

ROLE OF NUTRACEUTICAL & HERBAL ADJUDANT IN THE CHEMOTHERAPY OF THE CANCER

Dr. Prof. Md.Waasiullah¹, Piyush Yadav^{2*}, Sachin Yadav³ and Pratiksha Mishra⁴

¹Principal Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur -222001 (U.P.), India.

²Principal Dept. of Pharmacy, Prasad Polytechnic, Jaunpur -222001 (U.P.), India.

³Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur -222001 (U.P.), India.

⁴Assistant Professor Dept. of Pharmacy, Prasad Institute Jaunpur -222001 (U.P.), India.

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***Corresponding Author**

Piyush Yadav

Principal, Department of
Pharmacy, Prasad
Polytechnic, Jaunpur
(222001), U.P, India.

ABSTRACT

The third most common cause of mortality worldwide is cancer. The development of unanticipated side effects from existing cancer therapies like chemotherapy and radiotherapy lowers the quality of life and financial burden for oncology patients. Natural bioactive components in nutraceuticals and food value have reassuring medicinal capabilities in a number of ailments. Significantly interesting herbs have been shown to treat and prevent a variety of cancers as well as lessen the negative effects of radiotherapy and chemotherapy. The effectiveness of herbal remedies and nutraceuticals for chemotherapy and chemoprevention is emphasized. We draw the conclusion that

additional research is necessary to refute the specific strategies and effectiveness of herbs and nutraceuticals used as adjuvant therapy in cancer patients.

KEYWORDS: nutraceuticals, prevention, cancer, phytochemicals.

INTRODUCTION

The third greatest cause of mortality worldwide, particularly among established-relationship middle-aged people. In contrast to other deadly morbidities Due to changes in routine, eating habits, and approaches to treating serious illnesses and diseases, it is better.^[1] Such a high fatality rate highlights the difficulty of using traditional radiation and chemotherapy to treat this fatal condition. In addition to the typical side effects of radiation and chemotherapy, these treatment regimens promote resistance, and they also cause the majority of cancer cells to become more resistant to the treatment.

Through altering the distinct genetic code, a normal cell must go through many stages of initiation, development, and promotion in order to establish an invasive malignant phenotype. Even while a single item cannot reverse a propensity, certain people are at increased risk due to additional variables, such as a small number of high-risk cases that may share a genetic background, nutritional and dietary choices, and environmental factors.^[2]

Through altering the distinct genetic code, a normal cell must go through many stages of initiation, development, and promotion in order to establish an invasive malignant phenotype. Even while a single item cannot reverse a propensity, certain people are at increased risk due to additional variables, such as a small number of high-risk cases that may share a genetic background, nutritional and dietary choices, and environmental factors.^[3]

INDIA'S CANCER STANDARD

Since 1991, the "National Cancer Registry Program" has been reporting on epidemiological issues with Indian residents. Women were somewhat more likely to develop cancer than males, as expected. Esophageal, pharyngeal, stomach, lung, and oral cancers are some of the most complex diseases that affect men. In contrast, cervical and breast cancer are the two female malignancies with the highest incidence rates, followed by oral, gastric, and esophageal cancers.

The rising number of new cancer cases indicates the state of cancer research in India. The current research landscape includes everything from fundamental studies necessary for regulating carcinogens to research methods to assess various biological pathways and novel medications for therapy.

The most well-known cancer treatments with side effects

Chemotherapeutic drugs are known to have serious side effects that reduce the body's ability to fight off infection.

Personal satisfaction and financial strain. There aren't much detailed published data on the negative effects of anticancer medications in India.^[4] Since chemotherapy regimens are quite intricate and oncology patients tend to be a group with low tolerance, cancer patients experienced a great deal of side effects.^[5] Imatinib, docetaxel, gemcitabine, paclitaxel, oxaliplatin, capecitabine, 5-fluorouracil, vincristine, 6-mercaptopurine, and gefitinib are the anticancer medications most frequently associated with negative side effects, which can result

in cardiovascular toxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, gastrointestinal toxicity, and dermatological toxicity.^[6] Which may have adverse effects on the cardiovascular system, the liver, the nervous system, the kidneys, the gastrointestinal tract, and the skin.^[7] Depending on the location of the body being treated; radiation treatment may have particular or additional adverse effects. The negative effects of radiation to the brain can also manifest themselves, often between six months and many years following the course of therapy. Memory loss, stroke-like symptoms, and decreased brain function can all be serious delayed consequences. Radiation to the breast can harm the heart or lungs as well, leading to additional side effects including chemobrain and lymphedema. Some radiation treatment side effects, such skin issues and exhaustion, can occur regardless of the area of the body being treated.^[8]

NUTRACEUTICALS

Numerous epidemiological, biochemical, and clinical updates point to a consistent link between dietary components and a lower risk of acquiring cancer. Cancers can be prevented by diet, but they can also be brought on by it.^[9] Nutraceuticals are the typical (natural) bioactive foods that are considered to have nutritional value and employed in a variety of diseases based on their positive effects. Chemotherapy and radiation are two common cancer treatment modalities that have unforeseen side effects that might affect patients for the rest of their lives.^[10]

Numerous studies have shown that eating habits are among the most important determinants of chronic illnesses including diabetes, cardiovascular disease, neurodegenerative disorders, and Several forms of malignancy.^[11] Such connections between illness and eating practises show that nutrition directly affects health. Globally, cancer is becoming a gradually worsening health issue as a result of lifestyle choices, increased urbanisation, following environmental changes, and the desire to live longer. As a result, several studies and surveys demonstrate how a person's diet and environment may affect their health and cellular function.

Some dietary supplements help the body fight cancer by detoxifying it, while others work to lessen the side effects of radiation and chemotherapy. The adverse side effects of chemotherapy make nutritional problems worse, thus chemotherapy must include the proper quantity of vitamin supplement. By interfering with or modifying the biologic response, nutritional supplements protect you against the negative effects of both.^[12]

Up until 1990, the main tenet of nutraceuticals was that they were well-considered organic foods that could provide strength and were recommended daily for ingestion within the body for wellbeing. For instance, several food manufacturers started increasing the iodine content of table salt in the early 19th century to prevent goitre, which exemplifies the efforts made in the process of creating functional components.^[13]

Nutraceutical medicine is now acknowledged as a new discipline of "complementary and alternative medicine," thanks to the previous notion of nutraceuticals as potent medicinal supplements and their enormously growing recognition. Hippocrates, the founder of western medicine, said, "Let food be thy medicine and medicine be thy food," highlighting the link between nutrition and human health. In reality, this is one of the specific vitamins for health and their therapeutic benefits. Based on the separation stage, plant food products can be categorised as nutraceuticals, functional foods, and food supplements. Semi-purified plant products, which are not regarded to be conventional food, are referred to as nutraceuticals in place of pure, undisturbed plant molecules that have been removed as dietary supplements.^[14]

Food supplements are foods that can be regularly consumed as part of a diet to maintain general health. Phytonutrients, polyunsaturated lipids, and secondary metabolites such as flavonoids, glucosinolates, lignans, phytosterols, polyphenols, phytoestrogens, phytates, and terpenes are only a few of the components found in plant food.^[15]

PRESENT SITUATION

Natural and herbal extracts have been used for a variety of reasons since the dawn of civilisation. There are currently over 470 nutraceutical and functional food items on the market with verified health advantages. Currently, there is no recording plan for foods used to prevent diseases in the ancient past. Instead, clinical test findings from animal testing and research to establish the effects are legally necessary in the process of pharmaceutical development.

Typical cancer-related dietary supplements include the following.

- Isoflavones, which are found in soyfoods, have the ability to prevent cancer.
- Lycopene targets the testicles, skin, prostate, and adrenals to prevent cancer.
- Saponins have mutagenic and anticancer properties.

Turmeric's polyphenol curcumin has a number of health benefits, including being anti-inflammatory, antioxidant, and anticarcinogenic. There have been claims that fruits and vegetables including beetroot, cucumber fruit, and spinach leaves have anti-tumor properties.

Poor eating habits and sedentary lifestyles have indeed increased the incidence of certain diseases in India's nutraceutical market despite increasing public knowledge of the connection between eating and health issues, correct nutrition and diet are still important for lifespan and good health.

Numerous nutraceuticals are said to be extremely active, have a significant impact on cellular metabolism, and occasionally even have a little negative effect. They have always been innovative and have had to contend with India's nascent pharmaceutical businesses. The French physician observed that when large dosages of nutrients were combined with traditional chemotherapy in lung cancer patients, the tumor's chance of returning was cut in half, resulting in a decrease in cytotoxic levels.^[16]

Vitamin C

It greatly decreased the risk of stomach and esophageal cancers by reducing the production of nitrosamine in the intestinal tract.

People who are treated for terminal malignancies now have longer survival times. According to epidemiological research, ascorbate may be a potential chemopreventive for breast cancer. 748 cervical cancer patients and 1411 controls were compared in a Latin American study's analysis of nutritional consumption and dietary habits.^[17] The results supported a protective effect of Vitamin C against invasive cervical cancer. An inverse relationship between Vitamin C status and risk for cervical dysplasia was observed. esophageal cancer and 264 males with other diagnoses at Roswell Park Memorial Institute. Vitamins C, A, and intakes of fruits and vegetables were associated with decreased risks of esophageal cancer.^[18]

Fish oil

Eicosapentaenoic acid altered the cancer cell membranes to enhance susceptibility, which improved tumour inhibition during heat and chemotherapy.^[19]

Ginseng

To boost the effectiveness of the anticancer medication mitomycin, panax ginseng enhances its usage. Medical therapy can target tumour cells with the most targeted poisons (anticancer medications) thanks to nutrition therapy.^[20]

Avemar

Avemar is a fermented wheat gramme extract that is manufactured and "Approved dietary food for specific medical reasons of cancer patients," and it is strongly advised for use in adjuvant protocols (supported by the clinical trial) of patients with high-risk skin cancer.^[21]

HERBALS

Plants, plant mixtures, and green complexes are all examples of herbal medications. Herbal plants have been utilised in a number of ways across the ecosphere in both allopathic and conventional medicine. Herbal remedies are well-known for their effectiveness, affordability, practicality, and safety. Despite advances in synthetic chemistry, around 80% of the people of the ecosphere still rely on medicinal plants to alleviate illness.^[22] Any plant's biological activity is a result of its constituent phytochemicals, flavonoids, and phenols. They are plant-based components that alter certain molecular targets directly or indirectly as stable conjugates that change metabolic pathways to directly arbitrate their favourable health advantages.^[23] Natural anticancer medicines provide useful ways to improve the effectiveness of cancer treatment while minimising or eliminating negative side effects.^[24] In this era of pharmaceuticals, the precise application of phytochemicals may open up new possibilities for enhancing the effectiveness of chemotherapy. Natural products, particularly those from the plant kingdom, have been a crucial source of chemotherapy for the past 30 years.^[25] According to the axiom "Cancer is unfriendly to the human body, and hostile environment is malignant to plants," plants that can thrive in a variety of different situations may naturally be able to supply humans with essential anticancer chemicals.^[26]

ADVANTAGES OF CERTAIN HERBS AND HERBALS FOR CANCER

Ellagic acid

Black raspberries, pomegranates, walnuts, strawberries, raspberries, and almonds are just a few examples of the numerous nuts, seeds, and fruits that contain the polyphenol component ellagic acid. In a different research, Baradaran et al. demonstrated that ellagic acid's potent antioxidant capabilities have a chemoprotective impact and reduce OS.^[27] In the past, several investigations have found that ellagic acid exhibited chemoprotective, anti-apoptotic, and

anticarcinogenic effects that make it intriguing for future research in many illnesses, notably cancer cell systems.^[28]

Vinca rosea (periwinkle)

Catharanthus roseus, popularly known as periwinkle, is the most effective anticancer plant. Vinca alkaloids like vincristine (leurocristine), vinblastine, and reserpine are some of its constituents. The microtubule protein tubulin must connect with the alkaloids for them to manifest their anticancer properties, which stop the formation of microtubules and prevent the formation of spindles during the metaphase, which stops the division of cancerous cells.^[29] Vinblastine is used in treating Hodgkin's disease, a malignancy of kidney, and nonHodgkin's lymphoma. Nevertheless, vincristine is prescribed with a combination of other anticancer agents for the effective treatment of various cancers such as lung, breast, cervix, and liver.^[30] As of now, periwinkle's herbal compounds were legalized by the FDA for treating the neoplasm. In general, vincristine has used the drug during breast cancer.^[33]

Limitations

It has aftereffects like a loss of the need to eat, bone ache, unhappiness, giddiness, constipation, intestinal pain, and hair loss.^[31]

Curry leaf (turmeric)

The complete spectrum of therapeutic actions is confirmed by *curcuma longa*. It is hepatoprotective, anti-inflammatory, antioxidant, anti-mutagenic, anti-fungal, anti-viral, and anti-bacterial. Constituted curcumin prevents the production of eicosanoid (harmful) molecules like PGE-2, hence impeding the growth of cancer cells.^[32] Curcumin (Di-feruloyl-methane), one of the curcuminoids produced from turmeric, reduced cancer cells at every stage—including initiation, development, and metastasis—by preventing the spread of cancer cells in the G2/S phase and triggering death. Additionally, it slows angiogenesis, which is a rate-limiting stage in the development and spread of cancer.^[33]

Limitations

Up to nine months of daily consumption of 1 g of turmeric had a significant impact on the progression of palatal malignancies' precancerous lesions. Although there are no immediate hazardous symptoms seen after giving turmeric powder at doses up to 10 g/kg.^[34]

Anti-cancer properties

N. sativa functions like interferon and modulates and potentiates the immune system. Endothelial cells' ability to develop to malignancy has been reported to be inhibited in vitro by *N. sativa* ethanolic extract.^[35] Following treatment with an alcoholic extract or in conjunction with hydrogen peroxide, the MCF-7 breast cancer cell line was rendered inactive in vitro. Malignant cells are eliminated by *N. sativa* by adhering superficially to the asialofetuin (lectin), causing their clumping and aggregation.^[36]

Limitations of *N. sativa*

Acutely poisonous after oral administration of 25 g/kg. However, toxic symptoms start to show after receiving 25 g/kg intravenously.^[37]

The onion sativum (garlic)

The founder of western medicine, Hippocrates, was the first to support the useful use of *A. sativum* for the treatment of cancer. It participates in immune system enhancement and has defensive potential.^[38] Anticancer properties are shared by allicin, S-allyl cysteine, di-allyl-di-sulfide, and di-allyl-trisulfide cristine. In the chemotherapy for intestinal cancer, it is crucial. Garlic's antiproliferative properties are caused by metabolic byproducts of its organic sulphur components.^[39]

Papaya carica

When tested against the MCF-7 cell line, the fruitless variety of *C. papaya* extract reduced cell proliferation at various doses (25, 50, 100, 200, and 400 g/ml). The concentration-dependent inhibition of cell growth showed exponential growth, with the lowest growth inhibition at 25 g/ml being 9.38% and the greatest at 400 g/ml being 71.76%. Over 233.01 g/ml was the IC50 value. According to this investigation, *C. papaya* extract has anticancer activity.^[40]

Ganoderma lucidum

It has long been a significant source of organic mycological treatments. However, there is little information available about *Ganoderma*'s use in cancer immunotherapy. The polysaccharide included in *ganoderma*, betaglucan, is crucial for immunological surveillance. and cancer chemoprevention.^[41] NF- κ B and MAPK have been the major pathways that have received the most in-depth research. Because of *Ganoderma*'s wide range of uses and its ability to regulate the immune system, we may utilise it to treat immunological diseases,

cancer, and as a supplement to contemporary cancer therapies.^[42] The information that is currently available indicates that Ganoderma due to its function as an activator of the species as an anticancerimmunological reactions There is a tonne of literature about the other. natural resources, including marine and microbial sources, that can be utilisedeither directly or indirectly, as chemotherapeutic drugs.^[43]

Mangifera sp (Mango)

For their ability to protect Swiss albino mice's livers against 7, 12-dimethylbenz (a) anthracene-induced changes, mango pulp extract (MPE) and lupeol were studied. By modifying cell-growth regulators that were generated by oxidative stress, MPE was found to be helpful in preventing cellular damage to mouse liver.^[44] Mangiferin reportedly improved doxorubicin's effectiveness in MCF-7, according to Prasad et al.^[45]

Indica Azadirachta (neem)

Pre-clinical research on extracts from the neem plant's primary components, including the leaves, flowers, fruits, and seeds, has demonstrated positive chemopreventive and therapeutic properties.^[46] With more and more research, the fundamental mechanisms of neem's anticancer activities are starting to become clear. Neem extract is an useful natural resource since it is readily available, inexpensive, and safe for humans, all of which make neem-derived chemicals promising candidates for anticancer treatment.^[47] Neem has mainly been proven to be a potential preventative and therapeutic agent against several forms of cancer in preclinical investigations.^[48]

Intriguingly, neem has been demonstrated to enhance the effectiveness of various anticancer medications in addition to its anticancer effects when used alone.^[49–50] In comparison to cells treated with simply cisplatin, the combination of neem-derived gedunin and cisplatin further reduces the growth of treated ovarian cancer cells by over 50%.^[46] Compared to the effects of the two drugs alone, a sub-lethal dosage of ethanolic NLE and cisplatin also has synergistic effects on reducing the viability of breast and cervical cancer cells.^[51,52] It is necessary to do more research to find out whether neem might make cancer cells more susceptible to the cytotoxic effects of other treatment plans and whether combination therapy would have any possible clinical advantages.

HOW IMPORTANT IS ADJUVANT THERAPY?

All cancer treatments have evolved to the point where they can target individual molecules, but the intricacy of cell communication and the severe side effects of antitumorigenic drugs render the present treatments ineffective. It is clear that some malignancies are resistant to standard chemotherapy drugs. Adjuvant therapy that have also raised quality of life have helped patients get the desired objectives with the fewest negative effects. Although there are dose-relationships involved. As a result, mechanistic and focused techniques are required to enhance the quality, effectiveness, and minimise side effects, which is essential throughout the chemotherapeutic therapy. Although the rate-limiting stage to achieving effective adjuvant synergism will always be narrowing down the proper adjuvant.

In recent years, various dietary supplements and a select few nutraceuticals have been shown to mimic the effects of anticancer medications and can be utilised as adjuvants in chemotherapy. A select few substances influence different cell signalling pathways, which alters the course of biological systems. Due to the fact that several of these compounds have been shown to be benign and beneficial when combined with various anticancer medication classes. It follows that these compounds can be effectively used in combination with anticancer medications to treat cancer and its adverse effects.

CONCLUSION

Although the use of herbs and nutraceuticals is expanding quickly every day, there is still a dearth of extensive clinical evidence about the molecular and mechanistic activities of the corresponding classes from natural sources. Adjuvant treatment, for example, is therefore required in addition to traditional chemotherapy. The public should be made aware of the potential use of some herbs and nutraceuticals as an adjuvant, as it may be beneficial in the urgent need of the hour, as it not only boosts the effectiveness of conventional chemotherapy but also improves the quality of life for patients.

REFERENCE

1. Cancer. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>.
2. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The Aarhus statement: Improving design and reporting of studies on early cancer diagnosis. *Br J Cancer*, 2012; 106: 1262-7.
3. Cancer and Aging the Inflammatory Connection. Available from: <http://www.aginganddisease.org/article/2017/2152-5250/ad-8-5-611.html>.

4. Kirthi C, Afzal A, Reddy M, Aamir Ali S, Yerramilli A, Sharma S. A study on the adverse effects of anticancer drugs in an oncology center of a tertiary care hospital. *Int J Pharm Pharm Sci*, 2014; 6: 580-3.
5. Sunny S. Assessment of adverse effects of most commonly prescribed anticancer drugs in a tertiary care teaching hospital. *Indian J Pharm Pract*, 2017; 10: 270-5.
6. Chopra D, Rehan HS, Sharma V, Mishra R. Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. *Indian J Med Paediatr Oncol*, 2016; 37: 42-6.
7. Baldo P, Fornasier G, Ciolfi L, Sartor I, Francescon S. Pharmacovigilance in oncology. *Int J Clin Pharm*, 2018; 40: 832-41.
8. How Radiation Therapy Can Affect Different Parts of the Body. Available from: <https://www.cancer.org/treatment/treatments-and-sideeffects/treatment-types/radiation/effects-on-different-parts-of-body.html>.
9. Baena Ruiz R, Salinas Hernández P. Diet and cancer: Risk factors and epidemiological evidence. *Maturitas*, 2014; 77: 202-8.
10. Wargovich MJ, Morris J, Brown V, Ellis J, Logothetis B. Nutraceutical use in late-stage cancer. *Cancer Metastasis Rev*, 2012; 29: 503-10.
11. Willett WC, Koplan JP, Nugent R, Dusenbury C, Puska P, Gaziano TA. Prevention of chronic disease by means of diet and lifestyle changes. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, editors. *Disease Control Priorities in Developing Countries*. 2nd ed. Washington, DC: World Bank, 2006.
12. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev*, 2010; 4: 118-26.
13. Santini A, Novellino E. To nutraceuticals and back: Rethinking a concept. *Foods*, 2017; 6: e74.
14. Varzakas T, Zakyntinos G, Verpoort F. Plant food residues as a source of nutraceuticals and functional foods. *Foods*, 2016; 5: 88.
15. Kitts D. Bioactive substances in food: Identification and potential uses. *Can J Physiol Pharmacol*, 1994; 72: 423-34.
16. Arruebo M, Vilaboa N, Sáez-Gutierrez B, Lambea J, Tres A, Valladares M, et al. Assessment of the evolution of cancer treatment therapies. *Cancers (Basel)*, 2011; 3: 3279-330.

17. Herrero R, Potischman N, Brinton LA, Reeves WC, Brenes MM, Tenorio F, et al. A case-control study of nutrient status and invasive cervical cancer. I. Dietary indicators. *Am J Epidemiol*, 1991; 134: 1335-46.
18. National Research Council (US) Committee on Nutrition, and Cancer. 17th Relationship of Diet to Cancer at Specific Sites. United States: National Academies Press, 1982.
19. Chemo and Radiation. Nutrition and Cancer. Available from: <https://www.nutritioncancer.com>.
20. Chen S, Wang Z, Huang Y, O'Barr SA, Wong RA, Yeung S, et al. Ginseng and anticancer drug combination to improve cancer chemotherapy: A critical review. *Evid-Based Complement Altern Med*, 2014; 2014: 168940.
21. Demidov LV, Manziuk LV, Kharkevitch GY, Pirogova NA, Artamonova EV. Adjuvant fermented wheat germ extract (Avemar) nutraceutical improves survival of high-risk skin melanoma patients: A randomized, pilot, phase II clinical study with a 7-year follow-up. *Cancer Biother Radiopharm*, 2008; 23: 477-82.
22. Jain R, Rao B. Critical analysis of India's national mission on medicinal plants (NMMP) in providing access to quality botanical drugs to improve public health. *J Ayurveda Integr Med*, 2015; 6: 198-207.
23. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview. *Medicines*, 2018; 5: e93.
24. Al-Snafi AE. Chemical constituents and pharmacological activities of *Lantana camara* a review. *Asian J Pharm Clin Res*, 2019; 12: 10-20.
25. Demain AL, Vaishnav P. Natural products for cancer chemotherapy. *Microb Biotechnol*, 2011; 4: 687-99.
26. Greenwell M, Rahman PK. Medicinal plants: Their use in anticancer treatment. *Int J Pharm Sci Res*, 2015; 6: 4103-12.
27. Safarzadeh E, Shotorbani SS, Baradaran B. Herbal medicine as inducers of apoptosis in cancer treatment. *Adv Pharm Bull*, 2014; 4 Suppl 1: 421-7.
28. Ismail T, Calcabrini C, Diaz AR, Fimognari C, Turrini E, Catanzaro E, et al. Ellagitannins in cancer chemoprevention and therapy. *Toxins*, 2016; 8: 151.
29. Sharma P, McClees SF, Afaq F. Pomegranate for prevention and treatment of cancer: An update. *Mol J Synth Chem Nat Prod Chem*, 2017; 22: 177.
30. Moudi M, Go R, Yien CY, Mohd N. Vinca Alkaloids. *Int J Prev Med*, 2013; 4: 1231-5.

31. Quintão NL, Santin JR, Stoeberl LC, Corrêa TP, Melato J, Costa R. Pharmacological treatment of chemotherapy-induced neuropathic pain: PPAR γ agonists as a promising tool. *Front Neurosci*, 2019; 13: 907.
32. Periwinkle: A Herbal Powerhouse, Side Effects and Dosage, HealthXP. Available from: <https://www.healthxp.in/periwinkle-a-herbal-powerhouseside-effects-dosage>. [Last accessed on 2020 Jan 14].
33. Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Antitumour and antioxidant activity of natural curcuminoids. *Cancer Lett*, 1995; 94: 79-83.
34. Klinger NV, Mittal S. Therapeutic potential of curcumin for the treatment of brain tumors. *Oxid Med Cell Longev*, 2016; 2016: 9324085.
35. Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. *Nigella sativa* L. (Black cumin): A promising natural remedy for wide range of illnesses. *Evid Based Complement Altern Med* 2019;2019:1528635.
36. Majdalawieh AF, Fayyad MW. Recent advances on the anti-cancer properties of *Nigella sativa*, a widely used food additive. *J Ayurveda Integr Med*, 2016; 7: 173-80.
37. Salim EI. Cancer chemopreventive potential of volatile oil from black cumin seeds, *Nigella sativa* L., in a rat multi-organ carcinogenesis bioassay. *Oncol Lett*, 2010; 1: 913-24.
38. Tariq AL, Reyaz AL. Isolation of cannabinoids from the plant *Cannabis sativa* and its potential anticancer activity. *Int J Drug Dev Res*, 2012; 4: 241-6.
39. Lamm DL, Riggs DR. The potential application of *Allium sativum* (garlic) for the treatment of bladder cancer. *Urol Clin North Am*, 2000; 27: 157-62, 11.
40. Ariga T, Seki T. Antithrombotic and anticancer effects of garlic-derived sulfur compounds: A review. *Biofactors*, 2006; 26: 93-103.
41. Banu KS, Cathrine DL, Britto DJ. In vitro Anticancer Activity of *Carica papaya*. 6th International Conference on Emerging Trends in Engineering, Technology, Science and Management, 2017.
42. Yuen JW, Gohel MD. Anticancer effects of *Ganoderma lucidum*: A review of scientific evidence. *Nutr Cancer*, 2005; 53: 11-7.
43. Sohretoglu D, Huang S. *Ganoderma lucidum* polysaccharides as an anti-cancer agent. *Anticancer Agents Med Chem*, 2018; 18: 667-74.
44. Harhaji Trajković LM, Mijatović SA, Maksimović-Ivanić DD, Stojanović ID, Momčilović MB, Tufegdžić SJ, et al. Anticancer properties of *Ganoderma lucidum* methanol extracts in vitro and in vivo. *Nutr Cancer*, 2009; 61: 696-707.

45. Prasad S, Kalra N, Shukla Y. Hepatoprotective effects of lupeol and mango pulp extract of carcinogen induced alteration in Swiss albino mice. *Mol Nutr Food Res*, 2007; 51: 352-9.
46. Deep A, Mruthunjaya K, Manjula SN. Antitumor activity of *Crateva magna* in transplantable tumor models in mice. *Asian J Pharm Clin Res*, 2019; 12: 233-40.
47. Moga MA, Bălan A, Anastasiu CV, Dimienescu OG, Neculoiu CD, Gavriș C. An overview on the anticancer activity of *Azadirachta indica* (Neem) in gynecological cancers. *Int J Mol Sci*, 2018; 19: 3898.
48. Hao F, Kumar S, Yadav N, Chandra D. Neem components as potential agents for cancer prevention and treatment. *Biochim Biophys Acta*, 2014; 1846: 247-57.
49. Alzohairy MA. Therapeutics Role of *Azadirachta indica* (Neem) and their active constituents in diseases prevention and treatment. *Evid Based Complement Alternat Med*, 2016; 2016: 7382506.
50. Gupta SC, Reuter S, Phromnoi K, Park B, Hema PS, Nair M, et al. Nimbolide sensitizes human colon cancer cells to TRAIL through reactive oxygen species- and ERK-dependent up-regulation of death receptors, p53, and Bax. *J Biol Chem*, 2011; 286: 1134-46.
51. Bodduluru LN, Kasala ER, Thota N, Barua CC, Sistla R. Chemopreventive and therapeutic effects of nimbolide in cancer: The underlying mechanisms. *Toxicol In vitro*, 2014; 28: 1026-35.
52. Sharma C, Vas AJ, Goala P, Gheewala TM, Rizvi TA, Hussain A. Ethanolic neem (*Azadirachta indica*) leaf extract prevents growth of MCF-7 and HeLa cells and potentiates the therapeutic index of cisplatin. *J Oncol*, 2014; 2014: 321754.