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A scoping review of Ayurvedic rasayana adaptogens in oncology

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ABSTRACT

Introduction: Rasayanas are Ayurvedic natural products that have adaptogenic effects. The extensive research on rasayanas in oncology is not currently well summarized. The aim of this review is to investigate the range and nature of the current body of research, identify gaps in knowledge, and to summarize the existing literature as it relates to Ayurvedic rasayanas and oncology.

Materials and methods: A comprehensive literature search of fifteen Ayurvedic adaptogen rasayanas was conducted using three main concepts: Ayurvedic herbal terms, neoplasm terms, and oncological pathways. After screening was performed, key variables were extracted (tagged) including type of adaptogen, cancer type, type of study design, constituent type, and mechanisms of action (MOA). The results were synthesized and summarized using descriptive statistics and narrative summaries.

Results: Five hundred and eighty-four articles were reviewed and tagged. The two most tagged adaptogens were *Glycyrrhiza glabra (Yashthimadhu/licorice)* (n = 166 (28.4 %)) and *Withania somnifera* (*Ashwagandha*) (n = 151 (25.9 %)). The most frequently tagged cancer diagnostic categories were gastrointestinal (n = 175 (30 %)), and breast (n = 126 (21 %)). Most of the articles focused on *in vitro* studies (n = 470 (80.3 %)). Of the 12 MOA tags, the most frequently tagged was apoptosis (n = 298 (29.2 %)).

Conclusion: A large body of pre-clinical literature exists on adaptogen rasayanas in oncology, indicating this field of research is still in its early phase. Comparatively few studies focused on the effects on the immune system. Given the growing interest in immuno-oncology therapeutics and the potential impact of adaptogen rasayanas on the immune system, future research may focus more in this area, along with work that is more directly linked to future clinical studies.

1. Introduction

Natural products (NP) have historically played a unique and significant role in traditional and indigenous medicine and continue to be utilized in modern integrative health settings. NPs are naturally derived substances that include medicinal plants, dietary supplements, vitamins, and minerals. NPs are the most popular and commonly used form of integrative health in the US, where nearly $12.8 billion is spent annually on them [1,2]. Though ongoing research focuses on individual NPs and their effects, less is known about the field of research on NPs as a whole.

Adaptogens are a category of NPs that are broadly defined by their ability to aid in the response to stress [3]. Adaptogens are known by three defining characteristics [4]. They increase resistance to stressors. They help the mind and body return to a state of homeostasis. Thirdly, they are non-toxic. At normal doses, adaptogens do not cause harm or adverse effects. Adaptogens have been used for millennia in traditional

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systems of medicine like Ayurvedic Medicine and Traditional Chinese Medicine.

Ayurveda is a whole system of medicine from South Asia rooted in a holistic world-view. In addition to nutrition and lifestyle practices, NPs are a key therapeutic modality in Ayurveda. One important group of Ayurvedic NPs are called rasayanas. Many Ayurvedic rasayanas have therapeutic effects that overlap with adaptogens and, therefore, can also be classified as such. Rasayanas are focused on producing rejuvenating and anti-aging effects. According to the Ayurvedic tradition, NP rasayanas work by enhancing the nourishment of the body tissues (*dhatus*), optimizing digestion and metabolism (*agni*), increasing inner vitality/immunity (*ojas*), and opening the body channels (*srotas*), thereby promoting longevity. Similar to the concept of adaptogens, rasayanas address stress experienced in the mind and body, work to help the mind-body achieve and maintain homeostasis, and can generally be used long-term without toxicity. Differences in the concepts of adaptogens and rasayanas lie mostly in the difference in language used by biomedicine and Ayurveda to describe their effects [5].

The concept of rasayana is appealing for its applications in oncology because the effects of rasayanas match some of the needs of cancer patients. Cancer patients commonly suffer from symptoms like fatigue, sleep disturbance, and problems with emotional health [6–8]. Recovery from cancer treatment and the associated symptoms are a key concern for cancer patients. The rejuvenating properties of rasayanas may produce a favorable effect on cancer recovery. Additionally, immune system functioning is critical in oncology, and evidence suggests that adaptogens and rasayanas may impact favorably on immune functioning [9]. Rasayanas have been shown in pre-clinical studies to have anti-cancer effects of their own [10,11].

There has been a steady increase in the number of research studies investigating rasayanas over the years. However, a lack of scoping reviews and the associated lack of a comprehensive mapping of these studies represents a gap in the literature. Addressing this gap would provide a more comprehensive understanding of the current landscape and guidance for future research in the field. This study will map the existing literature and apply standardized methods and terminology to the field of research on rasayanas. This study aims to examine the extent, range, and nature of research activity; identify gaps in knowledge; and summarize the existing literature as it relates to Ayurvedic adaptogen rasayanas in oncology.

2. Methods

This scoping review followed the framework set out by Arksey and O'Malley [12]. The study consisted of six phases: defining the research question; study identification through searching the current body of literature; selection of relevant studies based on inclusion and exclusion criteria; tagging of studies based on pre-specified tags; collating, summarizing, and reporting results; and consultation with area experts to validate findings. An *a priori* protocol was developed as part of the preliminary steps to help guide the scoping review process. Each step was documented for reproducibility.

2.1. Research question

The research question motivating this review was to characterize the research landscape on Ayurvedic rasayana natural product adaptogens in oncology with the aim of addressing gaps in knowledge and to comprehensively map the existing literature to guide next steps in research.

2.2. Study identification

A health sciences librarian (PT) was consulted to assist in selecting relevant databases, identifying key terms, and building comprehensive searches for the initial literature search. Search terms included both keywords and index terms (Mesh, Emtree) as applicable to the individual databases (see Supplementary Table A1). The searches included three main concepts: Ayurvedic herbal terms, neoplasm terms, and oncological pathways. Searches were conducted with no date limitation. The PRISMA Extension for Scoping Reviews (PRISMA-ScR) was used to guide the process [13].

2.2.1. Electronic resources

The research question and protocol were referenced in developing the electronic search strategy. The search was conducted using the following databases:

1. PubMed
2. Web of Science
3. Cochrane
4. Science Direct
5. Embase

Please see Supplementary Materials for Database Search Strategies.

2.2.2. Data collection and analysis

For data collection, organization, management, and analysis, Endnote and Zotero citation management, Airtable (built-in data collection forms), Box Drive, Google Docs, and Excel were utilized.

2.2.3. Citation management process

Duplicate records were immediately removed through Endnote before the review process. After all abstracts were reviewed and screened for inclusion, the final studies were moved to Airtable for further evaluation.

2.3. Study selection

The studies included met the following criteria: publications completed within the time frame; pre-clinical, clinical, *in vivo*, and *in vitro* studies; pertinence to oncology and oncological pathways; use of adaptogen or constituent of interest. Both inclusion and exclusion criteria were applied to all studies.

Inclusion criteria was pre-determined in the study protocol. The included adaptogens of interest met the following criteria: the adaptogen is classified in Ayurveda as a rasayana, the rasayanas as a group must cover uses for all three doshas (*vata*, *pitta*, and *kapha*), and is readily available. The Ayurvedic tri-dosha concept is at the heart of Ayurvedic theory and practice. The tri-doshas are self-regulatory principles that represent both physiologic processes (*vata* – movement; *pitta* – transformation; and *kapha* – structure) and define pathophysiology in the mind-body. Botanical natural products can be classified according to their effects on *tri-dosha*. Additionally, we used the results of a prior qualitative study in which we interviewed Ayurvedic practitioners to identify rasayanas that they felt were most promising for use in oncology based on their clinical experience [14]. Based on this study, the proposed rasayanas were of greatest interest due to their Ayurvedic properties and potential applications in oncology as well as their current widespread use and availability. In the current study, we focused on single herbs (with the exception of one combination – *triphala*) rather than combinations of herbs. *Triphala* is a core Ayurvedic formulation that is also a combination of three rasayanas that were also included in our review individually (*Amalaki, Haritaki, and Bhibhitaki)*.

The adaptogen rasayanas included in this study were similar to those included in prior work [3]. Adaptogen rasayanas included in this study based on the criteria outlined above were:

1. *Tinospora cordifolia* (*Guduchi*)– AH, Ut.St. 39.44
2. *Phyllanthus emblica* (*Amalaki*)– AH, Ut.St. 39.24–27
3. *Terminalia chebula* (*Haritaki*) –AH, Ut.St. 39.28–32
4. *Terminalia bellirica* (*Bhibhitaki*)–AH, Ut.St. 39.42–43

5. *Asparagus racemosus* (*Shatavari*) –AH, Ut.St. 39.60-6, 157
6. *Sida cordifolia* (*Bala*) –AH, Ut.St. 39.60–61
7. *Tribulus terrestris* (*Gokshura*)–Rajanighantu, Shatahvadi Varga, 43
8. *Ipomoea digitata* (*Vidari*)–AH, Ut.St. 39.60–61
9. *Boerhavia diffusa* (*Punarnava*)–AH, Ut.St. 39.60–61, 155
10. *Glycyrrhiza glabra* (*Yashtimadhu/licorice*)*–AH, Ut.St. 39.44
11. *Aloe vera* (*Kumari*)–Bhavaprakasha Nighantu, Guduchyadi Varga, 116-117
12. *Withania somnifera* (*Ashwagandha*)–AH, Ut.St. 39.60-6, 158
13. *Bacopa monnieri* (*Brahmi*) –AH, Ut.St.39.50–53
14. *Centella asiatica* (*Gotu kola*) –AH, Ut.St. 39.44, 165
15. *Triphala* (a combination of *Amalaki, Haritaki, and Bhibhitaki*)–AH, Su.St. 6.159

(AH – Astanga hridayam, Ut.St.–Uttara Sthanam, Su.St. – Sutra Sthanam)

*During the manuscript tagging process, it was determined that *Glycerrizha glabra, Glycerrizha uralensis, and Glycerrizha inflata* have similar properties and constituents and therefore were merged under the *Glycyrrhiza glabra* (*Yashtimadhu/licorice*) tag.

Publications in the form of case studies, editorials, conference abstracts, gray literature, letters, and peer reviews were excluded. Publications prior to the year 2000 were also excluded. Additionally, manuscripts were excluded if they were not published in English.

2.3.1. Abstract screening

Prior to the abstract screening phase, duplicate manuscripts were removed. The abstract screening phase was informed by the study's protocol and the inclusion criteria. Eligibility was first determined by a one of four investigators (AM, PC, SS, and NK) and was performed twice to ensure accuracy. These reviewers evaluated the title and abstract of each manuscript as a first pass. Each study was added to a "yes," "maybe," or "no" category in EndNote/Zotero. "Maybe" studies were further evaluated through group discussion with the entire study team to determine whether to move the manuscript to the "yes" or "no" category. Any dispute over eligibility was discussed and resolved by the group or the study PI (AD), who is a content expert in Ayurvedic Medicine, Oncology, and Integrative Medicine.

Once this was complete, the "yes" manuscripts were uploaded to Airtable, where designated tags were assigned. Airtable, a cloud interface that provides a collaborative application for database tagging and pattern synthesizing, was chosen to streamline this process.

2.4. Tagging studies

Five investigators (AM, PC, SS, AS, and NK) independently performed formal evaluation of full-text literature for tagging. During the full-text evaluation process, it became clear that some abstracts were not representative of full-text manuscripts and so were deemed irrelevant and removed from the list. During the review process, Airtable was coded with pre-determined tags for labeling. The tags were developed based on the research question being investigated, along with the inclusion and exclusion criteria. Manuscripts were tagged to sort studies by identifiable key words, extract themes and patterns, and allow for quantification of findings.

2.5. Collating, summarizing, and reporting of results

The results were synthesized and presented using descriptive statistics of general characteristics and narrative descriptions. Graphical reporting is shown with structured figures and tables to highlight the most salient patterns. The graphics feature a distribution of studies that focused on cancer categories, rasayana types, and mechanisms of action. The number of manuscripts tagged under each category were quantified, and cross-tabulations were performed.

2.6. Expert validation of results

The findings from the tagging process were discussed with experts (RM and CE), who have expertise in Ayurveda research and practice as well as expertise in conducting scoping reviews. Expert suggestions were discussed and incorporated into the final manuscript.

3. Results

3.1. Search and selection of manuscripts

The initial literature search resulted in a total of 3547 manuscripts (Fig. 1). A second search was performed to include manuscripts that were published since the time of the initial search. This resulted in an additional 441 manuscripts. Of the total manuscripts identified (n = 3988), 1255 manuscripts were found to be duplicates, which were subsequently removed from the total count. After removal of the duplicate manuscripts, the remaining 2733 manuscripts were screened for relevance. Five-hundred eighty-four manuscripts in total met the eligibility criteria and were tagged for further full-text review (Fig. 1).

3.2. General characteristics of included manuscripts

The manuscripts were sorted into 11 major categories for tagging, 5 of which are shown in Table 1. The tagging categories are as follows: cancer type, type of study design, comorbidities, publication year, type of botanicals, type of adaptogen, constituent type, method of administration, period of treatment, mechanisms of action, and ineffective mechanism. "Ineffective mechanism" was tagged if a study investigated a mechanism of action for an adaptogen but the results of the study showed that it was not active on that particular pathway.

Within the final 584 manuscripts, there were 657 tags of various types of cancer, as some studies assessed more than one cancer type. The most frequently tagged cancer category was gastrointestinal (n = 175), which includes pancreatic, colon, colorectal, liver, biliary, and gastric cancer. The second most frequently tagged cancer was breast cancer (n = 126). The third most common type of cancer tagged was gynecological (n = 73), which includes cervical, ovarian, and uterine cancers. When cross-tabulating the cancer type and adaptogen type, it was found that the most common association of these two categories was between the adaptogen *W. somnifera (Ashwagandha)* and breast cancer (n = 35), followed by *G. glabra* (*Yashthimadhu/licorice*) and breast cancer (n = 34).

Manuscripts were categorized by experimental type: *in vivo*, *in vitro*, or clinical. The total number of tags in this category reflect a number that is greater than the total number of manuscripts due to some manuscripts belonging to multiple tagging categories. Of the 584 manuscripts, *in vitro* studies were the most frequently tagged (n = 470) accounting for 80.3 % of the manuscripts tagged, followed by *in vivo* studies (n = 192) accounting for 32.9 % of the manuscripts tagged. Lastly, clinical studies accounted for the least number of tags (n = 17), or 2.9 % of all manuscripts tagged. The study of adaptogen rasayanas is currently at varying levels. A map of the top five, most studied adaptogens and the number of manuscripts for each experimental category are shown in Fig. 2.

The methods of administration investigated through *in vivo* studies include the following routes–oral, topical, or injection. The most frequent method of administration was oral (n = 58), which consisted of 41.1 % of tags. The next most frequent method of administration was injection (n = 51), which consisted of 31.9 % of tags, The least frequent method of administration was topical (n = 17), which consisted of 2.9 % of tags. The last method of administration category was unknown method of administration (n = 21), with 3.6 % of tags. Of the 584 manuscripts, 49 manuscripts studied the adaptogen in different settings. Of the 49 manuscripts, n = 39 (80.0 %) involved rasayanas being administered concomitantly with radiation and n = 10 (20.0 %), whereby the rasayanas were administered prior to either inducing

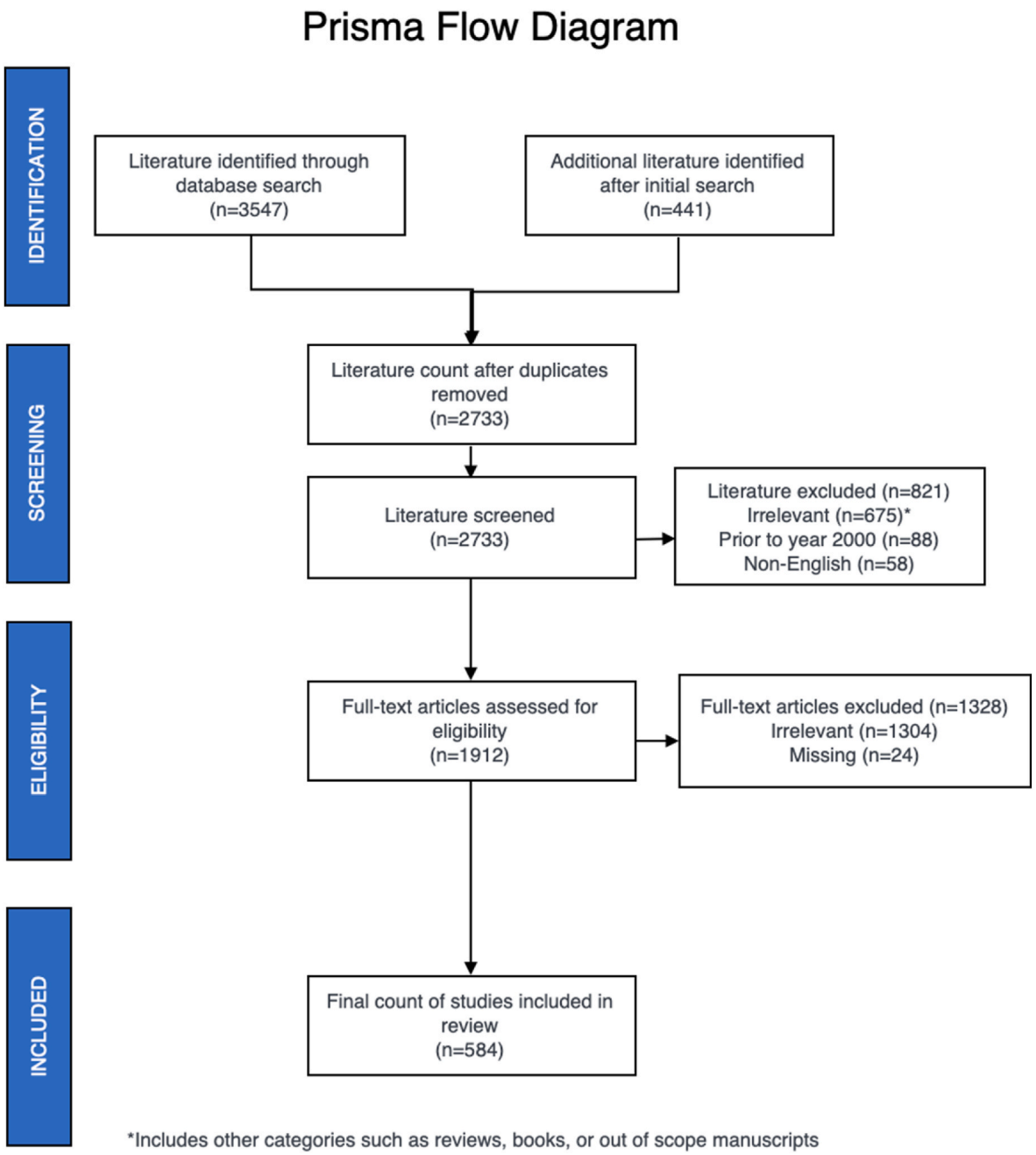

Fig. 1. Prisma Flow Diagram
*Missing (n = 24) indicates abstracts that were included in the initial screening process, but the associated manuscript could not be found for further eligibility screening.

carcinogenesis or undergoing chemotherapy or radiation in animal studies.

Manuscripts were also tagged to identify the form in which botanicals were administered in each study, either as a whole-plant formulation or as a constituent of the botanical. Of the 584 tagged manuscripts, n = 219 examined the whole plant, n = 348 examined a single constituent, and n = 17 examined both.

Of the adaptogens tagged, *G. glabra* (*Yashtimadhu/licorice*) was the most frequently tagged adaptogen (n = 166), accounting for 27.9 % of total manuscripts. *W. somnifera* (*Ashwagandha*) was the second most frequently tagged adaptogen (n = 151) in the literature search, consisting of 25.8 % of the total manuscripts. *A. vera* (*Kumari*) was the third most frequently tagged adaptogen (n = 79), appearing in 13.5 % of the total manuscripts. Of the 151 manuscripts that tagged *W. somnifera* (*Ashwagandha*), 110 manuscripts investigated a specific constituent, Withaferin A. In general, Withaferin A was the most tagged constituent. Of the 166 manuscripts tagged under *G. glabra* (*Yashthimadhu/licorice*), 114 of these manuscripts investigated a specific constituent of this adaptogen. Isoliquiritigenin (from *licorice*) was the second most studied constituent in the literature search (n = 57), followed by Asiatic acid (from *Centella asiatica)* (n = 27), then glycyrrhetinic acid (from *licorice*) (n = 24). Of the 79 manuscripts tagged with *A. Vera* (*Kumari*), 23 investigated a specific constituent, aloe emodin, making it the fifth of the top five most investigated constituents.

Additionally, 40 manuscripts investigated whether adaptogen rasayanas could enhance the effects or reduce the toxic effects of cancer treatment – either with chemotherapy or radiation therapy. Of the 40 manuscripts tagged, the most common chemotherapy drug utilized was

Table 1
General characteristics of included studies.

Characteristics	Number (N = 584)	Percentage (%)
Cancer type		
GI[a]	175	29.9 %
Breast	126	21.4 %
Gyn[b]	73	12.5 %
Thoracic	69	11.8 %
GU[c]	57	9.8 %
Hematologic[d]	49	8.4 %
Skin	39	6.7 %
Sarcoma	27	4.6 %
Brain	25	4.2 %
Head and Neck[e]	19	3.3 %
Endocrine System[f]	3	0.5 %
Type of study design		
In vitro	470	80.3 %
In vivo	192	32.9 %
Clinical	17	2.9 %
Clinical Context		
Adjuvant to/reducing side effects of radiation	16	2.7 %
Adjuvant to/reducing side effects of chemotherapy	14	2.4 %
Publication year		
2000–2005	43	10.0 %
2006–2010	86	17.9 %
2011–2015	194	39.9 %
2016-present	262	52.6 %
Type of botanicals		
Whole plant	219	37.5 %
Constituent	348	59.6 %
Combinations[g]	17	2.9 %

[a] GI includes pancreatic, colon, colorectal, liver, biliary, and gastric cancer.
[b] Gyn includes cervical, ovarian, uterine cancer.
[c] GU includes prostate, bladder, renal and kidney cancer.
[d] Hematologic includes leukemia, lymphoma.
[e] Head and Neck includes oral, eye, and nasopharyngeal cancer.
[f] Endocrine includes pituitary and adrenal cancer.
[g] Combinations indicates mixtures of phyto-molecular constituents from adaptogen rasayanas. For example, withaferins from Ashwagandha.

cisplatin (n = 5), which made up 12.5 % of the 40 manuscripts. The next highest were doxorubicin (n = 3) and cyclophosphamide (n = 3), each consisting of 7.5 % of the 40 tagged manuscripts. Additionally, fluorouracil (n = 2) and sorafenib (n = 2) each accounted for 5 % of the chemotherapy drug count. Lastly, it should also be noted that a number of manuscripts dealt with radiation alone (n = 22), accounting for 55.0 % of the 40 manuscripts.

Though most of manuscripts were tagged with effective mechanisms of action, some manuscripts demonstrated ineffective mechanisms of action (n = 44, 7.5 %). Eleven manuscripts were tagged with apoptosis being an ineffective mechanism of action and 11 more manuscripts were tagged with anti-oxidant being an ineffective mechanism of action. The third highest category tagged with an ineffective mechanism of action was anti-proliferative/anti-growth.

The mechanisms of action (MOA) investigated in the literature across all 15 rasayanas were (in order of most frequently tagged in total to least): apoptotic (n = 298,29.2 %), anti-proliferative/anti-growth (n = 249, 24.5 %), antioxidant (n = 167, 16.4 %), anti-metastatic/anti-invasive (n = 68, 6.8 %), anti-inflammatory (n = 47, 4.6 %), DNA/RNA degeneration (n = 41, 4.0 %), anti-angiogenic (n = 36, 3.5 %), cell-cycle arrest (n = 32, 3.1 %), anticarcinogenic/anti-metastatic (n = 26, 2.6 %), and immunomodulatory (n = 24, 2.4 %).

3.3. Adaptogen type versus mechanisms of action

In Fig. 3, the top five adaptogens and oncologic mechanisms of action (MOA) are represented as a bubble plot. The values in the chart do not represent discrete numbers of studies, but rather the number of times, or instances, certain mechanisms of action appeared (tagged) across all manuscripts. There are a total of 739 instances illustrated in the plot. The plot excludes studies related to symptom management where there was no mention of MOA.

The three most common MOA among the top 5 adaptogens were apoptotic (n = 236, 31.9 %%), anti-proliferative/anti-growth (n = 204, 27.6 %), and anti-oxidant (n = 119, 16.1 %), respectively. The least common MOA among the top 5 adaptogens were anti-carcinogenic/anti-mutagenic (n = 16, 2.2.4 %), immunomodulatory (n = 14, 1.9 %), and DNA/RNA degeneration (n = 26, 3.5 %). The two most commonly studied adaptogens in this tagging study were *G. glabra* (*Yashthimadhu/licorice*) (n = 260, 35.1 %) and *W. somnifera (Ashwagandha)* (n = 151, 28.3 %) respectively. The three most common combinations of adaptogens and MOA are *G. glabra (Yashthimadhu/licorice*) and apoptotic (n = 89, 12.0 %), *G. glabra* (*Yashthimadhu/licorice*) and anti-proliferative/anti-growth (n = 85, 11.7 %), and *W. somnifera* (*Ashwagandha*) and apoptotic (n = 87, 9.2 %). Immunomodulatory mechanisms is a key effect of adaptogens, but consisted of only 1.9 % of tags (n = 14). Results from the bubble plot indicate the most studied MOA were apoptotic and anti-proliferative/anti-growth mechanism, each studied most with *G. glabra* (*Yashthimadhu/licorice*) and *W. somnifera* (*Ashwagandha*).

Table 2 shows contrasting Ayurvedic and pharmacologic MOA. The four most common MOAs are shown. Overall, few areas of overlap are seen between Ayurvedic and pharmacologic MOAs.

4. Discussion

This scoping review maps the current body of literature on the use of Ayurvedic rasayana adaptogens, as it pertains to oncology. This is the first scoping review on this topic. There are several implications from this study.

G. glabra (*Yashthimadhu/licorice*) and *W. somnifera* (*Ashwagandha*) were the most commonly studied adaptogens in our scoping review. For *G. glabra* (*Yashthimadhu/licorice*), the most common mechanisms of action studied were apoptosis (n = 89), followed by anti-proliferative/anti-growth. *Glycyrrhiza glabra* (*Yashthimadhu/licorice*) is thought to have anti-inflammatory effects via a proposed mechanism of reduced activation of NFkB [15]. *G. glabra* (*Yashthimadhu/licorice*) has demonstrated apoptotic effects by influencing the mTOR pathway via proposed Bcl-2 phosphorylation and downregulation [16]. For *W. somnifera* (*Ashwagandha*) the most common mechanisms of action studied were apoptosis (n = 87), followed by antiproliferative/antigrowth (n = 63), and anti-oxidant (n = 39). To elicit its apoptotic effects, *W. somnifera* (*Ashwagandha*) was found to inhibit the NFkB pathway. These results suggest that there is a correlation between biomarkers related to particular apoptotic pathways and *W. somnifera* (*Ashwagandha*) administration, including BCL-2 downregulation, Bax upregulation, and caspase regulation (specifically caspase-3 and caspase-9 cleavage) indicating this adaptogen may affect cancer cells via apoptosis. Based on the data, *W. somnifera* (*Ashwagandha*) and *G. glabra* (*Yashthimadhu/licorice*) are promising for further study, including in combination.

From an Ayurvedic perspective, *Ashwagandha* and *Yashthimadhu* have overlapping and unique qualities and effects (Table 2). *W. somnifera* (*Ashwagandha*) balances *vata* and *kapha*. Its primary actions are to increase strength and vitality. Additionally, it works on the mind to instill a calming effect, strengthens the reproductive system, and is said to improve pain symptoms and improve energy. *G. gladbra (Yashthimadhu/licorice)*, which is *vata* and *pitta* balancing, has similar effects according to Ayurveda. It also improves strength, vitality, and reproductive function. The overlapping (supporting strength and vitality) and contrasting (balancing different dosha profiles) Ayurvedic

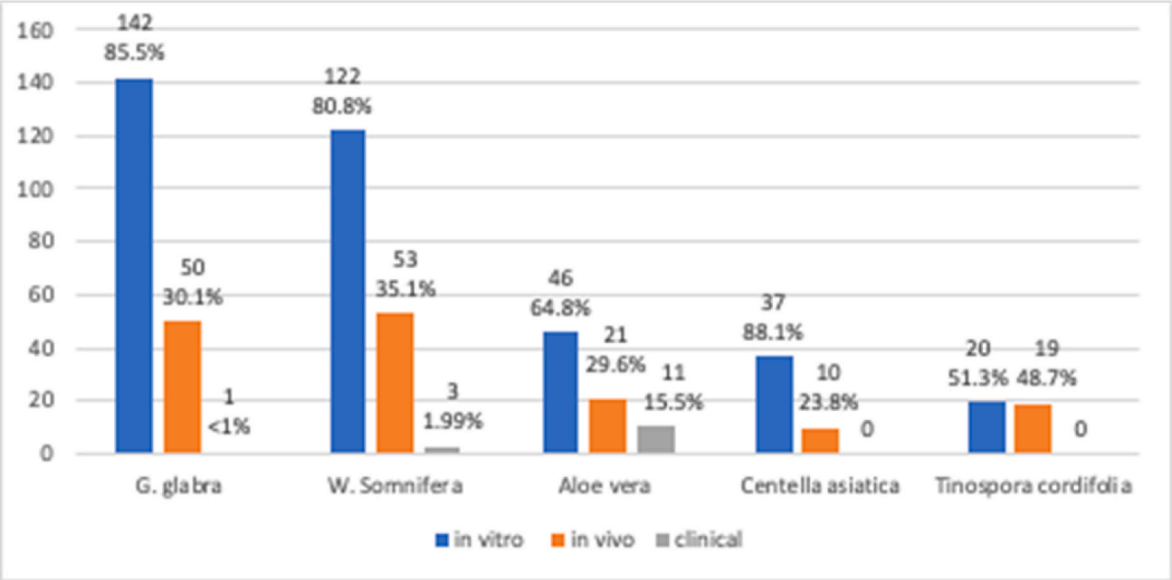

Fig. 2. Map of Most Studied Adaptogens From *In vitro* to Clinical
*Several studies involved more than one category

effects of *Ashwagandha* and *Yashthimadhu* suggest that they may complement each other. These Ayurvedic effects for *Ashwagandha* and *Yashthimadhu* - are interesting when juxtaposed with the biomedical effects described above. One area of overlap is in terms of immune function. Both Ayurveda and biomedicine suggest that these natural products improve immune function. In this way, traditional/indigenous and biomedical knowledge overlap, and represent an area for future research.

The mechanisms of action (MOA) that was most frequently tagged was apoptotic, followed by anti-proliferative/anti-growth then antioxidant in descending order. Cancer cells manipulate the apoptotic pathway and its inhibition through various mechanisms including overexpressing antiapoptotic proteins and under expressing proapoptotic proteins [17]. Thus, activation of the apoptotic pathway is one therapeutic approach that has potential in the treatment of cancer and is exemplified by specific plant compounds. Notably, a majority of the apoptosis mechanisms that were found in the literature were in association with *G. glabra* (*Yashthimadhu/licorice*). Recent *in vitro* research on *licorice* root extract highlighted its effects on apoptosis and cell cycle arrest [18].

Anti-carcinogenic/anti-mutagenic, immunomodulatory, and anti-inflammatory were the least commonly tagged MOA categories. Adaptogens are believed to act by providing an immunomodulatory effect [5, 9]. In one study, *G. glabra* (*Yashthimadhu/licorice*) had immunomodulatory activity by suppressing tumor growth and improving the health of mice as well as increasing antitumor cytokines (IL2, IL6, and IL7) and decreasing pro-tumor cytokine TNFalpha [19]. The unique ability of adaptogens to modulate the immune system is an area that merits additional research. This additional work is further justified by the growing importance of immunotherapy in oncology. Future research questions include not only whether adaptogen rasayanas can modulate the immune system in cancer patients but also whether rasayanas can be used in combination with immunotherapy.

Contrasting Ayurvedic and pharmacologic MOA (Table 2) on the surface showed little overlap. The unique language of the two systems of medicine – Ayurveda and biomedicine – may explain this apparent lack of coherence. However, adaptogen rasayanas showing apoptotic and anti-proliferative effects on cancer cells is consistent with the primary function of adaptogen rasayanas to return biological systems to homeostasis and balance. In this way, the Ayurvedic and biomedical views are aligned. Anti-oxidant pharmacologic MOAs may be explanatory for Ayurvedic effects – such as the longevity promoting effects of rasayanas. Oxidative stress plays a role in aging and the development of age-related illnesses [20]. Anti-oxidant rasayanas may offset some of these effects thereby potentially contributing to healthy aging and longevity. Further study of adaptogen rasayanas in this setting is therefore of interest.

Gastrointestinal (GI) cancer was the most studied cancer category in the scoping review (n = 175; 29.9 %). From the GI cancer category, liver cancer was the most tagged sub-category (n = 78), followed by colon cancer (n = 47). This finding may reflect the increasing global burden of GI cancers and of specific GI cancers, such as liver cancer, in Asia [21, 22]. Of the manuscripts from this cancer category, the majority were *in vitro* studies, which matched general trends in our dataset. Similarly, the top two adaptogens tagged within GI cancers were *G. glabra* (*Yashthimadhu/licorice*) and *W. somnifera (Ashwagandha*), and the key mechanisms tagged for the GI cancer category were apoptosis (n = 89) and anti-proliferative/anti-growth (n = 74).

Preclinical research currently dominates the field of adaptogen rasayana research, which reflects broader trends in the field of natural products research. The high number of *in vitro* (80.3 %) and *in vivo (*32.9 %) studies found in this scoping review, along with few clinical studies (2.9 %), reflects the nascent stage of this field of research (see Fig. 2). This finding was echoed in a recent article referring to the challenges in translating natural product pre-clinical research into clinical trial outcomes [23]. These challenges are due in part to the high cost and rigorous planning required to conduct clinical trials. The influence of the drug development model for pharmacologics – where drugs are tested in phase I, II, and III trials – likely colors the process for natural products. Natural products require unique considerations in their clinical development due to their unique characteristics [24]. Further discussion is needed to determine best practices for appropriately moving promising natural products into the clinical trial arena. Additionally, the extensive pre-clinical research that exists on these rasayana adaptogens can be used to guide translational studies of mechanisms and biological signatures.

The large number of pre-clinical studies on adaptogen rasayanas may also be due to the significant interest in identifying single molecules from the plant world that can be developed as pharmacologics. Though this effort in the past has led to the development of a number of prominent drugs, caution should be raised relating to bioprospecting practices and the biopiracy of natural products [25]. This complex issue relates to who benefits from biological resources and indigenous

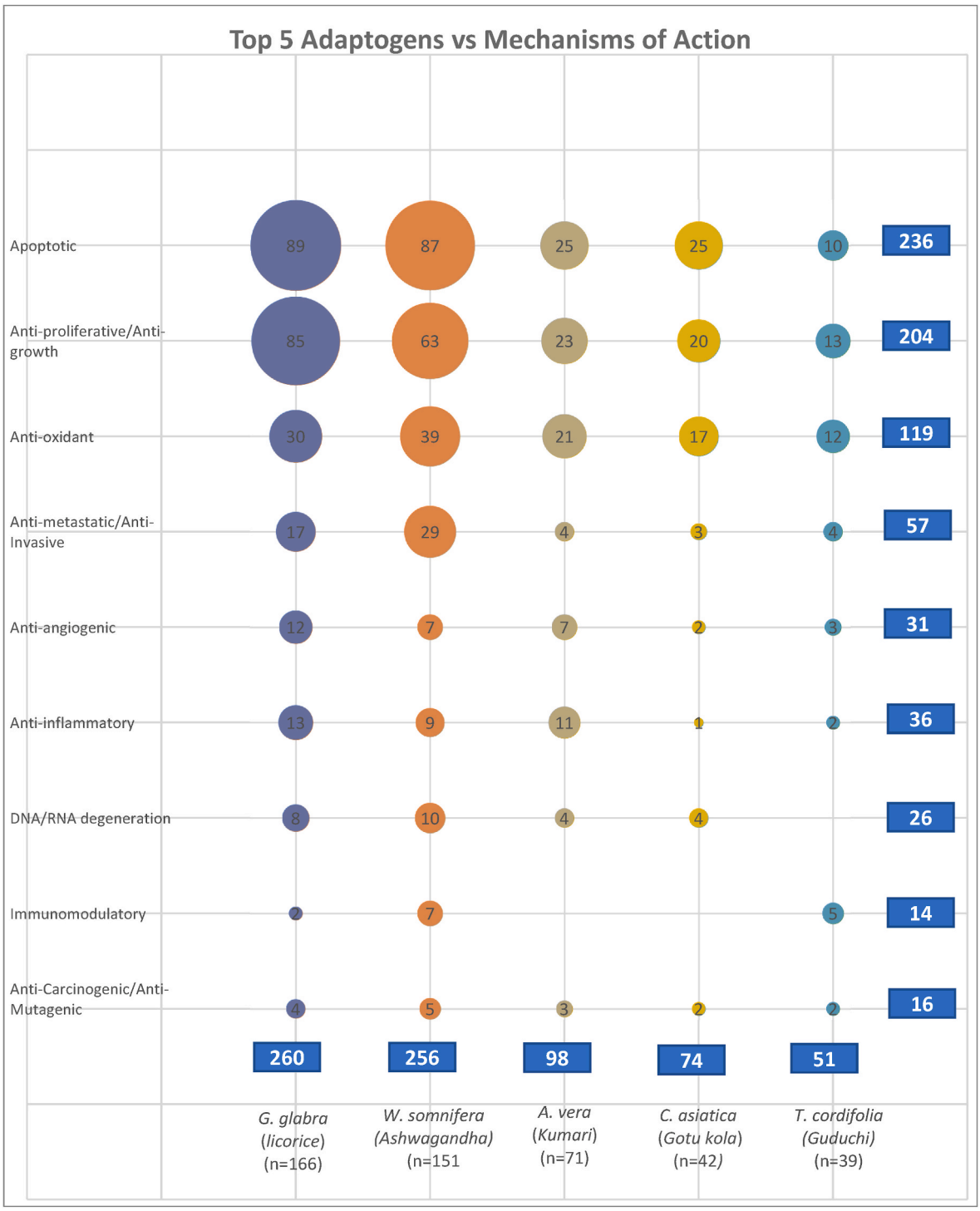

Fig. 3. Top 5 Adaptogen types and mechanisms of action.

knowledge of plant medicines when those plant medicines form the basis of lucrative pharmaceutical industry products.

Of the 17 clinical studies, 15 investigated adaptogen rasayanas administered concurrently with chemotherapy and radiation. For example, several investigated *A. vera* (*Kumari*) topically to mitigate the skin toxicity of radiation (n = 11). Among the studies that investigated adaptogen rasyanas concurrent with chemotherapy, most demonstrated that the adaptogen rasayanas either improved the effects of the drug or counteracted negative side effects induced by the drug [26–29]. One study showed that the adaptogen rasayana, *Triphala*, was able to act as a tumor proliferation suppressant where the chemotherapy agent 5-Fluorouracil could not [30]. These findings support the further investigation of adaptogen rasayanas to mitigate cancer treatment side effects. In addition, future research should investigate the effects of adaptogen rasayanas concurrent with chemotherapy to test if there is additive or synergistic anti-cancer effects, along with mitigation of side effects of chemotherapy.

There were a few limitations to this study. We focused our review predominantly on single herb adaptogen rasayanas from the Ayurvedic pharmacopeia, except for the herbal combination *Triphala*. By necessity, we also had to narrow our scope in terms of the number of adaptogen rasayanas that we included. However, we used clear and consistent

Table 2
Contrasting ayurvedic and pharmacologic actions

Rasayana	Ayurvedic Actions	Pharmacologic Mechanisms of Action[a]
Yashtimadhu	*Yashtimadhu* is sweet with a bitter aftertaste and cool in potency. It is an eye and hair tonic. It pacifies pitta and vata, and is useful in management of cardiac ailments, hoarseness of voice, recovery from inflammation and wounds.	Apoptotic Anti-proliferative/Anti-growth Anti-oxidant Anti-metastatic/Anti-invasive
Ashwagandha	*Ashwagandha* is astringent and bitter, hot in potency, and pacifies Vata and Kapha. It is alexipharmic, helpful in management of emaciation, and enhances complexion, potency and strength. It is helpful in management of inflammation and is a reproductive tonic.	Apoptotic Anti-proliferative/Anti-growth Anti-oxidant Anti-metastatic/Anti-invasive
Kumari	*Kumari* is cool in potency, bitter in taste and pacifies Kapha and Pitta. It is alexipharmic, pacifies cough, dyspnea, skin diseases, burns, and wounds. It is helpful in the management of menstrual disorders and liver diseases.	Apoptotic Anti-proliferative/Anti-growth Anti-oxidant Anti-inflammatory
Gotu Kola	*Mandukaparni* is astringent, sweet, cooling in potency, laxative, and light to digest. It enhances higher mental functions and memory. It improves voice and is helpful in management of skin diseases, diabetes, cough, poisoning, inflammation, and fever.	Apoptotic Anti-proliferative/Anti-growth Anti-oxidant DNA/RNA Degeneration
Guduchi	*Guduchi* is bitter, astringent and hot in potency. It is heavy to digest and pacifies all the three Doshas. It is helpful in management of fevers, anemia, rheumatoid arthritis, vomiting, diabetes, and skin diseases	Apoptotic Anti-proliferative/Anti-growth Anti-oxidant Immunomodulatory

References:
Yashtimadhu (*Glycyrrhiza glabra* – licorice): Bhavaprakasha Nighantu, Haritakyadi Varga, 128–129; Raja Nighantu, Pippalyadi Varga, 144-145.
Ashwagandha (*Withania somnifera*): Dhanvanthri Nighantu, Guduchyadi Varga, 302–303, Madanapala Nighantu, Abhayadi Varga, 173-174.
Kumari (*Aloe vera*): Rajanighantu, Parpatadi Varga, 47–49, Bhavaprakasha Nighantu, Guduchyadi Varga, 196-197.
Gotu Kola (*Centella asiatica)*: Bhavaprakasha Nighantu, Guduchyadi Varga, 236-237.
Guduchi (*Tinospora cordifolia)*: Dhanvanthri Nighantu, Guduchyadi Varga, 5-7.
[a] Top 4 pharmacologic actions are listed.

criteria to determine which adaptogen rasayanas were included in the study (see Methods Section). Lastly, the quality of the studies included was not assessed as this was beyond the scope of this review.

5. Conclusion

The goal of this study was to investigate the role of adaptogen rasayanas within the field of oncology. A vast majority of the literature focuses on pre-clinical studies reflecting that this area of study is still currently in its beginning phase. *W. somnifera* (*Ashwagandha*) and *G. glabra* (*Yashthimadhu/licorice*) had the largest body of evidence. Suggestions for future research include systematic reviews of both *ashwagandha* and *licorice* in the oncology setting, with the goal of evaluating quality of evidence, to inform the development of early phase clinical trials. Adaptogen rasayanas appear to target important oncologic pathways and have favorable impacts on the immune system. The results of this study lays the groundwork for future research on Ayurvedic adaptogen rasayanas in oncology, especially in these areas.

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Declaration of generative AI in scientific writing

There was no use of AI or AI-assisted technology in the writing of this manuscript.

CRediT authorship contribution statement

Cairn Wu: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Ashley Mulakaluri:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Project administration. **Pranay Chaurasia:** Formal analysis, Investigation, Data curation, Writing – original draft. **Sindhu Suryanarayana:** Software, Formal analysis, Investigation, Data curation, Writing – original draft. **Ambreen Singh:** Formal analysis, Investigation, Data curation, Writing – original draft. **Nicole Krauss:** Formal analysis, Investigation, Data curation, Writing – original draft. **Peggy Tahir:** Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Charles Elder:** Validation, Formal analysis, Writing – review & editing. **Rammanohar Puthiyedath:** Validation, Formal analysis, Writing – review & editing. **Anand Dhruva:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

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

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