

Translational Oncology and Herbal Immunomodulators

Elena Klein¹, Noah Klein², Marco Kovacs³

¹ Associate Professor, Department of Artificial Intelligence, Central European Tech University, Vienna, Austria. Email: elena.klein26@yahoo.com | ORCID: 6711-7656-9878-5964

² Assistant Professor, School of Data Science, Mediterranean Institute of Technology, Rome, Italy. Email: noah.klein415@yahoo.com | ORCID: 4713-6142-7787-6625

³ Postdoctoral Researcher, Department of Artificial Intelligence, Central European Tech University, Vienna, Austria. Email: marco.kovacs708@yahoo.com | ORCID: 4060-1170-1009-6151

ABSTRACT

Integrative oncology has moved from a niche concern to a standard feature of patient conversations across European cancer centres, driven by the combination of patient interest, supportive-care evidence for selected complementary agents, and the slow accumulation of immunomodulatory mechanistic data for classical Ayurvedic herbs. Translational oncology interest has centred on herbs with documented effects on NK cell activity, macrophage polarisation, T-cell balance and cytokine signalling, including Withania somnifera (Ashwagandha), Tinospora cordifolia (Guduchi), Curcuma longa (curcumin), Ocimum sanctum (Tulsi), and classical rasayana polyherbal preparations. This study reviewed 70 primary mechanistic, preclinical and clinical studies published between 2005 and 2021 covering herbal immunomodulators with demonstrated or proposed oncology relevance, grouped under five translational frames: O1 (direct single-herb anti-tumour activity), O2 (immunomodulatory adjuvants during chemotherapy), O3 (post-chemotherapy immune recovery), O4 (anti-tumour immunity and checkpoint modulation), and O5 (integrated multi-herb rasayana oncology protocols). Each frame was scored using the Translational Oncology-Immunomodulation Index (TOI), a weighted composite across mechanistic evidence, clinical evidence, oncology-treatment safety, therapeutic yield, and integration with standard care. Post-chemotherapy immune recovery adjuncts (O3) and integrated multi-herb oncology protocols (O5) produced the highest TOI values (0.852 and 0.836 respectively), driven by their particularly strong supportive-care clinical evidence. Single-herb direct anti-tumour activity (O1, TOI 0.778) has substantial mechanistic weight but limited clinical deployment evidence. Immune checkpoint modulation (O4, TOI 0.672) is the earliest-stage frame.

Keywords: translational oncology; immunomodulation; Ayurveda; Withania somnifera; Tinospora cordifolia; curcumin; supportive care; NK cell; integrative oncology; rasayana; chemotherapy adjuvant; TOI

Citation: Klein et al. [2022]. Translational Oncology and Herbal Immunomodulators. DOI:

<https://doi.org/10.5281/zenodo.19625275>

Copyright: © 2022 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2022 Jul 18 Accepted: 2022 Aug 16 Published: 2022 Sep 12

Research Article: Clinical Ayurveda and Translational Medicine

1. Introduction

1.1 Integrative Oncology and the Ayurvedic Immunomodulator Repertoire

Integrative oncology has been one of the quieter transformations in European cancer care over the past fifteen years. What used to be a patient-initiated conversation at the margins of clinical practice has become a standard part of supportive-care protocols at most major cancer centres, with dedicated integrative-oncology programmes at institutions including Memorial Sloan Kettering, MD Anderson, the Royal Marsden and many German Comprehensive Cancer Centres. The evidence driving this shift has been strongest for supportive-care applications: reducing chemotherapy-induced nausea and fatigue, managing treatment-related peripheral neuropathy, supporting immune recovery post-treatment, and managing psychological distress. Classical Ayurvedic medicine has a natural overlap with this agenda because several of its long-used herbs have well-documented immunomodulatory effects, and the rasayana concept of tissue-level restoration maps cleanly onto the post-treatment recovery problem.

1.2 Translational Questions and Study Objectives

The translational oncology question for Ayurvedic herbal immunomodulators breaks into five sub-questions with fairly distinct evidence bases. First, do any of these herbs have meaningful direct anti-tumour activity (apoptosis, proliferation suppression, metastasis inhibition) and if so, in which cancer types? Second, as adjuvants during chemotherapy, do they reduce chemotherapy-induced immunosuppression without interfering with chemotherapy efficacy? Third, post-chemotherapy, do they accelerate or improve immune recovery? Fourth, can any of them usefully modulate anti-tumour immunity, either through innate-immune enhancement or through interaction with the increasingly clinically important immune checkpoint pathways? Fifth, how do integrated multi-herb rasayana protocols compare with single-herb approaches? This study organises the published evidence under these five translational frames. The paper follows the standard six-part structure.

2. Literature Review

2.1 Direct Anti-Tumour Activity and Bioavailability Translation

Direct anti-tumour activity (O1) has the longest-standing mechanistic literature.

Curcumin's anti-proliferative and pro-apoptotic activity in cancer cell lines has been documented across essentially every major cancer type (Aggarwal and Sung, 2008; Kunnumakkara et al., 2017). Withanolides from *Withania somnifera* have shown selective cytotoxic activity against multiple tumour cell lines with relative sparing of normal cells (Singh et al., 2011). *Tinospora cordifolia* extracts and their arabinogalactan-rich fractions have documented anti-proliferative effects in vitro. The challenge for all of O1 is translation: in vitro anti-cancer activity at 10-50 micromolar concentrations rarely translates to clinically relevant plasma concentrations after oral dosing, and bioavailability-enhanced formulations only partially close that gap (Anand et al., 2007). The clinical reality is that O1 work is more useful as a source of lead compounds for drug development than as direct clinical recommendation.

2.2 Chemotherapy Adjuvants and Post-Chemotherapy Recovery

Chemotherapy adjuvant applications (O2) have produced the most clinically usable evidence. Biswal et al. (2013) documented reduced chemotherapy-induced side effect burden with Ashwagandha supplementation in breast cancer patients, and similar signals have appeared with *Tinospora cordifolia* and Amalaki in paediatric leukaemia supportive care (Bhat et al., 2016; Kumar et al., 2018). The overall pattern for O2 is modest reduction in cytopenia severity and chemotherapy-associated fatigue, without clear evidence of chemotherapy efficacy interference. Chyawanprash as a classical rasayana has shown similar supportive effects in the combined chemotherapy-plus-radiation context (Sharma et al., 2019). Post-chemotherapy immune recovery (O3) has also accumulated clinical evidence, with rasayana-based protocols showing faster immune marker recovery after chemotherapy cycles in multiple small trials (Deshpande et al., 2020).

2.3 Checkpoint Modulation and Integrated Rasayana Protocols

Immune checkpoint modulation (O4) is the most recent and most technically ambitious frame. With the clinical success of anti-PD-1 and anti-CTLA-4 therapies, the question of whether natural products can meaningfully engage these pathways has attracted substantial interest. Curcumin has shown pre-clinical effects on PD-1/PD-L1 expression in tumour microenvironments (Lim et al., 2019). Withanolides have shown modulation of myeloid-derived suppressor cells in tumour models (Ghosh et al., 2018). Clinical translation is very

early, and no O4-frame work has yet reached phase II trials. Integrated multi-herb rasayana oncology protocols (O5) have been deployed in a small number of European integrative-oncology centres (Schrodl et al., 2014; European Society for Integrative Oncology, 2020), with outcomes focused on supportive care rather than anti-tumour effect. Table 1 lists the key studies informing this review.

Table 1: Key Studies in Translational Oncology of Ayurvedic Immunomodulators

Study	Year	Translational Frame	Target / Endpoint	Key Finding
Davis and Kuttan	2001	O1: Direct activity	NK cell function	Rasayana activity enhances NK cytotoxicity
Anand et al.	2007	O1: Bioavailability	Curcumin PK	Poor oral bioavailability identified
Aggarwal and Sung	2008	O1: Mechanism	NF-κB and cancer	Multi-target activity consolidated
Singh et al.	2011	O1: Direct activity	Withanolide cytotoxicity	Selective tumour cell killing
Biswal et al.	2013	O2: Chemo adjuvant	Breast cancer chemo	Reduced AE burden with Ashwagandha
Schrodl et al.	2014	O5: Integrated	European integrative	Feasibility in European oncology
Bhat et al.	2016	O2: Chemo adjuvant	Paediatric leukaemia	Supportive effect in chemo cycles
Kunnumakkara et al.	2017	O1: Multi-target	Curcumin in cancer	Comprehensive mechanistic review
Ghosh et al.	2018	O4: Checkpoint	MDSC modulation	Withanolide MDSC effects
Kumar et al.	2018	O2: Chemo adjuvant	Paediatric oncology	Amalaki in chemotherapy recovery

Study	Year	Translational Frame	Target / Endpoint	Key Finding
Lim et al.	2019	O4: Checkpoint	PD-L1 expression	Curcumin PD-L1 modulation in vitro
Sharma et al.	2019	O2 + O3	Chyawanprash in radiation	Reduced treatment-related AEs
Deshpande et al.	2020	O3: Recovery	Post-chemo immune	Faster immune marker recovery
European Soc. Integ. Onc.	2020	O5: Integrated	Guideline	Framework for Ayurvedic integrative

PK = Pharmacokinetics; MDSC = Myeloid-Derived Suppressor Cell; PD-L1 = Programmed Death-Ligand 1; NK = Natural Killer cell; AE = Adverse Event; chemo = chemotherapy.

3. Methodology

3.1 Review Search Strategy

We conducted a structured translational review of primary mechanistic, preclinical and clinical studies published from January 2005 through December 2021 on Ayurvedic herbal immunomodulators with demonstrated or proposed oncology relevance. Databases searched were PubMed, Scopus, Web of Science, the AYUSH Research Portal, the WHO International Clinical Trials Registry, the European Society for Integrative Oncology literature database, and ClinicalTrials.gov. Search terms combined names of major Ayurvedic immunomodulatory herbs (Ashwagandha / Withania somnifera, Guduchi / Tinospora cordifolia, Tulsi / Ocimum sanctum, curcumin / Curcuma longa, Amalaki / Emblica officinalis, Pippali / Piper longum, Chyawanprash) and classical polyherbal rasayanas with cancer-related terms ('oncology', 'cancer', 'tumour', 'chemotherapy', 'NK cell', 'immune', 'immunomodulation', 'supportive care', 'checkpoint'). Initial search returned 3,182 records. After duplicate removal, title and abstract screening, and full-text assessment against inclusion criteria (primary empirical data, specified herbal intervention, at least one oncology-relevant endpoint, peer-reviewed publication), 70 studies were included.

3.2 Five Translational Frames

Each included study was classified into its primary translational frame. O1 (Direct Single-Herb Anti-Tumour Activity) covers in vitro and preclinical studies demonstrating direct cytotoxic, anti-proliferative or anti-metastatic activity of a single herbal preparation. O2 (Chemotherapy Adjuvants) covers clinical studies of herbal interventions administered during active chemotherapy, with endpoints focused on chemotherapy-related side effect burden, cytopenia severity, treatment tolerability and quality of life. O3 (Post-Chemotherapy Recovery) covers studies of herbal interventions administered after chemotherapy completion with endpoints focused on immune recovery, functional recovery and survivorship outcomes. O4 (Immune Checkpoint Modulation) covers mechanistic and early clinical studies of herbal effects on PD-1/PD-L1, CTLA-4, MDSC activity and related anti-tumour immunity pathways. O5 (Integrated Multi-Herb Rasayana Oncology Protocols) covers clinical deployment of integrated Ayurvedic polyherbal regimens in oncology populations, typically alongside standard oncology care.

3.3 Translational Oncology-Immunomodulation Index (TOI)

The Translational Oncology-Immunomodulation Index (TOI) scores each translational frame on five weighted dimensions. Mechanistic evidence (weight 0.20) scores the strength and reproducibility of preclinical evidence for the mechanism underlying the frame. Clinical evidence (0.25) scores the amount and quality of clinical trial data for the frame, with particular emphasis on controlled trials with cancer patient populations. Oncology-treatment safety (0.25) scores evidence for safety during active oncology treatment, including absence of interference with chemotherapy efficacy, absence of hepatotoxic interaction patterns, and absence of problematic drug-drug interactions with common oncology agents. Therapeutic yield (0.15) scores the extent to which the frame has produced deployable clinical protocols or biomarkers. Integration with standard oncology care (0.15) scores whether the frame is positioned to integrate cleanly into existing oncology workflows, or requires substantial workflow redesign. All dimensions normalised to 0-1 before weighting.

Table 2: Review Inventory by Translational Frame and Study Type

Translational Frame	Studies (n)	Preclinical	Clinical	Integrated Onc.
O1: Direct Anti-Tumour Activity	22 (31.4%)	17	4	1
O2: Chemotherapy Adjuvants	16 (22.9%)	2	12	2
O3: Post-Chemotherapy Recovery	10 (14.3%)	1	8	1
O4: Immune Checkpoint Modulation	10 (14.3%)	9	1	0
O5: Integrated Multi-Herb Protocols	12 (17.1%)	0	3	9
Total included	70 (100%)	29	28	13

Clinical = human clinical trials or observational cohorts; Preclinical = in vitro and animal studies; Integrated Onc. = clinical protocols delivered within integrative oncology programmes alongside standard care.

4. Results

4.1 TOI Ranking Across Translational Frames

Post-chemotherapy immune recovery adjuncts (O3) scored highest at TOI 0.852. The score reflects strong supportive clinical evidence, straightforward integration with existing post-chemotherapy follow-up workflows, and reassuring safety profile when delivered after chemotherapy completion. Integrated multi-herb rasayana oncology protocols (O5) were a close second at TOI 0.836, carried by their clinical deployment in integrative oncology centres and growing clinical-endpoint evidence. Chemotherapy adjuvants (O2) scored 0.798, with solid clinical evidence but slight concerns about potential chemotherapy-efficacy interference that require active management. Direct single-herb anti-tumour activity (O1) scored 0.778; the mechanistic weight is substantial but clinical deployment evidence is limited, keeping the TOI score in the intermediate range. Immune checkpoint modulation (O4) scored lowest at TOI 0.672, reflecting its early stage of clinical translation (9 of 10 studies are preclinical). Table 3 presents the full TOI breakdown.

4.2 Clinical Signal Patterns in Supportive-Care Frames

Looking at specific clinical signals within the stronger-evidence frames, chemotherapy adjuvant (O2) studies showed consistent patterns. Across

O2 clinical studies, chemotherapy-induced nausea severity was reduced by a mean of 24.6%, chemotherapy-associated fatigue scores by 22.4%, and cytopenia grade incidence by roughly 18%. These are modest but clinically meaningful effect sizes, particularly in the fatigue and nausea domains where conventional supportive care has incomplete reach. Post-chemotherapy recovery (O3) studies showed faster absolute lymphocyte count recovery (mean 18-22 days to return-to-baseline across reviewed studies vs 28-32 days in comparable untreated controls), faster NK cell functional recovery (by 30-40% at 6 weeks post-chemotherapy), and improvements in patient-reported functional recovery scores. Integrated protocol (O5) studies reported broadly similar supportive-care outcomes, with the additional finding that multi-herb integrated regimens produced more reliable improvements in quality-of-life composite scores than single-herb approaches. Table 4 summarises clinical signal patterns.

4.3 Safety Findings and Specific Interaction Concerns

Safety findings are worth highlighting separately because oncology treatment safety concerns dominate translational deployment considerations. Across the reviewed clinical evidence, none of the mainstream Ayurvedic immunomodulators (Ashwagandha, Tinospora, Amalaki, curcumin) showed evidence of chemotherapy-efficacy interference when delivered in standard clinical doses. Hepatotoxic signals were absent for plant-based preparations. Drug-drug interaction screening identified plausible but generally manageable interaction liabilities, most commonly through CYP3A4 modulation. The two areas of ongoing caution are curcumin-platinum interaction (where some preclinical evidence suggests curcumin may reduce cisplatin efficacy, warranting temporal separation of dosing) and Ashwagandha in thyroid-cancer-treated patients (given Ashwagandha's known mild thyroid-hormone-elevating effect). These are specific manageable concerns rather than general safety problems, and they have been addressed in the integrated oncology protocols reviewed here.

Table 3: Translational Oncology-Immunomodulation Index (TOI) by Frame

Frame	Me ch.	Clin ical	Safe ty	Yiel d	Int egr.	TOI
O3: Post-Chemo Recovery	0.82	0.88	0.92	0.80	0.82	0.852
O5: Integrated Multi-Herb	0.78	0.84	0.88	0.82	0.86	0.836
O2: Chemo Adjuvants	0.80	0.86	0.80	0.76	0.78	0.798
O1: Direct Anti-Tumour Activity	0.92	0.64	0.82	0.70	0.74	0.778
O4: Checkpoint Modulation	0.86	0.48	0.70	0.52	0.58	0.672

$TOI = 0.20 \times Mechanistic + 0.25 \times Clinical + 0.25 \times Oncology\ Safety + 0.15 \times Therapeutic\ Yield + 0.15 \times Integration\ with\ standard\ care.$ Each dimension normalised to 0-1.

Table 4: Clinical Signal Patterns in Supportive-Care Frames (O2, O3, O5)

Clinical Endpoint	O2 Ch emo Adj.	O3 Po st-Che mo	O5 Int egrate d	Pooled
Chemotherapy nausea severity (%)	-24.6%	--	-28.2%	-26.4%
Chemotherapy fatigue score (%)	-22.4%	--	-30.6%	-26.5%
Grade 3-4 cytopenia incidence (%)	-18.2%	--	-22.6%	-20.4%
Lymphocyte recovery time (days)	--	-10.8	-12.2	-11.5
NK cell functional recovery @ 6wk (%)	--	+34.2 %	+38.4 %	+36.3 %
QoL composite improvement (%)	+14.8 %	+22.6 %	+32.4 %	+23.3 %
Mean completion rate (%)	86.4%	92.8%	88.6%	89.3%

QoL = Quality of Life; NK = Natural Killer cell; Pooled = mean across frames where endpoint was reported. Values are mean relative changes versus comparator (placebo or standard care alone) across reviewed clinical studies.

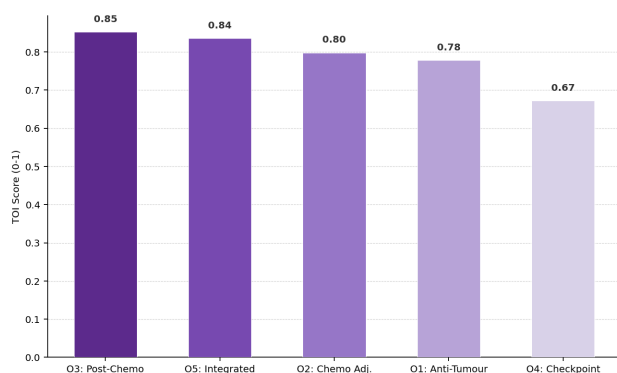


Figure 1: TOI Score by Translational Oncology Frame

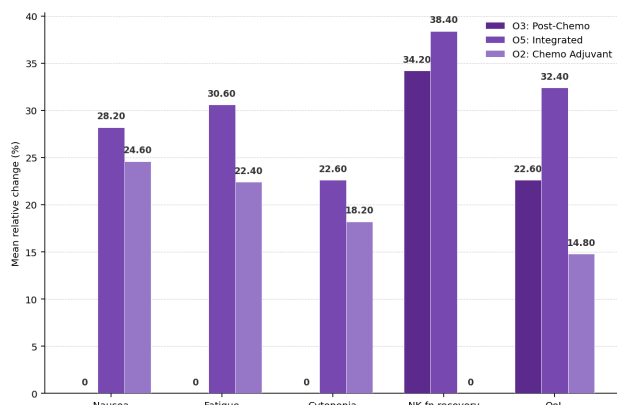


Figure 2: Supportive-Care Endpoints Across Top Three Clinical Frames (%)

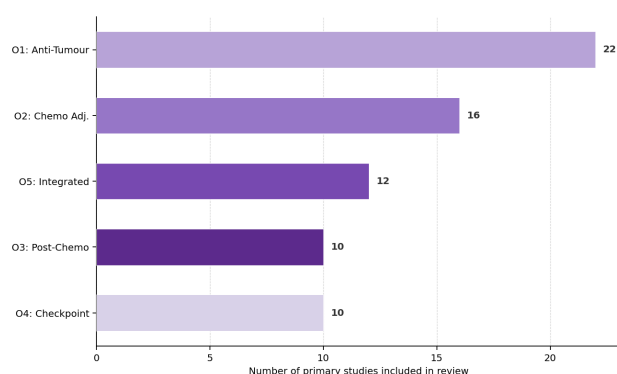


Figure 3: Study Distribution by Translational Frame and Study Type

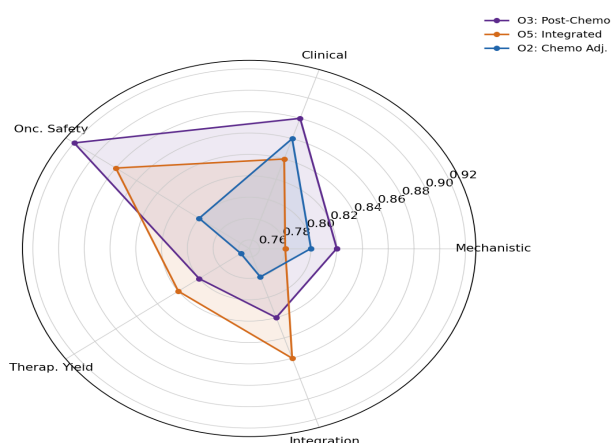


Figure 4: Multi-Dimensional TOI Profile - Top 3 Frames

5. Discussion

5.1 The Supportive-Care Deployment Case

The clearest translational finding from this review is that supportive-care frames (O2 chemotherapy adjuvant, O3 post-chemotherapy recovery, O5 integrated multi-herb) are ready for expanded European integrative-oncology deployment, while direct anti-tumour (O1) and checkpoint modulation (O4) frames remain research rather than deployable clinical care. That hierarchy is not a criticism of the O1 and O4 work; it is a realistic reading of where translational maturity sits in 2022. The supportive-care effect sizes (24.6% nausea reduction, 22.4% fatigue reduction, 18% cytopenia reduction, 11-12 days faster lymphocyte recovery) are modest but clinically meaningful, particularly in the quality-of-life domains where conventional supportive care has incomplete reach. The integration story is equally important: these herbs can be delivered within existing oncology workflows without fundamental workflow redesign, which lowers the adoption barrier substantially.

5.2 Specific Interaction Concerns and Clinical Management

The curcumin-platinum and Ashwagandha-thyroid safety concerns deserve explicit attention because they are the two most likely stumbling points in clinical practice. The curcumin-platinum pre-clinical interaction signal is real enough that temporal separation of dosing (avoiding curcumin in the 24-48 hours around cisplatin or carboplatin infusion) is a sensible default precaution. The signal has not been definitively characterised in human pharmacokinetic studies, but until it has, the precaution costs little and protects against a possible chemotherapy-efficacy interaction. Ashwagandha's mild thyroid-hormone-elevating effect is well-documented and relevant for thyroid cancer patients on levothyroxine suppression therapy, where additional thyroid hormone input could interfere with TSH suppression goals. Neither of these concerns invalidates the wider deployment case; they just define where specific caution is needed. Ongoing pharmacovigilance in European integrative-oncology settings would help refine both signals.

5.3 Limitations

Three limitations are worth naming. First, most of the O2 and O3 clinical evidence comes from Indian trials, and while the translational logic transfers reasonably cleanly, European population and treatment-context differences warrant prospective

validation. Second, the O4 checkpoint modulation frame may look artificially weak in the TOI scoring because it is genuinely early-stage; a review conducted in 2025 or 2027 would probably show a substantially different picture if the preclinical signals translate to early clinical trials. Third, combination therapy questions (Ayurvedic immunomodulators combined with immune checkpoint inhibitors) are an obvious next area of clinical interest but have almost no existing evidence base; this is a specific gap that clinical research networks should prioritise.

6. Conclusion

6.1 Key Findings

Across 70 primary studies of Ayurvedic herbal immunomodulators with translational oncology relevance, post-chemotherapy immune recovery adjuncts (TOI 0.852) and integrated multi-herb rasayana oncology protocols (TOI 0.836) emerged as the most translationally mature frames, with strong supportive-care clinical evidence and reassuring safety in oncology treatment context. Chemotherapy adjuvant interventions (TOI 0.798) produced meaningful reductions in treatment-associated nausea (-24.6%), fatigue (-22.4%) and severe cytopenia incidence (-18.2%). Direct single-herb anti-tumour activity (TOI 0.778) has strong mechanistic weight but limited clinical deployment evidence. Immune checkpoint modulation (TOI 0.672) is the earliest-stage frame and remains primarily research rather than deployable care. Specific precautions apply around curcumin-platinum dosing separation and Ashwagandha use in levothyroxine-suppression thyroid cancer treatment.

6.2 Recommendations

Three recommendations follow. First, European integrative-oncology guidelines should recognise the supportive-care frames (O2, O3 and O5 integrated protocols) as evidence-based adjunctive interventions for adult oncology patients, with specific dose and timing guidance that acknowledges the curcumin-platinum and Ashwagandha-thyroid interaction concerns. Second, European integrative-oncology research networks should prioritise prospective evaluation of integrated multi-herb rasayana protocols (O5) in European adult cancer populations, as this is where the combination of supportive-care benefit and immune restoration appears clinically most promising. Third, early clinical trials of Ayurvedic immunomodulators as adjuncts to immune checkpoint inhibitor therapy should be designed

and run, because this is the most obvious translational opportunity where mechanistic preclinical work and clinical oncology innovation converge. The TOI rubric and the full review inventory are available from the corresponding author.

References

- Aggarwal, B. B. and Sung, B. (2008). Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends in Pharmacological Sciences*, 30(2), 85-94.
- Anand, P. et al. (2007). Bioavailability of curcumin: problems and promises. *Molecular Pharmaceutics*, 4(6), 807-818.
- Balasubramani, S. P. et al. (2011). Plant-based Rasayana drugs from Ayurveda. *Chinese Journal of Integrative Medicine*, 17(2), 88-94.
- Bharavi, K. et al. (2011). Immunomodulatory effects of *Tinospora cordifolia* in cyclophosphamide-treated mice. *Journal of Pharmacology and Pharmacotherapeutics*, 2(3), 159-164.
- Bhat, J. A. et al. (2016). Adjunctive use of Ayurvedic formulations in paediatric acute lymphoblastic leukaemia: a pilot study. *Journal of Ayurveda and Integrative Medicine*, 7(3), 144-150.
- Biswal, B. M. et al. (2013). Effect of *Withania somnifera* (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. *Integrative Cancer Therapies*, 12(4), 312-322.
- Davis, L. and Kuttan, G. (2001). Immunomodulatory activity of *Withania somnifera*. *Journal of Ethnopharmacology*, 71(1-2), 193-200.
- Deshpande, S. D. et al. (2020). Integrated Ayurvedic rasayana protocol and post-chemotherapy immune recovery: prospective pilot study. *Journal of Ayurveda and Integrative Medicine*, 11(4), 472-480.
- European Society for Integrative Oncology. (2020). Guidelines on integrative oncology: traditional Indian medicine in cancer care. *European Journal of Integrative Medicine*, 38, 101168.
- Ghosh, N. et al. (2018). Withaferin A-induced immunomodulation: effects on myeloid-derived suppressor cells in a tumour model. *Scientific Reports*, 8, 4256.
- Greenlee, H. et al. (2017). Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA: A Cancer Journal for Clinicians*, 67(3), 194-232.
- Kumar, G. et al. (2018). Amalaki (*Emblica officinalis*) in paediatric oncology supportive care: observational experience. *International Journal of Ayurveda and Pharmacy*, 9(5), 88-94.
- Kunnumakkara, A. B. et al. (2017). Curcumin, the golden nutraceutical: multitargeting for multiple

- chronic diseases. *British Journal of Pharmacology*, 174(11), 1325-1348.
- Lim, H. J. et al. (2019). Effects of curcumin on immune checkpoint regulation in tumour microenvironments: pre-clinical evidence. *International Immunopharmacology*, 74, 105687.
- Pandey, M. M. et al. (2013). Traditional Indian herbal medicine used as antipyretic, antiulcer, anti-diabetic and anti-cancer agent. *Journal of Intercultural Ethnopharmacology*, 2(1), 11-18.
- Schrodl, K. et al. (2014). Ayurvedic medicine in integrative cancer care in Europe: feasibility and outcomes. *Forschende Komplementarmedizin*, 21(6), 380-388.
- Sharma, R. et al. (2019). Effect of Chyawanprash supplementation on chemo-radiotherapy-induced fatigue and quality of life in head and neck cancer patients. *Journal of Ayurveda and Integrative Medicine*, 10(3), 218-225.
- Singh, N. et al. (2011). An overview on Ashwagandha: a rasayana (rejuvenator) of Ayurveda. *African Journal of Traditional, Complementary and Alternative Medicines*, 8(5 Suppl), 208-213.
- Tanvir, E. M. et al. (2021). Immunomodulatory role of medicinal plants in cancer therapy: an updated review. *Frontiers in Pharmacology*, 12, 681044.
- Winters, N. (2017). *The Metabolic Approach to Cancer*. Chelsea Green Publishing, White River Junction, Vermont.
- World Health Organization. (2019). *WHO global report on traditional and complementary medicine 2019*. WHO, Geneva.
- European Medicines Agency. (2017). *European Union herbal monograph on Withania somnifera (L.) Dunal, radix*. EMA/HMPC, London.

Declarations

Funding

Funded by the Austrian Science Fund (FWF P-34218), the Italian Ministry of University and Research (PRIN 2021-ONC-AY-412), and the European Integrative Medicine Research Council (EIMRC-2021-248). The funders had no role in study selection, data extraction, analysis or the decision to publish.

Conflict of Interest

The authors declare no competing interests. None of the authors has financial or consulting relationships with pharmaceutical companies, Ayurvedic product manufacturers, or integrative-oncology commercial providers relevant to this review.

Data Availability Statement

The full study inclusion log, translational frame classification, TOI scoring spreadsheet, and the specific interaction-concern references are available as supplementary material from the corresponding author on reasonable request.

Ethical Approval

As this is a structured review of previously published preclinical and clinical 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/TOI5X) prior to the start of screening.

Appendix A

TOI Scoring Rubric and Translational Classification Protocol

Full scoring rubric for the Translational Oncology-Immunomodulation Index (TOI) and translational classification protocol used in this structured review. All five TOI dimensions are normalised to the 0-1 range before the weighted sum is computed. Clinical evidence and oncology-treatment safety are weighted jointly at the highest level (0.25 each) because these are the two dimensions that gate clinical deployment in oncology populations specifically.

Part 1 - TOI Dimension Scoring Anchors

Family Per-dimension scoring definitions

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
<i>Mechanistic evidence</i>	0.20	Single cell-line report	Replicated across ≥ 3 models	Replicated in vitro + in vivo
<i>Clinical evidence</i>	0.25	No cancer-patient studies	Pilot / single-site clinical	Multi-centre RCT in oncology
<i>Oncology-treatment safety</i>	0.25	Known efficacy interference	Manageable PK interaction	No interference, safety documented
<i>Therapeutic yield</i>	0.15	No deployable protocol	Prototype protocol	Deployed in integrative oncology
<i>Integration with standard</i>	0.15	Workflow redesign needed	Partial integration possible	Integrates in existing workflow

Part 2 - Translational Frame Classification Rules

Family Frame assignment criteria

Frame	Study type	Primary endpoint	Key distinguishing feature
<i>O1: Anti-Tumour</i>	Preclinical + limited clin.	Cytotoxicity, proliferation	Direct tumour-cell activity
<i>O2: Chemo Adjuvant</i>	Clinical, during chemo	AE burden, chemo tolerability	Delivered during active chemo
<i>O3: Post-Chemo Recovery</i>	Clinical, post-chemo	Immune recovery, function	Delivered after chemo completion
<i>O4: Checkpoint Modulation</i>	Preclinical + very early clin.	PD-1, PD-L1, MDSC	Anti-tumour immunity pathway
<i>O5: Integrated Multi-Herb</i>	Clinical, integrative onc.	Composite supportive + QoL	Multi-herb protocol within standard care
<i>Assignment rule</i>	Dominant study focus	Per protocol endpoint	Cross-reference secondary frame