NIH/NCI OCCAM SPECIAL LECTURE

June 15, 2022

TRADITIONAL MEDICINES FOR COVID-19 AND CANCER

EFFECTS ON IMMUNITY AND INFLAMMATION

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National Research Professor – Ayush

Savitribai Phule Pune University, Pune, India

CENTER FOR COMPLEMENTARY AND INTEGRATIVE HEALTH
CENTER OF EXCELLENCE – MINISTRY OF AYUSH

ACTIVITY

Policy Analysis
Advocacy and Translation

Transdisciplinary
Scientific Research

Teaching
and Training

Collaborative
Consortia

SCIENTIFIC CONTRIBUTIONS TO INTEGRATIVE HEALTH

1986 — Immunology

1994 — Rheumatology

1994 — Public Health

2002 — AyuSoft

2006 — Maternal & Child Health

2005 — Vaccine Adjuvant

2004 — Cancer Adjuvant

2002 — AyuGenomics

2010 — QC & Herb-Drug Interaction

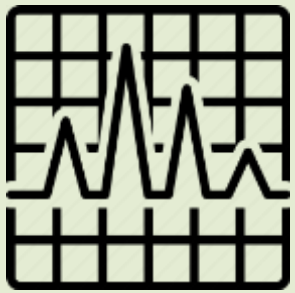
2011 — Aging

2015 — Network Pharmacology

2020 — COVID-19

CCIH- ISHS-PUNE UNIVERSITY
CAPACITY BUILDING

In silico Techniques



Bio-Analytical

Public Health

Epidemiology

Publication Ethics

Yoga Studies

Meta-research

Health policy

IMMUNITY
AYURVEDA PERSPECTIVE

Ayurveda

- Ancient Indian traditional '**health**' system
- **Restoration of health** using personalized approach
- Focuses on achieving **physiological homeostasis** through *Rasayana* therapy

Patwardhan. EPMA. 2014; 5(19).
Patwardhan. J Ayu Integr Med 2018; 9:85–6.

Rasayana

- **Tissue nourishment** to the optimum level
- Achieves **longevity**, cognizance and physique
- **Regeneration and adaptogenic** property by immunomodulation

Balasubramani. Chin J Integr Med. 2011; 17(2):88–94.
Chulet. Pharmacogn Rev 2009; 3:229–34

Immunomodulation

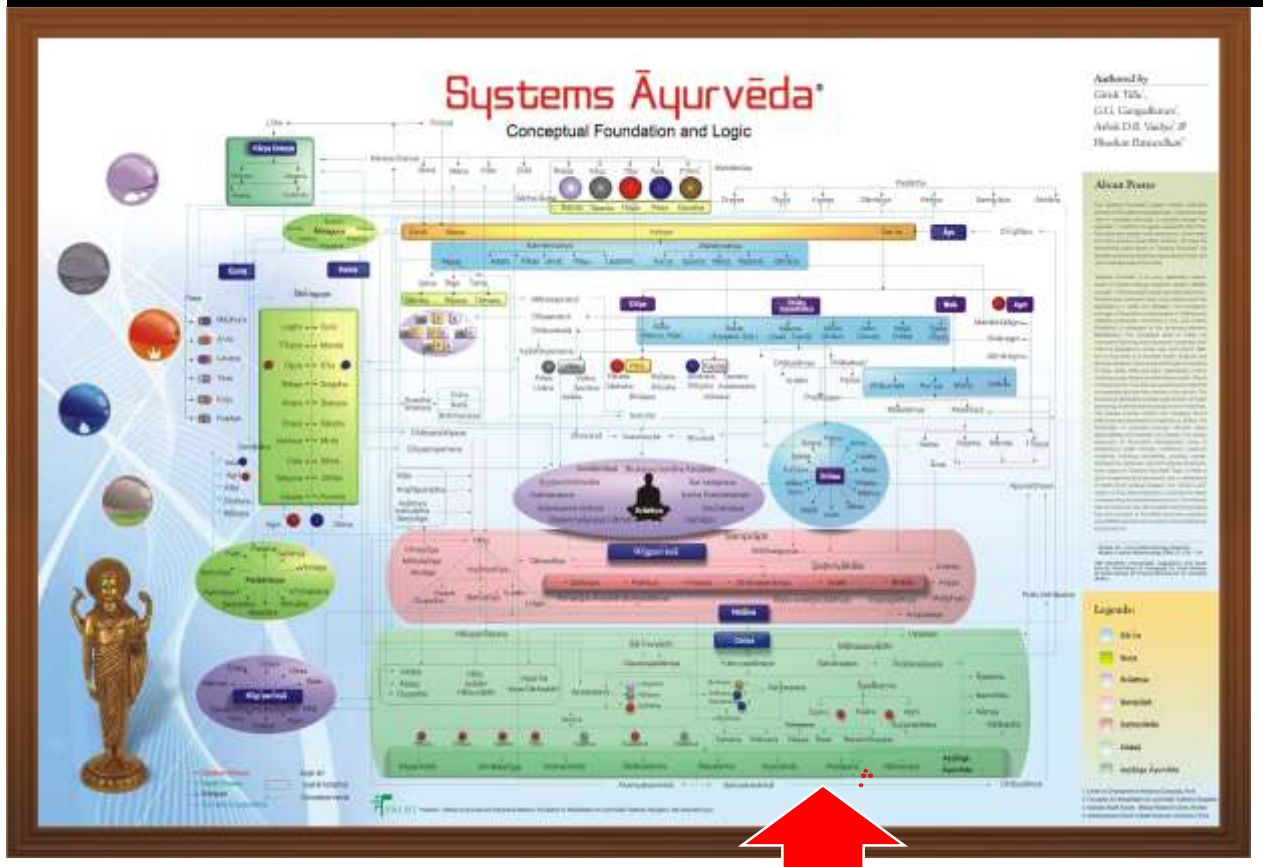
- **immune-homeostasis** balancing T & B cell and Th1/Th2 responses
- **Immunoadjuvants** for vaccines and chemo
- **Optimisation** of immune cells and immune markers

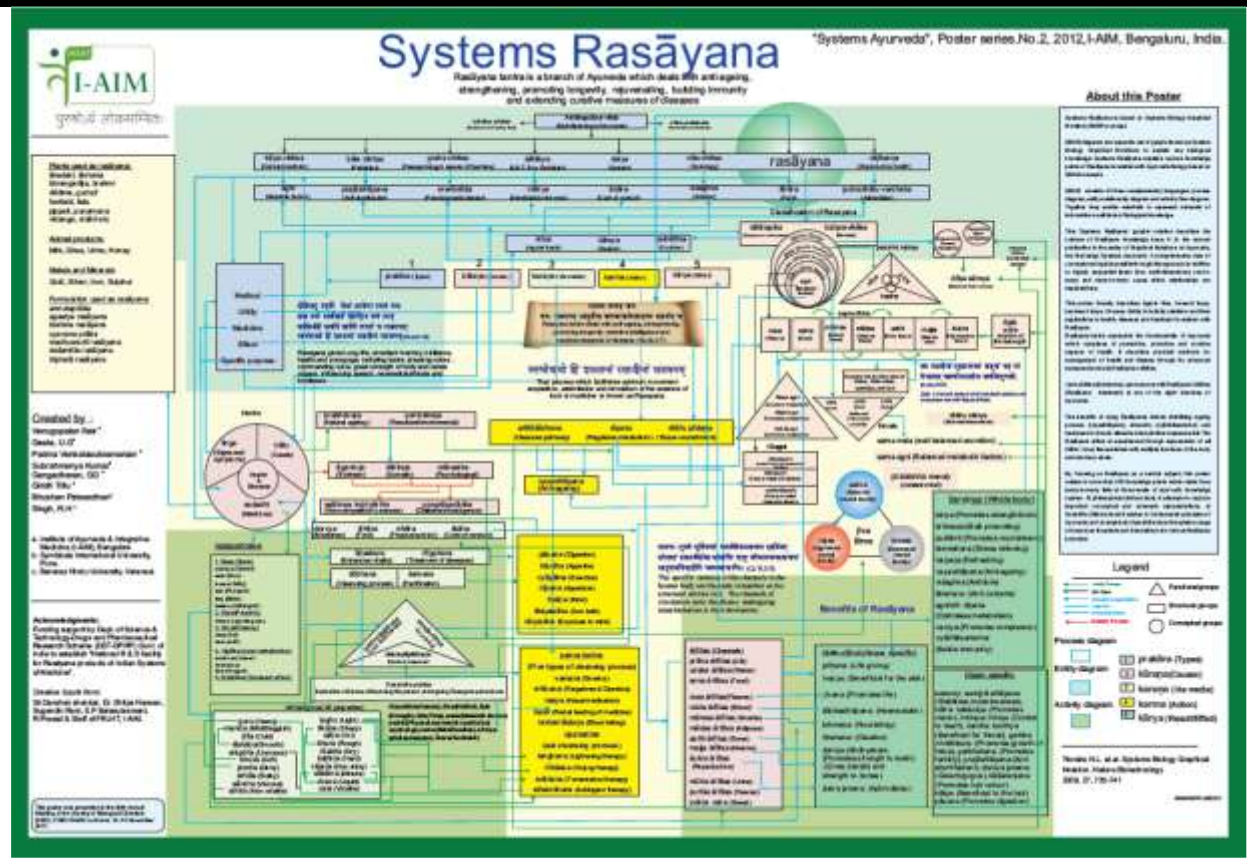
Patwardhan. Curr Sci 2020; 19:1158–60.
Tripathi. Anc Sci Life. 1999; 19(1-2):59-63.

Overview of Ayurveda

Holistic Personalized Medicine

4 Classic Books - 230 Knowledge points - 25000 Sutras - Systems Biology Graphical Notation Framework





IMMUNOMODULATION
AYURVEDA-BASED BOTANICALS

Representative Botanicals with Immunomodulatory Action

Asparagus racemosus

शतावरी गुरुः शीता तिक्ता स्वाद्वी रसायनी ।
मेधाऽग्निपुष्टिदा स्निग्धा नेत्र्या गुल्मातिसारजित् ।।

Tinospora cordifolia

गुडूची कटुका तिक्ता स्वादुपाका रसायनी ।
संग्राहिणी कषायोष्णा लघ्वी बल्याऽग्निदीपनी ।।

Withania somnifera

अश्वगन्धाऽनिलश्लेष्मश्वित्रशोथक्षयापहा ।
बल्या रसायनी तिक्ता कषायोष्णाऽतिशुक्रला ।।

Curcuma longa

हरिद्रा कटुका तिक्ता रूक्षोष्णा कफपित्तनुत् ।
वर्ण्या त्वग्दोषमेहास्रशोथपाण्डुव्रणापहा ।।

Emblica officinalis

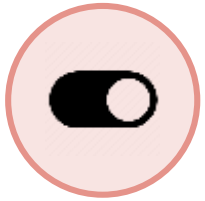
रक्तपित्तप्रमेहघ्नं परं वृष्यं रसायनम् ।
हन्ति वातं तदम्लत्वात्पित्त माधुर्यशैत्यतः ।।

Glycyrrhiza glabra

यष्टी हिमा गुरुः स्वाद्वी चक्षुष्या बलवर्णकृत् ।
सुस्निग्धा शुकला केश्या स्वर्या पित्तानिलास्रजित् ।।

IMMUNOMODULATION
SCIENTIFIC EVIDENCE

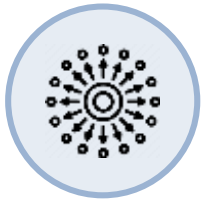
Immune-activation



- T-cell and macrophage activation
- Increase in phagocytosis and neutrophil functioning
- Hemolytic antibody responses

Bani. J Ethnopharmacol. 2006;107(1):107–15.
Patwardhan. Drug Discov Today. 2005;10(7):495–502.
Ziauddin. J Ethnopharmacol. 1996;50(2):69–76.

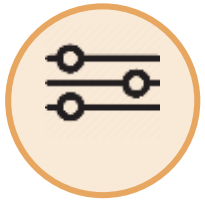
Cell proliferation



- Proliferation of selective Th1 cells
- Increase in count of CD4 and CD8 cells
- Increase in $CD3^+$ and $CD4/CD8^+$ percentages

Patwardhan . J Ayu Integr Med. 2021;12(2):227–8.
Gautam. J Ethnopharmacol. 2009;121(2):241–7.

Marker modulation

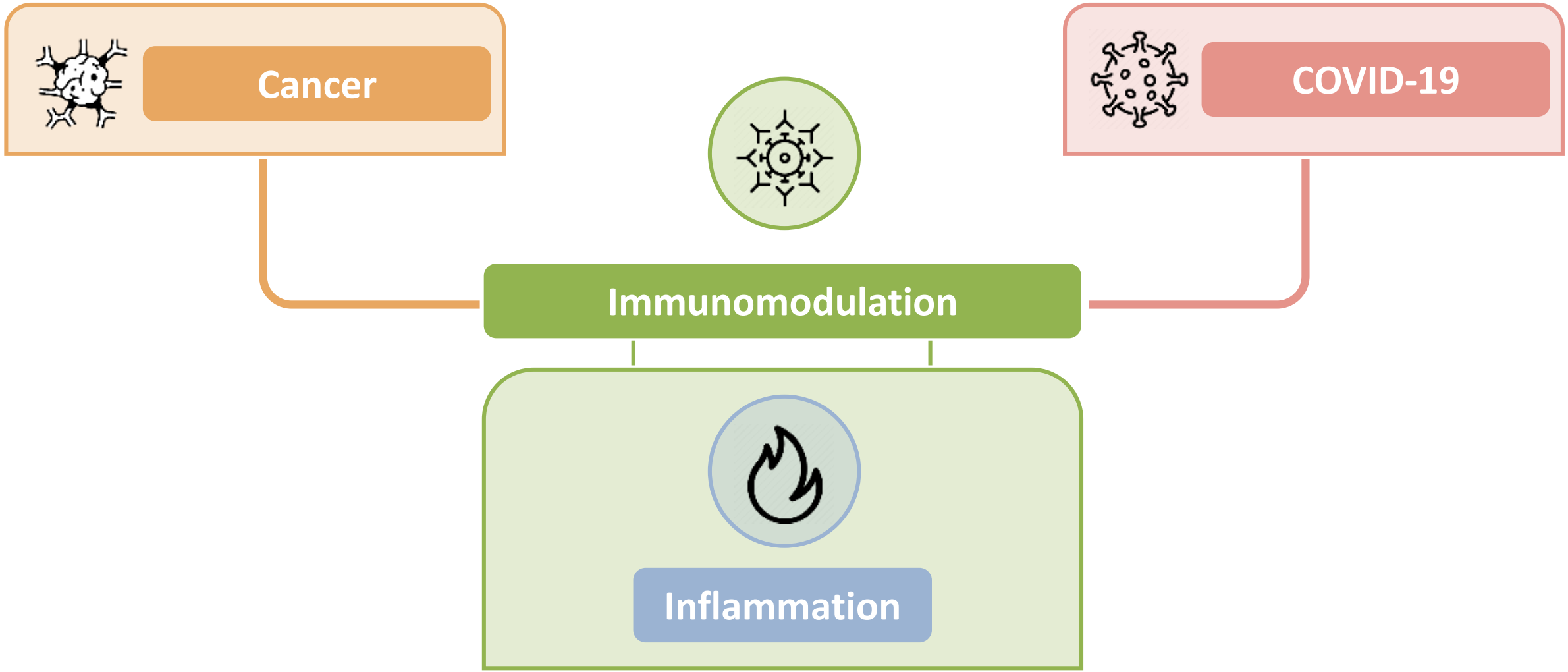


- Upregulation of IL-2, IFN-γ, IL-4, and GM-CSF
- Downregulation of NF-κB and IL-10
- Increase in agglutinin antibody titre and immunoglobulins

Bani. J Ethnopharmacol. 2006;107(1):107–15.
Patwardhan. Drug Discov Today. 2005;10(7):495–502.
Ziauddin. J Ethnopharmacol. 1996;50(2):69–76.

IMMUNE-INFLAMMATION

PHYSIOLOGICAL BRIDGE BETWEEN CANCER AND COVID-19



IMMUNOMODULATION
CANCER ADJUVANT

Immunity

- Increase in **NK cell activity** and antibody dependent **cellular cytotoxicity**
- **Interference** with tumor growth and **metastasis**
- Downregulation of **inflammatory** markers

Diwanay. Curr Med Chem Anticancer Agents. 2004;4(6):479–90.

Chemoprotection

- **Prevention** of **myelosuppression**
- **Increase** in bone marrow **cellularity**
- **Increase** in haemolytic and hemagglutinating **antibody** titers

Saggam. Front Pharmacol. 2022;13:835616.
Diwanay. J Ethnopharmacol. 2004;90(1):49–55.
Diwanay. Curr Med Chem Anticancer Agents. 2004;4(6):479–90.

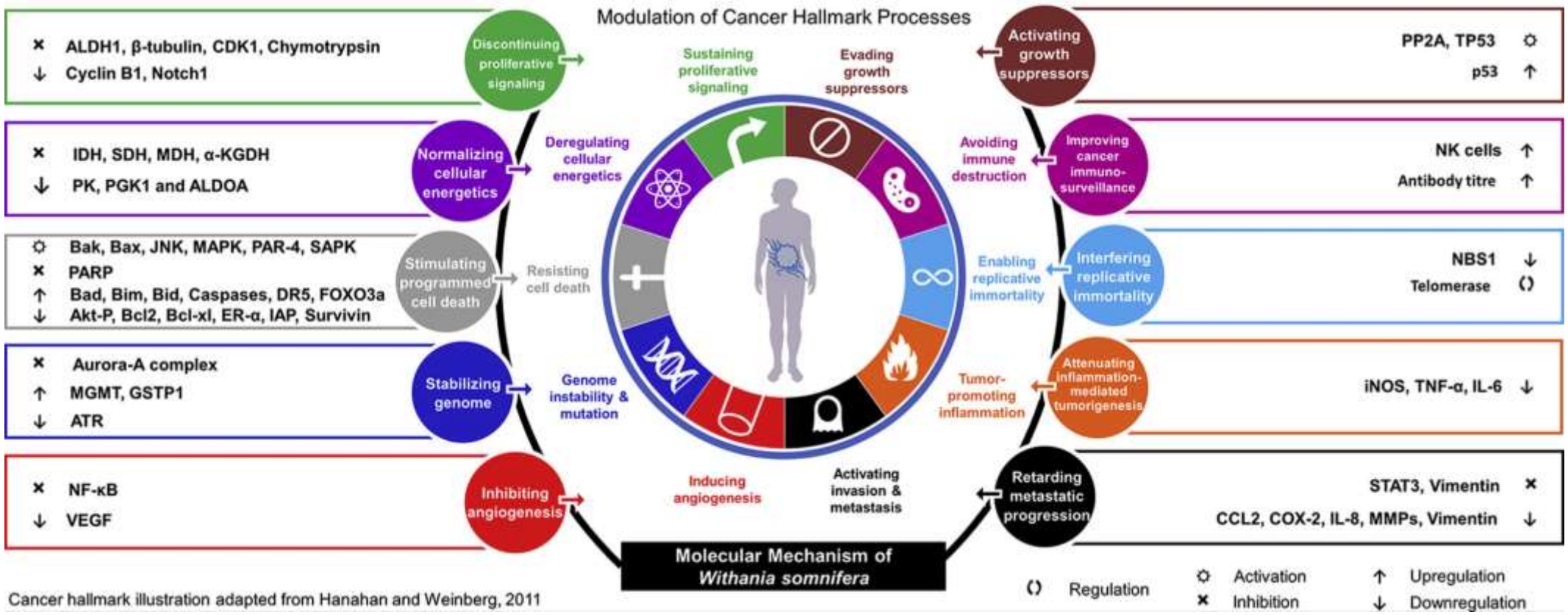
Quality of Life

- **Reduction** in post-therapeutic **pain**
- **Alleviation** of nausea, constipation, and **fatigue**
- Recovery of **appetite**
- **Improvement** in functional **activities** in daily routine

Deshmukh. Support Care Cancer. 2014;22(11):3007-15.
Biswal. Integr Cancer Ther. 2013;12(4):312-22.

IMMUNOMODULATION
CANCER ADJUVANT

Role of Ashwagandha in Cancer



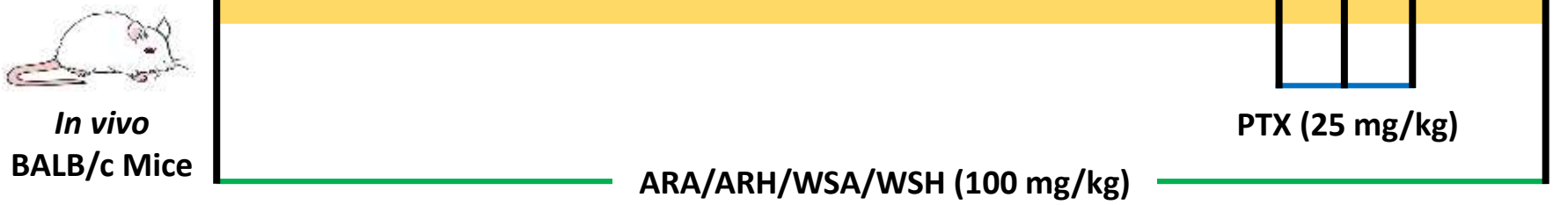
Saggam. J Ethnopharmacol 2020; 255: 112759.

CANCER ADJUVANT

ASHWAGANDHA AND SHATAVARI IN CHEMOTHERAPY-INDUCED MYELOSUPPRESSION

METHODOLOGY
EXPERIMENTAL DESIGN

Extrapolation of clinical dose of PTX and extracts to mice dose



Groups (N=10)	ARA/ARH/WSA/WSH (100 mg/kg) (oral)	Crem. : EtOH (1:1) (intraperitoneal)	PTX (25 mg/kg) (intraperitoneal)
Vehicle Control	-	Day 16-18	-
PTX25	-	-	Day 16-18
PTX25 + ARA100	Day 1-20	-	Day 16-18
PTX25 + ARH100	Day 1-20	-	Day 16-18
PTX25 + WSA100	Day 1-20	-	Day 16-18
PTX25 + WSH100	Day 1-20	-	Day 16-18

PTX- paclitaxel; **ARA**- *A. racemosus* aqueous extract; **ARH**- *A. racemosus* hydroalcoholic extract; **WSA**- *W. somnifera* aqueous extract; **WSH**- *W. somnifera* hydroalcoholic extract; **Crem.**- Cremophor® EL (polyoxyethylated castor oil vehicle); **EtOH**- Ethanol

METHODOLOGY
OUTCOME VARIABLES

Hematology Analysis

Total Leukocyte Count | Absolute Neutrophil Count | Cytokine Profiling

Morbidity Analysis

Clinical adverse effect of PTX	Observations and signs in animals	Parameter
Fatigue (extreme tiredness)	Reduction of general wandering of animal in cage	Activity
Peripheral neuropathy (numbness, weakness)	Abnormal behaviour and lack of relocation	Behaviour
Hair loss (alopecia)	Ruffled and fur loss represents alopecia	Fur aspect
	Adult mice huddle in response to cold	Huddling
Painful muscles and joints	Hunched posture is a sign of to pain or distress	Posture

Marupudi NI et al. **Paclitaxel: A review of adverse toxicities and novel delivery strategies**. Vol. 6, Expert Opinion on Drug Safety. 2007. p. 609–21.

Banipal RPS et al. **Assessment of Cancer-related Fatigue among Cancer Patients Receiving Various Therapies: A Cross-sectional Observational Study**. Indian J Palliat Care. 2017;23(2):207–11.

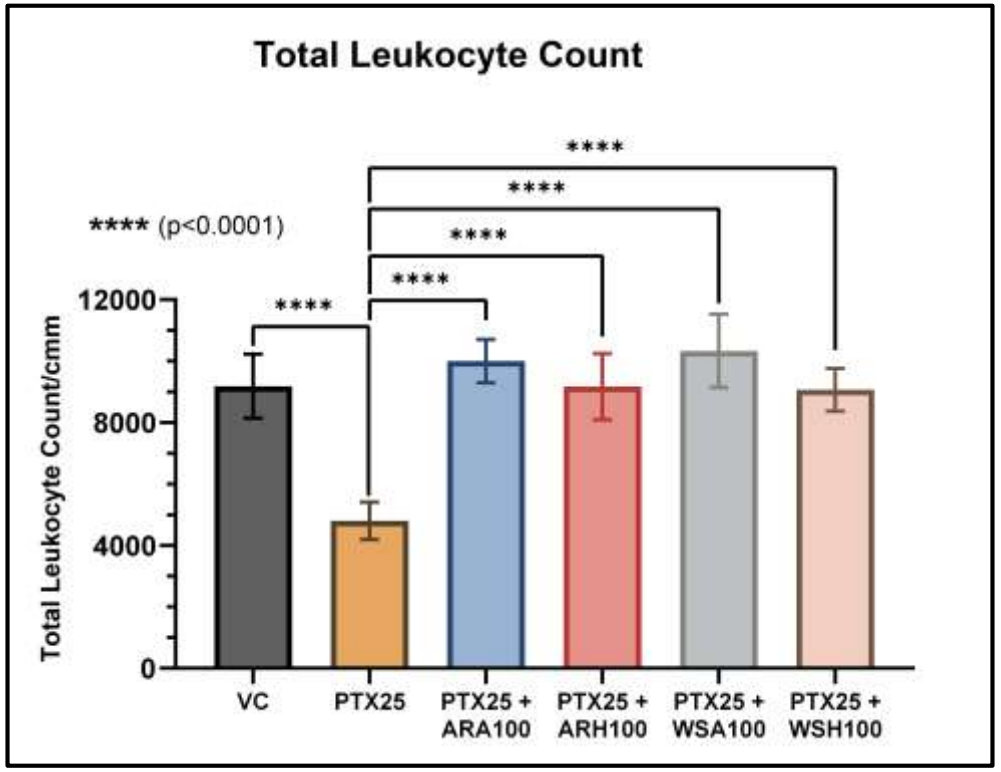
Banerjee R et al. **Are Observational, Real-World Studies Suitable to Make Cancer Treatment Recommendations?** JAMA Netw Open. 2020 Jul 30;3(7):e2012119–e2012119.

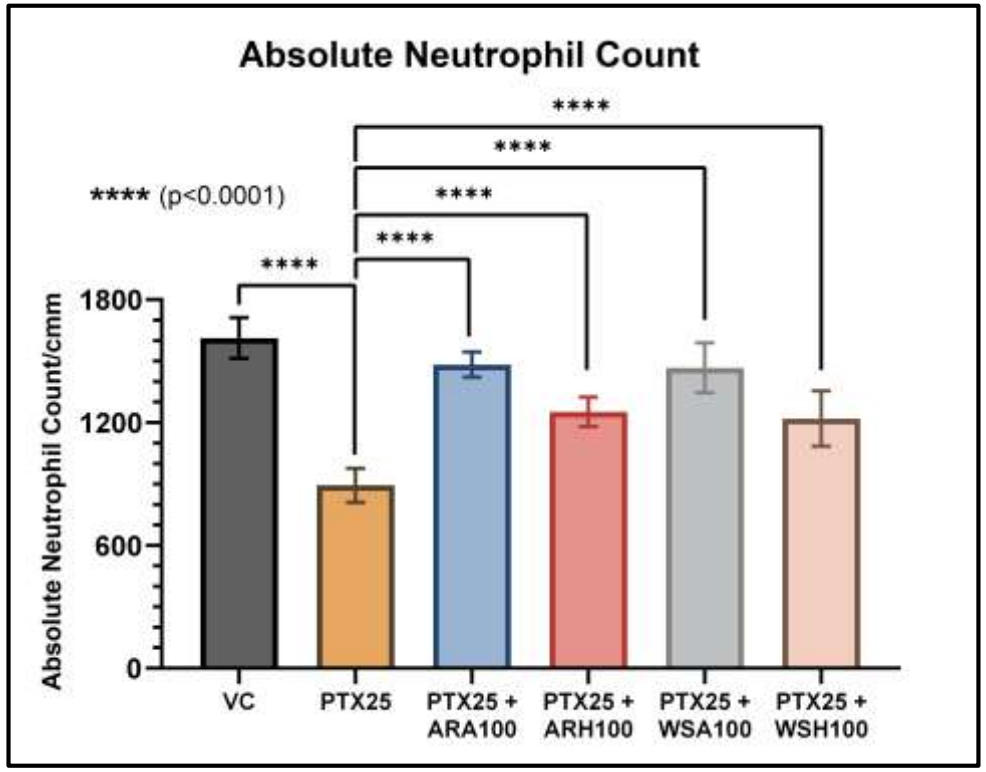
Paclitaxel (Taxol) | Breast Cancer Now. Available from: https://breastcancernow.org/information-support/facing-breast-cancer/going-through-treatment-breast-cancer/chemotherapy/paclitaxel-taxol

Clinical Signs of Pain and Disease in Laboratory Animals | It's Your Yale. Available from: https://your.yale.edu/policies-procedures/guides/4446-clinical-signs-pain-and-disease-laboratory-animals

Batchelder P et al. **Effects of temperature and social interactions on huddling behavior in Mus musculus**. Physiol Behav. 1983 Jul;31(1):97–102.

RESULTS
HEMATOLOGY ANALYSIS





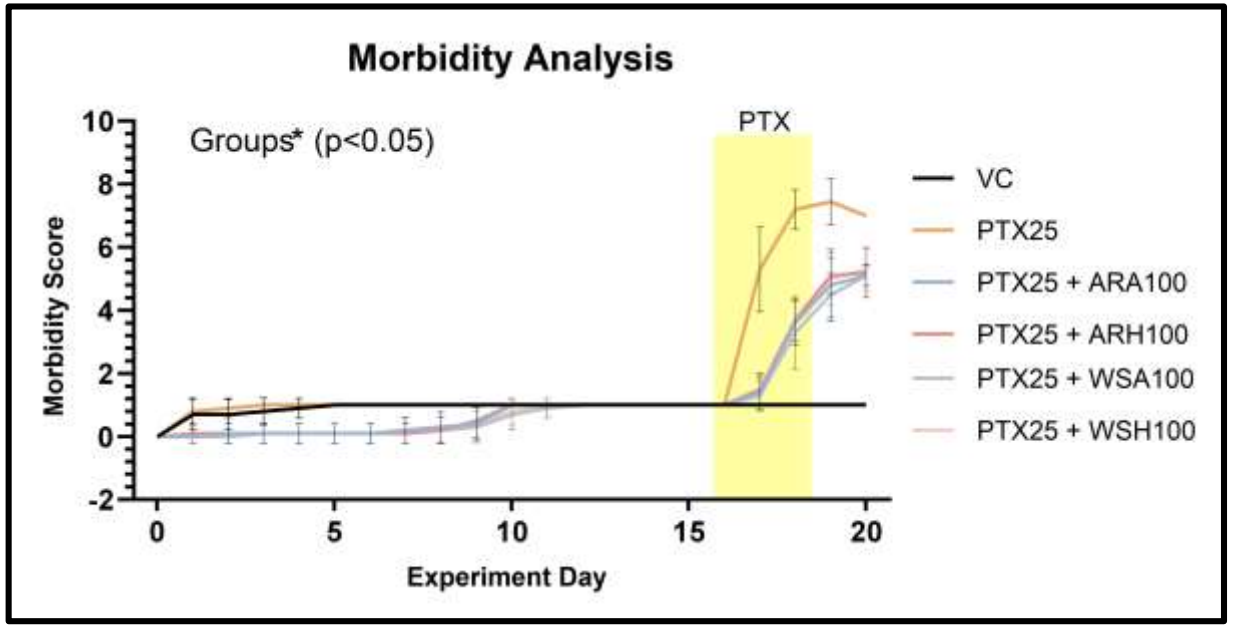
- Significant induction of leukopenia by PTX25
- Extracts prevented PTX-induced leukopenia

- Significant induction of neutropenia by PTX25
- Extracts prevented PTX-induced neutropenia

AR and WS significantly prevents PTX-induced myelosuppression.

RESULTS
MORBIDITY ANALYSIS

Scoring	0	1	2	3
Activity	Normal	Reduced	Only when provoked	Little or none with provocation
Behaviour	Normal	Slow normal on disturbed	Abnormal on disturb and relocation	Abnormal on disturb and no relocation
Fur aspect	Normal	Slightly ruffled or mild fur loss	Ruffled fur, moderate loss fur loss	Ruffled fur, piloerection, significant fur loss
Huddling	Normal	Mild grouping/ social proximity	Moderate grouping/ social proximity	High grouping/ social proximity
Posture	Normal	Slightly hunched, moving freely	Hunched with stiff movement	Hunched with little or no movement



PTX administration on day 16-18 increase morbidity by-

- Decrease in activity and behaviour
- Increase in huddling and hair loss
- Change to hunched posture

AR and WS significantly prevents PTX-induced morbidity.

Endo. Commun. Biol. 2018;1, 225. **Huet**. Shock. 2013;39, 488–494. **Mai**. Intensive care Med. Exp. 2018;6, 20. **Paster**. Comp. Med. 2009;59, 234–241. **Thomas-Stonell**. Dysphagia. 1988;3(2):73–78

RESULTS

CYTOKINE PROFILING (A panel of 20 cytokines)

Cancer Progression

- Invasiveness & metastasis
- Inflammation

- ↓ GM-CSF #
- ↓ IL-1α # #
- ↓ IFN-γ #
- ↓ IL-13 #
- ↓ IL-1β # #

Hematopoiesis

- Granulopoiesis
- Cell proliferation

- ↑ G-CSF #
- ↑ KC ##
- ↑ IL-2 #
- ↑ MCP-1 ###
- ↑ IL-3 #
- ↑ TNF-α ##
- ↑ IL-17A #

Morbidities

- Fatigue, pain & alopecia
- Peripheral neuropathy

- ↓ Eotaxin #
- ↓ IL-10 #
- ↓ IL-4 #
- ↓ MIP-1α #
- ↓ IL-5 #
- ↓ MIP-1β #
- ↓ IL-6 ###
- ↓ RANTES #

↑ Upregulation

↓ Downregulation

\# Hematopoietic cytokines

\# Inflammatory cytokines

\# Morbidity cytokines

AR and WS modulates PTX-induced altered cytokine levels.

Singh. 2017. BMC Musc Dis 18 (1): 17
Voloshin 2015 Mol Can Ther 14 (6):1385–94
Shi. 2018 Acta Cirurgica Bra 33 (6): 491–98
Bower 2014 Clin Onc 11 (10): 597–609
Manjavachi 2014 Neuropharma 79: 17–27
Cook 1996 J Leuko Bio 59 (1): 61–66.

Watari. 1989 Blood 73 (1): 117–22
Metcalf 2008 Blood 111 (2): 485–91
Ito. 2020 Exp Derm 29 (8): 726–32
Tiwari 2017 Biomed Pharma 86: 555–61
Piotrowska 2019 Fron Imm 10: 2198.
Broxmeyer 1993 J Imm 150: 3448-58.

Tsavaris. 2002 B Jour Can 87 (1): 21–27
Groopman 1989 N E J M 321 (21): 1449–59
Zheng 2021 E Clin Med 31
Krstic 2012 Imm Res 52 (1–2): 34–41
Deshmane 2009 J Int Cyt Res 29 (6): 313-26.
Liou 2013 J Pain 14 (1): 24–35

Harmon 1993 Lymph Cyto Res 12 (4): 197–203
Murphy 1993 Tox Path 21 (2): 229–30
Pusztai 2004 Cytokine 25 (3): 94–102
Mojsilović 2015 Med Infla 2015: 470458
Zhang 2013 J Pain 14 (10): 1031–44.
Yamashita 2019 Stem Cell 25(3): 357-372

SUMMARY

TRADITIONAL MEDICINES PREVENT PACLITAXEL-INDUCED MYELOSUPPRESSION

- Dose limiting toxicities of Chemotherapy- **leukopenia** and **neutropenia**
- **Prevention** of chemotherapy-induced **leukopenia** and **neutropenia**

Prevention of Myelosuppression

- **Downregulation** of **oncogenesis-** and **morbidity-**associated **cytokines**
- **Upregulation** of **hematopoietic** cytokines to achieve **immune-homeostasis**

Normalization of Cytokines

- **Decrease** in chemotherapy-associated **morbidity parameters**, such as-
  - Joint pain and fatigue
  - Peripheral neuropathy
  - Alopecia

Amelioration of Physical Morbidity

A. racemosus **and** ***W. somnifera*** **are potential chemotherapeutic adjuvants.**
The *Rasayana* effect can reduce adverse drug effects and maintain immune-homeostasis.

COVID-19 ADJUVANT

INFLAMMATION AND IMMUNOMODULATION

IMMUNOMODULATION
COVID-19 ADJUVANT

Viral Load Prevention

- **Inhibition** of host **receptor**
- Antioxidant property to maintain **oxidative balance**
- Improvement in **Th1 cell response**
- Enhancing **immune** cell **functioning**

Patwardhan. Curr Sci. 2020;118(8):1158-60.

Immune-homeostasis

- **Balancing** immune cell **activities**
- **Mitigation** of cytokine **storm**
- **Downregulation** of **inflammatory** markers
- **Prevention** of **pyrexia**

Saggam. Front Pharmacol. 2021;12:623795.

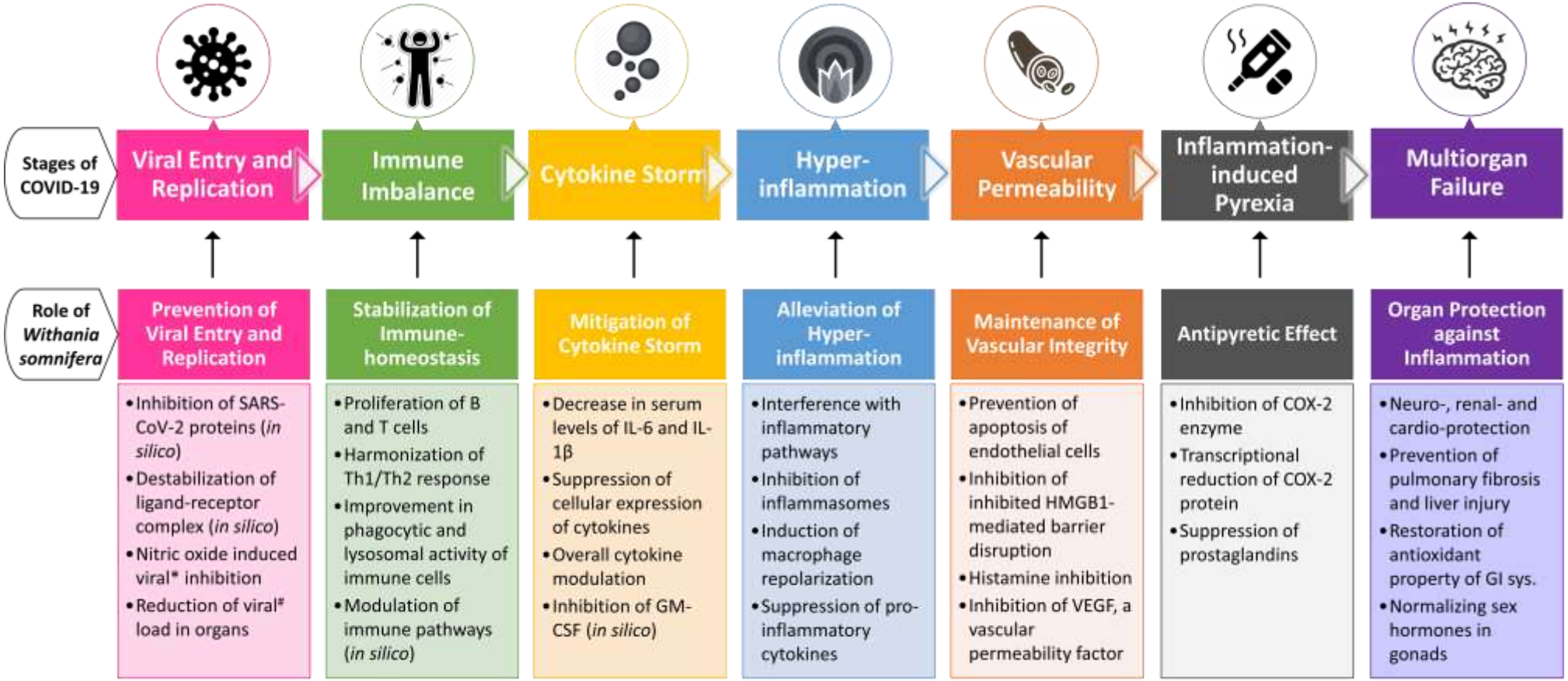
Organ Protection

- **Prevention** of inflammation -induced **organ failure**
- **Inhibition** of pulmonary **fibrosis**
- Neuro-, renal- and cardio-**protection**
- **Normalizing** sex **hormones**

Borse. PLoS One. 2021;16(6):e0248479

IMMUNOMODULATION
COVID-19 ADJUVANT

Probable Role of Ashwagandha in COVID-19



* infectious bursal disease virus; * chicken anaemia virus

Saggam. Front Pharmacol. 2021;12:623795.

AYUSH IN COVID-19
INTERVENTIONS AND STUDIES

Interventions

- **Ayurveda-** AYUSH 64, Kabasura Kudineer, Guduchi, Pippali, Yashti, Ashwagandha, Shunthi, Sanshamani Vati
- **Industry Products-** Anu Tail, Sudarshan Vati, Ayush Kwath, Chyavanprash
- Homeopathy, Unani, Siddha, Sowa Rigpa, Yoga

Clinical Studies

126 Studies

1,30,000 Participants

150 Sites

Prophylaxis
(42 Studies)

22 RCTs

Prospective	Retrospective
Observational	Population-based

Therapy
(50 Studies)

30 RCTs

Prospective	Retrospective
Observational	Open Label

Preclinical Studies

- **Immunomodulation-** innate and adaptive
- **Pharmacology-** anti-inflammatory effect, cytotoxicity
- **Anti-viral Activity**- Syrian hamster model
- **Co-morbidities**- obesity, IR, pulmonary and blood
- **Toxicity Studies-** CNS, CVS, respiratory studies
- ***In-vitro-*** PK studies

A-66, Y13, U8, S13, H26 Robust Protocols, GCP, CTRI, DSMB, CROs, External Audits

AYUSH IN COVID-19
CLINICAL TRIAL

Ashwagandha as Adjuvant to COVID-19 Vaccine

- 1200 Sample size
- 7 Collaborators
- Study sites: CRD-Pune, CCRAS institutions and THSTI
- Approved by CEC/IECs
- Study registered in CTRI
- Protocol in Frontiers in Medicine

AYUSH TASK-FORCE FOR COVID-19
PUBLICATIONS

Publications: AYUSH in COVID-19

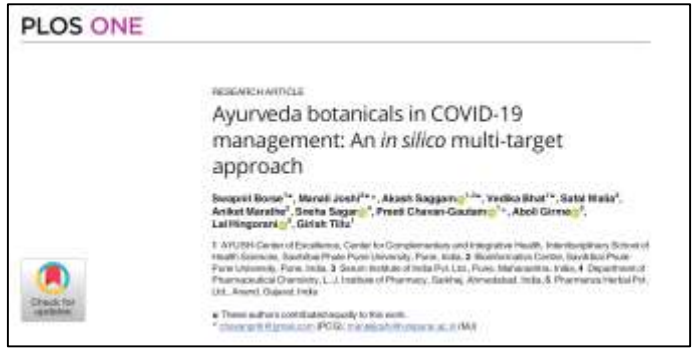
30 Online Preprints

15 Journal Publications

37 Under Peer Review


frontiers in Pharmacology

Withania somnifera (L.) Dunal: Opportunity for Clinical Repurposing in COVID-19 Management

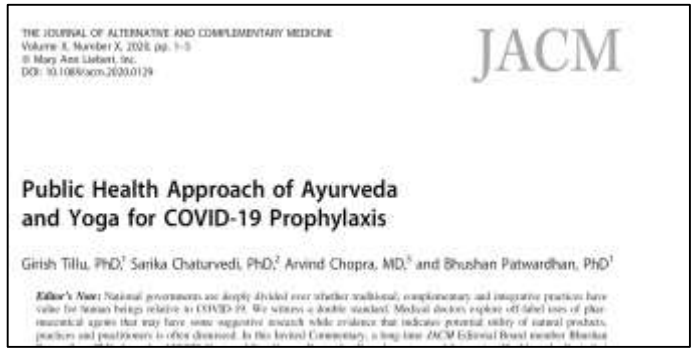

PLOS ONE

Ayurveda botanicals in COVID-19 management: An *in silico* multi-target approach


Journal of Ayurveda and Integrative Medicine

Editorial

Significance of AYUSH; India's first line of defence against COVID-19


JACM

Public Health Approach of Ayurveda and Yoga for COVID-19 Prophylaxis

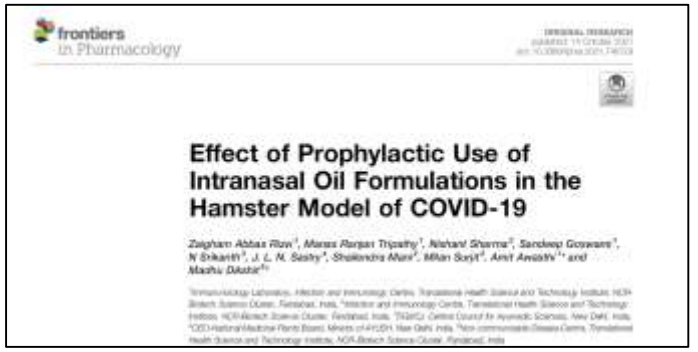
Girish Tillu, PhD; Sarika Chaturvedi, PhD; Arvind Chopra, MD; and Bhushan Patwardhan, PhD


Complementary Therapies in Medicine

Short Communication

Withania somnifera as a safer option to hydroxychloroquine in the chemoprophylaxis of COVID-19: Results of interim analysis

Arvind Chopra, Narayanam Srikanth, Bhushan Patwardhan, AYUSH CCRAS Research Group

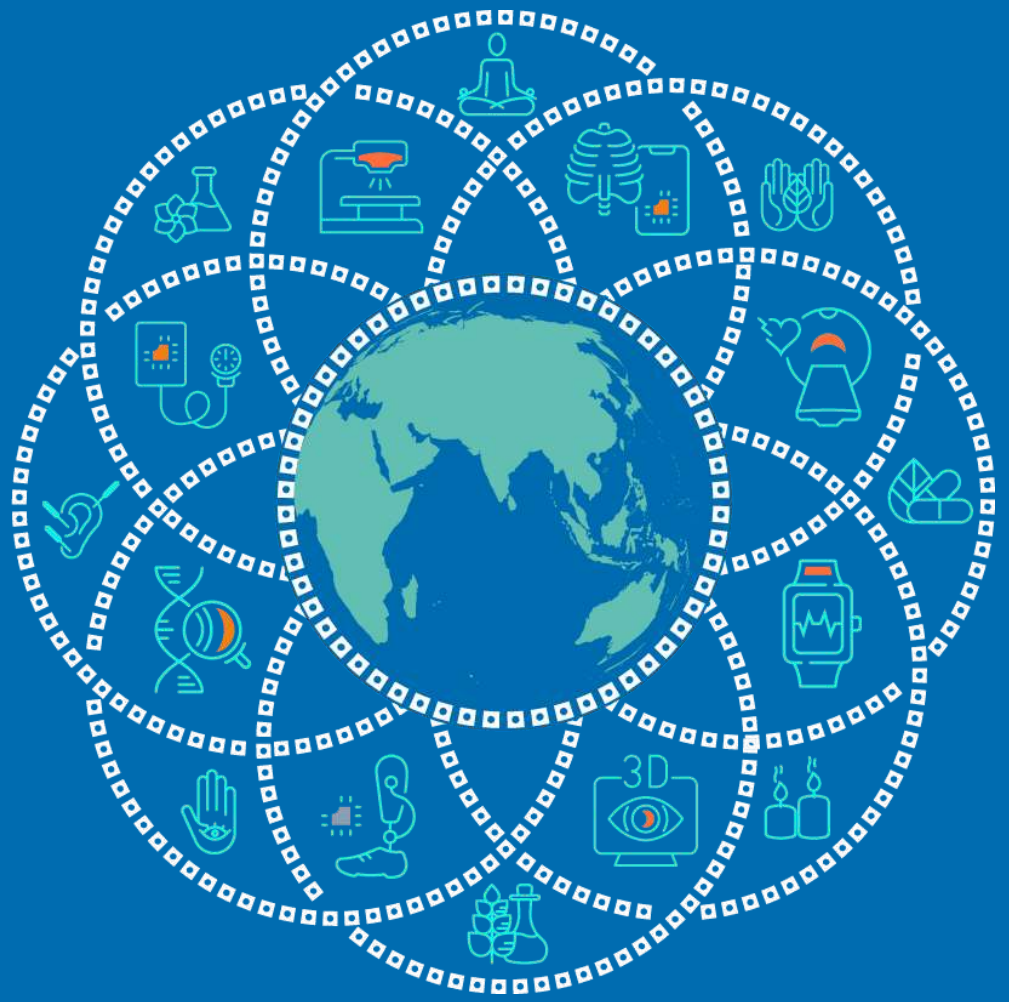

frontiers in Pharmacology

Effect of Prophylactic Use of Intranasal Oil Formulations in the Hamster Model of COVID-19

AYUSH RESOURCES
APP AND REPOSITORY

AYUSH Sanjivani App

- **15M** Health seekers data captured
- **75K** Physicians utilized AYUSH for prophylaxis
- **85%** AYUSH users for COVID-19 prevention
- **63%** Improvement in wellbeing & health status



World Health Organization

WHO GCTM INDIA

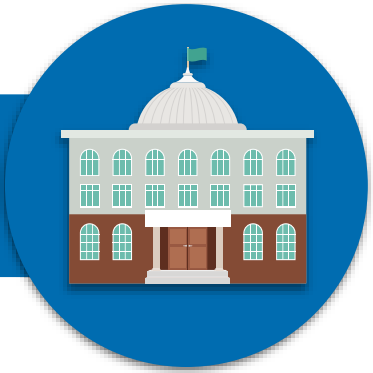
Catalysing Ancient Wisdom and Modern Science for the Health of People and the Planet

June 2022

Traditional Medicine in WHO Regions

ILLUSTRATIVE EXAMPLES

AFRO	AMRO	EMRO	EURO	SEARO	WPRO
E.g. African Traditional Medicine	E.g. Osteopathy, Chiropractic	E.g. Traditional Arab and Islamic Medicine	E.g. Naturopathy, Homeopathy	E.g. Ayurveda, Yoga, Unani, Nuad Thai	E.g. TrCM, Acupuncture, Tuina
					



170 WHO Member States report the use of traditional medicine; top priority request to WHO for evidence, data, standards and regulatory frameworks

Around 80% of the world's population is estimated to use traditional medicine

GCTM Foundation

Prime Minister Shri. Narendra Modi

PM Modi's leadership vision to establish a new WHO Global Centre for Traditional Medicine, during the historic 75th year national anniversary celebrations 'Azadi Ka Amrut Mahotsav', as a global good.

WHO DG Dr. Tedros Adhanom Ghebreyesus

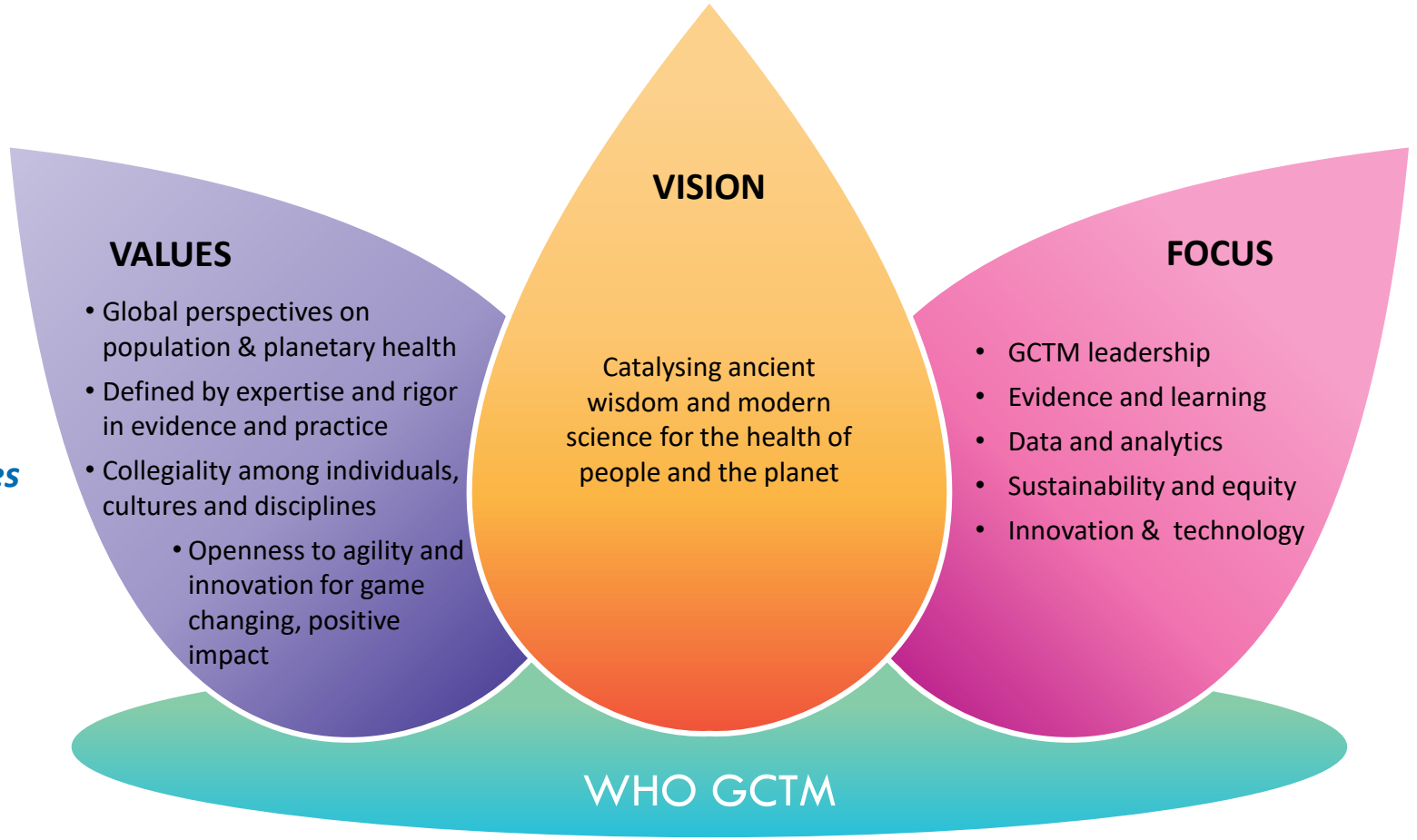
WHO DG's leadership vision that harnessing the potential of traditional medicine would be a game changer for the health of people and the planet when founded on evidence and equity.

Vasudhaiva Kutumbakam | **"The World is One Family".**

WHO GCTM Strategic Vision

Contributory to WHO's Mission, GPW Targets, Traditional Medicine Strategy and Sustainable Development Goals

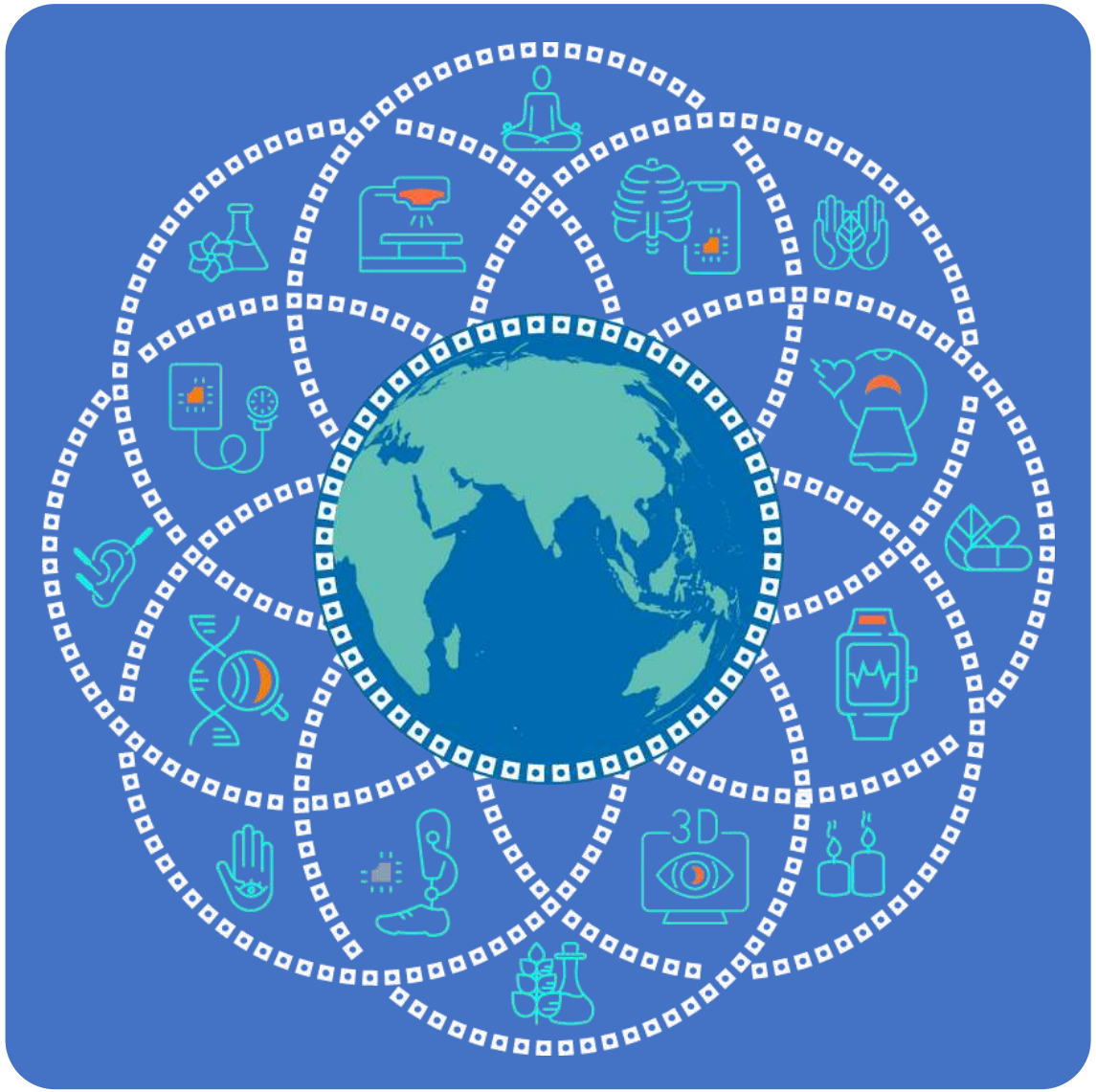
Aligned with WHO's global values



Complementary to WHO's core functions

Responsive to countries' needs to improve population and planetary health

WHO GCTM Focus Area



Evidence and Learning

Evidence syntheses and reviews with WHO Science Division, Cochrane Collaboration, Lancet Citizens' Commission etc. Links with WHO academy on TM courses

Data and Analytics

Updating global surveys on traditional medicine – on TM policies, education, and practice and inclusion of TM questions in WHO World Health Survey + household survey

Sustainability and Equity

Country profiles for all WHO MS, supported by regions, that highlight biodiversity, social- cultural heritages, scientific advances and equity and sustainability considerations.

Innovation and Technology

Artificial Intelligence (AI) mapping of TM trends, innovations, patents; developing and updating apps WHO's m-yoga app, linking to WHO Innovation Hub etc.

Thank You All and NIH/NCI-OCCAM

Faculty, Students, Collaborators, Funders

Faculty & Students

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Looking Forward to Continued Interactions and Collaborations!

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