Hindawi
BioMed Research International
Volume 2020, Article ID 8602879, 7 pages
https://doi.org/10.1155/2020/8602879

Review Article

Phytochemicals as Potential Anticancer Drugs: Time to Ponder Nature's Bounty

Mohammad Arif Ashraf

Department of Biology, University of Massachusetts, Amherst 01003, MA, USA

Correspondence should be addressed to Mohammad Arif Ashraf; arif.ashraf.opu@gmail.com

Received 31 August 2019; Accepted 13 January 2020; Published 31 January 2020

Guest Editor: Mohammad Nazim

Medicinal plants have been used from the beginning of human civilization, which is mostly evident from the ancient script and traditional herbal medicine recipe. Despite the historically enriched demonstration about the use of plant as therapeutics, the pharmaceutical industries lack interest on phytochemical research compared with synthetic drug. Mostly, the absence of information about plant-based medicinal therapeutics is responsible to draw the attention of researchers to think about natural products as potential drug for detrimental diseases, such as cancer. This review will cover about clinically successful plant-based anticancer drugs and underappreciated, but potential, drugs to bridge the information gap between plant biologists and clinical researchers. Additionally, unprecedented advancement of synthetic chemistry, omics study to pin point the target genes/proteins, and efficient drug delivery system have made it easier for researchers to develop a phytochemical as an efficient anticancer drug.

1. Introduction

Undoubtedly, we are living in a time when cancer is epidemic and one of the medical challenges of this century. Statistically, it is a devastating number to deal. According to the Cancer Research UK, 17 million new cases had been reported, and among them, 9.6 million patients ended up to death in 2018. If it continues in such a rate, by 2040, there will be 27.5 million new cancer patient each year. At the same time, if we wonder, how far we came to cure cancer—forget about that—because our understanding about cancer is like looking at the White House from the international space station, where we certainly do not realize the color or the power of the stuff we are looking at. However, if we take a step back before meddling our mind with thousands of target genes, proteins, and possible or probable drugs, the fundamental idea of different types of cancer is "uncontrolled cell division" [1]. In short, cell division is a rudimentary process from the very beginning of the existence of life in the universe. Symmetric cell division leads to proliferation and asymmetric cell division is an informative step for differentiation. It has been reported that uncontrolled symmetric cell division is the major factor for causing cancer [2]. It is quite reasonable to aim anticancer drugs to control the cell cycle machineries [3]. In recent years, along with the effort of traditional anticancer drug discovery approaches, which is time-consuming and expensive, there is a search for anticancer drug from plant-derived bioactive compounds. Furthermore, drug discovery and development from plant-based compounds are also inexpensive compared with conventional synthetic compounds [4].

The plants are visibly an efficient provider of food and shelter, but the role of plants as a source of medicine is underappreciated. Human civilization is using plant as a source of food, shelter, and medicine for almost same time [5]. The contribution of plant as medicine was neglected due to the lack of precise biochemical and pharmacological mechanisms. Surprisingly, in nature, plants are continuously and extensively exposed to natural pollutants, carcinogens, and toxic metals [6–9] compared with human. Apart from the classic crown gall disease [10], the example of uncontrolled cell division in plant is insignificant compared with the animal system. At the same time, plants

synthesize divergent of secondary metabolites, mostly used for their defense and response to environmental cues, such as biotic and abiotic stresses [11–14]. In most of the cases, we have limited idea how plants tightly regulate their cell cycle machineries endogenously even after enormous exposure to hazardous components. Till date, several plant-derived compounds such as taxol [15], vinblastine [16], topotecan [17], and many more have been used as anticancer drugs successfully in clinical studies.

In this review, the existing successful plant-based anticancer drugs will be explored first and then the future direction of this emerging area and how the advancement of drug delivery system and cell type-specific production of anticancer drugs will uplift plant-based compounds as anticancer agents will be discussed.

2. Plant-Based Cancer Treatment

2.1. Looking Back to the Past to Find the Future. The most ancient text described the use of plant material as medicine was found in the Sumerian clay slab from Nagpur, India, and written approximately 5000 years ago. It contains information about using recent days' popular poppy, henbane, and mandrake as therapeutics [18]. Next, oldest evidence of medicinal plant was demonstrated in ancient Chinese literature written by Emperor Shen Nung circa 2500 BC [19, 20]. In a continuous historical effort, Theophrastus, known as "the father of botany," first established the botanical science, documented in his book "*De Causis Plantarum*," and classified several hundred medicinal plants [21, 22]. In addition, historically prominent Greek physician, pharmacologist, and botanist Pedanius Dioscorides wrote a 5-volume book, "*De Materia Medica*," on the medicinal use of plant [23]. His book and research were enormously successful, and he was hired by Roman army as a physician. The legacy of Roman Empire on medicinal plant study was further carried by Muslim scholars during the Islamic Golden Age. For instance, Islamic scholar Ibn Baitar described more than thousand medicinal plants in his book, "*Liber Magnae Collectionis Simplicum Alimentorum Et Medicamentorum*" [24]. The knowledge of medicinal plants from ancient literature and text came to light through Carl Linnaeus's classification system, described in his book "*Species Plantarum*" [25].

In the early 19th century, the advent of advanced synthetic chemistry helps us to decipher the mechanism, isolation and synthesis of active compounds from popular medicinal plants, such as poppy, ipecacuanha, strychnos, quinine, and pomegranate [26]. Despite the enriched history and success of medicinal plants, during the late 19th and early 20th centuries, the research on medicinal plant did not progress as it was supposed to. The reluctance of pharmaceutical industries about plant-based components caused a significant shift of focus from plant to synthetic chemistry on drug development [27].

Fortunately, the gear has been shifted in recent years. In 2015, the Nobel Prize in physiology and medicine was awarded to Tu Youyou for her discovery of artemisinin and dihydroartemisinin as antimalarial drug and highlight of the importance of plant-based components as a potentially powerful source of drug discovery. During the Vietnam War, Ho Chi Minh urged to develop antimalarial drugs for his soldiers. Tu Youyou became the part of that project to find the antimalarial treatment, and she screened over 2,000 traditional herbal medicines and discovered *Artemisia annua* recipe [28].

The success story of antimalarial drug based on traditional herbal medicine is not an isolated story; rather, it is a tiny part of plant-based arsenal as potential drugs. As a result, the significant effort on finding therapeutic agents for cancer treatment has been focused on plant-based compounds by the National Cancer Institute (NCI), USA. NCI-initiated Cancer Moonshot^{SM} project, aimed to accelerate the cancer research by making more cancer therapeutics available for patients, is focused on phytochemicals. As a part of this project, they have established a repertoire of natural products, and their purified chemical components to make them available for researchers to find new anticancer drugs.

Till date, several plant-based compounds have been reported for their anticancer activity, and among them, a good number of compounds is clinically successful as well. I have tried to summarize some important phytochemicals as potential anticancer drugs in Table 1 and Section 2.2.

2.2. Success Stories of Medicinal Plant-Based Anticancer Drug. Till date, more than thousand plants species have been identified with noteworthy anticancer potential [90, 91]. The isolation of the vinca alkaloids, vinblastine [92] from the Madagascar periwinkle, and *Catharanthus roseus* G. Don. (Apocynaceae) is one of the major examples of anticancer medication. This along with vincristine and other cancer chemotherapeutic drugs are used for the treatment of a range of cancers such as leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma [30, 91]. The discovery of paclitaxel (Taxol) [93] from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), is another major success story in natural product drug discovery. Utilization of various parts of *Taxus brevifolia* from which paclitaxel was discovered and other *Taxus* species (e.g., *Taxus Canadensis* Marshall and *Taxus baccata* L.) by several Native American Tribes kindle the idea of indigenous knowledge-based medicinal plants [30, 91]. Another potent plant-acquired active compound, Homoharringtonine [94], was extracted from the Chinese tree *Cephalotaxus harringtonia* var. drupacea (Sieb and Zucc.) (Cephalotaxaceae) and has been used successfully for a long time in China in a racemic mixture with harringtonine for the treatment of acute myelogenous leukemia [30]. Elliptinium, a derivative of ellipticine, isolated from a Fijian medicinal plant *Bleekeria vitensis* A. C. Sm., is shipped to France for the treatment of breast cancer [30, 91]. These events represent only the surface of the success story of plant-based anticancer drug discovery with a promise to find more in the near future [91].

Table 1: Known phytochemicals, their source, and therapeutic use.

Phytochemical	Source	Therapeutic use	Reference
5-Fluorouracil	*Withania somnifera*	Human cervical cancer cell	[29]
Vindesine	*Catharanthus roseus*	Leukemias, testicular, breast and lung cancer	[30]
Vincristine	*Catharanthus roseus*	Lymphocytic leukemia	[30]
Vinblastine	*Catharanthus roseus*	Lymphocytic leukemia	[30]
Colchicine	*Colchicum autumnale*	Multiple solid tumors	[31]
Larotaxel	*Taxus baccata*	Breast, bladder, and pancreatic cancer	[32]
Cabazitaxel	*Taxus baccata*	Prostate cancer	[33]
Paclitaxel	*Taxus brevifolia*	Breast and ovarian cancer	[30]
Bullatacin	*Annona squamosa*	Liver cancer	[34]
Bryophyllin A	*Bryophyllum pinnatum*	Cervical cancer	[35]
Harmine	*Peganum harmala*	Breast cancer	[36]
Artemisinin	*Artemisia annua*	Liver, breast, and pancreatic cancer	[37]
Tannins	*Debregeasia saeneb*	Internal tumors	[38]
Theabrownin	*Camellia sinensis*	Lung cancer	[39]
Solamargine	*Solanum nigrum*	Breast, liver, lung, and skin cancer	[40]
Psoralidin	*Psoralea corylifolia*	Stomach and prostate cancer	[41]
Xanthatin	*Xanthium strumarium*	Lymphocytic leukemia and liver cancer	[42]
Thymoquinone	*Nigella sativa*	Colon, prostate, breast, and pancreas cancer	[43]
Kaempferol galactoside	*Bauhinia variegata*	Breast, lung, and liver cancer	[43]
Withaferin A, D	*Withania somnifera*	Breast, cervix, prostate, and colon cancer	[44]
Ginger	*Zingiber officinale*	Ovary, cervix, colon, liver, and urinary caner	[45]
Silibinin	*Sylibum marianum*	Lung, liver, skin, colon, and prostate cancer	[46]
Luteolin	*Capsicum annuum*	Colorectal cancer	[47]
Colchicine	*Colchicum autumnale*	Hodgkin's lymphoma, chronic granulocytic leukemia	[48]
Skimmianine	*Aegle marmelos*	Liver cancer	[49]
Boswellic acid	*Boswellia serrata*	Prostate cancer	[50]
Silymarin	*Sylibum marianum*	Colorectal cancer and colon cancer	[51]
Curcumin	*Curcuma longa*	Colon adenocarcinoma	[52]
Podophyllotoxin	*Podophyllum peltatum*	Non-small-cell lung carcinoma	[53]
Andrographolide	*Andrographis paniculata*	Colon cancer	[47]
Podophyllotoxin	*Podophyllum hexandrum*	Breast, ovary, lung, liver, bladder, and testis cancer	[54]
Betulinic acid	*Betula utilis*	Melanomas	[55]
Panaxadiol	*Panax ginseng*	Human colon cancer	[56]
Gossypol	*Gossypium hirsutum*	Colorectal cancer	[57]
Chrysin	*Passiflora caerulea*	Colorectal cancer	[58]
Plumbagin	*Plumbago zeylanica*	Liver, fibrosarcoma, leukemia, and breast cancer	[59]
6-Shogaol	*Zingiber officinale*	Ovary cancer	[60]
Curcumin	*Curcuma longa*	Breast, lung, colon, prostate esophagus, liver, and skin cancer	[61]
Ursolic acid	*Oldenlandia diffusa*	Lungs, ovary, uterus, stomach, liver, colon, rectum, and brain cancer	[62]
Isoliquiritigenin	*Glycyrrhiza uralensis*	Human lung cancer	[63]
Punarnavine	*Boerrhavia diffusa*	Malignant melanoma cancer	[64]
Procyanidins	*Vitis vinifera*	Human colon cancer	[65]
Resveratrol	*Polygonum cuspidatum*	Colorectal, skin, and liver cancer	[66]
Damnacanthal	*Morinda citrifolia*	Lung cancer, sarcomas	[67]
Gossypol	*Gossypium hirsutum*	Breast, stomach, liver, prostate, and bladder cancer	[68]
Niazinine A	*Moringa oliefera*	Blood cancer	[69]
Amooranin	*Amoora rohituka*	Lymphocytic leukemia	[70]
Betulinic acid	*Ziziphus rugosa*	Cytotoxicity against human melanoma cells	[71]
Asiatic acid	*Centella asiatica*	Melanoma, glioblastoma, breast cancer	[72]
Gallic acid	*Leea indica*	Ehrlich ascites carcinoma	[73]
Combretastatins	*Combretum caffrum*	Colon, leukemia, and lung cancer	[74]
Lycopene	*Solanum lycopersicum*	Prostate and colon cancer	[75]
Plumbagin	*Plumbago zeylanica*	Blood and skin cancer	[76]
Cannabinoid	*Cannabis sativa*	Lung, pancreas, breast, prostate, and colorectal cancer	[77]
Silymarin	*Sylibum marianum*	Colorectal cancer	[78]
Tylophorine	*Tylophora indica*	Breast cancer	[74]
Saffron	*Saffron crocus*	Liver, lung cancer and pancreatic cancer	[79]
nab-paclitaxel	*Taxus brevifolia*	Ovarian and breast cancer	[80]
Cyanidin	*Vitis vinifera*	Colon cancer	[81]
Actein	*Actaea racemosa*	Liver and breast cancer	[82]

Table 1: Continued.

Phytochemical	Source	Therapeutic use	Reference
Betulinic acid	*Betula Sp.*	Human melanoma xenografts and leukemia	[30]
Allin	*Allium sativum*	Carcinoma of human mammary gland	[83]
Neferine	*Nelumbo nucifera*	Liver cancer	[84]
Calcaelin	*Calvatia caelata*	Breast and spleen cancer cells	[85]
Lentinan	*Lentinus edodes*	Sarcoma-180 in mice	[86]
Schizophyllan	*Schizophyllum commune*	Head and neck cancer	[87]
Apigenin	*Matricaria chamomilla*	Colorectal cancer	[88]
Vitex	*Vitex agnus-castu*	Human uterine, ovarian, cervical, and breast cancer	[89]

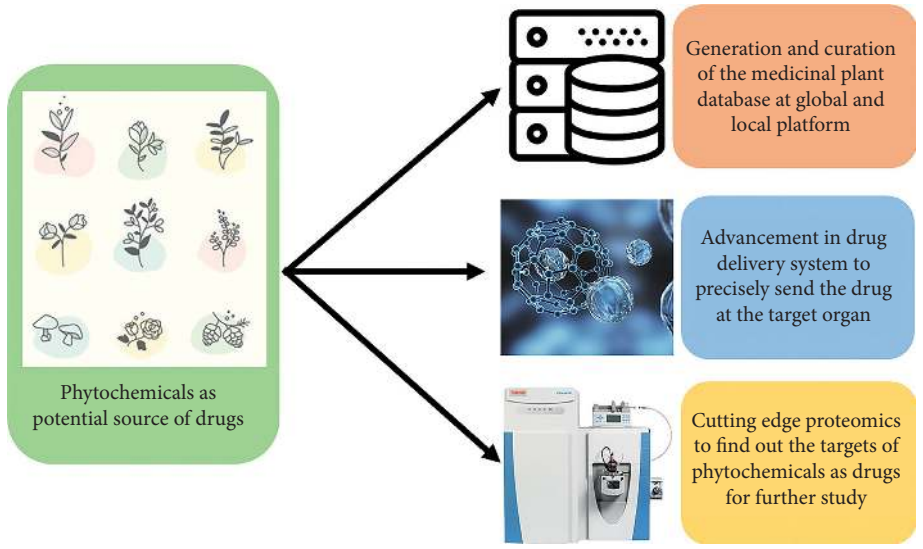

Figure 1: Phytochemicals can be used as drugs based on medicinal plant database, omics study to find the target, and efficient drug delivery system.

2.3. Toddler's Step Leads to the Unknown Horizon. The question is whether long-term ignorance of natural products for drug development can fit into the multibillion-dollar pharmaceutical industry? The answer certainly depends on multiple factors. However, the bright side is that the recent advancement of multiple medicinal plant database from local and global researchers, cutting edge omics technique to accelerate to find the drug targets and unprecedented improvement on drug delivery system (Figure 1).

Over the last decade, along with the effort of Moonshot[SM] project, local scientists from different parts of the work tried to curate the information of traditional herbal practice, preparation, recipe, and their ailments [12, 95–97]. Furthermore, to find out the target of potential phytochemicals is easier than ever, because of advancement of genomics, proteomics, transcriptomics, and metabolomics in recent years [91, 98–100]. The final frontier of using natural products as cancer treatment depends on the efficient drug delivery system. Fortunately, the advent of nanotechnology for drug delivery system has fast-forwarded this sector over the last few years [101, 102].

3. Conclusions

If we assume the research avenue of phytochemicals as potential cancer therapeutics as an image of a pyramid, this review has demonstrated a piece of stone from that pyramid. However, the idea of pushing natural products' research on drug discovery and development requires constant update and well-documented literature. This review paper will take the reader from the ancient history of herbal medicinal practice to the modern day's isolation, purification, identification, biosynthesis, in vitro or in vivo study, drug development, efficient delivery of drugs, and therapeutic trial.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The author is grateful to Md. Mostafa Kamal, United Graduate School of Agricultural Sciences, Iwate University, Japan, for his critical comments on the manuscript. This review article is fundamentally inspired by "Why *Arabidopsis* Why" series of http://www.aribidopsis.com blog. The author is thankful to the enthusiastic readers and their comments on this series over the last few years.

References

[1] K.-C. Tay, L. T.-H. Tan, C. K. Chan et al., "Formononetin: a review of its anticancer potentials and mechanisms," *Frontiers in Pharmacology*, vol. 10, 2019.

[2] L. Shahriyari and N. L. Komarova, "Symmetric vs. asymmetric stem cell divisions: an adaptation against cancer?," *PloS One*, vol. 8, Article ID e76195, 2013.

[3] J. Bai, Y. Li, and G. Zhang, "Cell cycle regulation and anticancer drug discovery," *Cancer Biology & Medicine*, vol. 14, p. 348, 2017.

[4] A. Rayan, J. Raiyn, and M. Falah, "Nature is the best source of anticancer drugs: indexing natural products for their anticancer bioactivity," *PLoS One*, vol. 12, Article ID e0187925, 2017.

[5] M. Fridlender, Y. Kapulnik, and H. Koltai, "Plant derived substances with anti-cancer activity: from folklore to practice," *Frontiers in Plant Science*, vol. 6, p. 799, 2015.

[6] A. Manara, "Plant responses to heavy metal toxicity," in *Plants and Heavy Metals*, pp. 27–53, Springer, Berlin, Germany, 2012.

[7] M. Maleki, M. Ghorbanpour, and K. Kariman, "Physiological and antioxidative responses of medicinal plants exposed to heavy metals stress," *Plant Gene*, vol. 11, pp. 247–254, 2017.

[8] M. A. Ashraf, S. Kumagai, K. Ito, R. Sugita, K. Tanoi, and A. Rahman, "ATP binding cassette proteins ABCG37 and ABCG33 are required for potassium-independent cesium uptake in arabidopsis roots," 2019, https://www.biorxiv.org/content/10.1101/823815v1.

[9] M. A. Nabi, K. Umetsu, O. Ponomarenko et al., "PIN FORMED 2 facilitates the transport of arsenite in *Arabidopsis thaliana*," 2019b, https://www.biorxiv.org/content/10.1101/710160.

[10] J. Gohlke and R. Deeken, "Plant responses to *Agrobacterium tumefaciens* and crown gall development," *Frontiers in Plant Science*, vol. 5, p. 155, 2014.

[11] D. M Pereira, P. Valentao, G. Correia-da-Silva, N. Teixeira, and P. B Andrade, "Plant secondary metabolites in cancer chemotherapy: where are we?," *Current Pharmaceutical Biotechnology*, vol. 13, pp. 632–650, 2012.

[12] M. A. Ashraf, A. Khatun, and T. Sharmin, "MPDB 1.0: a medicinal plant database of Bangladesh," *Bioinformation*, vol. 10, no. 6, pp. 384–386, 2014.

[13] M. A. Ashraf and A. Rahman, "Hormonal regulation of cold stress response," in *Cold Tolerance in Plants*, pp. 65–88, Springer, Berlin, Germany, 2018.

[14] M. A. Ashraf and A. Rahman, "Cold stress response in *Arabidopsis thaliana* is mediated by GNOM ARF-GEF," *The Plant Journal*, vol. 97, no. 3, pp. 500–516, 2019.

[15] W. J. Slichenmyer and D. H. Von, "Taxol," *A New and Effective Anti-cancer Drug*, vol. 2, no. 6, pp. 519–530, 1991.

[16] L. Caputi, J. Franke, S. C. Farrow et al., "Enzymes in the biosynthesis of the anticancer drug vinblastine in Madagascar periwinkle," *Science*, vol. 360, no. 6394, pp. 1235–1239, 2018.

[17] J. R. Brahmer and D. S. Ettinger, "The role of topotecan in the treatment of small cell lung cancer," *The Oncologist*, vol. 3, no. 3, pp. 11–14, 1998.

[18] K. Kelly, *The History of Medicine*, Facts on File, New York, NY, USA, 2009.

[19] H. Bottcher, *Miracle Drugs*, pp. 23–139, Zora, Zagreb, Croatia, 1965.

[20] C. Wiart, *Ethnopharmacology of Medicinal Plants: Asia and the Pacific*, Springer Science & Business Media, Berlin, Germany, 2007.

[21] R. Katic, *La Medicine En Serbie Au Moyen Age*, pp. 7–36, Scientific work, Beograd, Serbia, 1958.

[22] V. Pelagic, *Pelagic Folk Teacher*, pp. 500–502, Freedom, Beograd, 1970.

[23] J. Thorwald, *Power and Knowledge of Ancient Physicians*, pp. 10–255, August Cesarec, Zagreb, Croatia, 1991.

[24] J. Tucakov, *Pharmacognosy*, pp. 8–21, Academic books, Cambridge, MA, USA, 1948.

[25] R. Jancic, *Botanika Farmaceutika. Farmaceutski Fakultet*, Zavod za botaniku, Beograd, Serbia, 2002.

[26] Gupta V. Contemporary treatment with medicinal plants. skopje tabernakul, 5–43, 1992.

[27] L. Lasagna, "The pharmaceutical revolution: its impact on science and society," *Science*, vol. 166, no. 3910, pp. 1227–1233, 1969.

[28] X.-Z. Su and L. H. Miller, "The discovery of artemisinin and the nobel prize in physiology or medicine," *Science China Life Sciences*, vol. 58, no. 11, pp. 1175–1179, 2015.

[29] B. Yadav, A. Bajaj, M. Saxena, and A. Saxena, "In vitro anticancer activity of the root, stem and leaves of *Withania somnifera* against various human cancer cell lines," *Indian Journal of Pharmaceutical Sciences*, vol. 72, no. 5, p. 659, 2010.

[30] G. M. Cragg and D. J. Newman, "Plants as a source of anticancer agents," *Journal of Ethnopharmacology*, vol. 100, no. 1-2, pp. 72–79, 2005.

[31] J. M. Atkinson, R. A. Falconer, D. R. Edwards et al., "Development of a novel tumor-targeted vascular disrupting agent activated by membrane-type matrix metalloproteinases," *Cancer Research*, vol. 70, no. 17, pp. 6902–6912, 2010.

[32] V. Diéras, S. Limentani, G. Romieu et al., "Phase II multicenter study of larotaxel (XRP9881), a novel taxoid, in patients with metastatic breast cancer who previously received taxane-based therapy," *Annals of Oncology*, vol. 19, no. 7, pp. 1255–1260, 2008.

[33] J. S. De Bono, S. Oudard, M. Ozguroglu et al., "Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial," *The Lancet*, vol. 376, no. 9747, pp. 1147–1154, 2010.

[34] V. Biba, M. P. W. Jeba, and P. Remani, "Differential effects of annona squamosa seed extracts: antioxidant, antibacterial, cytotoxic and apoptotic study," *International Journal of Pharma and Bio Sciences*, vol. 4, pp. 899–907, 2013.

[35] S. Mahata, S. Maru, S. Shukla et al., "Anticancer property of *Bryophyllum pinnata* (Lam.) Oken. leaf on human cervical cancer cells," *BMC Complementary and Alternative Medicine*, vol. 12, p. 15, 2012.

[36] I. Ayoob, Y. M. Hazari, S. H. Lone et al., "Phytochemical and cytotoxic evaluation of peganum harmala: structure activity relationship studies of harmine," *ChemistrySelect*, vol. 2, no. 10, pp. 2965–2968, 2017.

[37] T. Efferth, "From ancient herb to modern drug: artemisia annua and artemisinin for cancer therapy," *Seminars in Cancer Biology*, vol. 46, pp. 65–83, 2017.

[38] A. Tariq, S. Sadia, K. Pan et al., "A systematic review on ethnomedicines of anti-cancer plants," *Phytotherapy Research*, vol. 31, no. 2, pp. 202–264, 2017.

[39] F. Wu, L. Zhou, W. Jin et al., "Anti-proliferative and apoptosis-inducing effect of theabrownin against non-small cell lung adenocarcinoma A549 cells," *Frontiers in Pharmacology*, vol. 7, p. 465, 2016.

[40] S. S. Al Sinani, E. A. Eltayeb, B. L. Coomber, and S. A. Adham, "Solamargine triggers cellular necrosis

selectively in different types of human melanoma cancer cells through extrinsic lysosomal mitochondrial death pathway," *Cancer Cell International*, vol. 16, p. 11, 2016.

[41] P. Pahari, U. P. Saikia, T. P. Das, C. Damodaran, and J. Rohr, "Synthesis of psoralidin derivatives and their anticancer activity: first synthesis of Lespeflorin I1," *Tetrahedron*, vol. 72, no. 23, pp. 3324–3334, 2016.

[42] R. L. Thangapazham, S. Sharad, and R. K. Maheshwari, "Phytochemicals in wound healing," *Advances in Wound Care*, vol. 5, no. 5, pp. 230–241, 2016.

[43] L.-Y. Tu, J. Pi, H. Jin, J.-Y. Cai, and S.-P. Deng, "Synthesis, characterization and anticancer activity of kaempferol-zinc (II) complex," *Bioorganic & Medicinal Chemistry Letters*, vol. 26, no. 11, pp. 2730–2734, 2016.

[44] I.-C. Lee and B. Choi, "Withaferin-A-A natural anticancer agent with pleitropic mechanisms of action," *International Journal of Molecular Sciences*, vol. 17, no. 3, p. 290, 2016.

[45] N. Rastogi, S. Duggal, S. K. Singh et al., "Proteasome inhibition mediates p53 reactivation and anti-cancer activity of 6-gingerol in cervical cancer cells," *Oncotarget*, vol. 6, p. 43310, 2015.

[46] C.-C. Tsai, T.-W. Chuang, L.-J. Chen et al., "Increase in apoptosis by combination of metformin with silibinin in human colorectal cancer cells," *World Journal of Gastroenterology*, vol. 21, no. 14, p. 4169, 2015.

[47] N. H. A. Osman, U. Z. Said, A. M. El-Waseef, and E. S. A. Ahmed, "Luteolin supplementation adjacent to aspirin treatment reduced dimethylhydrazine-induced experimental colon carcinogenesis in rats," *Tumor Biology*, vol. 36, no. 2, pp. 1179–1190, 2015.

[48] X. Lin, Z. Peng, and C. Su, "Potential anti-cancer activities and mechanisms of costunolide and dehydrocostuslactone," *International Journal of Molecular Sciences*, vol. 16, no. 12, pp. 10888–10906, 2015.

[49] M. Mukhija, M. P. Singh, K. L. Dhar, and A. N. Kalia, "Cytotoxic and antioxidant activity of Zanthoxylum alatum stem bark and its flavonoid constituents," *Journal of Pharmacognosy and Phytochemistry*, vol. 4, p. 86, 2015.

[50] P. Garg and A. Deep, "Anti-cancer potential of boswellic acid: a mini," *Journal for Drugs And Medicines*, vol. 7, pp. 18–27, 2015.

[51] K. Ramasamy and R. Agarwal, "Multitargeted therapy of cancer by silymarin," *Cancer Letters*, vol. 269, no. 2, pp. 352–362, 2008.

[52] N. G. Vallianou, A. Evangelopoulos, N. Schizas, and C. Kazazis, "Potential anticancer properties and mechanisms of action of curcumin," *Anticancer Research*, vol. 35, no. 35, pp. 645–651, 2015.

[53] J. Y. Shin, W. G. Hong, J. H. Cho et al., "Podophyllotoxin acetate triggers anticancer effects against non-small cell lung cancer cells by promoting cell death via cell cycle arrest, ER stress and autophagy," *International Journal of Oncology*, vol. 47, no. 4, pp. 1257–1265, 2015.

[54] Y.-Q. Liu, J. Tian, K. Qian et al., "Recent progress on C-4-modified podophyllotoxin analogs as potent antitumor agents," *Medicinal Research Reviews*, vol. 35, no. 1, pp. 1–62, 2015.

[55] S. K. Król, M. Kiełbus, A. Rivero-Müller, and A. Stepulak, "Comprehensive review on betulin as a potent anticancer agent," *BioMed Research International*, vol. 2015, Article ID 584189, 11 pages, 2015.

[56] C.-Z. Wang, Z. Zhang, J.-Y. Wan et al., "Protopanaxadiol, an active ginseng metabolite, significantly enhances the effects of fluorouracil on colon cancer," *Nutrients*, vol. 7, no. 2, pp. 799–814, 2015.

[57] L. Lan, C. Appelman, A. R. Smith et al., "Natural product (-)-gossypol inhibits colon cancer cell growth by targeting RNA-binding protein Musashi-1," *Molecular Oncology*, vol. 9, no. 7, pp. 1406–1420, 2015.

[58] I. E. León, J. F. Cadavid-Vargas, I. Tiscornia et al., "Oxidovanadium (IV) complexes with chrysin and silibinin: anticancer activity and mechanisms of action in a human colon adenocarcinoma model," *Journal of Biological Inorganic Chemistry*, vol. 20, no. 7, pp. 1175–1191, 2015.

[59] C.-H. Yan, F. Li, and Y.-C. Ma, "Plumbagin shows anticancer activity in human osteosarcoma (MG-63) cells via the inhibition of S-Phase checkpoints and down-regulation of c-myc," *International Journal of Clinical and Experimental Medicine*, vol. 8, p. 14432, 2015.

[60] A. Ghasemzadeh, H. Z. Jaafar, and A. Rahmat, "Optimization protocol for the extraction of 6-gingerol and 6-shogaol from Zingiber officinale var. rubrum Theilade and improving antioxidant and anticancer activity using response surface methodology," *BMC Complementary and Alternative Medicine*, vol. 15, p. 258, 2015.

[61] D. Perrone, F. Ardito, G. Giannatempo et al., "Biological and therapeutic activities, and anticancer properties of curcumin," *Experimental and Therapeutic Medicine*, vol. 10, no. 5, pp. 1615–1623, 2015.

[62] Ł. Woźniak, S. Skąpska, and K. Marszałek, "Ursolic acid-a pentacyclic triterpenoid with a wide spectrum of pharmacological activities," *Molecules*, vol. 20, pp. 20614–20641, 2015.

[63] S. K. Jung, M.-H. Lee, D. Y. Lim et al., "Induces apoptosis and inhibits xenograft tumor growth of human lung cancer cells by targeting both wild type and L858R/T790M mutant EGFR," *Journal of Biological Chemistry*, vol. 289, no. 52, pp. 35839–35848, 2014.

[64] S. Mishra, V. Aeri, P. K. Gaur, and S. M. Jachak, "Phytochemical, therapeutic, and ethnopharmacological overview for a traditionally important herb: boerhavia diffusa linn," *BioMed Research International*, vol. 2014, Article ID 808302, 19 pages, 2014.

[65] K. Y. Cheah, G. S. Howarth, K. A. Bindon, J. A. Kennedy, and S. E. Bastian, "Low molecular weight procyanidins from grape seeds enhance the impact of 5-Fluorouracil chemotherapy on Caco-2 human colon cancer cells," *PLoS One*, vol. 9, Article ID e98921, 2014.

[66] I. Ali and D. P. Braun, "Resveratrol enhances mitomycin C-mediated suppression of human colorectal cancer cell proliferation by up-regulation of p21WAF1/CIP1," *Anticancer Research*, vol. 34, no. 34, pp. 5439–5446, 2014.

[67] M. Y. A. Bhat, A. R. Omar, T. Subramani et al., "Damnacanthal is a potent inducer of apoptosis with anticancer activity by stimulating p53 and p21 genes in MCF-7 breast cancer cells," *Oncology Letters*, vol. 7, no. 5, pp. 1479–1484, 2014.

[68] Y. Zhan, G. Jia, D. Wu, Y. Xu, and L. Xu, "Design and synthesis of a gossypol derivative with improved antitumor activities," *Archiv der Pharmazie*, vol. 342, no. 4, pp. 223–229, 2009.

[69] M. M. Khalafalla, H. M. Dafalla, A. Nassrallah, K. M. Aboul-Enein, H. A. El-Shemy, and E. Abdellatef, "Dedifferentiation of leaf explants and antileukemia activity of an ethanolic extract of cell cultures of moringa oleifera," *African Journal of Biotechnology*, vol. 10, pp. 2746–2750, 2011.

[70] L. L. Chan, S. George, I. Ahmad et al., "Cytotoxicity effects of amoora rohituka and chittagonga on breast and pancreatic cancer cells," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 860605, 8 pages, 2011.

[71] U. Shah, R. Shah, S. Acharya, and N. Acharya, "Novel anticancer agents from plant sources," *Chinese Journal of Natural Medicines*, vol. 11, no. 1, pp. 16–23, 2013.

[72] M. Heidari, H. Heidari-Vala, M. R. Sadeghi, and M. M. Akhondi, "The inductive effects of *Centella asiatica* on rat spermatogenic cell apoptosis in vivo," *Journal of Natural Medicines*, vol. 66, no. 2, pp. 271–278, 2012.

[73] M. Raihan, S. M. Tareq, A. Brishti, M. Alam, A. Haque, and M. Ali, "Evaluation of antitumor activity of leea indica (burm. F.) merr. extract against ehrlich ascites carcinoma (EAC) bearing mice," *American Journal of Biomedical Sciences*, vol. 4, 2012.

[74] C. Lauritano, J. H. Andersen, E. Hansen et al., "Bioactivity screening of microalgae for antioxidant, anti-inflammatory, anticancer, anti-diabetes, and antibacterial activities," *Frontiers in Marine Science*, vol. 3, p. 68, 2016.

[75] E.-R. Hahm, M. B. Moura, E. E. Kelley, B. Van Houten, S. Shiva, and S. V. Singh, "Withaferin A-induced apoptosis in human breast cancer cells is mediated by reactive oxygen species," *PloS One*, vol. 6, Article ID e23354, 2011.

[76] R. Checker, D. Sharma, S. K. Sandur et al., "Plumbagin inhibits proliferative and inflammatory responses of T cells independent of ROS generation but by modulating intracellular thiols," *Journal of Cellular Biochemistry*, vol. 110, no. 5, pp. 1082–1093, 2010.

[77] G. Appendino, G. Chianese, and O. Taglialatela-Scafati, "Cannabinoids: occurrence and medicinal chemistry," *Current Medicinal Chemistry*, vol. 18, no. 7, pp. 1085–1099, 2011.

[78] V. Colombo, M. Lupi, F. Falcetta, D. Forestieri, M. D'Incalci, and P. Ubezio, "Chemotherapeutic activity of silymarin combined with doxorubicin or paclitaxel in sensitive and multidrug-resistant colon cancer cells," *Cancer Chemotherapy and Pharmacology*, vol. 67, no. 2, pp. 369–379, 2011.

[79] F. Ververidis, E. Trantas, C. Douglas, G. Vollmer, G. Kretzschmar, and N. Panopoulos, "Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: chemical diversity, impacts on plant biology and human health," *Biotechnology Journal*, vol. 2, no. 10, pp. 1214–1234, 2007.

[80] M. Caruso, A. Colombo, L. Fedeli et al., "Isolation of endophytic fungi and actinomycetes taxane producers," *Annals of Microbiology*, vol. 50, pp. 3–14, 2000.

[81] D. Y. Lim and J. H. Y. Park, "Induction of p53 contributes to apoptosis of HCT-116 human colon cancer cells induced by the dietary compound fisetin," *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 296, no. 5, pp. G1060–G1068, 2009.

[82] L. S. Einbond, M. Soffritti, D. D. Esposti et al., "Actein activates stress-and statin-associated responses and is bioavailable in Sprague-Dawley rats," *Fundamental & Clinical Pharmacology*, vol. 23, no. 3, pp. 311–321, 2009.

[83] M. Sabnis, *Chemistry and Pharmacology of Ayurvedic Medicinal Plants*, Chaukhambha Amarabharati Prakashan, Varanasi, India, 2006.

[84] J.-S. Yoon, H.-M. Kim, A. K. Yadunandam et al., "Neferine isolated from *Nelumbo nucifera* enhances anti-cancer activities in Hep3B cells: molecular mechanisms of cell cycle arrest, ER stress induced apoptosis and anti-angiogenic response," *Phytomedicine*, vol. 20, no. 11, pp. 1013–1022, 2013.

[85] T. B. Ng, Y. W. Lam, and H. Wang, "Calcaelin, a new protein with translation-inhibiting, antiproliferative and antimitogenic activities from the mosaic puffball MushroomCalvatia caelata," *Planta Medica*, vol. 69, no. 3, pp. 212–217, 2003.

[86] P. H. K. Ngai and T. B. Ng, "A ribonuclease with antimicrobial, antimitogenic and antiproliferative activities from the edible mushroom Pleurotus sajor-caju," *Peptides*, vol. 25, no. 1, pp. 11–17, 2004.

[87] J. Smith, N. Rowan, and R. Sullivan, *Medicinal Mushrooms: Their Therapeutic Properties and Current Medical Usage with Special Emphasis on Cancer Treatments*, Cancer Research, London, UK, 2002.

[88] J. K. Srivastava and S. Gupta, "Antiproliferative and apoptotic effects of chamomile extract in various human cancer cells," *Journal of Agricultural and Food Chemistry*, vol. 55, no. 23, pp. 9470–9478, 2007.

[89] M. Imai, H. Kikuchi, T. Denda, K. Ohyama, C. Hirobe, and H. Toyoda, "Cytotoxic effects of flavonoids against a human colon cancer derived cell line, COLO 201: a potential natural anti-cancer substance," *Cancer Letters*, vol. 276, no. 1, pp. 74–80, 2009.

[90] A. Mukherjee, S. Basu, N. Sarkar, and A. Ghosh, "Advances in cancer therapy with plant based natural products," *Current Medicinal Chemistry*, vol. 8, no. 12, pp. 1467–1486, 2001.

[91] R. K. Chando, N. Hussain, M. I. Rana et al., "CDK4 as a phytochemical based anticancer drug target," 2019, https://www.biorxiv.org/content/859595.

[92] M. J. Balunas and A. D. Kinghorn, "Drug discovery from medicinal plants," *Life Sciences*, vol. 78, no. 5, pp. 431–441, 2005.

[93] M. S. Butler, "The role of natural product chemistry in drug discovery†," *Journal of Natural Products*, vol. 67, no. 12, pp. 2141–2153, 2004.

[94] N. R. Kronenberg, O. Akerele, A. S. Bingel, D. D. Soejarto, and Z. Guo, "Medicinal plants in therapy," *Bulletin of the World Health Organization*, vol. 63, no. 63, pp. 965–81, 1985.

[95] A. R. S. Brito and A. A. S. Brito, "Forty years of Brazilian medicinal plant research," *Journal of Ethnopharmacology*, vol. 39, pp. 53–67, 1993.

[96] P. A. Babu, G. Suneetha, R. Boddepalli et al., "A database of 389 medicinal plants for diabetes," *Bioinformation*, vol. 1, no. 4, pp. 130-131, 2006.

[97] K. Mohanraj, B. S. Karthikeyan, R. Vivek-Ananth et al., "IMPPAT: a curated database of Indian medicinal plants, phytochemistry and therapeutics," *Scientific Reports*, vol. 8, p. 4329, 2018.

[98] C. Manach, J. Hubert, R. Llorach, and A. Scalbert, "The complex links between dietary phytochemicals and human health deciphered by metabolomics," *Molecular Nutrition & Food Research*, vol. 53, no. 10, pp. 1303–1315, 2009.

[99] A. C. Tan, I. Konczak, D. M.-Y. Sze, and I. Ramzan, "Molecular pathways for cancer chemoprevention by dietary phytochemicals," *Nutrition and Cancer*, vol. 63, no. 4, pp. 495–505, 2011.

[100] V. S. Thakur, G. Deb, M. A. Babcook, and S. Gupta, "Plant phytochemicals as epigenetic modulators: role in cancer chemoprevention," *The AAPS Journal*, vol. 16, no. 1, pp. 151–163, 2014.

[101] K. Cho, X. Wang, S. Nie, Z. Chen, and D. M. Shin, "Therapeutic nanoparticles for drug delivery in cancer," *Clinical Cancer Research*, vol. 14, no. 5, pp. 1310–1316, 2008.

[102] M. Moniruzzaman, M. A. Ashraf, and M. M. Morshed, "Nanotechnology: a possible healer in drug delivery system," *Asian Journal of Biomedical and Pharmaceutical Sciences*, vol. 4, p. 1, 2014.