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Review on medicinal plants of Sikkim Himalayan region with emphasis on anticancer study

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ABSTRACT

Plants are still not only important in health care, but they are also the finest and safest hope for future medicine. These local ethnomedicinal plants discovered in Sikkim have been scientifically studied, and the results have been widely disseminated so that people can learn more about effective drug treatments and improve their health. The focus of the prevailing study was to find maximum local ethnomedicinal plants that are found in Sikkim Himalayan region with anticancer study. Published data in this review were all gathered from the online bibliographical databases: PubMed, Science direct, Google Scholar, Research gate, Cochrane, Core, and 1 Library. With the extensive literature review data, it was revealed that 77 medicinal plants found in the Sikkim Himalayan region have proven anticancer activity summarized in Table 1 by considering their local name (Nepali), part used for the treatment procedure, active extracts/study models (both *in-vitro and in-vitro*) and cell culture assay (diverse cell lines studies). Out of 77 selected ethno-medicinal plants, 27 plants were active in the *in-vivo* model remaining 50 plants were active in the *in-vitro* model. As per the activity found in the active extracts, activity was highest in alcohol (methanol and ethanol extracts), followed by aqueous and ethyl acetate, chloroform, etc. Further research can be conducted on those plants that have shown the most promising anti-cancer efficacy in previous clinical tests, perhaps leading to low-cost plant-derived drugs to combat the expanding cancer epidemic.

INTRODUCTION

Mutations that are inherited, generated by environmental factors, or occur from DNA replication errors cause cancer. In multi-cellular animal creatures, including humans, aging is the most important risk factor for carcinogenesis. Cancer is the first or second leading cause of death in 91 of the 172 nations studied, and third or fourth in another 22 [1]. In 2040, an estimated 28.4 million new cancer cases (including non-melanoma skin cancer, except basal cell carcinoma) are expected to be diagnosed worldwide, up to 47% from the 19.3 million cases diagnosed in 2020, assuming national rates remain constant [2]. In both urban and rural India, cancer is the second and fourth major cause of adult deaths, respectively. Cancer is currently the leading explanation for ruinous health payment, distress funding, and increasing expenditure before death in every country of the world [3]. From 1990 to 2016, India's cancer death rate more than doubled. India's cancer incidence was estimated to be 1.15 million new patients in 2018, and by 2040, it is expected to nearly triple due to demographic changes alone [4]. The northeast region of India has the highest cancer incidence rate [six population based cancer registries (PBCRs) for males and four PBCRs for females] compared to other parts of the country. The nasopharynx, hypopharynx, esophagus, stomach, liver, gallbladder, larynx, lung, breast, and cervix uteri were the most common cancer sites in northeast India. As seen by the low 5-year survival rates of breast, cervical, and head and neck cancer in the northeast compared to the rest of India, the region lacks the necessary infrastructure in terms of specialized treatment facilities and human resources. A significant number of cancer patients

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from the northeast travel beyond the region for treatment and care [5]. A lot of work has gone towards reducing the detrimental side effects of medications during cancer treatment, such as limiting side effects on adjacent cells and tissues, improving drug accumulation and efficacy in the lesion, and developing novel drug delivery and targeting systems [6]. Medicinal plants are a gift from nature to humanity, assisting them in their quest for improved health. Plants and their bioactive substances have been used in traditional medicine since the dawn of humanity. Phyto chemicals found in some medicinal plant species suppress the progression and development of cancer [7]. According to studies, the plant kingdom contains over 250,000 plant species, of which only about 10% have been explored for the treatment of various diseases and approximately 60%–80% of the world's population still relies on traditional remedies for the treatment of common disorders and diseases [8]. Sikkim extends between 270 4′46″ to 280 7′48″ N and 880 58′00″ to 880 55′25″ E containing 4,000 flowering species [9]. The extraordinary geographical position and wide range of topography, high fertile soil, sufficient rainfall, and presence of a large number of perennial streams make the state of Sikkim one of the treasure houses of biodiversity in the country. Sikkim boasts an abundance of medicinal herbs and traditional medicine. About 550 medicinal plants are used by locals in the Sikkim Himalayas region for various ailments, of which only a few are commercially exploited. Plants are still not only important in health care, but they are also the finest and safest hope for future medicine. These local ethnomedicinal plants discovered in Sikkim have been scientifically studied, and the results have been widely disseminated so that people can learn more about effective drug treatments and improve their health.

RESULTS

Table 1. Plants found in Sikkim Himalayan region with reported anticancer activity.

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
1	*Abrus precatorius* L.	Lalgeri	Seeds	Petroleum ether	*In vivo*	EAC cells [10]
	Family: Fabaceae					
2	*Acorus calamus* L.	Bojho	Rhizome	Methanol	*In vitro*	MDA-MB-435S and Hep3B [11]
	Family: Acoraceae					
3	*Aegle marmelos* (L.) Corrêa	Bael	Fruit pulp	Water	*In vitro*	Michigan Cancer Foundation-7 (MCF7) [12]
	Family: Rutaceae		Bark	Hydromethanolic	*In vivo*	Chemical-induced skin papillomagenesis [13]
4	*Allium wallichii* Kunth	Ban Lasun	Whole plant	Ethanol	*In vitro*	MCF-7, PC3, HeLa cells [14]
	Family: Amaryllidaceae					
5	*Alstonia scholaris* (L.) R.Br.	Chatiwan	Root bark	Methanol	*In vivo*	MOR-P, COR-L23, MCF-7 [15]
	Family: Apocynaceae					
6	*Amomum subulatum* Roxb.	Elaichi	Seed	Ethyl acetate, hexane	*In vitro*	MCF-7, HeLa cells [16]
	Family: Zingiberaceae			Ethanol	*In vitro*	HeLa cells [17]
7	*Artemisia vulgaris* L.	Titaypati	Aerial flowering Part	Methanol	*In vitro*	SW-480 [18]
	Family: Asteraceae		Leaves and buds	Essential oil	*In vitro*	HL-60 [19]
8	*Asparagus racemosus* Willd.	Kurilo	leaves	Chloroform	*In vitro*	UOK 146 [20]
	Family: Asparagaceae		Root	Methanol		A549 [21]
9	*Azadirachta indica* A.Juss.	Nimpati	leaves	Ethanol	*In vivo*	Hamster buccal pouch carcinogenesis model [22]
	Family: Meliaceae		Leaves and flower	Limonoid	*In vitro*	BeWo cells [23]
			Edible part	Nimbolide	*In vitro*	U937, HL-60, THP1 and B16 [24]
10	*Bauhinia variegata* L.	Koirala	Whole plant	Methanol	*In vivo*	B16F10 [25]
	Family: Fabaceae		Leaves	Glucokinin	*In vitro*	HepG2, WRL and A549 [26]
11	*Berberis aristata* DC.	Chutro	Bark	Distilled water	*In vitro*	HeLa Cells [27]
	Family: Berberidaceae		Steam	Methanol	*In vitro*	MCF-7 [28]
12	*Betula utilis* D.Don	Bhojpatra	bark	Ethyl acetate cytotoxic triterpenes	*In vitro*	A172, MCF-7, DLD-1, PLC/PRF/5, A549, SK-OV-3, BxPC-3 DU145, Caki-1 [29]

Continued

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
13	*Bombax ceiba* L Family: Malvaceae	Simal	Flowers	Light petroleum and diethyl ether	*In vitro*	MCF-7, HeLa, COR-L23, C32, A375, ACHN, and LNCaP [30]
			Leaves	Methanol	*In vitro*	HL-60 [31]
14	*Buddleja asiatica* Lour. Family: Scrophulariaceae	Bhinsenpatee	Leaves	Methanol	*In vitro*	HepG2 [32]
15	*Calendula officinalis* L. Family: Asteraceae	Calendula	Flowers/Flos	Methanol, ethyl	*In vitro*	T47D [33]
			Flowers	acetate, and heptane	*In vitro*	HeLa, Fem-X, MDA-MB-361, LS174, and K562 [34]
				Distilled water Methanol	*In vivo*	Croton oil-promoted skin carcinogenesis model in Swiss albino mice [35]
16	*Callicarpa arborea* Roxb. Family: Lamiaceae	Guahelo	Leaves	Chloroform	*In vitro*	A549 [36]
17	*Carica papaya* L. Family: Caricaceae	Mewa	Leaves	Water	*In vitro*	K562, HeLa, HepG2 and Huh7 [37]
			Leaves	Water	*In vitro*	Atypical glandular cells (AGS), Capan1, DLD1, DOV13, Karpas, MCF7, T98G, HeLa, CD26 [38]
18	*Cassia fistula* L. Family: Fabaceae	Raj Briksha	Fruits	Ethyl acetate and *n*-butanol	*In vitro*	SiHa and MCF-7 [39]
			Flower	Rhein	*In vitro*	COLO 320 DM [40]
19	*Catharanthus roseus* (L.) G.Don Family: Apocynaceae	Sadabahar	Leaves	Aqueous and methanol	*In vitro*	MCF-7 [41]
				Endophytic fraction	*In vivo*	DMH induced colon cancer [42]
20	*Centella asiatica* (L.) Urb. Family: Apiaceae	Gora taprey	Leaves	Aqueous	*In vitro*	B16F1,MDA MB-231, C6 cell lines [43]
21	*Chenopodium album* L. Family: Amaranthaceae	Bethu saag	Leaves	Methanol	*In vivo*	EAC [44]
			Leaves	Methanol	*In vitro*	MCF-7 and MDA-MB-468 [45]
22	*Chromolaena odorata* (L.) R.King & H.Rob. Family: Asteraceae	Seto banmara	Leaves	Ethanol	*In vitro*	MCF-7, HeLa, HCT116 [46]
			Leaves	Methanol	*In vitro*	HT 29 [47]
23	*Cinnamomum tamala* (Buch.-Ham.) T.Nees & Eberm. Family: Lauraceae	Sinkauli	Leaves	Methanol Aqueous and pet. ether	*In vitro*	A549, MCF-7, COLO 205 [48]
			Leaves	Pet. ether fraction, chloroform fraction, ethyl acetate	*In vitro*	A549, MCF-7 and U-87 MG [49]
				fraction, n-butanol fraction	*In vivo*	Mouse fibrosarcoma [49]
24	*Citrus medica* L. Family: Rutaceae	Bimbira	Fruit	Fruit juice	*In vitro*	Human astrocytoma cell line [50]
25	*Clerodendrum infortunatum* L. Family: Lamiaceae	Chitu	Leaves and root	Hexane, chloroform, ethyl acetate and ethanol	*In vitro*	PC3, A549, HCT-116, T47D [51]
			Leaves	Terpenoids of methanol extract	*In vivo*	EAC [52]
26	*Digitalis purpurea* L. Family: Plantaginaceae	Fox glove	Leaves	Hexane, chloroform, methanol, water	*In vitro*	TK-10, MCF-7, UACC-62 [53]
27	*Dillenia indica* L. Family: Dilleniaceae	Ramphal	Fruit	methanol	*In vitro*	Human leukemic cell lines U937, HL60 and K562 [54]

Continued

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
28	*Dioscorea bulbifera*	Gittha	Rhizome	Ethanol extract	*In vitro*	Mouse epidermal JB6 cell lines [55]
	Family: Dioscoreaceae		Root	Ethyl acetate and acetone	*In vitro*	MCF-7 [56]
29	*Entada phaseoloides* (L.) Merr.	Pangra	Seed kernels	Phaseoloideside E,	*In vitro*	Ec-109 esophageal cancer cells [57]
	Family: Fabaceae			*N*-butanol fraction	*In vitro*	HepG2 [58]
30	*Eucalyptus globulus* Labill.	Tarpin	Aerial parts	water	*In vitro*	PANC-1, NCI-H460
	Family: Myrtaceae					And HCT-15 [59]
31	*Eupatorium cannabinum* L.	Banmara	Whole plant	Aqueous extract	*In vitro*	HepG2, Caco-2 [60]
	Family: Asteraceae		Aerial parts	Chloroform extract Methanol	*In vitro*	MCF-7 [61]
32	*Fagopyrum esculentum* Moench	Mithey Phapur	seeds	Antifungal peptide	*In vitro*	Hep G2, L1210, MCF 7, WRL 68 [62]
	Family: Polygonaceae			Recombinant buckwheat trypsin inhibitor	*In vitro*	
					In vivo	H22 [63]
33	*Ferula narthex* Boiss.	Hing	Whole plant	*n*-hexane fraction	*In vitro*	PC3 [64]
	Family: Apiaceae					
34	*Gloriosa superba* L.	Langarey tarul	seeds	Colchicine	*In vitro*	A549, MCF-7, MDA-MB231, PANC-1, HCT116, and SiHa [65]
	Family: Colchicaceae					
35	*Glycyrrhiza glabra* L.	Jathimadhu	Root	Ethanol	*In vitro*	HT-29 [66]
	Family: Fabaceae		Root	Isoliquiritigenin	*In vivo*	1,2-dimethylhydrazine-induced colon and lung tumors in mice [67]
36	*Hippophae salicifolia* D.Don	Achuk	Coarse bark	Methanol	*In vivo*	EAC [68]
	Family: Elaeagnaceae					
37	*Holarrhena antidysenterica* Wall.	Anley khirrn	Bark	Methanol	*In vitro*	Ca9-22 and HSC-3 cells [69]
	Family: Apocynaceae		Leaves	Chloroform soluble fraction	*In vitro*	A549, COLO205, DU145, HeLa, HEP2, IMR32, KB, MCF7, NCI-H23, OVCAR5, SiHa, SK-N-MC, SW 620, ZR-75-1 [70]
38	Hymenodictyon excelsum (Roxb.) Wall.	Latikaran	Bark	Methanol	*In vitro*	lung fibroblast (L-929) cell line [71]
	Family: Rubiaceae		Stem bark	Methanol	*In vivo*	EAC [72]
39	*Jatropha curcas* L.	Hathikane	Whole plant	Methanol	*In vitro*	HT-29 [73]
	Family: Euphorbiaceae		Seeds and latex	Curcin	*In vitro*	MCF-7, HepG2 and HCT-116 [74]
40	*Juglans regia* L.	Okhar	Fruits leaves	Methanol	*In vitro*	A-498 and 769-P and Caco-2 [75]
	Family: Juglandaceae		Leaves	Hexane	*In vitro*	PC3 [76]
41	*Kaempferia rotunda*	Bhui champa	rhizome	Lectin	*In vitro &*	EAC and U87 [77]
	Family: Zingiberaceae				*In vivo*	SW480 and SW48 [78]
						T47D [79]
42	*Litsea cubeba* (Lour.) Pers. Family: Lauraceae	Siltimbur	Heartwods and fruits	n-hexane, ethylacetate, and ethanol	*In vitro*	T47D [80]
			Leaves and fruit oil	water	*In vitro*	OEC-M1, J5, A549 [81]
43	*Lycopodium clavatum* L.	Nagbeli	Whole plant	Lycopodine	*In vitro*	HeLa [82]
	Family: Lycopodiaceae			Ethanolic extract		

Continued

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
44	*Melia azedarach* L.	Bakaina	Bark	Hexane	*In vivo*	A549 [83]
	Family: Meliaceae					
45	*Mentha spicata* subsp. spicata	Nageswari	Aerial plant	Essential oil	*In vitro*	HCT 116, MCF7, T47D [84]
	Family: Lamiaceae					
46	*Mesua ferrea* L.	Nageeswari	Leaves	Essential oil	*In vitro*	KB, MCF7, NCI-H [85]
	Family: Calophyllaceae		Leaves	Dichloromethane, ethyl acetate, methanol, aqueous	*In vitro*	PANC1 [86]
47	*Mimosa pudica* L.	Lajjawanti	Whole plant	Hydroalcoholic	*In vitro*	DAUDI [87]
	Family: Fabaceae			methanol	*In vitro*	MCF7, MDA-MB-231 [88]
48	*Moringa oleifera* Lam.	Sajana	Leaves	Water	*In vitro*	A549, COS-7 [89]
	Family: Moringaceae		Leaves	Hydromethanolic and methanolic	*In vivo*	B16F10 mouse melanoma [90]
49	*Nyctanthes* arbor-tristis L.	Parijat	Leaves	Ethanol and ethyl acetate	*In vitro*	HeLa [91]
	Family: Oleaceae					
50	*Ocimum tenuiflorum* L.	Tulasi	Leaves	Water and methanol	*In vitro*	MCF-7 and MDA-MB-231 [92]
	Family: Lamiaceae					
51	*Oroxylum indicum* (L.) Kurz	Totola	Stem bark	Hydro-alcoholic	*In vitro*	Budding yeast Saccharomyces
	Family: Bignoniaceae		Bark	Chrysin	*In vitro*	Cerevisiae [93]
						MCF7, HaCaT, TIG-3, and AT2KY [94]
52	*Oxalis corniculata* L.	Chariamilo	Whole plant	Ethanol	*In vivo*	EAC [95]
	Family: Oxalidaceae					
53	*Phyllanthus emblica* L.	Amla	Fruit pulp	Aqueous	*In vitro*	SiHa and HeLa [96]
	Family: Phyllanthaceae		Fruit	Aqueous	*In vitro*	HepG2, HeLa, A549, MDA-MB-321, SKOV3, SW620, MRC5
					In vivo	Mouse skin tumourigenesis model [97]
54	*Physalis minima* L.	Jangali phokphakey	Whole plant	Chloroform	*In vitro*	NCH-H23, T-47D, Caov-3 [98]
	Family: Solanaceae		Whole plant	Chloroform	*In vitro*	NCH-H23 [99]
55	*Picrorhiza kurrooa* Royle	Kutki	Rhizome	Dichloromethane fraction	*In vitro*	MCF7, SiHa, HeLa, MDA-MB231
	Family: Plantaginaceae				*In vivo*	EAC [100]
56	*Piper longum* L.	Pipla	Fruits	Water	*In vitro*	HCC-827 [101]
	Family: Piperaceae		Fruits	Ethanol	*In vitro*	SKOV3, HeLa, HepG2 [102]
57	*Podophyllum hexandrum* Royle	Bankankari	Leaves	Methanol	*In vitro*	MCF7 [103]
	Family: Berberidaceae					
58	*Punica granatum* L.	Darim	Peels	Methanol	*In vitro*	MCF7 [104]
	Family: Lythraceae					
59	*Rhododendron arboreum* Sm.	Laligurans	Bark	Ethyl acetate fraction	*In vitro*	HepG2, A498, NCI-H226, H157 and MDR-2780AD [105]
	Family: Ericaceae					
60	*Ricinus communis* L. Family: Euphorbiaceae	Rairi	Seeds	Crude protein extracts	*In vivo*	EAC [106]
			Aerial part	Essential oil	*In vitro*	HeLa [107]

Continued

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
61	*Rubia cordifolia* L.	Majito	roots	Pet-ether fraction	*In vitro*	HEK293, HeLa, HEp2 [108]
	Family: Rubiaceae		Roots and aerial part	Methanol fraction	*In vitro*	MCF7 [109]
			Root	Dichloromethane fraction	*In vitro*	Human epithelial carcinoma (HEp-2) [110]
				Methanol		
				Methanol		
62	*Rubus ellipticus* Sm.	Aeiselu	Fresh ripe fruit	Methanol, acid	*In vitro*	C33A and HeLa [111]
	Family: Rosaceae		Leaves	Methanol, acetone, acid acetone	*In vivo*	EAC and Dalton's lymphoma ascite (DLA) solid tumors [112]
				Methanol		
63	*Sapindus mukorossi* Gaertn.	Ritha	Seeds	Methanol, ethyl acetate, hexane	*In vitro*	Human melanoma cell lines A375. S2 (ATCC CRL-1872) and
	Family: Sapindaceae		Leaves and stem		*In vitro*	MeWo (ATCC HTB-65) [113]
				Aqueous	*In vivo*	A549
						Lewis lung cancer LL/2 [114]
64	*Smilax zeylanica* L.	Kukur	Root	Water	*In vitro*	HepG [115]
	Family: Smilaxcaceae		Leaves	Methanol	*In vivo*	Benzo[a]pyrene induced lung carcinoma [116]
			Stems	Methanol, Pet. ether	*In vitro*	MCF7 [117]
65	*Solanum nigrum* L	Kalobehi	Whole plant	hydro-alcoholic extracts	*In vitro*	HepG2, CT26 [118]
	Family: Solanaceae		Fruits			MCF7 [119]
				Aqueous	*In vitro*	Hep3B and HepJ5 [120]
				Aqueous	*In vitro*	
66	*Stephania glabra* (Roxb.) Miers	Taubarkey	Tuber	Methanol, aqueous	*In vitro*	A549, PC3 [121]
	Family: Menispermaceae					
67	*Tamarindus indica* L.	Titari	Seeds	Methanol	*In vitro*	Rhabdomyosarcoma, Human lymphoma [122]
	Family: Fabaceae					
68	*Taxus baccata* L.	Dhengre salla	Leaves, seeds cones	Water and methanol,	*In vitro*	HCT-116 and MDA-MB-231 [123]
	Family: Taxaceae			acetone, ethyl acetate and petroleum ether		
69	*Terminalia chebula* Retz.	Harra	Fruits	Ethanol	*In vivo*	EAC [124]
	Family: Combertaceae			Ethanol	*In vivo*	MCF-7, MCF-10 [125]
70	*Thysanolaena maxima* (Roxb.) Kuntze	Amliso	Whole plant	dichloromethane:	*In vitro*	Vero cell line [126]
	Family: Poaceae			methanol (1:1)		
71	*Tinospora cordifolia* (Willd.) Miers	Gurjo	Stem	dichloromethane fractions and ethanol	*In vitro*	HeLa [127]
	Family: Menispermaceae			Methanol: water	*In vivo*	HCA-7 [128]
				Water		AW13516 [129]
				Dichloromethane extract	*In vitro*	EAC [130]
				Methanol		MDA-MB-231, Vero [131]

Continued

Sl. No	Botanical name and family	Common name (Nepali)	Plant part	Active extract/ fraction/ compound	Study model	Cell line
72	*Trichosanthes tricuspidata* subsp. *tricuspidata* Family: Cucurbitaceae	Indreyni	Roots	chloroform	*In vitro*	PC3, MCF7 and L1210 [132]
73	*Urtica dioica* L. Family: Urticaceae	Sisnu	Leaves	Aqueous	*In vitro*	Human prostate Carcinoma LNCaP cells [133]
74	*Viscum articulatum* Burm.fil. Family: Viscaceae	Harchur	Whole plant	Aqueous	*In vitro*	Jurkat E6.1 and THP1 cells [134]
75	*Woodfordia fruticosa* (L.) Kurz Family: Lythraceae	Dhayeroo	Flower	Methanol	*In vivo* *In vitro*	Hepatocellular carcinoma [135]
76	*Zanthoxylum alatum* Steud. Family: Rutaceae	Bokey timbur	Leaves Stem bark	Zanthonitrile Ethyl acetate	*In vitro* *In vitro*	EAC [136] A-549 and MIA-PaCa [137]
77	*Zingiber officinale* Roscoe Family: Zingiberaceae	Aduwa	Rhizome	Ethanol Methanol	*In vitro* *In vivo* *In vitro*	CCA (CL-6) [138] HeLa cell and MDA-MB- 231 [139]

Table 2. Plant based anti-cancer marketed drugs.

Sl. No.	Anti-cancer agents	Natural source	Applications and targets	References
1.	Paclitaxel (PTX)	*Taxus brevifolia Nutt.*	Ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi's sarcoma, cervical cancer, and pancreatic cancer	[140,141]
2.	Vinblastine (VBS)	*Vinca rosea L.*	Breast cancer, testicular cancer, neuroblastoma, Hodgkin's and non-Hodgkins lymphoma, mycosis fungoides, histiocytosis and Kaposi's sarcoma	[142]
3.	Vincristine (VCS)	*Vinca rosea L.*	Leukemia, malignant lymphoma, Hodgkin's disease, acute erythraemia, and acute panmyelosis	[143]
4.	Podophyllotoxin (PTOX)	*Podophyllum*	Testicular, breast, pancreatic, lung, stomach, and ovarian cancers	[144,145]
5.	Camtothecin (CPT)	*Camptotheca acuminata*	Nuclear enzyme DNA topoisomerase type I inhibitor	[146]
6.	Eucalyptin A	*Eucalyptus globulus*	Breast, ovary, prostate, bladder, skin, and oral cavity	[147]
7.	Parthenolide (PN)	*Tanacetus parthenium*	Thyroid cancer cells	[148]
8.	Trabectedin	*Ecteinascidia turbinate*	Sarcoma or ovarian cancer	[149,150]

DISCUSSION

In drug development and therapy, particularly cancer research, plants and their secondary metabolites play a significant role. The goal of this review article is to list out the medicinal plants, their extracts, and metabolites that have recently attracted attention for their anticancer effects *in vitro* and *in vivo* from Sikkim Himalaya. Although the actual compounds isolated from the plant are frequently not used as medications, they provide clues for the creation of prospective novel agents [151]. Plants have been a major source of extremely successful conventional drugs for the treatment of many types of cancer [152]. Some of the drugs that failed earlier clinical tests are now igniting renewed interest as new technologies are created. The potential for attaching medications to carrier molecules targeted at certain cancers is demonstrated [153]. Natural products might be an important source of antitumor drugs for contemporary cancer treatment. It is anticipated that new anticancer phytopharmaceuticals made from medicinal plants will be useful for both cancer therapy and prevention [154]. The plant extracts having rich flavonoids have shown a chemopreventive role in cancer through their effects on signal transduction in cell proliferation and angiogenesis [155]. Some of the potential marketed plant-based drugs are highlighted in Table 2. As shown in Table 2, certain cancerous targets, such as ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi's sarcoma, cervical cancer, and pancreatic cancer, are targeted by Paclitaxel (PTX) obtained from *Taxus brevifolia* Nutt., Vinblastine (VBS), and Vincristine (VCS) obtained from *Vinca rosea* Linn. used for breast cancer, testicular cancer, neuroblastoma, Hodgkin's and non-Hodgkins lymphoma, mycosis fungoides, histiocytosis and Kaposi's sarcoma, leukemia, malignant lymphoma, Hodgkin's disease, acute erythraemia, and acute panmyelosis. Certain cancer like testicular, breast, pancreatic, lung, stomach, and ovarian cancers are treated by Podophyllotoxin (PTOX) obtained from *Podophyllum* spp. Camtothecin (CPT) obtained from *Camptotheca acuminate* is used for molecular targets such as nuclear enzyme DNA topoisomerase type I inhibitor. Eucalyptin A obtained from *Eucalyptus globulus*, Parthenolide (PN) obtained from *Tanacetus parthenium*, and Trabectedin obtained from *Ecteinascidia turbinate* have shown the potential for breast, ovary, prostate, bladder, skin, and oral cavity, thyroid cancer cells, and sarcoma or ovarian cancer. Most of the plant extracts were observed to have growth inhibition effects in the particular cell line, whereas other plant extracts inhibit DNA synthesis. The extract of *Morus alba* leaves, which includes several phenolic compounds in various solvents, inhibited the proliferation of the HepG2 cell line by stopping the cell cycle in the G2/M phase. This was accomplished by expressing the protein p27Kip1, activating caspases to cause cell death, and inhibiting topoisomerase II activity [156]. To investigate the impact of curcumin on the expression of COX-2, human HT-29 colon cancer cells were treated with various amounts of curcumin derived from *Curcuma longa*. Curcumin reduced the proliferation of HT-29 cells in a concentration- and time-dependent manner. Although COX-2's mRNA and protein expression were inhibited by curcumin, COX-1 was not similarly altered [157]. In addition, lactate dehydrogenase and 3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H-tetrazolium bromide tests to measure cytotoxicity and cell viability were used to evaluate the anticancer effects of curcumin on human breast cancer cell lines (MCF-7) [158]. HeLa and AGS cell lines were examined with the *Artemisia annua* extracts. In comparison to leaf extracts, stem extracts had less effectiveness inhibiting cell proliferation. At a dosage of 500 mg/ml, the ethanolic extract of leaves causes growth inhibitions in HeLa and AGS cells (57.24% and 67.07%), respectively [159]. In terms of toxicity studies, many plants showed some extent of toxicity, *Albizia coriaria* (Welw. ex) Oliver is used to treat skin conditions, jaundice, cough, sore eyes, postpartum hemorrhage, menorrhagia, threatening abortion, and venereal illnesses-syphilis, HIV, and gonorrhea [160]. *Catharanthus roseus* L. is an example, as it contains alkaloids that are neurotoxic, particularly VCS [161]. Highly toxic antimitotics-VCS and VBS prevent mitosis in metaphase after attaching to microtubules [162]. It is obvious that adverse symptoms such myelosuppression, alopecia, abdominal pains, constipation, nausea, paralytic ileus, mouth ulcers, hepatocellular damage, kidney impairment, pulmonary fibrosis, urine retention, amenorrhea, azoospermia, orthostatic hypotension, and hypertension might occur. These plants have been documented for the commercial medications made from this plant, VCS and VBS. In essence, meticulous monitoring of these medications' administration is required to minimise their negative effects [163–166]. From one study, luteolin obtained from *Daucus carota*, *Salvia rosmarinus,* shielded breast cancer cells from doxorubicin-induced toxicity by decreasing reactive oxygen species production [167]. Colchicine was previously considered as a cancer treatment, but it has a few disadvantages: it is highly toxic and exhibits little tumor cell specificity, which causes it to target normal cells. Colchicine hence has a limited role in treating cancer [168]. Cucurbitacins I and D undergo acetylation, which increases their hydrophobicity and cytotoxicity, to produce cucurbitacins E and B. In addition to reducing tumor size and weight, cucurbitacin E and doxorubicin are effectively cytotoxic for tumor cells in culture and *in vivo* [169–171]. A once-daily intraperitoneal injection of 1,100 mg/kg of *Withania somnifera* extract did not cause any death within 24 hours in Swiss albino mice. However, an acute toxicity investigation found that a small dose increase results in death, with an LD50 of 1,260 mg/kg/body weight. The components of peripheral blood did not alter. But the weights of the spleen, thymus, and adrenal glands were significantly decreased [172]. *Artemia salina* larvae were poisonous to the ethanolic leaf extract of *Hyptis capitata* Jacq., with the greatest toxicity value being 196,772.7 g/ml [173]. Although an analysis of the literature for *Astragalus bruguieri* revealed no records of acute toxicity, an acute toxicity test conducted on *Astragalus membranaceus* on Wister rats demonstrated the plant's safety up to 1,200 mg/kg bw/day [174]. Total 77 medicinal plants found in the Sikkim Himalayan region have proven anticancer activity in diverse cell lines. From this short review work, authors have highlighted the ethno medicinal plants found in Sikkim Himalaya region having potent anti-cancer activity summarized in Table 1 by considering their local name (Nepali), part used for the treatment procedure, active extract/study models (both *in-vitro and in-vitro*) and cell culture assay (diverse cell lines studies). Out of 77 selected ethno-medicinal plants, 27 plants were active in the *in-vivo* model and the remaining 50 plants were active in the *in-vitro* model. As per the activity found in the active extracts, activity was highest in

alcohol (methanol and ethanol extracts), followed by aqueous and ethyl acetate, chloroform, etc.

CONCLUSION

Mother Nature has given humans a gift in the form of plants. Most of today's medicines are derived from plant sources. However, whether the effect of a plant and its extract revealed in experimental animals and *in vitro* research can be expected in humans is a significant concern. Alkaloids, terpenoids, and flavonoids, which are found in certain plants from the Sikkim Himalayan region, are essential for fighting various ailments. Total 77 medicinal plants found in the Sikkim Himalayan region have proven anticancer activity in diverse cell lines. Further research can be conducted on those plants that have shown the most promising anti-cancer efficacy in previous studies, perhaps leading to low-cost plant-derived drugs from the Sikkim Himalayan region to combat the expanding cancer epidemic. Therefore, we are hopeful that in the near future, the therapeutic benefits of medicinal plants will be useful in treating sickness and displacing chemotherapy.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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