wjpmr, 2023,9(5), 149-154

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

THERAPEUTIC POTENTIAL OF HERBS AS ANTICANCER AGENTS

Tanya Yadav, Tofeeq Khan, Umesh Patel, Ubhay Pandey, Abhishek Soni*

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

***Corresponding Author: Abhishek Soni**

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

Article Received on 08/03/2023 **Article Revised on 28/03/2023** **Article Accepted on 18/04/2023**

ABSTRACT

Cancer is the second leading cause of death worldwide. Although great advancements have been made in the treatment and control of cancer progression, significant deficiencies and room for improvement remain. A number of undesired side effects sometimes occur during chemotherapy. Natural therapies, such as the use of plant-derived products in cancer treatment, may reduce adverse side effects. Currently, a few plant products are being used to treat cancer. However, a myriad of many plant products exist that have shown very promising anti-cancer properties in vitro, but have yet to be evaluated in humans. Further study is required to determine the efficacy of these plant products in treating cancers in humans. This review will focus on the various plant-derived chemical compounds that have, in recent years, shown promise as anticancer agents and will outline their potential mechanism of action. Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. With the success of these compounds that have been developed into staple drugs for cancer treatment new technologies are emerging to develop the area further. New technologies include nanoparticles for nano-medicines which aim to enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration. This review discusses the demand for naturally-derived compounds from medicinal plants and their properties which make them targets for potential anticancer treatments.

KEYWORDS: Medicinal plants, Natural products, Ayurveda, Cancer, Alternative medicine.

INTRODUCTION

Cancer has been a constant battle globally with a lot of development in cures and preventative therapies. The disease is characterised by cells in the human body continually multiplying with the inability to be controlled or stopped. Consequently, forming tumors' of malignant cells with the potential to be metastatic.[1] Current treatments include chemotherapy, radiotherapy and chemically derived drugs. Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer .Cancer remains one of the leading causes of morbidity and mortality globally. Amongst the non-communicable diseases, cancer is the second leading cause of death, after cardiovascular disease. Cancer is responsible for one in eight deaths worldwide more than AIDS, tuberculosis, and malaria together.[2] Overall cancer incidence and mortality are higher in North America, Australia, New Zealand and Western Europe compared to the rest of the world. In the United States, one in four deaths is attributed to cancer. Globally, the number of cancer deaths is projected to increase from 7.1 million in 2002 to 11.5 million in 2030. Chemotherapy is routinely used for cancer treatment. Since cancer cells lose many of the regulatory functions present in normal cells, they continue to divide when normal cells do not. This feature makes cancer cells susceptible to chemotherapeutic drugs. Approximately five decades of systemic drug discovery and development have resulted in the establishment of a large collection of useful chemotherapeutic agents. However, chemotherapeutic treatments are not devoid of their own intrinsic problems. Various kinds of toxicities may occur as a result of chemotherapeutic treatments. For example, 5-fluorouracil, a common chemotherapeutic agent, is known to cause myelotoxicity, cardiotoxicity and has even been shown to act as a vasospastic agent in rare but documented cases. Another widely used chemodrug, doxorubicin causes cardiac toxicity, renal toxicity and myelotoxicity. Similarly, bleomycin a well known chemotherapeutic agent is known for its pulmonary toxicity. In addition, bleomycin shows cutaneous toxicity. Cyclophosphamide, a drug to treat many

malignant conditions, has been shown to have bladder toxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia and at high doses cardiotoxicity.[3]

The toxicity of chemotherapeutic drugs sometimes creates a significant problem in the treatment of cancer using allopathy or established medicine. Various therapies have been propounded for the treatment of cancer, many of which use plant-derived products. There are four classes of plant-derived anticancer agents in the market today, the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptotecin and irinotecan). Plants still have enormous potential to provide newer drugs and as such are a reservoir of natural chemicals that may provide chemoprotective potential against cancer. Recently, Taneja and Qazi, have suggested a number of compounds from medicinal plants with potential anti-cancer activities.

For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment.[4] Plants have been used in medicine for their natural antiseptic properties. Thus, research has developed into investigating the potential properties and uses of terrestrial plants extracts for the preparation of potential nanomaterial based drugs for diseases including cancer. Many plant species are already being used to treat or prevent development of cancer. Multiple researchers have identified species of plants that have demonstrated anticancer properties with a lot of focus on those that have been used in herbal medicine in developing countries. Compounds which are characteristic to the plant kingdom and are necessary for plant survival and "housekeeping" of the organism are being investigated for their ability to inhibit growth and initiate apoptosis of cancerous cells. This article aims to take an overview of current plant derived compounds that have anticancer therapeutic properties and their developments in the field. The step towards development of cancer involves alterations of epigenetic processes and their deregulation. The control of hypermethylation of tumour-suppressor genes on CpG islands is deregulated in cancer cells. This can result in gene silencing and inactivation of tumour-suppressor genes. Drugs which can inhibit or reverse epigenetic alterations have been in development over recent years.[5] Chemically derived epigenetic drugs have been developed and undergone trials such as 5-azacytidine (azacitidine; Vidaza) and 5-aza-2'-deoxycytidine (decitbine; Dacogen) which are both DNMTi and HDACi such as suberoyanilde hydroxamic acid (SAHA, Vorinostat, Zolinza) and FK228 (Romidespin, Istodax).[6] However, it is difficult to engineer a chemically derived drug which is non-toxic to normal cells and is specific to cytotoxicity of cancer cells. Therefore, development and research into naturally derived compounds to be used for anticancer treatment is becoming high in demand with a focus on those derived from plant species and their natural products. There are many forms of cancer amongst the human population but they share similar characteristics or genotypes such as insensitivity to signals which inhibit cell growth making their replication limitless. Apoptosis is evaded and never induced in cancer cells and angiogenesis is sustained within the tumour tissue allowing survival of cancer cells. Plant derived compounds have demonstrated properties to inhibit cancer cell activity such as inhibiting proliferation of cancer cells and inducing apoptotic cell death.[7]

Medicinal plants use as anticancer agents

Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organisation (WHO) some nations still reply of plant-based treatment as their main source of medicine and developing nations are utilizing the benefits of naturally sourced compounds for therapeutic purposes. Compounds which have been identified and extracted from terrestrial plants for their anticancer properties include polyphenols, brassinosteroids and taxols. Many studies have focused on the chemoprotective properties of plants such as anticarcinogenic properties of *Abrus precatorius* on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells.[8] Similarly, Dhar *et al*. have examined the anticancer properties of *Albizzia lebbeck* on sarcoma in mice and *Alstonia scholaries* on benzo[a]pyrene-induced forestomach carcinoma in humans. Other plants that have shown anticarcinogenic properties include *Anacardium occidentale* in hepatoma, *Asparagus racemosa* in human epidermoid carcinoma, *Boswellia serrata* in human epidermal carcinoma of the nasopharynx, *Erthyrina suberosa* in sarcoma, *Euphorbia hirta* in Freund virus leukemia, *Gynandropis pentaphylla* in hepatoma, *Nigella sativa* in Lewis lung carcinoma, *Peaderia foetida* in human epidermoid carcinoma of the nasopharynx, *Picrorrhiza kurroa* in hepatic cancers, and *Withania somnifera* in various tumors.[9]

***Andrographis paniculata* (Burm. F.) Nees**

Andrographis paniculata, commonly known as bhunimba and kalmegha in Sanskrit, kiryat in Hindi and the king of bitters and chiretta in English, is found in India and Sri Lanka. The parts of the plant generally used for medicinal purposes are the roots and the leaves. *A. paniculata* extract contains diterpenes, flavonoids and stigmasterol. The primary medicinal component of Andrographis is the diterpene andrographolide (chemical structure shown below). Andrographolide, described as a "diterpene lactone" due to its ring like structure, has a very bitter taste and has a colorless crystalline appearance. *Andrographis* leaves contain the highest concentration of andrographolide (~ 2.25%), while the seeds contain the lowest.[10]

***Phyllanthus amarus* Schumach. & Thonn**

Phyllanthus amarus is found in tropical Asia, especially in warmer parts of India and is known as bhumyamalaki in Sanskrit, jaramla in Hindi and stone breaker in English. The whole plant, leaves, roots and shoots are reportedly used for their medicinal values. *P. amarus* contains various lignans, flavanoids and tannins, and evidence suggests that *P. amarus* extract may exert antitumor effects. Oral administration of *P. amarus* extract significantly increased the life span and reduced tumor size in mice bearing Dalton's lymphoma ascites (DLA) and Erlich ascites carcinoma (EAC). The chemoprotective properties of this plant may be related to its ability to inhibit metabolic activation of carcinogenic compounds, induce cell cycle arrest and interfere with DNA repair. *P. amarus* plant extract has been reported to result in a significant decrease in n-nitrosodiethylamine (NDEA)-induced tumor incidence.[11] Additionally, a decrease in tumor marker enzymes and liver injury markers has been reported *P. amarus* extract has been shown to inhibit DNA polymerase of hepatitis B virus and related hepatitis viruses and down regulates hepatitis B virus mRNA transcription and translation. The extract of *P. amarus* has been shown to inhibit aniline hydroxylase, a P-450 enzyme responsible for the activation of carcinogens. The extract of *P. amarus* inhibited the activity of cdc 25 tyrosine phosphatase, which is a key enzyme involved in cell cycle regulation. The extract of *P. amarus* resulted in the inhibition of the activity of topoisomerase I and II in *Sacchromyces cerviacae* mutant cell cultures. *P. amarus* extract has also been reported to have anti-angiogenic effects in mice bearing Lewis lung carcinoma with evidence to interfere with the migration of vascular endothelial cells.[12]

***Centella asiatica* Linn**

Centella asiatica, known as mandukaparni in Sanskrit, brahmamanduki in Hindi and asiatic pennywort in English, is another plant that has shown potential as an anticancer agent. This plant is commonly found in India, Australia, Pacific Islands, New Guinea, Malaysia, and Iran. The whole plant or its leaves are being traditionally used for their therapeutic properties. Partially purified fractions of *C. asiatica*, dose-dependently inhibited the proliferation of transformed cell lines, including Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells. However, practically no toxic effects were detected in normal human lymphocytes.[13] Partially purified fractions of *C. asiatica* also significantly suppressed the proliferation of mouse lung fibroblast cells in long-term culture. Oral administration of *C. asiatica* extracts slowed the development of solid and ascites tumors and increased the total life span of tumor-bearing mice. The mechanism underlying the antitumor activity of *C. asiatica* is suggested to be a direct inhibition of DNA synthesis. Pretreatment with *C. asiatica* is protective against radiation-induced liver damage. Pretreatment with *C. asiatica* significantly increases the survival time of irradiated animals. *C. asiatica* extract contains a number of compounds such as asiaticoside, hydrocotyline, vallerine, pectic acid, sterol, stigmasterol, flavonoids, thankunosides and ascorbic acid. *C. asiatica* is an inhibitor of lipid peroxidation in various organs such as liver, lung, brain, heart, kidney, and spleen as well as in serum.[14] In addition, it exhibits anti-elastase activity and acts as a free radical scavenger. *C. asiatica* reduces the level of total ATPase, Mg^{+2} ATPase, Na^{+}-K^{+} ATPase, and increases the level of Ca^{+} ATPase. These processes are suggested to defend the tissue against peroxidation reaction and thus protect it against cell damage. Oral consumption of leaves of *C. asiatica* has been shown to provide protection against oxidative damage.

***Tinospora cordifolia* (Wild) Miers**

Tinospora cordifolia, also known as guduchi in Sanskrit, giloya in Hindi and heartleaf moonseed plant in English, is a bulky, smooth, climbing deciduous shrub lacking bristles. The most commonly used part of the shrub is the stem, but roots are also known to contain important alkaloids.[15] This shrub is commonly found in India, Myanmar, Sri Lanka and China. According to ancient Ayurvedic lexicons, *T. cordifolia* is also referred to as "*amrita"*. The term "*amrita"* is ascribed to this plant due to its ability to impart youthfulness, vitality and longevity. The stem of *T. cordifolia* is used for general debility, dyspepsia, fever, urinary disease, and jaundice. The extract of its stem is used in treating skin diseases. There are certain curative properties of the root of *T. cordifolia* which allow for its use as antidote in snake bite, in combination with other drugs. *T. cordifolia* is well known in modern medicine for its adaptogenic, immunomodulatory and anti-oxidant activities. *T. cordifolia* is also known to have anti-inflammatory, anti-arthritic, anti-allergic properties. This plant is also useful in treating skin diseases, vomiting, anemia, piles, chronic fever, and emaciation. The methanol extract of *Tinospora* contains phenylpropanoids, norditerpene furan glycosides, diterpene furan glycosides and phytoecdysones. The roots of *T. cordifolia* are also reported to contain other alkaloids like choline, tinosporin, columbin, isocolumbin, palmatine, tetrahydropalmatine and magnoflorine.[16]

***Ziziphus nummularia* Wight**

Ziziphus nummularia, also known as bhukamtaka sukhsharanphala in Sanskrit, harbor in Hindi and wild jujube in English, is a thorny small bush or a divaricating shrub, with pale-purplish stems and or grey-velvety stipular prickles in pairs. The different parts of the plant that are used for medicinal purposes are root, bark, stem, flowers and seeds.[17] This shrub is generally found in India, Pakistan, Afghanistan, Egypt, Iran, Iraq, and Israel. Betulin and betulinic acid (chemical structures shown on next page) are present within the bark and stem of Z. *nummularia* and have been shown to have antitumor activity. Betulinic acid glycosides produce differential cytotoxicity, such that cancer cell lines are

more sensitive than normal cells. Similarly, betulinic acid, a naturally occurring pentacyclic triterpenoid, shows selective cytotoxicity against a variety of tumor cell lines. Betulinic acid has been suggested to induce apoptosis by generation of reactive oxygen species, inhibition of topoisomerase I, activation of the mitogen activated protein kinase (MAP kinase) cascade, inhibition of angiogenesis, and modulation of pro-growth transcriptional activators and aminopeptidase-N activity . Furthermore, betulinic acid has been shown to induce apoptosis by a p53- and CD95-independent mechanism. These mechanisms may be responsible for the ability of betulinic acid to effectively kill cancer cells that are resistant to other chemotherapeutic agents.[18]

Curcuma longa

Curcuma longa is popularly known as turmeric in English, haridra in Sanskrit and haldi in Hindi. The rhizome of the plant is traditionally used in cooking. The active ingredient of this plant is curcumin (diferuloylmethane, chemical structure shown below), a polyphenol derived from the rhizome of the plant. Turmeric is used for both cancer prevention and treatment. The anticancer potential of curcumin is associated with its ability to inhibit proliferation in a wide variety of tumor cell types. The anti-proliferative properties of curcumin may be related to its ability to down-regulate the expression of a number of genes, including NF-kappa B, Activator Protein 1 (AP-1), Epidermal growth receptor 1 (EGR-1), cycloxygenase 2 (COX2), lysyl oxidase (LOX), nitric oxide synthase (NOS), matrix metallopeptidase 9 (MMP-9), and tumor necrosis factor (TNF) [19]. Moreover, turmeric reduces the expression of various chemokines, cell surface adhesion molecules, cyclins and growth factor receptors, including epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2) . In addition to its effects on gene expression, turmeric inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. Turmeric has also been shown to inhibit tumor cell invasion and metastasis *in vitro* by reducing MMP-2 activity and by inhibiting HEp2 (epidermoid carcinoma cell line) cell invasion.[20]

***Annona atemoya* Mabb./ *Annona muricata* Linn**

Annona atemoya/muricata is a native of Caribbean, Central and South America. It is also commonly grown in South East Asia especially in eastern part of India. This plant is traditionally known as mamaphal in Hindi and sour-sop of America in English. The parts of the plant that are generally used for medicinal purposes are the root, bark, leaf and fruit. The fruit of *A. atemoya* contains bullatacin (chemical structure shown below), an acetogenin known to have antitumor properties. Bullatacin induces chromatin margination and tumor cell condensation, followed by apoptosis. *A. atemoya* contains two annomuricins namely A and B, which have shown cytotoxicity in human solid tumor cell lines A-549 lung carcinoma, MCF-7 breast carcinoma, and HT-29 colon adenocarcinoma cell lines. *A. atemoya* contains several other acetogenins that have also been shown to selectively induce cell death in tumor cells *in vitro*. In particular, two annonaceous acetogenins were found to produce cell death in the human hepatoma cell line HepG2 and hepatoma 2.2.15 cells.[21]

***edrus deodara* (Roxb. Ex. D. Don) G. Don**

Cedrus deodara (deodar cedar, himalayan cedar, or deodar in Hindi, devdar in Sanskrit, xue song in Chinese) is native to the western Himalaya (Hind Kush mountains), eastern Afghanistan, northern Pakistan, northwest and northcentral India, southwestern Tibet and western Nepal.[22,23] It is widely grown as an ornamental tree and planted in parks and large gardens for its drooping foliage. The name "deodar" is derived from modern Indian language derivatives of the Sanskrit name "devdar", meaning "timber of the gods". Bark of the *Cedrus deodara* is a good remedy in remittent and intermittent fevers, inflammation, rheumatoid arthritis, cancer, ulcers, diarrhea and dysentery. The oleo-resin from deodar is valued as a cure for skin diseases. Cedarwood oil is used as an expectorant, catarrhal of respiratory tract, anti-ulcer, arthritis pain reliever, anti-diabetic, anti-inflammatory, and to cure skin diseases.[24]

***Boswellia serrata* Roxb**

Boswellia serrata is a deciduous middle sized tree, which is most commonly found in tropical parts of Asia and Africa. The gum from the plant is tapped from incisions made on the trunk of the tree, which is then stored in specially made bamboo baskets and converted into different grades of material according to flavor, color, shape and size. A number of pharmacological properties of the gum have been documented.

***Mappia foetida* Miers. / *Nothapodytes foetida* Miers**

Mappia foetida/ Nothapodytes foetida is generally found in tropical countries. The medicinal properties of *M. foetida* have recently gained international attention.[25] The active component of *M. foetida* tree wood is camptothecin (chemical structure shown below), a potent chemotherapy drug used to treat leukemia. Recent studies have indicated that an endophytic fungus which grows on this plant also produces the camptothecine. Camptothecines have broad spectrum of antitumor activities both *in vitro* and *in vivo*. For example, camptothecines have been shown to be effective inhibitors of nucleic acid synthesis in HeLa cells and L-120 cells. The anti-neoplastic activity of camptothecine has been attributed to its inhibitory action on the nuclear enzyme type-1 DNA topoisomerase (topo-1) this alkaloid as well as several semisynthetic or fully synthetic analogues, are in various stages of preclinical and clinical trials. Irinotecan (7-ethyl-10-[4-(Ipiperidino)-I-piperidinol] carbonyloxycamptothecine) is a new potent semi-synthetic derivative of camptothecine, which is active against ascites and solid mouse tumors and induces partial or complete remission of breast carcinoma in the xenograft model system . A

series of Phase II clinical trials have been conducted to assess the anticancer activity of camptothecines and their analogues. The Phase II trials have revealed an extensive range of activities against lymphoma, leukemia, and solid epithelial tumors.[26] Topotecan, another synthetic modification of 10-hydroxycamptothecine, has been shown to slow the growth of human colon cancer cells, rhabdomyosarcoma cells, and osteogenic sarcoma xenografts.

***Withania somnifera* (Linn.) Dunal**

Withania somnifera (Linn.) Dunal (Solanaceae) known as ashwagandha in Sanskrit and Hindi, winter cherry in English, is a small subtropical shrub. The roots and leaves of *W. somnifera* have been used in the Indian traditional system of medicine Ayurveda, and the plant is marketed world-wide because of its medicinal properties. It is also one of the members of GRAS (generally regarded as safe) category of plants that has found several therapeutic uses. *W. somnifera* extract is suggested to modulate a variety of biological responses. Therefore, it has been extensively used in many indigenous preparations for its anti-ageing, aphrodisiac, cardiotonic, thyro-regulatory, anti-peroxidative, anti-inflammatory, antitumor, anti-stress, anti-oxidant, immuno-modulatory, hemopoietic, and rejuvenating properties.[27]

CONCLUSION

Any practical solution to controlling the initiation and progression of cancer is of paramount importance. The use of medicinal plant products to manage or arrest the carcinogenic process provides an alternative to the use of conventional allopathic medicine for treatment of the disease. Many herbs have been evaluated in clinical studies and are currently being investigated to understand their tumouricidal properties against various cancers. Cancer is becoming a high profile disease in developed and developing worlds. In 2007 the WHO published that in 2005, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries. In the United States cancer is the cause of 1 in 4 deaths and in 2010 it was estimated there were over 1.5 million new cases of cancer. Cancer Research UK said in 2012 14.1 million adults were diagnosed with cancer and 8.2 million people were killed by cancer globally. Therefore, the demand for a cure and the prevention of cancer is extremely high. Chemically-derived drugs have been developed and other cancer treatments pre-exist. However, current methods such as chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems. Therefore, there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source.

REFERENCES

1. W.H.O. Preventing chronic diseases: a vital investment, in WHO press. Geneva: WHO Global report, 2005.
2. Mathers CD, Loncar D. PLoS Med, 2006; 3(11): 442.
3. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Lancet. 2006; 367(9524): 1747–1757.
4. Hoyert DL, Heron MP, Murphy SL, Kung H-C. Natl. Vital Stat. Rep., 2006; 54(13): 1–120.
5. Jain S, Trivedi M, Raikwar M, Lodhi M, Ali MY, Purohit A, Nema P. A Review on Herbal Cosmetics and Cosmeceuticals. Asian Journal of Dental and Health Sciences, 2022 Dec 15; 2(4): 9-16.
6. Parkin DM. Oncogene, 2004; 23(38): 6329–6340.
7. Parkin DM, Bray F, Ferlay J, Pisani P. Int. J. Cancer, 2001; 94(2): 153–156.
8. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. CA: Cancer J. Clin, 2007; 57(1): 43–66.
9. Nema P, Jain S, Vishwakarma H, Purohit A, Jain PK. A complete review on aromatherapy: a complementary alternative medication therapy with recent trend. International Journal of Medical Sciences and Pharma Research, 2021; 7(4): 1-7.
10. Rexroth G, Scotland V. Med. Klin, 1994; 89(12): 680–688.
11. Seidel C, Florean C, Schnekenburger M, Dicato M, Diederich M. Chromatin-modifying agents in anti-cancer therapy. Biochimie, 2012; 94: 2264–2279.
12. Kumar S, Pathania AS, Saxena AK, Vishwakarma RA, Ali A, Bhunshan S. The anticancer potential of flavonoids isolated from the stem bark of Erythrina suberosa through induction of apoptosis and inhibition of STAT signalling pathway in human leukaemia HL-60 cells. Chemico-Biological Interactions, 2013; 205: 128–137.
13. Rajeswara Rao BR, Singh K, Sastry KP, Singh CP, Kothari SK, Rajput DK, Bhattacharya AK. Cultivation Technology for Economicaly Important Medicinal Plants. In: Reddy KJ, Bahadur B, Bhadraiah B, Rao MLN, editors. Advances in Medicinal Plants. University Press; Hyderabad, 2007; 112–122.
14. Azmi AS, Bhat SH, Hanif S, Hadi SM. Plant polyphenols mobilize endogenous copper in human peripheral lymphocytes leading to oxidative DNA breakage: A putative mechanism for anticancer Properties. FEBS Letters, 2006; 580: 533–538.
15. Apostolou A, Stagos D, Galitsiou E, Spyrou A, Haroutounian S, Portesis N, Trizoglou I, Hayes AW, Tsatsakis AM, Kouretas D. Assessment of polyphenolic content, antioxidant activity, protection against ROS-induced DNA damage and anticancer activity of Viti vinifera stem extracts. Food and Chemical Toxicology, 2013; 61: 60–68.
16. Siriwantanmetanon N, Fiebich BL, Efferth T, Prieto JM, Heinrich M. Traditionally used Thai medicinal plants: In vitro anti-inflammatory, anticancer and antioxidant activities. Journal of Ethnopharmacology, 2010; 130: 197–207.

17. Purohit A, Jain S, Nema P, Jain DK, Vishwakarma H, Jain PK. A comprehensive review on tailoring an herbal approach for treatment of poly cystic ovarian syndrome. Asian Journal of Dental and Health Sciences, 2022 Mar 15; 2(1): 27-32.
18. Gupta SC, Tyagi AK, Deshmukh-Taskar P, Hinojosa M, Prasad S, Aggarwal BB. Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols. Archives of Biochemistry and Biophysics, 2014; 559: 91–99.
19. Cao J, Xia X, Chen X, Xiao J, Wang Q. Characterization of flavonoids from Dryopteris erythrosora and evaluation of their antioxidant, anticancer and acetylcholinesterase inhibition activities. Food and Chemical Toxicology, 2013; 51: 242–250.
20. Agati G, Azzarello E, Pollastri S, Tattini M. Flavonoids as antioxidants in plants: Location and functional significance. Plant Science, 2012; 196: 67–76.
21. Huntely AL. The health benefits of berry flavonoids for menopausal women: Cardiovascular disease, cancer and cognition. Maturitas, 2009; 63: 297–301.
22. Wen L, Wu D, Jiang Y, Prasad KN, Lin S, Jiang G, He J, Zhao M, Luo W, Yang B. Identification of flavonoids in litchi (Litchi chinensis Soon.) leaf and evaluation of anticancer activities. Journal of Functional Foods, 2014; 6: 555–563.
23. Xia X, Cao J, Zheng Y, Wang Q, Xiao J. Flavonoid concentrations and bioactivity of flavonoid extracts from 19 species of ferns from China. Industrial Crops and Products, 2014; 58: 91–98.
24. Jain S, Purohit A, Nema P, Vishwakarma H, Jain PK. A brief review on nutraceuticals and its application. Asian Journal of Dental and Health Sciences, 2022 Mar 15; 2(1): 7-13.
25. Malíková J, Swaczynová J, Kolář Z, Strnad M. Anticancer and antiproliferative activity of natural brasinosteroids. Phtyochemistry, 2008; 69: 418–426.
26. Steigerová J, Oklešťková J, Levková L, Kolář Z, Strnad M. Brassinosteroids cause cell cycle arrest and apoptosis of human breast cancer cells. Chemico-Biological Interactions, 2010; 188: 487–496.
27. Steigerová J, Rárová L, Oklešťková J, Křížová K, Levková M, Šváchová M, Kolář Z, Strnad M. Mechanisms of natural brassinosteroid-induced apoptosis of prostate cancer cells. Food and Chemical Toxicology, 2012; 50: 4068–4076.