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Ayurveda & Bioactives as Adjuvant for Dna Modulation in Cancer Treatment & Adverse Drug Reaction [ADR] – A Glimpse of Traditional Indian Nanotechnology

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Bioactives such as Curcumin and Quercetin and herbs such as “Tulsi”/ Holy basil [*Ocimum sanctum* L.] can provide relief from Adverse drug reaction [ADR] caused by chemotherapy in cancer patients. About 50% patients face moderate ADR issues such as nausea, vomiting, headache, and fewer [20-30%] serious ones [hair loss, loss of fertility and immunity]. The growing recurrence or resistance of cancers to chemotherapy and antimicrobial resistance [AMR] are other emerging challenges in addressing the global cancer burden, among the top causes of death. Two targets of herbal/ bioactive actions include topoisomerase that affects cell replication and telomere length and it may reduce resistance/ recurrence also. Patients with special conditions the old, children and less developed countries with low health budgets can especially develop from it.

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Keyword: Herbs, bioactives, topoisomerase, telomerase, neoplasm, resistance.

Introduction

Cancer is the 2nd leading cause of death in the world causing 10 million i.e. 16% of global deaths in 2018 vide World health Organisation data. ^[1] There were 2 times as many new cases reported in 2022.^[2] About 1 in 5 people develop cancer in their lifetime, approximately 1 in 9 men and 1 in 12 women die from the disease, the study says.

Low and middle income countries like India have much less cancer burden [below 100 in 100,000 population i.e. below 0.1% while it is 2.5-3 times or more in highly developed nations in Europe & America [>250 per 100,000] vide latest WHO statistics. [3] The main cancer types by frequency of occurrence and contribution to death are as below:

Table 1. Main cancer types prevalence & mortality in India & the world

	India [4]		World [1]	
	Rank	% Incidence	Rank	% Incidence
1. Breast	2	10.5	2	11.6
2. Lung	1	10.6	1	12.4
3. Colorectal			3	9.6
4. Prostate			4	7.3
5. Stomach	5	5.2	5	4.9
6. Oral	4	5.7		
7. Oesophagus	3	5.8		

The new estimates available on IARC's Global Cancer Observatory above show that 10 types of cancer collectively comprised around 2/3rd of new cases and deaths globally in 2022. Data covers 185 countries and 36 cancers.[2]

Cancer prevalence are low among many poor/ middle income nations in Africa & Asia as per that map and developed world needs to explore its causes and best practices to follow. Better diet, in terms of natural, home cooked, fresh food, rich in spices such as Turmeric could be an important driver behind low cancer levels in India. [4][5][6]

Cancer was rare in the 20th century to occur few hundred or thousand cases annually in a city but is common today that it is common among every lane in cities. In fact, its is 3 most leading cause of deaths in India among non-communicable diseases with 8% of all deaths, after cardiovascular [28%] and respiratory diseases [10%], among the non-communicable diseases that together comprised 61% of all deaths in 2016 in India. [4] There are limitations of various cancer treatment prevalent regimes so search for new drugs is ongoing continually, including immunotherapy recently that has new promises as well as new problems despite the initial hope that it will avoid majority of the adverse drug reactions [ADR] caused by chemotherapy, the dominant treatment type.[5] Hence, search for safer medicines with lesser ADR is also continuing, including Botanicals. [6]

Complete cancer cure by Ayurveda medicine alone was a recent news and scientific publication[7]. It was a case of 51-year-old female patient, diagnosed with high-grade non Hodgkin lymphoma of type "Diffuse large B-cell lymphoma" [DLBCL] confirmed by PET-CT scan. She was started with Rasayana [special chemicals, vide Ayurvedic literature, for body rejuvenation/ anti-ageing] regimen.

Significant clinical improvement and regression in tumor size in this patient after treatment as will be discussed later. This, along with few other cases mentioned further triggered this article to explore the value of Ayurveda, the prevalent

traditional medicinal system in India for millennia, in the context of modern science.

The purpose of this article, a mini review, is to:

- a. Enlist top priority ayurvedic herbs & their bioactive ingredients in treating cancer,
- b. Mention briefly the pharmacological action of these herbs/ their ingredients in modulating cancer physiology,
- c. Highlight literature evidence regarding efficacy and safety of these herbs briefly.

Methodology

We enlist a few cases we have directly observed in the past decade with Ayurveda either solely or in combination with modern treatment [mostly chemotherapy]. We then enlist the major medicinal plants i.e. herbs used in these treatments and their bioactive ingredients from literature. We enlist their pharmacological actions as corroborative evidence of potential utility in cancer treatment. Finally, we mention some literature evidences regarding the safety of using these herbs and metal ash/ oxides in cancer treatment.

Cases Observed

Besides the above case have observed the following cases treated with Ayurveda along or with Chemotherapy.

Table 2. Cancer patients personally witnessed with treatment & outcome

PLACE	YEAR	SEX	AGE	CONDITION & STAGE	PHYSICIAN	THERAPY	RESULT
1. Gorakhpur	2,000	M	65	Colon- I	Clinic	Ayurveda	Lived 10 years, deceased
2. Pune	2,000	M	30	Lymphoma- II	Late Dr. Vilas Nanal	Integrated	Healthy, no recurrence yet
3. Pune	2,005	F	65	Colon- II		Integrated	Living 25 years
4. Bangalore	2018	M	60	Prostate- III	IAIM ^(a)	Ayurveda	Lived 6 months extra, deceased
5. Durg	2018	F		Myloma- III	Jiva Ayurveda co. ^(b)	Integrated	Lived 3 years extra, deceased
6. Nagpur	2020	F	60	Colon- II	GVAK ^(c)	Ayurveda	Healthy
7. Pune	2021	M	81	Pancrease- II ^(d)	Dr. Narendra Pendse	Ayurveda	Lived 6 months extra, deceased

(a) *Institute of Ayurveda & Integrative Medicine, Bangalore.*

(b) <https://ayurveda.jiva.com>

(c) *Cow urine therapy by GVAK- Go-Vigyan Anusandhan Kendra (Cow Science Research Centre), Nagpur.*
[\[https://govigyan.com/en/\].](https://govigyan.com/en/)

(d) *developed into ascites later, had mild COVID-19 fever & recovered at home few months before death.*

Chemotherapy was stopped by relatives after 3 and 6 cycles as the 3^d and 5th patient could not sustain the severe ADR. Patient no. 7 had mild COVID-19 fever & recovered at home 5 months before death.

Among the 4 Ayurveda only treated patients mentioned above, 3 are deceased of which 1 had -6 months longer life than estimated by modern physicians, another 3 years, the 1st lived 10 years since cure while 1 while 1 [cow urine] got completely cured and is healthy since the last 4 years. So the success rate appears to be 50% in these 4 and its 60% if the 1st case quoted at start is added. Notably, none suffered many ADR such as nausea, vomiting, headache, stomach ache, weight loss, hair loss, black circles around eyes, burning sensation of lips etc.

Of the 3 integrated medication patients [Ayurveda and Chemotherapy together], 1 is healthy after 25 years, another is healthy since 15 years, while 1 survived for only 3 years, indicating 70% success rate.

The medication provided in the above DLBCL case comprised mainly of the following ingredients- [a] Hirak [diamond], Suvarna [Gold], Ropya [Silver], Tamra [Copper], Loha [Iron], [b] Praval [coral] [c] Kamdudha [Calcium carbonate, Conch, iron oxide] [d] Surshekhar [Black Pepper- *Piper nigrum* L.], Ginger [*Zingiber officinalis* Roscoe], Cardamom [iL.], Yashtimadhu [Licorice- *Glycyrrhiza glabra* L.].

Some other herbs/ bioinputs commonly used in the Ayurvedic cancer medicines are depicted in table 3 with their bioactive ingredients and mechanism of action.

Table 3. Common Ayurvedic herbs/ bioinputs with bioactive ingredients and mechanism of action

HERB & BIOACTIVES	MECHANISM OF ACTION
Amla [as described below]- Ascorbic acid	increase in telomerase activity with no change in telomere length in peripheral blood mononuclear cells ^{[8](a)}
Ashwagandha {Indian Ginseng, <i>Withania somnifera</i> [L.] Dunn.- WS}- <i>Withanolides</i> ^(b)	Prevented leukopenia and neutropenia & PTX-induced myelo-suppression induced by PTX in BALB/c mice, promoted TNF- α , IL-2 and IL-3, maintained homeostasis, WS reduced the MIP-1 α expression ^[6] , enhance telomerase activity ~45% ^[8]
Neer Bramhi [<i>Bacopa monieri</i> [L.] Wettst.- Bacoside	scavenging superoxide anion and hydroxyl radicals and in reducing H ₂ O ₂ -induced cytotoxicity and DNA damage in human fibroblast cell ^[8]
Cow urine- Free fatty acid, Peptide	reduction in tumor burden and number of papillomas & Anticancer effect with <i>Taxus buccata</i> in mice ^[9] purification of toxic herbal and mineral drugs ^[10] , Apoptosis ^[11] , toxicity of peptides against nucleated cancer cells but protecting RBCs from lysis ^[12]
Giloy {Heart leaved moonseed, <i>Tinospora cordifolia</i> [Willd.] Miers}- Tinosporine, Berberin	DNA protective ability on genotoxicity in lymphocytes in mice ^[8] , activation of macrophages ^[13] , downregulation of anaphase-promoting complex [APC] & Bone morphogenetic proteins [BMPs] ^[14] , apoptosis of oral cancer cell line AW13516 ^[15]
Ginger [<i>Zingiber officinalis</i> Roscoe]- Gingerol, Shgaol	Apoptosis, arrests the G0/G1-phase, reduces DNA synthesis ^[16] , Telomere Shortening & cell senescence ^[17]
Gotu Kola/ Mandukparni [<i>Centella asiatica</i> L.]- Asiaticoside, Asiatic acid	Apoptosis in MCF-7 cells ^[18] , inhibition of DNA synthesis ^[19] , destroying mitochondria, reducing the expression of <u>proliferating cell nuclear antigen</u> [PCNA] ^[20] , reduced c-myc gene expression and enhanced of c-fos and c-erbB2 gene expressions ^[21] , decreased pro-inflammatory cytokine levels, increased anti-inflammatory cytokine levels ^[22] , down-regulation of mRNA and protein MMP-15 in renal carcinoma ^[23]
Licorice/ Yasthimadhu [<i>Glycyrrhiza glabra</i> L.]- Glycyrrhizin	Isoliquiritin [0.31-3.1 mg/kg], a licorice-derived flavonoid, inhibited the carmine content of granuloma tissue, by anti-tube formation effect ^[24]
Pepper, Black [<i>Piper longum</i> L.]- Piperine	Piperine is an alkaloid from black pepper that can inhibit human colon cancer cell growth by G1 arrest and endoplasmic reticulum stress induced apoptosis ^[25]
Turmeric [<i>Curcuma longa</i> L.] – Curcumin	<u>apoptosis</u> , reducing <u>oxidative stress</u> , <u>cell cycle arrest</u> in G2/M phase, modulating the <u>proteasome</u> , NF-KB, cytokine, and inflammatory responses ^[25]
Triphala^(d) - Acids- Ascorbic, Belleric, Chebulagic, Chebulinic, Gallic, Ellagic^(e)	increased constitutive DNA base excision repair and reduced clastogenicity ^[8] , cytotoxic to L 929 cells and able to reduce ascites tumor in mice & restored the production of IL-2 and interferon- γ ^[26] , inhibited growth of cancer cell lines A-549, SKOV-3, SK-MEL-2, XF-389, and HCT-15 ^[26] , cytotoxicity to cancer cell line [MCF-7] and a transplantable mouse thymic lymphoma [barcl-95], inhibition of MMP-9 ^{[27](f)} .
Tulsi [Holy basil- <i>Occimum sanctum</i> L.]- Eugenol	Inhibits the COX-2 gene in human colon HT-29 cell lines, Apoptosis in MCF-7, Diminished oxidation of DNA, inhibits MMP-9 action, Prevents the synthesis of prostaglandin-E2, Triggers cell apoptosis, Target surviving/E2F1 ^[28]

(a) also, neuroprotective effects from H₂O₂-induced DNA damage and repair in neuroblastoma cells.

(b) also *Asparagus/ Satavar* [*Asparagus racemosus* Willd.]- Saponin.

(c) US PATENTS #6410059, 6896907, 7235262- enhances the properties of cancer drugs. bioavailability facilitator and anticancer compounds, antibiotics.^[13]

(d) Mixture of 3 most valuable tree fruits in Ayurveda- *Embellic myrobylan* [*Phyllanthus emblica* L.], *Belleric Myrobylan* [*Terminalia bellerica* Rox.], *Chebulic Myrobylan* *Terminalia chebula* Retz.

(e) also tannoids, mainly emblicanins, organic acid gallates, B-sitosterol, Glycosides.

(f) Also noted- Radioprotective by scavenging ROS^[29], increased cytotoxic T cells and NK, suppressed the expression of oncogenes, c-Myc and Cyclin D1^[30], apoptosis in Dalton's Lymphoma Ascites [DLA] and CeHa cell lines & inhibited DNA topoisomerase I, inhibition against B16F10, HeLa and MK-1 cell growth.^[31]

Discussion

The published case of Lymphoma patient cured by Ayurveda mentions the “rasayana” [alchemy/ elixir/ rejuvenating chemicals] regimen consists of many bhasmas [incinerated ash of metals] and herbo-mineral formulations. [7] No the patient or others treated in that clinic or elsewhere in India showed any toxicity signs. After treatment of 23 months the hematological and biochemical values restored to normalcy. Significantly no adverse effects were reported, testifying the safety of the metallic formulations. Remarkably, biopsy after-treatment showed no evidence of lymphoma, The quality of life and physical performance of the patient improved with weight gain, unlike in the chemotherapy/ radiotherapy. The rasayana treatment can be administered orally, without injections or hospitalization at much lower cost- at 10-20% of the modern medicine. Conventional standard of care will improve therapeutic outcomes and the anecdotal evidence warrants further clinical studies.

Adverse effects and herbal adjuvants

ADR is a major issue faced by many cancer patients on modern treatment that commonly includes interstitial pneumonitis, lungs infections, colitis, diarrhea, and endocrine disorders as per USA data. [5] Another, early and large study says that long-term adult survivors may face more physical limitations [53% compared with 21% for controls without cancer]. [32] Muscle activity may be most likely be impaired and these survivors may face limited participation in social events, sports, shopping [31% vs 13% reported by controls].

An earliest large cross-sectional study in Germany of survivors 1 to 5 years after the diagnosis of stage I or II breast cancer who were disease-free, reported that the most frequent physical symptoms were general aches and pains [70%], muscle stiffness [64%], and joint pain [62%]. [33] Women who were prematurely postmenopausal and those who received chemotherapy had a higher risk of sexual dysfunction.

In India, a study of total of 500 patients who developed ADRs due to cancer chemotherapy during 2018-2019 in Uttarakhand state, reported 665 ADRs. [34] Commonest ADR was anemia was followed by nausea/vomiting and leucopenia. The most common drugs implicated were cisplatin, paclitaxel, carboplatin, and doxorubicin. Naranjo's scale showed 92% of ADRs as probable and 7% as possible. About 80% of ADRs were of moderate [level 3 and 4] severity, 11% mild [level 1 and 2] severity, and 8.2% of level 5 severity. Preventable ADRs comprised of only 27% and 73% not preventable, which is a cause for concern to address these. Another study from Bihar state in India however mentioned contradictory observation- with 49% patients complaining hair loss- alopecia, 27% nausea, vomiting & burning sensation, 24% of constipation. [35]

The common ADRs as indicated in the 1st Indian study above include nausea, vomiting [20%], diarrhoea [5%], headache [5%], hair loss [5%]. [34] The 2nd Indian subsequent study also mentioned these but with contrasting frequencies. [35] These ailments can be treated with common Ayurvedic/ herbal remedies such as Ginger as its phytochemicals Gingerols and shogaols show biological activity, like anticancer, oxidative stress reduction, antimicrobial, anti-inflammatory, and anti-allergic to multiple central nervous system activities [36]. Loss of both fertility [23] and

immunity [5][37] are major challenges. Consumption of more fruits, vegetables, herbs regularly can improve bioactives intake and improve immunity and wellbeing. [38][39][40]

Diet relation to cancer recovery and recurrence

There was relation “diet” mentioned earlier [32] but “healthy diet” is promoted now through Government advisory such as in the USA [Box 2]. [41] In fact, there is increasing trend and research globally towards complementary and alternative medicine [CAM] as evidenced as a study in Norway [42] comprising 315 women and 153 men with a response rate of 67% of the 706 cancer survivors. Most of the participants [83%] suffered from the effects of cancer treatment; both late and long-term. Commonest effects were fatigue [59%], sleep disorder [41%], hot flashes [39%], nerve damage [polyneuropathy, 38%], and pain [36%] with a mean number of 5.1 of different effects. Nearly half of the such participants complaining late and long-term effects [43%] reported using CAM for redressal. Self-help practices [26%] were commonest such as relaxation therapy [19%], yoga [14%] and meditation [13%], but 22% also visited to CAM providers. Herbal- and other natural remedies were used by 13% for redressal. Majority of the CAM users reported self-perceived improvements of their symptoms [86% for self-help practices, 90% for visits to CAM providers]. Few (<10%) experienced adverse effects of the CAM treatment.

Box 2. Healthy diet advisory for Cancer survivors, USA [41]

A healthy and balanced diet is important for overall wellness. This includes:

- eating a plant-based diet and have at least 5-9 servings of fruit and vegetables daily
- including beans in your diet
- eating whole grains [such as cereals, breads, and pasta] several times daily
- choosing foods low in fat and low in salt”

Recurrence of cancer is a risk is faced by considerable proportion of the cancer survivors and varies by cancer type, besides age of the patient and other factors. About 7-13% of breast cancer patients developed recurrent cancer within 5 years of adjuvant or neo-adjuvant treatment, with increasing risk seen for increasing breast cancer stage. [43] The study mentions prostate cancer has higher rate of 25% recurrence in patients who have had radical prostatectomy. Lung cancer recurrence has wider range [30-75%]. Adenomas, which are associated with colorectal cancer, have been reported to recur in 40-50% of patients. Colon cancer has been found to recur in approximately 33% of patients with stage II and III cancer. Polyphenol rich diet may reduce the risk of cancer recurrence, the authors argued and other too have demonstrated earlier. [44] The therapeutic action of polyphenols is enhanced or modulated by the gut microbiota and it is diet dependant. [45]

Polyphenols are among these supplements and can neutralize free radicals turning them in less dangerous and thereby, stopping side reactions. Polyphenols have broad applications such as the treatment of cancer or inflammations, anti-aging aims in cosmetics or nutraceutical purposes. Moreover, polyphenols are known to be nootropics, owing to be helpful in

several functions of the brain, such as learning, memory, attention or motivation, thereby protecting the brain against neurodegenerative diseases. [43]

Drug interactions

Exploring integration of herbs or Ayurveda [Rasayana] therapy or botanicals with chemotherapy/ radiotherapy to improve efficacy and reduce ADR is suggested by scientist in USA also. [25] Table 4 depicts these, with some interaction but overall benefits.

Table 4. Ayurvedic medicines/ herbs as adjuvants in chemotherapy

HERB	BIOACTIVES	TARGET/ MECHANISM	PLACE, YEAR	REMARK
Turmeric	Curcumin	<u>cytochrome P450</u>	USA, 2020	Interference, but can modulate side effects [25]
Ashwagandha & Asparagus	Withanoloide, Saponins	Pro-inflammatory cytokines, Hematological Homeostasis	Pune, 2020	evaluated as safe, desirable therapeutic adjuvants for cancer [6]
Heart leaved moonseed	Berberin, Tinospoine		Odisha, 2012	Similar effect to Doxorubicin [46]
Triphala	Polyphenols [Flavanoids], Gallates, Glycosides	Cytotoxic to cancer cell lines, protects normal ones, rejuvenates	USA, 2017, 2023	Adjuvant therapy to Radiation and Chemotherapy, [25][29][31]

A review of 115 articles on internet, using keywords, breast cancer, and medicinal plants, aggregated 64 therapeutic targets from 35 different plant species. [47] Among the molecular targets, 51 % [33/64] caused apoptosis and 37 % [24/64] demonstrated cell proliferation activity. The review provides evidence of data suggesting that 17 % therapeutic targets have carcinogen inactivation activity, 10 % have precancerous growth prevention activity, 9% have mutagenesis and gene expression activity, and 4 % regulate toxic metabolism. The authors further argue that Ayurveda/ herbal medicines can be beneficially incorporated with chemotherapy, the predominant regime to reduce ADR & improved recovery, better health of the survivors. A key feature of Ayurvedic medicine is its “Polyherbal” nature with synergistic effect and pre-empting the emergence of resistance. [48] The lower ADR makes them suitable for patients with special conditions such as children or elders. This is crucial as for instance, researchers are predicting that the number of persons over the age of 65 years diagnosed with cancer each year will double by the year 2050 in USA, and will quadruple among those aged ≥85 years then. [32] Similar pattern may occur in the developed nations/ globally due to wealth increase all over.

Govt. of Victoria in Canada enlists popular botanicals used in CAM and their interaction with cancer drugs. Of these, Turmeric is said to make no effect on the treatment while Black pepper, Garlic, Guggul tree gum, Licorice may influence the chemotherapy treatment outcomes, its cautioned. [49] However, another review suggested that Turmeric may influence negatively the outcomes. [50] Nevertheless, yet another analysis did not find serious ADR of combined use of herbals with chemotherapy but only 8% ADR as fatal and 5% avoidable. [51] Ginger or turmeric were not claimed for serious ADR and integrative therapy was recommended for the best outcomes with phytovigilance. This was based on the analysis of

VigiBase, a WHO database of individual case safety reports [ICSRs] which archives reports of suspected Adverse Drug Reactions [ADRs] when herbal products are used in conjunction with anti-cancer treatment. The possible interactions between antineoplastic [L01 ATC class] or hormone antagonists [L02B ATC class] with 10 commonly used herbs [Pineapple, Green tea, Cannabis, Black cohosh, Turmeric, Ginger, Echinacea, St John's wort, milk thistle] to compare ADRs described in ICSRs with the literature. A total of 1057 ICSRs were extracted from the database but only 134 were adequate [or did not concern too many therapeutic lines] so analysed, of which, 51 rationalizable ICSRs could be explained, leading to a pharmacokinetic or pharmacodynamic interaction mechanism. Reports concerned more frequently women and half of the admissible ICSRs involved *Viscum album* and *Silybum marianum*.

DNA modulation

The anti-cancer activity of Ayurvedic herbs is ascribed to either as topoisomerase inhibitors poisons such as *Phyllanthus amarus* Schum and Thonn. [bioactive Phyllanthin] or *Nothapodytes nimmoniana* [J Graham] Mabb. {syn. *Mappia foetida* [Wt.] Miers, bioactive Camptothecin}.^[19] Some other herbs target telomere instead that is earlier known as anti-aging target.^{[8][52][53][54]} Yet another potential emerging mechanisms is GLP-1 Agonist like Semaglutide, basically used in diabetes similar to the famous branded drug “Ozempic” is found useful in treating cancer also.^[55] It inhibits the cancer cell proliferation by the cAMP-PKA pathway, acting as molecular brake on the uncontrolled cell division, thereby impeding the relentless expansion of malignant cells^[56]. Impaired glucose metabolism may be a causal factor behind cancer so its is important to reduce sugar and glycation/ lipoxidation end products [AGE/ ALE] they argued and cited research showing that 20-40% of the cancers are diet dependent and preventable.^[57] Cinnamon, the routine Indian spice is a GLP-1 agonist and found useful in treating cancer, besides diabetes.^[58] Some other pathways of action include apoptosis as enlisted earlier and anti-oxidant activity thereby reducing the stress viz. reactive oxygen species [ROS], to help smooth physiological functioning.^{[59][60]}

Box 3. Indian herbs with Potential influence on Cancer treatment [Chemotherapy]^[49]

INTERACTIONS

Botanical Effect on CYP3A4 Enzyme
 Black pepper [Piper nigrum] Potential inhibitor
 Garlic [Allium sativum] Weak inhibitor
 Guggul tree [Commiphora mukul] Potential inducer
 Licorice [Glycyrrhiza uralensis] Potential inhibitor
 Turmeric [Curcuma longa] No effect
 Wheat bran [Triticum aestivum] Potential inhibitor

Many other herbs in India and Africa/ tropics are also found to be useful in addressing cancer e.g. Kalmegh *Andrographis paniculata* Nees, bioactive Andrographaloides,^{[61][62][63][64]} and Black cumin [Nigella sativa L., bioactive Thymoquinone].^{[65][66]} In fact, the former is found to even overcome the Gemcitabine Resistance through Regulation of

ERBB3 and Calcium Signaling Pathway in Pancreatic Ductal Adenocarcinoma. [67] The ever-growing resistance to synthetic molecules is a growing concern [68]. We suggest that herbals can possibly address it with more research.

Innovations- local and Global

Complete Ayurveda clinics are emerging across India tapping even the “medical tourism” concept emerging globally, in Kerala state, the so called “God’s own country” [69] or in cities such as Pune [70] or aforesaid Jain clinic at Indore city [11]. These usually run to the full capacity and/or are overbooked with few weeks/ months of waiting. Hence, some enterprises like aforesaid Jiva provide telemedicine consultation and courier the drugs. Another “Huma” therapy at Lucknow city is a completely Ayurvedic clinic for cancer using herbal mixture comprising *Azadirachta indica* A. Juss., *Curcuma longa* L., *Emblica officinalis gaertn.*, *Ocimum sanctum* L., *Semecarpus anacardium* L., *Tinospora cordifolia* [Willd.] Miers. [71] Most of these clinics employ Ayurvedic detox therapy named as “Panchkarma” [5 actions- Vamana [vomiting], Virechana [purgation], Niruham [decoction enema], Anuvaasan [oil enema], and Nasyam [nasal administration]. [72][73] An Ayurvedic tonic named “Chayavanprash” with “aforesaid Triphala” as the main drug and many other herbs is popular too for disease prevention and immunity building, especially since COVID-19 pandemic. [38][39]

Scientists have repurposed to treat cervical cancer “Panchvalkal”, an Ayurvedic traditional formulation has references in Charak Samhita and Bhavaprakasha Nighantu used for the treatment of women with endometriosis-related problems, leucorrhea and vaginal ailments [74]. The formulation comprises the barks of trees *Ficus glomerata* Roxb., *Ficus religiosa* L., *Ficus benghalensis* L., *Ficus virens* Aiton, and *Thespesia populnea* [L.] Soland ex. Correa. However, the 1st 3 tree species being sacred in India their bark harvest is a taboo. [75]

Similarly, traditional Chinese medicine [TCM] has developed formula PHY906, decoction of a mixture of the four herbs: *Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, *Scutellaria baicalensis* Georgi and *Ziziphus jujuba* Mill, for over 1800 years for treating a variety of gastrointestinal distress such as diarrhoea, cramps, nausea, vomiting etc. [76][77]

A concern raised about Ayurvedic drugs was the content of heavy metals considered toxic such as mercury leading to prohibition of import of some Ayurvedic medicines in USA about 2 decades ago. However atomic and biochemical studies found that these “*bhasma*” when given in higher doses to rats does not get absorbed in the gastrointestinal tract but gets excreted. [78] Further it said that a study on the neurotoxic effect and accumulation of methyl mercury and mercuric sulfide [HgS] in rats indicates that inorganic HgS can be absorbed in the insoluble form in the G-I tract and that its neurotoxic potency is about 1,000 times less than that of the soluble MeHg. Zinc oxide nanoparticles [nZnO] Experiments showed selective toxicity to different bacterial systems and human T lymphocytes. A standardized colloidal gold preparation [Tyndall's purple, Au, 27 nm] is found to be a far more effective anti- arthritic agent in rats than the sodium aurothiomalate used in the treatment of rheumatoid arthritis. *Swarna bhasma* [42 iterations, 900 C] was prepared brown red in colour following the classic texts. An infrared spectrum showed no presence of organic compounds and transmission electron microscope [TEM] measurements revealed average particle size to be 57 nm with globular morphology. An atomic absorption spectroscopy indicated the *bhasma* to be free of any mercury but having 92% zerovalent gold [Au] in the *bhasma*. These nanogold particles should be able to reach the affected site even if administered orally and provide a slow

and sustained release of Au [I] ions. Further, recent research has also ascertained the safety of even mercury as well as higher efficacy as nano-carriers due to the traditional nanotechnology said to be used. [79][80][81]

The southern Indian traditional medicine branch called “Siddha” that developed mainly in the Tamil nadu state was supposedly most expert in employing heavy metals in highly processed, no-toxic forms such use of vermilion, a lead compound [Pb₃O₄] for treating hepatitis C virus [HCV] and found ot be non toxic to humans.[82] Another *in vitro* study showed that Rasagenthi Mezhu [RGM], a popular Siddha medicine containing toxic metals such as mercury, lead, and arsenic is useful to cure cervical cancer cells and not toxic to the healthy cells. [83]

Unani is another traditional medicine system in India that also has similar herbal and/ or metallic medicines found to be effective for millennia and found to be useful in treating even cervical cancer. [84] Other studies have also shown the anticancer potential of Islamic medicine. [85] Other traditional medical practices worldwide may also have useful elements to integrate into the modern medicine for better efficacy/ relief to the patient from ADR.[25]

Bioactives such as Curcumin,[40] Quercetin[86] and Resveratrol[87] are also now being proposed to address cancer, the latter being at low cost, almost painless by the Premier cancer research institute in India! Further, innovative, natural products based therapies in cancer are being proposed such as using vitamin C [88] and vitamin D [89]. Chemotherapy is likely to produce *de novo* antimicrobial resistance [AMR] in gut microbiota by activating the bacterial SOS system. [90][91] Chemotherapy is damaging to the commensal gut microbiota and changes in gut microbiota are significant precursors to sepsis in cancer patients. Microbiome-based therapeutic interventions may be able to correct dysbiosis and prevent carriage of antimicrobial-resistant pathogens. The global spread of antibiotic-resistant pathogens threatens to increase the mortality of cancer patients significantly. We propose that chemotherapy contributes to the emergence of antibiotic-resistant bacteria within the gut and, in combination with antibiotics, drives pathogen overgrowth and translocation into the bloodstream. In our model, these processes are mediated by the effects of chemotherapy on bacterial mutagenesis and horizontal gene transfer, the disruption of commensal gut microbiology, and alterations to host physiology. Herbal medications may be helpful in addressing AMR issues their use in cancer treatment is worth exploring urgently, including in veterinary care given the rising importance of zoonotic diseases as COVID-19 showed. [92] Bioactive from common crop plants such as spices such as Coriander can alleviate the ecological risk of species extinction due to overharvest as proposed in the case of Asoca tree {*Saraca asoca* [Roxb.] De Wilde} used to treat menorrhagia in Ayurveda across south-east Asia contribute to environmental sustainability. [93] The study also quotes its utility in cancer therapy. Of course, cultivation as pesticide free, with organic inputs is a prerequisite to minimize the cancer risk.

Global and public health outlook

Tobacco use, alcohol consumption, unhealthy diet, physical inactivity, air pollution and microbial infections are identified as major causes behind cancer [1] and these need to be addressed on priority basis. Cancer burden puts unequal burden in poorer countries as evident from the fact that In developed countries, 8% women are diagnosed with breast cancer and 1 in 71 women die of it say WHO. [2] By contrast, in less developed countries; only 4% women is diagnosed with breast cancer, 1 in 48 [2%] women die from it. In the less developed countries, there were 543,337 deaths & 811,014 new cancer

patients the ration being 70% in 2018 while in the highly developed countries of there were 9,296,171 new cancer cases and 3,643,502 cancer deaths, at 40%. **WHO estimates that the number of new cancer cases in 2050 will rise 77% to a total of 35 million cases.** ^[94] WHO further estimates that in 2050, the mortality amounts in the low and medium human development index countries may almost double. WHO referenced survey data from 115 countries on components of their universal health coverage, only 39% of these countries included basic cancer management as part of health benefit packages [HBP] for their citizens! The less developed countries with lower healthcare budget can benefit from the herbal medicines. The traditional medicine policy of WHO is a step in that direction. ^[95]

Statements and Declarations

Acknowledgements

We acknowledge Mr. Darshan Shanker, Dr. Amita Wele, late Mr V M Ghate, late Dr. D K Ved, Dr. Jaffri, late Dr. Vilas Nanal, Dr. Sudha Agarwal, late Mr. Shashank Karekar, Mr. Raghu V, Dr. Narendra Pendse for the useful insights and our organisations for the moral support.

Funding

The desk review study was not externally funded.

Conflict of Interest

The authors declare no conflict of interest.

References

1. ^{a, b, c} WHO. *Cancer-Key Fact. 2018. World Health Organization, Geneva.* <https://www.who.int/news-room/fact-sheets/detail/cancer>
2. ^{a, b, c} WHO. *Global cancer burden growing, amidst mounting need for services. 2024. WHO [2018]. Cancer-Key Fact. World Health Organization, Geneva.* <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services>
3. [^] IARC. *GLOBOCAN 2020: New Global Cancer Data. 2020. International Agency for Research on Cancer IARC.* <https://www.uicc.org/news/globocan-2020-global-cancer-data>.
4. ^{a, b, c} Kulothungan, V., Sathishkumar, K., Leburu, S. et al. *Burden of cancers in India - estimates of cancer crude incidence, YLLs, YLDs and DALYs for 2021 and 2025 based on National Cancer Registry Program. BMC Cancer 2022. 22, 527.*
5. ^{a, b, c, d} Kroschinsky F, Stölzel F, von Bonin S, Beutel G, Kochanek M, Kiehl M, Schellongowski P. *New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. Crit Care.*

2017 Apr 14;21[1]:89. doi: 10.1186/s13054-017-1678-1.

6. ^{a, b, c, d}Saggam A, Kale P, Shengule S, Patil D, Gautam M, Tillu G, Joshi K, Gairola S, Patwardhan B. Ayurveda-based Botanicals as Therapeutic Adjuvants in Paclitaxel-induced Myelosuppression. *Front Pharmacol*. 2022. Feb 22;13:835616.
7. ^{a, b}Bendale Y, Kadam A, Patil A, Kantilal Birari-Gawande P. Complete tumor regression with exclusive Ayurvedic rasayana regimen in high-grade diffuse large B-cell lymphoma: A case report. *Clin Case Rep*. 2022. Apr 14;10[4]:e05696.
8. ^{a, b, c, d, e, f}Sharma R., Martins, R. Telomeres, DNA Damage and Ageing: Potential Leads from Ayurvedic Rasayana [Anti-Ageing] Drugs. *J Clin Med*. 2020; 9[8]: 2544.
9. [^]Singh, S. Pharmacotherapeutics of gomutra [Cow urine]. *The Pharma Innovation Journal* 2019. 8[6]: 707-712.
10. [^]Singh S. Biochemical appraisal of Gomutra [Cow urine]. *Journal of Pharmacognosy and Phytochemistry* 2019; 8[3]: 4089-4092.
11. ^{a, b}Jain [N.D]. Discover Cow Urine Therapy's Cutting-Edge Approach To Cancer Treatment. <https://clinic.ayurvedacowurine.in/cancer.html>
12. [^]Raj A. K., Upadhyay V, Lokhande K B, Venkateswara K, Bhonde R, Sarode S C, Sharma N K. Free Fatty Acids from Cow Urine DMSO Fraction Induce Cell Death in Breast Cancer Cells without Affecting Normal GMSCs. *Biomedicines* 2023, 11[3], 889.
13. ^{a, b}Kumar R, Ali S A, Singh S K, Bhushan V, Kaushik J K, Mohanty A K, Kumar S. Peptide profiling in cow urine reveals molecular signature of physiology-driven pathways and in-silico predicted bioactive properties. *Sci Rep*. 2021; 11: 12427.
14. [^]Palmieri A, Scapoli L, Lapichino A, Mercolini L, Mandrone M, Poli F et al, 2019. Berberine and *Tinospora cordifolia* exert a potential anticancer effect on colon cancer cells by acting on specific pathways. *Int J Immunopathol Pharmacol*. 2019: 33: 2058738419855567.
15. [^]Patil S, Ashi H, Hosmani J, Almalki AY, Alhazmi YA, Mushtaq S, Parveen S, Baeshen HA, Varadarajan S, Raj AT, Patil VR, Vyas N. *Tinospora cordifolia* [Thunb.] Miers [Giloy] inhibits oral cancer cells in a dose-dependent manner by inducing apoptosis and attenuating epithelial-mesenchymal transition. *Saudi J Biol Sci*. 2021; 28[8]: 4553-4559.
16. [^]Khanam S, Prakash A. An overview of medicinal plants as anticancer agents. *IP International Journal of Comprehensive and Advanced Pharmacology* 2021; 6[2]:53–62.
17. [^]Kaewtunjai N, Wongpoomchai R, Imsumran A, Pompimon W, Athipornchai A, Suksamrarn A, Lee T R, Tuntiwechapikul W. Ginger Extract Promotes Telomere Shortening and Cellular Senescence in A549 Lung Cancer Cells. *ACS Omega* 2018, 3, 12, 18572–18581.
18. [^]Babykutty S, Padikkala J, Sathiadevan P P, Vijayakurup V, Abdul azis T K, Srinivas P, Gopala S. Apoptosis Induction of *Centella Asiatica* on Human Breast Cancer Cells. *Afr J Tradit Complement Altern Med*. 2009; 6[1]: 9–16.
19. ^{a, b}Desai A G, Ghulam N Q, Ganju R K, El-tamer M, Singh J, Saxena A K et al. Medicinal Plants and Cancer Chemoprevention. *Curr Drug Metab*. 2008; 9[7]: 581–591.
20. [^]Wu T, Geng J, Guo W, Gao J, Zhu X., Asiatic acid inhibits lung cancer cell growth in vitro and in vivo by destroying mitochondria. *Acta Pharmaceutica Sinica B*, 2017. 7[1]: 65-72.

21. ^aHussin, F., Eshkoor, S.A., Rahmat, A. et al. *The centella asiatica juice effects on DNA damage, apoptosis and gene expression in hepatocellular carcinoma [HCC]. BMC Complement Altern Med 2014: 14, 32.*
22. ^aNaidoo, D.B., Chuturgoon, A.A., Phulukdaree, A. et al. *Centella asiatica modulates cancer cachexia associated inflammatory cytokines and cell death in leukaemic THP-1 cells and peripheral blood mononuclear cells [PBMC's]. BMC Complement Altern Med 2017. 17, 377.*
23. ^{a, b}Huang C F, Hung T W, Yang D F, Tsai y L, Yang J T, Lin C L, Hsieh Y H. *Asiatic acid from centella asiatica exert anti-invasive ability in human renal cancer cells by modulation of ERK/p38MAPK-mediated MMP15 expression. Phytomedicine. 2022. Volume 100, no. 154036.*
24. ^aLim T K. *Edible Medicinal and Non-Medicinal Plants. Edible Medicinal and Non-Medicinal Plants. 2015. 22: 354–457.*
25. ^{a, b, c, d, e, f}Arnold J. T, *Integrating ayurvedic medicine into cancer research programs part 2: Ayurvedic herbs and research opportunities, Journal of Ayurveda and Integrative Medicine, 2023. 14[2]: 100677.*
26. ^{a, b}Wongnoppavich A, Jaijoi K, Sireeratawong S. *Triphala: The Thai traditional herbal formulation for cancer treatment. Songklanakarin J. Sci. Technol. 2009. 31 [2], 139-149.*
27. ^aVerma N, Singh AP, Amresh G, Sahu PK, Singha, Mishra N, *Review on wonderful and miraculous Triphala. Journal of Pharmacy Research 2011, 4[3], 690-694.*
28. ^aHasan MR, Alotaibi BS, Althafar ZM, Mujammi AH, Jameela J. *An Update on the Therapeutic Anticancer Potential of Ocimum sanctum L.: "Elixir of Life". Molecules. 2023 Jan 25;28[3]: 1193.*
29. ^{a, b}Baliga MS, Meera S, Vaishnav LK, Rao S, Palatty PL. *Rasayana Drugs From the Ayurvedic System of Medicine as Possible Radioprotective Agents in Cancer Treatment. Integrative Cancer Therapies. 2013. 12[6]:455-463.*
30. ^aPeterson CT, Denniston K, Chopra D. *Therapeutic Uses of Triphala in Ayurvedic Medicine. The Journal of Alternative and Complementary Medicine. 2017: 607-614.*
31. ^{a, b}Khan K H, *Roles of Emblica officinalis in Medicine - A Review. Botany Research International, 2009. 2 [4]: 218-228.*
32. ^{a, b, c}Stein KD, Syrialia KL, Andrykowski MA. *Physical and Psychological Long-Term and Late Effects of Cancer. Cancer. 2008 Jun 1; 112[11 Suppl]: 2577–2592.*
33. ^aGanz PA, Rowland JH, Desmond K, et al. *Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol. 1998. 16: 501–514.*
34. ^{a, b}Ramasubbu SK, Pasricha RK, Nath UK, Das B. *Frequency, nature, severity and preventability of adverse drug reactions arising from cancer chemotherapy in a teaching hospital. J Family Med Prim Care. 2020; 9[7]: 3349–3355.*
35. ^{a, b}Singh S, Dhasmana DC, Bisht M, Singh PK. *Pattern of adverse drug reactions to anticancer drugs: A quantitative and qualitative analysis. Indian J Med Paediatr Oncol 2017. 38: 140-5.*
36. ^aAL-ataby IA and Talib WH. *Daily Consumption of Lemon and Ginger Herbal Infusion Caused Tumor Regression and Activation of the Immune System in a Mouse Model of Breast Cancer. Front. Nutr. 2022. 9:829101.*
37. ^aDuck_hee K, Weaver MTPark NJ, Smith B, McArdle T, Carpenter J, *Significant Impairment in Immune Recovery Following Cancer Treatment. 2009. Nurs Res, 2009. 58[2]: 105–114.*
38. ^{a, b}Ghate U and Kulkarni H. *Polyphenols, Spices and Vegetarian Diet for Immunity and Anti-Inflammatory Drug Design. 2021. In L. Q. Zepka et al [Eds], Bioactive Compounds–Biosynthesis, Characterization and Applications. London: Intechopen, pp. 63-76.*

39. ^{a, b}Ghate U. and Kulkarni H. [2023] *Spices, Unpacked Diet, Bio Actives and Immunity: Indian Health and Pandemic. European J Science innovation Tech. 3[3]: 422-441.*
40. ^{a, b}Aggarwal B. et al [2011]. *Identification of Novel Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic Diseases- "Reverse Pharmacology" and "Bedside to Bench" Approach. Curr Drug Targets. 12[11]: 1595-1653.*
41. ^{a, b}Anon. *Cancer survivorship guidelines- Diet. National Cancer Institute, USA, Maryland .*
<https://www.cancer.gov/about-cancer/coping/survivorship/follow-up-care>
42. [^]Kristoffersen, A.E., Wider, B., Nilsen, J.V. et al. *Prevalence of late and long-term effects of cancer [treatment] and use of complementary and alternative medicine in Norway. BMC Complement Med Ther 22, 322 [2022].*
43. ^{a, b}Cordova FM, Watson RR, *Polyphenols in Human Health and Disease. Chapter 16 in Editor[s]: Watson R R, Preedy V R, Zibadi S [eds.] Food and Supplement Polyphenol Action in Cancer Recurrence, 2014. Vol. 1, pp. 191-195.*
44. [^]Shahidi F. and Abul Hossain. *Bioactives in spices, and spice oleoresins: Phytochemicals and their beneficial effects in food preservation and health promotion, Journal of Food Bioactives, 2018. Vol. 3, pp. 8-75.*
45. [^]Bié, J.; Sepodes, B.; Fernandes, P.C.B.; Ribeiro, M.H.L. *Polyphenols in Health and Disease: Gut Microbiota, Bioaccessibility, and Bioavailability. Compounds 2023, 3, 40-72.*
46. [^]Saha S, Ghosh S. *Tinospora cordifolia: One plant, many roles. Anc Sci Life. 2012; 31[4]: 151–159.*
47. [^]Dash MK, Joshi N, Gautam DND, Jayakumar R, Tripathi YB. *Ayurvedic supportive therapy in the management of breast cancer. Journal of Herbal Medicine, Vol. 29, October 2021, 100490.*
48. [^]Khan M, Pandit S, Saha A, Somani R, Joshi V, et al. [2022] *Perspective of using Indian Polyherbal Medicine in the Treatment of Cancer. Curr Res Cmpl Alt Med 6: 165.*
49. ^{a, b}Anon [n.d.]. *Botanicals interaction with cancer treatment. Govt. of Vancouver, Canada.*
<https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Supplemental-Botanical-Interactions-with-Chemotherapy-and-Radiation.pdf>.
50. [^]Chan, WJ.J., Adiwidjaja, J., McLachlan, A.J. et al. *Interactions between natural products and cancer treatments: underlying mechanisms and clinical importance. Cancer Chemother Pharmacol 91, 103–119 [2023].*
51. [^]Pochet S, Lechon AS, Lescrainier C, De Vriese C, Mathieu V, Hamdani J, Souard F. *Herb-anticancer drug interactions in real life based on VigiBase, the WHO global database. Scientific Reports, 2022 Aug, 12[1]:14178.*
52. [^]Patil S A, Wele A, Gadgil S S. *Dietary agents AND telomerase Spices AND telomerase Inhibition inhibition. VI th International Conference on Ayurved for Cancer. 2023. DOI: 10.13140/RG.2.2.24601.80483*
53. [^]Dhyani, P., Quispe, C., Sharma, E. et al. *Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell Int 22, 206 [2022].*
54. [^]Kaewtunjai N, Wongpoomchai R, Imsumran A, Pompimon W, Athipornchai A, Suksamrarn A, Lee RT, Tuntiwechapikul W. *Ginger Extract Promotes Telomere Shortening and Cellular Senescence in A549 Lung Cancer Cells. ACS Omega 2018, 3, 12, 18572–18581.*
55. [^]Akl MM, Ahmed A. *Semaglutide, a GLP-1 Agonist Like Ozempic, and Its Potential Role as a Preventive Anti-Cancer Agent, 2023. Qeios ID: L9AQQC.*
56. [^]Zhang H, Kong Q, Wang J, Jiang Y, Hua H. *Complex roles of cAMP-PKA-CREB signaling in cancer. Exp Hematol Oncol. 2020; 24; 9[1]:32.*

57. [^] Kulkarni H, Ghate U, *Plant Based Diet for Better Immunity, Elderly Health and Environment: Indian Insights. Europ Jr of Sci, Innov Tech* vol. no 4 pp. 366-384.
58. [^] Perng D, Tsai Y, Chheng J, Wang J, Chou K, Shih C, Chheng J. *Discovery of a novel anticancer agent with both anti-topoisomerase I and II activities in hepatocellular carcinoma SK-Hep-1 cells in vitro and in vivo: Cinnamomum verum component 2-methoxycinnamaldehyde. Drug Des Devel Ther.* 2016; 10:141-153.
59. [^] Chan, WJ, Adiwidjaja, J., McLachlan A.J. et al. *Interactions between natural products and cancer treatments: underlying mechanisms and clinical importance. Cancer Chemother Pharmacol* 2023. 91, 103–119.
60. [^] Fatima, N.; Baqri, S.S.R.; Alsulimani, A.; Fagoonee, S.; Slama, P.; Kesari, K.K.; Roychoudhury, S.; Haque, S. *Phytochemicals from Indian Ethnomedicines: Promising Prospects for the Management of Oxidative Stress and cancer. Antioxidants* 2021, 10, 1606.
61. [^] Shimura, T., Sharma, P., Sharma, G.G. et al. *Enhanced anti-cancer activity of andrographis with oligomeric proanthocyanidins through activation of metabolic and ferroptosis pathways in colorectal cancer. Sci Rep* 11, 7548 [2021].
62. [^] Miyazaki K, Xu C, Shimada M, Goel A. *Curcumin and Andrographis Exhibit Anti-Tumor Effects in Colorectal Cancer via Activation of Ferroptosis and Dual Suppression of Glutathione Peroxidase-4 and Ferroptosis Suppressor Protein-1. Pharmaceuticals* 2023, 16[3], 383.
63. [^] Zhao, Y.; Roy, S.; Wang, C.; Goel, A. *A Combined Treatment with Berberine and Andrographis Exhibits Enhanced Anti-Cancer Activity through Suppression of DNA Replication in Colorectal Cancer. Pharmaceuticals,* 2022. 15, 262.
64. [^] Zhao Y, Wang V, Goel A, *A combined treatment with melatonin and andrographis promotes autophagy and anticancer activity in colorectal cancer, Carcinogenesis,* 2022, 43 [3]: 217–230.
65. [^] Al-Obeed, O., El-Obeid, A.S., Matou-Nasri, S. et al. *Herbal melanin inhibits colorectal cancer cell proliferation by altering redox balance, inducing apoptosis, and modulating MAPK signaling. Cancer Cell Int* 2020. 20, 126.
66. [^] Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhour ZA, Anwar F. *A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pac J Trop Biomed.* 2013 May; 3[5]:337-52.
67. [^] Okuno K, Xu C, Pascual-Sabater S, Tokunaga M, Takayama T, Han H, Fillat C, Kinugasa Y, Goel A. *Andrographis Reverses Gemcitabine Resistance through Regulation of ERBB3 and Calcium Signaling Pathway in Pancreatic Ductal Adenocarcinoma. Biomedicines.* 2023 Jan; 11[1]:119.
68. [^] Sharma, N.K.; Bahot, A.; Sekar, G.; Bansode, M.; Khunteta, K.; Sonar, P.V.; Hebale, A.; Salokhe, V.; Sinha, B.K. *Understanding Cancer's Defense against Topoisomerase-Active Drugs: A Comprehensive Review. Cancers* 2024, 16, 680.
69. [^] <https://ayurvedapayyanur.com/oncology/>
70. [^] <https://www.rasayucancerclinic.com>
71. [^] Pal S K, *Cancer Alternative Therapy Huma: A Clinical Perspective. Annals Ayurvedic Med.* 2013:2 [3] P- 80-88.
72. [^] <https://www.dabur.com/blog/detoxification/what-panchakarma-treatment>
73. [^] <https://www.ayurwakeup.com/what-is-panchakarma-panchakarma-treatment-benefits/>
74. [^] Aphale S, Shinde K, Pandita S, Mahajan M, Raina P, Mishra JN, Ghanekar-Kail R. *Panchvalkala, a traditional Ayurvedic formulation, exhibits antineoplastic and immunomodulatory activity in cervical cancer cells and C57BL/6*

mouse papilloma model. *J Ethnopharmacol.* 2021 Nov;280: 114405.

75. [^]Ghate U, Genus Figs. *Resonance*, 1999 Dec. 90-100.
76. [^]Lam, W., Jiang, Z., Guan, F. et al. PHY906[KD018], an adjuvant based on a 1800-year-old Chinese medicine, enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment. *Sci Rep.*, 2015. 5, 9384
77. [^]Shwu-Huey Liu, Yung-Chi Cheng, Old formula, new Rx: The journey of PHY906 as cancer adjuvant therapy, *Journal of Ethnopharmacology*, 2012. 140(3): 614-623.
78. [^]Kapoor RC. Some observations on the metal-based preparations in the Indian Systems of Medicine. *Indian Journal of Traditional Knowledge Vol. 9 [3], 2010. pp. 562-575.*
79. [^]Srikanth N., Singh A., Ota S., Sreedhar B. and Dhiman KS. Chemical characterization of an Ayurvedic herbo-mineral preparation-Mahalaxmivilas Rasa. *Journal of Ayurveda. and integrative medicine*, 2019. 10[4], 262-268.
80. [^]Ramanan N., Lahiri D., Rajput P., Varma RC., Arun A., Muraleedharan T S., et al. Investigating structural aspects to understand the putative/claimed non-toxicity of the Hgbased Ayurvedic drug Rasasindura using XAFS. *Journal of synchrotron radiation*, 2015. 22[5]: 1233-1241.
81. [^]Ghate U, Wele A, Globalization of AYUSH Products: Status, Challenges and Suggestions for Growth. *Jr Traditional Medicine Rreview*, 2022. 1(2): 21-34.
82. [^]Al-Ansari MM, Ranjit Singh AJA, Al-Khattaf FS, Michael JS. Nano-formulation of herbo-mineral alternative medicine from *linga chenduram* and evaluation of antiviral efficacy. *Saudi J Biol Sci.* 2021 Mar. 2 8[3]: 1596-1606.
83. [^]Riyasdeen A, Vaiyapuri S. Periasamy, Preethy Paul, Ali A. Alshatwi, Mohammad A. Akbarsha, Chloroform Extract of *Rasagenthi Mezhugu*, a Siddha Formulation, as an Evidence-Based Complementary and Alternative Medicine for HPV-Positive Cervical Cancers, *Evidence-Based Complementary and Alternative Medicine*, 2012. Article ID 136527, pp. 10.
84. [^]Sharma N, Raina P, Mulla G, Shindikar A, Patil P, Bhalerao S, Ghanekar Kaul R. Phytochemical Profiling and Assessment of *Habbe Musaffe Khoon* Against Cervical Cancer. *Pharmacognosy Magazine.* 2024; 20[1]:179-188.
85. [^]Zaid H, Silbermann M, Ben-Arye E, Saad B. Greco-Arab and Islamic Herbal-Derived Anticancer Modalities: From Tradition to Molecular Mechanisms. *Evidence-Based Complementary and Alternative Medicine*, 2012, Article ID 349040, pp. 13.
86. [^]Ghate U, Kulkarni H, Quercetin- herbal bioactive nanotechnology for osteoarthritis & elderly health. *Brazilian Journal of Development*, 2023. 9[12]: 31772-31783.
87. [^]Agarwal A, Khandelwal A, Pal K, Khare NK, Jadhav V, Gurjar M et al. A novel pro-oxidant combination of resveratrol and copper reduces transplant related toxicities in patients receiving high dose melphalan for multiple myeloma [RESCU 001]. *PLoS One.* 2022 Feb; 17[2]:e0262212.
88. [^]Roa FJ, Peña E, Gatica M, Escobar-Acuña K, Saavedra P, Maldonado M, Cuevas ME, Moraga-Cid G, Rivas CI, Muñoz-Montesino C. Therapeutic Use of Vitamin C in Cancer: Physiological Considerations. *Front Pharmacol.* 2020 Mar 3;11:211. doi: 10.3389/fphar.2020.00211.
89. [^]Mukherjee S, Das S, Sriram N, Chakraborty S, Sah MK. In silico investigation of the role of vitamins in cancer therapy through inhibition of MCM7 oncoprotein. *RSC Adv.*, 2022,12, 31004-31015.
90. [^]Papanicolas LE, Gordon DL, Wesselingh SL, Rogers GB, Not Just Antibiotics: Is Cancer Chemotherapy Driving

Antimicrobial Resistance? Trends in Microbiology, 2018. 26 [5]: 393-400.

91. [^]Nanayakkara AK, Boucher H, Fowler VG, Jezek A, Outtersson K, Greenberg DE. *Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. CA: A cancer journal for Clinicians, 2021. 71[6]: 488-504.*
92. [^]Ghate U. and Kulkarni H. 2024. *Antimicrobial Ayurveda Crops as Superfoods as For Export, Conservation & Farmers' Benefit. Qeios, 3G4GP7.3 DOI- <https://doi.org/10.32388/3G4GP7.3>*
93. [^]Ghate U., H Kulkarni, M Deshpande, M Akkalkotkar, 2022. *Threatened Ayurvedic Herb [Seeta Ashoka] Substitution Options for Menorrhagia- based on Bioactive Principle's Molecular Docking Study, Int. J. Pharm. Investigation, 12[3]: 1-5.*
94. [^]<https://www.medicalnewstoday.com/articles/an-estimated-35-million-new-cancer-cases-to-occur-in-2050-who-warns#77%-rise-in-cancer-cases-by-2050>.
95. [^]Qi, Z. *WHO traditional medicine strategy. 2014-2023. World Health Organization, Geneva, 2013. pp. 188.*