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A Research on the Exploration of Some Anti-Cancerous Medicinal Plants of in the Northern Hemisphere Atmosphere

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Abstract:- Since earlier times of human history, many plants have been known, identified, studied, and used for various medicinal purposes and can be regarded as the basis of modern medicine. Kingdom Plantae has an essential metabolism thatcan develop various types of compounds on a large scale, which can be utilized by various industries like pharmaceuticals toobtain and produce a new variety of innovativemedicines. Various compounds like vinca, taxol, camptothecin, and epipodophyllotoxin can be extracted from various species of plants as anti-cancer properties are present in them having the ability to treat the cancer cells.

The mostpopular as well as essential anticancer drugs extracted from the plants are Taxol, camptothecin, vinca alkaloids,as well as podophyllotoxins along with their semisynthetic and synthetic derivatives. The continuous search for antitumor and anticancer agents from plant sources is essential to figure out various ways for safe and effective treatment for many health-related problems.

In India as well as in other countries, herbal plants serve as essential contributors, especially in the pharmaceutical industries. Plants found at higher altitudes like the Himalayas have an assault for diverse testing, including mutagenic UV radiations, droughts, strong winds, and desiccation. Even the secondary metabolites extracted from certain plant parts, such as polyphenols, terpenes, and alkaloids,are well known to possess various antimutagenic and anticancer properties.

According to ethnobotanical historical sources, various uses and wide applications of medicinal plants have led to more attention. Many natural products having various significant chemical structures are isolated as anticancer agents. Certain side effects occur due to chemotherapy whereas natural therapies like the utilization of plant-derived products in cancer treatment do not cause such adverse effects. Thus, the protection of medicinal plants by import and export monitoring trade is highly symbolic and the best way tothe conservation of medicinal plants is through plant cultivation.

Keywords:- *Modern medicine, Medicinal plants, UV radiations, Droughts, Strong winds, etc.*

I. INTRODUCTION

Cancer is acting as an aggressive killer in the world.Clinically, the novel synthetic chemotherapeutic agents are not working so well tomeet expectations, and instead of their consideration costs about 17 million deaths occur due to cancer per year(Thun et al.,2010). In spite ofthe decade ofmedical research and advancements, problems like cancellation remain a big huddle in the healthcare system (Yabroff et al.,2011).

India is known as a leading country for having scientific literaturehighlighting concealed phytochemical, ethnomedicinal,and pharmacological aspects.Moreover,a large part of the Himalayan region comes beneathh Indian Territory constituting a strong and effective traditional system (Mathur and Joshi, 2013).

Cancer is regarded as a primordial disease which is evident from the record of fossil bones and mummies found in Egypt(Mackay et al.,2006).According to studies, after cardiovascular diseases, cancer is regarded as the highest cause ofdough(Park et al.,2008).

About 50% of anticancer drugs employed these days are obtained fromnaturally occurring products or are isolated as either semisynthetic or synthetic compounds,out of which plants act as essential sources(Newman&Cragg,2012).

6500 years old text from Rigveda has an emphasis on the use of Himalayan plants for various medicinal uses (Malla and Shakya, 1984). Himalayas serve as the planet's largest biodiversity zone accounting for plant resource diversity(Kala&Mathur,2002).Every year of deaths due to cancer are reporting various Himalayan countries such as India, Nepal,and Pakistan (Akhtar,2007;BBhatia et al.,2011).

Identification, as well as evaluation of effective anticancer plants along with their mechanisms and uses, may be beneficial for novel drug development which will then be employed for the treatment of cancer(Krishnaswamy,2008 About 10 million new cases are diagnosed every year with occurrence of approximately 6million deaths all over the world(Hanif et al.,2009;Ismail et al.,2012).By 2030,WHO projected about 11 milliondeaths(WHO.,2007).

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Approximately more than ten thousand medicinal plants reported from the Himalayas are known to support primary health care as well as the livelihoods of about a 600million people in the area(Shengji,2001). The Indigenous aspect of knowledge is applied for the formation of different ethnomedicine is essentialfor the treatment of cancer(Gautam,2011).Medicinal plants have contributed a lotto the discovery of anticancer drugs like camptothecin, podophyllotoxin, paclitaxel, and taxol (Oberlies & Kroll, 2004; Singh et al.,2013).

The International Agency for Research on Cancer has estimated the chances of prevalence and mortality about the disease. About 14.1 million cases of cancer were reported and then they further resulted in about 8.2 milliondeaths along with 32.6 million patients suffering froma disease like cancer as per the 2012 census of 184 countries worldwide.(WHO,2016)

Globally, cancer is known to be the major mortality as well as morbidity cause.Moreover, apart from cardiovascular diseases,cancer has become the 2nd most leading consequence of death among communicable diseases (Sener et al.,2005). Incidence, as well as mortality of cancer, is more in countries likeNew Zealandand Australia if compared with other parts of the world (Parkin&DM,2004). Thecases of deaths occurring because of cancer are supposed to elevate from 7.1 millionin 2002 to 11.5 million in 2030 across the globe(Mathers&Loncar,2006).

Medicinal plants form an essential constituent of health care for the population as they are greatly used in terms of traditional and modern medicines(Luseba etal.,2010).An important income source is being provided to rural as well as urban people as a trade value for global trade whose estimation is accounted to be 32.6 billion per year(Brinckmann.,2016).Apart from accessibility and productivity,climate change affects the phytochemical content of the existing populations which potentially affects the pharmaceutical properties(Gairola et al.,2010).

Despite the considerable development cost, novel synthetic chemotherapeutic agents which are in use were unavailable to fulfilling expectations(Coseri,2009).Thus, a need for developing new, effective, and affordable anticancer drugs arises. Over the past 30years, natural products have been receiving much attention for having great efficiency as a cancer therapeutic cum preventive agent(Newman,2008).The plant kingdom act as the most significant source as about sixty percent of drugs employed in the treatment of cancerisextractedfromnaturally occurring sources(Gordaliza et al.,2007).

II. TOXICITY DUE TO CHEMOTHERAPEUTIC TREATMENT

Consistent discovery and development have given rise to the collection of various chemotherapeutic agents although treatments involving such drugs are not even devoid of their self-intrinsic problems. As a result of chemo therapeutic treatment, many toxicities are produced like 5-fluorouracil which also behaves like a vasospastic and may cause myelotoxicity and cardiotoxicity. (Macdonald,1999)

Cardiac toxicity(Rexroth&Scotland,1994) toxicity of the renal system(Manila et al,1995), as well as myelotoxicity(Andreux et al.,1994), may be caused by Doxorubin whereas Bleomycin causes pulmonary toxicity(Golding et al.,1982)along with cutaneous toxicity(Klaus et al.,1973).Cyclophosphamide helps in the treatment of many malignant conditions and may cause bladder toxicity and which may be in the form of immune suppression, alopecia, hemorrhagic cystitis, and cardiotoxicity (Fraiser,Kanekal&Kehrer,1991).

Medicinal plants serve to have a common alternative for the treatment of cancer among different countries and more than 300 plantsare being identified to exhibit anti-cancer properties worldwide. Data reflects products duct derived from plants have a 10% to 40% incidence of cancer treatment at the global level,reporting about 50% of patients from Asia(Cassileth&Deng,2004)whereas the estimation of anticancer herbal product cost is approximately about 5 billion dollars per year(Jong et al.,2006).

III. PLANTS AS A SOURCE OF DRUGS

The natural compounds obtained from plant source has an essential role in pharmacological activities and Taxol, Vina alkaloids, Camptothecin and podophyllotoxins along with their semisynthetic derivatives are examples of such cooperation(Malik et al.,2014).

Compounds having therapeutic properties in plants were identified by scientists andare thus used to treat various diseases(Shankari&Gurunathan,2015).

As per World Health Organization,curcumin can be taken into consideration to study the decreased rates of cancers likecolorectal,lung, and prostate in India and it is under clinical trials to study its safety and effectiveness(Dahmke et al.,2014).The anticancer action of green tea from Camellia Sinensisalong with its main constituent like an epigallocatechin-3-gallate about various tumor cell-relatedmodels, althoughmanystudies are still required forprovingtheir role as anticancer drugs(Rahmani et al.,2015).

IV. DEMANDS FOR MEDICINAL PLANTS

Successful trials have been made in drug development originating from plants concerning clinical development. As they have non-toxic effects on normal cells while cytotoxic effects on cancer cells and keeps them under the huge requirement. Some species are investigated and selected by various developing countries like Africa or Asia practicing herbal therapies with their enormous use in cancer treatment(Ochwang et al.,2014).

It was estimated by the World Health Organization in 2007 that the trade based on plant-derived drugs contributed about US$100 billion approximately and by 2050,it is expected to reach US$5 trillion.Factors like deforestation, population growth along with rapid urbanization are

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contributing to an issue of protecting medicinal plants which is a need oeveryan hour as many medicinal plants having high value are being threatened and are on the verge of extinction due to over-exploitation(Parveen et al.,2013).

V. PLANT METABOLITES EXTRACTED FROM THE NATURAL SOURCES

For about 60,000 years approximately, plantshave been used as medicines having the ability of cocktail production by secondary metabolites accounting for a broad and wide range of pharmacological properties exhibiting anticancer activity (Kuttan et al.,1997).Phenolic compounds such as flavonoids account to be the most pro mis plant-derivativessecondary metabolites which are useful in treating cancer(Asensi et al.,2011;Wahl et al.,2011)

All the extracts which have been reported so far would be able to show replication in their anti-cancer effects in larger-scale tests, and that may be essential in making them compatiblewithvarious strategies employed duringthe treatment of cancer(Fritz et al., 2013; Ioannidis, 2005).

Tubulin depolymerization is inhibited by Paclitaxel which stabilizes the microtubule cytoskeleton and block mitosis in a manner depending upon concentration(Wani &Horwitz,2014).There are various other molecular anti-cancer agents which are found in plants naturally like genistein,lycopene, and resveratrol which are under further clinical trials(Bosviel et al., 2012; King-Batoon et al., 2008).

Several pregnane glycosides as well as alkaloids are some other examples of plant-obtainedmetabolites that show anticancer activity in vitro and serve to inhibit breast growth and prostate cancer lines(Jagadeesh et al., 2007).

Non-psychoactive cannabinoids have also been reported to show anti-tumor activities (McAllister et al., 2015) and likewise, such activities are beingreported foran increasing number of secondary plant metabolites (Schnekenburger et al., 2014).

VI. SOME ANTI-CANCER MEDICINAL PLANTS OF THE NORTHERN HEMISPHERE ARE AS FOLLOWS

S. No.	Botanical Name	Common Name	Plant part used
1.	*Tinospora cordifolia*	Miers	Stem, root
2.	*Curcuma longa*	Turmeric	rhizome
3.	*Ziziphus nummularia*	jujube	root,stem,bark,seed and flower
4.	*Cedrus deodara*	Deodar	Resins, bark
5.	*CentellaAsiatica*	Pennywort	The w*hole* plant, especially leaves
6.	*Andrographis paniculata*	creat	Roots, leaves
7.	*Phyllanthus amarus*	Gale of wind	Whole plant
8.	*Mappia foetida amruta*	Amruta	Whole plant
9.	*Taxus baccata*	English yew	pollen,needles,root,stem,bark, and wood
10.	*Podophyllum peltatum*	Indian May apple	rhizomes
11.	*Taraxacum officinale*	Common dandelion root	root

A. Tinospora cordifolia (Wild) Miers

- **Botanical name**-Tinospora cordifolia
- **Common name**-Miers
- It is also known as -Guduchi, Giloya, Heartleaf moonseed plant
- **Plant part used**-stem,roots

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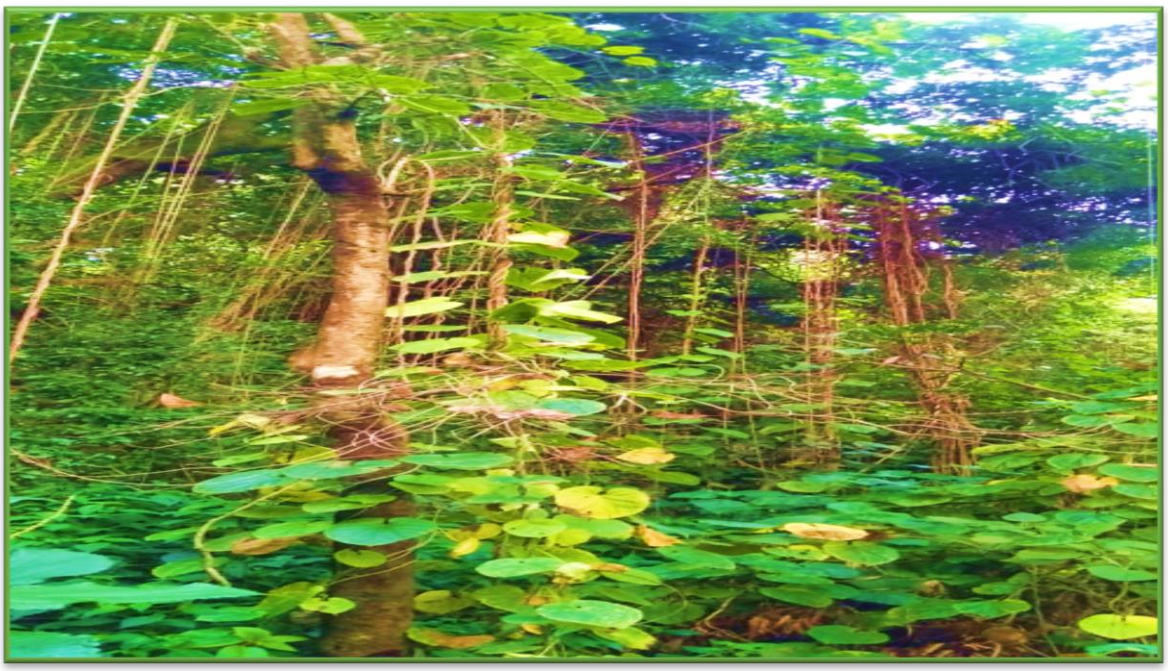

Fig. 1: *Tinospora cordifolia* (Captured at district MANDI)

It is a smooth, bulky, deciduous shrub devoid of bristles.

Tinospora cordifolia is among the noncontroversial and largely used herbs in Ayurveda medicine. It belongs to the Menispermaceae family. It is also known as amrita because of its ability of imparting vitality andlongevity.The stem of this plant is beneficial in treating debility,fever,jaundice,dyspepsia,jaundice,anemia,vomiting, piles,and certain skin diseases(Srivastava et al.,2003).It's roots have curative properties useful as an antidote for snakebites (Wang et al.,1991).Apart from this it also has some beneficial properties in modern medicine as it is immunomodulatory and adaptogenic along with essentialanti-inflammatory, antiarthritic as well as anti-oxidant properties(Chitre et al.,2004).The roots of this plant contain various alkaloids such as choline, Neosporin,isocolumbin,columbin,palmatine tetrahydropalmatine, and magnoflorine(Qazi et al.,2008).

Tinosporacordifolia helps in killing HeLa cells in vitro and this indicates that it can act as an anti-cancer agent thus its extract shows an increase in tumor-free survival capacity which is dose-dependentalong with the highest survivors(Vidyasagar et al.,1998).

Leaves of Tinospora are protein-rich which accounts for 11.2% and also constitutes calcium as well as phosphorus.Diterpene compounds are active adaptogenic constituents that include diasporic acid,Tinospora,cordifolisides,yellow alkaloid,groin,and berberine along with certain polysaccharides like arabinogalactan polysaccharide(Winston et al.,2007).

VII. ANTI-CANCER ACTIVITY IN *T.CORDIFOLIA*

Response Surface methodology(RSM) is used Methodology alkaloid palmatine from Tinospora cordifolia species which then indicates anticancer efficiency in dimethylbenz anthracene DMBA inducing skin cancer concerning animal models like mice.Before 24 hours of cyclophosphamide(50mg/kg) administration,a single dose of Tinospora extract that is 200,400 and 600mg/kg dry weight respectively helps in preventing the formation of micronucleus in the bone marrow of mice(Ali& Dixit,2013).

An increase in the life span along with a decrease in the size of the turn with comparison to the control was studied at a dose of 750mg/kg body weight C57 BI mice were administrated with 50% of Tinospora cordifolia methanolic extract consecutively for 30 days(Verma et al.,2011).It was also found in a study that anti-brain cancer potential accounts for 50% ethanolic Tinospora cordifolia extract along with the use of C6 glioma cells (Mishra&Kaur,2013).

Cell proliferation was reduced by TCE ina dose-dependent manner whereas it helped in inducing differentiation in C6 glioma cells.Then it was reported that all the extracts taken were much more active in response to KB as well as CHOK-1 cells while palmatine was known to be much more responsive against the KB and HT-29;yangambin against the KB cells whereas tinocordiside against the KB and CHOK-1(Bala et al.,2015).

Two molecules were marked as hexane and methanol fractions and represented as T1 and T2. Tinospora cordifolia plant showed that inthe case of MCF-7 cells,T1 treatment suppresses the process of proliferation and invasion,thereby increasing E-cadherin transcription while the migration of MCF-7 cells is mainly regulated by T1 as compared with T2(Shilpa et al.,2015).

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VIII. VARIOUS CHEMICAL CONSTITUENTS OF *T.CORDIFOLIA* ARE AS FOLLOWS

CHEMICAL	PRESENT IN(plant part)	ACTIVE COMPOUND PRESENT
Sesquiterpenoid	Stem	Tinocordifolin
Glycosides	Stem	Furanoid diterpene glucoside, 18-norclerodane glucoside,Cordioside, Cordifolioside A, Cordifolioside B,Cordifoliside C, Cordifoliside D, Cordifoliside E Palmatosides C, Palmatosides F, Syringin, Syringin-apiosylglycoside, Tinocordiside,
Steroids	Aerial part Stem	β -sitosterol, δ-sitosterol, 20 β- hydroxy ecdysone. Ecdysterone, Makisterone A, Giloinsterol
Diterpenoid lactones	Whole plant	Furanolactone, Clerodane derivatives, Tinosporon, Tinosporides, Jateorine, Columbin
Alkaloids	Stem as well as Root	Palmatine,Choline, Berberine, Tembetarine, Magnoflurine, Tinosporin, Tetrahydropalmatine,Isocolumbin, Palmatine,Magnoflurine
Aliphatic compound	Whole plant	Heptacosanol, Octacosanol

A. Curcuma longa

- **Botanical name-**Curcuma longa
- **Common name-** Turmeric
- It is also known as Haridra, Haldi
- **Plant part used-** rhizome

Fig. 2: Curcuma longa (Captured at YS Parmar University, SOLAN)

It has the ability of proliferation inhibition in a large variety of tumor cells which accounts for its anticancer potential (Aggrawal & Kumar et al.,2015).This anti-proliferative potential can be related to the property of down-regulating the expression of various genes like NF-kappa B,Activator Protien1 or AP-1,Lysyl oxidase(LOX),Cycloxygenase 2(COX2),Nitric Oxide Synthase(NOS),Epidermal Growth Receptor 1(EGR-1),Matrix Metallopeptidase 9(MMP-9) as well as Tumor Necrosis Factor (Shen et al,2002).

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It also causes inhibition of the action of c-Jun kinase present at the N-terminal as well as inhibits kinase and serineproteins.Turmeric causesa reduction in the expression of surface adhesion molecules,chemokines,cyclins, and growth receptors such as EGFR,and HER2 (Agrawal&Kumar et al.,2015).

Turmeric also helps in the inhibition of tumor cell invasion along with themetastasis process occurringin vitro as it reduces MMP-2 action and also inhibits cell invasion of HEp2 (Chakrabati, Banerji, Chatterjee & Das et al.,2006).Various studies show that apoptosis is induced by curcumin.It also leads to proliferation inhibition andinterrupts the progression of thecell cycle(Chen&Huang,1998).Inhibition of proteinslike tyrosine kinase and kinaseCalong with suppression of(c-myc mRNA)and up-regulation (of B-cell lymphoma 2 mRNA expression);curcumin is supposed to exert its anti-proliferative as well as apoptotic effects(Chen&Huang,1998).

A rapid decrease in membrane potential of mitochondria is caused due to Curcumin, the release of cytochrome c,caspases3, and 9activation along with anti-apoptotic protein downregulation and inhibition of Apoptosis protein leading to apoptosis occurring in vitro(Goswami et al.,2004;Kumar et al,2004)

Multiple molecular targets along with enzymes, proteins, transcription factors,cytokines, and cell cyclesare revealed as experimental evidence (Sharma et al.,2005;Shishodia et al.,2005).

IX. ANTI-CANCER ACTIVITY

A polyphenol (Diferuloylmethane) Curcumin is derived from the Curcuma longa plant called turmeric whose constituents are much more active.Out of all such constituents,curcumin is the most active as found in research.Rawturmeric, it is present between 0.3 to 5.4% and it is non-toxic comprising numerous therapeutic properties(Cikrikci et al.,2008).

Anti-cancer pigment known as curcumin is exhibited by Curcuma longa that can cause inhibition of cancer growth under in-vivo as well as in-vitro conditions(Sharma et al.,2006). The activityof proliferation of cells is suppressed by it in different cancer cell lines and is also known to cause tumor inhibition(Sahu et al;Mehta et al).

G1/S arrest along with induction of apoptosis is also seen as an effect of curcumin apart from a mitotic block found in various cell lines of tumors(Shishodia et al.,2005; Sa&Das et al.,2008).

It shows the effect on various biological pathways which are involved in activities like oncogene expression, mutagenesis, apoptosis, metastasis, tumorigenesis, and regulation of the cell cycle.It also acts as a radiotherapy enhancer as it leads to cancer cell arrest during phase G2/M in the cell cycle,where various cells show increased susceptibility towards various cytotoxic effects caused because of radiotherapy (Wilken et al.,2011).

A. Ziziphus nummularia

- **Botanical name-***Ziziphus nummularia*
- **Common name-**jujube
- It is also known as bhukamtaka,harbor, and wild jujube.
- **Plant part used-**root,stem,bark,seed and flower

Fig. 3: *Ziziphus nummularia* (Captured at HAMIRPUR)

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It is a shrub or can be called a thorny bushhaving purplish stems with velvet-like prickles present in pairs.It is found in the countries like India, Afghanistan, Pakistan, Iraq, Iran, Egypt, and Israel.

Within the bark and stem of this plant, some chemicals are present like Betulin and Betulinic acid which exhibit antitumor properties(Urban et al.,2005).Cytotoxicity is generated by glycosides of Betulinic acid so that cancer cell lines aremuch more sensitive as compared to the normally occurring cells(Legault et al.,2006).Betulinic acid is a pentacyclic triterpenoid that occurs naturally and marks cytotoxicity in response to different cell linesabout tumor(Eiznhamer et al.,2004)

Betulinicacid can cause destruction of cancer cells which are even muchmore resistant towards some other chemotherapeutic agents.It is also known for inducingthe apoptosis process through the production of ROS,inhibiting topoisomeraseI,activating mitogen protein kinase cascade,inhibiting angiogenesis,modulating pro-growth transcriptional activators along with aminopeptidase-N activity(Eiznhamer,ZQ,Xu et al.,2004).

The effect as a result of apoptosis of anticancer drugs targeting various cell lines of tumor is potentiated by betulinic acid, which includes *p53* mutant cells, along with primary tumor cells, and not byfibroblast cells of humans,which indicatesthe specificity of the tumorto some extent (Simone et al.,2005).

B. Anti-cancer activity

In Z.nummularia medicinal properties are present in a tremendous amount which can be confirmed by the presence of secondary metabolites having a unique and wide number of therapeutic properties.This plant constitutes of 16 glycosides and flavonoids along with 64 glycosides as well as 14 terpenoids.

C. Phytochemistry (Ziziphus nummularia)

The presence of various alkaloids, flavonoids, saponins, triterpenoids, and fatty acids has been marked about the phytochemistry of *Ziziphus nummularia.*

PHYTO-CHEMICALS	COMPOSITION	REFERENCE
Alkaloids	Nummularine-T, a 13-membered formylcyclopeptide alkaloid is extracted from the bark of Z. nummularia with spectroscopic as well as chemical methods used to establish its structure.	(Singh&Pandey,1995)
Cyclopeptide alkaloids	Two peptide alkaloids namely nummularine-M as well as nummularine-N are extracted by the Z.nummularine.Out of these two Nummularine-M is a 14-membered cyclopeptide belonging to intergerrinine while nummularine-N is a 13-membered cyclopeptide similar to nummularine-B.	(Pandey et al.,1984)
Glycosides& saponin	A newly synthesized dammarane saponin called Zizynummin is extracted by the dry leaves of the Ziziphus nummularia designated as structure β-Dglucopyranosyl-(1 → 2)-6-deoxy-α-L-talopyranosyl-(1 → 3)-α-Larabinopyranosyl-(1 → 3)-jujubogenin.	(Sharma et al.,1983)
Glycosides	25S-spirostane was known to be extracted as well as characterized as nummularogenin,25S-3 alpha-hydroxy-5 alpha-spirostane-2,12-dione.	(Srivastava et al.,1984)

D. Cedrus deodara

- **Botanical name-** Cedrus deodara
- The name ‘Deodar’ is derived from the Sanskrit name ‘deodar which means ‘timber of the god’.
- **Common name-** Deodar
- It is also known as Himalayan cedar,Devdar.
- **Plant part used-**Resins,bark

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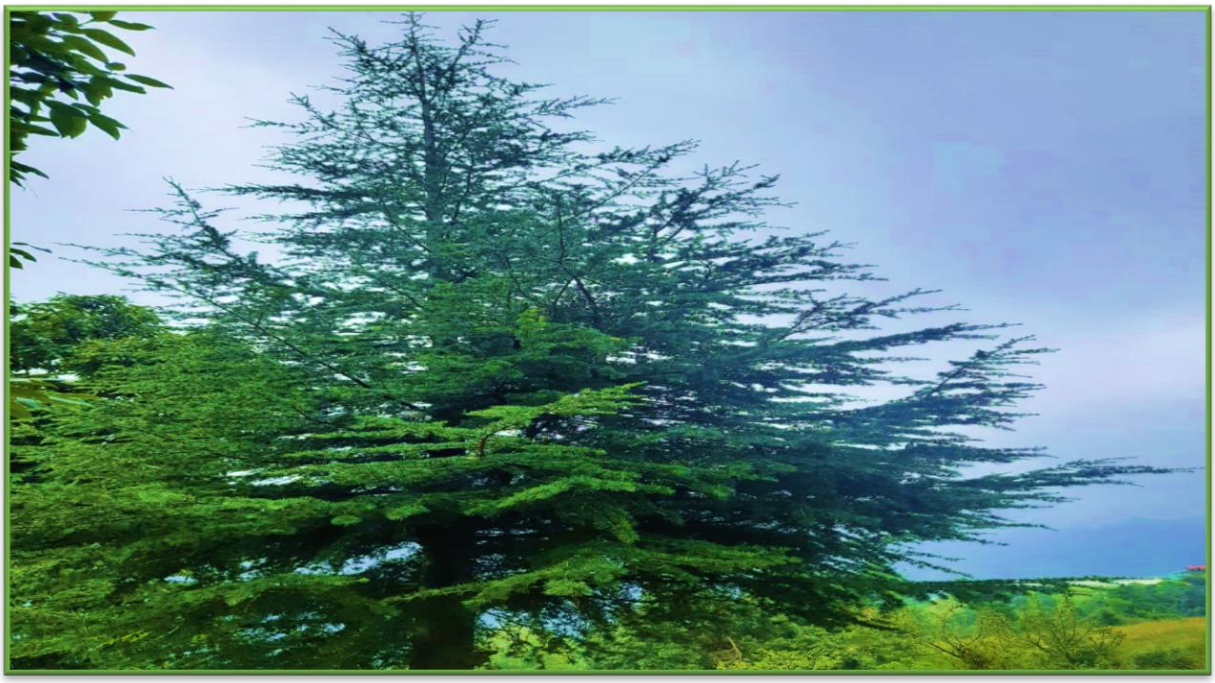

Fig. 4:*Cedrus deodara*(Captured at queen of hills, SHIMLA)

It is found in countries like Afghanistan, Pakistan, India, Nepal, and Tibet.

Its bark is used in the treatment of fevers,rheumatoid arthritis,ulcers,diarrhea,dysentery, and cancer as a remedy (Kirtikar et al.,1918).Oil is extracted from Cedarwood and it has various applications as it exhibits anti-inflammatory,anti-diabetic as well as anti-ulcer properties and acts as an expectorant, arthritis pain reliever and catarrhal in the respiratory tract(Desai et al.,2008).

Resins have anti-obesity properties which areeffective in cleaning the respiratory tract by reducing cough and cold. Insecticidal as well as antifungal properties are also exhibited by the*Cedrus*oil. Stem wood leads to the production of lignin composition which exhibits cytotoxicity in cancer cell lines of humans (Jaswant et al.,2006).

Some studies show that the lignin mixture mediates early formation of NO which leads to the activation of caspases,generation of peroxides along with depolarization of mitochondria which is ultimately the reasonfor mitochondrial-dependent as well as independent apoptotic pathways that result in destroying leukemia cells(Shashi et al.,2006).

E. Centella Asiatica

- **Botanical name**-*Centella asiatica*
- **Common name**- pennywort, leafspade
- It is also known as mandukaparni,brahmamanduki
- **Plant part used**-Whole plant especially leaves

Fig. 5:*CentellaAsiatica* (Captured at YS Parmar University,SOLAN)

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It is found in various countries like Australia, Malaysia,India,New Guinea,Iran,India, and the Pacific islands. Transformed cell lines proliferation along with the Ehrlich tumor cells ascites along with Dalton's lymphoma tumor cellsascites are inhibited by partially purified C.Asiatica dose fractions(Kuttan et al.,1995).It is also known to suppress the proliferation of fibroblast cells present in mouse lungs. Studies also show that development ofsolid and ascites tumors was slowed and the span of life in the case of tumor-bearing mice was increased through the oral administration of C.Asiatica extract and this mechanism which showsemphasis on the antitumor activity exhibited byC.*Asiaticaa*andwas recommended to cause a direct inhibition inthe synthesis of DNA(TD Babu,1995).

A number of compounds like hydrocotyline, ballerina, asiaticoside,sterol ,thankunosides,stigmasterol, flavonoids, and ascorbic acid are present in C.*asiatica* extract(R Sharma&J Sharma,2005)

Anti-elastase activity is exhibited by this plant and thus it acts like a free radical scavenger.It decreases the ATPase, Mg^{+2} ATPase, Na^{+}-K^{+} ATPase levelsand leads to an increase in the Ca^{+} ATPase level and such processes then help in defending the tissue against the reaction of peroxidation, showing protection from cell damage and highlighting its anticancer property(Singh et al,2008).

F. Andrographis paniculata

- **Botanical name-** *Andrographis paniculata*
- **Common name-**creat
- It is also calledbhunimba,kalmegha,Kiryat,king of bitters, and chiretta.
- **Plant part used-** roots and the leaves

It is found in various countries like India and Sri Lanka.

Extract of A. paniculata constitutes of flavonoids,diterpenes, and stigmasterol. It is identified as diterpene lactone because of its structure which seems ring-like. It also hasa colorless crystalline structure with a bitter taste(Taylor et al.,1992).It has the ability to activate both antigen-specific as well as non-specific immune responses thus it is also regarded as potent-stimulator.It acpotentstimulatorive agent and is much effective against many infectious as well as oncogenic agents(Saxena et al,1993).

Cytotoxic activity is observed in response to different cancer cell varieties(Tewari et al.,2010).Examples of such cells where andrographolide has cytotoxic activity are p388 lymphocytic leukemia cells,KB human epidermoid cancer cells,HCT-116 colon cancer cells along with MCF-7 cancer cells(Surbur et al.,2007).It causes growth inhibition in cancer cells of the colon and further enhances development along withperipheral blood lymphocyte divisions exerting prodifferentiative effects upon myeloid leukemia M1 cell line present in mouse(Kuroyangi et al.,1994).In immune-competent Swiss albino mice, in-vivo results showed that andrographolide leads to inhibition of proliferative cancer cells devoid of any toxicity symbols even at increased doses(Nirmal et al.,2016).

Fig. 6: *Andrographis paniculata*(Captured at YS Parmar University,SOLAN)

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G. Phyllanthus amarus

- **Botanical name-** Phyllanthus amarus
- **Common name**-Gale of wind
- It is also known as bhumyamalaki and jaramla
- **Plant part used**-The whole plant including leaves, roots, and shoots

It can be found at tropical Asia, especially in the warmer regions ofcountries like India.

Various constituents like lignans, flavonoids, and tannins are present in*P. amarus*.Itsextract is known to exert antitumor effects while its oral administration leads to an increase in the life span and reduce the size of the tumor in mice having DLA(Dalton;s lymphoma ascites) and EAC(Erlich ascites carcinoma).This plant has the property to cause metabolic inhibition of carcinogenic compounds,inducing the arrest of cell cycle arrest and interference inthe DNA repair process (Joy et al.,2002).

P.amarus extract shows DNA polymerase inhibition in the hepatitis B virus and it also causes down-regulation of the hepatitis B virus, mRNA transcription along withtranslation (Gupta et al.,1996).It has been shown to cause inhibition ofaniline hydroxylase,a P-450 enzyme that contributes to a reason for carcinogen activationand its extract also inhibits CDC 25 tyrosine phosphate activity which accounts for the key enzyme employed in the regulation ofthe cell cycle(Kuttan et al.,2000).

It has an anti-angiogenic effect on mice having Lewis lung carcinoma and is known to interrupt vascular endothelial cell migration(Yang et al.,2006)

Fig. **7:** *Phyllanthus amarus* (Captured at YS Parmar University,SOLAN)

H. Mappia foetida

- **Botanical name**-Mappia foetida amruta,
- **Common name**-Amruta,Kalgur,Narkya whole plant
- **Plant part used**- whole plant

It is found in tropical countries and has acquired attention at the international level.An active and effective constituent of its tree wood is camptothecin which is a potent chemotherapy drug employed for leukemia treatment(Wall&Wani.,1996).Moreover, an endophytic fungus that grows on such plants also produces substances like camptothecin(Verma et al.,2005).Camptothecin serve to have a broad spectrum of antitumor activities.They also exhibit anti-neoplastic activity which leads to inhibitory action upon nuclear enzymes like DNA topoisomerase and topo-1(Potmesil,1994).Various clinical trials have been done in order to access the anti-cancer action of camptothecinalong with their analogs and such trials have revealed a wide range of actions against leukemia, lymphoma, and epithelial tumors(Rowinsky et al.,1993).

I. Taxus

It is a genus of 12 species that are distributed across thenorthern hemisphere,amongwhich about 4 species are present in North America,1 in Europe,and others are native to Southeast Asia.

- **Botanical name**-Taxus baccata
- **Common name-** English yew
- **Plant part used**-pollen,needles,root,stem,bark and wood

Taxus has been into consideration after several studies(Triangle Research Institute,NC,USA) and as novel anticancer dipteaene amide which is also known as ‘taxol’ was discovered from the extract obtained from the yew bark(Wani et al., 1971; Edgington, 1991). Taxus constitutes various compounds including taxane, derivatives,flavonoids, and polysaccharides.An oxygen-rich diterpene known as taxol is of great significance as it can be employed in the inhibition of cancer cell growth.

Taxus species show slow growth with 1.5-2 years of seed dormancy(Steinfeld, 1992).Taxol shows significant action inmalignant melanoma treatment, lung cancer, and other kinds oftumors(Wickremesinghe&Arteca, 1993, 1994).

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It is a diterpene alkaloidthat has been derived from Taxus spp. having a high market value which is approximately more than $1 billion each year(Malik et al.,2011).Taxol stabilizes microtubules and inhibits the process of depolymerization into tubulin that then stops the cell cycle atthe G2/M phase causing the death of cells(Schiff et al.,1979;Horwitz,1994).

Yew trees related to taxus are common and distributed in the Northern Hemisphere and are classified into eight species based on their geographical location (Cope 1998; Gupta 2015).

Plant culture is regarded as the most relevant and efficient way for sustainable production of thetaxol along with concerned taxoids at the industrial level.(Exposito et al.,2009)Since 1990,the taxol's biotechnological production had been started through cell culture obtained from the taxus.(Fett-Neto et al. 1992; Wicremesinhe and Arteca 1993).

Successfully it has been isolated from other Taxus speciesincluding various plant parts like pollen,needles,bark,root,stem, and wood (Wani et al., 1971; Vidensek et al., 1990; Wither up et al., 1990; Fett-Neto et al., 1992;Wickremesinghe&Arteca, 1994).Extraction procedures show that about 7,000kg of bark is required in order to produce 1Kg taxol(Cragg et al.,1993).

J. Podophyllum

- **Botanical name**-Podophyllum peltatum
- **Common name**-Indian May apple
- **Plant part used**- rhizomes

It is found in Indian Himalayas,Bhutan,Pakistan,Afghanistan,Nepal,China, and Taiwan. Podophyllum in India has beendistributed amongthe restricted regions of the Himalayan zone at an altitude ranging from2000-4000m.a.s.l.(Bhadula et al.,1996)It is an herbaceous as well as rhizomatous species with much medicinal importance which was announced to be in danger of getting extinct by CITES in 1989(Foster,1993).Its rhizomes are used for extraction of podophyllotoxin lignin which then produces semi-synthetic by products, teniposide, etoposide that are used for cancer treatment(Bruneton,2009).

Since 1966,routes for podophyllotoxin synthesis have been improved(Gensler&Gatsonis,1966) although this is still not viable commercially because of its complicated and complex structure thus there is a need for podophyllotoxin production as along with that derived anticancer drugs have also been known to stimulate exploration of another sources of the plant(Gordaliza et al.,2004;Malik et al.,2014).

K. Taraxacum officinale

- **Botanical name**- Taraxacum officinale
- **Common name**-Common dandelion root
- **Plant part used**- root

It is quite popularfor its medicinal properties existing invarious cultures and is employed for treating diseases like anemia, hepatitis, cirrhosis, cancer and inflammation. It has also been used in Jordan folk medicine for male infertility treatment(Tahtamouni et al.,2016).

An effective antimicrobial as well as anti-cancer drugs having cheap cum eco-friendly nature can be developed by dandelion-mediated synthesis of nanoparticles as stated in a study(Saratale et al.,2018)and some recent in-vitro studies also show that anti-cancer potential for an aqueous dandelion root extract constitutes of cancer cell-killing effect on colon cancer cell models(Bahrambeygi et al.,2014).

In vitro apoptosis activity can be induced in hepatocellular carcinoma cells of humans(Yoon et al.,2016).It has thepotential which leads to induction of apoptosis and autophagy in case of human pancreatic cells causing no specific effect on the noncancerous cells(Venezuela et al.,2021).

It contains taraxerol,saponins,taraxasterol,sesquiterpenes,flavonoids as well as phenoliccompounds which are known to have the anticancer property(Ivanov et al.,2018).

X. PLANTS ACTING AS EXPRESSION SYSTEMS

Tropical rainforests as well as coral reefs are well known to harbor moleculeplethora which is undiscovered along with similar or greater efficiency as anti-cancer reagents although modes of action are still unknown (Mukherjee et al.,2001;Pereira et al.,2018).This perspective is endowed with much huge damage as well as the destruction of forests and reefs concerning extinction of various species(van Oppen et al.,2017)

Many plant species are employed as an expressionsystem for the recombinant therapeutic proteins inaddition to native protein production along with anti-cancer activity(Spiegel et al.,2016).The plant used in case of recombinant therapeutic proteins is regarded as molecular farming whereas the medical relevance in association with such proteinsis of therapeutic importance(Buyer,2015;Fischer et al.,2013).

Plants are beneficial in context with biopharmaceutical manufacturing as they are capable of producingvarious complex proteins along with thesignificant post-translational modifications having low-cost upstream production inheriting safety based on human pathogen inability to cause replication in the plants giving rise to the potential for smooth as well as flexible production accounting at a larger scale(Buyer et al.,2017).

Some natural compounds obtained from plant source show an essential part in the activities related to pharmacology and Taxol, Vina alkaloids, Camptothecin, and podophyllotoxins along with their semi-synthetic derivatives are examples of suchcooperation (Malik et al.,2014).

Plant-derived drugs contributing tovarious types of research as well as clinical trials are as follows:

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ANTICANCER AGENT	EXTRACTED FROM	ACTIVITY	REFERENCE
Paclitaxel	*Taxus*	Block mitosis, induce apoptosisand cause inhibition of translational machinery	(Jordan et al.,2005;Che et al.,2015;Park et al.,2002)
Pomiferin	*Maclurapomifera*	inhibits oxidative damage of DNA, Pro-apoptotic effects, DNA fragmentation, Pro-apoptotic effects	(Amin et al.,2009)
Epigallacotechin-3-gallate	*Catechin* (green tea)	Inhibition of cyclin-dependent kinases	(Raza&John,2005;Hakim et al.,2003)
Roscovitine	*Raphanus sativus(Brassicaceae*)	decrease in cell cycle progression	(Cragg et al.,2005;Shah et al.,2013)
Flavopiridol	*Dysoxylumbinectariferum((Meliaceae*)	growth inhibitory effects, Anti-inflammatory, activate tyrosine kinase	(Newcomb,2004;Cragg et al.,2005)
Noscapine	Opium poppy (*Papaver somniferum*)	inhibits tumor growth and progression&shows antiproliferative properties	(Kaur et al.,2015;Henary et al.,2014)
Combretastatin A-4 phosphate	*Combretum caffrum*	Anti-angiogenic, shows vasuclar shut-down of tumors and tumor necrosis	(Shah et al.,2013;Cragg et al.,2005)
Sulphoraphane	cruciferous vegetables	Induces phase II detoxification enzymes, tumor growth inhibition in breast cancers, showingantiproliferate effects	(Tracy et al.,2007;Comblatt et al.,2007;Heiss et al.,2001)
Epipodophyllotoxin	*Podophyllum peltatum*	Pro-apoptotic effects; cell cycle interference	(Shah et al.,2013)

XI. NANOPARTICLES ACTING AS CARRIERS IN ANTI-CANCER AGENTS RELATED TO PLANT VIRUSES

Nanoparticles acting as carriers in the site-specific delivery of anti-cancer agents have gained much interest since many years (VanderMeel et al.,2017).These particles are proteinaceous and biodegradable in nature. With only about 104 formulations of polymers in the field of the clinical trials in comparison to 2800 trails for mAbs,thus it can be stated that success as anapplicable approval of anti-cancer nanoparticles is stillinadequate (Venditto&Szoka,2013).

Size of nanoparticles may have hindered the success rate by reducing tumor penetration efficiency,or even due to some uncertainties regarding biocompatibility as well as biodegradability of nanoparticles in vivo,potentially causing their accumulation inside the body with long term side-effects which are still unknown(Lammers et al., 2012).

Study shows that particles of Cowpea mosaic virus with different lengths deprived of cargo anticancer drugs lead to spectacular collapse in case of solid tumors within the three days, when directly administrated into the tumors(Lizotte et al.,2016).

Based on native research, plant virus nanoparticles like Potato virus X or Cowpea mosaic virus are used for presenting HER2 epitopes as an anti-cancervaccine(Shukla et al.,2017)and for delivery of compounds constituting small molecules targeting towards specific cells which is leads to the reduction in side effects related with chemotherapy(Le et al.,2017).

XII. ENVIRONMENTAL CONDITIONS AFFECTING MEDICINAL PLANTS

Environmental conditions are being altered at some areas which create unideal and unsurvival conditions for species inhabiting them although suitable range for species is specified and medicinal plants then narrow and move substantially as per changes in the climate. The risk due to which species won't be able to migrate increases because of habitat fragmentation (Pompe et al.,2008).

Phenological change leads to disruption in relationship between pollinators and other commensal organisms(Kharouba et al.,2018). Factors like smoking tobacco,alcohol consumption, infections caused due to the Helicobacter pylori,Hepatitis B &C,environmental polluntantsleading to genetic mutations(Futreal et al., 2004; Park et al., 2008).

An additional threat of unsustainable harvesting pressures is exhibited by medicinal plants of high value(Cho et al.,2014).There is a wide demand for the medicinal plants including illegal harvesting has become a serious problem leading to decline in species abundance as well as average stature(McGraw,2001);(Case et al.,2007). Complete extinction of valued species occurs due to factors like commercial harvest and destruction of habitat including decline in size as well as abundance(Kiehn,2007).For example snow lotus (*Saussurealaniceps* Hand.-Mazz), goldenseal (*Hydrastis canadensis*), *silphium* (*Ferula* sp.)(Law&Salick,2005);(Albercht&McCarthy,2006);(Brinckmann et al.,2020).

About more than ten thousand Himalayan medicinal plants are known to support primary health care as well as livelihoods of about 600million people of the area(Shengji,2001).Indigenous knowledge is essential in the preparation of different ethnomedicines for treating cancer like diseases(Gautam,2011).Medicinal plants have contributed muchto the discovery of anticancer-related drugs like camptothecin, podophyllotoxin, paclitaxel, and taxol (Oberlies&Kroll,2004;Singh et al.,2013).Conservationists have recognized the unsustainability of herbaceous root harvesting and have regarded related medicinal plants to be under a higher threat(Verma et al.,2007;Maori,2011).Secondary metabolite production like polyphenols,alkaloids, and terpenes have been reported for anticancer properties on tbasicsisof physiological adaptations in the biochemical profile of plant tissues(Bhatia et al., 2011).

XIII. SUMMARY & CONCLUSION

Only chemotherapy is the most preferred way for cancer treatment despite many side effects this idea of using natural as well as harmless ways like ethno-plants exhibiting anti-cancerous properties is of significant importance to health as well as biodiversity exploration.

The study states that there is a huge variety of discovered and undiscovered anti-cancerous plants in the northern hemisphere. More research and exploration in this regard would be highly beneficial to pharmaceutical industries which would contribute towards the increase in the economy and improvement in health-relatedsectors.

Such actions will lead to the promotion of medicinal plant cultivation to maintain access for local people along with the preservation of traditional knowledge and values preserving their sustainable use.Ex situ seedbanking as well as assisted migration can be beneficial for preventing the extinction of useful species at the global level.

XIV. FUTURE ASPECTS

Access to medicinal plants creates resilience which focuses on the decline due to the increase in environmental extremes and economic losses as a result of climate change. Thus,actions by local and national governments and ethnobotanical communities are of great significance in helping the people as well as communities who are dependent upon medicinal plants for income, medicine, or health care.

- Medicinal plants are considered rich resources of ingredients that can be used in drug development of pharmacopeial, non-pharmacopeial, or synthetic drugs.
- Part of that, these plants play a critical role in the development of human cultures around the whole world.
- Medicinal plants are also used for water purification.
- Medicinal Plants can be used in big sewage treatment plants for pure water instead of using chemical components.

- **DATA AVAILABILITY:** No data were used to support this study.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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