Medicinal Plants of the Himalayas

Subjects: Medicine, General & Internal

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WHO recommends cancer is the leading cause of death worldwide, with nearly 10 million deaths predicted in 2020(1). The bioactivities of phytocompounds for various health benefits have been studied for decades. Synthetic drugs are being replaced by phytocompounds which have great advantages due to their effects on a wide range of target cells with lower cell cytotoxicity effects or side effects compared to synthetic anticancer compounds, which are a single-target effect for prevention and treatment of carcinoma. Various medicinal plants and their nanoparticles have anticancer activity, namely *Murraya koenigii* leaf extract ZnO nanoparticlets. Most modern drugs used to treat cancer originate from various medicinal plants; 50% of the anticancer drugs originate from medicinal plants. In developing countries, more than 80% of people use medicinal plants as traditional medicinal therapy and 60% of cancer patients use herbal treatment as an option to cure cancer. Currently, for high-risk breast cancer patients, tamoxifen and related compounds such as raloxifene are prescribed. The phytocompounds most studied in different research papers for the treatment of cancer (anti-proliferative activity) are curcumin, polyphenols, Withaferin A (WFA), a triterpenoid, celastrol, and berry bioactives. Vinca alkaloids, podophyllotoxin, taxanes, campothecin, homoharringtonine, saponin, isoquinoline, shatavarine IV, stigamsterola, calotropin, and shikonin phytocompounds are discussed as follows. Cancer as well as boosting the immune system.

Keywords: cancer medicinal plants ; Himalayas ; phytocompounds ; cytotoxicity ; immunotherapies

1. Vinca Alkaloids

According to the declaration of WHO Model List of Essential Medicines on 8 December 2016, from the plant kingdom the first antimitotic agent used in the pharmaceuticals and drugs market and known to be highly effective in the treatment and utilized medicines was Vinca alkaloids. Vinblastine, vinca alkaloids, and leurocristine extracted from *Catharanthus roseus* were the first drugs utilized for cancer treatment purposes. These drugs were extracted from the Catharanthus roseus plant species during an investigation for the development of oral hypoglycemic agents, even though the extracts reduced white blood cell count and caused bone marrow depression in rats instead of the oral hypoglycemic treatment effect. The extracts obtained from this plant increase the life expectancy of mice treated with transplantable lymphocytic leukemia. Vindesine (VDS) and vinorelbine (VRLB) are the semi-synthetic analogs of vinca alkaloids, useful to treat various cancers by mixing with other chemotherapeutic drugs. Vinblastine is used to treat Kaposi's sarcoma, breast cancer, leukemia cancer, testicular cancer, lung cancers, and lymphomas [1]. Vincristine is used to treat leukemia, and childhood acute lymphocytic leukemia [2].

2. Podophyllotoxin Derivatives

The derivatives of podophyllotoxin (PTOX) etoposide [3], teniposide [4], and etoposide phosphate [5], are used for anticancer chemotherapy that is extracted from *Podophyllum peltatum* L. (Berberidaceae) and *Podophyllum emodi* Wall. (syn. *P. hexandrum*). PTOX is an aryltetralin-lignan with strong cytotoxic activity [6]. The podophyllotoxin derivatives have antiproliferative activity against germ cell tumors and small cell and non-small cell lung cancers. 4β-aminoalkyl-4′-*O*-demethyl-4-desoxypodophyllotoxin, TOP-53, is a podophyllotoxin derivative with antitumor activity and anticancer activity against lung cancer and lung metastatic cancer. The cytotoxicity activity of TOP-53 was determined using IC_{50} and showed 0.016–0.37 µg/mL against murine tumors and 0.26–8.9 µg/mL against human non-small cell lung cancer (NSCLC) cell lines. TOP-53 podophyllotoxin derivative is also potent in antitumor activity for lung localized tumors and metastatic tumors in the lungs [7].

These derivatives prevent the polymerization of tubulin and thereby could induce cell cycle arrest at mitosis and inhibit the formation of the mitotic-spindles microtubules. The therapeutic use of a plant species of the *Podophyllum peltatum* Linn., *P. emodii* Wallich family Podophyllaceae, has been used for the treatment of warts and skin cancer. Native Americans used topical administration of alcoholic extract of dried roots of *Podophyllum peltatum* for the treatment of warts by its topical administration in the 1940s. The first isolated major cytotoxic therapeutic component was

podophyllotoxins in the 1880s. During the development of spectroscopic techniques, the exact structure of podophyllotoxins was determined in the 1950s. Lignans, which are almost like podophyllotoxins, were also applied during clinical trials, but the effect was unsatisfactory concerning high cytotoxicity and absence of effectiveness. Later on between the 1960s and 1970s, Teniposide ($C_{32}H_{32}O_{13}S$) and Etoposide ($C_{29}H_{32}O_{13}$) were discovered and used as clinical agents to treat testicular, bronchial, and lymphomas cancer, as reported by Sandoz Laboratories in Switzerland [8].

3. Taxanes

The first isolated compound from *Taxus brevifolia* Nutt. (Taxaceae) bark was taxol or Paclitaxel. Various parts of *Taxus* species, such as *T. canadensis* Marshall, *T. baccata* L., and *T. brevifolia*, have been used for anticancer activity, for instance for the treatment of ovarian and breast cancers [9]. This has led to substantial demand for it. In the ancient Indian holistic and natural medicine called Ayurveda, the leaves of *T. baccata* were used in the treatment of cancer. Taxanes from *T. wallichiana* plant species have anti-inflammatory, analgesic, antipyretic, antiallergic, immunomodulatory, anticonvulsant, anti-conceptive, anti-osteoporotic, antiplatelet, antifungal, and antibacterial activities, as well as antispasmodic effects [10][11][12]. A *Taxus* species constituent, paclitaxel, is found in the leaves. Baccatins exist in high amounts and are converted to paclitaxel and active paclitaxel analogs such as docetaxel or Taxotere, which are a significant source and major category of the drugs, and are utilized to treat Kaposi sarcoma, lung cancer, ovarian and breast cancer. Paclitaxel also has the potential to treat non-cancerous diseases, such as rheumatoid arthritis, psoriasis, and multiple sclerosis. Breast cancer is mainly treated using a semisynthetic derivative of docetaxel. The effectiveness of the docetaxel anticancer agent was analyzed statistically by developing a clinical trial of more than one dozen taxanes analogues. The National Cancer Institute (NCI) recorded 2069 cancer clinical trials in July 2004 and stated that 105 with docetaxel (Taxotere), 10 with miscellaneous taxanes, 134 with Taxol (paclitaxel), and 23 taxanes, and in total around 248 listed as taxanes-derived drugs, are in preclinical development in single or combined with other anticancer agents [13]. The cytotoxicity effects of paclitataxel and docetaxel on a lymphoblastoid cell line were assessed in half maximal cell growth (IC_{50}) to indicate the drug sensitivity as a phenotype and shown to be 3.98–21.36 nmol/L for paclitaxel and 1.54–13.32 nmol/L for docetaxel in the IC_{50} range [14].

4. Camptothecin Derivatives

For the first time, In the early 1960's a phytochemical called camptothecin was extracted from a Chinese ornamental tree called *Camptotheca acuminata Decne (Nyssaceae)* species and used as an anticancer agent. This shows the advancements in anticancer drug development. An extract camptothecin from *Camptotheca acuminata species* showed high anti-tumor and anticancer activity out of 1000 different plant extracts tested for the same activities. This is considered the unique character of the *Camptotheca acuminata plant* species. The active chemicals isolated from it were identified as camptothecin, declared in the 1970s by the NCI (National Cancer Institute) as a candidate for clinical trials However, it displayed a flaw in bladder toxicity and was no longer in use. SmithKline Beecham (now Glaxo SmithKline) develops Topotecan (Hycamtin) and effective camptothecin derivatives, and Japanese company developed Irinotecan, Yakult Honsha, which are more effective than camptothecin. Irinotecan is utilized to treat colorectal cancers, whereas whereas lung and ovarian cancer are treated by topotecan [15]. TDP1 (Tyrosyl-DNA phosphodiesterase 1) inhibitors have a moderate inhibitory effect with IC_{50} which is the concentration of a compound required to reduce the enzyme activity by 50% in the concentration range of 0.4–100 µm [16][17][18]. A natural quinoline, camptothecin (CPT) has anticancer activity and inhibits Topoisomerases 1 [19]; it is also used as a chemotherapeutic drug to treat tumors and metastatic colorectal cancer and is known as a bioavailable derivative of irinotecan [20]. Topotecan is also a CPT derivative that treats ovarian cancer and small cell lung cancer [21]. TDP1 helps to prevent the DNA damage caused by Top1 inhibitors, hence TDP1 is responsible for drug resistance of some cancers. TDP1 activity and the percentage of non-small-cell lung cancer tumor cells in human tissue have a positive correlation [22]. The synergistic effect of TDP1 and TOP1 inhibitors is expected to increase treatment or decrease the traditional drug dose [23].

5. Homoharringtonine

Cephalo taxus harringtonia var *drupacea* (Cephalotaxaceae) is a Chinese tree by which semisynthetic cephataxine homoharringtonine was originally obtained and clinically used. Elliptinium is extracted from the Apocynaceae, a family containing *Bleekeri avitensis*, a medicinal plant from Fiji having anticancer activity. Chronic myelogenous leukemia treatment and myelogenous leukemia in China are achieved through the mixture of homoharringtonine (HHT) and harringtonine. For effective treatment of leukemias, purified homoharringtonine has been used because some cancers are drug-resistant. Breast cancer has been treated using Elliptinium in France [24]. HHT possesses antitumor activity. For instance, the administration of HHT 25 mg/kg inhibits the growth of tumor volume in the same way as in concentration of

cisplatin [25]. In addition, cisplatin also possesses body weight reduction ability whereas HHT lacks this effect. From the experiment of a lung cancer xenograft mouse model, the effects of 10 mg/kg cisplatin administration and 15 mg/kg and 25 mg/kg HHT on tumors were 69.6%, 40.5%, and 74.6% respectively. From this, HHT is an effective drug to treat lung cancer [26]. Omacetaxine mepesuccinate is a drug mainly used to treat breast cancer and leukemia. This drug works by blocking the synthesis in the peptidyl transferase center and leads to cell apoptosis [27].

6. Saponin Extract from Albizia Lebbeck Plant

Albizia lebbeck is a fast-growing deciduous and dispersed umbrella-shaped plant with a thin foliage crown with smooth, grayish-brown and fissured bark, found in Bangladesh, Africa, India, Australia, and subtropical and tropical Asia [28]. In traditional medicine, the *Albizia lebbeck* plant parts such as the leaves and pods part were utilized in cancer prevention. In addition, seeds, bark, pods, and leaves were applied for cytotoxic activity in colon, cervical, hepatic, breast, and larynx cancer [29]. Parts of *Albizia lebbeck* such as flowers, roots, bark, and seeds are utilized for the treatment of edema, poisoning, bone fracture [30][31], arthritis [32], skin disease, cough, and cold, wound healing, pruritis [33], malaria [31], abscess, abdominal tumors, leprosy, boils, and gonorrhea [34] in traditional medicine. Traditionally, the leaves of *A. lebbeck* were used for cancer treatment [35], and the pods also showed anticancer activity [36]. The poisonous and medicinal plants of east and South Africa declared *A. lebbeck* uses for its anticancer activity [37]. Stem bark methanolic extract of *A. lebbeck* has a cytotoxic effect against cervical carcinoma, larynx carcinoma, hepatocarcinoma, breast carcinoma cell lines, and colon carcinoma [38]. A saponins area secondary metabolite of glycosidic nature shows an anticancer effect [39]. Programmed cell death is caused by an enzyme called caspases which is from a family of proteases that activate and influence the executioner mode of apoptosis [29][40].

7. Isoquinoline Alkaloid Extract from Annona squamosa

Annona squamosa or custard apple, a small green tree, 6–8 m tall, is found specifically in deciduous forests. The medical applications are constipation, dysentery, antibacterial infection, epilepsy, dysuria, cardiac problems, hemorrhage, abortifacient properties, ulcers, fever, antifertility, antitumor, and worm infection treatments [41][42][43]. Constitutes a compound of acetogenins having anti-microbial, anti-neoplastic, pesticidal, parasiticidal, and parasiticidal effects [44][45]. Squamostatin and squamocin extracted from *A. squamosa* seeds compounds of acetogenins show a cytotoxic effect [46] [47]. By the activation of caspase 3, squamocin prevents human leukemia cell line proliferation and leads to apoptosis. Another part of acetogenin called ascimicin can inhibit and is cytotoxic to 9KB, A549, HT-29, and 9ASK tumor cells [48]. To treat chronic diseases like such as skin complaints, insect bites, and cancerous tumors, all parts of *A. squamosal* were used in traditional medicine [49][50][51][52]. The phytochemicals existing in the leaves are anti-ulcer, anti-diabetic, anti-fungal, anti-inflammatory, anti-depressant, and antimicrobial [53][54][55][56][57][58]. The chemical compounds constituted in *Annona squamosa* are phenolic compounds, terpenoids, alkaloids, flavonoids, glycoside, saponin, and steroids which are all-natural products [59][60][61]. The alkaloids obtained from the aerial part showed anticancer activity in 0.01 to 100 µg/mL concentration ranges on liver, breast, and colon cancer cell lines. Isoquinoline alkaloid extract possesses a high anticancer activity against colon cancer cells (HCT116) and human breast cancer cells (MCF-7) [62].

8. Shikonin and its Derivatives

Traditionally, for anti-inflammatory and antimicrobial effects, and as a tonic for chronic diseases, remitting cough and cold purposes, *Arnebia euchroma* liquid extract is mixed with bees' wax [63][64]. Phytochemicals constituted in the *Arnebia euchroma* which have great importance in anti-immune deficiency, anti-microbial and anticancer activity are arnebin-7, acetyl-shikonin, isovaleryl-shikonin, shikonincoumarins, B-hydroxy-isovaleryl-shikonin, deoxy-shikonin, β,β-di-methylacryl-shikonin, iso-butyryi-shikonin, stigma sterol, arnebinone, and isobutyl-shikonin [65][66][67][68][69]. A secondary metabolite of *Arnebia euchroma* called shikonin, found mainly in the root, prevents a compound that malfunctions and deletes the process of action in the cell, rapidly causing carcinomas [70]. Researchers also investigated some derivatives of the Sh+ikonin component and their cytotoxic effect and antioxidant activity [71][72]. From the plant species the methanol extracted has antioxidant and antimicrobial effects, and hydroxyl radicals for DNA damage protection [73]. The phytochemicals existing in the *Arnebiaeu chroma* plant are utilized for treating carcinogenic diseases. The phytochemicals utilized for treatment are acetyl-shikonin, teracryl-shikonin, and β,β-dimethylacryl-shikonin [74][75][76][77]. A phytochemical compound shikonin is utilized for various activities such as analgesic, anti-tumor, anti-fungal, anti-bacterial, wound healing, anti-inflammatory, anti-diabetic, anti-pyretic, and chemo-preventive [23][78][79][80][81]. For the preparation of various drugs effective inwith anti-inflammatory, anti–HIV, anti-microbial and anticancer effects, isovaleryl-alkannin, acetyl-shikonin, benzoquinone, shikonin-angelate, naphthoquinone, deoxy-shikonin, arnebin-5, arnebin-6, and alkannin are utilized from the phytochemical shikonin. The roots of *Arnebia euchroma* also constitute a dimeric naphthoquinone

compound called Shikometabolin H, epoxyarnebinol, and 2,3-secodiplopterol dioic acid helps to reduce the STAT3 transcriptions, the activators of human carcinogenic cells, and increase the antitumor immunity [82][83].

9. Calotropin in Asclepias curassavica

A plant species *Asclepias curassavica* constitutes a wide variety of biologically active compounds such as flavonol glycosides, carbohydrates, triterpenes flavonols, cardenolides, amino acids, etc. The chemical called cardenolides has the constitutents calotropin, coroglaucigenin, calactinasclepin, asclepain CI, asclepiadin CII, curassavogenin, asclepogenin, calotropagenin, uzarin, uzarigenin, uscharidin, corotoxigenin, uscharidin, calotroposide, kidjolanin, clepogenin, and desglucouzarin, which are applicable for pharmacological purposes such as anticancer, antipyretic, analgesic, antimicrobial, cardiovascular, and many other pharmacological activities [84]. Calotropin (a cardiac glycoside), an alcoholic extract of *Asclepias curassavica* species, has a cytotoxic effect against nasopharynx carcinoma cells. A pronounced cytotoxicity activity against four different types of cancer cells was shown by cardenoliedes phytocompounds extracted from the aerial and root part of *Asclepias curassavica.* Significant cytotoxic activity was shown by asclepin and 12 beta-hydroxycalotropin (a cardenolide) had a strong cytotoxic effect against HepG2 and Raji cell lines [83][85][86].

10. Shatavarin IV in Asparagus racemosus

Compounds having anticancer activity include terpenoids, lignans, alkaloids, and flavonoids. Terpenoids (steroids) are the major group and widely applicable in chemotherapy cancer treatment, e.g., Taxol can be mentioned [87]. Steroidal saponin with few steroids and their glucosides, triterpenoids, alkaloids, and flavonoids exist in *Asaparagus racemosus* species [88]. Shatavarin I to X (shatavarins) are the major steroidal glucosides or saponins extracted from the root [89][90]. The non-polar and polar extracts from the total extracts and their formulation are capable of immune–pharmacological activity in cancer chemotherapy [91]. 7,12-dimethylbenzanthracene (DMBA)-induced mammary carcinogenesis can be inhibited by the *Asparagus racemosus* plant species extract, as investigated in rats. The compound shatavarin IV (84.69 %) with its fraction, codedAR-2B containing 5.05% shatavarin IV, is capable of cytotoxicity. Shatavarin IV from shatavarin's rich fraction has a tremendous anticancer effect in vivo and in vitro [92].

11. Stigmasterol in Bacopa monnieri Linn

The plant *Bacopa monnieri* constitutes bacosides A and B, alkaloids, namely herpestine and brahmana, tetracyclic triterpenoid saponins, flavonoids, hersaponin, [93], triterpenes such as bacosine [94], and sterols like bacosterol [95]. A natural product, phytoserols extracted from the aerial part of the plant species *Bacopa monnieri* have anticancer activity [96]. The activity of stigmasterol tested on the growth of murine models of cancer, which becomes transplantable by decreasing the viable cell count, a packed cell volume, tumor volume, inhibiting EAC (Ehrlich ascites carcinoma), was investigated in vivo and increases the life expectancy of the victim, protecting the liver of the EAC tumor-bearing mice. The antitumor mechanism functioned by the initiation of PP2A by ceramide causing apoptosis, as is indicated by a structure analogous to phytosteroids [97]. The main criteria to prove the value of the anticancer agent is increasing the age of the animals [98].

12. Methanolic Extract of Bauhinia Racemose Plant

The methanolic extract of Bauhinia racemose plant (MEBR) from the family of Caesalpiniaceae shows a significant inhibiting activity on the HeLa cancer cell line by decreasing the cell viability $p < 0.001$, IC_{50} = 80 µg/mL in reference to tamoxifen, which accounts $p < 0.001$, IC_{50} = 48 µg/mL according to the concentration dependency. The methanolic extract of Bauhinia racemose plant (MEBR) shows cytotoxic activity against the HeLa cancer cell line and leads to apoptosis. The TPC, or total phenolic content, obtained from the dried extract of the Gallic acid calibration curve is high in value, 886.8252 mg GAE/g. When the concentration of extract becomes high, membrane permeability will decrease and with separation of cells from the well surface will become either necrotic or circular and have a condensed cytoplasm of the clumped cells, a significant characteristic of showing a concentration-dependent anti-HeLa cancer cell line cytotoxic effect of the extract. To determine the degree of comparative cytotoxic potential, the half maximum inhibitory concentration (IC_{50}) values of both tamoxifen and MEBR must be known. An image from an inverted fluorescent microscope shows cancer cells liable to MEBR and stained with Dichloro-dihydro-fluorescein diacetate in diacetate; it is unstructured morphology and releases bright fluorescence because of the reactive oxygen species production and intracellular mass formation [99].

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