Phytochemicals in Cancer Chemoprevention: A Brief Perspective

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Praveen Kumar and Anita Thakur

Abstract

Cancer is one of the leading causes of deaths globally. There are various treatment options available to cure cancer such as radiotherapy, chemotherapy, and immunotherapy. Despite being the primary choices of usage, current cancer therapies suffer with tremendous side effects with yet poor patient survival. Further, with the development of drug resistance in cancer cells, there is requirement to develop new therapeutics against cancer. A number of studies either on plant extracts or purified phytochemicals have shown promise towards cancer therapy directly or in combination with existing drugs. Several plant-derived compounds have been reported with anti-proliferative activities against various types of cancers by modulating complex cellular pathways. Since, phytochemicals are generally regarded as safe and easily available to consume; they are perceived as therapeutic agents with much less side effects. In this chapter we are presenting a very brief summary of relevance of plant products as therapeutic agents against cancer.

Keywords

Cancer · Cancer chemoprevention · Phytochemicals · Bioavailability · Biphasic effects

1.1 Introduction

Cancer is a highly morbid disease causing 9.6 million deaths worldwide in 2018. Lung cancer, breast cancer, and colorectal cancer are the major cancer types and among top five cancers resulting in the mortality [1, 2]. Various carcinogens present in the environment cause cancer initiation, e.g. tobacco consumption, ionizing

P. Kumar (✉) · A. Thakur
Technion – Israel Institute of Technology, Technion City, Haifa, Israel

M. Kumar et al. (eds.), *Pharmacotherapeutic Botanicals for Cancer Chemoprevention*, https://doi.org/10.1007/978-981-15-5999-0_1

radiations, and industrial chemicals. Cancer can also be caused by certain infections and it can also be genetic. There are several progressive changes that occur in cells undergoing tumorigenesis in spatio-temporal manner referred to as the hallmarks of cancer. Cancer hallmarks include modulation of signaling pathways for sustained proliferation (e.g., PI3K signaling), evading tumor suppressors (p53 and pRB regulation), activation of invasion and metastasis, enabling replicative immortality, angiogenesis induction, and resisting death [3]. All of these features help cancer cells to proliferate rapidly resulting in unchecked growth.

Cancer chemoprevention is the process of chronic administration of a natural, synthetic, or a biological agent in order to suppress, delay, or reduce the occurrence of malignancy [4, 5]. The interest in cancer chemoprevention is increased by the studies elucidating a better mechanistic understanding of the cancer biology, which led to the development of new drugs. Cancer chemo-preventive agents have been broadly classified into hormonal, dietary, medications, and vaccines [5]. Anti-estrogens such as selective estrogen receptor modulators (SERMs) are used against breast cancer [6]. Medications like aspirin, metformin, and statins have been implicated with anticancer effects. Several dietary agents such as vitamins and phytochemicals have shown anti-proliferative activity against various cancers. There are vaccines against infections that cause cancers, e.g. hepatitis B virus [5]. Cancer exhibits various progressive stages, viz. initiation, promotion, conversion, progression, invasion, and metastasis. [7]. Most of the drugs target the last stages of the cancer progression. There are severe limitations to target the advanced stages, e.g. severe side effects, high cost, and single target. For some tumors (sarcomas and leukemias), single target is enough for chemoprevention; however, for others multiple targets are required. Therefore most of advanced therapeutic strategies suggest targeting more than one stage including multiple targets for cancer treatment with the aid of computational models [8].

Remarkably high proliferation of cancer cells is contributed by diverse mechanisms altered in these cells. These alterations also make cancer cells vulnerable to therapeutic interventions. Most of the cancer drugs available in the market target the abnormally functional pathways to halt the proliferation of cancer cells. The various classes of anticancer drugs such as kinase inhibitors, metabolic inhibitors, immune checkpoint inhibitors, radiation therapy (summarized in great details in the review [9]) are important to mention here but are beyond the scope of this chapter. Since these drugs also target the normal pathways, patients suffer from severe side effects from prolonged therapy [10]. Further, currently prescribed therapy promises only a very limited life span for cancer patients. Therefore, despite achievement of significant advances in medical research aiming at cancer drugs, there is still shortage of a promising therapy, which can be prescribed to cure or prevent cancer without causing significant side effects. Since, cancer is a tremendously heterogeneous disease, one uniform treatment regimen might not be suitable for all the cancer types. Drug resistance to the existing therapies curbs the patient life span drastically necessitating the need for the discovery of alternative drug choices. Plant and plant-derived products are very promising as an alternative and complementary to the currently available drug options.

1.2 Phytochemicals in Cancer Therapy

About 25–28% of the currently available drug compounds are derived from higher plants [11] demonstrating the potential of plant products in cancer therapeutics and further encourages the scope of research to develop additional drugs from plants. Phytochemicals are plant derived non-nutritive chemicals synthesized as defense mechanism against harsh environment including various pathogens [2]. The phytochemicals exhibiting various medicinal properties are classified as polyphenols, terpenoids, and alkaloids, which are also a part of human diet.

There is a large number of publications that describe the potential of plant metabolites against cancers [2, 7, 12]. Many of plant products exhibit a great deal of activity against various types of cancers (resveratrol). There are several known phytochemicals exhibiting a specific activity against a tumor, e.g. epigallocatechin-3-gallate exhibits an increase in caspase-3, p27, and calpain I activities in human Jurkat T, prostate cancer (PC-3, LNCaP) cells, and breast cancer (MCF-7) [13]. Capsaicin showed inhibition of growth and reversal of transformed phenotype in H-ras MCF-10A as reviewed in [2].

1.3 Potential of Phytochemicals for Cancer Chemoprevention

Phytochemicals exhibit a number of modulatory effects on the cancer cells that make them suitable as drug candidates. Plant products act as blocking agents to suppress the interaction of molecules leading to carcinogenic phenotype, e.g. DNA damage or production of ROS.

1.3.1 Phytochemicals as ROS Scavengers and Redox Modulators

Rapidly proliferating cancer cells result in the production of several free radical (H_2O_2, OH^- O_2^-) known as reactive oxygen species (ROS). While ROS promote the cancer cell proliferation, they are deleterious for normal cells inducing DNA damage and cell death. There are several studies demonstrating the protection provided by phytochemicals against ROS. For example, Tea polyphenols normalized the levels of superoxide dismutase (SOD) and catalase; *Curcuma longa* normalized SOD and CAT in mice [14] and rats [15], respectively. Some phytochemicals exploit the fact that cancer cells have high levels of ROS. These phytochemicals help elevate ROS even further and cause cell death, e.g. gallic acid mediated cell death due to elevated ROS in DU145 human prostate cancer cells [16].

1.3.2 Phytochemicals in DNA Damage and Repair

Cancer cells exhibit continued ROS production, which leads to cancer driving mutations in cancer cells and DNA damage in normal cells. Phytochemicals exhibit

dual function of DNA damage and DNA repair depending upon the genomic stability of the cells and can be selective against cancer. For example, curcumin induced both mitochondrial and nuclear DNA damage after 72 h incubation in G2 hepatoma cells [17]. Also, there are several reports exhibiting DNA damaging effect like *Tinospora* extracts and turmeric [2], sulforaphane exhibited DNA protection on certain embryonic derived cells [18].

1.3.3 Phytochemicals Control Gene Expression

Oncogenes and tumor suppressor genes dictate whether the outcome of a cellular phenotype would be cancerous or not. p53 tumor suppressor gene is a master regulator of cell division and is mutated in a large number of cancer types. Further, tumor cells hyperactivate various oncogenes, which are responsible for uncontrolled tumor growth. Plant metabolites exhibit activities to restore or upregulate tumor suppressor functions and downregulating the oncogene function to keep tumor growth in check. For example, in a study using 26 medicinal plants on MDR leukemia cells, many plant extracts such as *Leonotis leonurus*, *Hypoestes aristata*, *Salvia apiana* showed increased p53 expression and cells death and lower levels of RAS and EGFR [19]. Similarly growth inhibition of breast cancer cells such as myoblasts and MCF7 was observed using plant extracts which either upregulate p53 expression or downregulate oncogene function or both [2].

1.3.4 Phytochemicals Modulate Phase 1 and Phase 2 Enzymes

Upon ingestion, a xenobiotic compound undergoes detoxification process in liver. Three sets of enzymes are involved in detoxification process: phase I enzymes mainly cytochrome p450 (oxidoreduction step); phase II includes glutathione S-transferase (conjugation step); and phase III, as example Multidrug Resistance Protein (MRP) (excretion step) [20]. Typically, phase I enzymes make the non-polar xenobiotic compound more hydrophilic thereby often increasing the toxicity of the xenobiotic. Phase II enzymes conjugate with the products of phase I reactions rendering them less toxic. Phase III enzymes help excretion of the waste products. Dietary plants contain a number of anti-oxidants that through nuclear (factor erythroid 2) related factor 2 (nrf2) pathway induce the production of cytoprotective antioxidant enzymes such as glutathione S transferase and superoxide dismutase [21]. Many plant products have been reported to decrease expression of phase I and increase the expression of phase II enzymes promoting more cytoprotection. For example, *Brassica oleracea* increases GST enzymes in nrf2 background mice [22].

1.3.5 Phytochemicals Inhibit Cell Proliferation

Cancer cells typically exhibit very high proliferation rates, which is responsible for various manifestations of the cancers. Therefore, major therapeutic aim is to reduce the proliferation of cancer cells. A number of phytochemicals have been reported that reduce the proliferation rate of the cancerous cells. For example, MCL (Mantle cell lymphoma) growth was inhibited in a dose dependent treatment with curcumin by suppressing cyclin D1, NFkB, and Survivin protein expression, which caused G1 phase arrest [23]. Breast cancer cell line MCF-7 was growth inhibited by treatment with phenolic compound rich cranberry extract effected by reduction in CDK4 and cyclin D1 levels [24].

1.3.6 Phytochemicals Promote Autophagy

Autophagy, also known as macroautophagy, is a highly conserved and regulated process that targets proteins and damaged organelles for lysosomal degradation to maintain cellular homeostasis at a basal state, as well as during cellular stress [25]. The role of autophagy in cancer is complex and is primarily dictated by tumour type and stage. Numerous studies have associated its role constrains to tumor initiation in normal tissue and to tumor promotion and maintenance in certain tumor types. Furthermore, several synthetic autophagy modulators have been identified as potential candidates for cancer treatment. Emerging evidence has allied phytochemicals targeting the autophagic pathway as promising agent against various malignancies with minimal side effects. Paclitaxel, a taxane class diterpenoid, triggers early autophagy in both normoxic and hypoxic conditions in breast cancer cells and is associated with apoptosis. [26, 27]. In addition, diverse phytochemicals derived from natural sources, such as curcumin, ursolic acid, apigenin (4′,5,7-trihydroxyflavone), resveratrol, quercetin, thymoquinone, celastrol, and γ-tocotrienol, also have attracted attention as potential autophagy modulators and therefore can help to overcome chemoresistance and radioresistance [28].

1.3.7 Phytochemicals Exhibit Anti-inflammatory Effects

Onset of cancer is associated with a systemic inflammatory response. The inflammatory response possibly interferes with drug metabolism as inflammation hinders cytochrome P450 activity. Therefore anti-inflammatory drugs are given to the cancer patients. However, they also present patient with side effects over prolonged usage [29]. There are several phytochemicals that are known to inhibit known pathways (NFkB, Cox II and iNOS) thereby lowering the inflammation (reviewed in [2]). Quercetin inhibited NFkB in mouse derived inflamed intestinal epithelial cells and reduced inflammation [30].

1.3.8 Phytochemicals Modulate Tumor Metabolism

In the recent years it is being increasing clear that tumor cells exhibit remarkably different metabolism compared to the normal cells due to requirement of unique pathways operating in tumor cells in order to proliferate at enormous rates. Therefore recently, targeting the altered cancer cell metabolism is a very attractive target for the development of cancer therapy. Cancer cells display addiction to glycolytic pathway even in the presence of oxygen called as the Warburg effect [31, 32]. Various phytochemicals were shown to modulate cancer cell metabolism, e.g. resveratrol was shown to partially reverse Warburg effect and resulted in more oxygen consumption and caused cell death [33]. Curcumin and docetaxel treatment lead to an altered glucose, lipid, and glutathione metabolism in cancer cells [34]. A recent study demonstrated phloretin specifically inhibited GLUT2 and resulted in cell cycle arrest in breast cancer cell line, MDA-MB-231, but not in a normal cell line, MCF-10A [35].

1.3.9 Phytochemicals Modulate Gut Microbiota to Prevent Cancer

The role of gut microbiota in cancer is being gradually discovered. Healthy gut microbiota leads to healthy metabolism and offers protection from several diseases including cancer. Dietary phytochemicals such as polysaccharides and phenolic compounds were found to regulate the gut microbiota under stress conditions which led in the reduction of stress related diseases such as inflammatory bowel disease, cancer obesity, and risk of cancer by self-regulation of microbiota [7, 36, 37].

1.4 Limitations of Phytochemicals as Therapeutics for Chemoprevention

As we covered the potential of phytochemicals briefly as anticancer compounds and their potential in chemotherapy, phytochemicals do suffer with certain limitations.

1.4.1 Complex Mixture of Metabolites

Phytochemicals are typically isolated using various extraction procedures employing a variety of solvent systems. When ingested as crude water extract, the efficacy of the mixture might be limited due to less relative abundance of the active compound. Therefore, the separation of active ingredients is needed to achieve the desirable effects. However, it is not always easy to separate and identify the mixture and is a very complicated process requiring a specific expertise in compound separation and identification.

1.4.2 Bioavailability of Phytochemicals

Despite the demonstrated therapeutic potential of phytochemicals, they resulted in limited efficiency in preclinical or clinical trials. One of the biggest reasons that can affect the therapeutic potential is the bio-availability of the active compounds to the target tissues. There are several barriers that affect the bioavailability of the active compounds: indigestibility, rate of metabolism and kinetic stability, interaction with other molecules and phytochemicals [38]. Upon administration, the phytochemicals are subjected to liberation, absorption, distribution, metabolism, and elimination processes. Using computational models depending upon the necessary parameters related to the compounds, better bioavailability could be achieved. To enhance the bioavailability of the compounds, active compounds should be separated, purified, tested and suitable target delivery strategies should be employed. For example, delivery of pH sensitive nanoparticles coated with paclitaxel were more effective compared to neutral nanoparticles [39].

1.4.3 Biphasic Effects

Many plant derived products exhibit biologically opposite effects at different concentrations (hormesis), i.e. they are biphasic as the response changes according to the concentration of the phytochemical. As an example, Genistein exhibits biphasic effects on a number of cell lines. Genistein at lower concentrations (1 μM) promotes cell proliferation, while higher concentration (10 μM) is cytostatic for estrogen dependent MCF-7 cells [40]. Therefore, a titration of dose for phytochemicals is required for desired effects.

1.5 Phytochemicals in Clinical Trials and the Therapies

Although there are enormous reports on anticancer properties of phytochemicals against a variety of cancers, only a few get to the clinical trials and are prescribed for the treatment [41]. There are several plant derived compounds that show promise for cancer treatment in preclinical studies in various models tested, e.g. curcumin, genistein, allicin, etc. Phytochemicals serve three purposes in clinical trials: to improve the effects of chemotherapy and radiotherapy, to reduce the side effects of the drugs, and to check the unwanted drug interactions. Despite the limited preliminary usage, the phytochemicals have been used in clinical trials, e.g. curcumin is used in phase II clinical trial for advanced pancreatic cancers [42]. There are many plant products, which have made it to the different preclinical and clinical trials based on their antitumor and anti-proliferative effects by virtue of the pleiotropic effects on numerous pathways in the cells. This has been nicely summarized in many detailed reviews [41, 43].

1.6 Future Directions: Filling in the Gaps

Despite the availability of reports on phytochemicals proven to be effective against various cancers, the studies were not very well organized and typically used crude plant extracts in a certain solvent systems are documented in popular traditional medicine systems such as Ayurveda medicine system and Chinese medicine system.

There are several reports indicating the ability of phytochemicals to act as signaling molecules against cancers, reviewed in [2]. However, there are only limited studies that properly document the isolation of bioactive phytochemicals in preclinical studies to be used in clinical trials [41]. The complex mixture of the crude plant extracts needs to be separated using suitable separation techniques, such as HPLC or other separation methods. Individual bioactive components should be tested for their biological activities against cancer in preclinical studies and their dosage should be established. High-throughput testing of compounds will enable faster results and should be considered wherever possible. Further, combinations of phytochemicals in addition to the individual screening should be done to check the effects. To enhance the bioavailability of the compounds for optimal effects targeted delivery strategies such as nanoparticles; liposomes or similar strategies should be tested and developed. Further, combination of different phytochemicals or existing therapies should be examined for better efficacy.

1.7 Conclusions

Plants not just constitute our daily food but are sources of valuable phytochemicals with demonstrated potential for cancer chemoprevention in different in vitro, in vivo, preclinical and clinical studies. There are several factors making phytochemicals an attractive choice for the development of an alternative or synergistic approach with conventional cancer therapies. However, to develop a suitable drug from plants organized studies are required. Identification of the bioactive constituents, separation, in vitro and animal testing are required before the clinical studies. The selected plant derived drug candidates should be tested for several pharmacotherapeutic parameters such as pharmacokinetics, drug metabolism, stability, drug–drug interactions dosage, and other required screening.

Conflict of interest Authors declare no conflict of interest

References

1. WHO (2018) Latest global cancer data. WHO, Geneva
2. Kaur V, Kumar M, Kumar A et al (2018) Pharmacotherapeutic potential of phytochemicals: implications in cancer chemoprevention and future perspectives. Biomed Pharmacother 97:564–586. https://doi.org/10.1016/j.biopha.2017.10.124
3. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674. https://doi.org/10.1016/j.cell.2011.02.013

4. Steward WP, Brown K (2013) Cancer chemoprevention: a rapidly evolving field. Br J Cancer 109:1–7. https://doi.org/10.1038/bjc.2013.280
5. Benetou V, Lagiou A, Lagiou P (2015) Chemoprevention of cancer: current evidence and future prospects. F1000Research. https://doi.org/10.12688/f1000research.6684.1
6. Vogel VG (2014) Role of hormones in cancer prevention. Am Soc Clin Oncol Educ B. https://doi.org/10.14694/edbook_am.2014.34.34
7. Koh Y-C, Ho C-T, Pan M-H (2020) Recent advances in cancer chemoprevention with phytochemicals. J Food Drug Anal 28:14–37. https://doi.org/10.1016/j.jfda.2019.11.001
8. Brouwer AF, Meza R, Eisenberg MC (2017) Parameter estimation for multistage clonal expansion models from cancer incidence data: a practical identifiability analysis. PLoS Comput Biol. https://doi.org/10.1371/journal.pcbi.1005431
9. Falzone L, Salomone S, Libra M (2018) Evolution of cancer pharmacological treatments at the turn of the third millennium. Front Pharmacol 9:1300
10. Nurgali K, Jagoe RT, Abalo R (2018) Adverse effects of cancer chemotherapy: anything new to improve tolerance and reduce sequelae? Front Pharmacol 9:245
11. Fridlender M, Kapulnik Y, Koltai H (2015) Plant derived substances with anti-cancer activity: from folklore to practice. Front Plant Sci 6:799
12. Wang H, Oo Khor T, Shu L et al (2012) Plants vs. cancer: a review on natural phytochemicals in preventing and treating cancers and their druggability. Anti Cancer Agents Med Chem 12:1281–1305. https://doi.org/10.2174/187152012803833026
13. Nam S, Smith DM, Dou QP (2001) Ester bond-containing tea polyphenols potently inhibit proteasome activity in vitro and in vivo. J Biol Chem. https://doi.org/10.1074/jbc.M004209200
14. Hu Y, Guo D-H, Liu P et al (2011) Bioactive components from the tea polyphenols influence on endogenous antioxidant defense system and modulate inflammatory cytokines after total-body irradiation in mice. Phytomedicine 18:970–975. https://doi.org/10.1016/j.phymed.2011.02.012
15. Singh H (2011) Hepatoprotective activity of turmeric and garlic against 7-12, dimethylbenzanthracene induced liver damage in wistar albino rats. European J Med Plants. https://doi.org/10.9734/ejmp/2011/587
16. Yordi EG, Pérez EM, Matos MJ, Villares EU (2012) Antioxidant and pro-oxidant effects of polyphenolic compounds and structure-activity relationship evidence. Nutr Well-Being Heal. https://doi.org/10.5772/1864
17. Cao J, Liu Y, Jia L et al (2007) Curcumin induces apoptosis through mitochondrial hyperpolarization and mtDNA damage in human hepatoma G2 cells. Free Radic Biol Med 43:968–975. https://doi.org/10.1016/j.freeradbiomed.2007.06.006
18. Benedict AL, Knatko EV, Dinkova-Kostova AT (2012) The indirect antioxidant sulforaphane protects against thiopurine-mediated photooxidative stress. Carcinogenesis 33:2457–2466. https://doi.org/10.1093/carcin/bgs293
19. Saeed MEM, Meyer M, Hussein A, Efferth T (2016) Cytotoxicity of South-African medicinal plants towards sensitive and multidrug-resistant cancer cells. J Ethnopharmacol. https://doi.org/10.1016/j.jep.2016.04.005
20. Jancova P, Anzenbacher P, Anzenbacherova E (2010) Phase II drug metabolizing enzymes. Biomed Pap. https://doi.org/10.5507/bp.2010.017
21. Thomas H. Rushmore, A.-N. Tony Kong (2005) Pharmacogenomics, regulation and signaling pathways of phase I and II drug metabolizing enzymes. Curr Drug Metab. https://doi.org/10.2174/1389200023337171
22. McWalter GK, Higgins LG, McLellan LI, et al (2004) Transcription factor Nrf2 is essential for induction of NAD(P)H:quinone oxidoreductase 1, glutathione S-transferases, and glutamate cysteine ligase by broccoli seeds and isothiocyanates. J Nutr. https://doi.org/10.1093/jn/134.12.3499s
23. Shishodia S, Amin HM, Lai R, Aggarwal BB (2005) Curcumin (diferuloylmethane) inhibits constitutive NF-κB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. Biochem Pharmacol. https://doi.org/10.1016/j.bcp.2005.04.043

24. Sun J, Hai Liu R (2006) Cranberry phytochemical extracts induce cell cycle arrest and apoptosis in human MCF-7 breast cancer cells. Cancer Lett. https://doi.org/10.1016/j.canlet.2005.10.027
25. Kimmelman AC (2011) The dynamic nature of autophagy in cancer. Genes Dev 25 (19):1999–2010
26. Horwitz SB (1994) Taxol (paclitaxel): mechanisms of action. Ann Oncol 5(Suppl 6):S3–S6
27. Notte A, Ninane N, Arnould T, Michiels C (2013) Hypoxia counteracts taxol-induced apoptosis in MDA-MB-231 breast cancer cells: role of autophagy and JNK activation. Cell Death Dis. https://doi.org/10.1038/cddis.2013.167
28. Sohn EJ, Park HT (2017) Natural agents mediated autophagic signal networks in cancer. Cancer Cell Int 17:110
29. Roxburgh CSD, McMillan DC (2014) Cancer and systemic inflammation: treat the tumour and treat the host. Br J Cancer 110(6):1409–1412
30. Ruiz PA, Braune A, Hölzlwimmer G, et al (2007) Quercetin inhibits TNF-induced NF-κB transcription factor recruitment to proinflammatory gene promoters in murine intestinal epithelial cells. J Nutr. https://doi.org/10.1093/jn/137.5.1208
31. Liberti MV, Locasale JW (2016) The Warburg effect: how does it benefit cancer cells? Trends Biochem Sci 41(3):211–218
32. Warburg O (1956) On the origin of cancer cells. Science. https://doi.org/10.1126/science.123.3191.309
33. del Blanquer-Rosselló MM, Hernández-López R, Roca P et al (2017) Resveratrol induces mitochondrial respiration and apoptosis in SW620 colon cancer cells. Biochim Biophys Acta. https://doi.org/10.1016/j.bbagen.2016.10.009
34. Bayet-Robert M, Morvan D (2013) Metabolomics reveals metabolic targets and biphasic responses in breast cancer cells treated by curcumin alone and in association with docetaxel. PLoS One. https://doi.org/10.1371/journal.pone.0057971
35. Wu KH, Ho CT, Chen ZF, et al (2018) The apple polyphenol phloretin inhibits breast cancer cell migration and proliferation via inhibition of signals by type 2 glucose transporter. J Food Drug Anal. https://doi.org/10.1016/j.jfda.2017.03.009
36. Li Y, Hao Y, Gao B, et al (2019) Chemical profile and in vitro gut microbiota modulatory, anti-inflammatory and free radical scavenging properties of chrysanthemum morifolium cv. Fubaiju. J Funct Foods. https://doi.org/10.1016/j.jff.2019.04.053
37. Malik A, Sharma D, Malireddi RKS, et al (2018) SYK-CARD9 signaling axis promotes gut fungi-mediated inflammasome activation to restrict colitis and colon cancer. Immunity. https://doi.org/10.1016/j.immuni.2018.08.024
38. Estrela JM, Mena S, Obrador E, et al (2017) Polyphenolic phytochemicals in cancer prevention and therapy: bioavailability versus bioefficacy. J Med Chem. https://doi.org/10.1021/acs.jmedchem.6b01026
39. Shenoy D, Little S, Langer R, Amiji M (2005) Poly(ethylene oxide)-modified poly(β-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs. 1. In vitro evaluations. Mol Pharm. https://doi.org/10.1021/mp0500420
40. Jodynis-Liebert J, Kujawska M (2020) Biphasic dose-response induced by phytochemicals: experimental evidence. J Clin Med 9:718. https://doi.org/10.3390/jcm9030718
41. Choudhari AS, Mandave PC, Deshpande M et al (2020) Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Front Pharmacol 10:1614
42. Dhillon N, Aggarwal BB, Newman RA, et al (2008) Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res. https://doi.org/10.1158/1078-0432.CCR-08-0024
43. Russo M, Spagnuolo C, Tedesco I, Russo GL (2010) Phytochemicals in cancer prevention and therapy: truth or dare? Toxins 2(4):517–551