Anticancer Compounds from Selected Medicinal Plants: An update

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Abstract

Globally cancer is one of the leading causes of mortality. Although, rapid progression and advancement in treatment have been made to combat this life-threatening disease. Conventional therapies like chemotherapy and radiation therapy have several adverse side effects on healthy cells, therefore, a novel alternative and effective treatment regime is required to treat cancer. Currently, the benefits of using medicinal plant-derived products over synthetic medicine have significantly increased in the field of healthcare. Several medicinal plants and their bioactive compounds have shown to possess potent anti-cancer properties *in vitro* and *in vivo*. Additionally, they are less toxic, very effective and, safe when administered in cancer patients**.** Some of the well-established anti-tumor compounds include vinblastine, curcumin, vincristine, podophyllotoxin, taxol, orientin, camptothecin vinflunine ditartrate, anhydrovinblastine, poliglumex, combretastatins, and triptolide. Many of them are in clinical trial, only a few have been clinically approved. This chapter

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summarizes the benefits of medicinal plants and plant-derived products in anti-cancer therapeutics. Clinical investigations, as well as *in vitro* and *in vivo* activity screening of anticancer effects of medicinal plants and their bioactive components, are presented with up-to-date information here.

Keywords
Medicinal plants, Cancer, Anticancer compounds

1. Introduction

Cancer is simply defined as the abrupt and uncontrollable growth of cells in any part of the body. This growth of tumour or cancer cells can occur in any part of the body resulting in different types of cancers, such as breast cancer, kidney cancer, lung cancer, colorectal cancer, lymphoma etc. According to the global cancer statistics of 2020, there occurred approximately 19.3 million cases of cancer and almost 10 million cancer deaths worldwide (Sung et al. 2021). The causes of commencement of this abnormal growth include radiations, infections, smoking or tobacco or genetic factors. The conventional methods of treatment of cancer are increasingly causing side effects pertaining to normal cells. Thus, there is an urgent need to find the treatment with higher efficacy and lower side effects.

Medicinal plants are a rich source of bioactive compounds. Many of the pharmaceutical industries are exploring the wealth of traditional knowledge that exists in our communities for new potential therapeutic substances that can be exploited commercially. In traditional Ayurvedic medicine particularly Ayurveda, plants and their products are used to cure many diseases. Plants are an excellent source for biologically active molecules which can be further used as a structural template for obtaining the modified derivatives with increased activity with minimum toxicity. It is essential to determine the active compound and its mechanism of action in order to process it further for determining their role as therapeutic agents (Wagh et al. 2020). It also requires specific evaluation in terms of the safety as they may possess toxic elements, pesticides etc. Since the actual chemical composition may vary seasonally and is also climate dependent, therefore it is essential to isolate and analyze the therapeutic potential of different plant metabolites/active constituents.

The plant phytochemicals have found numerous applications as anti-inflammatory, analgesic, anti-cancer, antimicrobial, anti-diabetic, antineurogenesis, anti-adipogenesis, hepatoprotective, cardioprotective and effective for arthritis and wound healing (Figure 1). The frequently used plants for anti-cancerous properties are *Withania somnifera*, *Artemisia annua, Taxus wallichiana, Calotropis procera, Citrullus colocynthis, Nigella sativa, Pulicaria crispa, Urtica dioica, Arum palaestinum*, *Catharanthus roseus* etc. (Aumeeruddy et al. 2021; Khan et al. 2020). The bioactive compounds extracted from these plants can act independently or they are also explored for their synergistic cancer effects when used in combination with other bioactive components.

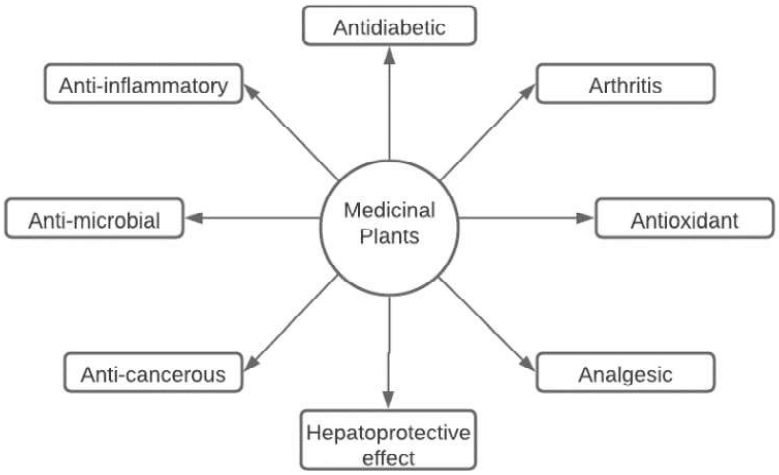

Figure 1: Therapeutic applications of medicinal plants

Some of the most commonly exploited phytochemicals for their anticancerous properties are summarized in Table 1. They exhibit their therapeutic role by different mechanisms of action at different stages of carcinogenesis in addition to their protective role. Therefore, the use of phytochemicals and bioactive compounds is being established in therapies due to their anti-proliferative and anti-apoptotic properties, their protective role as antioxidants and improving immune response and reducing inflammation. These anti-cancerous agents may act by blocking signalling pathways that are necessary for cancer progression with the involvement of p53 and p21, Bcl-2, Bax, cytochrome c and caspases, etc. They selectively inhibit the proliferation and induce cell death through various pathways (Nguyen et al.

2020). Compounds like curcumin, paclitaxel, resveratrol, quercetin, vincristine, ingenol mebutate have been put to use against cancer and have shown success in clinical trials and therapeutic applications (Seca and Pinto 2018; Wagh et al. 2020). Plant derived compounds have long been used in the treatment of cancer and it is well documented in literature (Table 1). FDA data showed that 40% of the approved molecules are natural compounds or their derivatives, out of which 1/3rd are used for anticancer therapy (Seca and Pinto 2018). It is well established that these products have more significance than the other therapies as they are safe and target mostly the malignant cells.

Table 1: A list of anticancer compounds derived from plants

Anticancer compounds	Plant Source	References
Diallyl Disulphide, Diallyl trisulphide	*Allium sativum*	(Forma et al. 2021)
Taxol	*Taxus brevifolia*	(Sarli et al. 2020)
Betulin	*Betula alba*, *B. pendula*, *B. pubescent* and *B. platyphylla*	(Król et al. 2015)
Curcumin	*Curcuma longa*	(Tomeh et al. 2019)
Ingenol Mebutate	*Euphorbia peplus* L., *Euphorbia paralias* L., *Euphorbia millii* Des Moul., *Euphorbia palustris* L., *Euphorbia marginata* Pursh, *Euphorbia helioscopia* L., and *Euphorbia myrsinites* L.	(Seca and Pinto 2018)
Homoharringtonine	*Cephalotaxus harringtonii, Cephalotaxus fortunei*	
Garcinol	*Garcinia indica*	(Saadat and Gupta 2012)
Eugenol, Orientin, Vicenin	*Ocimum sanctum*	(Iqbal et al. 2017)
Silibinin	*Sylibum marianum*	
Colchicine	*Colchicum autumnale*	
Podophyllotoxin	*Podophyllum peltatum*	
Viscumin	*Viscum album*	
Cannabinoid	*Cannabis sativa*	
Vincristine, vinblastine	*Catharanthus roseus*	
Paclitaxel	*Taxus brevifolia*	
Andrographolide	*Andrographis paniculata*	
Scutellarin	*Scutellaria barbata*	
Berberine	*Berberis vulgaris*	

This chapter presents four medicinal plants namely, *Catharanthus roseus, Andrographis paniculata, Oroxylum indicum* and *Scutellaria barbata* which are

known for their anticancer properties in addition to being used for the various other health benefits.

2. *Catharanthus roseus*

The medicinal plant *Catharanthus roseus* comes from the plant family Apocynaceae. *Catharanthus* means "pure flower" in Greek language and *roseus* means "red, rose or rosy". It is a native flowering plant of Madagascar, which is an island in Indian Ocean, therefore, also commonly known as Madagascar periwinkle. Generally, it is seen to be growing in a warm climate. It is a dicotyledonous plant, from which two famously used phytochemicals can be extracted, namely, vincristine and vinblastine. Other than the popularized used of the plant in treatment of cancer, it is characterized by properties of being anti-microbial, anti-diabetic, anti-diarrhoeal, healing wounds, anti-oxidant, and hypotensive. So, being a medicinal plant, it can be used in the possible treatment of vast variety of diseases all over the world, including diabetes, cancer, Hodgkin's disease, heart diseases, leishmaniasis, menorrhagia etc. (Mishra and Verma 2017; Aslam et al. 2010).

2.1 Medicinal uses of *Catharanthus roseus*

C. roseus holds chemical compounds like carbohydrates, flavinoids, saponin and alkaloids and can be used to treat a wide variety of diseases. There are more than 400 alkaloids found in the plant which are used in the fields of pharmaceuticals, agrochemicals, as flavouring agents, for fragrance, act as ingredients and additives in food products and are also used in pesticides (Sain and Sharma 2013; Aslam et al. 2017; Mishra and Verma 2017). The extract from its leaf can be used against a bee or wasp sting in a few countries like India. The leaf infusion is used for menorrhagia in Philippines and Africa. Other than leaf, in Bahamas, the flower decoction is used as a cure for asthma, tuberculosis and flatulence. The plant is also renowned for its use to treat diabetes in various parts of the world. Alkaloids like reserpine and serpentine, extracted from the plant are powerful tranquilizers. While some of them like catharanthine, locherine, vindoline and vindolinine lower the blood sugar level, others also help in haemostatics i.e., stop bleeding (Gupta et al. 2017; Aslam et al. 2017). As for the antidiabetic activity, its ethanolic extracts of leaves and flower play a role in lowering of blood sugar which is due to the increased utilization in the liver as has been suggested by various studies (Aslam et al. 2017). Studies

revealed that leaf extracts of this plant also possess antimicrobial activities against microorganisms like *Pseudomonas aeruginosa* NCIM 2036, *Salmonella typhimurium* NCIM 2501, *Staphylococcus aureus* NCIM 5021. The same extract could also be used in the form of a prophylactic agent in treatment of number of diseases (Dwivedi and Sharma 2013; Baran et al. 2017).

2.2 Phytochemicals and use against cancer

In modern medicine, *C. roseus* is gradually making its place as an effective source of chemical constituents for treatment of various types of cancers. The two major anticancer alkaloids produced by the plant are vinblastine and vincristine (Table 2), which are extracted from its stem, root and leaf (Baran et al. 2017). They are dimeric alkaloids and belong to a group called vinca alkaloids, antimitotic drugs employed in cancer chemotherapy (Jordan et al. 1985). Vinblastine, also called vincaleukoblastine, was first used in 1960 for treatment of Hodgkin's disease, non-Hodgkin lymphomas, testiscarcinomas, and occasionally breast cancer and choriocarcinomas. Vincristine, also known as leurocristine, is the oxidized form of vinblastine and is used against leukaemia in children. Vinblastine and vincristine are sold as Velban and Oncovin, respectively (Mishra and Verma 2017). The plant doesn't initially contain these compounds in large quantities. It possesses precursor alkaloids-vindoline and catharanthine. These precursors are mixed for synthesis of chemicals that work against cancer (Baran et al. 2017).

2.3 Screening and isolation of bioactive compounds

Various traditional techniques such as centrifugal partition chromatography, ultrasonic-assisted extraction, soxhlet extraction etc. involving alcoholic extracts of freeze-dried roots are in use for the isolation and extraction of bioactive compounds mainly vinblastine, vincristine, vindoline, catharanthine from *C. roseus* (Pham et al. 2020; Tikhomiroff and Jolicoeur 2002). Recently, a comparatively novel and improved method involving negative-pressure cavitation extraction followed by high-pressure liquid chromatography has been suggested for isolation as well as quantification of bioactive compounds (Mu et al. 2012).

Vinca alkaloids are a type of cytotoxic drugs that specifically affect the cell cycle. They induce changes in a cell and inhibit the cancer cells to divide further by acting upon tubulin and prevent formation of microtubules, which play a significant role in cell division (Ingalwad et al. 2020). By inhibiting the polymerization of mitotic spindle microtubules, they suppress the process of mitosis or cause

metaphase arrest, thereby leading to apoptosis of actively-dividing cells (Choudhari et al. 2020; Seca and Pinto 2018; Wang et al. 2016). The microtubules are composed of basic units; alpha-tubulin and beta-tubulin. The dynamic assembly and disassembly of the structure is caused by continuous polymerization and depolymerization of these units by a process called "treadmilling" which is regulated by binding of GTP (Guanosine 5-triphosphate) to tubulin. The vinca alkaloids and their derivatives depolymerize the MTs by attaching to the surface between two tubulin heterodimers near the exchangeable GTP-binding site. Such interference in MT dynamics causes programmed cell death or apoptosis. When these alkaloids are present in high concentrations, they form large tubulin polymers referred to as "Paracristal", causing the mitosis of tumor cells to stop immediately leading to death. Whereas, when they are present in lower concentrations, mitosis is arrested and cell death occurs after a significant incubation period (Almagro et al. 2015; Hadfield et al. 2003; Takanari et al. 1990).

3. *Andrographis paniculata*

Andrographis paniculata is a medicinal plant belongs to the family Acanthaceae and is commonly known as "kalmegh" in India. It is a part of traditional medicinal system in India, Pakistan, China, Malaysia, Indonesia and Thailand. It is a branched, annual plant that produces phytochemicals like flavonoids, diterpenoids and polyphenols from different parts which contribute towards its medicinal properties. It can be used against inflammation, common cold, burns, liver diseases, vitiligo, diabetes, hypertension, fever etc. (Nagajothi et al. 2018). A specific diterpenoid produced by it, namely andrographolide can be used for treatment of various types of cancerous growths like carcinoma and leukaemia (Akbar 2020; Boopathi 2000; Borhanuddin et al. 1994; Liaqat 2021).

3.1 Medicinal uses of *Andrographis paniculata*

The plant has been traditionally used to treat fever, cough, skin diseases, ulcers, breathing difficulties, worms and wound healing (Rajalakshmi et al. 2016; Theresa et al. 2020). The use of the whole plant has been seen for poisonous stings, dysentery, malaria, influenza and respiratory infections, while leaf extract is used as a remedy for infectious diseases, loss of appetite, diarrhoea etc. In some countries like Malaysia, the decoction of the plant's aerial parts is used for treatment of diabetes, common cold, hypertension, malaria, cancer etc. It is the cold property of this herb that makes it efficient against fever. In India, it can also be used

against some complex ailments such as gonorrhea, jaundice, leucorrhoea, pre and post-natal care (Alagesaboopathi et al. 1999; Chopra et al. 1956; Okhuarobo et al. 2014; Saxena et al. 1998). Isolates of *A. paniculata* like andrographolide, neoandrograholide, dehydroandrographolide, isoandrographolide, etc. showcase anti-inflammatory, astringent, hypoprotective and anti-pyloric features which act against influenza, bronchitis, cholera, piles and other diseases mentioned above (Niranjan et al. 2010). The root extract is used in the form of a tincture that is aperient, stimulant, tonic and is administered on poisonous bites. The leaf decoction can also be used for general debility and dyspepsia (Boopathi 2000).

3.2 Phytochemicals and use against cancer

A. paniculata has major phytochemicals such as alkaloids, phenols, flavonoids, terpenoids, tannins and saponins (Nagajothi et al. 2018). The principal flavonoids obtained are 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 7-O-methywogonin, 2'-methyl ether (Kishore et al. 2003; Liaqat 2021). As for its antimicrobial activity, a study by Polash et al. (2017) revealed that the antibacterial activity against gram-positive *B. subtilis* and gram-negative *E. coli* was maximum by aqueous stem extract followed by ethanolic stem extract in both, while maximum activity in *S. typhi* was shown by ethanolic stem extract followed by aqueous leaf as well as stem extracts.

Some bitter compounds have been isolated from the plant like andrographolide, neoandrographolide and deoxyandrographolide which are diterpenoids and diterpenoid glycosides. Andrographolide is considered the major medicinal phytochemical produced which is present in maximum amounts in leaves i.e., 2.39% and the minimum in seeds (Mishra et al. 2007). It is a diterpenoid and possesses a lactone function and it is shown to be antiviral, anti-inflammatory, anticancer, antidiabetic, analgesic, choleretic and anti-allergic in nature (Mu et al. 2012). It shows anti-cancer activity by inducing cell cycle arrest at G_0/G_1 phase and eventually leading to apoptosis with inhibition of tumor growth. It acts against leukaemia, breast cancer, oral cancer, lung cancer, pancreatic cancer and colon cancer (Liaqat 2021; Malik et al. 2021). A study involving observation of *in vitro* anticancer properties of *Andrographis paniculata* showed that different extracts of its leaves like water, ethanol and acetone extracts affected the cancer cell lines differently. Ethanol extracts showed the most cancerous cell inhibition out of the three, which can be reasoned due to the presence of alkaloids and flavonoids (Shanmugam et al. 2015).

3.3 Screening and evaluation of bioactive compounds

A number of experiments have been carried out for isolation and extraction of anticancer bioactive compounds from *A paniculata*, most of which use chromatography as the primary procedure. Andrographolide is mainly found in the aerial parts of the plant. Extraction methods like solid-liquid extraction, ultrasound and microwave-assisted solvent extraction are reported in literature. An experiment conducted by Mulukuri et al. (2011) involved application of column chromatography on chloroform and methanolic extracts. The three compounds obtained were Andrographolide (AND-4), 14-Deoxy andrographolide (AND-6) and neoandrographolide, respectively, when compared to authentic samples. Using MTT assay, the efficiency of each of these compounds was tested against cancer cell lines Hep G2, HCT-116, revealing that AND-4 possessed cytotoxic activities against the cancer cell lines. In another study, an extract of freeze-dried *A. paniculata* leaves was chromatographed using acetone, showed that AND-6 exhibited enhanced proliferation and interleukin-2 (IL-2) induction in human peripheral blood lymphocytes, whereas, 14-deoxy-12-hydroxy andrographolide was reported to act against human lung carcinoma (Tan et al. 2016). Siripong et al. (1992) obtained three compounds namely 14-deoxy-11,12-didehydroandrographolide, andrographolide and neoandrographolide after chromatographic fractionation for isolating diterpenoids which were evaluated for cytotoxicity against KB cells (Human epidermoid carcinoma of nasopharynx) and P388 cells. Andrographolide was the only compound which showed the highest cytotoxicity against both cell lines.

The major bioactive compound of the plant andrographolide inhibits cancerous growth by cell-cycle arrest, inducing apoptosis or necrosis (done via mitochondria and TRAIL pathways) and NF-κβ inhibition. Antiangiogenic behaviour of the compound also plays a role in its possible use in treatment of cancer. Cell cycle arrest is usually made at G_0/G_1 stage effectively. This is done mainly by inducing cell cycle inhibitory proteins such as p16, p21, p27 which is associated with a decline in cyclin A, cyclin D, CDK4 and CDK2 expression. In breast cancer cell lines and lymphoma cells, tumor growth was inhibited by inducing apoptosis through mitochondrial pathway and the TRAIL pathway was followed in human prostate cancer cells.

Angiogenesis occurs for cancer cells to get nutrient supply for growth. This results as a response to chronic inflammation. The anti-inflammatory activity of AG prevents angiogenesis, leading to eventual death of cancer cells. Treatment with AG inhibits

NF-κβ to bind to DNA which down regulates the pro-inflammatory proteins expression. Therefore, this anti-inflammatory activity can prevent further angiogenesis successfully (Malik et al. 2021; Sharma et al. 2011).

4. *Oroxylum indicum*

Oroxylum indicum is an endangered medicinal herb which is mainly distributed in Asian regions such as India, Japan, Thailand, Vietnam, Malaysia, Indonesia, Philippines, Taiwan and Indonesia. This plant belongs to the family of Bignoniaceae, also known as Trumpet creeper family (Deka et al. 2013; Dev et al. 2010; Salleh et al. 2020). Initiating with the studies in Ayurveda, this potent medicinal plant has found applications in different areas of medical and research fields. Chemical compounds found in different parts of *O. indicum* treat various kinds of diseases such as inflammation, cancer, diabetes, ulcers, arthritis and other microbial diseases. It also show photocytotoxic, immunostimulant, hepatoprotective, gastroprotective, anthelmintic, cardioprotective, antiobesic and antiproliferative properties (Harminder Singh et al. 2011).

4.1 Medicinal uses of *Oroxylum indicum*

All parts of the *O. indicum* like stem, root, leaves, and seeds exhibit medicinal properties. It is also known to be safe for human consumption and is effective against many types of diseases in proper dose. Therefore, it is used in a well-known commercial product Chyawanprash. However, most of the compounds in *O. indicum* show anticancer properties based on the studies done by different researchers and scientists. Medicinal plants like *O. indicum* are now used with advanced treatment to prevent cancer. There are numerous approaches available nowadays for cancer treatment e.g. chemotherapy, but due to nonselectivity of drugs, a large number of healthy cells get destroyed along with the malignant cells. There is a need to achieve better cancer treatment, so that healthy cells would not get destroyed with malignant cells. Compounds extracted from medicinal plants are the best fit for this goal. Plant-derived compounds make the cancer treatment procedures more effective and have less side effects (Kooti et al. 2017; Rafieian-Kopaie and Nasri 2015).

Studies has shown that *O. indicum* possess anticancer properties and provide effective treatment against different types of cancer. It has been involved as a promising enemy of cancer, specialist for disease therapy including cervical malignancy (Wahab et al. 2019; Zazali et al. 2013). It has been shown that this plant had the option to

hinder the multiplication of disease cells by going about as hostile to Human Papilloma Virus (HPV) and an apoptosis inducer (Wahab and Mat 2018).

4.2 Phytochemicals and use against cancer

Various parts of *O. indicum* consists of chemical compounds such as, flavonoids, alkaloids, tannin, glycosides, saponins, phenols and quinones (Lalrinzuali et al. 2018; Salleh et al. 2020). Flavonoids are the most significant class of secondary metabolites present in major amount in all parts of *O. indicum*. They are mainly constitutes of baicalein, baicalein-7-O-glucosice, baicalein-7-O-diglucoside, scutellarin chrysin, and oroxylin-A (Salleh et al. 2020; Yadav et al. 2012). Various examinations directed on phytochemicals of *O. indicum* have shown that stem, barks, root barks, leaves, fruits and seeds contain a large amount of baicalein ($C_{15}H_{10}O_5$), a flavone with chemical name 5,6,7-trihydroxyflavon, that possess anti-cancerous properties (Chen et al. 2003; Lalrinzuali et al. 2018; Salleh et al. 2020).

4.3 Screening and evaluation of bioactive compounds

Many studies suggest that baicalein extracted from *O. indicum* has a potential effect against cervical cancer (Wahab et al. 2019; Zazali et al. 2013). This compound showed anticancer activity against HPV. It provides anti-proliferation and firmly induces apoptosis in treated cervical malignant growth cell lines, SiHa and HeLa, by down regulating the expression of HPV oncoproteins, E6 and E7 and up regulating the expression of tumor suppressor proteins, p53 and pRb (Wahab and Mat 2018). Methanol leaf concentrate of *O. indicum* at convergence of 3.87 µg/mL repressed cervical cancer (HeLa cell line) development by instigating G_1/S cell cycle capture and apoptosis by means of p53-mediated pathway (Salleh et al. 2020; Zazali et al. 2013).

In vitro studies has shown that it has anti-proliferative activity against liver cancer (Hep G2 cell line) (Chassagne et al. 2018; Salleh et al. 2020). It also suppress the viability of bladder cancer cells by lowering the number of anti-apoptotic genes- B-cell lymphoma 2 (BCL2), B-cell lymphoma extra-large (Bcl-xL) and X-linked inhibitor of apoptosis protein (XIAP) (Salleh et al. 2020; Yang et al. 2018). Chrysin ($C_{15}H_{10}O_4$) is a dihydroxyflavone with chemical name 5,7-dihydroxyflavone. It has different roles such as anti-inflammatory, hepatoprotective, anticancer and anti-tumorigenic. It has an anti-tumorigenic effect. p53 is a transcription factor that suppresses tumour, it also plays a significant role in cell apoptosis and cell cycle regulation. Therefore, up-regulation of p53 can help in effective treatment of tumour.

A study revealed that treatment with chrysin increases p53 protein expression and its target genes. It also suppress growth of MCF7, breast cancer cell lines (Nagasaka et al. 2018). The antitoxic, antimicrobial and anticancer properties of stem bark of *O. indicum* is more thoroughly done by Moirangthem et al. (2013).

Methanol extract of stem bark showed effective antioxidant activity with the highest amount of phenolic and flavonoid compounds. It also showed cytotoxic effect and apoptosis against HeLa cell lines. However, petroleum ether extract of stem bark of *O. indicum* exhibit highest cytotoxicity and apoptosis on HeLa cell lines (Moirangthem et al. 2013). Parts such as leaf, bark, pod and seeds are also proved to be effective against MCF-7, breast cancer cell (Buranrat et al. 2018). The extract of these parts cause cell death of MCF-7 cells and also act as anti-proliferative against these cells. Highest activity was shown in seeds extract of *O. indicum*, which shows effective results in less doses. The study inferred that these extracts can stop the spread of MCF-7 cells, and provide an effective treatment against breast cancer (Buranrat et al. 2018). *O. indicum* extract does not exhibit hepatotoxic effect. In C57BL/6J mouse model, an *O. indicum* extract sabroxy was given at the dose of 500 mg/kg, every day for 4 weeks. Results shown that sabroxy does not induce any hepatotoxic effect in the mice, as it does not affect the level of enzymes present in liver. The study concluded that relevant dosage of *O. indicum* extract is safe to consume, without any risk of hepatotoxicity (Pondugula et al. 2021).

5. *Scutellaria barbata*

Scutellaria barbata is a traditional Chinese medicinal herb, which is perennial or annual herbs of Lamiaceae family. It is native to the places of Southern China and used as a traditional medicine in parts of China and Korea (Shen et al. 2020). The genus *Scutellaria* is widely distributed in Europe, North America, East Asia, and South America and has 536 species. Different types of chemical compounds are extracted from different parts of *S. barbata* to further analyze their functional properties.

5.1. Medicinal uses of *Scutellaria barbata*

Different chemical compounds of *S. barbata* has found applications in different pharmacological studies such as, antibacterial, antioxidant, anticancer, anti-inflammatory and immunostimulant (Chen et al. 2019). *S. barbata* is also used to treat pimples and hepatitis in Vietnam. As an anticancer medicinal plant, it is found to be effective against human breast cancer and prostate cancer cells, as it inhibits

their proliferation (Tao and Balunas 2016). This medicinal herb tends to exhibit effective antimicrobial properties for example, *S. barbata* showed significant results against XDRAB pneumonia, caused by *Acinetobacter baumannii* (Tsai et al. 2018). Various effective functional properties of *S. barbata* have been exploited to make its way for further clinical researches. A number of phytochemicals from *S. barbata* are exploited for medicinal properties including flavonoids, diterpenoids, polysaccharides and essential oils. A polysaccharide extracted from *S. barbata,* B3-PS1, can potentially treat diseases such as rheumatoid arthritis, Alzheimer's and adult respiratory distress syndromes (Wang 2012; Wu and Chen 2009). Apigenin and luteolin exhibit antibacterial properties (Sato et al. 2000). Scutellarian flavone also showed its cardioprotective effect during *in vitro* studies (Chen et al. 2019; Wang et al. 2016). *S. barbata* is enriched with a range of essential oils. A major volatile oil which is found in *S. barbata* is oxygenated monoterpene. Steroids extracted from the roots of *S. barbata* are cholesterine, stigmasterol and B-sitosterol and various steroid compounds that are extracted from whole herb are soybean steroid-4-alkene-3-ketone; stigmasta-5,22-dien-3-ol; cholesta-6,22,24-triene,4,4-dimethyl chloestric-6,22,24-triene; ergosta-4,6,22-trien-3-alpha-ol; stigmastan-3, 5,22-triene; stigmasta-5,22-dien-3-ol acetate; erogosta-4,6,22-trien-3-ol; sitosterol acetate, phytosteryl-β-D-glucoside and so on (Chen et al. 2019; Yu et al. 2004). Amount of trace metals which are important for human body are also extracted from whole grass of *S. barbata*, which includes Fe, Cu, Mn, Mg, Ca and Zn (Zhan-yu et al. 2008).

5.2 Phytochemicals and use against cancer

At least 130 phytochemicals are present in different parts of *S. barbata* with major amount of flavonoids, alkaloids, polysaccharides, volatile oils and steroids (Chen et al. 2019; Wang 2012; Dai et al. 2013). Flavonoids are the one of the chemical compounds found majorly in *S. barbata* with its derivatives. About 49 derivatives of flavonoids are detected (Wang 2012), out of which 2.1% of flavonoids are present in *S. barbata,* where most of the flavonoid content is present in leaves (Chen et al. 2019). Root of *S. barbata* is also a main store house for various flavonoids. Other main flavonoids isolated from *S. barbata* are wogonin, apigenin, luteolin, naringenin, scutellarian, hispidulin and eriodicytol (Chen et al. 2019). Flavonoids exhibit different pharmacological properties. Wogonin and baicalein showed effective treatment against cancer and have anti-inflammatory actions (Chen et al. 2008; Wang et al. 2018). Studies suggest that flavonoids also have antioxidant properties.

Diterpenoids are the hydrocarbons which consists of 20 carbon atoms and formed of four isoprene units (Jones 2017). *S. barbata* is a source of diterpenoids. Different types of scutellones– A, B, C, D, E, F, G, H, I with A, B, C_1, C_2, D types of scuterivulactones are extracted from *S. barbata* (Chen et al. 2019). Diterpenoid compounds, neo-clerodane are also isolated. There are more than 50 neo-clerodane compounds are present (Wang 2012). Main neo-clerodane diterpenoids compounds extracted from *S. barbata* are different derivatives of scutebarbataine (Type- B,C, D,E, F, G, H, I, J, K, L, M, N, and O), barbatin (Type-A, B, C, D, and E) and scuteliquanine (Type- A, B and C) (Chen et al. 2019). These isolated compounds have pharmacological applications in cancer treatment. Most of the neo-clerodane compounds showed antitumor properties against colon cancer, breast cancer and hepatoma cancer (Chen et al. 2019; Wang et al. 2019).

Other polysaccharides extracted from *S. barbata* are: *S. barbata* polysaccharides SBP, which constitutes of- mannose, arabinose, xylose, rhamnose, glucose and galactose. Second one is, *S. barbata* polysaccharides SPS4, consists of: rhamnose, arabinose, xylose, fucose, glucose, mannose and galactose (Wang et al. 2020; Chen et al. 2019). Polysaccharides exhibit antitumor and immune-stimulatory properties (Linh 2015). The compounds that are extracted from oxygenated monoterpene are: globulol, menthol, thymol, linalool, β-terpineol and hydrocarbon sesquiterpene, including β-bourbonene and β-himachalene (Chen et al. 2019; Li et al. 2013). Hexahydrofarnesylacetone is also detected in significant amount along with 3,7,11,15-tetra- methyl-2-hexadecen-1-ol, 1-octen-3-ol and methyleugenol in aerial parts of *S. barbata* (Yu et al. 2004). Palmitic acid and formylofuran is also isolated in high concentration from the volatile oil, extracted from whole grass of *S. barbata*. Essential oil play a key role in antimicrobial actions. The MIC experiment done by Yu et al. (2004) which showed highly effective antibacterial effect against methicillin-resistant *Staphylococcus aureus* (MRSA).

5.3 Screening and evaluation of bioactive compounds

The chemical compounds of *S. barbata* play a key role against cancer. Their pharmacological activities have been tested against a range of cancers including lung, liver, colorectal, gastric, ovarian, leukemia and others. The flavonoids are further exploited to determine their anticancer properties. Dai et al. (2013) studied the effect of total flavonoids of *S. barbata* on hepatocarcinoma. Matrix

Metalloproteinases (MMPs) leads to metastasis however, tissue inhibitors of metalloproteinase (TIMP) down-regulate the expression of MMPs (Quintero-Fabián et al. 2019). Results revealed that the total flavonoids inhibit the multiplication and invasion of hepatocarcinomic (MCC97H) cells by reducing the expression of MMP-2 and MMP-9 while increasing the expression of TIMP-1 and TIMP-2. Therefore, total flavonoids of *S. barbata* can be effective in treatment of metastasized hepatocarcinoma (Dai et al. 2013). Phytochemical such as BZL101, extracted from *S. barbata,* also exhibit anticancer properties. Marconett et al. (2010) showed how BZL101 of *S. barbata* can be used for therapeutic purposes for breast cancer and prostate cancer. The effect of BZL101 is studied on the early and late-stage breast and prostate cancer cell lines. BZL101 in both the cases of early and late-stage cancers, inhibit the proliferation of cells by regulating the expression of main components of cell cycle. In early stage breast cancer cell line (MCF7), BZL101 arrested cell cycle in G_1 phase and arrested the cell cycle at G_2/M phase in case of early prostate cancer cells (LNCaP) and down-regulated the expression of main components of G_1 and G_2/M phase regulation. Similarly, in late stage breast cancer (MDA-MB-231) cell lines and prostate cancer (PC3) cell lines, it arrested the cell cycle in S phase and down-regulated the expression of main components of S phase regulation (Marconett et al. 2010). Extract of *S. barbata* decreases the expression level of Bcl-2 protein, cause apoptosis and also reduce the malignancy of A2780 ovarian cancer cells by increasing the level of expression Caspase3/9 simultaneously (Chen et al. 2019; Zhang et al. 2017; Shim et al. 2016). *S. barbata* extract also proved to be effective against leukemia. For example, it inhibits the growth by increasing sub-G2 DNA content and induce apoptosis through mitochondrial signaling pathway in U937 leukemic cells (Cha et al. 2004; Chen et al. 2019). Neo-clerodane diterpenoids barbetallarine B and scutebarbatine are evaluated to determine cytotoxic activity against some cancer cell lines 6 HL-60 (human leukaemia) cells, MCF-7 (Human breast cancer) cells, LLC (Lewis lung carcinoma) cells, where barbetallarine B showed less cytotoxicity against HL-60 cell line and scutebarbatine B was inactive against all three cancer cell lines (Lee et al. 2010).

Table 2: Anticancer compounds and their mode of action from the medicinal plants

Medicinal Plant	Genus Name	Common Name	Anticancer Compound	Mode of Action
Catharanthus roseus	*Catharanthus*	Bright eyes	Vinblastine and Vincristine	Affect the cell cycle and inhibit cell divison by acting upon tubulins, prevent formation of microtubules.
Andrographis paniculata	*Andrographis*	Green chiretta	Andrographolide	Inhibits cell growth by cell cycle arrest, induces apoptosis and necrosis via mitochondria and TRAIL pathways and NF-κβ inhibition. Also, act as an antiangiogenic agent.
Oroxylum indicum	*Oroxylum*	Indian trumpet flower	Baicalein	Baicalein showed antiproliferative activity and induces apoptosis in cervical cancer cell lines, SiHa and HeLa by down regulating the expression of HPV oncoproteins, E6 and E7.
			Chrysin	Exhibit anti-tumorigenic property by up-regulating the expression of p53 protein.
Scutellaria barbata	*Scutellaria*	Barbed skullcap	Flavonoids	Inhibits multiplication of hepatocarcinoma by reducing the expression of MMP-2 and MMP-9 while increasing the expression of TIMP-1 and TIMP-2
			BZL101	Inhibits proliferation of breast and prostate cancer cells by down regulating the expression of key components at different phases of cell cycle.

Other than having anticancer properties, *S. barbata* also exhibit various antimicrobial, anti-inflammatory and antioxidant properties. Essential oils provide bactericidal effect against some gram-positive bacteria and methicillin- resistant *Staphylococcus aureus* (Yu et al. 2004) and also *S. barbata* extract has antibacterial effect against XDRAB pneumonia (Tsai et al. 2018). Flavones such as apigenin and luteolin are proved to be toxic against strains of Methicillin-resistant *Staphylococcus aureus* and Methicillin-sensitive *Staphylococcus aureus* (Sato et al. 2000). *S. barbata* has been proved to an antiinflammatory agent to some extent. A study by Liu et al. (2018) suggests that mainly phenolic and flavonoid constituent present in ethanol and ethyl extract of *S. barbata* help in inhibition of expression of different

inflammatory mediators in RAW 264.7 cells such as, lipopolysaccharide-induced nitric oxide, prostaglandin E2, interleukin-6, interleukin-1, phosphor extracellular signal-regulated kinase and phosphor-c-Jun N-terminal kinase (p-JNK). Thus, these phytochemicals of *S. barbata* can be further exploited as antiinflammatory agents. Polysaccharides present in *S. barbata* exhibit antioxidant properties, where a statistical evaluation of polysaccharides present in *S. barbata* by Ye et al. (2012) suggested that they can be a potential anti-oxidative agent for future relevance. Also, flavones apigenin and luteolin have strong antioxidative properties against DPPH (2,2'-diphenyl-1-picrylhydrazyl) radical (Linh 2015).

6. Conclusion and Future Prospects

Cancer is the most fatal disease in both developing and developed countries. It is characterized by irregular cell proliferation. Several therapeutic procedures used to treat cancer have a limitation due to undesirable side effects on normal healthy cells. Thus, there is a growing demand for alternative medicine and holistic approach with higher effectiveness and lower side effects to treat cancer. Recently, medicinal plants and their bioactive products have shown remarkable contributions to human beings' health and have very promising potential towards numerous disease treatments. Myriad benefits like immunomodulatory, antioxidant, and anti-inflammatory properties of medicinal plant-derived natural products and bioactive compounds have led them to be an anti-cancer drug. Medicinal plants like *Catharanthus roseus, Andrographis paniculata, Oroxylum indicum, Scutellaria barbata* secretes numerous phytochemicals. These phytochemicals include vinblastine, vincristine, terpenoids, tannins, saponins, flavonoids (5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 7-O-methywogonin, 2'-methyl ether, moslosooflavone, 7-hydroxy-5-methoxy flavonoid, rivularin, scutevulin, and 1,3 flavonoid glycosides, wogonin, apigenin, luteolin, naringenin, scutellarian, hispidulin and eriodicytol), baicalein diterpenoids (scutebarbatain, barbatin, and scuteliquanine), polyphenols, andrographolide, glycosides, phenols, quinones, polysaccharides, volatile oils, and steroids, that have an anti-cancer effect. These compounds have antioxidant properties, inhibition of DNA damage, cell cycle arrest especially at G_0/G_1; G_2/M phase, eventually leading to apoptosis induction, inhibits proliferation of cancerous cells, and inhibition of angiogenesis in a tumor cell. Thus, the use of medicinal plant-derived compounds is the therapeutic approach to lower the side effects and

increases the effectiveness of treatment with minimal risk. In this chapter, efforts have been made to summarize the significantly important medicinal plants derived phytocompounds with their potent anti-cancer activity and mechanism of their action. It will also provide a baseline for the discovery of novel anticancer drugs and establishment of their analogs. Therefore, more research is required on medicinal plants to explore their anticancerous activity with minimal side effects, and minimum cytotoxicity for the therapeutic intervention.

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