Phytochemicals - a New Pipeline for Anticancer Drug Development

Foram Patel*, Denni Mammen, Elizabeth Robin and Darshee Baxi

School of Science, Navrachana University, Vasna-Bhayli Road, Vadodara-391 410, Gujarat, India

Received: 26 August 2021 Revised: 12 January 2022 Accepted: 20 January 2022 Published: 3 March 2022

*Corresponding Author: foramp@nuv.ac.in

Abstract

In spite of advance interventions and novel strategies, cancer is still one of the major causes of mortality worldwide. The constant increase in cancer patients, failure of conventional chemotherapeutics due to toxicity clearly demands an alternative approach. In past decades, scientific community is engrossed in the discovery of new agents from natural sources. The phytochemicals have recently gained the attention because of their potential to modulate cascades of molecular mechanisms that governs the tumor growth and progression. The protective effects of phytochemicals have gained attention due to less side effects and greater safety index. The present review summarizes the perspective of the scientific evidences as well as their potential druggability. The approach aimed to examine the current status of phytochemical compounds currently used to treat cancer and their potential at a preclinical and clinical level. It also addresses current challenges that lie ahead for their use. The methodology adopted for this review was comparative analysis of the papers published in the areas of antitumor plant-based products or plant compounds or dietary phytochemicals, anticancer phytochemicals or anticancer herbs. The analysis involved papers published from 2010 to 2020 for the recent understanding.

Keywords

Cancer, Secondary metabolites, Phytochemicals, Phyto-agents

Introduction

Cancer is a significant public health problem worldwide and is the second leading cause of death. Cancer is a large group of diseases that begin in any organ or tissue of the body when abnormal cells grow wildly, go past their usual limits to attack connecting parts of the body and/or spread to other organs. The latter process is called metastasizing and is a significant reason of death from malignancy. A neoplasm and malignant tumors are commonly considered for cancer. According to the World Health Organization (WHO), it is estimated that globally 9.6 million deaths occur due to cancer and its complications. Lung, colorectal, prostate, liver and liver cancer are well known types of cancer in men, while breast, cervical, thyroid, lung and colorectal cancer are well known among the women. The economic burden continues to grow due to lack of proper health management systems. The current treatment options available for treatments are chemotherapy and radiation therapy while sometimes surgical removal is also opted. The major disadvantage due to the chemotherapeutics is relapse of cancer, drug resistance and toxicity to the non-targeted tissues. These problems resist the use of the currently available chemotherapeutics drugs as it ultimately impairs the quality of life. Therefore, there is urgent need to search new lead anticancer agents with better potency and lesser complications. There are many scientific evidences available which shows that natural compounds are good sources for the development of new remedies for cancer.[1] There has been investigation that floral kingdom consists of approximately 250000 plant species and nearby 10% have been researched for the cancer treatment.[2] The plant derived analogues are present in different plant and have several pharmacological functions. There is wide research gap and investigation is needed to identify the molecules involved in cell signaling network and better assessment is needed in understanding their mechanism of action. Another research need is dosage concentration and frequency of intake at human trials. However, an important research need is testing in vitro dosage which are unachievable in human trials.[3-6] Phytochemicals serve as the promising candidate for the treatment of the cancer. For example, currently Taxol analogues, Vinca alkaloids and podophyllotoxins analogues has been used for the treatment. This paper aims to review the available biological actions of phytoconstituent in relation to cancer treatments. It also attempts to investigate the current concerns of chemotherapeutics being used in practice.

Challenges and introspection into the current cancer treatment regimen:

There are three major aspects for clinical trials with phytochemicals: 1) adjuvant for chemo and radiotherapy. 2) reduction of chronic side effects of chemotherapy, and 3) unwanted interaction with chemo and radiotherapy. The array of compounds like berberine, curcumin, epigallocatechin, quercetin, resveratrol and sulphorafane are currently in clinical trials on various cancers. The major classes of plant-based anticancer compounds clinically used include epipodophyllotoxin, camptothecin derivatives, vinca alkaloids, and taxane diterpenoids. However, there still remains the key concern of poor solubility, poor penetration in target cells, limited therapeutic potential and toxicity. In this regard, prodrugs, combination therapy with conventional chemotherapeutics, synthetic metal analogues and nano-formulations could be targeted to enhance the bioactivity. These major limitations can be overcome with the advent of nanotechnology and micro-encapsulation of phytochemical for targeted delivery, longer circulation period in the bloodstream and lesser side effects over free compounds. The combinational approach with mixture/single of phytochemicals and chemotherapeutic drugs induce synergistic effect and may be efficient at the lower dose compared to an individual drug which increases toxicity in normal cells. The use of cholesterol/sphingomyelin liposomal vincristine (Mariqbo®) for the treatment of acute lymphoblastic leukemia was approved by Food and Drug Administration (FDA).[7] Paclitaxel is considered to be a magic pill in chemotherapeutic not only used as a single drug but combined with other anticancer drugs. The hormone-refractory metastatic breast and prostate cancer is treated with Cabazitaxel (Jevtana®) approved by FDA.[8] These modifications in delivery system have increased accumulation of drugs in target cells and improved their cytotoxicity. When docetaxel combined with curcumin administered in mice having breast cancer showed reversal in drug resistance.[9] Recently it has been reported that the gingerol increased the sensitivity of cisplatin in gastric cancer and doxorubicin in liver cancer.[10-11]

An overview of Phytochemicals

Phytochemicals, or 'plant chemicals', are bioactive non-nutrient plant compounds that has ability to interact with at least one component of a living tissue introducing enormous scope of credible effects. They shield plants from destructive microorganisms and also from ultraviolet (UV) irradiation and extreme temperatures. Additionally, birds and insects are attracted to promote seed dispersal, pollination and germination. Phytochemicals are responsible for

colours to plants and range of flavours both pleasant and unpleasant when consumed. They are explicit to specific plants and parts of plants, and that they usually synthesis is increased during stressful events. Phytochemicals additionally provide health benefits when plant or its part are devoured. They consist of biomolecules essential for well-being (e.g., proteins, carbohydrates, vitamins, and minerals) and other supplements (e.g., phenolic acids, flavonoids, and other phenolics).[12] Phytochemicals are classified as primary metabolites and secondary metabolites. Primary metabolites comprise of the common sugars, amino acids, proteins, nitrogenous bases pyrimidines and purines, chlorophylls etc. Secondary metabolites include alkaloids, flavonoids, steroids, terpenes, lignans, saponins, phenolics and glucosides. The detailed classification is represented in Fig 1.

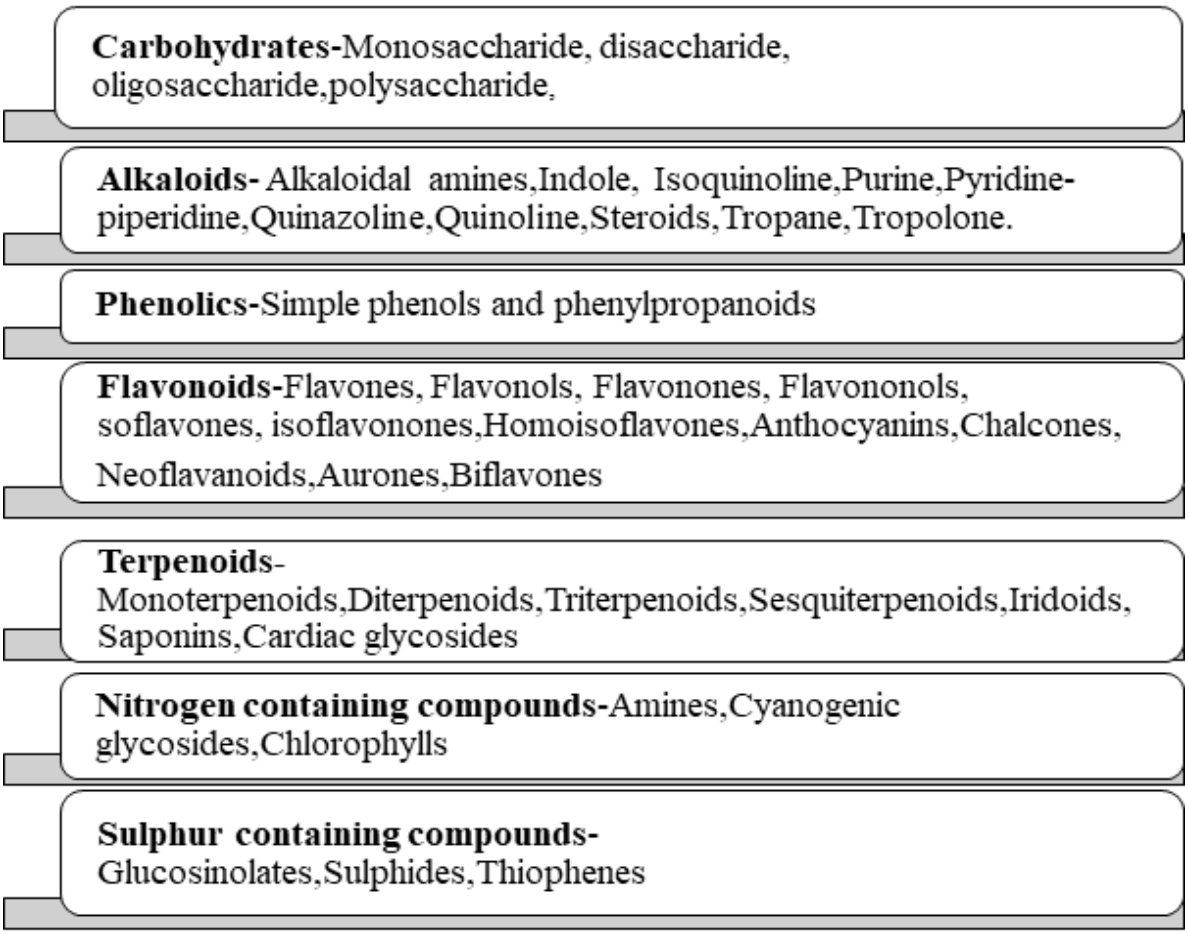

Figure 1: Classification of Phytochemicals

Role of Phytochemicals in cancer treatment

Plants are indispensable sources for anticancer drug development. Natural dietary phytochemicals are broadly utilized in in vitro, in vivo, and preclinical cancer prevention and treatment studies. In number of clinical trials have shown various degrees of success. Since ancient times plants and their formulations are used for its probable effects. In any case, therapy of plant-based compounds for the treatment of cancer can be followed back to 1950s. Some of the very first anticancer agents derived from plants are vinca alkaloids such as vinblastine, vincristine, and cytotoxic podophyllotoxins. Modern drug development program based on Ayurveda and has acquired acknowledgement in present healthcare settings. Plant derived natural products are nontoxic to normal cells and also better endured henceforth they have acquired consideration for modern drug discovery. Alkaloids, flavonoids, phenolics, tannins, glycosides, gums, resins and oils and their derivatives present in root, stem, bark leaf, and flower perform many pharmacological functions in human systems. Vinblastine, vincristine, taxol, elliptinium, etoposide, colchicinamide, 10-hydroxycamptothecin, curcumol, gossypol, ipomeanol, lycobetaine, tetrandrine, homoharringtonine, monocrotaline, curdione, and indirubin are astounding phyto molecules in this scenario.[13] The extraordinary potential of plant-based compounds for the treatment and counteraction of cancer is ascribed to their safety, low cost, and oral bioavailability. However, a couple of plant-based compounds induce some side effects. It also has been elucidated that phytochemical can modulate key cellular signalling pathways from initiation to progression by targeting different stages. The exposure of carcinogen at cellular, genetic and epigenetic levels triggers the multistep carcinogenesis process. The initial uptake of carcinogenic agent and its assimilation in tissues where its activation and detoxification occur, interaction with the DNA, results in genetic damage and transformation into neoplastic cells.[14] The tumour promotion on other hand is relatively expanded proliferation of cancerous cells regulated by mediators of cell signalling pathways like receptors, regulatory proteins, kinases and cyclins. The tumour promotion on other hand is relatively expanded proliferation of cancerous cells regulated by mediators of cell signalling pathways like receptors, regulatory proteins, kinases and cyclins. The final stage is progression of neoplastic transformation characterized by metastatic potential and migration to the distant location in the body. Thus this bidirectional communication between cells and their secondary sites serve as one of the promising target for the action of phytocompounds.[15] For instance, to name a few dietary phytochemicals like quercetin from onion, apple, lemon, Epigallocatechin

from green tea, genistein from soya bean, caffeic acid from coffee, resveratrol from red grapes, berries, Indol-3-carbinol from cruciferous vegetables have been proved in extensive range of anti-proliferation, cell cycle blockage, DNA repair alterations, apoptosis induction, free radical scavenging, anti-inflammation, activation of tumour suppressor genes, suppression of oncogenes, regulation of growth factors and hormones and inhibition of invasion, angiogenesis and metastasis.[16] The molecular connection between the phytochemicals and regulatory check points of cancer progression is illustrated in the fig.2. Several crude phytochemicals which are obtained from medicinal plants and has multifactorial effects on the many types of cancer are as depicted below.

Important phytochemicals and their effect on types of cancer:

1. Andrographolide

Species: *Andrographis paniculata*

Andrographolide is one of the diterpene lactone found in the Andrographis paniculata which is reported to exert the anti-proliferative activity on various human cancer cells.[17] The anti-cancer activity is modulated through cell-cycle arrest by induction of p27 accompanied with decrease in cyclin dependent kinase 4 (CDK4) expression. Further, the immunomodulatory activity was reported by increase in cytokine levels and enhanced natural killer cell activity. These demonstrate andrographolide as an opportunistic pharmacophore with potent anticancer/immunomodulatory activity.[18]

2. Berberine

Species: *Berberis vulgaris*

Berberine is a benzylisoquinoline alkaloid present in the roots, rhizomes, stem and bark of *B. vulgaris.* Berberine has multifaceted role like cell cycle arrest, autophagy, inhibition of cell invasion and metastasis, regulation in tumour microenvironment and immunomodulatory activity.[19] Also it has been demonstrated *in vivo* levels of catalase and glutathione peroxidase enzymes increased which proves berberine as a potent anti-oxidant.[20]

3. Crocetin

Species: *Crocus sativus*

Crocetin is a diterpenoid and natural carotenoid found in crocus flower. There are reports which shows that crocetin have significant effect on Breast, Cervical, Colorectal, Leukemia, Liver, Lung, Pancreas, Skin.[21] Crocetin exert anti-proliferative, anti-apoptotic, and decrease the

activity of RNA and DNA polymerase. It also decreases the lipid peroxidation with concomitant increase in GST, catalase and superoxide dismutase.[22-23]

4. Curcumin

Species: *Curcuma longa*

Curcumin is polyphenol extracted from rhizome of Curcuma longa also known as turmeric. Several studies demonstrated curcumin's anti-cancer activity on leukemia, breast, gastric, pancreas, colorectal, prostate, cervical, liver and lung.[24] The curcumin mainly exerts its activity by prompting apoptosis and restraining proliferation and invasion of tumors by suppressing cellular signalling pathways like including Wnt/β-catenin, PI3K/Akt, JAK/STAT, MAPK, p53 and NF-κB.[25]

5. Aloe emodin

Species: *Aloe barbadensis*

Aloe emodin *is* dihydroxyanthraquinone present in sap of aloe vera. It exhibits an array of deleterious effect on cancers like ovary, colorectal carcinoma, gastric carcinoma, liver, glioma, leukemia, breast, small cell lung cancer including reduction in cell viability, induction in cell cycle arrest, apoptosis, cell cycle arrest through downregulation of cyclin dependent and independent kinase. Additionally, emodin related compounds also served as adjuvants with chemotherapy in treatment of certain cancers.[26-27]

6. Magniferin

Species: *Mangifera indica*

Magniferin is xanthoid present in the peel, stalks, leaves, barks, kernel, and seed of mango fruit. Magniferin showed anti-proliferative effect on breast, prostate, pancreas, lung, colon, leukemia and cervical cancer.[28] Further it causes cell cycle arrest at G2/M phase accompanied with the inhibition of expression levels of proteins like ATR, Chk1, Wee1, Akt, and Erk1/2. It also relieves the oxidative stress, suppress metastatic potential, decrease the expression of MMP-7 and 9, and inhibit b-actin pathway by reversing epithelial-mesenchymal transition (EMT).[29]

7. Plumbagin

Species: *Plumbago zeylanica*

Plumbagin is a naphthoquinone isolated from roots of Plumbago zeylanica. There are reports which demonstrated the role of Plumbagin against gastric, breast, melanoma, promyelocytic leukemia cancer. It has been reported that plumbagin suppress malignant activity of tumour

cells through cascade of mechanism such as the inhibition of growth, invasion, metastasis and anti-angiogenesis.[30] Flow cytometric analysis of human cancer cell lines revealed that Plumbagin arrest cell cycle at G1 phase with concomitant inhibition of cyclin D1, cyclin E, and upregulation of p53.[31]

8. Piperine

Species: *Piper longum*

Piperine is an alkaloid transcendently found in the fruits and roots of Piper longum. Black pepper has been exploited as king of spices in Indian system of medicine for various ailments.[32] Piperine not only exhibits anti-proliferative activity but also regulates the fundamental proteins involved in the cancer progression. Piperine inhibits cell proliferation via cell cycle arrest, triggers reactive oxygen species production which in turn activates intrinsic and extrinsic apoptosis pathways. Piperine at the molecular level block the Akt phosphorylation leading to inhibition of angiogenesis and vascular endothelial growth factor (VEGF).[33]

9. Epigallocatechin

Species: *Camellia sinensis*

Epigallocatechin (type of catechin) is a polyphenol extracted from tea plant. The epigallocatechin mediates the anti-cancer activity via inhibition of nuclear factors associated with the inhibition of migration, invasion and angiogenesis. It has dual function of anti-oxidant and pro-oxidant potential which modulates the production of reactive oxygen species leading to epigenetic modification, regulation of histone acetylation and upregulation of apoptosis.[34-35]

10. Resveratrol

Species: *Vitis vinifera*

Resveratrol is trans-stilbenoid polyphenol present predominantly in grapes but also found in mulberries, blueberries, cranberries and peanut. Resveratrol activates apoptotic pathways which includes increase in levels of Bax and decrease in levels of Bcl-2 and cyclin D1. In addition to this it regulates cell differentiation, DNA repair, cell cycle arrest, autophagy, angiogenesis and metastasis.[36] It also modulates the balance of cyclins as well as cyclin-dependent kinases (CDKs) which inhibits cell cycle at G0-G1 phase. It activates the STAT3 which promotes the proliferation, survival, invasion, angiogenesis, and metastasis of tumour cells.[37]

Phytochemical	**Type of cancer**	**Biological action**
Andrographolide[38-39]	Breast, Liver, Lung, Ovarian, Cervical	suppression of heat shock protein 90, cyclins and cyclin-dependent kinases, metalloproteinase and growth factors, and the induction of tumour suppressor proteins p53 and p21.
Berberine[40-42]	Breast, Liver, Lung, Ovarian, Cervical, Prostate, Colorectal	Caspase activation; ROS production, Cytochrome c release; Bcl-2/Bcl-xL decrease, COX-2 downregulation
Crocetin[43-45]	Breast, Cervical, Colorectal, Leukemia, Liver, Lung, Pancreas, Skin.	suppression of Bcl-2 and up-regulation of Bax expression,
Curcumin[46-48]	Blood, Breast, Gastric, Pancreas, Colorectal, Prostate, Cervical, Liver, Lung, Skin	interfere with multiple cellular signalling cascades including Wnt/β-catenin signalling, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling pathway, mitogen-activated protein kinase (MAPK) pathway, p53 signalling and nuclear factor-κB (NF-κB) pathway
Aloe emodin[49-50]	Ovary, Colorectal carcinoma, Gastric carcinoma, Liver, Glioma, Blood, Breast	cell cycle arrest through downregulation of cyclin dependent and independent kinase and suppression of Bcl-2 and up-regulation of Bax expression
Magniferin[51]	Breast, Liver, Lung, Blood, Prostate, Brain, Gastric, Kidney	down-regulation of inflammation, cell cycle arrest, reduction of proliferation/metastasis, promotion of apoptosis in malignant cells and

		protection against oxidative stress and DNA damage.
Plumbagin[52-54]	Breast, Liver, Lung, Blood, Prostate, Brain, Gastric, Kidney	Cell cycle arrest, DNA damage, apoptosis, and suppression of telomere and telomerase activity, inhibition of proteasome, Inhibition of COX-2 and STAT3 signalling pathway
Piperine[55-56]	Breast ,Lung, Prostate, cervical, Ovary, colorectal	induction cell cycle arrest, increased cell apoptosis, disruption of redox homeostasis, inhibition of angiogenesis, modulation in stress, and autophagy, influence on the Wnt/β-catenin and inhibition of PI-3K/Akt signalling pathways.
Epigallocatechin[57-58]	Breast, Lung, Pancreatic, Ovary, Oral, Prostate, Blood, Colorectal,	induction of apoptosis, inhibiting NF-κB activation and downregulate the key genes associated with angiogenesis, tumour metastasis and survival.
Resveratrol[59-60]	Breast, Colon, Liver, Lung, Prostate, Blood	induction cell cycle arrest, increased cell apoptosis, inhibition of COX-2 and STAT3 signalling pathway

Table 1: Summary of phytochemicals used in cancer treatment.

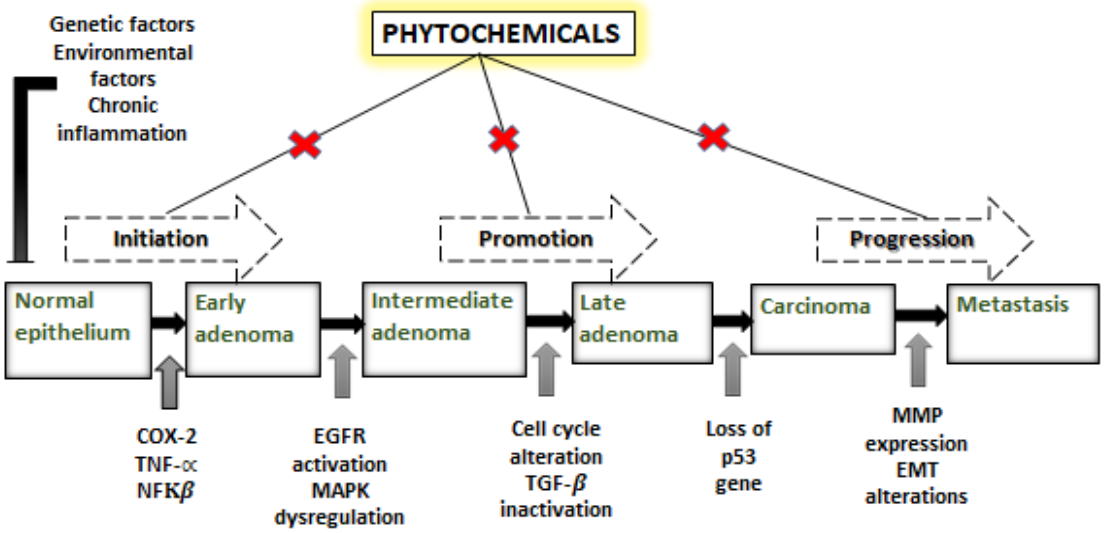

Figure 2: Phytochemicals alterate the key signalling pathways of cancer from initiation to progression.

Conclusion and Future perspective:

The high biodegradability and biocompatibility of phytocompounds have open the new avenues in cancer therapy. The phytochemicals can be categorized as signalling molecules and imposition of serving as phyto-chemotherapeutics is still needed to be investigated. The phytocompounds could be combined with the conventional therapies to enhance the potency and prevent tumour recurrence after achieving a successful treatment. The pleotropic properties of Phyto agents can be considered as pioneering adjuvant line of action that can be in combination with chemotherapeutics. In conventional approach of research, efficacy of phytochemicals is evaluated in vitro and then in vivo followed by mechanistic studies. This screening only suffices the cytotoxic effect on cancer cells. To overcome these limitations, the approach should be developed to predict the pharmacological activities by using OMICS analyses. Although there are many known phytochemicals having cytotoxic effects, but the exact molecular/cellular targets and systematic mechanisms for many of them is questionable. With the advancement of bioinformatics, the in-silico approaches to study the pharmacokinetics properties of molecules should be opted. So due to large scale use of traditional healthcare products and their demand by humans, it is very essential to scrutinize different formulations for anticancer therapy in vitro as well as in vivo.

Glossary:

- **Neoplasm-** an abnormal growth of tissue caused due to rapid cell division. It is also known as tumour.
- **Malignant tumors-** cancerous tumor
- **Chemotherapeutics-** drugs for treatment of cancer.
- **Adjuvant-** substance which help or aid to increase the potency of the drug.
- **Alkaloid-** a class of naturally occurring heterocyclic nitrogen bases in plants having pharmacological effects.
- **Flavonoids-** a class of complex polyphenolic compounds naturally present in plants.
- **Terpenoids-** also known as isoprenoids.
- **Tannins-** water soluble polyphenol naturally present in plants.
- **Apoptosis-** It's a programmed cell death.
- **Metastasis-** It's a process through which cancer cells spreads to other body parts.
- **Adenoma-** structurally unorganized neoplasm consisting of fibrous, glandular and fat tissues.
- **Carcinoma-** most common type of malignancy starts at inner or outer epithelium of the organs.

References:

1. Solowey, E., Lichtenstein, M., Sallon, S., Paavilainen, H., Solowey, E., & Lorberboum-Galski, H. (2014). Evaluating medicinal plants for anticancer activity. *The Scientific World Journal*, *2014*, Article ID 721402 ,12-24. DOI: https://doi.org/10.1155/2014/721402
2. Singh, S., Jarial, R., & Kanwar, S. S. (2013). Therapeutic effect of herbal medicines on obesity: herbal pancreatic lipase inhibitors. *Wudpecker J Med Plants*, *2*(1), 53-65.
3. Yadav, V. R., Prasad, S., Sung, B., & Aggarwal, B. B. (2011). The role of chalcones in suppression of NF-κB-mediated inflammation and cancer. *International Immunopharmacology*, *11*(3), 295-309.
4. Tanaka, T., Shnimizu, M., & Moriwaki, H. (2012). Cancer chemoprevention by carotenoids. *Molecules*, *17*(3), 3202-3242.

5. Zhuang, S. R., Chen, S. L., Tsai, J. H., Huang, C. C., Wu, T. C., Liu, W. S., & Wang, C. K. (2009). Effect of citronellol and the Chinese medical herb complex on cellular immunity of cancer patients receiving chemotherapy/radiotherapy. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *23*(6), 785-790.
6. Sharma, H., Parihar, L., & Parihar, P. (2011). Review on cancer and anticancerous properties of some medicinal plants. *Journal of Medicinal Plants Research*, *5*(10), 1818-1835.
7. Wang, X., Song, Y., Su, Y., Tian, Q., Li, B., Quan, J., & Deng, Y. (2016). Are PEGylated liposomes better than conventional liposomes? A special case for vincristine. *Drug Delivery*, *23*(4), 1092-1100.
8. de Morrée, E., van Soest, R., Aghai, A., de Ridder, C., de Bruijn, P., Ghobadi Moghaddam-Helmantel, I. & van Weerden, W. (2016). Understanding taxanes in prostate cancer; importance of intratumoral drug accumulation. *The Prostate*, *76*(10), 927-936.
9. Aung, T. N., Qu, Z., Kortschak, R. D., & Adelson, D. L. (2017). Understanding the effectiveness of natural compound mixtures in cancer through their molecular mode of action. *International Journal of Molecular Sciences*, *18*(3), 656.
10. Luo, Y., Zha, L., Luo, L., Chen, X., Zhang, Q., Gao, C., & Qiao, T. (2019). [6] -Gingerol enhances the cisplatin sensitivity of gastric cancer cells through inhibition of proliferation and invasion via PI 3 K/AKT signaling pathway. *Phytotherapy Research*, *33*(5), 1353-1362.
11. Martin, A. C. B. M., Tomasin, R., Luna-Dulcey, L., Graminha, A. E., Naves, M. A., Teles, R. H. G., & Cominetti, M. R. (2020). [10]-Gingerol improves doxorubicin anticancer activity and decreases its side effects in triple negative breast cancer models. *Cellular Oncology*, *43*(5), 915-929.
12. Huang, Y., Xiao, D., Burton-Freeman, B. M., & Edirisinghe, I. (2016). Chemical changes of bioactive phytochemicals during thermal processing. *Reference Module in Food Science, Elsevier, 77*(9),1-6. DOI:10.1016/B978-0-08-100596-5.03055-9
13. Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2020). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. *Frontiers in Pharmacology*, *10*(1614), 1-17. DOI:https://doi.org/10.3389/fphar.2019.01614

14. Quail, D. F., & Joyce, J. A. (2013). Microenvironmental regulation of tumor progression and metastasis. *Nature Medicine*, *19*(11), 1423-1437.
15. Arends, M. J. (2013). Pathways of colorectal carcinogenesis. *Applied Immunohistochemistry & Molecular Morphology*, *21*(2), 97-102.
16. Afrin, S., Giampieri, F., Gasparrini, M., Forbes-Hernández, T. Y., Cianciosi, D., Reboredo-Rodriguez, P., & Battino, M. (2020). Dietary phytochemicals in colorectal cancer prevention and treatment: a focus on the molecular mechanisms involved. *Biotechnology Advances*, *38*(2020),1-38. DOI: 10.1016/j.biotechadv.2018.11.011.
17. Lee, Y. C., Lin, H. H., Hsu, C. H., Wang, C. J., Chiang, T. A., & Chen, J. H. (2010). Inhibitory effects of andrographolide on migration and invasion in human non-small cell lung cancer A549 cells via down-regulation of PI3K/Akt signalling pathway. *European Journal of Pharmacology*, *632*(1-3), 23-32.
18. Rajagopal, S., Kumar, R. A., Deevi, D. S., Satyanarayana, C., & Rajagopalan, R. (2003). Andrographolide, a potential cancer therapeutic agent isolated from Andrographis paniculata. *Journal of Experimental Therapeutics and Oncology*, *3*(3), 147-158.
19. Imenshahidi, M., & Hosseinzadeh, H. (2019). Berberine and barberry (Berberis vulgaris): a clinical review. *Phytotherapy Research*, *33*(3), 504-523.
20. Wang, Y., Liu, Y., Du, X., Ma, H., & Yao, J. (2020). The anti-cancer mechanisms of berberine: a review. *Cancer Management and Research*, *12*(1) 695-702. DOI: https://dx.doi.org/10.2147%2FCMAR.S242329
21. G Gutheil, W., Reed, G., Ray, A., Anant, S., & Dhar, A. (2012). Crocetin: an agent derived from saffron for prevention and therapy for cancer. *Current Pharmaceutical Biotechnology*, *13*(1), 173-179.
22. Wang, C. J., Shiah, H. S., & Lin, J. K. (1991). Modulatory effect of crocetin on aflatoxin B1 cytotoxicity and DNA adduct formation in C3H10T12 fibroblast cell. *Cancer Letters*, *56*(1), 1-10.
23. Chryssanthi, D. G., Lamari, F. N., Iatrou, G., Pylara, A., Karamanos, N. K., & Cordopatis, P. (2007). Inhibition of breast cancer cell proliferation by style constituents of different Crocus species. *Anticancer Research*, *27*(1A), 357-362.
24. Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. *Nutrients*, *11*(10), 2376.

25. Wang, M., Jiang, S., Zhou, L., Yu, F., Ding, H., Li, P., & Wang, K. (2019). Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. *International Journal of Biological Sciences*, *15*(6), 1200.
26. Sanders, B., Ray, A. M., Goldberg, S., Clark, T., McDaniel, H. R., Atlas, S. E., & Rasul, A. (2018). Anti-cancer effects of aloe-emodin: a systematic review. *Journal of Clinical and Translational Research*, *3*(3), 283.
27. Lissoni, P., Rovelli, F., Brivio, F., Zago, R., Colciago, M., Messina, G., & Porro, G. (2009). A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus Aloe arborescens in patients with metastatic cancer. *In Vivo*, *23*(1), 171-175.
28. Ahmad, A., Padhye, S., & Sarkar, F. H. (2012). Role of novel nutraceuticals garcinol, plumbagin and mangiferin in the prevention and therapy of human malignancies: mechanisms of anticancer activity. *In Nutraceuticals and Cancer* (pp. 179-199). *Springer*, Dordrecht.
29. Imran, M., Arshad, M. S., Butt, M. S., Kwon, J. H., Arshad, M. U., & Sultan, M. T. (2017). Mangiferin: a natural miracle bioactive compound against lifestyle related disorders. *Lipids in Health and Disease*, *16*(1), 1-17.
30. Cao, Y. Y., Yu, J., Liu, T. T., Yang, K. X., Yang, L. Y., Chen, Q., & Zhang, Y. (2018). Plumbagin inhibits the proliferation and survival of esophageal cancer cells by blocking STAT3-PLK1-AKT signaling. *Cell Death & Disease*, *9*(2), 1-13.
31. Zhang, X. Q., Yang, C. Y., Rao, X. F., & Xiong, J. P. (2016). Plumbagin shows anti-cancer activity in human breast cancer cells by the upregulation of p53 and p21 and suppression of G1 cell cycle regulators. *European Journal*, *37*(1), 30-35. DOI: 10.12892/ejgo2765.2016
32. Rafiq, R. A., Ganai, B. A., & Tasduq, S. A. (2015). Piperine promotes ultraviolet (UV)-B-induced cell death in B16F10 mouse melanoma cells through modulation of major regulators of cell survival. *RSC Advances*, *5*(16), 11884-11894.
33. Doucette, C. D., Hilchie, A. L., Liwski, R., & Hoskin, D. W. (2013). Piperine, a dietary phytochemical, inhibits angiogenesis. *The Journal of Nutritional Biochemistry*, *24*(1), 231-239.

34. Kwak, T. W., Park, S. B., Kim, H. J., Jeong, Y. I., & Kang, D. H. (2017). Anticancer activities of epigallocatechin-3-gallate against cholangiocarcinoma cells. *OncoTargets and Therapy*, *10*(1), 137-144.DOI: https://dx.doi.org/10.2147%2FOTT.S112364
35. Min, K. J., & Kwon, T. K. (2014). Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate. *Integrative Medicine Research*, *3*(1), 16-24.
36. Udenigwe, C. C., Ramprasath, V. R., Aluko, R. E., & Jones, P. J. (2008). Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutrition Reviews*, *66*(8), 445-454.
37. Varoni, E. M., Lo Faro, A. F., Sharifi-Rad, J., & Iriti, M. (2016). Anticancer molecular mechanisms of resveratrol. *Frontiers in Nutrition*, *3*(8),1-15. DOI: https://dx.doi.org/10.3389%2Ffnut.2016.00008
38. Preet, R., Chakraborty, B., Siddharth, S., Mohapatra, P., Das, D., Satapathy, S. R., & Chowdhury, C. (2014). Synthesis and biological evaluation of andrographolide analogues as anti-cancer agents. *European Journal of Medicinal Chemistry*, *85*(2014), 95-106.
39. Lim, J. C. W., Chan, T. K., Ng, D. S., Sagineedu, S. R., Stanslas, J., & Wong, W. F. (2012). Andrographolide and its analogues: versatile bioactive molecules for combating inflammation and cancer. *Clinical and Experimental Pharmacology and Physiology*, *39*(3), 300-310.
40. Tillhon, M., Ortiz, L. M. G., Lombardi, P., & Scovassi, A. I. (2012). Berberine: new perspectives for old remedies. *Biochemical Pharmacology*, *84*(10), 1260-1267.
41. Zhang, X., Gu, L., Li, J., Shah, N., He, J., Yang, L., & Zhou, M. (2010). Degradation of MDM2 by the interaction between berberine and DAXX leads to potent apoptosis in MDM2-overexpressing cancer cells. *Cancer Research*, *70*(23), 9895-9904.
42. Li, J., Gu, L., Zhang, H., Liu, T., Tian, D., Zhou, M., & Zhou, S. (2013). Berberine represses DAXX gene transcription and induces cancer cell apoptosis. *Laboratory Investigation*, *93*(3), 354-364.
43. Bathaie, S. Z., Hoshyar, R., Miri, H., & Sadeghizadeh, M. (2013). Anticancer effects of crocetin in both human adenocarcinoma gastric cancer cells and rat model of gastric cancer. *Biochemistry and Cell Biology*, *91*(6), 397-403.

44. Li, C. Y., Huang, W. F., Wang, Q. L., Wang, F., Cai, E., Hu, B., & Li, H. H. (2012). Crocetin induces cytotoxicity in colon cancer cells via p53-independent mechanisms. *Asian Pacific Journal of Cancer Prevention*, *13*(8), 3757-3761.
45. Mohan, C. D., Kim, C., Siveen, K. S., Manu, K. A., Rangappa, S., Chinnathambi, A., & Ahn, K. S. (2021). Crocetin imparts antiproliferative activity via inhibiting STAT3 signaling in hepatocellular carcinoma. *IUBMB Life*, *73*(11), 1348-1362.
46. Singh, S., & Khar, A. (2006). Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, *6*(3), 259-270.
47. Wang, M., Jiang, S., Zhou, L., Yu, F., Ding, H., Li, P., & Wang, K. (2019). Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. *International Journal of Biological Sciences*, *15*(6), 1200.
48. Bhatia, M., Bhalerao, M., Cruz-Martins, N., & Kumar, D. (2021). Curcumin and cancer biology: Focusing regulatory effects in different signalling pathways. *Phytotherapy Research*, *35*(9), 4913-4929. DOI:10.1002/ptr.7121.
49. Thimmegowda, N. R., Park, C., Shwetha, B., Sakchaisri, K., Liu, K., Hwang, J., & Kim, B. Y. (2015). Synthesis and antitumor activity of natural compound aloe emodin derivatives. *Chemical Biology & Drug Design*, *85*(5), 638-644.
50. Guo, J., Xiao, B., Zhang, S., Liu, D., Liao, Y., & Sun, Q. (2007). Growth inhibitory effects of gastric cancer cells with an increase in S phase and alkaline phosphatase activity repression by aloe-emodin. *Cancer Biology & Therapy*, *6*(1), 85-88.
51. Dilshara, M. G., Kang, C. H., Choi, Y. H., & Kim, G. Y. (2015). Mangiferin inhibits tumor necrosis factor-α-induced matrix metalloproteinase-9 expression and cellular invasion by suppressing nuclear factor-κB activity. *BMB Reports*, *48*(10), 559.
52. Yin, Z., Zhang, J., Chen, L., Guo, Q., Yang, B., Zhang, W., & Kang, W. (2020). Anticancer effects and mechanisms of action of plumbagin: Review of research advances. *BioMed Research International*, *2020*, Article ID 6940953, 1-10. DOI:https://doi.org/10.1155/2020/6940953
53. Padhye, S., Dandawate, P., Yusufi, M., Ahmad, A., & Sarkar, F. H. (2012). Perspectives on medicinal properties of plumbagin and its analogs. *Medicinal Research Reviews*, *32*(6), 1131-1158.

54. Jamal, M. S., Parveen, S., Beg, M. A., Suhail, M., Chaudhary, A. G., Damanhouri, G. A., & Rehan, M. (2014). Anticancer compound plumbagin and its molecular targets: a structural insight into the inhibitory mechanisms using computational approaches. *PLoS One*, *9*(2), e87309.
55. Rather, R. A., & Bhagat, M. (2018). Cancer chemoprevention and piperine: molecular mechanisms and therapeutic opportunities. *Frontiers in Cell and Developmental Biology*, *6*(10), 1-12. DOI:10.3389/fcell.2018.00010.
56. de Almeida, G. C., Oliveira, L. F., Predes, D., Fokoue, H. H., Kuster, R. M., Oliveira, F. L., & Abreu, J. G. (2020). Piperine suppresses the Wnt/β-catenin pathway and has anti-cancer effects on colorectal cancer cells. *Scientific Reports*, *10*(1), 1-12.
57. Narayanan, S., Mony, U., Vijaykumar, D. K., Koyakutty, M., Paul-Prasanth, B., & Menon, D. (2015). Sequential release of epigallocatechin gallate and paclitaxel from PLGA-casein core/shell nanoparticles sensitizes drug-resistant breast cancer cells. *Nanomedicine: Nanotechnology, Biology and Medicine*, *11*(6), 1399-1406.
58. He, L., Zhang, E., Shi, J., Li, X., Zhou, K., Zhang, Q., & Tang, X. (2013). (−)-Epigallocatechin-3-gallate inhibits human papillomavirus (HPV)-16 oncoprotein-induced angiogenesis in non-small cell lung cancer cells by targeting HIF-1α. *Cancer Chemotherapy and Pharmacology*, *71*(3), 713-725.
59. Tsai, H. Y., Ho, C. T., & Chen, Y. K. (2017). Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. *Journal of Food and Drug Analysis*, *25*(1), 134-147.
60. Xiao, Q., Zhu, W., Feng, W., Lee, S. S., Leung, A. W., Shen, J., & Xu, C. (2019). A review of resveratrol as a potent chemo protective and synergistic agent in cancer chemotherapy. *Frontiers in pharmacology*, *9*(1534), 1-10 DOI:10.3389/fphar.2018.01534