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Review Article

Perspective of using Indian Polyherbal Medicine in the Treatment of Cancer

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Abstract

Body Revival is a composite traditional herbal medicine with multiple phytoconstituents recognized as anticancer therapeutic potentials. These bioactive anticancer phytoconstituents are β-asarone, cucurbitacin B, 1-hydroxytectoquinone, marmelin, methylglyoxal, mollugin, quercetin, withanone, withanolid, withaferin A etc. This review is based on mechanistic analysis of individual phytoconstituents as chemotherapeutics and their synergistic impacts on the management of cancer. The possible modes of anticancer actions of Body Revival are multifactorial. It stimulates the immune system, protects DNA from injury, restores damaged DNA, lowers oxidative impairment, antiproliferation, cancer cell cycle arrest, initiation of apoptosis, suppression of angiogenesis and metastasis, chemo preventive or restore/protects normal cells from harmful effects of radiation. Furthermore, it is devoid of any toxic effect. The goal-oriented programmed clinical approaches are desirable to strengthen its anticancer efficacies as a safe chemotherapeutic agent.

Keywords: Cancer; Chemotherapeutics; Apoptosis; Phytochemicals; Herbs

Abbreviations: Bcl-xL=B-cell lymphoma extra large; Erα=Estrogen receptor-α; HCC=*hepatocellular carcinoma*; MAP kinase=mitogen-activated protein kinase; MMP=matrix metalloproteinase; NF-KB=Nuclear factor kappa B; ROS=reactive oxygen species; STAT3=signal transducer and activator of transcription 3; TGF-β=transforming growth factor β; TRIM16=Tripartite motif-containing protein 16; VEGF=vascular endothelial growth factor; Wnt=wingless-type.

Cancer cell lines: breast: MCF-7, MDA-MB-231, MDA-MB-435S; cervical: HeLa, WRL68; colon: LoVo, HCT116, HCT-15, CoLo-05; colorectal: HT29; fibroblast: HSKMC; gastric: AGS; hepatic: Hep3, HepG2; laryngeal: HEp-2; leukaemia: K562, P338,

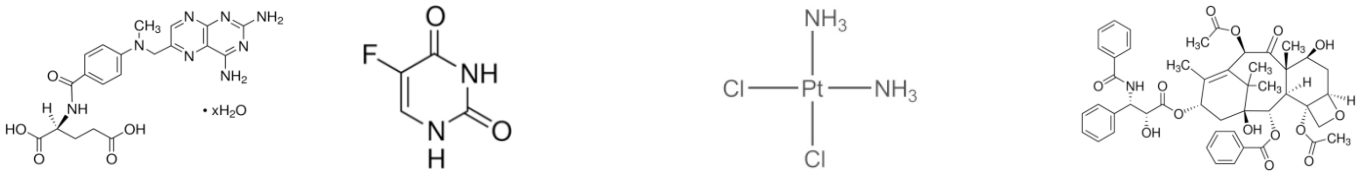
THP-1, U937, Jurkat; lung: A-375, A-549; lymphoma: BC-1/KMC; melanoma: B16F10; neuroblastoma: IMR-32; pancreatic: BxPC-3 and prostrate: DU-145, PC3, LNCaP.

Introduction

Cancer is a global health problem because of its high prevalence and poor prognosis. It can affect any part of the body and spread one part to other organs. Widespread metastases are the most imperative reason of death in cancer [1]. The Cancer registry specifies 18.1 million new cases and 10 million global deaths due to cancer in 2020. Although the most common cancers are breast, lung, colorectal and prostate, contributing 12.5%, 12.2%,10.7% and 7.8% respectively to the total number of new cases diagnosed in 2020 [2]. Moreover, in India, 1.3 million new cancer cases and 0.85 million deaths were reported [3]. The burden of cancer incidence and mortality is rapidly growing worldwide [4].

Cancer occurs due to over expression of oncogenes or damage in DNA. Conversely, oxidative stress or reactive oxygen species (ROS) play a considerable role in key cellular pathways of DNA damage, mutagenesis and apoptosis. Besides genetic injury, habitual use of tobacco, alcohol dependence, inadequate diet, physical apathy, radiation, chemical and environmental pollutants are the major threats considered for any type of cancer [5]. The International Agency for Research on Cancer (IARC) has already identified more than 150 chemicals, drugs, foods, airborne particles, ionizing radiation and other consumer products as potential carcinogens [6].

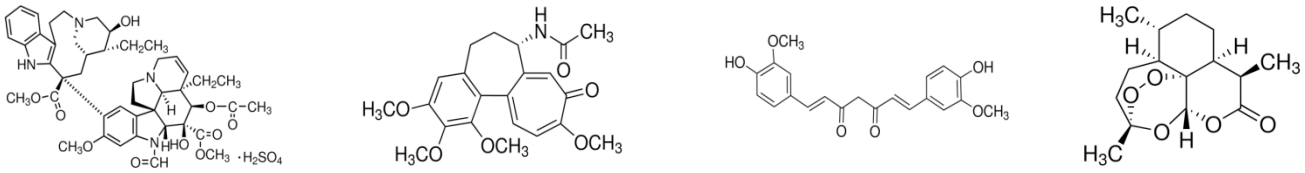
There are four types of therapeutic modalities in cancer depending upon the nature, progression of disease conditions and possibilities of recovery, viz. surgery, chemotherapy, radiation therapy and palliative care. In the early 1900s, the term "chemotherapy" was first introduced by German chemist Paul Ehrlich to treat specific infective conditions like cancer with chemicals. After several attempts, methotrexate (1948), chlorambucil (1957), cyclophosphamide (1959), 5-fluorouracil (1970), Doxorubicin (1974) and Cisplatin (1978) were developed for the treatment of cancers [7]. Cytotoxic chemotherapeutics target directly to DNA; while the target chemotherapeutics aim at the abnormal protein expression inside the malignant cells [8]. At this time, although chemotherapy is the most powerful weapon to treat deadly cancers, causes widespread cytotoxicity of healthy cells and causes severe side effects, such as nausea, emesis, anorexia, diarrhoea, skin damage and hair loss. To overcome these unwanted side effects, searching for novel and safe chemotherapeutics for cancer is crucial. Consequently, alternative medicine may provide a safe chemotherapeutic to treat cancer without undesirable side effects.



Methotrexate **5-Fluorouracil** **Cisplatin** **Paclitaxel**

Figure 1: Anticancer medicines

The anticancer properties of plants have been recognized from ancient times. The innovation of the application of the plant alkaloids (Vincristine and Vinblastine from *Vinca rosea)* for both leukaemia and Hodgkin's disease has been considered a major breakthrough in the research of chemotherapeutics (1963). From that time to till now, numerous chemotherapeutics have been isolated, identified or developed from natural resources. Paclitaxel (Texol) was obtained from the bark of *Taxus baccata* (2002), while colchicine alkaloid was first isolated from the corn of *Colchicum autumnale* (2009) and has exhibited clinical significance against different cancers such as ovarian, breast, prostate and lung cancer [9,10]. There are reports that several natural supplements, including single or mixed herbal extracts and pure compounds are able to reduce the harmful side effects of chemotherapy and can improve the quality of life (QoL) of cancer patients [11-13].



Vincristine **Colchicine** **Curcumin** **Artemisinin**

Figure 2: Anticancer phytoconstituents

Furthermore, phytochemicals derived from secondary metabolites of medicinal herbs, such as alkaloids, terpenes, quinones, steroids, polyphenolics etc. have shown promising clinical efficacy in cancers [14]. Artesunate derived from *Artemisia annua,* β-Asarone from *Acorus calamus*, Crocetin from *Crocus sativus,* Cucurbitacin B from *Cucumis melo*, Curcumin from *Curcuma longa*, Mollugin from *Rubia cordifolia*, Resveratrol from *Vitis vinifera,* Roscovitine from *Raphanus sativus,* Silibinin from *Silybum marianum,* Withanolids and Withaferin from *Withania somnifera,* etc. have been reported for their potential therapeutic role in cancer and metastasis [15,16].

Materials and Methods

A bibliographic search of PUBMED, MEDLINE, Academic Google, and other relevant websites (2010-2022) was performed for the present study. Indian medicinal plants employed in the Indian herbal formulation (Body Revival) have been the top search terms. Following the rigorous reading of the titles and abstracts used in the original search, only fully published papers were selected to take part in this review.

Results and Discussion

Herbal extracts consisting of multiple herbs for the management of cancer have been used in Ayurveda, Indian System of Medicine, since immortal time. These formulations are reported to work on multiple biochemical pathways simultaneously [17]. It is observed that mixed herbal formulations are more effective than any single herb due to their similar cumulative actions. On this concept Body Revival (Health Reactive, Rajasthan, India), a formulated herbal liquid suspension has been developed based on immunotherapy to treat cancers as mentioned in ancient Ayurvedic texts. The nine natural ingredients of Body Revival are selected from the traditional medicines as mentioned in Ayurvedic Pharmacopoeia of India [18]. The composition of Body Revival suspension (5 ml) contained pure extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Rubia cordifolia* root (200 mg), *Cucumis melo* seed (200 mg), *Symplocos racemosa* stem bark (95 mg) and honey (Q.s). Earlier preclinical studies reported, it has potent antiinflammatory, immunomodulatory, chemo preventive and antithrombotic actions. Body Revival contained polyphenolic compounds and exhibited beneficial action on myelosuppression and cardiac ischemia [19-21]. It has been reported that Body Revival therapy unquestionably better the health condition in general and mental disabilities and illness due to weak immune circumstances by modulating signalling pathways or/and cellular functions. In due course, it is helpful to fight infections from environmental pathogens or chemicals that suppress physical immunity [21].

Body Revival is used to improve the body's defence mechanism, repair damaged tissues, flush out harmful metabolites through excretion and rejuvenate healthy cells and helpful to improve quality of life and enhance longevity during palliative care in cancer patients in the last 25 years. In this juncture, we are trying to focus on the importance and the perspective of the use of Body Revival in cancers with comprehensive evidence and justification. The main part of this review is based on underlying plausible mechanistic analysis of its individual phytoconstituents as chemotherapeutics/or adjuncts and their synergistic impacts on the management of cancer.

Table 1: Bioactive anticancer components present in the ingredients of Body Revival

Natural Ingredients	Part	Extract/Active component	Anticancer action	Reference
Aegle marmelos	fruit	extract marmelin	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7, MDA-MB-231, HEp-2, PC3, A549, CoLo-05, THP-1	22,25-28
Acorus calamus	rhizome	extract β-asarone	• apoptosis • antiproliferative activity • cytotoxicity: MDA-MB-435S , Hep 3B, HeLa, HCT116, AGs, HSKMC, LoVo, HT29, LNCaP • down-regulate mitochondrial membrane potential • down regulate VEGF mRNA expression • down regulate Bcl-2/Bax ratio • up regulate caspase-9 and caspase-3 cascades	29-35
Withania somnifera	root	extract withaferin withanolide withanone	• apoptosis • antiproliferative activity • cytotoxicity: DU-145, HCT-15, A-549, IMR-32, A375, • inhibit cancer cell G2/M cycle • inhibit angiogenesis • inhibit proteosomal enzymes • inhibit tumor growth • activate TRIM16 expression • inhibits JAK1, MAP kinase P38, Bcl-xL	37-44
Blumea lacera	fruit	extract glycoalkaloids	• apoptosis • antiproliferative activity • cytotoxicity: MDA-MB-435S, BBC-1/KMC, B16F10 • anti-leukemic activity • anti-HSV activity	45-49
Rumex vesicarius	whole plant	extract	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7 and WRL68 • inhibits angiogenesis • inhibit tumors	50-52
Rubia cordifolia	root	extract mollugin furomollugin dehydro-a lapchone 1-OH tectoquinone	• apoptosis • antiproliferative activity • cytotoxicity: HEp-2, MDA-MB-231, HepG2, HeLa, MCF-7, P338, A-375, BxPC-3, U937 • protect radiation	53-59
Cucumis melo	seed	extract cucurbitacin B	• apoptosis • antiproliferative activity • cytotoxicity: K562, PC3, HCT116, HeLa, Jurkat • inhibits STAT3 activation • inhibit Raf/MEK/ERK pathway • effective in hepatocelluar cancer	60-64

Symplocos racemosa	bark	extract glycosides	• apoptosis • antiproliferative activity • cytotoxicity: Hep3B	65-68
Honey		polyphenols methylglyoxal	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7, MDA-MB-231, HepG2 • suppress angiogenesis • arrest cell cycle • inhibit tumor growth • down regulate ATP production in cancer cells • protect against mutagen-induced DNA damage • protect from harmful effect of radiation	69-74

Anticancer activities of phytochemicals present in the ingredients of Body Revival

The anticancer properties of the ingredients present in Body Revival are pure aqueous extracts of *Aegle marmelos* fruit pulp, *Acorus calamus* rhizome, *Withania somnifera* root, *Blumea lacera* fruit, *Rumex vesicarius* whole plant, *Rubia cordifolia* root, *Cucumis melo* seed, *Symplocos racemosa* stem bark and honey.

Aegle marmelos

Aegle marmelos known as "bael" or "wood apple" is associated with in the family of Rutaceae. It contains marmelin, lupeol, marmelosin, furocoumarins and scopoletin [22]. It has antioxidant, antiproliferative, cytoprotective, anticancer, radio-protective, immunomodulatory, hepatoprotective and cardioprotective properties [23]. Marmelin stimulates tumor necrosis factor-α (TNF-α) and caspases to triggers apoptosis in the malignant cells [24]. Fruit pulp extract of *Aegle marmelos* exhibited anti-proliferative activity through suppressing the breast tumor growth rate [25]. It did not increase ERα mRNA levels in MCF7 and MDA-MB-231and thereby reduced the viability of cancer cells [26]. It can protect blood lymphocytes from γ-radiation [27]. It can protect buccal epithelial DNA from oxidative stress [28].

Acorus calamus

Acorus calamus well-known as "bach" or "sweet flag" is associated in Acoraceae family. The rhizome contains two main bioactive principles, (α)-asarone and (β)-asarone [29]. It has antioxidant, anti-inflammatory, anti-cancer, radioprotective, gastoprotective, neuroprotective and cardioprotective effects [30]. (β)-Asarone showed chemo preventive and anticancer effect on all kinds of cancer cell lines, such as Hep3 (hepatic carcinoma), MDA-MB-435S (breast cancer), AGS (gastric cancer), HSKMC (fibroblast), LoVo (Colon cancer), HT29 (colorectal cancer) and HeLa (cervical cancer) cells. Recently, it has been reported that β-asarone by activating the innate immune system can successfully inhibit liver metastasis and proliferative action in HCT116 colon cancer cells [31]. The underlying mechanism of β-asarone involves suppression/inhibition of cell proliferation and angiogenesis, while exaggerating apoptosis [32-35].

Withania somnifera

Withania somnifera familiar as "ashwagandha" or "winter cherry" or "Indian ginseng" is belongs to the family of Solanaceae. It exhibits antioxidant, anti-inflammatory, anti-stress, immunomodulatory, adaptogenic, chemo preventive effects, anti-cancer activity. The rhizome/root contains two main bioactive anticancer components, Withanolide and Withaferin A [36]. *W. somnifera* is a promising therapeutic agent for a broad range of cancers. It showed cytotoxicity against four human cancer cell lines such as prostrate DU-145, colon HCT-15, lung A-549 and neuroblastoma IMR-32 [37]. Several studies demonstrated that Withaferin A (WA) has the potential to restrict the genesis and proliferation of cancer cells via controlling the non-genetic influences on gene expression [38,39]. It also reduced the side effects of some cancer chemotherapeutic agents, viz. cyclophosphamide and paclitaxel without interfering with the cancer-reducing actions of the drugs [40]. Recently, it has been reported WA inhibited cell cycle, angiogenesis, proteasomes and tumor growth in the prostate [41]. Nagy and his co-workers (2020) reported that WA activates TRIM16 (tripartile motif 16) expression, which acts as tumor suppression in melanoma [42]. In molecular docking studies, Withanolide, WA and Withanone showed the best binding affinity against Protein kinase C and (ii) NF-KB. Furthermore, enzyme ligand binding affinity have also been noted against Tyrosine-protein kinase JAK1, Mitogen-activated protein kinase P38, Glutathione Reductase and Glutathione S-Transferases [43,44]. Molecular docking study also provides evidence that Withanolide, Withaferin A and Withanone robustly attach to the macromolecules to restrain escalation of cancer cells, as a promising anticancer medicine.

Blumea lacera

Blumea lacera frequently known as "kakronda" or "lettuce"

is associated in the family of Asteraceae. It possesses antioxidant, anti-ulcer, anti-diarrheal, hepatoprotective, antiviral activities [45]. It contains phenolics, glycoalkaloids and essential oils [47,48]. *B. lacera* leaves have shown non-selective cytotoxic activity against MDA-MB-435S, BBC-1/KMC, B16F10 cells [45, 48]. It exhibited a broad spectrum of anti-leukemic activity and strong anti-HSV activity [49].

Rumex vesicarius

Rumex vesicarius also known as "amlabet" or "bladder dock" is belongs to the family of Polygonaceae. It is used in the treatment of tumors, liver diseases, cardiovascular disease, asthma, bronchitis and nausea [50]. It possessed a promising anticancer potential against MCF-7 and WRL68 cell lines and HCC induced hepatic carcinoma model. It showed potent antiangiogenic and antiproliferative activities [51,52].

Rubia cordifolia

Rubia cordifolia commonly known as "manjishtha" or "Indian maddar" is belongs to the family of Rubiaceae. It contains anthraquinones, glycosides, terpenes and carboxylic acid groups of compounds such as mollugin, furomollugin, dehydro-α lactone, 1-hydroxytectoquinone, alizarin, rubuadin, lucidine, manjisthin and bicyclic hexapeptides [53,54]. The active constituent, Mollugin, exhibited considerable activity against P338 lymphoid leukemia [53,55]. Tripathy and Singh (2007) reported the herb has radioprotective action. Aqueous root extract of *R. cordifolia* exhibited cytotoxcity on HeLa cells [56]. Moreover, 1-hydroxytectoquinone isolated from *R. cordifolia* cytotoxic has an effect against A375 human malignant melanoma [57]. The methanolic extract of *Rubia cordifolia* demonstrated antiproliferative and apoptotic properties on HEp-2 (human laryngeal carcinoma) cell line in a dose-dependent manner [58]. Furthermore, it showed cytotoxic action on MDA-MB-231, HepG2, BxPC-3 and MCF-7 cancer cells [59].

Cucumis melo

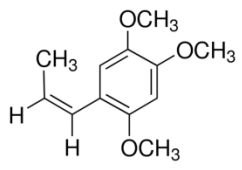
Cucumis melo or "madhuphala" or "muskmelon" is belongs to the family of Cucurbitaceae. Cucurbitacin B (CuB) is a tetracyclic-triterpenes present in *Cucumis melo* [60]. The anticancer activity of CuB in human leukemia cells has been observed. It restrains STAT3 activation and the Raf/MEK/ERK pathway in K562 leukemic cells [61]. It is also used as a liver protection medicine in curing hepatic lesions and liver cancer [60,62]. CuB also inhibited multiple myeloma cells in the G2/M phase [63]. *Cucumis melo* exhibited cytotoxicity against PC3, HCT116, HeLa, and Jurkat cell lines [64].

Symplocos racemosa

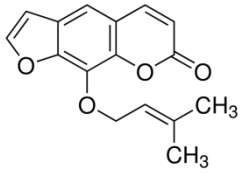
Symplocos racemosa or "Lodhra" is associated with the family of Symlocaceae. It has been extensively applied in traditional medicine for gastro-intestinal and liver problems, uterine complaints, menstrual disorders and solid tumors. It has several bioactive glycosides such as symplocomoside, symponoside, benzoyl salireposide, salireposide etc. [65,66]. *Symplocos racemosa* bark showed cytotoxic action on Hep3B hepatocellular carcinoma cells [67]. Raval and his coworkers (2009) evaluated the chloroform, butanol and methyl acetate bark extracts for their cytotoxicity assay against leukemia and cervical cancer cell lines. They reported that the butanol extract had the highest cytotoxicity activity against HeLa cell line [68].

Honey

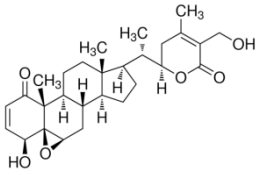
Honey is composed of sugars, amino acids, proteins, enzymes, vitamins, flavonoids, phenolic acids and other compounds. Bioactive polyphenolic compounds such as kaempferol, quercetin, chrysin, luteolin, apigenin, naringenin etc are present in honey [69]. Honey has potential apoptotic, antiproliferative and immunomodulatory activities [70]. It antagonizes estrogenic activity, restricts cell proliferation, exaggerates apoptosis and reduces mitochondrial membrane potential in the two most widely used breast cancer cell lines, MCF-7 and MDA-MB-231[71,72]. It inhibits cell proliferation, suppresses angiogenesis, induces apoptosis, protects against mutagen-induced DNA damage in HepG2 liver cancer cells and HT 29 colorectal cancer [73]. Honey contains other anticancer molecules such as methylglyoxal, which inactivates glyceraldehyde-3-phosphate dehydrogenase (GA3PD) and down regulates ATP production in cancer cells and thereby accelerating the death of cancer cells [74]. Hence, honey is potentially helpful to resist cancer via controlling three key steps of carcinogenesis: initiation, proliferation and progression.



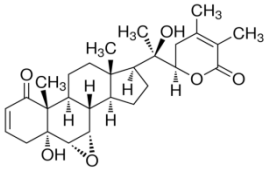
β-Asarone



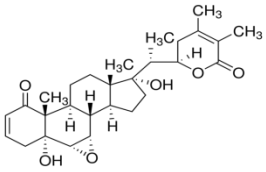
Marmelin



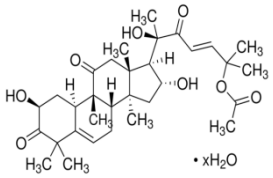
Withaferin A



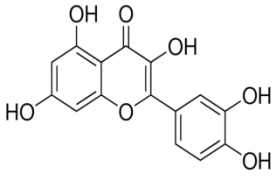
Withanolide



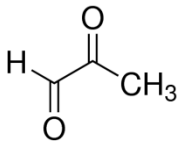
Withanone



Cucurbitacin B



Quercetin



Methylglyoxal

Figure 3: Anticancer phytoconstituents present in Body Revival

Body Revival: Possible modes of anticancer actions

Body Revival is a composite of herbal medicines and honey with multiple phytoconstituents recognized as anticancer therapeutic potentials. It is assumed that herbal formulations with multiple phytochemicals may have better therapeutic effects than the same phytochemicals taken alone. Based on this thought, a combination of the anticancer phytochemicals is blended in suspension to get a more potent therapeutic anticancer agent. Some of the known bioactive anticancer phytoconstituents present in Body Revival are β-asarone, cucurbitacin B, furomollugin, 1-hydroxytectoquinone, luteolin, marmelin, methylglyoxal, mollugin, naringenin, quercetin, symplocomoside, withanone, withanolid, withaferin A etc. Most of them target in the plasma membrane, transmembrane receptors, tyrosine kinases and G-protein coupled receptors. Therefore, possible modes of anticancer actions of Body Revival are (i) stimulate the immune system; (ii) prevent DNA damage and repair damaged DNA; (iii) reduce oxidative damage; (iv) antiproliferation; (v) cancer/tumor cell cycle arrest; (vi) induction of apoptosis and (vii) inhibition of angiogenesis; (viii) inhibition of metastasis; (ix) restore normal cell from toxic chemicals (chemoprevention); and (x) restore/protect normal cell from harmful effect of radiation. It is presumed that natural resource derived components in amalgamation with anticancer agents have immense potential to fight with tumour/cancer cells without affecting normal cells like lymphocytes or fibroblasts. But still, it is not fully understood whether Body Revival suspension is cytotoxic anticancer medicine or targeted anticancer medicine.

Therapeutic Application of Herbal Formulations in Cancer

Herbal formulations frequently composed with some primary herbs which are responsible for the target therapeutic actions and accessory herbs which have either synergetic actions to improve the therapeutic properties of primary herbs or nullifying the other effects related to disease. There are multiple scientific evidences and clinical trial reports of using herbal formulations on cancers. In this juncture, some marketed anticancer drugs are tabulated in the Table 2. Most of these formulations are now applied as a combination therapy with the conventional chemotherapy, radiotherapy or palliative care treatment to enhance the therapeutic advantages by reducing the side effects or complications.

Herbal Formulation	No. of Ingredients	Country Origin	Anticancer Actions	Reference Number
PC-SPES	8	China	Prostate cancer	75
Sho saiko-to (TJ-9)	7	Japan	Hepatic cancer	76
Compound 861	10	China	Hepatic cancer	77
Bu-Zhong-Yi-Qi	8	China/Japan	Lung, ovarian and colorectal cancer	78
Goshajinkigan	10	Japan	Colorectal cancer	79
Rikkunshito	8	Japan	Chemotherapy induced nausea and vomiting	80
HUMA	8	India	Oral cancer, chemotherapy	81
Carctol	8	India	Chemotherapy induced nausea and vomiting	82
MaZiRenWan	6	China	Palliative care	83
HC-9	9	India	Breast cancer	84
BASANT	7	India	Cervical cancer	85
Varunadi Ghritha	18	India	Head-neck cancer	86

Table 2: Herbal formulations used in cancer therapy.

Anorexia, vomiting, constipation, diarrhoea, anaemia, headache, fatigue, pain, infection and hair loss are the common sign and symptoms of conventional therapy in cancers. A substantial number of meta-analysis and review of randomized control trials specifically informed that herbal medicines and formulations could improve the quality of life of cancer patients during conventional therapy and palliative care [87-90]. Other than that life style modifications including food habits, exercise, meditation and Yoga can improve the quality of life of cancer patients, particularly during palliative care [91,92].

Conclusions

The burden of cancer in society can be lowered by early detection and to starting effective and specific treatment management of cancer. Most cancers have high possibility of curing if diagnosed early and preventing the spread of disease. Body Revival is a polyherbal medicine intended to use broad spectrum cancer patients. From literatures based on ancient knowledge and modern research, strongly admits that Body Revival is able to stimulate the immune system, protect DNA from injury, restores damaged DNA, lower oxidative impairment, anti-proliferation, cancer cell cycle arrest, initiation of apoptosis, suppression of angiogenesis and metastasis, chemo preventive or restore/protects normal cells from harmful effects of radiation. The goal-oriented programmed clinical approaches are highly desirable in future to conclude the effectiveness and nature of the anticancer drug of natural origin.

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