Acta Scientific Veterinary Sciences (ISSN: 2582-3183)

Volume 6 Issue 3 March 2024

Review Article

A Review on Anti-Cancer Properties of Medicinal Plants Endemic to the Himalayas

Reshma Sinha*, Babita Rana and Deepa Sharma

Department of Animal Sciences, Central University of Himachal Pradesh, India

***Corresponding Author:** Reshma Sinha, Department of Animal Sciences, Central University of Himachal Pradesh, India.

Received: January 29, 2024

Published: February 29, 2024

Abstract

Introduction: Cancer ranks high amongst the topmost causes of mortality globally. Several factors such as stressful living, pollution, irregular habitual activities, UV exposures and ionizing radiations, toxic drugs, and genetic alterations are contributing to enhanced incidences of cancer. Surgery, chemotherapy, and radiation therapy are conventional cancer therapies that often cause serious side effects on human health. Scientists are moving towards alternatives and exploring natural remedies such as plant extracts and natural products for both treatment and prevention.

Methodology: For the present article, research, review and official documents were referred which followed the keywords- endemic, herbal, extract, anti-cancer and Himalayas.

Results: The Himalayan region is the hub of endemic medicinal floras, which can be utilized in the curing of multiple ailments and disorders including cancer without causing serious side effects. In the current review article, we have documented 8 endemic medic herbs namely Bergenia ciliata, Cedrus deodara, Gentiana kurroo, Podophyllum hexandrum, Osmunda regalis, Nardostachys jatamansi, Coptis teeta, and Saussurea costus. Studies reporting the cytotoxic efficacies of extracts of these floras have shown significant results in the suppression of cancer cells in various animal models through DNA damage and activation of apoptosis-inducing enzymes. The review will provide basic information to the researchers interested in developing newer, safe, and standard herbal drugs to prevent and cure cancer.

Conclusion: Further greater extensive researches are required to document the unique medicinal floras of the Himalayan region and to explore their hidden potentials, bioactive compounds, and mechanism of anticancer activities to develop herbal drugs.

Keywords: Anticancer; Cytotoxicity; Endemic plants; Himalayas; Phytochemicals

Introduction

In the modern era, consuming processed and fermented food consisting of preservatives, and various types of ripening agents have led to the development of tumors over prolonged use [1]. Accumulation of toxins from fast food, and sodas; habits such as smoking, drinking, and chewing paan, unhealthy style of living, exposure to UV and ionizing radiations, toxic drugs, and pollution weaken the immune system making it prone to diseases such as cancer [1]. Cancer is a degenerative disease characterized by excessive cell development and multiplication. It ranks high amongst the topmost causes of mortality globally with roughly ten million fatalities attributed to it in the year 2020 (Table 1) [2].

It arises due to genetic alterations that disrupt the orderly process of cell division. These cells may form a mass called a tumor that can be either benign or malignant. A benign tumor can grow but cannot spread. While malignant cancerous tumors can migrate from their place of origin, attacking neighbouring tissues, and producing aggregates at the body's distant localities through a process called "metastasis". Tumors consisting of such malignant cells become more invasive and deadly gradually, destroying the tissues as well as organs necessary for an individual's survival. Cancer formation is essentially influenced by two kinds of genes: tumour suppressor genes and proto-oncogenes. When mutated, proto-oncogenes (HER2, BRCA1, BRCA2) can become carcinogenic oncogenes that

S. No.	Type of cancer	Cases of cancer (In millions)	Number of deaths
1	Breast cancer	2.26 million	6.85 lakhs
2	Lung cancer	2.21 million	1.80 million
3	Colon and rectum cancer	1.93million	9.16 lakhs
4	Gastric cancer	1.09 million	7.69 lakhs
5	Non-melanoma cancer	1.20 million	-
6	Prostate cancer	1.41 million	7.69 lakhs

Table 1: Global data on cancer types and cases recorded in 2020 [2].

induce excessive multiplication [3]. These mutations may cause the proto-oncogenes to produce too many growth-stimulatory proteins that are expressed incorrectly or inappropriately in normal cells. In contrast, tumor suppressor genes (p53, APC, INK4) contribute to cancer when they are inactivated by mutations [3]. Surgery, chemotherapy, and radiation therapy are traditional cancer treatments often complimented by other alternative remedies [1, 4]. Conventional therapies often possess potential side effects such as toxicity, sleep disturbance, limited bioavailability, depression, hair loss, anxiety, nausea, and vomiting. But at best, it adds a few years to the patient's life [1]. Therefore, alternative approaches need to be explored for cancer prevention and curing. Studies have exemplified the impact of natural remedies comprising of plants and herbal products to have a certain level of curative effect [1].

The Himalayas are a range of mountains in Southeast Asia that span roughly 2400 kilometres passing through various nations such as China, Afghanistan, Bhutan, India, Nepal, and Pakistan. The Indian Himalayas are divided into three longitudinal belts

- Outer Himalayas (the Shivalik range).
- Lesser Himalayas (lower/middle Himalayas).
- Greater Himalayas (higher Himalayas).

In the Himalayas Indian region, around 18,440 species are reported out of those 30% are endemic [5]. In the Kashmir Himalayas region of the north-western Himalayas, 312 plant species have been reported, out of which 153 are endemic including *Lilium polyphyllum, Aconitum chasmanthum, Gentiana kurroo,* and *Saussurea costus* (Table 2) [6].

S. No.	Botanical Name	Local Name	Name of family
1	*Lilium polyphyllum D. Don*	Kakoli/ksheerkakoli.	Liliaceae
2	*Aconitum chasmanthum*	Mohru/patis kauri	Ranunculaceae
3	*Gentiana kurroo Royal*	Trayman	Gentianaceae
4	*Saussurea costus*	Koot/Kushta	Asteraceae

Table 2: Endemic flora of Kashmir Himalayan region [6].

A report entitled "Conservation of Endemic Threatened Flora" has been released by the Research wing of Uttarakhand State Forest Department in 2020 [7] stating that out of 1145 total conserved species in the state, 46 species are endemic, of which 25 species are near-endemic, 10 are endemic to Uttarakhand, and 10 are endemic to the Himalayan region of India (Table 3).

Various endemic medicinal plants such as *Cedrus deodara* (Himalayan cedar), *Coptis teeta* (Indian goldthread), *Podophyllum* (Himalayan mayapple), *Saussurea costus* (Indian costus or kuth), *Pittosporum ericocarpum* (Doon cheese wood), and *Bergenia ciliata* (Winter begonia) have been found in the Himalayas [5, 6]. Most of these plants have anti-cancerous properties and are utilized in curing diverse cancers types like colon, breast, laryngeal, and tongue cancer (Table 4) [8-10]. Moreover, compared to modern symptomatic treatments, medicinal plants are readily available, inexpensive, and non-toxic [4,11].

Anti-cancerous medicinal plants endemic to the Himalayas

Gentiana kurroo

It is an annual plant with sturdy, fully formed, white to brown rhizomes that give rise to blooming stems, each having one to four blue-coloured blooms (Figure 1). The aerial section of the plant primarily consists of radical leaves at the base while the shoot is characterized by blooming branches containing cauline leaves [12].

Phytochemicals constituents

Gentiana plants are well recognized for their bittering flavour just because of the existence of key active compound secoiridoids in the form of swertiamarin, gentiopicroside, and sweroside [8]. Iridoid glycosides like gentiopicrin, 6-o-vaniloyl, aucubin, gen-

S. No.	Scientific Name	Local Name	Endemism
1	*Indopiptadenia oudhensis*	Gainti	Endemic to Western Himalaya
2	*Nardostachys jatamansi*	Jatamansi	Endemic to Himalaya (IHR)
3	*Aconitum hetrophyllum*	Atees	Pan Endemic in Himalaya
4	*Saussurea costus*	Koot/Kushta	Endemic to Himalaya (IHR)
5	*Gentiana kurroo*	Trayman	Endemic to Western Himalaya
6	*Cyathea spinolosa*	Tree fern	Pan Endemic in Himalaya
7	*Osmunda regalis*	Royal fern	Endemic to central and southern India
8	*Utricularia brachiata*	-	Endemic to northeast India
9	*Utricularia striatula*	-	Endemic to northeast India
10	*Angelica glauca*	Choru	Endemic to Himalaya (IHR)

Table 3: List of Uttarakhand region species endemic to the Himalayas' Indian Region [7].

Figure 1: *G. kurroo* a) Plant b) Flower [12].

tiamarin, and gentianin have also been discovered in *Gentiana*'s roots [12]. Additional phytochemicals extracted are gentiside, swertianolin, swertisin, and isogensitin [9].

Anti-cancer properties

Gentiana kurroo is widely utilized in ayurvedic therapies due to the anticancer efficacies of its phytoconstituents. It has been reported that the dose-dependent administration of root extracts suppress the development of cancer cells [8]. Extracts of root-stock and aerial sections of *G. kurroo* exhibited *in-vitro* cytotoxicity in pancreatic cancer, lung cancer, acute monocytic leukemia, breast, prostate, colon cancer, and lung carcinoma cells [8-9]. A study investigating the anti-cancer efficacy of the plant revealed its tetraploid cytotype with more cytotoxic potential than the diploid cytotype. Moreover, methanolic root-stock extract displayed higher anticancer efficacy in the colon cancer HCT-116 cell line at IC_{50} 5.65 µg/ml [9]. In another study, it has been revealed that methanolic root extract (10-100 µg/ml) suppress cancer cell growth in a dosage-related mode. At higher values (100 µg/ml), the extract suspended the growth of the THP-1 (87 ± 2.40) and HCT-116 (74 ± 2.57) cell lines while, at small doses (10 µg/ml), the extract exhibited anti-proliferative effect on the MiaPaCa-2 (39 ± 4.55) and THP-1 (37 ± 1.80) cells [8]. The extract induced the effect by reducing mitochondrial membrane potential along with the inducing apoptosis in MiaPaCa-2 cell lines and simultaneously blocked cell cycle progression thereby enhancing sub-resting phase/interphase cell populace, possibly by DNA fragmentation which resulted in apoptotic cell death (Figure 2) [8].

Nardostachys jatamansi

It is a tiny, annual, rhizomatic plant with long, stalkless, and oval-elliptical leaves (Figure 3b). Blooms are faded blue or pink colored; roots are present in form of deep grey-colored rhizomes capped with reddish to brown tuft-like petiole remnants of the radical leaves (Figure 3a) [20].

Phytochemical constituents

Nardostachys' plants reported to contain various phytochemical constituents such as α-patchoulenese, β-eudesemol, β-patchoulenese, β-sitosterol, jatamansin, jatamansinol, valeranal, valeranone, n-hexacosanol isolverate, nardol, norsechelanone, seychelane, volatile essential oils, etc. [4,11].Other phytoconstituents include nardin, nardal, patchouli alcohol, jatamol, jatamansic acid, malline, dihydrojatamansin, nardostachone, nardosinone, spirojat-

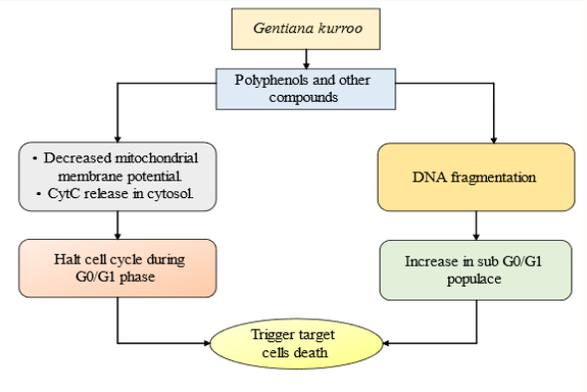

Figure 2: Mechanism of *Gentiana Kurroo* induced apoptosis in cancer cells [8].

Figure 3: *Nardostachys jatamansi* (a) Roots (b) Plant [20].

amol, jatamansinone, jatamansone, lupelol, pyrnocoumarin A and B, sesquiterpene acid, calarenol, coumarin, jatamansinol have also been discovered [4,11,20].

Anti-cancer properties

Several traditional medical systems have documented *N. jatamansi's* efficacy in treating lung, ovary, prostate, and liver cancer. In an investigation, the *N. jatamansi* methyl-alcohol extract exhibited higher cell growth suppression in MDA-MB-231cells (*half maximal inhibitory concentration*: 23.83 ± 0.69 micrograms/millilitres) and in MCF-7 cells (*half maximal inhibitory concentration*: 58.01 ± 6.13 micrograms/millilitres) as revealed by the MTT test. Fractions of petroleum ether and diethyl ether have demonstrated higher cytotoxic efficacy in MDA-MB-231cells (*half maximal inhibitory concentration*: 25.04 ± 0.90 micrograms/millilitres) and MCF-7 Cells (*half maximal inhibitory concentration:* 60.59 ± 4.78 micrograms/millilitres) [11]. *High-performance thin-layer chromatography* revealed the existence of lupeol, beta-sitosterol and other sesquiterpenes in *Nardostachys jatamansi* extracts/fractions which exhibited *in-vivo* cytotoxicity on these cancerous cells (Figure 4) [11]. In a comparative investigation analyzing the potency of different solvents, N-hexane *Nardostachys jatamansi* extract revealed maximum potency as the suppressor of neuroblastoma IMR-32 and SK-N-SH cells development in concentration-related mode [4]. It displayed 91% inhibition in the IMR-32 cells and 82% in the SK-N- SH cells at IC_{50} of 100 micrograms/millilitres [4].

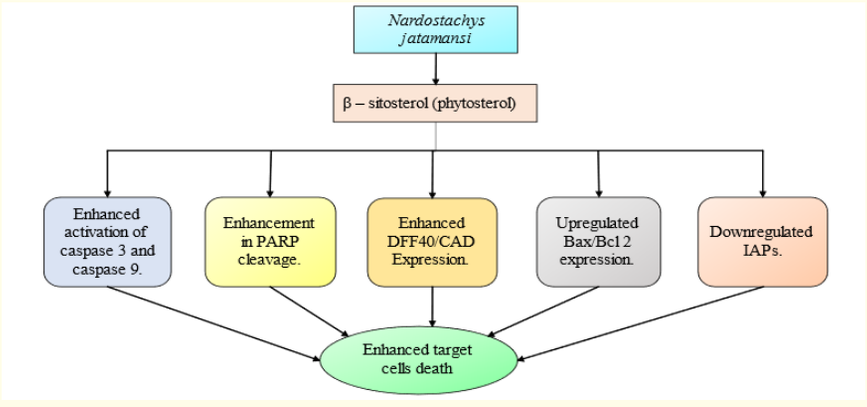

Figure 4: Mechanism of β-sitosterol-induced cell death in cancer cells [11].
Abbreviations: PARP: Poly-ADP ribose polymerase; IAPs: Inhibitor of apoptosis is protein

Podophyllum hexandrum

It is a smooth, upright, juicy plant with crawling, knotty rhizomes having several yellow to darkly brown roots; inexactly thirty to ninety cm long stem; ten to twenty cm long, circular leaves that look alike umbrellas; white to faded pink coloured blooms (Figure 5a); and two to five cm broad, and ovoid to ellipsoidal berry-like fruit (Figure 5b) [21].

Phytochemical constituents

Several lignans like podophyllotoxin, 4'-dimethyl-podophyllotoxin and 4'-dimethyl-deoxypodophyllotoxin, glycosides, tannins, flavonoids such as quercetin, terpenes, saponins, D-glycosides, proteins, calcium oxalate, mineral salts, wax, and volatile oils been reported in *P. hexandrum*'s rhizomes [21].

(a) (b)

Figure 5: *Podophyllum hexandrum* (a) Plant (b) Fruit [21].

Anti-cancer properties

Podophyllotoxin is widely used to develop newer carcinopreventive medications like etopophose, etoposide, and teniposide that are nowadays widely utilized in neuroblastoma, leukemia, moderate lung, liver and testicular cancer therapies [21,22] The semisynthetic derivatives of podophyllotoxin mainly function as DNA topoisomerase II blockers (Figure 6) [22].

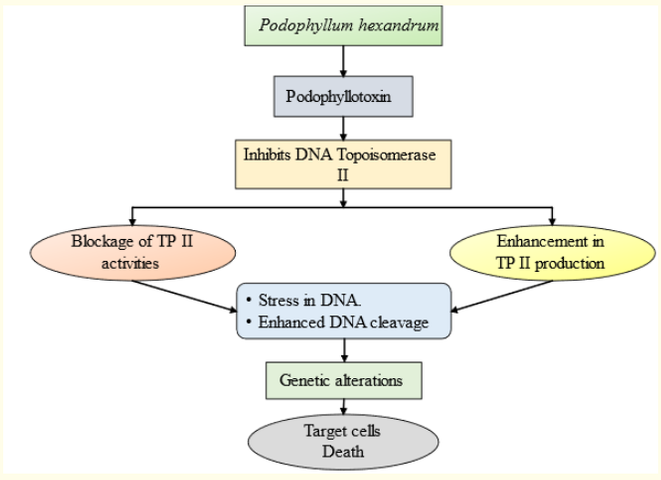

Figure 6: Mechanism of action of Podophyllotoxin against cancer cells [22].

Abbreviation: TP II: DNA Topisomerade II

In an ATP-dependent reaction, Topoisomerase II relaxes both +ve and -ve supercoils by incorporating a dual-stranded gap in one DNA duplex and transiting another duplex through it. The semisynthetic derivatives (teniposide and etoposide) of podophyllotoxin attach to this complex and inhibit the repair of the double-stranded gap, halting the cells in the late synthesis or early pre-mitotic stage [22]. In another investigation, methyl-alcohol and ethanolic extracts of *P. hexandrum* rhizomes displayed dose-dependent growth inhibitory effects in neuroblastoma, colon, lung, central nervous system, breast, and prostate cell lines [13]. At 100 µg/ml concentration, 70% ethanolic and methanolic extracts displayed higher growth suppression of 86% and 85% growth suppression against the Colo-205 colon cancer cells [13].

Saussurea costus

It is a thin, erect, and up to two meters tall annual plant (Figure 7a). Roots are extended with a conspicuous fragrance (Figure 7b); membranous blooms are black or darkish violet coloured, sticky, and asymmetrically marked, while the fruit is hair-covered [14,23].

(a) (b)

Figure 7: *S. costus* (a) Plant (b) Dried roots.

Phytochemical constituents

On phytochemical analysis of *S. costus* roots various secondary metabolites namely terpenoids, lignans, flavonoids, glycosides, steroids, and essential oils (lactone, costunolide, and sesquiterpenes), aldehydes, alcohols, ketones, lupeol, palmitates, dihydroneoclovene, saussureal, and betulinic acid have been reported [14,23-24].

Anti-cancer properties

On administration, the root extract of costus demonstrated anti-cancerous effects on several cancer types including lung, prostate, oral, stomach, and esophageal cancer due to the existence of cancer-suppressing agents like dehydrocostus lactone, cynaropicrin, costunolide, and sesquiterpenes [14,23]. It has been revealed that by suspending TNF-alpha-instigated phosphorylation and destruction of I-kappa B alpha proteins in HL-60 cells, dehydrocostus lactone blocks NF Kappa B activities and enhances the activities of caspase-8 and caspase-3 which make HL-60 cells vulnerable to TNF-alfa induced apoptosis (Figure 8) [23]. It was also discovered that Costunolide, which is an efficient apoptosis inducer expresses its action by instigating reactive oxygen species-mediating mitochondrial permeability transition and releasing cytochrome complex in the cytosol (Figure 8) [24]. Thus *S. costus* instigated cancer cells' demise by halting them in the post-mitotic gap phase of the cell cycle or by the intrinsic mitochondrial route [14].

Coptis teeta

It is an annual, stemless, flowering herb that grows up to 30-50 cm (Figure 9a). Compound leaves are five to twenty cm in size, smooth, and with lobular epipodium; small, white to yellow blooms; rhizomes bear adventitious roots and are up to fifteen cm in length (Figure 9 b). Blooming occurs in the spring season while fruiting occurs in late spring-early summer [25].

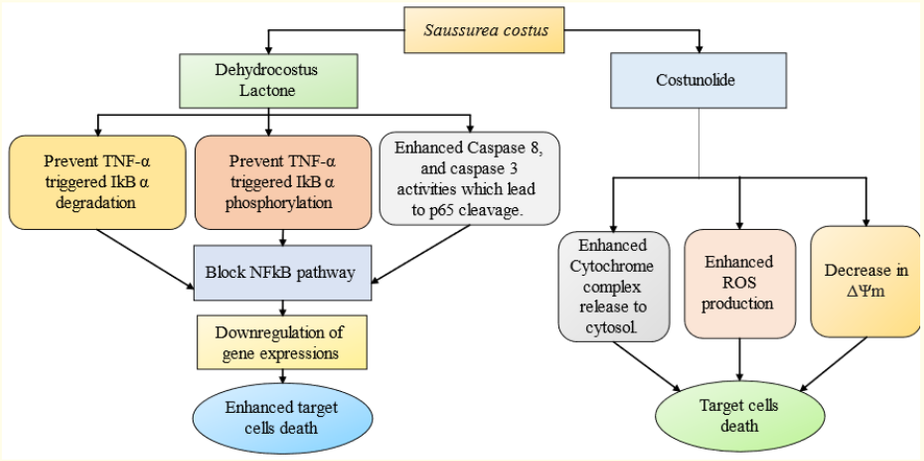

Figure 8: Mechanism of dehydrocostus lactone and costunolide- induced cell death in cancer cells [23,24].
Abbreviations: ROS: Reactive Oxygen Species, ΔΨm: Mitochondrial memnrane potential.

Figure 9: *C. teeta* (a) Plant (b) Dried rhizomes [25].

Phytochemical constituents

In the roots of *C. teeta*, 6.0-8.5% berberine and various alkaloids including coptina and epiberberine have been reported. It was also reported to contain jatrorrhizine, trans linoleic acid, fatty acid esters, ketones, phytosterols fixed oil, albumin, coloring compounds, lignin, extractive sugars, phenylpropanoids, saccharides, and steroids [15,25-26].

Anti-cancer properties

Multiple investigations demonstrated that berberine *via* the production of ROS causes apoptosis in diverse cancer cells like the pancreas, breast, lung, cervix, colon, leukemia, liver, ovary, and prostate cancer [15,25-26]. It has been reported to regulate the actions of Bcl-2 and Bax in the colon cancer cells (Figure 10) [26]. It was also revealed to exhibit anti-cachectic activities which were explored in athymic mice.

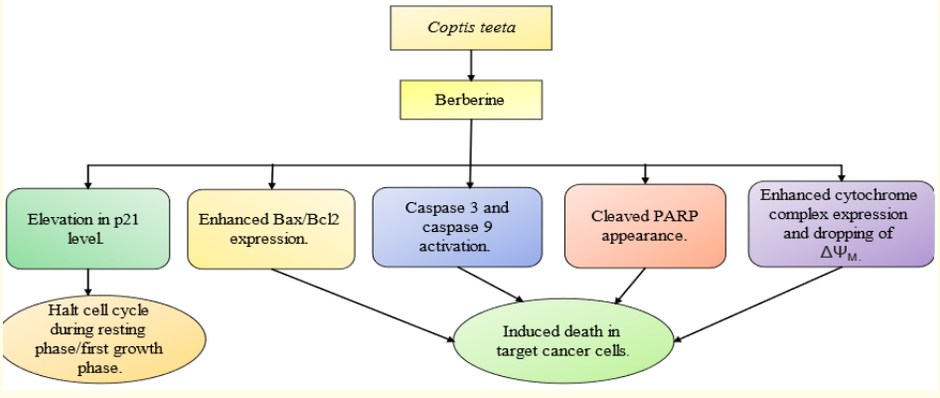

Figure 10: Mechanism of action of berberine-induced cell death in cancer cells [26].
Abbreviations: PARP: Poly-ADP Ribose Polymerase, ΔΨm: Mitochondrial Membrane Potential

Bergenia ciliata

It is a straight, fleshy, perennial rhizomatous plant found growing on rocky cliffs up to 35cm. Leaves are spreading, glabrous, and few in number (Figure 11 b); petioles are 1-2 cm long, with a hook-like outgrowth occurring at the lower or upper half; flowers are white or pink (Figure 11a), and fruits are capsule-like Solid, and rigid rhizomes are covered with root scars; have a pungent taste and a characteristic, slightly camphoraceous odour [16,27].

Phytochemical constituents

In the preliminary phytochemical screening of *Bergenia ciliata* rhizomes flavonoids, glycosides, saponins, sterols, and terpenoids, compounds like (-)-3-O-galloylcatechin, (-)-3-O-galloylepicatechin, arbutin, bergenin, phenols, leucocyanidin, tannins, gallic acid, tannic acid, paashanolactone, afzelechin, and catechin, were discovered [16,17,27].

Figure 11: *B. ciliata* (a) Flowers (b) Leaves.

Anti-cancer properties

When administered to Hep3B, and PC-3 cancer cell lines *B. ciliata* rhizomes exhibited dose-dependent cytotoxicity with methyl-alcohol (IC_{50}: 29.25 ± 2.50 µg/ml, 27.68 ± 1.32 µg/ml), and aqueous extracts (IC_{50}: 75.53 ± 3.68 µg/ml, 25.46 ± 2.95 µg/ml), and triggered apoptosis [17]. It has been demonstrated that *B. ciliata* ethyl acetate fraction with IC_{50} 0.76 and 0.773 mg/ml is a potent anti-cancerous as evident in Ht144 and H157 cell lines, and the aqueous extract having IC_{50} 0.3-0.36 mg/ml in H157 cell line [16]. *B. ciliata* ethanolic root extract also triggered cell death in cancer cells by targeting UPR pathways (Figure 12) [27].

Osmunda regalis

It is a tall, perennial, deciduous, herbaceous fern (Figure 13a) characterized by a short, erect, and scaleless rhizome (Figure 13b). Sporangia are devoid of indusium and occur at the outer edge of pinnules and on the underside. The chlorophyll-bearing spores are trilete, green, and dispersed in the form of a ball-shaped tetrad [28].

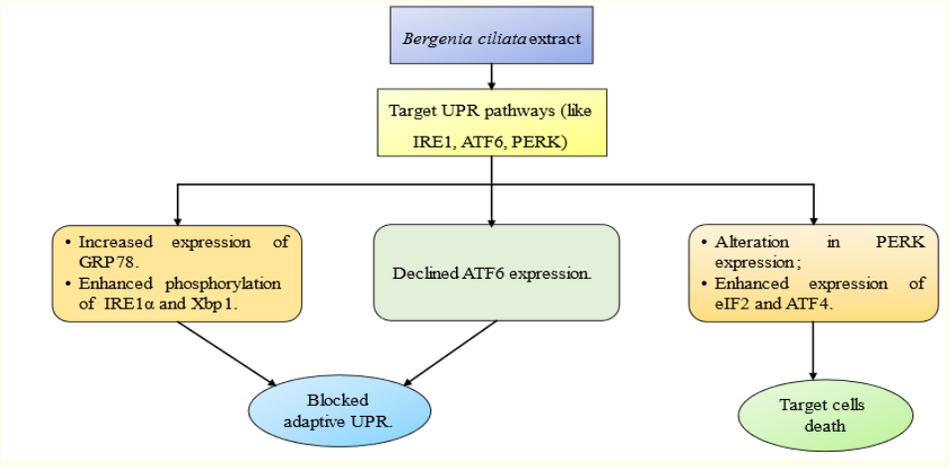

Figure 12: Mechanism of action *B. ciliate* ethanolic induced cell death in cancer cells [27].
Abbreviations: UPR: Unfolded Protein Response, PERK: Protein Kinase R-Like Endoplasmic Reticulum Kinase

Figure 13: *O. regalis* a) Plant [28] (b) Rhizome [18].

Phytochemical constituents

On the phytoconstituents assessment of German-origin *O. regalis*, ketoaldehydes, alkanediols, and esters have been reported [28]. About 39 components including hexacosanal, hexahydrofarnesyl acetone, γ-palmitolactone, tricosane, 1-heptacosene, butylphenol, and phytol have been reported in the essential oils [28]. In the volatile oils, alkylated phenol, carbonylic compounds, diterpene alcohol, hydrocarbons, monoterpene, and terpenoid ketones have been reported [28].

Anti-cancer properties

It has been reported that the roots of *Osmunda regalis* have anticancer efficacies and are used to heal tumors [18,28]. At 6µg/ml-90µg/ml concentrations, ethanolic root extracts exhibited significant anti-proliferative action on different neck and head carcinoma cells. Higher growth suspension was reported in HlaC78 with an EC_{50} value of 21.4 µg/ml followed by FaDu cells with an effective concentration of 8.5µg/ml. Toxic effects have been reported to be regulated by p-glycoprotein and by suppressing migration on ECM [18]. Higher motility inhibition on laminin was evident in the HlaC78 cell line coupled with gene expression alteration of integrins, proteases, VCAN, KAL1, and other genes participating in metastases and adherence of cells (Figure 14). *The* extract was revealed to instigate HNSCC cells' demise and to prevent endothelial cell tube development [18].

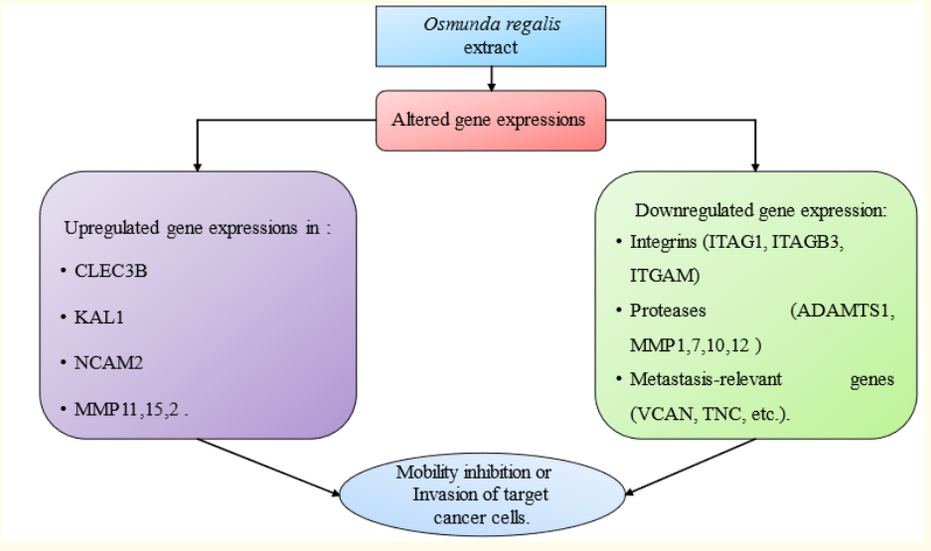

Figure 14: Mechanism of action *O. regalis* mediated mobility inhibition or invasion of cancer cells [18].

Cedrus deodara (C.D.)

It is a large annual tree, up to eighty-five meters tall with broad, spreading, wrinkled-black branches (Figure 15a); triangular leaves that resemble needles (narrow, large, and conical); shoots are dimorphous; blooms are typically bisexual; however, few trees or tree-limbs usually have unisexual blooms and cones are usually elongated to bell-like or may be circular (Figure 15b) [10,19,29].

Phytochemical constituents

Almost 105 phytoconstituents like terpenoids (Himachalol, Allohimachalol, Himadrol, Dewarol, Dewardiol), flavonoids (Cedeodarin, Dihydromyricetin, Cedrin, Cedrinoside), phytosterols, lignans, volatile oils, and few multifarious constituents have been identified in multiple portions of *Cedrus.* In the needle and wood oil, terpenoids were the most typical category of the constituents that have been extracted [29]. A sesquiterpene named himachalol was extracted from the needle's chloroform extract and in wood oil [29]. Additionally, β-himachalene was also explored in deodar's essential oil [10,29]. Likewise, in needle oil, eight flavonoids like 2R, cedrusone A, myricetin, 3R-DMY, quercetin, and cedrin were discovered [19, 29]. Additionally, four dihydroflavonols namely cedrin, cedrinoside, dihydromyricetin, and cedeodarin were explored in the cedarwood [29]. Besides these phytoconstituents, some lignans like cedrusinin, wikistromol, dibenzylbutyrolactol, and benzyrolactol have been reported in cedarwood powder [19].

Figure 15: *Cedrus deodara* (a) Tree (b) Cones [29].

Anti-cancer properties

Traditionally, *Cedar* was utilized in curing colon, ovarian, and liver carcinoma [10,19,29]. In an investigation, remarkable concentration-dependent suppression was observed in colon, prostate, liver, cervix, neuroblastoma, and breast cells at 10, 30, and 100 µg/ml of lignan concentration. On comparing the IC_{50} values, each constituent (wikistromol, matairesinol, and Benzylbutyrolactol) of *C. deodara* lignan compositions demonstrated cytotoxic efficacy by synergism effect [19]. The cytotoxic efficacy of phytoconstituents isolated from Cedar was accompanied by the triggering of cell death [19]. In another study, the MTT assay evaluated the *cytotoxic* efficacy of total flavonoids (needles) and indicated a dose-dependent inhibitory activities in liver carcinoma HepG2 cells at IC_{50} of 114.12 µg/ml. The study revealed total flavonoids exhibit cytotoxic efficacy by regulating the cell cycle and triggering cell death (Figure 16) [30].

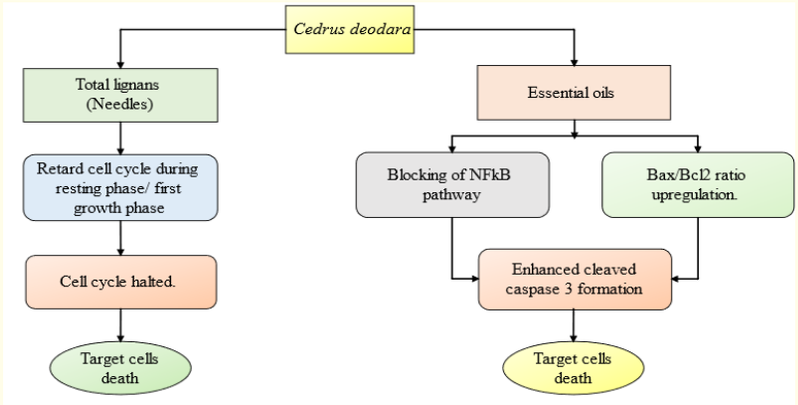

Figure 16: Mechanism of action *C. deodara* total and essential oils induced cell death in cancer cells [10,30].

Another study revealed the *in-vitro* anticancer efficacy of *C. deodar* essential oil against colon cancer HCT-116 (IC_{50}:11.88 µg/ ml) and SW-620 (IC_{50}:14.63 µg/ ml) cells. It was reported that essential oil's cytotoxic efficacy might be accredited to the termination of the NFKB signaling route which suppressed cancer cells' growth thereby instigating their demise [10].

Future Prospectives and Conclusion

After reviewing the existing literature available on the floras of the Himalayan region it has been concluded that the Himalayan region is extremely abundant in medicative floras. Most of these medicinal herbs including *Aconitum hetrophyllum, Angelica glauca, Bergenia ciliata, Cedrus deodara, Coptis teeta, Gentiana kurroo, Lilium polyphyllum, Osmunda regalis, Nardostachys jatamansi, Podophyllum hexandrum, and Saussurea costus*, are endemic to the Himalayas. Since ancient times, many of these plants including *Bergenia ciliata, Cedrus deodara, Osmunda regalis, and Saussurea costus* have been used in treating several diseases and disorders including cancer without causing any serious side-effect. The anticancer efficacies of these medicative floras are due to existing secondary metabolites or bioactive compounds including flavonoids, polyphenols, tannins, lignans, and essential oils. In addition to anticancer properties, these plants also have anti-diabetic, antimicrobial, antioxidant, hepatoprotective, and several other medicinal benefits. But, many of the endemic medicinal plants are still not documented. Hence there is a greater need of documenting and establishing a record of the current status of medicative floras endemic to the Himalayas and to explore their hidden potential, bioactive compounds, and mechanism of anticancer activity in order to develop newer herbal drugs useful in cancer treatment.

Declarations

- **Funding:** No funding was received for current project.
- **Competing Interest**: Authors declare non-conflict.
- **Animal Ethics:** Nil.

Bibliography

1. Nataru S., *et al*. "A review on medicinal plants as a potential source for cancer". *International Journal of Pharmaceutical Sciences Review and Research* 26 (2014): 235-248.

2. World Health Organisation report on Cancer (2022).

3. Weinberg RA. "How cancer arises". *Scientific American* 275 (1996): 62-70.

4. Pandita RM., *et al*. "Evaluation of in vitro Cytotoxicity of Nardostachys jatamansi Roots extracts and Fractions against neuroblastoma human cancer cell lines". *Journal of Pharmacy Research* 5 (2012): 2720-2722.

5. Singh P and Dash SS. "Plant Discoveries 2013: New Genera, Species and New Records". Botanical Survey of India, Kolkata (2014).

6. Hussain Mir A., *et al*. "Ecology, distribution mapping and conservation implications of four critically endangered endemic plants of Kashmir Himalaya". *Saudi Journal of Biological Sciences* 27 (2020): 2380-2389.

7. Forest Research, Uttarakhand. "Conservation of endemic threatened floras: List of endemic species to Indian Himalayan region (2020).

8. Wani BA., *et al*. "Induction of apoptosis in human pancreatic MiaPaCa-2 cells through the loss of mitochondrial membrane potential (ΔΨm) by Gentiana kurroo root extract and LC-ESI-MS analysis of its principal constituents". *Phytomedicine* 20 (2013): 723-733.

9. Jeelani SM., *et al*. "*In-vitro* cytotoxicity in relation to chemotypic diversity in diploid and tetraploid populations of Gentiana kurroo Royle". *Journal of Ethnopharmacology* 274 (2021): 113966.

10. Bhagat M., *et al*. "*Cedrus deodara* (Bark) Essential Oil Induces Apoptosis in Human Colon Cancer Cells by Inhibiting Nuclear Factor Kappa B". *Current Topics in Medicinal Chemistry* 20 (2020): 1981-1992.

11. Chaudhary S., *et al*. "Evaluation of antioxidant and anticancer activity of extract and fractions of Nardostachys jatamansi DC in breast carcinoma". *BMC Complementary and Alternative Medicine* 15 (2015): 1-13.

12. Sharma A., *et al*. "Gentiana kurro's physiology and pharmacological properties: Recent update and future perspective". *Maejo International Journal of Energy and Environmental Communication* 4 (2022): 12-22.

13. Ganie SA., *et al*. "Long dose exposure of hydrogen peroxide (H2O2) in albino rats and effect of Podophyllum hexandrum on oxidative stress". *European Review for Medical and Pharmacological Sciences* 15 (2011): 906-915.

14. Shati AA., *et al*. "Secondary metabolites of saussurea costus leaf extract induce apoptosis in breast, liver, and colon cancer cells by caspase-3-dependent intrinsic pathway". BioMed Research International (2020).

15. Zhu M., *et al*. "Up-regulation of microRNAs, miR21 and miR23a in human liver cancer cells treated with Coptidis rhizoma aqueous extract". Experimental and Therapeutic Medicine 2 (2011): 27-32.

16. Ahmed M., *et al*. "Antioxidant, anticancer and antibacterial potential of Zakhm-e-hayat rhizomes crude extract and fractions". Pakistan Journal of Pharmaceutical Sciences 29 (2016): 895-902.

17. Rajkumar V., *et al*. "Anti-neoplastic activities of Bergenia ciliata rhizome". *Journal of Pharmacy Research* 4 (2011): 443-445.

18. Schmidt M., *et al*. "The influence of Osmunda regalis root extract on head and neck cancer cell proliferation, invasion and gene expression". *BMC Complementary and Alternative Medicine* 17 (2017): 1-12.

19. Singh SK., *et al*. "Chemically standardized isolates from Cedrus deodara stem wood having anticancer activity". *Planta Medica* 73 (2007): 519-526.

20. Shati AA., *et al*. "Secondary metabolites of saussurea costus leaf extract induce apoptosis in breast, liver, and colon cancer cells by caspase-3-dependent intrinsic pathway". BioMed Research International (2020).

21. Kalam MA., *et al*. "Medicinal importance of Papra (Podophyllum hexandrum Royle) in Unani system of medicine". *Journal of Complementary and Integrative Medicine* 18 (2021): 485-490.

22. Kumar J., *et al*. "Conservation Status, Anticancer Compounds and Pharmacological Aspects of Royle: A Review Podophyllum hexandrum". *Indian Journal of Ecology* 49 (2022): 1096-1102.

23. Oh GS., *et al*. "Dehydrocostus lactone enhances tumor necrosis factor-α-induced apoptosis of human leukemia HL-60 cells". *Immunopharmacology and Immunotoxicology* 26 (2004): 163-175.

24. Lee MG., *et al*. "Constunolide Induces Apoptosis by ROS-mediated Mitochondrial Permeability Transition and Cytochrome C Release". *Biological and Pharmaceutical Bulletin* 24 (2001): 303-306.

25. Payum T. "Distribution, Ethnobotany, Pharmacognosy and Phytoconstituents of Coptis teeta Wall.: A Highly Valued and Threatened Medicinal Plant of Eastern Himalayas". Pharmacognosy Journal 9 (2017): S29.

26. Murthy KNC., *et al*. "The natural alkaloid berberine targets multiple pathways to induce cell death in cultured human colon cancer cells". *European Journal of Pharmacology* 688 (2012): 14-21.

27. Qadri O., *et al*. "The methanolic extract of Bergenia ciliata attenuates cancer by modulating Unfolded Protein Response in HeLa cells". *International Journal of Advanced Research in Science, Engineering* 7 (2018): 2711-2719.

28. Bouazzi S., *et al*. "Cytotoxic and antiviral activities of the essential oils from Tunisian Fern, Osmunda regalis". *South African Journal of Botany* 118 (2018): 52-57.

29. Bisht A., *et al*. "Cedrus deodara (Roxb. ex D.Don) G.Don: A review of traditional use, phytochemical composition and pharmacology". *Journal of Ethnopharmacology* 279 (2021): 114361.

30. Lee MG., *et al*. "Constunolide Induces Apoptosis by ROS-mediated Mitochondrial Permeability Transition and Cytochrome C Release". *Biological and Pharmaceutical Bulletin* 24 (2001): 303-306.