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Unani Medicine for Cancer Care: An Evidence-Based Review

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ABSTRACT

Cancer is a significant global healthcare problem, with an estimated worldwide incidence of 10 million new cases per year, 46% of which are in developed countries. Mortality is high, with >7 million deaths per year. The goal of cancer treatment is first to eradicate the cancer. If this primary goal cannot be accomplished, the therapeutic goal shifts to palliation, the amelioration of symptoms, and preservation of the patient's quality of life (QOL). In the last two decades, great advances have been made in cancer therapy; however, the success rates still remain unsatisfactory. Current conventional anticancer therapies are associated with adverse effects, drug resistance, and cancer recurrence. Therefore, there is still an urgent need for new therapeutic options for cancer. Current evidence, based on preclinical studies suggests that some Unani medicinal plants have anticancer potential. This review offers an evidence-based perspective of 20 Unani herbal drugs for the prevention and treatment of cancer. Several mechanisms are likely to account for the observed pharmacological effects, the most important being direct cytotoxicity, apoptosis induction, anti-oxidation, and immunomodulation. These Unani herbal drugs when combined with conventional anticancer therapy may help to synergize the anticancer effects, and reduce the side effects of conventional drugs, to improve the patient's QOL, and to prevent cancer recurrence. However, well-designed and well-executed randomized controlled clinical trials (RCTs) are required to validate their usefulness and to make their use acceptable clinically in different types of cancers. Thus, these Unani medicinal plants may have turned into anticancer drugs.

Keywords: Anticancer, Chemoprevention, Medicinal plants, Preclinical, Unani.

INTRODUCTION

Cancer is a significant global healthcare problem, with an estimated worldwide incidence of 10 million new cases per year, 46% of which are in developed countries. Mortality is high, with more than 7 million deaths per year[1]. According to National Cancer Registry Programme estimates, 700,000 to 900,000 new cancer cases occur in India every year. The WHO has estimated that about 15 million new cancer cases will be diagnosed each year by 2020 worldwide[2]. Also by 2020, overall mortality from cancer will increase by 104%, and the increase will be 5-fold higher in developing than in developed countries[3].

In the last two decades, great advances have been made in cancer therapy; however, the success rates still remain unsatisfactory. Current conventional treatment options are accompanied by adverse effects, drug resistance, and cancer recurrence. Therefore, there is still an urgent need for new therapeutic options for cancer.

Unani medicine is a holistic approach to cancer care. Current evidence, based on preclinical in vitro and in vivo studies suggests that some Unani medicinal plants have anticancer potential. This review offers an evidence-based perspective of 20 Unani herbal drugs for the prevention and treatment of cancer. Several mechanisms are likely to account for the observed pharmacological effects, the most important being direct cytotoxicity, apoptosis induction, anti-oxidation, and immunomodulation. These Unani herbal drugs when combined with conventional anticancer therapy may help to synergize the anticancer effects, and reduce the side effects of conventional drugs, to improve the patient's QOL, and to prevent cancer recurrence. However, well-designed and well-executed randomized controlled clinical trials (RCTs) are required to validate their usefulness and to make their use acceptable clinically in different types of cancers. Thus, these Unani medicinal plants may have turned into anticancer drugs.

CANCER: AN OVERVIEW

Malignant tumors are collectively referred to as cancers. The term 'cancer' is derived from the Greek and Latin words for a crab, because a cancer "adheres to any part that it seizes on in an obstinate manner, similar to a crab" [4,5]. Cancer is a clonal acquired genetic disease caused by alterations in genes that are important for normal cellular functions (proto-oncogenes and tumour suppressor genes), and characterized by uncontrolled cell growth and metastasis. In addition to uncontrolled cell proliferation, some cancer cells have the ability to invade other tissues through direct cell migration or through the blood and lymph systems and may affect other distant tissues/organs[6].

Cancer is known as *Sartān* in Unani system of medicine. *Sartān* is an Arabic word which means crab. According to Unani medicine, cancer is essentially a disease of black bile (*Sawdā'*), i.e., excessive production and collection of black bile. The eminent Unani physicians notably, Galen (129-199AD), Rhazes (854-925), Abulcasis (936-1013), and Avicenna (980-1037) were acquainted with cancer. Galen (Jālinūs) was the first to deal with tumors, including cancer, in a systematic way. He adopted Hippocrates' basic theory of cancer as an excess of black bile. Avicenna and Rhazes (Al-Rāzi) described most types of cancers known at their time and suggested several treatments based on their belief that cancer is a result of excess of burned black bile in the affected tissue. The Andalusian scholar Al-Zahrāwī (Abulcasis) was the first to conduct classic removal of breast cancer. He recognized that cancer can be treated surgically only in its early stages when complete removal is possible[7]. Cancer has become the second leading cause of death worldwide after heart disease[3,6]. The major organ sites affected are shown in Table 1.

Table 1: Estimated Cancer Incidence by site and sex, US, 2010

Rank	Male			Female		
	Sites	%	Number	Sites	%	Number
1	Prostate	28	217,730	Breast	28	207,090
2	Lung	15	116,750	Lung	14	105,770
3	Colorectal	9	72,090	Colorectal	10	70,480
4	Bladder	7	52,760	Endometrial	6	43,470
5	Melanoma	5	38,870	Thyroid	5	33,930
6	Lymphoma	4	35,380	Lymphoma	4	30,160
7	Kidney	4	35,370	Melanoma	4	29,260
8	Oral cavity	3	25,420	Kidney	3	22,870
9	Leukemia	3	24,690	Ovary	3	21,880
10	Pancreas	3	21,370	Pancreas	3	21,770
	Other sites	19	149,190	Other sites	20	153,260
	All sites	100	7,89,620	All sites	100	7,39,940

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database[3]

Cancer may have multiple causes (Table 3). It has been estimated that nine modifiable risk factors are responsible for more than one-third of cancers worldwide. These include smoking, alcohol consumption, obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, air pollution, indoor smoke from household fuels, and contaminated injections[3].

Table 2: Selected Known Causes of Cancer and the Associated Cancer Types

Category	Suspected carcinogens	Associated cancer
A. Radiation		
	Ionizing Radiation (Therapeutic or Diagnostic)	Leukaemia, thyroid, breast, lung, liver, bone cancer
	Non-ionizing Radiation (Ultraviolet light)	Skin cancer
B. Occupational Carcinogens		
	Aromatic amines (Dyes)	Bladder Cancer
	Asbestos	Lung, pleural, peritoneal cancer
	Benzene	Acute myeloidleukaemia

	Chromium	Lung cancer
	Nickel dust	Nasal sinuses, Lung cancer
	Vinyl chloride (PVC)	Liver cancer
C. Therapeutic Agents		
1. Chemotherapy	Cyclophosphamide	Bladder cancer, leukaemia
	Chlorambucil&Melphalan	Acute nonlymphocyticleukaemia
2. Hormones	Androgens	Prostate cancer
	Diethylstilbestrol	Vaginal, endometrial, breast cancer
	Oestrogens	Endometrial, breast, liver cancer
3. Other drugs	Phenacetin	Kidney, bladder cancer
	Azathioprine & Cyclosporine	Non-Hodgkin's lymphoma
D. Infectious Agents		
1. Bacteria	*Helicobacter pylori*	Gastric cancer
2. Viruses	Human papilloma virus (HPV)	Cervical cancer
	Epstein-Barr virus (EBV)	Burkitt's lymphoma, Hodgkin's lymphoma
	Hepatitis B or C virus	Liver cancer
	Human immunodeficiency virus (HIV)	Kaposi's sarcoma, non-Hodgkin's lymphoma
	Human T-lymphotropic virus type 1 (HTLV-1)	Adult T-cell leukaemia/lymphoma
3. Parasites: Flukes	*Schistosomahaematobium*	Bladder cancer
	Clonorchissinensis *Opisthorchisviverrini*	Cholangiocarcinoma
E. Miscellaneous		
1. Tobacco	Cigarette smoking	Lung, bladder cancer
	Tobacco chewing	Oropharyngeal cancer
2. Alcohol	Excessive alcohol consumption	Oropharyngeal, laryngeal, oesophageal, liver cancer
3. Dietary factors	Low-fibre/ High fat diet	Colorectal cancer
	Inadequate folic acid intake, excess red or processed meat consumption	Colon cancer
	High Nitrosamine intake	Gastric cancer
	Aflatoxins (food contaminant)	Liver cancer
4. Lifestyle risk factors	Obesity (BMI >30 kg/m^2)	Males: esophagus, colon cancer Females: gallbladder, endometrial, breast (postmenopausal) cancer
	Physical inactivity	Colon, breast cancer

Adapted from Colledge et al, 2010, Munjal et al, 2012, Longo et al, 2012, Goldman et al, 2012

The goal of cancer treatment is first to eradicate the cancer. If this primary goal cannot be accomplished, the goal of cancer treatment shifts to palliation, the amelioration of symptoms, and preservation of the patient's quality of life while striving to considerably prolong life.

Chemotherapy and radiotherapy, together with surgery, are the major modalities of cancer therapy. Although exciting advances continue to be made in cancer therapeutics, nearly 40% of patients diagnosed with cancer will die of their disease. Virtually all patients diagnosed with advanced stage cancers will succumb to their tumour or complications of its therapy. The majority of patients receive little or no benefit from current chemotherapies mainly because most of the cancer cells are either intrinsically chemo-resistant or they become resistant during therapy. Thus, the treatment success rates are very low; and the current standard therapeutic options for cancer are not adequate and still do not meet the criteria to cure patients suffering from this lethal disease.

UNANI MEDICINAL PLANTS WITH ANTICANCER ACTIVITY

Several preclinical in vitro and in vivo studies have been carried out to observe the anticancer effects of Unani medicinal plants. The phytochemicals present in these plants may have the potential to act as preventative or therapeutic agents against different kinds of human cancers. The present paper describes 20 Unani medicinal plants which have been shown to possess anticancer activity indicating that these could be possible agents to prevent or reduce the process of carcinogenesis.

1. Afsantīn

Botanical Name: *Artemisia absinthium* L.
Family: Asteraceae
Anticancer Activity: The crude extract of the aerial parts of *Artemisia absinthium* (AA) significantly inhibited cell proliferation and promoted apoptosis in two human breast cancer cell lines – an estrogenic-responsive cell line (MCF-7) and an estrogenic-unresponsive cell line (MDA-MB-231). Cells were incubated with various concentrations of AA, and anti-proliferative activity was assessed by MTT assays, fluorescence microscopy after propidium iodide staining, western blotting and cell cycle analysis. Cell survival assays indicated that the extract was cytotoxic to both MCF-7 and MDA-MB-231 cells. The morphological features typical of nucleic staining and the accumulation of sub-G1 peak revealed that the extract triggered apoptosis. Treatment with 25 μg/mL AA extract resulted in activation of caspase-7 and up-regulation of Bad in MCF-7 cells, while exposure to 20 μg/mL AA extract induced up-regulation of Bcl-2 protein in a time-dependent manner in MDA-MB-231 cells. Both MEK1/2 and ERK1/2 were inactivated in both cell lines after AA treatment in a time-dependent manner. These results suggest that AA-induced anti-proliferative effects on human breast cancer cells could possibly trigger apoptosis in both cell lines through the modulation of Bcl-2 family proteins and the MEK/ERK pathway. This might lead to its possible development as a therapeutic agent for breast cancer following further investigations[9].

2. Aftīmūn

Botanical Name: *Cuscuta reflexa* Linn.
Family: Convolvulaceae
Anticancer Activity: The water extract of *Cuscuta reflexa* showed anti-inflammatory and anticancer activities in cell lines. The extract down regulated lipopolysaccharide (LPS)-induced over expression of TNF-α and COX-2 in murine macrophage cell line (RAW264.7); blocked NF-κB binding to its motifs and induced apoptosis in Hep3B cells as evident from MTT, DAPI staining and annexin V staining assays. The extract up-regulated BAX and p53, and down-regulated Survivin and Bcl-2. In conclusions, *Cuscuta reflexa* inhibited LPS-induced inflammatory responses in murine macrophage cell line through interplay of TNF-α, COX-2 and NF-κB signaling; and it induced apoptosis in Hep3B cells through the up-regulation of pro-apoptotic factors (BAX and p53) and down-regulation of anti-apoptotic factors (Survivin and Bcl-2)[10].

The chloroform and ethanol extracts (at doses of 200 and 400 mg/kg body weight orally) of the whole plant of *Cuscuta reflexa* exhibited significant antitumor activity in Swiss albino mice against Ehrlich Ascites Carcinoma (EAC) cell line; and the effects were comparable to that of the reference standard antitumor, 5-fluorouracil. Administration of the extracts resulted in a significant ($p<0.05$) decrease in tumor volume and viable cell count, but increased non-viable cell count and mean survival time, thereby increasing the lifespan of the tumor-bearing mice. Restoration of haematological parameters, including Hb, RBC, WBC, and Lymphocyte counts to normal levels in extract-treated mice was also observed[11].

Methanolic extract of *Cuscuta reflexa* stems (MECR) and its Ethyl acetate soluble fraction (EAMECR) showed significant anti-inflammatory and cytotoxic activities with Inhibitory Concentrations IC50% values 277.83 μg/mL and 214.94 μg/mL in Human Red Blood Cell (HRBC) Stability Assay, and Lethal Concentration LC50% 257.73 μg/mL and 184.86 μg/mL in Brine Shrimp Lethality Assay (BSLA) respectively[12].

3. Āmla

Botanical Name: *Emblica officinalis* gaertn or *Phyllanthus emblica* L.

Family: Euphorbiaceae

Anticancer Activity: The aqueous extract of *Phyllanthus emblica* (PE) fruit showed the anti-metastatic activity in reducing proliferation, migration, invasion, and adhesion of human fibrosarcoma cells in both dose- and time-dependent manners, especially growth arrest with low IC50 value. A decrease in the expression of both MMP2 and MMP9 seems to be the cellular mechanism for anti-metastasis in this case. There is a high potential to use PE extracts clinically as an optional adjuvant therapeutic drug for therapeutic intervention strategies in cancer therapy or chemoprevention[13].

The total aqueous extract of *E. officinalis* showed protective effects in mice treated with Cyclophosphamide (CP). Plant extract, in particular, was very effective in reducing CP-induced suppression of humoral immunity. In CP-exposed animals, plant pretreatment showed the nephroprotective effect. The plant extract treatment resulted in restoration of antioxidant enzymes in CP-treated animals. It is suggested that *E. officinalis* or its medicinal preparations may prove to be useful as a component of combination therapy in cancer patients under the CP treatment regimen[14].

Emblica officinalis gaertn (*Phyllanthus emblica* L.) has been studied for its radioprotective effects using hydroalcoholic extract of its fruit against radiation-induced damages in mice. There was significant depletion in lipid peroxidation ($p<0.001$) in liver tissue and significant elevation in antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH) and glutathione S-transferase (GST) levels ($p<0.001$) in blood of mice in test group in comparison to control (radiation alone) group. These observations indicated a possible therapeutic use of the EO to prevent radiation-induced damage. Further evaluation of this and other radioprotective effects perhaps will make it a suitable radioprotector against sub-lethal doses[15-19].

4. Asgand

Botanical Name: *Withania somnifera* (L.) Dunal

Family: Solanaceae

Anticancer Activity: The 50% ethanol extract of root, stem and leaves of *Withania somnifera* showed growth inhibitory activity against five human cancer cell lines representing four different tissues, PC-3, DU-145, HCT-15, A-549 and IMR-32; and the effects were comparable to that produced by anticancer drugs paclitaxel, adriamycin and 5-fluorouracil (5-Fu) used as positive controls. This study gives support that 50% ethanol extract of *Withania somnifera* were highly cytotoxic to the human cell lines studied. The leaf extract produced anti-proliferative activity on NCI-H460 (lung), HCT-116 (colon), SF-268 (central nervous system) and MCF-7 (breast) human tumor cell lines (). Hence, this study has revealed remarkable anticancer potential in the rootm stem, and leaves of *Withania somnifera*[20,21].

Withania somnifera (leaves) showed significant cytotoxicity on MCF-7, PA-1, and A459 cancer cell lines. Standard drug Doxorubicin was used as a positive control[22].

5. Asl-us-Sūs

Botanical Name: *Glycyrrhiza glabra* Linn.

Family: Fabaceae

Anticancer Activity: In the preclinical in-vitro cytotoxic study three different extracts (chloroform, methanol and water) of *Glycyrrhiza glabra* showed significant cytotoxicity by MTT method as compared with reference standard 18 β-glycyrrhetic acid. Chloroform extract of *Glycyrrhiza glabra* showed good cytotoxicity (IC 50 value of 0.4485 µM) against human breast cancer cell line (MCF7) than the other two extracts (methanol and water) of *Glycyrrhiza glabra* because it was containing higher amount of 18 β-glycyrrhetic acid as quantified through HPTLC method. The cell viability of two different cell lines determined by two fold Trypan Blue method was 45.71% for normal cell line (VERO) and 78.78% for human breast cancer cell line (MCF7). From the results of the study, it can be concluded that 18 β-

glycyrrhetic acid could be considered as a potential source of natural anticancer component and the percentage of which was higher in the chloroform extract of *Glycyrrhiza glabra*[23].

Glycyrrhizin showed potential chemopreventive activity on 12-O-tetradecanoyl phorbol-13- acetate-induced coetaneous oxidative stress and tumor promotion in Swiss albino mice[24].

6. Balādur

Botanical Name: *Semecarpus anacardium* Linn.
Family: Anacardiaceae
Anticancer Activity: An active compound 3-(8'(Z),11'(Z)-pentadecadienyl) catechol isolated from the kernel of *Semecarpus anacardium* nut (SA-3C) showed anti-cancer activity in human tumor cell lines. The isolated SA-3C was cytotoxic to tumor cell lines with IC(50) values lower than doxorubicin and even multidrug resistant tumor cell lines were equally sensitive to SA-3C. SA-3C induced apoptosis in human leukemia cell lines in a dose-dependent manner and showed synergistic cytotoxicity with doxorubicin. The cell cycle arrest induced by SA-3C at S- and G(2)/M-phases correlated with inhibition of checkpoint kinases. SA-3C isolated from the kernel of *Semecarpus anacardium* can be developed as an important anti-cancer agent for single agent and/or multiagent cancer therapy[25].

Semecarpus anacardium nut extract showed restoration of energy metabolism in leukemic mice treated by *Semecarpus anacardium* (SA) nut milk extract. SA treatment was compared with standard drug imatinib mesylate. SA administration to leukemic animals resulted in clearance of the leukemic cells from the bone marrow and internal organs[26].

Semecarpus anacardium nut extract showed inhibitory effect on human breast cancer cell line (T47D). At the molecular level, these changes were accompanied by decrease in Bcl(2) and increase in Bax, cytochrome c, caspases and PARP cleavage, and ultimately by internucleosomal DNA fragmentation[27].

7. Balela

Botanical Name: *Terminalia bellirica* (Gaertn.) Roxb.
Family: Combretaceae
Anticancer Activity: The methanolic extract of fresh shade-dried powdered leaves of *Terminalia bellerica* showed significant anticancer effect in human hepatic cancer (HepG2), breast cancer (MCF 7), and colon cancer (HT 29) cell lines as revealed by (a) cell growth inhibition, (b) G2/M-phase cell cycle arrest, and (c) apoptosis. The extract inhibited the proliferation of human cancer cells in a dose-dependent manner as evident from the percentage of cell viability determined by MTT assay. The extract showed significant cytotoxicity with IC50 of 5.65µg/mL. Moreover, normal Monkey Kidney (VERO) cell line was less sensitive to the extract-induced cytotoxicity. The extract induced apoptosis by down-regulation of anti-apoptotic gene, Bcl-2, and up-regulation of pro-apoptotic proteins Bax, Caspase-9 and Caspase-3 in a dose dependent manner. The pro-apoptotic effect of the extract was also due to down-regulation of the AKT/mTOR signaling pathway. Flow cytometry analysis showed an increase in the percentage of G2/M arrest phase in HepG2 cell line compared to control cell line. Overall, these findings suggest that leaves of *Terminalia bellerica* can provide a source of potential therapeutic compounds for the treatment of cancer[28].

The crude aqueous methanolic extract of the dried powdered fruits of *Terminalia belerica* showed significant anticancer activity against DMBA-induced skin papillomas in Swiss albino mice as revealed by reduction in the number of papillomas and tumor yield. Group1: DMBA + Croton Oil. The DMBA was used as the cancer inducer and Croton oil 1% as cancer promoter. The 104 µg DMBA was dissolved in 100 µL acetone and a single application was given followed by 1% Croton oil applied on the skin twice a week up to 16 weeks. Group 2: DMBA + Croton Oil + Extract of *Terminalia belerica*. The extract was given at a dose of 100µl one hour before each application of 1% croton oil. The average number of papillomas was 13 and 6 in group 1 and group 2 respectively. The tumor yield was also reduced which was 1.8 and 1.1 in group 1 and group 2 respectively[29].

8. Chirchita

Botanical Name: *Achyranthes aspera* Linn.
Family: Amaranthaceae
Anticancer Activity: Methanolic extract of *Achyranthes aspera* leaves exhibited time and dose dependent cytotoxicity on several human cancer cells in vitro. Compared to cancer cells of colon, breast, lung and prostate origin, pancreatic cancer cells were significantly more sensitive to the extract. Preliminary mechanistic studies suggested that it selectively suppressed the transcription of metalloproteases (MMP-1 and -2), inhibitors of MMPs (TIMP-2) and angiogenic factors (VEGF-A and VEGF-B). Fractionation of the extract on methanol equilibrated silica gel column resolved into 3 fractions of which fraction (F3) was found to be enriched with anti-proliferative activity. In conclusion, methanolic extract of *Achyranthes aspera* contains potent anti-proliferative compound with specific activity against pancreatic cancer[30].

The extracts of *Achyranthes aspera* leaves showed significant anticancerous activity in Swiss albino mice with plasmacytomas, metastasized tumor in the head, and throat induced by mineral oil. The cancer symptoms were studied by observing the length of tail, swelling, uncontrollable growth in body parts and enumeration of T cell counts. The study clearly indicated that the ether extract at the concentration of 3 mg/ml was very effective in reducing the cancer symptoms[31].

9. Deodār

Botanical Name: *Cedrus deodara* (Roxb.) G.Don
Family: Pinaceae
Anticancer Activity: An isolate "CD lignan mixture" comprising lignans from stem wood of *Cedrus deodara* consisted of (-)-wikstromal (75-79%), (-)-matairesinol (9-13%) and benzylbutyro lactol (7-11%) in the in vitro cytotoxicity studies showed significant dose-dependent effects against several human cancer cell lines from different tissues such as breast, cervix, neuroblastoma, colon, liver, and prostate at 10, 30 and 100 microg/mL. CD lignan mixture had the most pronounced effect on CNS cell lines followed by colon. In the in vivo anticancer study, it induced the tumor regression, which was 53% in Ehrlich ascites carcinoma 54% in colon carcinoma (CA-51), when CD lignan mixture was given at 300 and 400 mg/kg, I.P. for 9 days in the Ehrlich ascites carcinoma and colon carcinoma (CA-51) models in mice respectively. It was comparable with 5-fluorouracil at 22 mg/kg and 20 mg/kg, respectively. It induced apoptosis as indicated by annexin V positive cells, induction of intracellular caspases, DNA fragmentation and DNA cell cycle analysis[32].

The hydro-alcoholic extract of *Cedrus deodara* wood showed anticancer activity against 3 human cancer cell lines – prostate (PC3), ovary (A2780), and breast (MCF7), and the effects were comparable with doxorubicin used as positive control[33].

AP9-cd, a standardized lignan composition from *Cedrus deodara* consisting of (-)-wikstromal, (-)-matairesinol, and dibenzyl butyrolactol inhibited human leukemia Molt-4 cell proliferation with 48-h IC(50) of approximately 15μg/ml, increased sub-G0 cell fraction with no mitotic block, produced apoptotic bodies and induced DNA ladder formation. AP9-cd caused 2-fold activation of caspase-3 in Molt-4 and 5-fold activation in HL-60 cells. Also caspases-8 and -9 were activated in human leukemia HL-60 cells. The studies indicated that AP9-cd mediated early NO formation leads to caspases activation, peroxide generation, and mitochondrial depolarization which may be responsible for mitochondrial-dependent and -in dependent apoptotic pathways involved in the killing of leukemia cells by AP9-cd[34].

10. Gilo

Botanical Name: *Tinospora cordifolia* (Thunb.) Miers
Family: Menispermaceae
Anticancer Activity: An alkaloid palmatine isolated from the methanolic extract of shaded-dried powdered stems of *Tinospora cordifolia* showed significant anticancer activity in DMBA (7,12-dimethylbenz (a)anthracene) induced skin carcinogenesis in Swiss albino mice. Alkaloid administration significantly decreased tumor size, number, and the activity of serum enzyme when compared with the control. In addition, depleted levels of reduced glutathione (GSH), superoxide dismutase (SOD), and catalase and increased DNA damage were restored in palmatine treated groups. In conclusion, the data of the present

study clearly indicate the anticancer potential of palmatine alkaloid in DMBA induced skin cancer model in mice[35].

The 50% ethanolic extract of *Tinospora cordifolia* (TCE) significantly reduced cell proliferation in a dose-dependent manner and induced differentiation in C6 glioma cells. Further, TCE showed antimigratory and anti-invasive potential as depicted by wound scratch assay and reduced expression of plasticity markers NCAM and PSA-NCAM along with MMP-2 and 9. On analysis of the cell cycle and apoptotic markers, TCE treatment was seen to arrest the C6 cells in G0/G1 and G2/M phase, suppressing expression of G1/S phase specific protein cyclin D1 and anti-apoptotic protein Bcl-xL, thus supporting its anti-proliferative and apoptosis inducing potential[36].

The 50% methanolic extract of the fresh shade-dried powdered stems of *Tinospora cordifolia* significantly prevented the micronucleus formation in bone marrow of Swiss albino mice in a dose-dependent manner, suggesting its antimutagenic activity. In melanoma assay in C57BL mice, the extract significantly reduced the melanoma size and increased the lifespan of mice as compared to control, suggesting its anticancer activity[37].

11. Gul-i-Nīlofer

Botanical Name: *Nymphaea alba* Linn.
Family: Nymphaeaceae
Anticancer Activity: Treatment of rats orally with *Nymphaea alba* (100 and 200 mg/kg body weight) resulted in significant decrease in gamma-glutamyl transpeptidase, lipid peroxidation, xanthine oxidase, H2O2 generation, blood urea nitrogen, serum creatinine, renal ODC activity, DNA synthesis ($p < 0.001$) and incidence of renal tumors. Renal glutathione content ($p < 0.01$), glutathione metabolizing enzymes ($p < 0.001$) and antioxidant enzymes were also recovered to significant level ($p < 0.001$). Thus, our results show that *Nymphaea alba* is a potent chemopreventive agent and suppresses Fe-NTA-induced oxidative stress, hyperproliferative response and renal carcinogenesis in Wistar rats[38].

Strong antitumor activity was observed with *Nymphaea alba*, in Agrobacterium tumefaciens-induced potato disc tumor assay. Inhibition of tumor formation of potato discs was caused by anti-tumorogenesis. Tumor formation was not observed with positive control camptothecin (100% inhibition). Best antitumor activity was obtained with methanolic extract of *Nymphaea alba* (100% inhibition) similar to positive control camptothecin. Alcoholic extracts (ethanol and methanol) of *Nymphaea alba* showed similar antitumor activity (between 99.4%-100% tumor inhibition)[39].

12. Halela

Botanical Name: *Terminalia chebula* Retz.
Family: Combretaceae
Anticancer Activity: The Chebulinic acid was extracted from 50% (v/v) ethanolic extract of the powder of dried fruits of *Terminalia chebula* by the Colum chromatography. The Chebulinic acid of *Terminalia chebula* showed significant in-vitro anti-cancer activity in Colon Adenocarcinoma (HT-29) cell lines as assessed by using MTT cell growth inhibition assay, and its effect was comparable with the standard drug 5-fluorouracil. It was found that the Chebulinic acid inhibited the growth of HT-29 cancer cells, and the maximum percentage inhibition was 41.2% at a dose of 200µg/ml. Hence, Chebulinic acid can be used as a potent anti-cancer agent[40].

In the preclinical in vitro and in vivo study, ethanolic extract of *Terminalia chebula* (ETC) fruits showed significant anticancer activity. The ETC showed in vitro cytotoxicity against Ehrlich Ascites Carcinoma (EAC) cells in a dose dependent manner as evident from the viability of cells determined using Trypan Blue Exclusion Method, and the percentage viability in EAC cells was 86% and 100% at the doses of 100 µg and 200 µg respectively. The ETC prolonged the lifespan of tumor bearing mice as determined by mean survival time; and the increase in the lifespan was 74.07% ($p<0.05$) with ETC (200 mg/kg/day orally), and 88.88% ($p<0.001$) with the positive control 5-fluorouracil (20 mg/kg IP/day) as compared to the negative control (normal saline) group. The ETC significantly reduced the tumor volume in EAC bearing male Swiss albino mice. The haematological parameters (Hb content, RBC count, and WBC count) were

also reversed to near normal values in the animals treated with ETC. These results suggest that *Terminalia chebula* might be a good choice for the treatment of cancer; and ETC may be used as a potential anticancer chemotherapeutic agent[41].

The ethanolic extract of *Terminalia chebula* fruits showed significant anticancer activity in human breast cancer (MCF-7) cell lines in a concentration- and time-dependent manner as evident from the percentage viability of MCF-7 cells determined by MTT assay. The extract at the doses of 200µg/ml and 400µg/ml showed the 43.06% and 36.20% viability of MCF-7 cells respectively as compared to the untreated control group (100% cell viability)[42].

13. 'Inab-us-Sā'lab

Botanical Name: *Solanum nigrum* Linn.
Family: Solanaceae
Anticancer Activity: An ethanol extract of *Solanum nigrum* (SNL) ripe fruits significantly suppressed the proliferative capacity of human breast cancer cells (MCF-7) assessed by Tritium Uptake proliferation assay. This was further confirmed through MTT assay and Trypan Blue exclusion experiments, which showed a very close correlation between the SNL extract concentration and the surviving cell numbers. The SNL extract-mediated suppression of cell growth was verified to be apoptotic, based on the appearance of DNA laddering, increase in DNA fragmentation, and low fluorescence intensity in nuclei after propidium iodide staining of the cells. Furthermore, the SNL extract was revealed to be a potential scavenger of hydroxyl radicals and DPPH (Diphenyl Picryl Hydrazyl) radicals rather than superoxide anions. Collectively, findings suggest that *Solanum nigrum* fruit extract could be used as an antioxidant and cancer chemo-preventive agent[43].

Lunasin, a bioactive component isolated from autoclaved *Solanum nigrum* inhibited core histone H3 and H4 acetylation, the activities of the HATs, and the phosphorylation of the Rb protein. It was concluded that consumption of *Solanum nigrum* may play an important role in cancer prevention[44].

14. Jangli Arand

Botanical Name: *Jatropha curcas* Linn.
Family: Euphorbiaceae
Anticancer Activity: The extract of the leaves of *Jatropha curcas* exhibited cytotoxic activity against human breast adenocarcinoma cells (BT-549) with IC50 value of 21.3 µg/ml. Similar cytotoxic activity was previously reported, where the root of *Jatropha curcas* inhibited the proliferation of human colon adenocarcinoma cells (HT-29, IC50 = 18.3 µg/ml) and human hepatocytes (Chang liver cells, IC50 = 33.3 µg/ml)[45].

Ethanolic extract of *Jatropha curcas* leaves showed inhibitory effect on the growth of cancer cells in DLA tumor bearing mice. Based on in vitro studies like brine shrimp lethality assay, potato disc method and onion root tip inhibition studies, the ethanolic extract of *Jatropha curcas* leaves was found to possess anticancer activity[46].

15. Kachnār

Botanical Name: *Bauhinia variegata* (L.) Benth.
Family: Fabaceae
Anticancer Activity: Ethanolic extract of *Bauhinia variegata* bark showed in vitro anticancer activity in HeLa cell lines. The IC50 value of the extract was 191.5µg/ml against HeLa cell lines determined by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) and SRB (sulforhodamine B) assays. The extract induced apoptotic cell death in malignant HeLa cell lines as determined by Ethidium bromide/Acridium orange fluorescent staining method. The extract also arrested the replication of cells at G0/G1 phase as evident from Flow cytometric analysis[47].

The leaf extracts of *Bauhinia variegata* showed in vitro cytotoxicity as determined by Sulforhodamine B (SRB) assay. Aqueous fraction of *B. variegata* showed significant cytotoxic effect

against human cancer cell lines with 99, 99, 94, 93, and 87% cell growth inhibitory activity against ovary (IGR-OV-1), prostate (DU-145), leukemia (THP-1), breast (MCF-7), and lungs (HOP-62) cell lines, respectively. Ethyl acetate extract showed marked cytotoxicity against THP-1 (93%) and MCF-7 (84%) cell lines. Benzene extract showed 75% cytotoxicity against THP-1, while acetone extract demonstrated 60% cytotoxicity against THP-1 and MCF-7 cell lines. The rest of the extracts (petroleum ether, chloroform, ethyl alcohol) showed lower anticancer activity (<50%). In general, breast (MCF-7) and leukemia (THP-1) cell lines exhibited greater sensitivity to *B. variegata* extracts[48].

The methanolic extracts from both natural in vivo garden plants and regenerated in vitro culture plants of *Bauhinia variegata* showed in vitro cytotoxicity in Ehrlich Ascites Carcinoma (EAC) cell lines[49].

16. Kutki

Botanical Name: *Picrorhiza kurroa*

Family: Plantaginaceae

Anticancer Activity: In a preclinical in vitro study, Nano encapsulated extract formulation from rhizome of *Picrorhiza kurroa* showed >100% increment in cell killing at a concentration of 100µg/ml recorded in two cell lines, 52.5% cytotoxicity in human hepatocarcinoma cell line (HePG-2) was recorded at 0.1µg/ml concentration, whereas 50.4% cytotoxicity was recorded in Madin Darby Canine Kidney (MDCK) cell lines at 1µg/ml of formulation concentration. Exhibited LC50 values of Formulation in HePG-2 and MDCK cell lines were recorded 1.2 µg/mL and 4.14µg/mL respectively. MDCK cytotoxicity results support that formulation is less cytotoxic in normal cell lines, as MDCK is a Non-Cancerous cell line. These effects were comparable with standard anticancer drug Doxorubicin, which was used as positive control[50].

The hydro-alcoholic extract of *Picrorhiza kurroa* roots showed anticancer activity against human colon cancer cell line (Colo205) and the effect was comparable with doxorubicin used as positive control[33].

Methanolic and aqueous extracts of *Picrorhiza kurroa* rhizome showed antioxidant and anti-neoplastic activities. Both extracts exhibited inhibition of lipid peroxidation, free radical scavenging activity (DPPH and OH), and ferric reducing antioxidant property (FRAP). The extracts showed cytotoxicity in human breast carcinoma (MDA-MB-435S), human hepatocellular carcinoma (Hep3B) and human prostate cancer (PC-3) cell lines as evident from XTT assay. The extracts induced apoptosis[51].

17. Sadābahār

Botanical Name: *Catharanthus roseus* (L.) G. Don

Family: Apocynaceae

Anticancer Activity: In a preclinical in vitro study, the ethanolic extract of powdered shade-dried aerial parts of *Catharanthus roseus* exhibited significant antitumor activity in MCF (breast cancer) cell lines as evaluated by MTT cell viability assay. In the preclinical in vivo study, ethanolic extract of *Catharanthus roseus* (EECR) in the doses of 50 and 100 mg/kg orally significantly increased the lifespan and decreased the tumor volume and cancer cell count in Ehrlich ascites carcinoma (EAC) bearing Swiss albino mice, and the effects of the extract were comparable with standard anticancer drug 5-Fluorouracil. The results of both in vitro and in vivo studies indicate that *Catharanthus roseus* possesses significant antitumor activity[52].

Vincristine and vinblastine have been isolated from *Catharanthus roseus* and each has been effectively used against a number of different forms of cancers including childhood leukaemia and Hodgkin's disease[53].

The 50% and 100% methanolic crude extracts of *Catharanthus roseus* (at <15 µg/mL) had significant anticancer activity against numerous cell types in vitro[54]. Greatest activity was seen against multidrug resistant tumor types, suggesting there were compounds in *Catharanthus* that were synergistic or additive with antineoplastic elements by inhibiting resistance to them. Crude decoction of (200 mg and 1 g herb/mL water) *Catharanthus* showed a moderate anti-angiogenesis affect in vitro[55].

18. Sibr Zard (Elva)

Botanical Name: *Aloe vera* (L.) Burm.f.

Family: Xanthorrhoeaceae

Anticancer Activity: The 50% ethanolic extract of the dried leaf powder of *Aloe vera* (at the dose of 100 mg/kg daily for 14 days) showed antitumor activity against Ehrlich ascites carcinoma (EAC) in Swiss albino mice. The extract treatment inhibited the increase in body weight and abdominal circumference and restored the serum biochemical parameters (ALT, AST, LDH, ALP and glucose) and haematological parameters towards normal levels in EAC bearing mice. The extract also decreased the levels of hepatic lipid peroxidation, and increased the levels of antioxidant – reduced glutathione (GSH) and antioxidant (free radical scavenging) enzymes, glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT)[56].

Aloe emodin (AE), present in highest concentration in the cortex of *Aloe vera* leaves, induces cell death in several tumor cell lines, as well as the regression of neuroectodermal tumors in mice with severe combined immunodeficiency without appreciable signs of acute and chronic toxicity[57].

19. Waj Turki

Botanical Name: *Acorus calamus* Linn.
Family: Acoraceae
Anticancer Activity: Among the five fractions (petroleum ether, chloroform, ethyl acetate, acetone, and water) of the crude hydro-ethanolic extract of *Acorus calamus* rhizomes, chloroform fraction showed reasonably good cytotoxicity against the human breast cancer (MCF-7) cell lines with CTC50 value of 110µg/mL, whereas the rest of the fractions were moderately cytotoxic to the MCF-7 cell lines with CTC50 values ranging from 170-360µg/mL. The cytotoxicity was measured as the growth inhibition and determined by Sulphorhodamine B (SRB) Assay. Thus, the chloroform fraction may be considered as a potential source of metabolites which could be developed as a precursor for anticancer drugs[58].

Methanolic extract of *Acorus calamus* showed cytotoxic effect in human breast cancer (MCF-7) cell lines as assessed by MTT Assay. The extract significantly reduced cell viability in malignant cells in a concentration dependent manner. The IC50 values in MCF-7 cells were determined as 52.07µg/mL[59].

The ethanolic extract of *Acorus calamus* roots showed significant in vitro cytotoxic activity as determined by Brine Shrimp Lethality Assay. The percent mortality (mean ± SD) of larvae (nauplii) was 61.25±26.66, which was increased with the increase of the doses of the extracts. The LC_{50} and LC_{90} values were found 50 and 300 μg/mL, and the results were statistically significant ($P < 0.0001$)[60].

20. Zarishk

Botanical Name: *Berberis aristata* Linn.
Family: Berberidaceae
Anticancer Activity: The extracts of *Berberis aristata* showed antineoplastic activity in Ehrlich ascites carcinoma (EAC)-bearing Swiss albino mice as determined by Brine shrimp lethality bioassay (BSL). Antineoplastic activity of the aqueous and ethanolic extracts (100 and 6.5 mg/kg IP, respectively) was compared with that of cisplatin (3.5 mg/kg IP) on the parameters such as percentage increase in weight, median survival time, and hematology. Ethanolic extract attenuated percentage increase in weight gain (-6.86 ± 1.50) due to tumor cell proliferation and increased the survival time (19.5 days) when compared to control group (19.10 ± 2.31 and 16 days, respectively). However, the effect was less than that of cisplatin. In vitro tumor cell viability assay and BSL test showed the cytotoxic effect of the extracts. Cisplatin and the extracts reversed the tumor-induced alterations in total white blood cell count, differential leukocyte counts, total red blood cell count, and hemoglobin contents[61].

The methanolic extract of the stems of *Berberis aristata* significantly inhibited proliferation of human colon cancer (HT29) cells in a dose-dependent manner as determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) microculture tetrazolium viability assay. Cisplatin was used as positive control and Dimethylsulfoxide (DMSO) as vehicle (negative) control. The extract at a dose of 100 µg/mL showed 54.89% cytotoxicity. The IC50 value of *Berberis aristata* methanolic extract was 1.8964 µg/mL after 72 h of incubation[62].

The hydro-alcoholic extract of *Berberis aristata* root showed anticancer activity against 3 human cancer cell lines – oral (DWD), lungs (Hop62), and ovary (A2780), and the effects were comparable with doxorubicin used as positive control[33].

SUMMARY

The best ways for cancer treatment are preventing its causes and diagnose it in earlier stages. So many cancers are either disseminated at diagnosis or too advanced locally to resect, that a systemic approach to treatment offers the only chance of remission/cure. Chemotherapeutic drugs are widely used in the treatment of cancer. However, they are not always effective and usually are accompanied with side effects. In the recent decades, there has been a dramatic increase in interest in the use of herbal drugs to kill cancer cells. Unani herbal drugs might be potentially safe therapeutic candidates for the treatment of cancer. Several preclinical in vitro and in vivo studies have reported anticancer activity of some Unani medicinal plants extracts on different human cancer cell lines and in animal models. However, there is currently no strong scientific evidence from clinical trials that these Unani herbal drugs can treat, prevent or cure cancer. This review provides the salient findings of preclinical studies of 20 Unani medicinal plants for their anticancer activity. These findings provide a good base for clinical trials. These Unani medicinal herbs may be valuable for optimizing the conventional anticancer therapy; and they can be used in combination with conventional anticancer drugs as a supportive therapy to improve health-related quality of life (HRQoL) of cancer patients. However, clinical studies of these herbs need to be conducted for possible alternative medical treatment of cancer.

CONCLUSION

Unani medicine is a holistic approach to cancer care. The primary aim of this review is to highlight and discuss the latest findings of studies conducted on Unani medicinal plants for their anticancer effects, in order to fight against this deadly disease by developing the safe and effective anticancer therapeutic agents. Unani herbal drugs can be considered as promising chemotherapeutic agents. The randomized controlled clinical trials may be conducted to evaluate the safety and efficacy of these Unani herbal drugs as an adjunct to conventional anticancer treatment. Thus, these Unani medicinal plants may have turned into anticancer drugs.

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