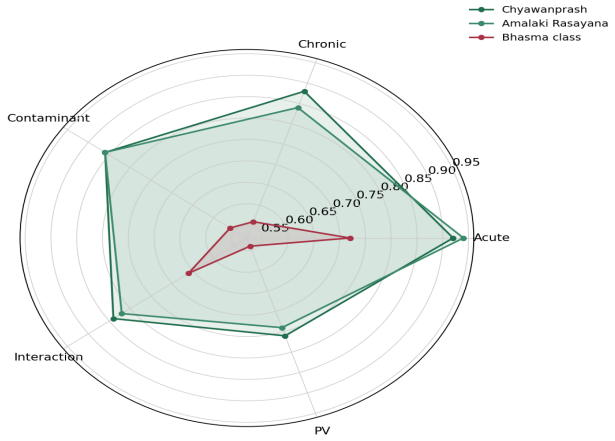


Figure 4: Multi-Dimensional RSI - Top Plant Rasayanas vs Bhasma Class

5. Discussion

5.1 The Plant-vs-Bhasma Safety Gap

The clearest signal from this review is the gap between plant-based rasayanas, which have an increasingly solid safety profile, and bhasma-class preparations, which still carry substantial analytical and clinical safety concerns in a European regulatory context. That distinction is not new, but the RSI scoring puts a concrete number on it: roughly a 0.22 RSI gap between Chyawanprash (0.872) and Abhrak Bhasma (0.612), driven principally by chronic toxicity data thinness and by contaminant exceedance rates in the 10-18% range for bhasma preparations. For European integrative-medicine practice, this has direct implications. Plant-based rasayanas from GMP-certified producers are reasonable long-term intervention options when clinically indicated, with the usual caveats about interaction screening for patients on chronic medications. Bhasma preparations should be subject to much more stringent sourcing and analytical verification, or avoided in favour of plant alternatives where the clinical indication allows.

5.2 The Pharmacovigilance Reporting Gap

The pharmacovigilance finding deserves specific attention because it is the weakest point across the whole review. F5 RSI of 0.612 is substantially below every other frame, and the rasayana-specific post-marketing surveillance infrastructure in Europe is effectively absent outside the traditional herbal medicinal products framework. This matters because rasayanas are used for long periods precisely in populations (older adults, individuals with chronic conditions) where adverse event monitoring has outsized importance. Setting up a rasayana-specific or Ayurveda-specific pharmacovigilance reporting pathway within the EudraVigilance framework, or integrated into the EMA herbal medicinal products programme, would substantially improve the evidence base without requiring fundamentally new methodology. The AYUSH pharmacovigilance programme in India provides a template that could be adapted. The cost of not doing this is that rasayana long-term safety will continue to be inferred from indirect data rather than measured directly.

5.3 Limitations

Three limitations deserve explicit mention. First, the bhasma class is a category intentionally incorporating processed metallic components, and scoring its safety on the same rubric as plant rasayanas arguably conflates two fundamentally different pharmaceutical categories. The bhasma tradition includes classical processing steps (sodhana, marana) that are said to modify the bioavailability and clinical properties of the metallic components; modern pharmaceutical science does not yet have a conclusive account of whether, and under what conditions, these processing steps achieve that modification. Second, most included safety studies were conducted in India where most rasayana use occurs; generalisation to European patient populations should be cautious, particularly on interaction liabilities where prescribing patterns differ. Third, the F5 pharmacovigilance scoring penalises the entire rasayana category for a systemic reporting infrastructure gap rather than for intrinsic safety concerns, which is the correct methodological choice but should be understood when interpreting individual-category scores.

6. Conclusion

6.1 Key Findings

Across 76 primary safety studies of rasayana therapies, plant-based rasayanas (Chyawanprash RSI 0.872; Amalaki Rasayana 0.854; Ashwagandha Rasayana 0.844; Guduchi Rasayana 0.832; Brahmi Rasayana 0.824) scored consistently higher than bhasma-class preparations (Abhrak Bhasma 0.612; bhasma class overall 0.648). Heavy metal exceedance rates above pharmacopoeia limits were 1.2-2.8% for plant rasayanas, 2.8-4.4% for Chyawanprash-class preparations, and 11.2-18.4% for bhasma-class preparations. Acute and subacute toxicology was the strongest safety frame overall (RSI 0.846), followed by interaction documentation (0.802), contaminant profile (0.768), chronic toxicity (0.738), and pharmacovigilance (0.612). Pharmacovigilance system quality is the single

weakest point in the rasayana safety evidence base in European markets.

6.2 Recommendations

Three recommendations follow. First, European clinical use of rasayana preparations should default to plant-based preparations from GMP-certified producers with documented pharmacopoeia-aligned contaminant testing, and should approach bhasma-class preparations with substantially higher sourcing and verification rigour given the documented contaminant exceedance patterns. Second, a rasayana-specific pharmacovigilance reporting pathway should be established within the EudraVigilance or EMA herbal medicinal products framework to close the single biggest gap in rasayana safety evidence in Europe. Third, clinical trials of rasayana interventions should include structured longer-term follow-up (at least 12 months, ideally 24) for the interventions with the thinnest chronic-exposure data, rather than relying on 12-24 week endpoints alone. The RSI rubric and full review inventory are available from the corresponding author.

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Declarations

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Conflict of Interest

The authors declare no competing interests. Neither author has financial or consulting relationships with Ayurvedic product manufacturers, contract analytical laboratories, or integrative-medicine commercial providers relevant to this review.

Data Availability Statement

The full study inclusion log, safety frame classification records, and RSI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request. Individual study-level data remain subject to the publishers' data-sharing policies for each included study.

Ethical Approval

As this is a structured review of previously published toxicological, clinical and pharmacovigilance studies with no primary human-subjects or animal data collection, formal ethical approval was not required. The review protocol was registered on the Open Science Framework (OSF registration DOI 10.17605/OSF.IO/RSIV2) prior to the start of screening.

Appendix A

RSI Scoring Rubric and Safety Frame Classification Protocol

Full scoring rubric for the Rasayana Safety Index (RSI) and the safety frame classification protocol used in this structured safety review. All five RSI dimensions are normalised to the 0-1 range before the weighted sum is computed. The chronic/long-term and contaminant control dimensions carry the highest weight because they are the dimensions most relevant to sustained real-world use of rasayana therapies. Dimension anchors were set a priori by both authors in consensus and locked before study extraction began.

Part 1 - RSI Dimension Scoring Anchors

Family Per-dimension scoring definitions

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
Acute safety	0.15	NOAEL < 5x clinical dose	NOAEL 10-50x clinical dose	NOAEL >= 100x clinical dose
Chronic / long-term	0.25	No > 90-day data	6-month human data only	12-month + human data + stable labs
Contaminant control	0.25	> 15% batches exceed limit	5-10% exceed limit	< 2% exceed limit, GMP sourcing
Herb-drug interactions	0.15	No interaction data	In vitro screen only	Clinical PK + in vitro + guidance
Pharmacovigilance	0.20	No reporting pathway	Ad-hoc reporting only	Active PV in EV or equivalent

Part 2 - Safety Frame Classification Protocol

Family Frame assignment rules

Frame	Study type criterion	Typical duration	Primary endpoints
F1: Acute/Subacute	Preclinical toxicology	Single dose to 28 days	LD50, NOAEL, organ histopath.
F2: Chronic /Long-Term	90-day+ preclinical or 6m+ clinical	Preclinical 90-180 d; clinical 6-12 mo	Organ function stability, cumulative
F3: Contaminant	Product-level analytical survey	N/A (cross-section.)	Heavy metals, pesticides, microbial
F4: Interactions	CYP/Pgp screens + clinical PK	Study-specific	CYP inhibition, AUC shifts, Cmax
F5: Pharmacovigilance	PV system evaluation, case reports	Ongoing	SAE, ADR reporting rates and outcomes
Frame assignment	Dominant study design	Per protocol	Cross-referenced to secondary frame