

## Bioactives & Traditional Medicinal Systems for Cancer Relief: A Global Glimpse

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### ABSTRACT

The growing the global cancer burden, 2<sup>nd</sup> leading cause of death, faces the challenge of the recurrence or resistance of cancers to chemotherapy, besides higher risk of antimicrobial resistance [AMR] due to the weakened immunity post chemotherapy. Bioactives such as Curcumin and Quercetin, among others from traditional Systems of Medicine such as Ayurveda, Chinese, Unani & Homeopathy can provide relief and aid in faster or better recovery during Cancer treatment, as adjuvant to the modern treatment viz. chemotherapy by alleviating its strong Adverse drug reaction [ADR] observed among majority of the cancer patients. ADR issues include nausea, vomiting, headache, and fever, loss of hair, loss of fertility and immunity. Bioactives influence the Endoplasmic reticulum (ER) stress leading to apoptosis of tumor cells to control the cancer, besides targeting topoisomerase the limiting the cell replication and telomere length.

**Keywords:** Ayurveda, Neoplasm peptides, Unani, Homeopathy

### INTRODUCTION

Cancer is the 2<sup>nd</sup> leading cause of death in the world causing 10 million i.e. 16% of global deaths in 2018 vide World health Organization data [1]. The International Agency for Research on Cancer (IARC) predicts 21.7 million cancer cases and 13 million deaths in 2030 [2]. The cancer incidence in the developing world is 55% of new cases today, and may rise to 60% by 2020 and 70% by 2050. The cost associated with cancer cases was about US\$1.16 trillion in 2010 globally, and >2% of the total global gross domestic product (GDP). This precludes the substantial longer-term costs to families and caregivers and suffering cost is hard to measure [3]. Surgery, radiation therapy, and chemotherapy is the current gold standard of care for cancer but with limitations that include the lack of screening tests for early diagnosis and tumor-specific drug delivery systems. Further, most classical anticancer drugs harm normal cells too, causing systemic toxicity and adverse drug reactions (ADR) such as nausea, vomiting, mucositis, alopecia, neuropathy and myelosuppression [4]. In addition, these drugs are associated with multidrug resistance (MDR), a problem responsible for more than 90% of cancer patient deaths in chemotherapy. Immunotherapy appears promising but its high cost and complexity may limit its reach or new challenges may surface [5]. Thus, Herbal remedies, with their long history of use in traditional medicine systems, are rich in bioactives and offer a potentially gentler and more

natural approach to symptom management. Patients seek such alternatives or complements to conventional treatments fraught with harsh side effects so nearly 50% lung cancer patients surveyed expressed willingness to participate in herbal clinical trials, it's said [4]. Such growing interest globally in bioactives including from traditional medicinal systems triggered this mini desk review of the topic, aimed to:

- Enlist top priority bioactives with clinical or strong *in vivo/ in vitro* evidence in treating cancer/ cell lines
- Depict the pharmacological action of these bioactives on cancer pathology
- Indicate future scope of natural products for the cancer patients for better cure/ Quality of Life (QOL).

### BIOACTIVES SCOPE IN CANCER TREATMENT

Selective and more efficient new drugs are urgently being

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exploded includes bioactive peptides from animals such as milk and dairy products [3] that contain bioactive peptides as amino acid sequences are that act in 3 ways:

1. Hydrolysis mediated by digestive enzyme
2. Proteolytic microorganisms derived Protein mediated hydrolysis
3. Digestion by proteolytic enzymes derived from microorganisms or plants.

Bovine skim milk digested with cell-free extract from the yeast *Saccharomyces cerevisiae* reportedly inhibits the proliferation of a human leukemia cell line (HL-60). Anticancer activity of casein fraction-derived casein o phosphopeptides (CPPs) is also reported, inhibiting the cancer cell growth and stimulate the activity of immunocompetent cells and neonatal intestinal cells [3]. The study further states that a yogurt fraction obtained by membrane dialysis has anti-proliferative effect on Coca-2 and IEC-6 mammalian intestinal cells and the bacterial hydrolysis of casein by commercial yogurt starter cultures yields bioactive peptides that influence colon cell kinetics *in vitro*. Milk contains “Lactoferrin” an iron-binding glycoprotein (80-kDa) of the transferrin family with many biological functions, including anticancer, and immunomodulatory.

Milk and especially clarified butter from it's an important component of Ayurveda, traditional medicinal system (TSM) in Asia [6]. Further, cow urine rich in peptides is also a famous Ayurvedic treatment for cancer [7-10]. Polyphenols in blocking the adaptive pathway endoplasmic reticulum (ER) stress or facilitating the apoptotic pathway is an emerging cancer management strategy [11]. ER stress i.e. accumulation of unfolded proteins in ER caused by the tumor-microenvironment such as hypoxia, low nutrients that disturb function of the ER to maintain cellular homeostasis, is associated with cancer. An adaptive pathway in cancer is the ER stress initiates unfolded protein response (UPR) to re-establish ER homeostasis as, Thus, an anti-cancer therapeutic strategy can be facilitating ER stress to initiate the apoptosis pathway. For, the cancer cells fail to re-establish ER homeostasis via UPR, if ER stress persists or is aggravated. Then ER stress switches from pro-survival to pro-apoptotic condition. The ER strategy covers mainly lung, breast, colorectal, gastric, prostate, and liver cancer comprising 55% of the global cancer incidence burden 2012. Others have reported the molecular mechanism of cancer management by bioactives [12] as depicted in **Table 1**, especially by alleviating the stress from Reactive Oxygen Species (ROS).

Bioactives such as Curcumin, Quercetin and Resveratrol are also now being proposed to address cancer including the use

of nanotechnology for higher efficacy due to the poor bioavailability of these small molecules [11-14]. Further, innovative, natural products-based therapies in cancer are being proposed such as using vitamin C [15], vitamin D [16] and vitamin E [17]. Antimicrobial resistance [AMR] in gut microbiota may be produced *de novo* by Chemotherapy by activating the bacterial SOS system [18]. Chemotherapy damages the commensal gut microbiota may cause sepsis in cancer patients. Such dysbiosis may be offset by microbiome-based therapeutic interventions and prevent carriage of antimicrobial-resistant pathogens. The mortality of cancer patients may significantly increase globally due to the global; spread of AMR. increase. Herbal medications may help to manage the AMR issues, including in veterinary care given the rising importance of zoonotic diseases as COVID-19 showed [19,20]. Sourcing bioactive from common crops such as spices such as Coriander can alleviate the ecological risk of wild medicinal plants species extinction due to overharvest as proposed in the case of “Seeta Ashoka” tree {*Saraca asoca* [Roxb.] De Wilde} used to treat menorrhagia in Ayurveda south & east Asia [21]. The study also quotes utility of the tree in cancer therapy also traditionally due to many useful phytochemicals content. Microbial production of the desired phytochemical using endophytes of threatened tree species tissue culture is industrial option today as being done in the of Taxol or proposed for Camptothecin [22] obtained from the small tree *Nothapodytes nimmoniana* {syn. *Mappia foetida*}.

Among bioactives, polyphenols are important and can neutralize free radicals thus reducing the reactive oxygen species (ROS) stress, thereby avoiding cancer proliferation. Polyphenols have broad applications such as the treatment of cancer or inflammations, anti-aging aims in cosmetics or nutraceutical purposes, being nootropic, and help in brain functions so reduce the risk of the neurodegenerative diseases [23]. Indian cancer incidence (89 per 100,000 population) was only 25% of the values in EU (363) and USA (387) and 50% of the global value (197). This indicates better immunity in India, which could be due to the 2 times higher spices consumption in India (2 kg/ year/ head) than USA, it is said [24].

Curcumin, a flavonoid from Turmeric roots is known to be anti-cancerous and may hold the key to this pattern [25] as Turmeric is among the commonest spice consumed daily in India and has high antioxidant value. Piperine from Black Pepper, a healthy spice than Chilly, Quercetin from onion, Eugenol from Clove, Ursolic Acid from Holy Basil, Gingerol from ginger are other important bioactives in Indian diet, causing better immunity & 90% lower COVID-19 incidence (31,000 per 1 million population) & only 1% mortality compared to 5-10% in European countries or USA.

**Table 1.** Some important bioactives and their molecular mechanism to address cancer [12].

Phytochemicals compounds	Plants# [13]	Cancer model	Concentrations	Molecular effects
<b>Berberine</b>	Indian Berberis*	Human glioma cell U251 and U87 GBM	100 nM	Inhibition of AMPK/mTOR/ULK1
<b>Cucurbitacin B</b>	Ashgourd	Breast cancer cell MCF-7	200 µM	Elevation of γH2AX, phosphorylation of ATM/ ATR, ROS
<b>Curcumin</b>	Turmeric	Malignant mesotheloma cancer cell MM-B1, H-Meso-1, and MM-F1	25 µM	Raise Bax/bcl-2 ratio, p53 expression, activation of caspase 9, cleavage of PARP-1
<b>Epigallocatechin-gallate (EGCG)</b>	Tea	Human glioblastoma cell T98G and U87MG	500 µM	Raise the level of ROS
<b>Gingerol</b>	Ginger	Human colon cancer cell SW-480 and HCT116	300 µM	Inhibition of JNK, ERK1-2, and P38 MAPK
<b>Hesperetin</b>	Orange, Lemon	Lung cancer cell H522	350 µM	Knockdown caspase-3/9, p53, Bax Upregulate Fas, FADD and caspase-8
<b>Kaempferol</b>	Beans, Grape, Tea, Spinach	Colorectal cancer cell HCT116, HCT15, and SW480	50 or 100 µM	Produced ROS and p53 signal
<b>Luteolin</b>	Carrot, Pumpkin,	Human liver cancer SMMC-7721	100 µM	Augment appearance of caspase-8, decline bcl-2
<b>Quercetin</b>	Grape, Onion,	Lymphoma cell BC3, BCBL1 and BC1	15 µM	Inhibits PI3K/Akt/mTOR and Wnt/β-catenin
<b>Thymoquinone</b>	Thyme	Oral cancer cell SASVO3, SCC-4, OCT, SAS	40–60 µM	Augment appearance of LC3-II and Bax
<b>Ursolic acid</b>	Holy Basil, Thyme	Prostate cancer cell PC3	10–40 µM	Augment Beclin-1/Atg5 and inhibits Akt/Mtor
<b>γ-tocotrienol</b>	Ashgourd	Breast cancer cell MCF-7 and MDA-MB-231	10 µmol/L	Activate AMPK, down regulate Ang-1/Tie-2

#: Majority are used in TM in India for cancer treatment; \*: *Tinospora cordifolia*

### AYURVEDA TREATMENT FOR CANCER

Complete cancer cure by Ayurveda medicine alone was a recently reported [26]. It was a 51- year-old woman patient, diagnosed with high-grade non-Hodgkin lymphoma of the type “Diffuse large B-cell lymphoma” [DLBCL] confirmed by the PET-CT scan. She was started with Rasayana [special

processed herbs, vide Ayurvedic literature, for body rejuvenation/ anti-ageing] regimen.

Significant clinical improvement and regression in tumor size in this patient after the treatment. This, along with few other cases mentioned further triggered this article to explore the value of TSM globally using preliminary desk review.

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

The patient improved in terms of the quality of life (QOL) and physical performance with weight gain, unlike in the chemotherapy/ radiotherapy. Oral administration of Raayana treatment is common, without injections or hospitalization and the cost is much lower- at 10-20% of the chemotherapy. Conventional standard of care will improve therapeutic outcomes and the anecdotal evidence suggests further clinical studies to be initiated.

We enlisted 7 case studies of cancer patients successfully treated in the past decade by Indian physicians with Ayurveda in another study either solely or in combination with modern treatment, mostly chemotherapy [27]. We mentioned in it evidences from literature regarding the safety of using herbs and metal ash/ oxides in cancer treatment, including as adjuvant by posing no adverse “drug interaction”, and depicted the mechanism of action of 12 top priority herbs species used in Ayurveda to address cancer.

The anti-cancer activity of Ayurvedic herbs is ascribed to either as topoisomerase inhibitors poisons such as *Phyllanthus amarus*. [bioactive Phyllanthin] or [28]. Some other herbs target telomere instead that is earlier known as anti-aging target. GLP-1 Agonist like Semaglutide, basically used in diabetes similar to the famous branded drug “Ozempic” is found useful in treating cancer also, as another potential emerging mechanism [29]. Cancer cell proliferation is inhibited by the cAMP-PKA pathway, to control the cell division, thus arresting the expansion of malignant cells [30]. Impaired glucose metabolism may be a causal factor behind cancer warranting reduction in sugar consumption and glycation/ lipoxidation end products [AGE/ ALE] they said. About 20-40% of the cancers are diet dependent and preventable [31]. Cinnamon, the routine Indian spice is a GLP-1 agonist and found useful in treating cancer, besides diabetes [32]. Apoptosis as enlisted earlier and anti-oxidant activity thereby reducing the ROS stress for smooth physiological functioning are other pathways for anti-cancer mechanism of herbs [33-35].

The growing popularity of Ayurveda motivated the Indian government to institute separate ministry of Indian systems of medicine termed as “AYUSH” (meaning Ayurveda, Yunani, Siddha & Homeopathy, <https://ayush.gov.in>). Ayurveda industry turnover has grown to \$ 4 billion/ year with exports comprising 25% in it due its ever-growing global popularity [35]. Corporate such as Dabur (<https://www.dabur.com>) and Patanjali (<https://patanjaliayurved.net/>) have turnover of \$ 1.3 billion and \$ 1.1 billion respectively vide annual financial reports

on their website. The A success in Ayurveda motivated them to jump in to health foods and few other fast-moving consumer goods (FMCG) such as soap, cosmetics, toiletries but herbal medicines form solid foundation of their success due the encouraging customer feedback. There are numerous Ayurveda clinic chains are emerging across India today specializing in cancer treatment such as Jiva (<https://www.jiva.com/>) and Shuddhi (<https://shuddhi.com>). Ayurvedic drugs are sold at premium price in plush kiosks at the Airports such as Forest Essentials co. (<https://www.forestessentialsindia.com/>). So, Ayurveda has got celebrity status today, by the results evident. The controversy over the use of heavy metals in Ayurveda is explained by the Bhabha Atomic research Centre (BARC), a premier research center at Mumbai metro police to be traditional nanotechnology and without any toxic effects observed on the patients but with higher efficacy due to the smaller particle size that better penetrates body tissues like precision medicine using cyclotron technique [36], which is also substantiated by other studies elsewhere with heavy metals such as Mercury besides Gold and Zinc and nontoxicity tests in the Zebrafish model [37].

The southern Indian and Sri Lankan traditional medicine branch similar to Ayurveda is called “Siddha” mainly practiced by the saints & Yogis (meditating persons), chiefly in the Tamilnadu state. It is highly reputed in employing heavy metals in highly processed, non-toxic forms such as use of vermilion, a lead compound [Pb3O4] for treating hepatitis C virus [HCV] and found it as non-toxic to humans [38].

## UNANI SYSTEMS OF MEDICINE

Unani is another traditional medicine system in India and central Asia that also has similar herbal and/ or metallic medicines and is found to be effective for millennia for health security including in treating even cancer, such as a case of cervical cancer [39]. Other studies have also shown the anticancer potential of Islamic medicine [40]. Central Council for Research in Unani Medicine (CCRUM) of the Indian Government has described using experimental evidence cancer management techniques in the Unani system using 20 Unani herbal drugs for the prevention and treatment of cancer, with proposed mechanisms such as being direct cytotoxicity, apoptosis induction, antioxidation, and immunomodulation [41]. Cancer is termed as “Sartan” (سرطان) in the Arabic word for crab [42].

## HOMEOPATHY TREATMENT OF CANCER

Ministry of health & family welfare scientists have explained the homeopathy mechanism of addressing cancer [43]. Homeopathy is traditional nanotechnology using ultra-dilution vide Avagardo’s principle, showed Indian Institute of Technology, Bombay (IIT-B) [44]. Homeopathy therapy was established by a German physician, Samuel Hahnemann at the end of the 18<sup>th</sup> century. It is widely used but became

controversial due to the use of extremely high dilutions, which may be as much as one part in  $10^{60}$ ,  $10^{400}$ ,  $10^{2000}$  and even ultra-high dilutions. IIT-B research above is first in the world to show the presence of starting ingredients even after ultra-high dilutions involved in the preparation of homeopathic medicines. Further, these active starting ingredients are found to be encapsulated with meso-microporous cross-linked silicates chains. Homeopathy has a holistic healing approach but its efficacy in modern techniques is yet often unproven.

An analysis of 8 controlled trials (7 placebo controlled and 1 trial against an active treatment) with a total of 664 participants was conducted [45]. Of these, 3 studied adverse effects of radiotherapy, 3 studied adverse effects of chemotherapy and 2 studied menopausal symptoms associated with breast cancer treatment. The preliminary data supported the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating of the efficacy or adverse effect of homeopathic medicines in cancer treatments is not yet demonstrated. No serious adverse effects or interactions are yet reported.

This study quoted a systematic review of 26 surveys from 13 countries that reported that up to 64% of patients with cancer (average 31.4%) used complementary therapies at some stage of their illness [46]. Another study found that homeopathy was in the top five most commonly used complementary therapies in 7 out of 14 European countries by patients with cancer [47]. Homeopathy is used by patients with cancer for symptomatic relief and general supportive care, and to address the adverse effects of the cancer treatment. About 1/3<sup>rd</sup> of European cancer patients used complementary or alternate medicine (CAM) the first Europe-wide study of CAM, a team of international researchers found [48]. Its use varied from a low of just under 15% of cancer patients in Greece to a high of nearly 75% of patients in Italy. Homeopathy improves the Quality of Life (QOL) and survival is improving in patients using homeopathy as adjuvant to chemotherapy, another study found in 98 patients with advanced non-small cell lung cancer (NSCLC) at the Vienna University [49]. It showed that:

- Conventional medicine and homeopathy work well together.
- Quality of life improves with additive homeopathy in patients with non-small cell lung cancer (NSCLC).
- Survival improves in patients with NSCLC with additive homeopathy.

Thus, additive homeopathy may alleviate side effects of conventional therapy as patients with advanced non-small cell lung cancer (NSCLC) have limited treatment options.

This prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter, phase III study, evaluated the possible effects of adjuvant homeopathic treatment compared to placebo in patients with NSCLC stage IV, in terms of QoL in the 2 randomized groups and survival time in all 3 (three) groups. QoL as well as functional and symptom scales showed significant improvement in the homeopathy group when compared with placebo after 9 and 18 weeks of homeopathic treatment ( $p < .001$ ). Homeopathy group had had significantly higher median survival time (435 days) versus placebo (257 days;  $p = .010$ ) and control (228 days;  $p < .001$ ). A higher QoL may have contributed to the prolonged survival. Further studies including other tumour entities are warranted.

## DRUG INTERACTIONS

The integration of herbs or Ayurveda (Rasayana) therapy or botanicals with chemotherapy/ radiotherapy to improve its efficacy and reduce ADR is suggested in USA [50]. **Table 2** depicts some interaction but largely benefits of such adjuvants.

A desk review of 115 articles on breast cancer, with 64 therapeutic targets and 35 different plant species showed apoptosis caused by 51% and 37 % 55 affected cell proliferation [55]. The review indicates that 17 % therapeutic targets have carcinogen inactivation, 10 % prevent precancerous growth, mutagenesis and gene expression activity is affected in 9%, while toxic metabolism is regulated in 4% which can help to the beneficial integration of Ayurveda/ herbal medicines with chemotherapy for improve recovery, and better health outcomes for the survivors.

“Polyherbal” nature with synergistic effect and pre-empting the emergence of resistance are key distinguishing features of Ayurvedic medicines [56]. Special condition patients such as children or elders may benefit by this due to lower ADR. As people above 65 years age diagnosed with cancer annually in USA will double by the year 2050, and will quadruple among those aged  $\geq 85$  years then [57]. Global trend may be similar. So, adding herbal remedies as adjuvants can benefit millions of patients.

Canadian Govt. of Victoria in enlists popular botanicals used in CAM and their interaction with cancer drugs and Turmeric is said to make no effect on the treatment while Black pepper, Garlic, Guggul tree gum, Licorice may influence the chemotherapy treatment outcomes [58]. No serious ADR is reported for Ginger or turmeric that are common spices globally today, and integrative therapy was recommended for the best outcomes with phytovigilance vide a WHO database [59].

**Table 2.** Herbs as adjuvants in chemotherapy.

Herb	Bioactives	Target/ Mechanism	Place, Year	Remark
Turmeric	Curcumin	Cytochrome P450	USA, 2023	Interference, but can modulate side effects [50].
Ashwagandha & Asparagus	Withanoloids, Saponins	Pro-inflammatory cytokines, Hematological Homeostasis	Pune, 2022	Evaluated as safe, desirable therapeutic adjuvants for cancer [51].
Heart leaved moonseed	Berberin, Tinospoin		Odisha, 2012	Similar effect to Doxorubicin [52].
Triphala	Polyphenols [Flavonoids], Gallates, Glycosides	Cytotoxic to cancer cell lines, protects normal ones, rejuvenates	USA, 2017, 2023	Adjuvant therapy to Radiation and Chemotherapy [53,54].

### ADVERSE EFFECTS AND HERBAL ADJUVANTS

Long-term adult survivors may face more physical ADR limitations (53% compared with 21% for controls without cancer), a study in USA found [57]. 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.

A 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, long ago found that the most frequent physical ADR symptoms included general ache and pain (70%), muscle stiffness (64%), and joint pain (62%) and women had a higher risk of sexual dysfunction in prematurely postmenopausal ones and those who received chemotherapy, it was found in a study in Germany [60].

A study of total of 500 patients in Uttarakhand state suffering from ADRs due to cancer chemotherapy during 2018-2019 in, reported 665 ADRs [61]. Anemia, nausea/vomiting and leucopenia were commonest. Preventable ADRs comprised of only 27%, which is a cause for concern. Contradictory observation was made in another study from Bihar state in India - about 49% patients complained the hair loss- alopecia, 27% nausea, vomiting & burning sensation, 24% of constipation [62].

Such ailments can be easily treated with common Ayurveda/ herbal remedies such as Ginger as its phytochemicals Gingerols and shogaols exhibit biological activity, such as anticancer, oxidative stress reduction, antimicrobial, anti-inflammatory, and anti-allergic.

### ALTERNATE MEDICINE, DIET, LIFESTYLE, CANCER

Consumption of more fruits & vegetables (F&V), herbs regularly can improve bioactives intake and improve

immunity and wellbeing [24]. Herbs like Lemon & Ginger are found to cause tumor regression and trigger immunity in mice model [63]. So even fresh herbs & spices consumption besides F&V can reduce the cancer risk/ recurrence.

Diet regime was given important in modern medicine advisory in the 20<sup>th</sup> century but “healthy diet” is promoted now through Government advisory such as in the USA (Box 2) [64]. There is globally move towards complementary and alternative medicine [CAM] especially in QOL in survivorship, post Cancer remission, as evidenced as a study in Norway of the 706 cancer survivors [65].

#### Box 2. Healthy diet advisory for Cancer survivors, USA [64]

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

1. Plant-based diet and have at least 5-9 servings of fruit and vegetables daily
2. Including beans in your diet
3. Eating whole grains [such as cereals, breads, and pasta] several times daily choosing foods low in fat and low in salt.

Recognizing the key importance of diet in Cancer occurrence and management, “Warburg” effect was hypothesized i.e. anaerobic glycolysis is the basis of the cancer cell energy metabolism [66]. But the cause and effect relation of the genetic dysregulation and cancer trigger in the Warburg effect is uncertain. The anticancer strategies based on the Warburg effect comprise dietary changes and drug compounds. Normal cells undergo glycolysis and oxidative phosphorylation in the presence of oxygen. However, an increased glucose uptake and glycolysis rate are observed in

the proliferating cancer cells and, undergo lactic acid fermentation mostly. The 2 diet-based strategies below are used. to target cancer metabolic processes

- a) Calorie Restriction (CR):** CR was the first method offered for cancer prevention by reducing tumor blood supply, in 1914. The reduction of lower circulating glucose lowers insulin levels and increases transcription of insulin-like growth factor binding protein- (IGFBP-) 1. Thus, the bioavailability of insulin-like growth factor-1 (IGF-1) is reduced. CR metabolic effects differ between normal and cancer cells, with energy source of the latter being shut off. Fasting based intervention is shown to protect normal cells but cancer cells are vulnerable to high-dose chemotherapy in both cell culture and the mice with neuroblastoma. Fasting weekly once to avoid “carbohydrate” was common in Indian diet for centuries and this may act like a preventive strategy for cancer, it seems.
- b) Ketogenic Diets (KDs):** In a KD, fats account for about 90% or more of total energy intake. The KD simulates fasting, increasing ketones in the blood and reducing glucose; while speedily increasing the fatty acid oxidation and acetyl-CoA production. KDs are popular today aimed at lowering blood sugar and insulin levels, targeting the Warburg effect. The ketogenic diet (or keto diet, for short) offers many health benefits and is a low carb, high fat diet. Many studies show that KD can help you lose weight and improve your health. Keto-diets may benefit against diabetes, cancer, epilepsy, and Alzheimer’s disease. Keto diet’s hallmark is the reduction in the blood sugar levels and an increase in ketones. In Keto diet, one burns fat and ketones as the main fuel source [67].

## INNOVATIONS & WAY FORWARD

Modern Indian scientists have repurposed “Panchvalkal”, an Ayurvedic traditional formulation to treat cervical cancer referred in basic Ayurvedic doctrines Charak Samhita and Bhavaprakasha Nighantu used for the treatment of women with endometriosis-related problems, leucorrhoea and vaginal ailments but not commercialized or patented yet [68]. The formulation comprises the barks of trees *Ficus glomerata*, *Ficus religiosa*, *Ficus benghalensis*, *Ficus virens*, and *Thespesia populnea*. However, the 1<sup>st</sup> 3 tree species being sacred in India their bark harvest is a taboo [69]. So raw material scarcity or controversy may arise.

Similarly, traditional Chinese medicine (TCM) has developed formula PHY906, decoction of a mixture of the four herbs: *Glycyrrhiza uralensis*, *Paeonia lactiflora*, *Scutellaria baicalensis* and *Ziziphus jujuba*, for over 1800 years for treating a variety of gastrointestinal distress such as diarrhea, cramps, nausea, vomiting etc. [70,71].

Finally, UK researchers have mapped using artificial intelligence (AI) the 110 cancer-beating molecules from a variety of chemical classes including flavonoids, terpenoids, and polyphenols [72], based on comprehensive analysis of 7,962 bioactive molecules. These were defined by anti-cancer drug likeness threshold of >70% using machine Learning (ML) with capacity like the clinically approved anti-cancer drugs. Bioactives with high anti-cancer likeness (ACL) score > 0.7 and their associated food sources in the above study published in “Nature” journal. The top anti-cancer drug like molecules (with ACL > 0.9) and their likely molecular mechanisms of anti-cancer actions is provided in literature. The multi-step process of carcinogenesis includes:

- Antioxidant and scavenging free radicals
- Anti-inflammatory
- Antibacterial and antiviral effects
- Pro-apoptotic effects
- Modulation of enzyme activities in detoxification, oxidation, regulation of hormone metabolism
- Regulation of gene expression in cell proliferation or differentiation, oncogenes, and tumor suppressor genes

For example, “3-indole-carbinol”, is a strong anti-cancer-like molecule abundant in the mustard/ Rapeseed vegetables’ Brassicaceae family members (including cabbage, broccoli and Brussels’ sprout). It targets multiple aspects of cancer cell cycle regulation and survival, including endoplasmic reticulum function, receptor signaling caspase activation and estrogen metabolism. Further, “Apigenin”, abundant in coriander, parsley and dill and “dydamin”, is a flavonoid glycoside in the lemon fruits are other important examples, besides Curcumin and Quercetin. These influence apoptotic pathways as well as cell cycle arrest mechanisms to suppress cancer cell migration and invasion. The maximum diversity of such bioactives is visible in the foods Tea, Grape, Carrot, Coriander, Orange, Dill, Cabbage and Wild celery. Their continued consumption in regular diet can reduce the cancer risk, it seems. These bioactives conform to the Lipinsky rules such as low molecular weight [73].

## PUBLIC HEALTH IMPLICATIONS

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 [74]. This may be attributed the rising obesity and packed food as found in COVID-19 higher disease burden also in Europe, USA than Asian or African nations consuming fresher, less processed, home cooked foods [75]. Medicinal plant use for cancer treatment is common even today in African countries like Morocco at 38% where women accounted for 80% of the user population against 20% of men (P<0.05) as per the study by

the study at the oncology unit of IBN Rochd University Hospital Centre in Casablanca, Morocco [76]. The plants used in cancer management are- White Horehound (*Marrubium vulgare*) Dutchman's Pipe (*Aristolochia longa*), Barbery (*Berberis vulgaris*), Resin Spurge (*Euphorbia resinifera*), Turmeric (*Cucuma longa*) were the most commonly, while anticancer activity has been demonstrated for Black Cumin (*Nigella sativa*), Ginger (*Zingiber officinale*), Olive (*Olea europaea*), Fenugreek (*Trigonella foenum-graecum*), Common Sage (*Salvia officinalis*), Resin Spurge. Tobacco use, alcohol consumption, unhealthy diet (including excess Sugar consumption), physical inactivity, air pollution and microbial infections are identified as major causes behind cancer to be addressed on priority basis through public awareness campaign [1]. Poorer countries have higher cancer burden as evident from the fact that as per WHO data in the developed countries, breast cancer affects 8% women and 1 in 71 women die of it [1]. By contrast, in less developed countries; breast cancer affects only half i.e. 4% women, but 1 in 48 i.e. 2% women die from it. 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 budget herbal medicines as shown above. The traditional medicine policy of WHO is a step in that direction [77].

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