Orchids as Potential Sources of Anticancer Agents: Our Experience

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ABSTRACT

Cancer is the second leading cause of death globally and the cancer burden continues to grow, exerting tremendous physical, emotional and financial strain on individuals, families, communities and health systems. Many health systems in low- and middle-income countries are ill-prepared to manage this burden, and around the world large numbers of cancer patients do not have access to timely quality diagnosis or treatment. Natural products, especially originated from plants, have been applied as remedies to treat various diseases, including cancer, for thousands of years. Several anticancer agents derived from plants, such as paclitaxel (taxol), vinblastine, vincristine, camptothecin derivatives, podophyllotoxins, are in clinical use and a number of other promising agents are in preclinical or clinical development. A growing number of bioactive compounds with cytostatic and cytotoxic activities to treat cancer have been isolated from several orchid species. The Annapurna Research Center in collaboration with other academic institutions is engaged in identifying and exploring anticancer compounds in orchids of Nepal. The center has identified ten different orchid species which contain high phenol and flavonoid contents evidently showing anticancer activities in our *in vitro* assays against different cancer cell lines viz cervical cancer, lung cancer and brain tumor cell lines. These findings demonstrate that orchids which have been used in in various formulations in traditional medicine since ancient times qualify as potential source for novel drug candidates or starting points for further lead optimization towards clinical candidates for the most urgently needed treatment of aggressive types of cancer. This review paper highlights that in all likelihood; our contributions in orchid research here in Nepal could bring great relief to patients with cancer globally.

Key words: Cancer; Orchids; Anticancer compounds; Natural products

INTRODUCTION

Cancer is a group of over 100 disease types leading to abnormal invading cell growth, which spreads to other parts in the body, referred to as metastasizing. Metastases are a major cause of death from cancer. Globally, cancer is one of the leading causes of death. Worldwide, one in five men and one in six women develop cancer during their lifetimes. The five-year-prevalence figure is estimated to be 43.8 million cases globally and is expected to rise by additional 22 million annually within the next two decades.[1] The International Agency for Research on Cancer (IARC) released on 14th December the updated Globocan 2020 with new estimates on the global cancer burden, indicating that it has risen to 19.3 million cases and 10 million cancer deaths in 2020.[2] Treatment of cancer currently includes the surgical removal of cancerous tissue, radiotherapy, chemotherapy and a combination of chemotherapy and targeted therapy. Many health systems in low- and middle-income countries are least prepared to manage this burden, and large numbers of cancer patients globally do not have access to timely quality diagnosis and treatment. The WHO reported that 30% of the deaths from cancer are preventable if people would not consume tobacco products and if they would eat a healthy diet, exercise regularly, limit the use of alcohol and protect themselves against cancer-causing infections.[1] The utilization of anti-cancer drugs in chemotherapy, while often more beneficial when used in conjugation with radiation therapy or surgery, is considered the first line of treatment. Because cytotoxic drugs are the mainstay of chemotherapy, it is important to discover novel cytotoxic or cytostatic agents with sufficient activity, novel mechanisms-of-action and minimal issues of toxicity and amenable to targeted therapies.[3,4,5]

Natural products, especially derived from plants, have been used to treat various diseases for thousands of years. The world market for medicinal plants and their products is increasing with rapidly escalating prices. The demand

for medicinal plants intended for use by traditional Ayurveda and modern pharmaceutical companies as source for novel drug candidates is on the rise. Therefore, the trade of medicinal plants becomes an important source of revenue to the Nepal government and supports substantially the livelihoods of communities, particular in rural settings. Medicinal plants have enormous therapeutic potential and may have few side effects.[6] The search for anticancer agents from plant sources started back in the 1950s, when cytotoxic vinca alkaloids (vinblastine and vincristine) and podophyllotoxins (etoposide and teniposide) were isolated.[7] Furthermore, several anticancer agents derived from plants, including taxol (*Taxus brevifolia*), vinblastine and vincristine *(Catharanthus roseus)*, camptothecin derivatives *(Camptotheca acuminata)*, podophyllotoxins *(Podophyllum peltatum)* are in clinical use, and followed by a number of promising agents in preclinical or clinical development. Examples are flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol. Since synthetic anticancer drugs are expensive and not easy to access for everybody in Nepal. There is a need to search for novel anticancer compounds in plants, particular herbs, which are rich in compounds with high polyphenol and flavonoid contents. Compounds rich in polyphenol and flavonoids exhibit high antioxidant activities, which property plays an important role for the treatment of cancers. [8]

Figure 1: Some orchid species of anticancer sources; *Dendrobium longicornu* (a), *D. transparens* (b), *Rhyncostylish retusa* (c) and *Vanda cristata* (d).

For this reason, Annapurna Research Center, in collaboration with various other academic institutions, is engaged in identifying and exploring anticancer compounds isolated from orchids, which are used in traditional medicine in various formulations. The center examines *in vitro* dose-dependent effects of orchid extracts with a high phenol and flavonoid content against cancer-cell lines, namely for glioblastoma, cervical and lung cancer. It is determined whether or not the compounds extracted arrests the proliferation of cancerous cells. In result ten different orchid species were identified where their extracts demonstrated strong antiproliferative activities in the assays. Some orchids of Nepal (Fig.1) have already been investigated for their anticancer activity in different cancer-cell lines.[8-11] Once there is a suggestion that antioxidants and anticarcinogens do indeed exist in a particular plant, it has been investigated further, using crude extracts from various plant parts as well as *in vitro* culture-raised tissue. Moreover, the center is conserving the germplasm of species with anticancer potential using *in vitro* culture technologies. Some of the species are amenable to mass propagation. Such highly interesting process of cultivation has been exercised in a partnering mode with different stakeholders of society.

Anticancer agents from orchids

A large number of bioactive compounds with anticancer and anti-tumorous activities have been isolated from several orchid species (Table 1). The methanolic extract obtained from *Anoectochilus formosanus* have shown to induce apoptosis of MCF-7 cells. Antitumor activity of *A. formosanus* may be associated with its potent immune stimulating effect.[12] A phenanthrene derivative 3,7-dihydroxy- 2,4,6trimethoxyphenanthrene was isolated from the all plant of *Bulbophyllum odoratissimum*. The compound displayed cytotoxicity against the growth of human leukemia cell lines K562 and HL-60, human lung adenocarcinoma A549, human hepatoma BEL-7402 and human stomach cancer cell lines SGC-7901 with IC50 values of 14.23, 10.02, 3.42, 15.36 and 1.13 mg/ml respectively.[13] A number of compounds such as 7,8-dihydro-4-hydroxy 12,13-methylenedioxy-11-methoxyldibenz[bf]oxepin, cumulating, densiflorol A and plicatol B isolated from *Bulbophyllum kwangtungense* have shown anti-tumor activities against Hela and K562 human tumor cell lines (Wang et al., 2006). Silbenoids,3,3'-dihydroxy-2',6'-bis(p-hydroxybenzyl)-5-methoxybibenzyl and 3',5-dihydroxy-2-(p-hydroxybenzyl)-3-methoxybibenzyl isolated from the tubers of methanol extract of *Bletilla striata* showed inhibitory effect of tubulin polymerization at IC50 10 µM. On the other hand, phenanthrene and dihydrophenanthrene with a benzyl moiety (1-(p-hydroxybenzyl)-4,8- imethoxyphenanthrene-2,7-diol and 2,7-dihydroxy-1,3-bis(phydr-oxybenzyl)-4-methoxy-9,10-dihydrophenanthrene), and dimeric

phenanthrenes blestriarenes B and C and blestrianol A were found to be three times less potent (IC50: 30 µM) than bisbenzyls indicating that the restricted diaryl ring system of phenanthrene is unfavorable for tubulin binding. Furthermore, bisbenzyl 3,3'-dihydroxy-2',6'-bis(p-hydroxybenzyl)-5-methoxybibenzyl potentiated the cytotoxicity of SN-38 in BCRP-transduced K562 (K562/BCRP) cells.[14] Studies were also carried out on microspheres of tubers of *B. striata* on angiogenesis. It produced a change of tumor microcirculation after trans-catheter arterial chemoembolization: first pass perfusion MR imaging and Chinese ink casting in a rabbit model. With Bletilla microspheres may enhance its anti-tumor effect by inhibiting the angiogenesis (Zhao et al., 2004). The same observations have been made in other experiment when tested *B. striata* colloid on angiogenesis. Inhibits angiogenesis, through binding inhibition of vascular endothelial growth factor to its receptor.[15]

The tuber of *Cremastra appendiculata* yield cirrohopetalanthrin and 2,7,2',7',2''-pentahydroxy-4,4'4''7''-tetramethoxy-1,8,1',1''-triphenanthrene which were found to have moderate cytotoxicity against human colon cancer, human stomach cancer, human hepatoma, human breast cancer, human lung adenocarcinoma and human ovarian cancer cell lines.[16] The homoisoflavanone 5,7-dihydroxy-3-(3-hydroxy-4methoxybenzyl)-6 methoxychroman isolated from *C. appendiculata* was found to be a potent inhibitor of angiogenesis.[17] Cephalinone F isolated from *Cephalanceropsis gracilis,* a native orchid of Taiwan, has significant cytotoxicity against human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines. Cirrhopetalanthrin isolated from tuber of *Cremastra appendiculata* showed non-selective moderate cytotoxicity with IC50 values of 8.4 -13.3 µM against human colon cancer (HCT-8), human hepatoma (Bel7402), human stomach cancer (BGC-823), human lung adenocarcinoma (A549), human breast cancer (MCF-7) and human ovarian cancer (A2780) cell lines.[17] A study to understand the molecular basis underlying the antitumor effects of C. appendiculata was performed by 5,7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-6-methoxychroman isolated from the bulb. Similar observations were obtained in a study with the ethanol extract of the tuber of C. appendiculata was subjected to column chromatography to yield 2,7,2',7',2'-pentahydroxy-4,4',4'',7''-tetramethoxy-1,8,1',1''- triphenanthrene and cirrhopetalanthin. Both compounds were evaluated against six human cancer cells; human lung adenocarcinoma (A549), human ovarian cancer (A2780), hepatoma (Bel7402), human stomach cancer (BGC-283), human colon cancer (HTC-8), and human breast cancer (MCF-7) cell lines. Both compounds were selectively active against the human cancer cell lines used.[16]

Denbinobin and 4,7-dihydroxy-2-methoxy-9,10-dihydrophenanthrene from *Dendrobium nobile* showed cytotoxicity against human lung carcinoma, human ovary adenocarcinoma and human promyelocytic leukemia cell lines.[17] Erianin obtained from the stem of *Dendrobium chrysanthum* was found to be a potent inhibitor of proliferation of HL-60 cells and the inhibition might be due to erianin-induced apoptosis and altered expression of bcl-2 and bax genes in HL-60 cells.[18] In another study, erianin leads to extensive tumor necrosis, growth delay and rapid vascular shutdown in hepatoma Bel7402 and melanoma A375.[19] Dendrochrysanene isolated from stems of *D. chrysanthum was* found to suppress the mRNA level of TNF-alpha, IL8, IL10 and iNOS in murine peritoneal macrophages.[20] Two pimaranediterpenoids, lonchophylloids A and B were isolated from the stems of *Ephemerantha lonchophylla* expressed the multidrug resistance phenotype to the toxicity of the anticancer isolated from the stems of *Ephemerantha lonchophylla* expressed the multidrug resistance phenotype to the toxicity of the anticancer drug doxorubicin. Subsequently, it has been reported that denbinobin also isolated from this plant exhibit anti-tumor and anti-inflammatory activity. Denbinobin displays anticancer effects in K562 cells through the increase of levels of tubulin polymerization and deregulation of BcrAbl signaling (Huang et al., 2005). Methanolic extract of *Gastrodia elata* prevents serum deprived apoptosis through activation of serine/threonine kinase dependent pathway and suppression of JNK activity. [21] whereas the ethanolic extract from the rhizomes have shown potent anti-tumor activity in vitro in a dose dependent manner.[22] According to Huang et al. (2007), bis-(4-Hydroxybenzyl) sulfide and N6-(4-hydroxybenzyl) adenine riboside were isolated from methanol extract of rhizomes of *G. elata* potently prevented PC12 cell apoptosis on ischemic/hypoxic model to screen neuroprotective in concentration dependent manners with EC50 values of 7.20 µM and 3.7 x 10-8 M, respectively. (2S)5,2',6'-trihydroxy-6-lavandulyl-4''-(γ,γdimethylallyl)-2'',2''-dimethylpyrano-[5'',6'',7,8] flavanone, a dihydroflavanoid isolated from *Spiranthes australis* inhibits human cancer cells growth including A498, A549, BEL-7402,SGC-7901,MCF-7, HT-29 and K562 cell lines.[23]

Table 1: Anticancer effect of extracts/compounds of different orchid species on different cancer cell lines.

S.N.	Orchid Species	Extract/Active Compound	Biological Target	References
1	*Agrostophyllum brevipes*	Callosinin		Majumder et al., 2001,2003[24,25]
2	*Anoectochilus formosanus*	Methanolic extract	MCF-7 cell lines	Tseng et al., 2006[26]
3	*Bletilla formosana*	4-Methoxy-9,10-dihydrophenanthrene-1,2,7-triol		Lin et al., 2005[27]
		1-(4-Hydroxybenzyl)-4,7-dimethoxy-9,10-dihydrophenanthrene-2-ol		
		1,3,6-tri(4-Hydroxybenzyl)-4-methoxydihydrophenanthrene-2,7-diol		
4	*B. striata*	3,3'-Dihydroxy-2',6'-bis(p-hydroxybenzyl)-5-methoxybibenzyl	K562 cell line	Morita et al., 2005[14]
		3',5-Dihydroxy-2-(p-hydroxybenzyl)-3-Methoxybibenzyl		
		1-(p-Hydroxybenzyl)-4,8-dimethoxyphenanthrene-2,7-iol		
		2,7-Dihydroxy-1,3-bis(p-hydroxybenzyl)-4-methoxy-9,10-dihydrophenanthrene		
		Blestrianol A		
		Blestriarene B		
		Blestriarene C		
5	*Bulbophyllum kwangtungense*	Plicatol B	Hela and K562 cell lines	Wu et al., 2006[28]
		Cumulatin		
		Densiflorol A		
6	*B. odoratissimum*	3,7-Dihydroxy-2,4,6-trimethoxyphenanthrene	K562, HL-60, A549,BEL-7402 and SGC-7901 cell lines	Chen et al., 2007[13]
7	*Coelogyne cristata*	Coeloginanthridin		Majumder et al., 2001[24]
		Coeloginanthrin		
8	*C. flaccida*	Callosinin		Majumder et al., 2001,2003[24,25]
9	*C. stricta*	Methanol extract	HeLa cell line	Thapa et al., 2020[10]
10	*Cremastra appendiculata*	Cirrhopetalanthin	HCT-8, Bel7402, BGC-823, A549, MCF-7 and A2780 cell lines	Xue et al., 2006[16]
		2,7,2',7',2'-Pentahydroxy-4,4',4'',7''-tetramethoxy-1,8,1',1''-triphenanthrene		
11	*Dendrobium amoenum*	Methanol extract	HeLa and U-251 cell lines	Paudel& Pant, 2017[29]
12	*D. brymerianum*	Moscatilin	H460 cell line	Klongkumnuankarn et al., 2015[30]
		Gigantol		
		Lusianthrindin		
		Dendroflorin		
13	*D. catenatum*	Protein extract	HepG2, SGC-7901, MCF-7 cell lines	Zheng et al., 2015[31]
		Peptides		
14	*D. crepidatum*	Methanol extract	HeLa, U-251 cell lines and T-cell lymphoma	Paudel et al., 2019[32]; Prasad & Koch, 2016[33]
		Ethanol extract		
15	*D. chrysanthum*	Ethanol extract	T-cell lymphoma and FaDu cell line	Nam et al., 2019[34]; Prasad & Koch, 2016[33]
		Moscatilin		
16	*D.chryseum*	Methanol extract	HeLa and U251 cell lines	Pant et al., 2021[11]

17	*D. chrysotoxum*	Erianin	T47D, 143B, HUVECs, HeLa, MG63.2, K562, HL-60, A549, BEL-7402, SGC-7901 cell lines	Chen et al., 2008[35]; Hu et al., 2012[36]; Li et al., 2018[37]; Sun et al., 2016[38]; Wang et al., 2016[39] Lin et al., 2005[27]
		1,4,5-trihydroxy-7-methoxy-9H-fluoren-9-one		
		Dendroflorin		
		Chrysotoxol B		
		Confusarin		
		Moscatin		
		Epheranthol B		
		Erianin		
		Gigantol		
		Tristin		
18	*D. denneanum*	Polysaccharides	S180 induced mice	Fan &Luo, 2011[40]
19	*D. densiflorum*	Cypripedin	H460 cell line	Wattanathamsan et al., 2018[41]
20	*D. draconis*	Gigantol	H460 cell line	Charoenrungruang et al., 2014a[42], 2014b[43]; Unahabhokha et al., 2016[44]
21	*D. ellipsophyllum*	4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl	H460, H292, H23 cell lines	chaotham&Chanvorchote 2015[44]: Chaotham et al.2014[45];Hlosrichok et al., 2018[46]
22	*D. falconeri*	Dendrofalconerol A	H460 cell line	Pengpaeng et al., 2014[47], 2015[48]
23	*D. fimbriatum*	4-(3-hydroxy-4-methoxyphenethyl)-2,6-dimethoxylphenol	HL-60, SMMC-7721, A-549, SW480, MCF-7 cell lines	Xu et al., 2014[49]
		Fimbriadimerbibenzyl A, B, E, F and G		
		Moscatilin		
24	*D. findlayanum*	4, 4′-dihydroxy-3, 3′,5-trimethoxy bibenzyl	A172, SHSY5Y and HeLa cell lines	Liu et al., 2020[50]
25	*D. formosum*	Ethanolic extract	T-cell lymphoma	Prasad & Koch, 2014[51]
26	*D. gratiosissimum*	Dengraols A and B	HL-60	Zhang et al., 2008[52]
		Gigantol		
		Moscatilin		
27	*D. loddigesii*	Moscatilin	HUVECs, A-549, H23, MDA-MB-231, HCT-116, SCC, A375 cell lines	Cardile et al., 2020[53]; Chen et al., 2013[54]; Chen et al., 2008[55]; Ho & Chen, 2003[56]; Kowitdamrong et al., 2013[57]; Tsai et al., 2010[58]
28	*D. longicornu*	Acetone extract	U-251 and HeLa cell lines	Paudel et al., 2017[29]
		Ethanol extract		
29	*D. moniliforme*	Methanol extract	HeLa, HCT-116, MCF-7, U-251, K562, HSC-T6, BNL CL.2, PC-3 and DU-145 cell lines, 26-M3.1 induced mice	Hsu et al., 2014[59]; Huang et al., 2005[60]; Li et al., 2014[61]; Paudel et al., 2018[62]; Sánchez-Duffhues et al., 2009[63]; Sun et al., 2016[64];
		Ethanol extract		
		Denbinobin		
		Moniliformediquinone		
30	*D. nobile*	Denbinobin	K562, PC-3, SNU-484, SK-Hep-1, HeLa, MCF-7, A549, HL-60, HepG2 cell lines and S180 induced mice	Huang et al., 2005[23]; Lu et al., 2014;[66] Luo& Fan, 2011[67]; Song et al., 2012[68]; Wang et al., 2010[69]; Zhou et al., 2016[70]
		Denobilone A		
		Lactone derivatives		
		Polysaccharides		
31	*D. officinale*	Aqueous extract	MNNG-induced gastric tumorigenesis in rats, HeLa cell line, and SGC-7901 xenograft mice	Ren et al., 2020[71]; Zhang et al., 2018[72]; Zhao et al., 2016[73]
		4,4'-dihydroxy-3,5-dimethoxybibenzyl		
		Dendrocandin B		
		Dendrocandin U		
		Denofficin		
		Gigantol		
		Moscatilin		
		Polysaccharides		

32	*D. polyanthum*	Moscatilin	A549, HL-60 cell lines	Hu et al., 2009[74]
33	*D. pulchellum*	Chrysotoxine	H460, H23 cell lines	Bhummaphan et al., 2018;[75]Chanvorachote et al.,
		Moscatilin		
34	*D. signatum*	Ethanol extract	MCF-7, NCI-H187, MDA-231, HepG2 and HT-29 cell lines	Chimsook, 2016[77]; Mittraphab et al., 2016[78]
		Dendrosignatol		
		3,4-dihydroxy-3',4'-dimethoxybibenzyl		
		Dendrocandin B		
		dendrocandin I		
		Dendrofalconerol A		
35	*D. sinense*	3,4,3'-trimethoxy-5,4'-dihydroxybibenzyl	SGC-7901, BEL-7402, K562 cell lines	Chen et al., 2014[79]
		5,3'-dihydroxy-3,4-dimethoxy-bibenzyl		
		Longicornuol A		
36	*D. transparens*	Methanol extract	HeLa and U251 cell lines	Joshi et al., 2020[9]
37	*Ephemerantha lonchophylla*	Ephemeranthone	K562 cell line	Chen et al., 2000[80]
		Erianthridin		
		Denbinobin		
38	*Eulophia macrobulbon*	Ethanol extract and fractions	MCF-7, HeLa and CaCo-2 cell lines	Schuster et al., 2017[81]
39	*E. nuda*	9,10-dihydro-2,5-dimethoxyphenanthrene-1,7-diol	MCF-7 and MDA-MB-231 cell lines	Shriram et al., 2010[82]; Bhatt et al., 2018[83]
		Alcohol extact		
40	*Gastrodiaelata*	N6-(4-hydroxybenzyl) adenine riboside	PC12 cell line	Huang et al., 2004[21]
41	*Gymnadeniaconopsea*	Gymconopin A		Matsuda et al., 2004[84]
		Gymconopin B		
		Gymconopin D		
		Dihydroxy-2,6-bis(4-hydroxybenzyl)-5-methoxy-bibenzyl		
42	*Maxillaria densa*	2,5-Dihydroxy-3, 4-Dimethoxyphenanthrene		Decigsa-campos et al., 2007[85]
		9,10-dihydro-2,5-dihydroxy-3, 4-dimethoxyphenanthrene		
		Nudol		
		Gymnopusin		
		Erianthridin		
		Fimbriol A		
43	*Papilionanthe uniflora*	Methanol extract	HeLa cell line	Joshi et al., 2020[9]
44	*Pholidota articulata*	Methanol extract	HeLa cell line	Joshi et al., 2020[9]
45	*P. yunnanensis*	2,4,7-Trihydroxy-9,10-Dihydrophenanthrene		Guo et al., 2007[86]
		3,7-dihydroxy-2,4,8-Trimethoxyphenanthrene		
		Coelonin		
		3,7-Dihydroxy-2,4-dimethoxyphenanthrene		
46	*Rhyncostylish retusa*	Methanol extract		Radhika et al., 2013[87]
47	*Spiranthes australis*	(2S)-5,2',6'-trihydroxy-6-lavandulyl-4"-(γ,γ -dimethylallyl)-2",2"-dimethylpyrano-[5",6": 7,8]-flavanone	A549, BEL-7402, SGC-7901, MCF-7, HT-29, K562, and A498 cell lines	Peng et al., 2007[23]
48	*Vanda cristata*	Methanol extract	HeLa and U251 cell lines	Joshi et al., 2020

CONCLUSION

It is documented that orchids are rich in potential anticancer agents and are on the forefront in terms of offering possibilities for new anticancer drugs. Many existing anticancer remedies based on traditional medicine are of orchid origin. In fact, orchids have exhibited anticancer activities in animal models of leukemia, skin cancer and sarcomas. For those plants which have shown promising results, further investigation has ensued but deeper investigations for single active molecular moiety must be undertaken. While cancer exerts a high mortality rate and may not be treatable by the usual arsenal of an oncologist, it is likely that orchids and their components may play a role in palliative care or reduce the side effects associated with currently available cancer treatments. By generating awareness regarding the use of herbs and exploring their natural product properties, healthcare professionals can play a significant critical role as knowledge resource for the masses. From literature-based information, our research findings show that particular orchids, used since ancient times in traditional medicine under various formulations, contain potential anticancer drug candidates in their plant material and may also experience eventual utilization as herbal product, depending on the specific data collected.

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