Ethnobotanical Study of Medicinal Plants of Kashmir Valley, India Having Anticancer Properties

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ABSTRACT

Kashmir valley is inhabited by various tribes living in close vicinity of enriched forests. These tribes have always used medicinal plants for the treatment of various diseases by traditional methods. Utilization of medicinal plants is directly linked to their culture and history. There are many tribes and villages that are repositories of indigenous knowledge and practice. With due attention to rapid progress in the phytochemical study of plants, they are becoming popular because of their anticancer effects. Documentation of such knowledge is required in view of day to day disappearing knowledge in the new generations. Therefore, in the present study an attempt has been made to document some locally available plants utilized traditionally by the inhabitants of the valley and are having anticancer properties. These plants are likely to provide effective anticancer agents. The aim of this study is to investigate the effective medicinal plants in the treatment of cancer and study their mechanism of action.

Keywords- Medicinal properties, Tribes, Phytochemical study, Anticancer agents.

I. INTRODUCTION

Ethnobotany is a multi-disciplinary natural science, which deals with human plant Importance of ethnobotany has been realized by mankind by means of various uses of plants in their day to day life science. Ethnobotany has more and more been recognized as a valid discipline that plays a very material role in the advancement of many aspects of scientific, sociological and historical studies.

There are simple herbs and roots that every family may use for themselves and no need to call a physician. Medicinal plants are a valuable natural resource and are regarded as potentially safe drugs they have been playing an important role in alleviating human sufferings by contributing herbal medicines in the primary healthcare systems of rural and remote areas where more than 70% of the population depends on folklore and traditional systems of medicines(1, 2). The reason for their popularity is due to high cost and side effects of allopathic medicines. The state of Jammu and Kashmir cradled in the lap of Himalayas has been recognized as heaven on earth and is also called the biomass state of India and harbors a rich diversity of medicinal plants(3, 4). This area has a diverse variety of plant species especially ethno medicinally important plants due to wide variety in its topography and microclimatic conditions(4, 5). Since ages in the need of hour, people in the valley have learned and practiced the medicinal usage of plants /herbs growing in their vicinity for the treatment of various ailments. Many studies have been carried out to document the indigenous knowledge of medicinal plants from different areas of the Kashmir valley.

Cancer is one of the major causes of death in the world, and it is the second leading cause of mortality after cardiovascular diseases(6). Cancer starts with the deformation of natural cells caused by genetic mutation in the DNA of normal cell. A few cancer syndromes are caused by inherited mutations of protooncogenes that cause oncogene to be turned on (activated). Mutated oncogenes are stimulated by the exposure to chemical, environmental or viral carcinogens which leads to wrongly expressed within their normal cell or expressed in inappropriate tissue which leads to cellular proliferation and there by result in cancer formation. Tumor suppressor genes are intended to keep oncogenes in check by halting uncontrolled cellular growth. When Tumor Suppressor genes are inactivated or attenuated, it leads to promotion or initiation of cancer (Table1).

Table 1: Types of cancer and their common oncogenic or tumor suppressor gene origin

| Cancer Type                                      | Common Oncogenic or Tumor Suppressor Gene Origin          |
|-------------------------------------------------|----------------------------------------------------------|
| Leukemia, breast, colon, gastric and lung Cancer | c-MYC amplification                                      |
| Renal cell cancer                                | Von Hippel-Lindaugene (VHL) dysfunction                   |
| Chronic myelogenous leukemia                     | Bcr-abl proto-oncogene translocation                      |
| Childhood neuroblastoma and small cell lung Cancer | n-MYC amplification                                     |

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Nowadays, there are various methods available in the medical field that are used for the treatment of cancer such as chemotherapy, but in these methods there is non-selectivity of medicines due to which a high percentage of healthy cells will be lost with cancer cells. The most important problem in cancer treatment is destroying tumor cells in the presence of normal cells, without damaging natural cells. In order to prepare anticancer medicines from natural resources like plants, testing cytotoxic compounds and screening raw extracts of plants is necessary(8). Therefore, natural products with higher effectiveness and lower side effects are desired (9). Various Medicinal herbs are important for cancer treatment due to their multiple chemical compound for discovering new active materials against cancer(10). Plants produce a wide range of chemical compounds called secondary metabolites such as alkaldoids, terpenoids, flavonoids, pigments, and tannins which have biologic effects such as anti-inflammatory, anticancer etc. The development of novel plant derived natural products and their analogs for anticancer activity details efforts to synthesize new derivatives based on bioactivity- and mechanism of action-directed isolation and characterization coupled with rational drug design – based modification(11).

II. METHODOLOGY

The study contains review of existing information on medicinal plants of Kashmir published in various journals, books, theses and reports. Frequent field trips have been made during last few decades in order to collect information about the traditional knowledge used by the local people to cure their various diseases. During field trips various methods used to document the traditional knowledge include interviews questionnaires and discussions with local knowledgeable persons, herbal healers called bhoris and tribes (gijjares and bakerwals). The data were recorded on the plant part used, local name and their use. The collected specimens have been identified and accessed from the KASH herbarium of Kashmir University Srinagar (J&K).

III. RESULTS/FINDINGS

1. Achillea Wihelmsii

Achillea Wihelmsii belonging to family Asteraceae is commonly known as Yarrow and locally known as Pahalgaeses. The Methanol extract of this plant have cytotoxic effects on colon cancer cells (HT-29)(12). It has also been found that methanol extracts of plant’s leaves effects cell lineage of colon cancer, stomach cancer and breast cancer(13). Plant extract also contains phenol compounds, especially flavonoids, which suppress reproduction of cancer cells through inducing apoptosis(14, 15). 1,8-cineole is one of the most important monoterpene compounds of this plant that causes apoptosis in human melanoma cells(16).

2. Allium Sativum

Allium sativum belonging to family Amaryllidaceae and subfamily Allianceae is commonly known as Garlic and locally known as Rhoahun and Lahsun. Garlic has been used as a food having a unique taste and odor. It has been revealed by the scientific research that the wide variety of dietary and medicinal functions of garlic can be attributed to the sulfur compounds present in or generated from garlic. Although garlic produces more than 20 kinds of sulfide compounds from a fewsulfur-containing amino acids, their functions are different from one another; e.g., allicin, methyl allylthiosulfide and diallyl trisulfide have antibacterial, antithrombotic, and anticancer activities, respectively(17). Research has been done to show that Allium sativum and organosulfuric compounds reduce the risk of cancer in breast, larynx, colon, skin, womb, gullet, bladder, and lung(18, 19). In other research, Allium sativum compound, Allicin has the antitumor effects on breast and prostate cancer by inducing planned death of cells(20, 21). It has been found When Allium sativum is crushed and cracked up, Allicin 1, under the effect of an enzyme, changes to Allicin 2. Allicin is a proliferation inhibitor of malignant human cells. Ajoene , another compound of Allium Sativum suppresses proliferation of leukemia and causes planned death of cell(22, 23).

3. Artemisia Absinthium

Artemisia absinthium belonging to Asteraceae family is commonly known as wormwood and sagebrush and in Kashmir it is known as ‘Tethwen’. In Kashmir it is traditionally used as a vermifuge, an insecticide, an antispasmodic, an antiseptic as well as in the treatment of chronic fevers and inflammation of the liver(24). The essential oil obtained from it has antimicrobial(25) and antifungal activity(26). Chemical analysis of Artemisia absinthium extracts has shown that its volatile oil is rich in thujone , which has been reported as an anthelmintic (27). The main compounds of Artemisia absinthiumare

| Cancer Type                          | Genetic Alterations                      |
|--------------------------------------|------------------------------------------|
| Follicular lymphoma                  | Bcl-2 amplification, myc mutation        |
| Sporadic thyroid cancer              | Ret mutation                             |
| Familial melanoma                    | P16NKKmutation                           |
| Familial breast and ovarian cancer   | BRCA1, BRCA2 mutation                    |
| Colorectal and gastric cancer        | APC gene mutation                        |
| Invasive ductal breast cancer        | HER-2 amplification                      |
Cannabis sativa is a dioicous plant of the Cannabaceae family and is commonly known as hemp and locally known as bhang. It has been used as a psychoactive drug, as a traditional medicine to treat ear-ache, scabies and piles(32), and as a source of textile fibre since ancient times(33). Equally highly interested in this plant are the pharmaceutical, since its metabolites show potent bioactivities on human health. The active components of Cannabis sativa are cannabinoids. Cannabinoids and their derivatives exert palliative effects in cancer patients by preventing nausea, vomiting and pain and also stimulate the appetite. These compounds have also been shown anti-tumor activity in cell culture and animal models by modulating key cell signaling pathways(34). Cannabinoid treatment promotes cancer cell death, impair tumor angiogenesis and block invasion and metastasis(35). It has been studied that cannabinoids inhibit the stimulation of the vascular endothelial growth factor (VEGF) pathway. Thus, various components of the VEGF-activated pathway, such as the active forms of its best-established receptors (VEGFR1 and VEGFR2), have been shown to be down-regulated in response to treatment with cannabinoids in different cancer types(36). Cannabinoid receptor activation inhibits migration and proliferation, and induces apoptosis in vascular endothelial cells which might also contribute to the antiangiogenic effect of cannabinoids(37).

5. Crocus Sativus

Crocus sativa, a perennial plant belonging to family Iridaceae is commonly known as saffron and locally known as Kung. Traditionally it is used to treat Asthma, arthritis, digestive disorders, diuretic, leukorrhoea etc. The part of the plant used is stigma, known as saffron. Various studies have been carried out on saffron extract showing anticancer effects in vitro; for example, materials separated from saffron such as crocin, crocetin, picrocrocin, and safranal were studied to effect on human cancer cells by inducing apoptosis in cancer cells(38, 39). In another study, the quercetin, plant substance of saffron showed cytotoxic effects on colorectal cancer cells(40). Studies has also revealed that crocus sativus has an antiangiogenic effects on breast cancer cells (MCF-7), and extract of this plant inhibits angiogenesis in these cells(41). Another research has been done to study effect of cellular toxicity and apoptotic properties of saffron extract on the cancer cells and thus showing that saffron can play an important role in cell death of HeLa and HepG2 cells and apoptosis. Saffron can be used as a chemotherapeutic agent to treat cancer in the human in future(41, 42).

6. Datura Stramonium

Datura stramonium is a wild weed belonging to family Solanaceae, its name derived from Sanskrit word “Dhutra”. It is commonly known as daturas, Jimson weed or devil’s snare and locally known as datur. Traditionally datura plant parts are used to treat various disorders including asthma, skin disorders, jaundice, piles, diabetes, Rheumatism, Frost bite, and toothache(32, 43). It has been found bychemical investigation of a methanol extract of the flowers of Datura that the isolated with anoliodes exhibit cytotoxic activities against various cancer cell lines including A549 (lung), BGC-823 (gastric) and K562 (leukemia)(44). In another study it was found that Datura stramonium agglutinin (DSA (lectin)) induced irreversible differentiation in C6 glioma cells. The differentiated cells had long processes, a low rate of proliferation and a high content of glial fibrillar acidic protein. Experiments were carried out with several other lectins which indicated that both recognition of linear Nacetyllactosamine repeats and recognition of multiantennary units of cell-surface glycans were required for the inhibition of C6 proliferation. Proliferation of four human glial tumor cells was also inhibited by DSA, which suggests its usefulness as a new therapy for treating glioma without side effects(45).

When isolated endophytic fungi from Datura stramonium was tested for the antitumor activities by MTT assay on human gastric tumor cell line BGC-823, it showed 100% growth inhibition rate(46). Further studies were carried out on human cancer cells lines in vitro on MDA-MB231 (breast), and FaDu (neck) which were treated with Datura stramonium aqueous leaf extract for 24 and 48 h and showed increase in GSSG in FaDu cells indicating oxidative stress in treated cells(47).

7. Lavatera Cashmeriana

Lavatera cashmeriana belonging to family Malvaceae is commonly known as Kashmiri Mallow and locally known as pash kul. Traditionally it is used to treat throat problems and is used as mild laxative. Four protease inhibitors viz LC-pi I, II, III and IV which are purified from seeds of Lavatera cashmeriana inhibits...
trypsin, chymotrypsin and elastase in vitro(48) and have antibacterial activity against Klebsiella pneumoniae and Pseudomonasaeruginosa(49). In a study, LC-pi I and II were found to significantly inhibit the in vitro growth of Human acute monocytic leukemia cell line (THP-1), Human lung carcinoma cell line (NCIH322), human colon cancer cell lines CoLO205, whereas only LC-pi I inhibited growth of human colon cancer cell lines (HCT-116) cells but not LC-pi II in a dose dependent manner. Further LC-pi III and IV could not inhibit the growth of these cells. Their pharmacological effects may be mediated through inhibition of the protease activity and the subsequent modulation of the protease pro-survival signaling as LC-pi I and II strongly inhibited the in vitro activity of trypsin, elastase and chymotrypsin(49).

8. Papaver Somniferum

Papaver somniferum belonging to the family Papaveraceae is commonly known as Opium Poppy and locally known as Khashkhash. Traditionally it is used for the treatment of Diarrhea, Dry Cough. It is widely used for medicinal purposes because it contains various alkaloids such as morphine, noscapine, narcotine, codeine, papaverine, and others(50, 51). Alkaloid, Noscapine obtained from Papaver somniferum is used in cancer treatment, which interacts with a-tubulin and has anticancer and antiangiogenetic properties(52). Another alkaloid, codeineone, obtained from Papaver somniferum which is an oxidative product of codeine has apoptotic effects through fragmentation of DNA(53). Morphine is other alkaloid obtained from Papaver somniferum shows anticancer activities by inhibiting NF-kB(54).

9. Rosa Damascenas

Rosa damascenas belonging to family Rosaceae is commonly known as Rose and locally known as Gulab or poosh in Kashmir. Traditionally it is used for coughts and colds. The flowers and leaves of the plant are its active ingredient is tannin. The ethanol extract of the plant cell has killing effect on cervical cancer cells (HeLa). It has also been reported that the essential oil obtained from it has toxic effects on lung cancer cell lines (A549) and breast (MCF7) cell lines(55). It’s essential oil affects gastric cancer cells in 2 specific phases, soluble phase and the vapor phase: the soluble phase increases cell viability, while the vapor phase decreases cell survival. Also by cytometry it has been showed that apoptosis is the important mechanism accompanied with cell death(56).

10. Saussureacostus

Saussureacostus belonging to family Asteraceae is commonly known as Costus and locally known as Kuth. Traditionally it is used to treat Joint pain, back pain, sole ulcers, dysentery, fever, urinary problems.C-17 polyene alcohol isolated from Saussureacostus exhibited moderate cytotoxicities against the human tumor cell linesA549, SK-OV3, SK-MEL-2, XF 498 and HCT 15(57). Costunolide, an active compound isolated from the root of Saussureacostus, has been investigated for its effect on the induction of apoptosis in HL-60 human leukemia cells and its putative pathways of action. It has studied that costunolide is a potent inducer of apoptosis, and facilitates its activity via ROS generation, thereby inducing mitochondrial permeability transition(MPT) and cytochrome C release to the cytosol(58). Costunolide also shows an anti-angiogenetic effect. This compound selectively inhibited the endothelial cell proliferation induced by vascular endothelial growth factor (VEGF). It has also found that it inhibits the VEGF-induced chemotaxis of human umbilical vein endothelial cells (HUVECs) in a dose-dependent manner. The results thus obtained show that costunolide might inhibit angiogenesis by blocking the angiogenic factor signaling pathway. VEGF interacts with its cognate receptors, KDR/Flk-1 and Flt-1, and exerts its angiogenic effect. Costunolide inhibited the auto phosphorylation of KDR/Flk-1 without affecting that of Flt-1. These results suggest that costunolide may prove useful for the development of a novel angiogenesis inhibitor(59). Studies have been carried out to understand the molecular basis of antitumor effects of Saussureacostus to analyze the effects of this medicinal herb on proliferation and on expression of cell growth/apoptosis related molecules, using an AGS gastric cancer cell line. When treated with Saussureacostus dramatically reduced cell viabilities in a dose andtime-dependent manner. Studies demonstrated that Saussureacostus induced growth inhibition and apoptosis of human gastric cancer cells, and these effects were correlated with down- and up-regulation of growth regulating apoptotic and tumor suppressor genes, respectively(60). The cytostatic effects of Saussureacostus root were attributed to the regulation of cyclins and pro-apoptotic molecules and suppression of anti-apoptotic molecules. The extracts of Saussureacostus root may thus be used for the treatment of gastric cancers either by traditional herbal therapy or by combinational therapy with conventional chemotheray(61). Lappadilactone and seven sesquiterpene lactones of Saussureacostus were examined against selected human cancer cell lines for cytotoxicity. Lappadilactone, dehydrocostus lactone and costunolide exhibited the most potent cytotoxicity withCD50 values in the range 1.6–3.5 micrograms/ml in dose- and time dependent manners. The cytotoxicities were not specific and showed similar activities against HepG2, OVCAR-3 and HeLacell lines. The structure–activity relationship showed that the alpha-methylene-gamma-lactone moiety is necessary for cytotoxicity, and activity is reduced with the presence of a hydroxyl group(62). Dehydrocostus lactone (DL) is the major sesquiterpene lactone and is isolated from the roots of Saussureacostus, inhibited NF-kappa B activation by preventing TNF-alpha induced degradation and phosphorylation of its inhibitory protein I-kappa Balpha in human leukemia HL-60 cells and that DL renders HL-60 cells susceptible to TNF-alpha induced apoptosis by enhancingcaspase-8 and caspase-3 activities(63). Cynaropicrin is the another active compound that is isolated from Saussurealappa, which exhibits
immunomodulatory effects on cytokine release, nitric oxide production and immunosuppressive effects. Cynaropicrin potently inhibited the proliferation of leukocyte cancer cell lines, such as U937, EoL-1 and Jurkat T cells. The combination treatment with cysteine and N-acetylcysteine, reactive oxygen species scavengers, or rottlerin, a specific protein kinase (PK) C-delta-inhibitor, abolished cynaropicin-mediated cytotoxicity and morphological change, and that cynaropicin-induced proteolytic cleavage of PKC-delta suggests that reactive oxygen species and PKC-delta may play an important role in mediating pro-apoptotic activity by cynaropicrin. Thus it can be concluded that cynaropicrin is a potential anticancer agent against some leukocyte cancer cells such as lymphoma or leukemia, through pro-apoptotic activity(64).

11. Trigonellafoenum-graecum

Trigonellafoenum graecum belonging to family fabaceae is commonly known as Fenugreek and locally known as Meth. Traditionally it is used treat back pain. It has been studied that the crude extract of fenugreek shows the selective cytotoxicity against some cell lines such as MCF7, TCP (T-cell lymphoma), FRO (thyroid papillary carcinoma), and brain tumors(65). It also shows protective effect against breast cancer induced by DMBA (7,12-dimethylbenz(a) anthracene) in mice(66). In another study, the extract of this plant shows inhibitory effects on the growth of cancer cell. The main mechanism of anticancer activity is apoptosis induction(65, 66).

12. Urticadioica

Urticadioica belonging to family urticaceae is commonly known as stinging nettle and locally known as soi or sadder. Traditionally it is used to excitity in paralyzed limbs and is also used as vegetable. Studies have been carried out that aqueous and ethanol extracts of the plant show cell proliferation inhibitory effect on prostate cancer cells (LNCaP and as hPCEs) (67). It has also referred that extract of this plant has anticancer effects against esophageal cancer(68). Phenol compounds of this plant are having antioxidant activity and may have an important role to prevent cancer. It has been studied that the root extract of this plant has the antiproliferative effect on human prostate cancer cells(69).

13. Viola Odorata

Viola odorata belonging to family violaceae is commonly known as garden violet and locally known as Bunufsha. Traditionally it is used to treat respiratory problems. The whole aerial part including stem, flowers and leaves are used in cancer. Viola has been reported as pharmacological tool and antitumor agents(70). CycloviolacinO2 (CYO2), a cyclotide from Viola odorata (Violaceae) has antitumor effects and causes cell death by membrane permeabilization. This study documents several cyclotides with robust cytotoxicity that may be promising chemo sensitizing agents against drug resistant breast cancer(71).

CycloviolacinO2 (CYO2). Cyclotide obtained from Viola odorata shows selective toxicity against cancer cell lines relative to normal cells, which indicates the possibility of its use as an anticancer agent(71). Analysis of the proposed mechanism of action shows that the disruption of cell membranes plays a crucial role in the cytotoxicity of cycloviolacinO2 (CYO2) because the damage to cancer cells (human lymphoma) can be morphologically distinguished within a few minutes, indicating necrosis(72).

IV. DISCUSSION

Life and diseases go together, where there is life, disease are bound to exist. Traditional use of plant remedies provides potential indicators of biological activities. The WHO has estimated that 8 %of population of developing countries rely on traditional medicines mostly plant drugs for their primary health care needs. Also modern pharmacopoeia still containsat least 25 % drugs derived from plants and many other synthetic analogies built on prototype compounds isolated from plants. Demand for medicinal plants is increasing in both developed and developing countries due to growing recognition of natural products being non-narcotic having no side effects, easily available at affordable prices and sometimes the only source of health care available to the poor. Medicinal plant sector has traditionally occupied an important position in the socio-cultural, spiritual and medical arena of rural and tribal lives of India. Medicinal plants as group comprise approximately 50% of all the higher flowering plants of India.

V. CONCLUSION

Keeping in view the high cost and side effects of allopathic medicine, the use of medicinal plants against different ailments play a significant role in meeting the primary health care needs of the rural communities of the Kashmir valley. An immensely valuable database could be the outcome of this knowledge which in turn could provide baseline information for the commercial exploitation of the bioresources. Besides, the information could prove a fruitful source the pharmacologists, phytochemists, botanists and to those interested in the development of the alternative therapies. Utilization of indigenous drug resources will increase the local industry on one hand and minimize the expenditure incurred on the purchase of foreign drugs on the other.

It is also suggested to document such vital and valuable knowledge for the future generations as this knowledge is found to be declining day to day.

DISCLOSURE/CONFLICT OF INTEREST

The author(s) declare no conflict of interest.
AUTHORS' CONTRIBUTIONS

SSH initiated the study, and designed the plan and edited the manuscript. SSH and BAB wrote the manuscript and designed the tables. All the authors read and approved the final manuscript.

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