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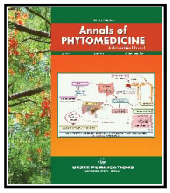

Review Article : Open Access

Anticancer structure activity relationship of podophyllotoxin of various species of Podophyllum

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Abstract

Since ancient times, Podophyllum species possess significant anticancer compounds. An Indian species of Podophyllum, it also goes by the name Himalayan mayapple. *Podophyllum hexandrum* Royale, sometimes known as *Podophyllum emodi* Wall. ex Hook. f. is a rare priceless Indian medicinal plant, spread between 2000-4000 meter an above sea level in the Himalayan foothills. It is a perennial herbaceous plant that is also seen in remote regions of India's cold desert (Ladakh). Podophyllotoxin (4 per cent dry weight), which has cytotoxic and antitumor effects; although is also employed, is one of the most important in the diagnosis of certain kinds of cancer. About 8% of the podophylloresin, from which many lignans were extracted is found in the rhizomes and roots of the plant because it has a higher concentration of podophyllotoxin than other plants, *P. hexandrum* is in higher demand both domestic and in international markets; *P. hexandrum*, *Podophyllum peltatum* (American Podophyllum) and other species further show the need for further research and development of this plant.

1. Introduction

Pharmaceutical discovery is increasing leaps and bounds (Ahmad *et al.,* 2023; Khan *et.al.,* 2023; Noor *et.al.,* 2023), especially the anticancer natural products are being explored (Choudhary *et al.,* 2023; Trivedi *et al.,* 2023; Yamini *et al.,* 2023). The herb. *P. hexandrum* is an evergreen member of Berberidaceae family. The genus "Podophyllum," comprises three species, *i.e., P. hexandrum, P. peltatum and P. sikkimensi* (Jagdish *et al.,* 2018). The *P. peltatum* is typically found in the Atlantic, North America and frequently observed in Asia's Himalayan regions (Sharma *et al.*, 2016). *P. hexandrum* is a high-altitude plant that grows between 2500 and 4000 meters above sea level in the Himalayan regions of China and India, is a succulent, glabrous, robust herbaceous plant that prefers the shade in Chinese and Ayurveda medicine. The plant's roots, fruit, leaves, and rhizome have been frequently utilized for the ailment of number of illnesses such as Hodgkin's disease, myeloid leukemia both the bacterial and viral infections genital herpes warts, autoimmune disease with limb nerve damage and numerous granulomatous skin diseases. Additionally, research has shown that *P. hexandrum* can be used as a successful remedy for cell and tissue damage due to radiation. Oral administration of rhizome and root paste can be used in cholera, gastritis, diarrhea, and dyspepsia and to treat peptic ulcers (Anand *et al*., 2022).

P. hexandrum is receiving an abundance of interest due to the presence of podophyllotoxin, a resinous extract that has been found to have therapeutic potential. The plant's growth parameters, including environmental elements like soil, pH, rainfall, temperature, and humidity, *etc*., also affect the amount of podophyllotoxin present **(**Srivastava *et al*., 2020). Its roots and rhizomes are indigenous to the Himalayas, Afghanistan, and southwestern China (Gupta *et al*., 2021) and they are prized for their aryltetraline lignans, which have anticancer, antifungal, and immune modulatory properties **(**Kushwaha *et al*., 2011**;** Broomhead *et al*., 1990).

Podophyllum has a long history of use in the indigenous Himalayas, with an aqueous extract of the roots being a popular cathartic. It has also been used to treat ophthalmic disease. Thomson tested the resin from the Indian plant in 1890 and found 56% podophyllotoxin content. Podophyllotoxin was isolated as pure in 1880 after Podwyssotzki demonstrated that it was the active ingredient in podophylline. *P. hexandrum* rhizomes are known to contain several lignans, which are intermediate phenylpropanoid pathway dimerization products bound by the central carbon of their side chain (Kamil *et al*., 1986; Jackson *et al*., 1984). It grows near the soil and has bright green obovate the few stiff branches have leaves on them. It has a pale pink blossom and a red-orange elongated fruit. It can proliferate through seeds or rhizomes division. The Himalayan plant can tolerate cold temperatures, as expected from a plant in the Himalayas, but it cannot tolerate dry conditions. This plant is named Podophyllum due to its leaves that resemble those of a duck's foot, which is derived from the Greek words podos and phyllon. The plant has attractive leaves with three lobes. It has attractive foliage with three lobes.

2. Geographical distribution

P. hexandrum is originally found in India and is thought to have originates from Himalayas. It has spread from India to China, Taiwan, Afghanistan, Bhutan, and Pakistan **(**Chaudhari *et al*., 2014; Chaurasia *et al*., 2012**)**. This plant species' distribution in India per state growing

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P. hexandrum to increase podophyllotoxin production (Kharkwal *et al*., 2008). Several widespread species of Podophyllum can be found around the world shown in Table 1 (Arora *et al.,* 2021; Nag *et al*., 2014; Nagar, 2011).

Table 1: Some common species of Podophyllum found in various parts of the world

Podophyllum species	Common names	Geographical distribution
P. hexandrum	Himalayan mayapple	Alpine regions of the north central and east Himalayas
P. sikkimensi	Mayapple	Northeast Himalayas
P. peltatum	Mayapple or western mandrake	Eastern north America
P. veitchii	Dysoma veitchi	Western china
P. verisipelle and P. pleianthum	Mayapple	China

3. Pharmacological activity

Indian Podophyllum resin, which is found in the plant's rhizome and is commonly used in trade, can be processed to produce the neurotoxin podophyllotoxin or podophylline. The main lignans, in the resin of podophyllotoxin and it is an average-dimerized compound. The etoposide (vepeside), a cancer drug with FDA approval medication, is derived from to cure lung and testicular cancer, podophyllotoxin inhibits the proliferation of malignant cells. Topoisomerase inhibitors that are semi-synthetic and used to treat skin conditions like tumors, pimples, and eczema, as well as leukemia, lung, and testicular cancer, use podophyllotoxin as a precursor. For implemented the FRAP and DPPH assay to measure the rhizome extracts' biochemical and antioxidative activities because the bioactive components have the most potent antioxidants were podophyllotoxin deoxy (PODD), podophyllotoxin (POD), as well as polyneuridine as shown in Figure 1 (Li Mengfei *et al*., 2012). Therapeutic action of podophyllotoxin and its analogue are mentioned in Table 2.

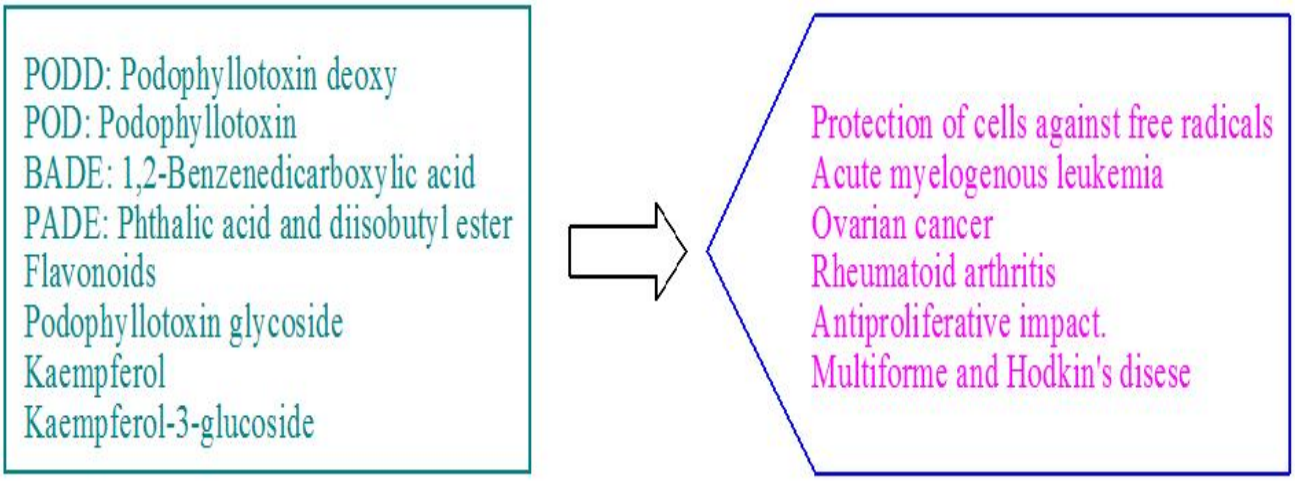


Figure 1: Biological characteristics of *P. hexandrum* bioactive substances.

Table 2: Therapeutic action of podophyllotoxin and its analogue

Podophyllotoxin and its analogues pharmacological actions				
Action	**Podophyllotoxin analogue**	**Method**	**Implication**	**Reference**
Cytotoxic action	Cleistantoxin	The MCF-7, MCF-7R, KB, and HT29 cell line from cancer were tested for action	Strong cytotoxicity has been demonstrated with cleistantoxin	Hensel *et al*., 2020
Antibacterial activity	Synthesized podophyllotoxin precursors	*Salmonella typhi, Escherichia coli, Streptococcus faecalis, Pseudomonas aeruginosa,*	Strong antibacterial activity	Thanh *et al*., 2012

		Klebsiella pneumoniae and *Shigella sonnei* were tested for action		
Antitumour action	VP16-213 (NSC-141540)	Non-obese diabetic mice were tested for action against the L1210 ascites tumour	VP16-213 is a cell cycle -particular medicine because it produced a considerable cure after every 3 h for 24 h	Nanjundaswamy *et al*., 2007
Insecticidal action	Twenty podophyllotoxin analogues were evaluated	*In vivo* action has been tested against *Brontispa longissima* larvae in their fifth instar	Deoxypodophyllotoxin between many 20 moieties, one demonstrated greater insecticidal activity than an info-mercial insecticide.	Dombernowsky *et al*., 1993
Antineoplastic action	Cycloligns are novel hybrids of indirubin and podophyllotoxin derived from podophyllotoxin	Action as just a multipurpose anti MDR drug against human leukemia cancer cells was evaluated. The action of A-549 human lung carcinoma, P-388 murine leukemia, and HT-29 colon carcinoma was all tested	The hybrid of podophyllotoxin and indirubin (Da-1) showed promise in overcoming medication protection. It is a brand-new hybrid with strong antiproliferative properties. Several compounds were active at concentrations lower than 1 pm; with Deoxy podophyllotoxin being the most effective molecule in every case.	Liu *et al*., 2011

4. Active constituents

P. hexandrum has medicinally significant lignans in its rhizomes and roots. It has been stated that the plant's main active ingredients, *P. hexandrum* root, contain 56% podophyllotoxin (Wang *et al*., 2018) numerous lignans with pharmacological effects have been found in the resin known as podophyllin, which is present in Podophyllum species, according to extensive chemical research. These include podophyllotoxin, epipodophyllotoxin, and podophyllotoxone toxin along with flavonoids that contain quercetin, quercetin-3-glucoside 4-demethylpodophyllotoxin, podophyllotoxin glucoside, quercetin and quercetin-3-glucoside are flavonoids. Along with kaempferol and kaempferol-3-glucoside, 4-demethylpodophyllotoxin, podophyllotoxin glucoside and 4-dimethylpodophyllotoxin glucoside as shown in Figure 2 (Tabassum *et al*., 2014; Rather *et al*., 2016).

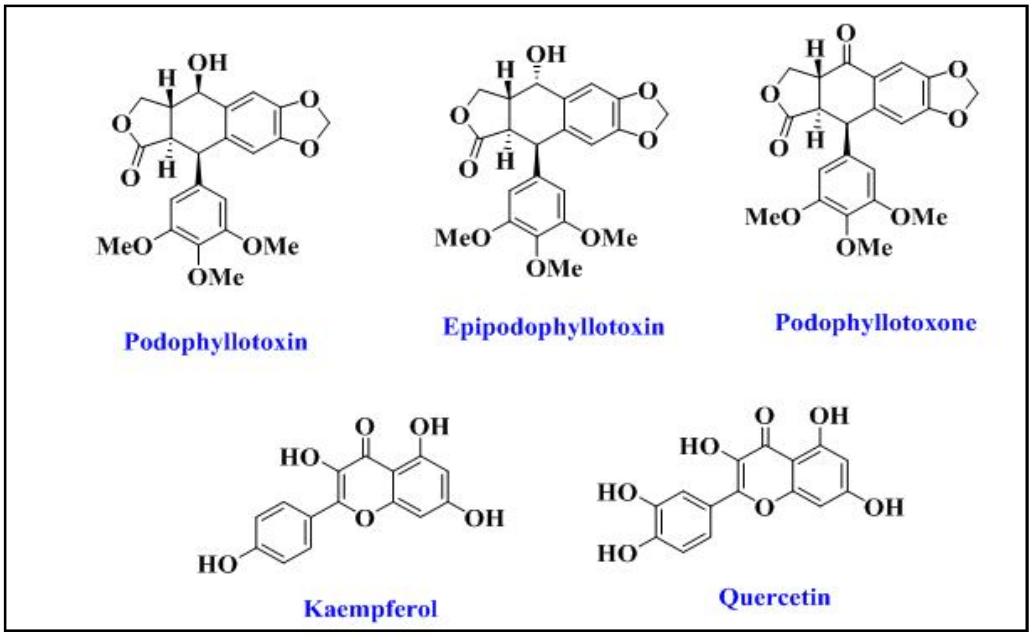


Figure 2: Chemical structure of Podophyllum species and its chemical constituents.

In the 1930, The structure of the selective cyclolignan podophyllotoxin ($C_{22}H_{22}O_8$) was discovered. Numerous structural modifications to podophyllotoxin resulted in the development of two therapeutically effective anticancer drugs, etoposide and teniposide as shown in Figure 3 (Stoll *et al*., 1930; Mounia *et al*; 2012). *P. hexandrum* is employed in the organic synthesis of etoposide (VP16-213) and teniposide (VM-26) and its congeners and analogue exhibit potent anticancer, antineoplastic and anti HIV activity (Stahelin *et al*; 1999). Podophyllotoxin has been known to interact with the replication cycle and DNA. However, it took another twenty years for the mechanism of action of these viable derivatives to be understood. Etiposide inhibits DNA topoisomerase I (T-DNA) and interrupts the s-phase cell cycle. It is also known that podophyllotoxin inhibits tubulin polymerization, which regulates how mitotic spindles are organized, resulting in decreased cell development (Ardalani *et al*., 2017). However, the cytotoxic effect of these medications on healthy body cells, myelosuppression and the development of drug resistance make them difficult to use therapeutically. According to these legends, the production of a novel powerful podophyllotoxin derivatives such as NK-611 (Mross *et al*., 1996), NPF (Huang *et al*., 1999), GL-311 (Lee *et al*., 2001), TOP-53 (Solary *et al*., 1993), F14512 (Ardalani *et al*., 2017), azatoxin and others.

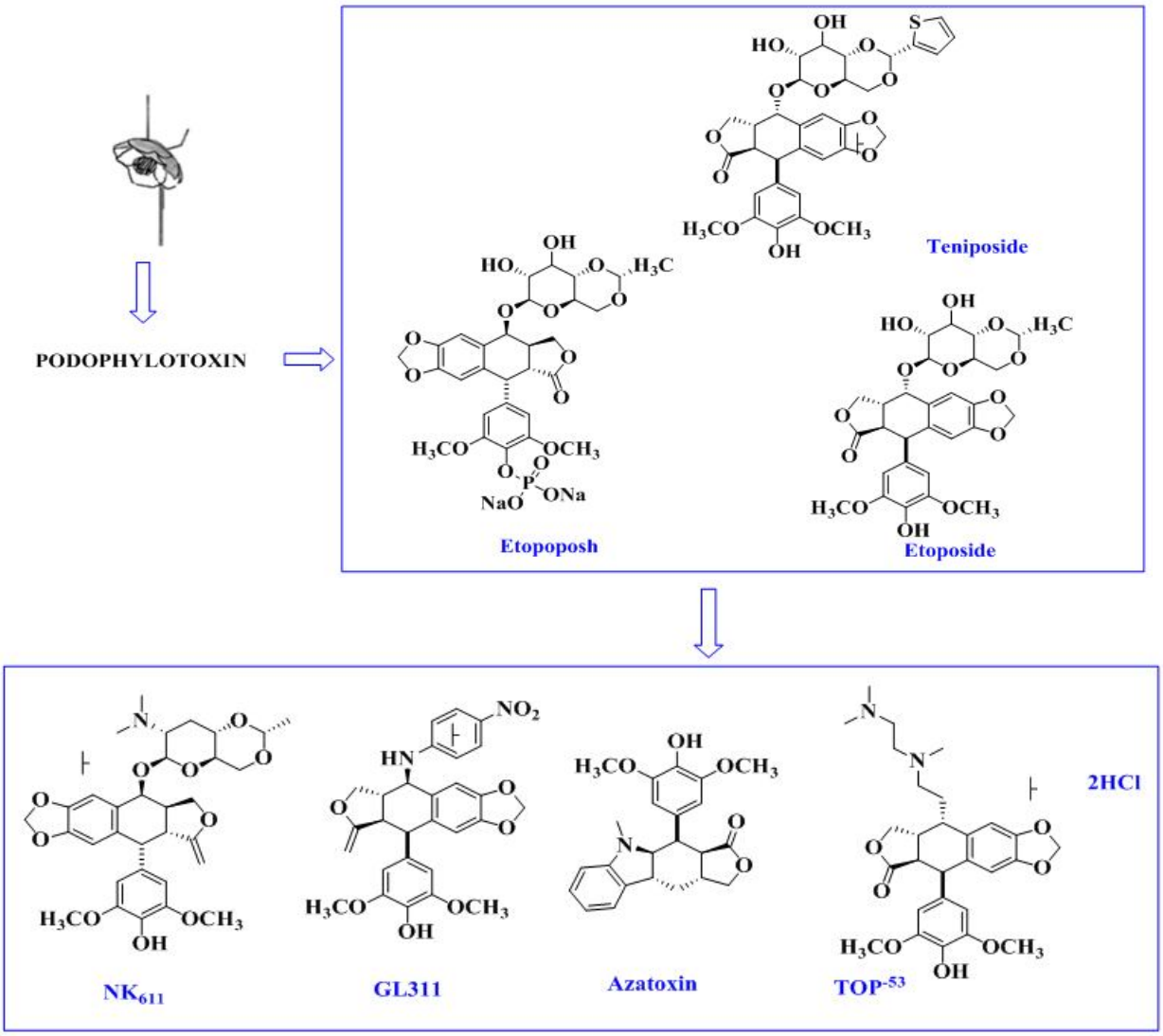


Figure 3: Podophyllotoxin based development of anticancer drugs.

The consecutive discovery of medicines from the podophyllotoxin group. Etoposide, teniposide and etopophos are anticancer medications that have received FDA approval.

They were developed according to parents' molecule podophyllotoxin that was initially from mayapple bushes as a cure for a variety of ailments. When the negative consequences of podophyllotoxin and its main derivatives have been discovered, less hazardous analogue products such as TOP-53, NK-611, GL-331, azatoxin and many more developed and commercialized.

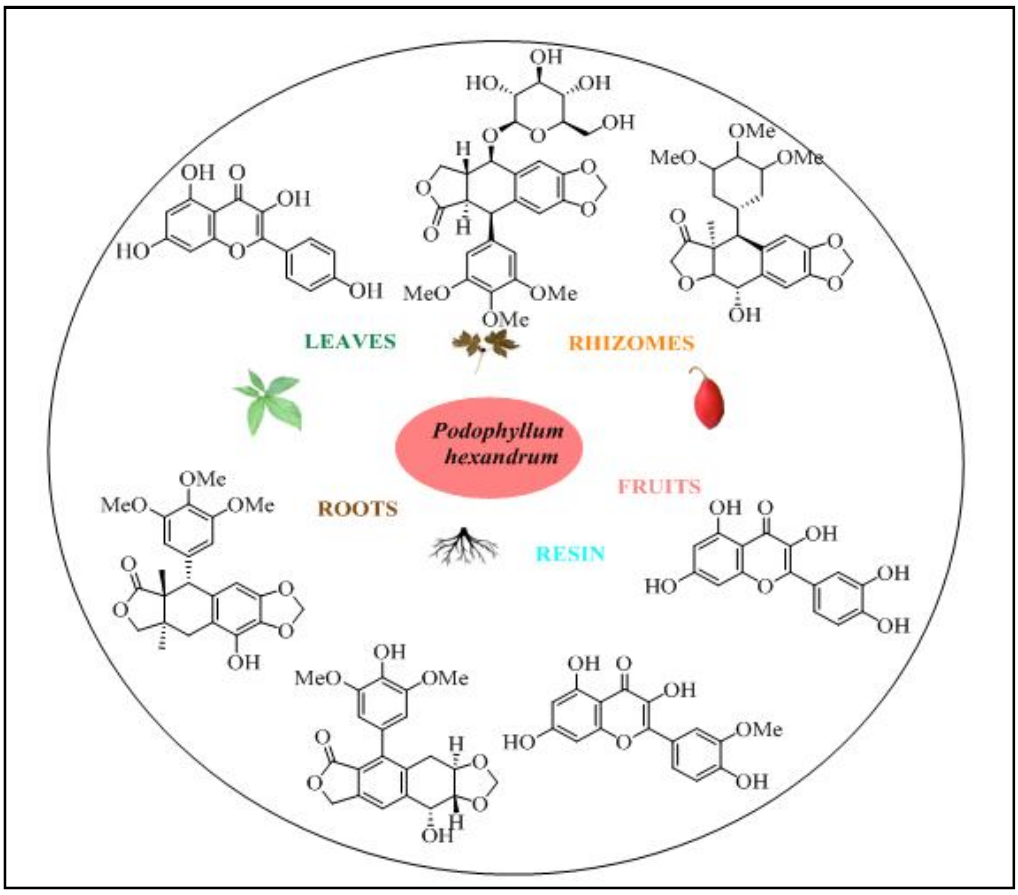
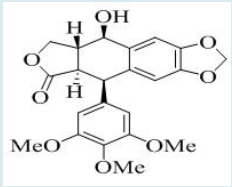
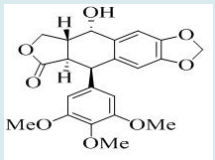
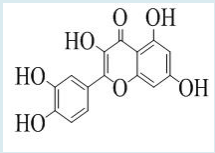
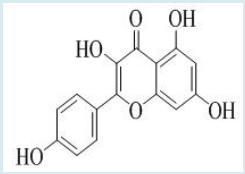


Figure 4: Sources of different podophyllotoxin derivatives from plant parts.

All these derivatives are derived from Podophyllum plant shown in Figure 4, which gives antibacterial activity such as kempferol, podophyllotoxin 4-o-glucoside', picropodophyllotoxin alpha-peltatin, 4-dimethylpodophyllotoxin, isorhamnetin, quercetin (Kumar *et al*., 2020).

Table 3: Physiochemical characteristics of the primary components found in Podophyllum extract

Physicochemical characteristics	Podophyllotoxin	Epipodophyllotoxin	Quercetin	Kaempferol
Structural formula				
Molecular formula	$C_{22}H_{22}O8$	$C_{32}H_{32}O_{13}S$	$C_{12}H_{10}O_7$	$C_{15}H_{10}O_6$
Molecular weight (g/mol)	414.405 g/mol	414.4 g/mol	302.236 g/mol	286.236
Solubility	Soluble in organic solvents, ethanol, DMF and DMSO	Soluble in organic solvents	Soluble in organic solvents	Slightly solubilized in water and highly soluble in hot ethanol, ether, DMSO
Melting point	183ºC	183ºC	316ºC	276-278ºC
Boiling point	597.9ºC	597.9 ± 50.0 ºC	642.0 – 643.0ºC	582.1 ± 50.0ºC

5. Podophyllotoxin

P. hexandrum has been extensive attention because of the presence of podophyllotoxin, a resin extract that has been found to have medical benefits. It is widely distributed in plant species 'roots and rhizomes. The plants growing parameters, including environmental elements like soil and pH, rail fall, temperature, humidity, *etc*., and effect the amount of podophyllotoxin present (Alam *et al*., 2009). This resin can be extracted from both *P. hexandrum* (Indian) and *P. peltatum* (American) specific plant species as shown in Figure 5, even though, it is commonly known that the Indian plant produces more than its American equivalent. Later, several parts of podophyllin isolated from both American and Indian species were discovered (Hartwell *et al*., 1947).

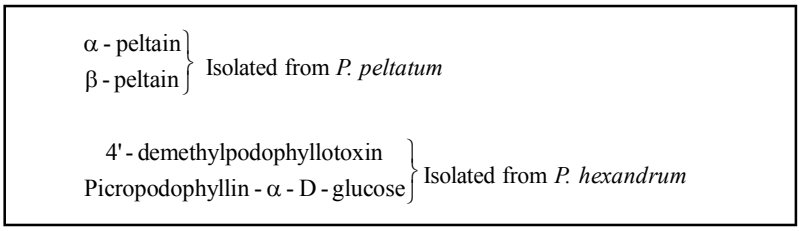


Figure 5: Isolation of compound through *P. hexandrum and P. peltatum*.

5.1 Phytochemical profile of podophyllotoxin

According to its chemical structure, podophyllotoxin belongs to the aryltetralin lignans family. It is made up of phenyl propane units linked by carbons in the side chain combined. Figure 6 depicts the podophyllotoxin's chemical structure both 2D and 3D formats (Hartwell *et al*., 1958) various compounds derived from podophyllotoxin or Podophyllum species include quercetin, kaempferol, isorhamnetin, and quercetin-3-galactoside. Chemically, these compounds can be lignin and flavonoids.

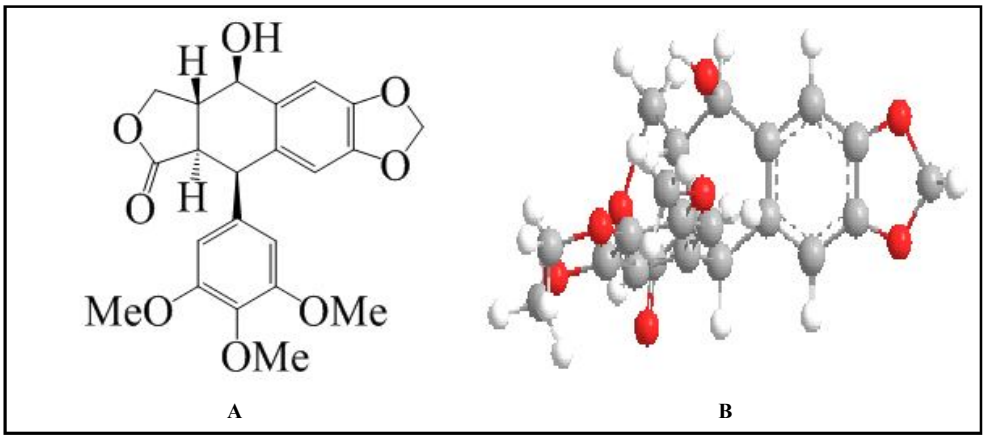


Figure 6: Podophyllotoxin resin chemical structure (a) and 3d representation (b).

Because podophyllotoxin is one of the most powerful naturally occurring cytotoxic chemicals, which is an important component of its semisynthetic derivatives that act as cytostatics and thus used to treat various types of cancer. Etoposide and teniposide are the most important anticancer drugs derived from toxin. The chemical structures of etoposide and teniposide are depicted in Figures 6 and 7. Podophyllotoxin prevents the formation of microtubules, which in turn prevents cell division.

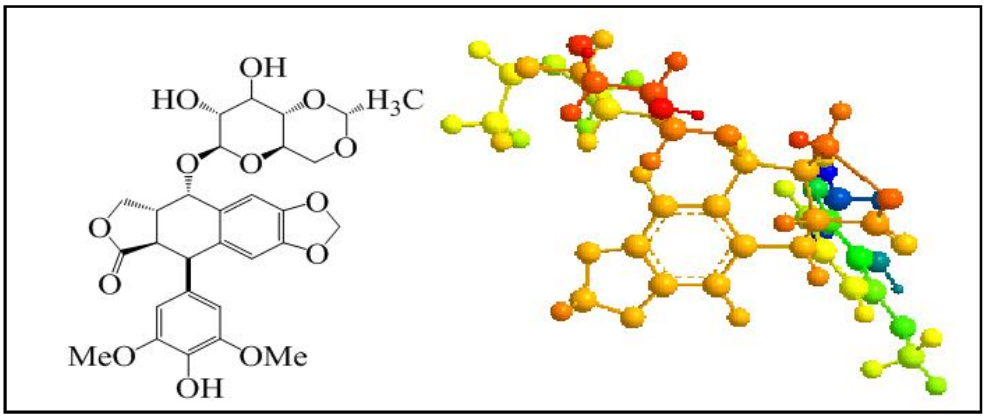


Figure 7: Teniposide's chemical structure in two dimensions and three dimensions.

The amount of resin collected varies depending on the time of year and location of selection toxin generate is highest in May, When the plant is about to flower, it drops by 7% and when the plant is about to fruit, it drops by 7%. Furthermore, the yield from young rhizomes is greater. As the rhizomes mature the quantity of podophyllotoxin concentration reduces (Giri *et al*., 2001).

5.2 Mode of action

Podophyllotoxin inhibits microtubule assembly and causes the cell cycle to stop on metaphase. These PDT lignans inhibit the catalytic activity of topoisomerase II DNA by stabilizing a cleavage enzyme-DNA complex in which the DNA was cleaved and covalently bound to the enzyme. It binds to the colchicine site of tubulin. Some chemical changes were made from podophyllotoxin to etoposide/teniposide, which resulted in a change mechanism of action, from the parent compound PDT's inhibitor of microtubule formation to etoposide and congeners' DNA topoisomerase II inhibitor. etoposide/teniposide are DNA topoisomerase II inhibitors, whereas podophyllotoxin is an ant microtubule agent (Nagar *et al*., 2011; Kumari *et al.*, 2016). The diagrammatic representation of mode of action of podophyllotoxin and its derivatives are depicted in Figure 8.

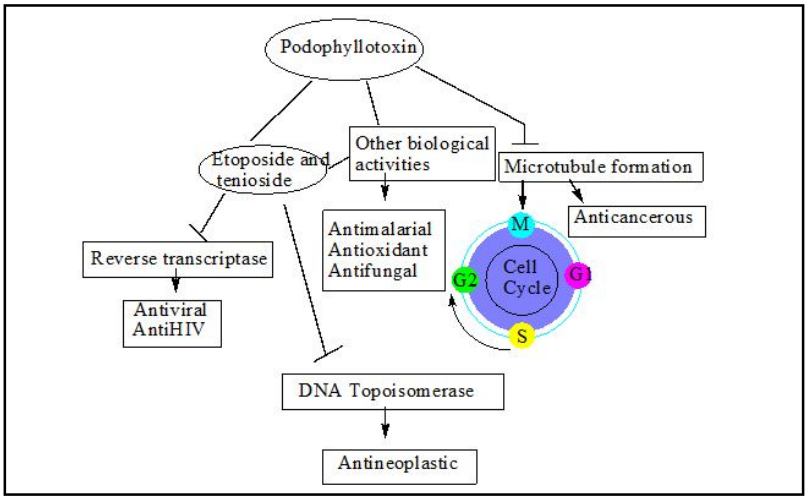


Figure 8: Mode of action of podophyllotoxin and its derivatives.

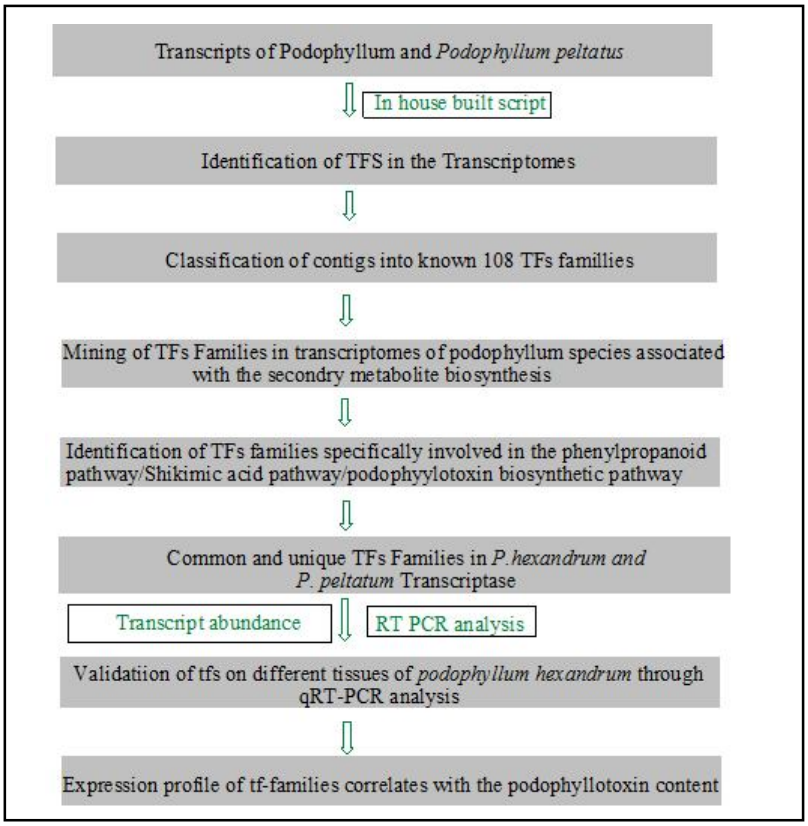


Figure 9: Workflow for identifying and analyzing TFs from Podophyllum species transcriptomes.

5.3 Identification of unique and common genes factors in podophyllum species transcriptomes

The Plant Fcat database was used to identify and classify transcription factors (TFs) comprised in the secondary metabolite biosynthesis. Figure 9 depicts the workflow for mining, identifying, and experimentally validating transcription factors for *P. hexandrum* transcriptomes (Kumar *et al*., 2017; Bhattacharyya *et al*., 2013).

5.4 Production of podophyllotoxin

The majority of the suggested mechanisms involve shickmick acid-mediated phenolic oxidative coupling of C6-C3 monomer. An enzyme-controlled reaction produces optically active lignin dimers. A number of chemicals with substantial economic and medical significance are created through the reductive dimerization of cinnamic acid or cinnamic alcohols and are clinically effective anticancer medicines. Figure 10 depicts the biosynthetic process by which podophyllotoxin is produced in species of Podophyllum (Kumar *et al*., 2015; Biswasa *et al*., 2020; Karuppaiya *et al*., 2015). The biosynthetic process that results in the podophyllotoxin quinate dehydrogenase (QD), aromatic amino acid transaminase (AAAT), phenylalanine ammonia lyase (PAL), cinnamate-4-hydroxylase (C_4H) and dirigent protein oxidase (DPO) due to the varied characteristics of the ring structures, derivative chemicals are created as secondary metabolites. Coniferyl alcohol is the first step in the manufacture of podophyllotoxin and when an oxidant is present, it transforms into pinoresinol through a series of events that includes dimerization of a stereospecific reaction intermediate. There is still a lack of a comprehensive and conclusive understanding of this pathway and research is underway to learn more about the genes and transcription factors that may play a role in its regulation (Xia *et al*., 2000; Marques *et al*., 2013).

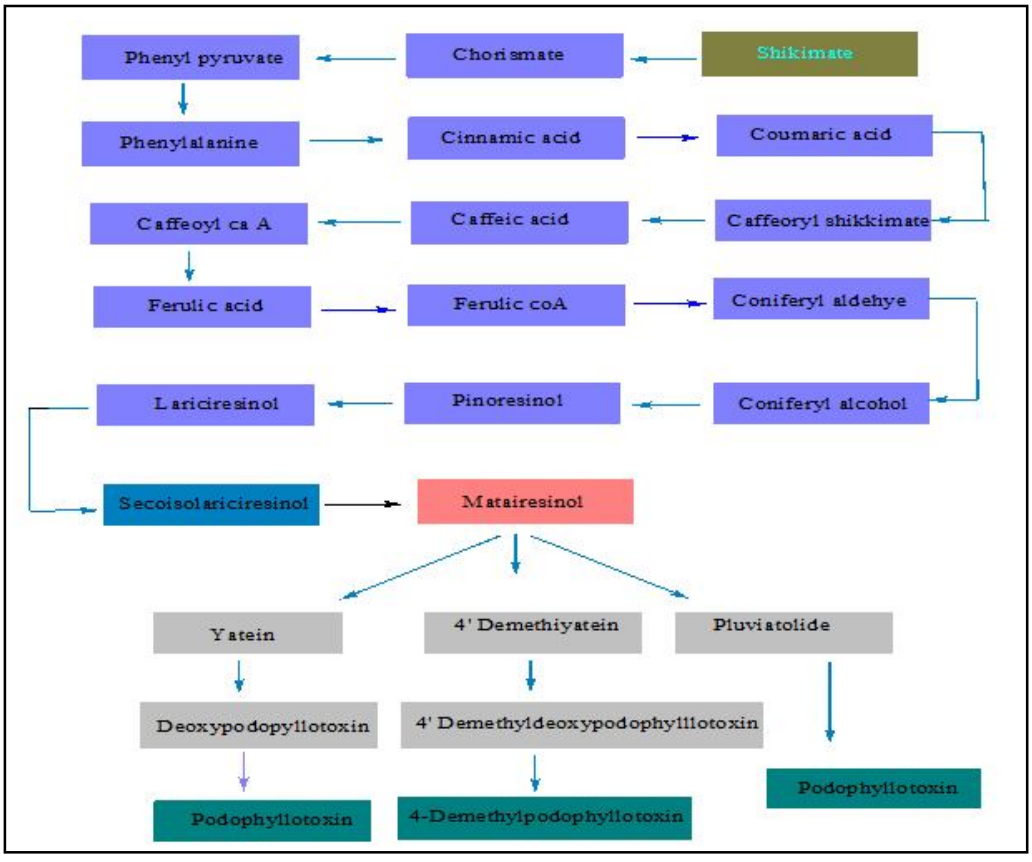


Figure 10: Synthetic routes of podophyllotoxin.

5.5 Structure activity of podophyllotoxin and its derivative

Podophyllotoxin is composed of five-ring structure (A, B, C, D and E rings). Only A and E rings are required to function. Previously, it was stated that all the rings are required for its activity, but this is no longer the case. For better activity, dring lactones are desired. Most C-ring alterations are permissible and big groups at this position improve anticancer and topoisomerase activities (Nagar *et al*., 2011; Shah *et al*., 2021).

The podophyllotoxin/epipodophyllotoxin hybrids (Figure 11) are split into two groups: podophyllotoxin/epipodophyllotoxine hybridization with or without linkage with another anticancer pharmacophore; 2. 1,2,3-triazole interaction with other anticancer pharmacophore. In this review, the phrase “type 2 hybrids” implies 1,2,3-triazole-tethered podophyllotoxin/epipodophyllotoxin anticancer pharmacophore hybrids, for example 1,2,3-triazole-tethered podophyllotoxin-sugar hybrids. Hybrid anticancer pharmacophores have two related pharmacophores for example coumarin and chromone, furan and pyrrole.

Most current developments anticancer activity, mechanisms of action and the structure activity connection of hybrid podophyllotoxin/epipodophyllotoxin molecules are covered in this study (Xiao *et al*., 2020).

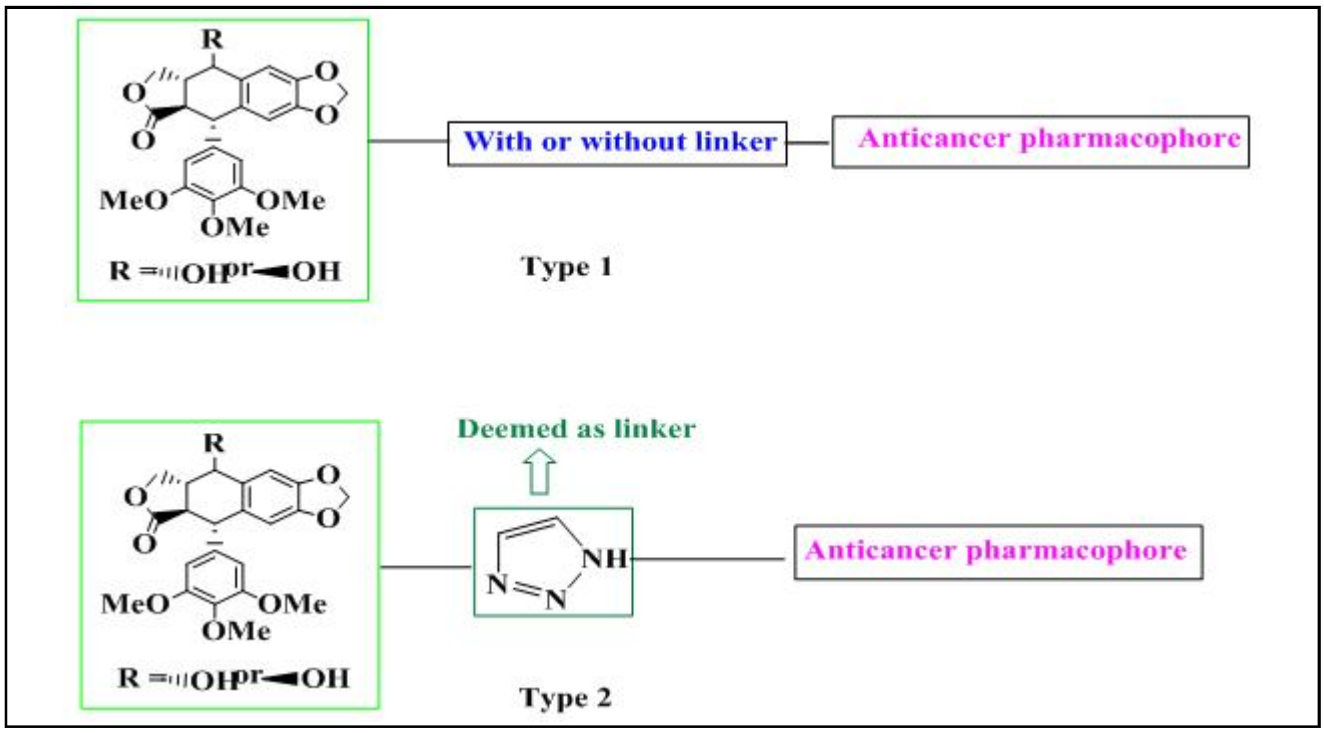


Figure 11: Two main categories of hybrids between podophyllotoxin and epipodophyllotoxin.

6. Hybrids of podophyllotoxin

By combining amino acids and peptides with podophyllotoxin/ epipodophyllotoxin, new anticancer medicines with improved effectiveness against both medication-sensitive and medication-resistant malignancies may be produced. Numerous combinations of amino acids, peptides and podophyllotoxin/epipodophyllotoxin had significant *in vitro* ant proliferative action and one of these was the hybrid with the amino acid glycine depicted in Figure 12.

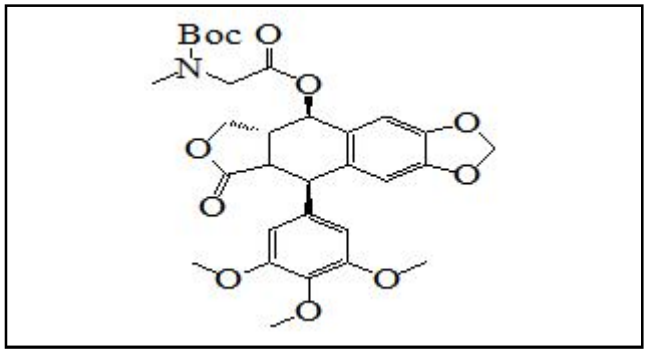


Figure 12: Chemical structure of podophyllotoxin glycine hybrid.

6.1 Podophyllotoxin/epipodophyllotoxin azole hybrids

The advantage of two nitrogen hetero atoms ring provided by the nitrogen-containing azole skeleton has a significant impact on biological interactions and structural modifications. One of the most popular pharmacophores used in the creation of new anticancer drugs is hetero aromatic rings (Bozorov *et al*., 2019). As putative anticancer medications, cefatrizine and carboxyamidotriazole are being studied in clinical trials or have been already used in clinics to treat cancer (Xu *et al*., 2019). These compounds' cytotoxicity towards human cancer cell lines HeLa, K562, & K562/A02 was assessed in vitro using MTT assay in the comparison of parent compounds, podophyllotoxin, VP-16 and ADM. Since the majority of 1,4-disubstituted triazole podophyllotoxin have been shown to strong antitumor activity, azole-mediated hybridization of podophyllotoxin and epipodophyllotoxin may be produce effective anticancer drugs.

Epi-podophyllotoxin-1,2,3-triazole hybrids 3 (IC_{50}: 0.69 >10 m, MTT test) have been significantly more powerful than their regioisomers (IC_{50}: 0.059 >100 m) against the cancer cell lines HeLa, K-562, and MDR K-562/AO2, indicating that the position of the substituent on the 1,2,3-tri incorporating ester groups into the 1,2,3-triazole pattern enhance the action of hybrids 3 (Chen *et al*., 2011) while phenyl containing compounds boosted the activity of hybrids 4, especially hybrid 4a (IC_{50}: 53-82 nm), which were both extremely effective against the cancer cell lines HeLa, K562 and K562/a02. Their effectiveness against every cancer cell line tested was like the etoposide (IC_{50}: 2.11-151.6 m) and doxorubicin (IC_{50}: 0.36-19.21 m).

Hybrids 3a, b and 4a, b were furthermore analysed as possible therapeutic candidates. The typical hybrids 5a and b demonstrated that the addition of an alkyl to the 1,2,3-triazole moieties C-4 position or the substitution of a methoxy group for a hydroxyl at the epipodophyllotoxin motifs' C-4' position was tolerated. (Figure 13, IC_{50}: 10-60 nm, MTT assay) were 35.8-1900 times more effective against the PC-3, HEP-2, AND MCF-7 cancer cell lines than standard etoposide (IC_{50}: 2.15-19 m) (Reddy *et al*., 2011).

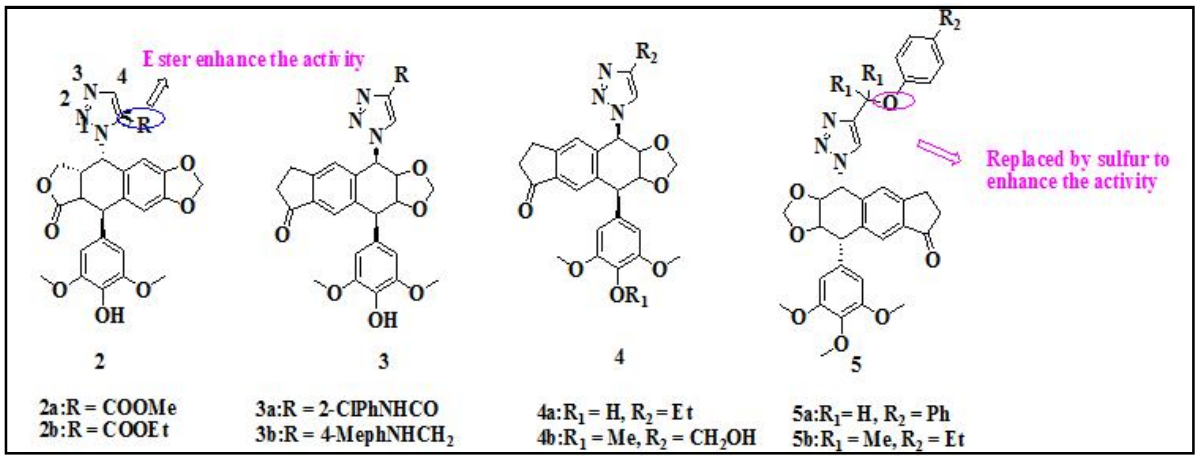


Figure 13: Chemical structure of 1, 2 and 3-triazole hybrids epipodophyllotoxin.

It should be highlighted that advances in click chemistry developments [Cu-AAC] (the copper-catalyzed azide-alkyne cyclo addition reaction) have resulted in the use of numerous synthetic methodologies for 1,2,3-triazole scaffolding shown in figure 14 (*e.g.,* derivatives, hybrids, and conjugates) in medicinal chemistry (Dheer *et al*., 2017). Several biological evaluations were performed and resulted in the identification of anticancer agents (Valdomir *et al*., 2017; Savanur *et al*., 2018).

Anti-microbial, anti-infective and antioxidant activities of 1,2,3-triazole-bearing hybrids considered (Tarawneh *et al*., 2018) consequently, triazole-linked derivatives were postulated to influence adenosine diphosphate ribosylation biology therefore have been frequently employed in peptides that mimicked a trans-amide bond, despite their destructive impacts on native peptide activity (Ben Haj Salah *et al*., 2018).

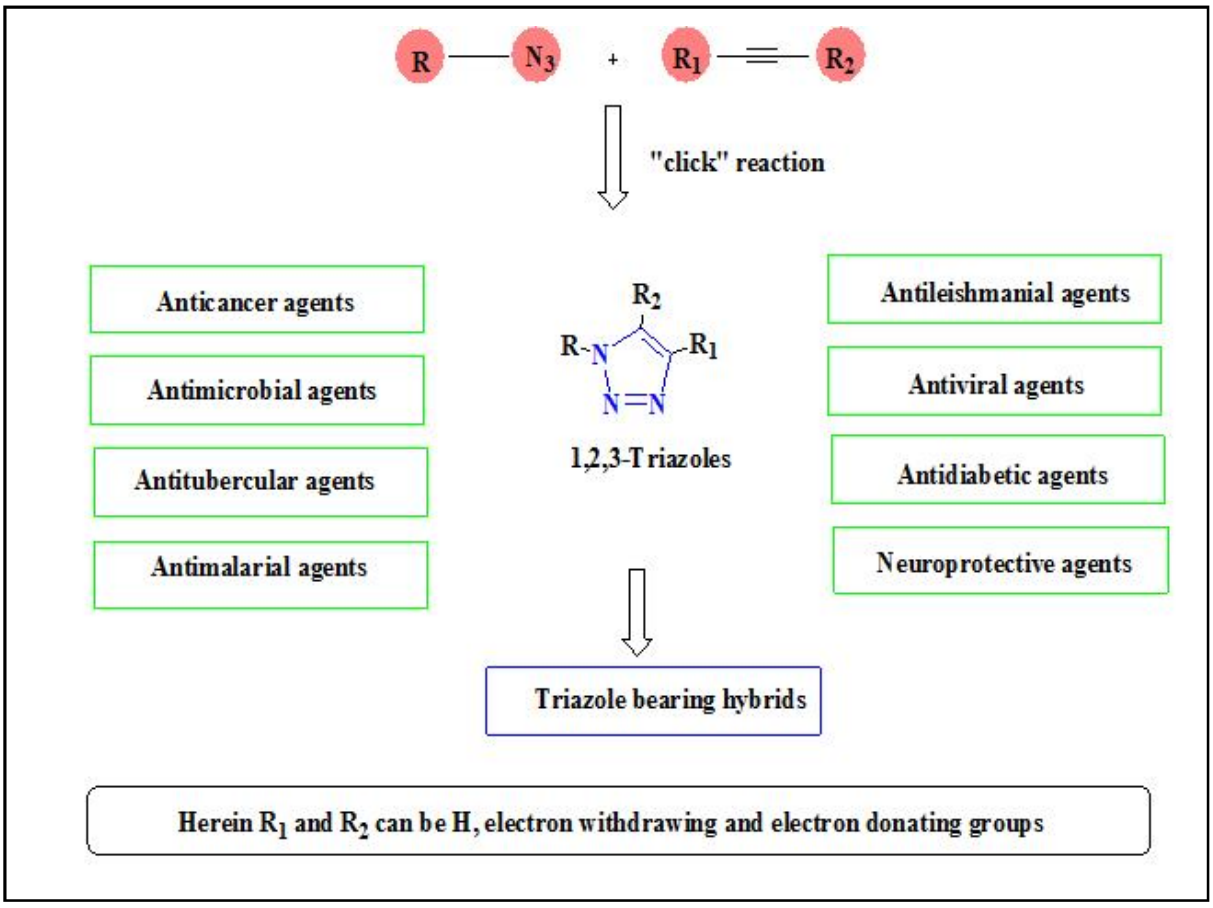
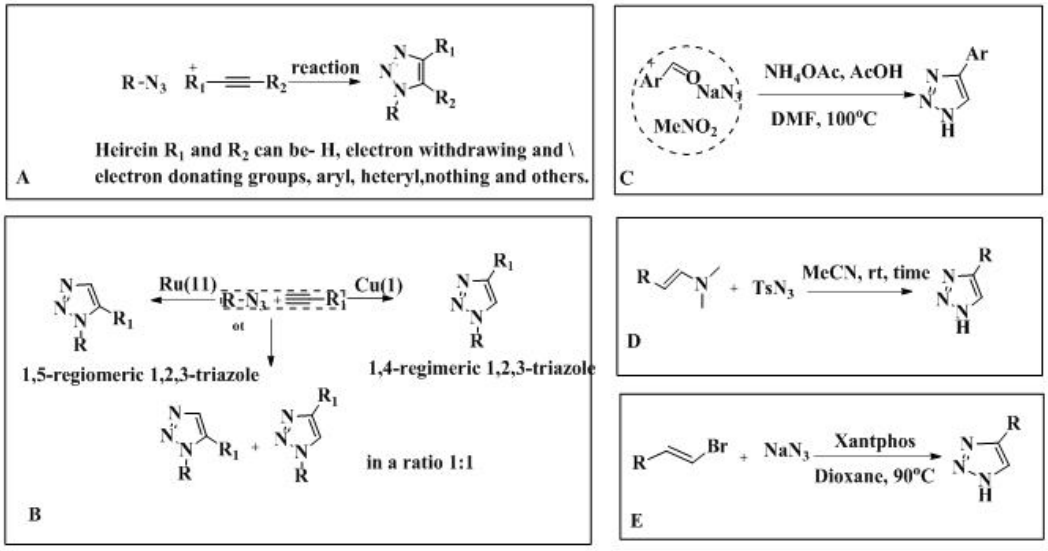


Figure 14: Bioactive 1,2,3 triazole using "click" reaction.

6.2 Chemistry: 1, 2, 3-triazole synthesis and properties

The standard click chemistry synthetic pathway for 1, 2, 3-triazoles is shown in scheme 1A. The Cu(I)-catalyzed Huisgen 1, 3-dipolar cyclo-addition of regioisomeric 1,2,3-triazoles is the most popular method for producing 1,2,3-triazoles (Kacprzak *et al*., 2016). The primary products of this reaction when ruthenium catalysts are used instead of Cu(I) the resulting compounds are 1,5-regioisomeric 1,2,3-triazoles (Johansson *et al*., 2016). A non-catalytic heat route yield gives both regioisomeric 1,2,3-triazoles.

In 2015, Totobenazara and Burke used traditional reactions to discover novel 'click' approaches for 1,2,3-triazoles (Totobenazara and Burke, 2015). Phytopharmaceutical research (Alam *et al.,* 2022; Khan *et al.,* 2022; Sharma *et.al.,* 2023; Singh *et al.,* 2022) may be furnished by podophyllotoxin, especially the anticancer therapy. The SAR study of podophyllotoxin/epipodophyllotoxin hybrid are shown in Figure 16.



Scheme 1 (A-E). Synthesis of 1,2,3-triazole.

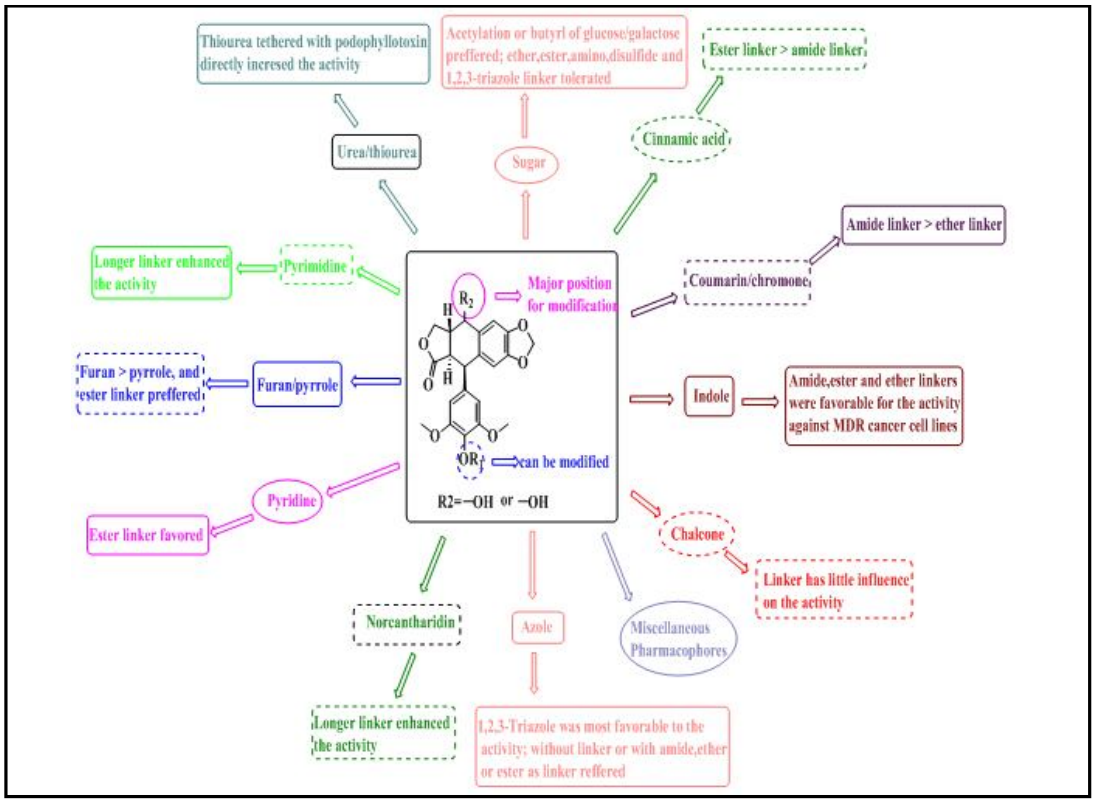


Figure 16: SAR of Podophyllotoxin/epipodophyllotoxin hybrid.

7. Conclusion

P. hexandrum is a medicinal plant from cold temperate climate zones of the world that is in danger of extinction. Due to their effectiveness in combating cancer and other dangerous ailments, plants are of almost importance. Derivatives of podophyllotoxin/epipodophyllotoxin showed notable anticancer properties, and several of them have already been employed in clinics to treat a variety of malignancies. Toxin analogue with α -configuration (podophyllotoxin) are potential inhibitors of the tubulin polymerization, whereas those with a configuration (epipodophyllotoxin) are inhibitors of topoisomerase II. Configuration at C-4 position of involvement of podophyllotoxin in the mechanism of action is significant, with the ability to cure a variety of malignancies, including MDR types, hybridizing podophyllotoxin and epipodophyllotoxin may provide new anticancer candidates with two or more modes of action when combined with another anticancer pharmacophore.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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