Complementary and Alternative Therapies in Oncology

Subjects: Oncology

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Cancer is the second leading cause of death worldwide, after cardiovascular diseases. Increasing patients' awareness and providing easier access to public information result in greater interest in alternative anticancer or unproven supportive therapies. Fear of cancer and limited trust in the treating physician are also important reasons leading patients to seek these methods. Complementary and alternative medicine (CAM), as opposed to evidence-based medicine (EBM), is not grounded in well-designed clinical studies, and thus may not be effective or may even harm patients. Complementary medicine is used in addition to standard medicine, whereas alternative medicine is used in lieu of standard methods. Patients diagnosed with cancer are frequently confused due to the unpredictability of the situation, stress, and fear of the future of themselves and their families. The willingness to actively participate in the therapeutic process may prompt them to seek allegedly effective CAM options. Patients attempt these methods to increase treatment efficacy, alleviate treatment side effects, or improve their physical and mental condition.

Keywords: cancer ; alternative and complementary medicine ; whole-body hyperthermia ; chlorella ; hemp ; vitamin C ; turmeric ; ozone therapy ; spirulina

1. Introduction

Cancer is the second leading cause of death worldwide after cardiovascular diseases, and its incidence is growing. The efficacy of cancer treatment is increasing due to a better understanding of its biology and improvements in diagnostic and therapeutic methods. Active participation by patients in the diagnostic and therapeutic process may increase their compliance and well-being. However, greater patient awareness, more accessible public data, and determination often prompt them to seek unproven alternative therapies.

Complementary and alternative medicine (CAM), as opposed to evidence-based medicine (EBM), is not grounded in well-designed clinical studies, and thus may not be effective or may even harm patients. Complementary medicine is used in addition to standard medicine, whereas alternative medicine is used in lieu of standard methods.

Patients diagnosed with cancer are frequently confused due to the unpredictability of the situation, stress, and fear of the future of themselves and their families. The willingness to actively participate in the therapeutic process may prompt them to seek allegedly effective CAM options. Patients attempt these methods to increase treatment efficacy, alleviate treatment side effects, or improve their physical and mental condition. However, in many instances, patients replace main treatments with alternative methods, which may considerably worsen their prognosis.

The use of CAM in cancer patients has been consistently increasing [1]. For example, in a nationwide survey carried out in the Nepal, 32% of cancer patients reported using alternative therapies [2]. In another study of almost 1500 cancer survivors, 67% reported ever using CAM, and 43% had used CAM in the past year [3]. Alternative therapies are not subject to any formal regulations in Poland, and no public education programs address this issue. Consequently, patients often rely on knowledge from the Internet, which is frequently untrustworthy. The growing popularity and heterogeneity of CAM methods make them an important issue for patient–doctor relations in Poland and other Central European countries [4]. A recent study from Poland demonstrated that an astonishing number of CAM practices offered to manage multiple entities [5].

One of the reasons for seeking unconventional methods is the lack of time and understanding of medical staff. Cancer therapy requires a complete understanding of both parties and a truthful dialogue to ensure the safety and well-being of the patient. In addition, a sincere relationship with the treating physicians and their basic knowledge of alternative treatments may significantly influence patients' decision-making process.

The increasing use of CAM by cancer patients constitutes a challenge for health care systems. Apart from social education, good communication between cancer patients and medical staff is crucial in managing this problem. This aim

may be achieved by competence, understanding, patience, and adequate support for patients.

Health care professionals generally question the value of CAM and see no need to increase their expertise on this subject. However, having a basic knowledge of CAM may facilitate discussion with patients and influence their decisions.

2. Chlorella

Chlorella is a unicellular alga from the class of green algae that is increasingly being added to yogurts, juices, and smoothies in powder form. It is rich in protein; vitamins (particularly B vitamins); trace elements such as magnesium, potassium, iron, calcium, and zinc; fiber; and omega-3 fatty acids. The antioxidant and immunomodulatory properties of chlorella result from increasing the activity of NK cells and stimulating the production of interferon-γ, interleukin-12, and interleukin-1β. Ref. [6] Hot water extract of *Chlorella vulgaris* induces apoptosis and DNA damage in non-small-cell lung cancer cell lines [7]. Animal and in vitro studies have shown its antiproliferative effects on liver and colorectal cancer cells [8][9]. Lycopene isolated from chlorella inhibited the growth of prostate cancer cells in [10]. In an animal model, chlorella extract reduced bone marrow suppression caused by cisplatin [11]. Clinical data on chlorella treatment include only a small group of breast cancer patients [12]. According to a survey, chlorella extract decreased the severity of chronic weakness and dry skin in this group. The anticancer activity of chlorella has not been the subject of clinical trials.

3. Beet Juice, Carrot Juice

Many studies confirm the role of diet, mainly in cancer prevention. A diet including high amounts of lutein-rich vegetables such as spinach, broccoli, lettuce, tomatoes, oranges, carrots, and celery has been proven to reduce the risk of developing proliferative diseases. The inclusion of these foods in the diet can reduce the risk of colorectal cancer [13]. A citrus-rich diet reduces the risk of laryngeal cancer, and a diet high in fruits and vegetables reduces the risk of pancreatic cancer [13][14]. Consumption of carotenoid-rich foods inhibits DNA damage, and the betanin in beet juice induces apoptosis in breast cancer cells [15][16].

In vitro studies have shown that beet juice may increase the anticancer effect of doxorubicin [17]. A case report suggested that the combination of chlorambucil with beet juice and carrot juice is beneficial in a B-CLL leukemia patient [18]. Finally, the consumption of large amounts of carrot juice and beet juice was shown to reduce the anticancer effects of cisplatin [19].

4. Hemp

Hemp and hemp-derived cannabinoids (i.e., substances that act on cannabinoid receptors) are available for medical treatment in many countries. Individual preparations differ in delta-9-tetrahydrocannabinol and cannabidiol (CBD) content. In Poland, an aerosol preparation containing THC and CBD is registered to treat spasticity symptoms in patients with multiple sclerosis, but is not refunded. Until recently, hemp was also available in Poland in a dried form containing 19% THC and <1% CBD. This medicine does not have the characteristics of a medicinal product, and thus the specific indications for its use cannot be listed. The dried form is registered as a prescription ingredient.

Some studies have shown that cannabinoids might reduce the severity of nausea and vomiting associated with chemotherapy [20] and carry analgesic effects [21]. THC and CBD have alleviated acute and chronic pain in animal studies, but results in cancer patients are inconclusive [22]. A small study reported improved anxiety, mood, and well-being with cannabinoids in cancer patients [23]. However, no extensive clinical trials have been undertaken to confirm the analgesic effect of THC and CBD [24].

Anticancer effects of cannabinoids have only been tested on cancer cell lines. The administration of CBD increased the sensitivity of multiple glioma cells to chemotherapy [25]. Antiproliferative effects of THC and CBD have also been shown in breast, uterus, gastric, colorectal, pancreatic, lung adenocarcinoma, prostate cancer, and lymphoma cell lines [23].

The side effects of cannabinoids are primarily related to their stimulant and depressant effects on the CNS. Patients may experience confusion, impaired memory, drowsiness, and perceptual disturbances. Interestingly, unlike opioid receptors, cannabinoid receptors are not present in the brain's respiratory center. Thus, in the case of cannabinoid overdose, there is no fear of respiratory depression [23]. However, THC and CBD affect receptors not only in the nervous system; they can cause tachycardia, hypotension, muscle relaxation, or impaired gastrointestinal motility [26]. The risk of cannabinoid addiction is lower than for tobacco, alcohol, or cocaine. Withdrawal symptoms such as irritability, restlessness, nausea, or

insomnia have been less severe than those accompanying benzodiazepines or opiates, and usually resolve after a few days [23].

5. Propolis

Propolis is a resinous substance collected by bees from the buds and shoots of young trees and green plants. It is available as a dietary supplement in several forms, including pills, capsules, tablets, drops, syrups, ointments, sprays, powders, or liquids for skin application.

Studies on cell lines and animal models have shown a cytotoxic effect of propolis on breast, cervical, skin, gastric, prostate, and leukemia cancer cells, and a protective effect on the DNA of healthy cells [27][28][29][30]. A Polish study claimed that ethanol extract of propolis has cytotoxic activity on glioblastoma cell lines [31].

Due to its anti-inflammatory and antimicrobial effects, propolis extract was also used to treat complications after radiotherapy. A small study showed that propolis extract allowed the healing of radiation skin ulcers resistant to standard treatments [32]. Finally, in a study involving over 200 patients with breast cancer and head and neck cancer, propolis solution was shown to be effective and safe in preventing and treating oral mucositis caused by radiotherapy or chemotherapy [33]. However, larger clinical studies have not confirmed any beneficial effects in patients with radiation or postoperative ulcers and oral mucositis. So far, no study has shown the anticancer effects of propolis.

6. Vitamin C

Vitamin C is one of the most potent antioxidants. The first reports of its potential anticancer effects were published in the 1970s. An increasing number of institutions offer intravenous vitamin C infusions for cancer patients, advertising them as an adjunctive or anticancer modality.

High doses of vitamin C inhibit the growth of prostate, colon, and pancreatic cancer, as well as mesothelioma cell lines [34][35][36][37]. In a phase I study, the addition of high vitamin C doses to anticancer therapies (e.g., gemcitabine) was claimed to increase their effectiveness [37]. However, in other studies conducted on cell lines and in animal models, high doses of vitamin C reduced the effectiveness of chemotherapy [38][39][40]. In a small study, intravenous vitamin C infusions reduced chemotherapy-related symptoms such as fatigue, nausea, vomiting, or loss of appetite [38]. Currently, there is no evidence to confirm the beneficial effects of intravenous vitamin C in cancer patients, and its use may even reduce the effectiveness of treatment.

Due to the risk of hemolysis, intravenous vitamin C is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency [41], and even its oral form in these patients should be used with caution. High doses of vitamin C should not be administered in patients with a predisposition to kidney stones [38][39]. Vitamin C infusions administered shortly before chemotherapy may cause adverse interactions [39].

7. Turmeric

Turmeric is a spice originating from India and has been used in traditional Chinese and Ayurvedic medicine since ancient times. This compound has attracted great interest in recent decades because it contains bioactive curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin). Laboratory studies have shown its antioxidant and anti-inflammatory effects [42][43].

Turmeric was shown to increase the sensitivity of cancer cells to cisplatin, 5-fluorouracil, paclitaxel, and radiotherapy [43][44][45][46][47]. Some studies also demonstrated a chemoprotective effect of turmeric against the development of head and neck cancer and colorectal cancer [48][49].

The clinical data on turmeric are scarce. In patients with colorectal cancer, turmeric reduced weight loss and decreased serum inflammatory parameters [50]. A phase II trial involving 44 patients claimed that 30-day turmeric therapy might reduce tumor size [51]. Other studies involving small groups of patients with prostate and pancreatic cancer, that investigated this compound alone or combined with radiotherapy and chemotherapy, have been inconclusive. In patients with head and neck cancer and breast cancer, turmeric reduced radiation skin reactions [52][53].

No severe side effects of turmeric have been observed, but there are interactions with antiplatelet agents [54], doxorubicin, or tacrolimus [55]. Turmeric also affects the activity of cytochrome P450 enzymes [56].

References

1. Horneber, M.; Bueschel, G.; Dennert, G.; Less, D.; Ritter, E.; Zwahlen, M. How Many Cancer Patients Use Complementary and Alternative Medicine: A Systematic Review and Meta-analysis. Integr. Cancer Ther. 2012, 11, 187–203.
2. Choi, S.J.; Kunwor, S.K.; Bin Im, H.; Hwang, J.H.; Choi, D.; Han, D. Traditional and complementary medicine use among cancer patients in Nepal: A cross-sectional survey. BMC Complement. Med. Ther. 2022, 22, 70.
3. Mao, J.J.; Palmer, C.S.; Healy, K.E.; Desai, K.; Amsterdam, J. Complementary and alternative medicine use among cancer survivors: A population-based study. J. Cancer Surviv. 2011, 5, 8–17.
4. Puskulluoglu, M.; Uchańska, B.; Tomaszewski, K.A.; Zygulska, A.L.; Zielińska, P.; Grela-Wojewoda, A. Use of complementary and alternative medicine among Polish cancer patients. Nowotw. J. Oncol. 2021, 71, 274–281.
5. Perdyan, A.; Wasiukiewicz, M.; Szastok, P.; Jassem, J. The scope of complementary and alternative medicine in Poland. Nowotw. J. Oncol. 2021, 71, 357–372.
6. Kwak, J.H.; Baek, S.H.; Woo, Y.; Han, J.K.; Kim, B.G.; Kim, O.Y.; Lee, J.H. Beneficial immunostimulatory effect of short-term Chlorella supplementation: Enhancement of Natural Killercell activity and early inflammatory response (Randomized, double-blinded, placebo-controlled trial). Nutr. J. 2012, 11, 53.
7. Zhang, Z.-D.; Liang, K.; Li, K.; Wang, G.-Q.; Zhang, K.-W.; Cai, L.; Zhai, S.-T.; Chou, K.-C. Chlorella vulgaris Induces Apoptosis of Human Non-Small Cell Lung Carcinoma (NSCLC) Cells. Med. Chem. 2017, 13, 560–568.
8. Azamai, E.S.M.; Sulaiman, S.; Habib, S.H.M.; Looi, M.L.; Das, S.; Hamid, N.A.A.; Ngah, W.Z.W.; Yusof, Y.A.M. Chlorella vulgaris triggers apoptosis in hepatocarcinogenesis-induced rats. J. Zhejiang Univ. Sci. B 2009, 10, 14–21.
9. Cha, K.H.; Koo, S.Y.; Lee, D.U. Antiproliferative effects of carotenoids extracted from Chlorella ellipsoidea and Chlorella vulgaris on human colon cancer cells. J. Agric. Food. Chem. 2008, 56, 10521–10526.
10. Hamouda, R.A.; El Latif, A.A.; Elkaw, E.M.; Alotaibi, A.S.; Alenzi, A.M.; Hamza, H.A. Assessment of Antioxidant and Anticancer Activities of Microgreen Alga Chlorella vulgaris and Its Blend with Different Vitamins. Molecules 2022, 27, 1602.
11. Lin, S.-H.; Li, M.-H.; Chuang, K.-A.; Lin, N.-H.; Chang, C.-H.; Wu, H.-C.; Chao, Y.-H.; Lin, C.-C.; Pan, I.-H.; Perng, M.-D.; et al. Chlorella sorokiniana Extract Prevents Cisplatin-Induced Myelotoxicity In Vitro and In Vivo. Oxid. Med. Cell. Longev. 2020, 2020, 7353618.
12. Noguchi, N.; Maruyama, I.; Yamada, A. The Influence of Chlorella and Its Hot Water Extract Supplementation on Quality of Life in Patients with Breast Cancer. Evid. Based Complement. Altern. Med. 2014, 2014, 704619.
13. Kamal, N.; Ilowefah, M.A.; Hilles, A.R.; Anua, N.A.; Awin, T.; Alshwyeh, H.A.; Aldosary, S.K.; Jambocus, N.G.S.; Alosaimi, A.A.; Rahman, A.; et al. Genesis and Mechanism of Some Cancer Types and an Overview on the Role of Diet and Nutrition in Cancer Prevention. Molecules 2022, 27, 1794.
14. Jansen, R.J.; Robinson, D.P.; Stolzenberg-Solomon, R.Z.; Bamlet, W.R.; De Andrade, M.; Oberg, A.L.; Rabe, K.G.; Anderson, K.E.; Olson, J.E.; Sinha, R.; et al. Nutrients from Fruit and Vegetable Consumption Reduce the Risk of Pancreatic Cancer. J. Gastrointest. Cancer 2013, 44, 152–161.
15. Azqueta, A.; Collins, A.R. Carotenoids and DNA damage. Mutat. Res. Mol. Mech. Mutagen. 2012, 733, 4–13.
16. Nowacki, L.; Vigneron, P.; Rotellini, L.; Cazzola, H.; Merlier, F.; Prost, E.; Ralanairina, R.; Gadonna, J.-P.; Rossi, C.; Vayssade, M. Betanin-Enriched Red Beetroot (Beta vulgaris L.) Extract Induces Apoptosis and Autophagic Cell Death in MCF-7 Cells. Phytother. Res. 2015, 29, 1964–1973.
17. Kapadia, G.J.; Rao, G.S.; Ramachandran, C.; Iida, A.; Suzuki, N.; Tokuda, H. Synergistic cytotoxicity of red beetroot (Beta vulgaris L.) extract with doxorubicin in human pancreatic, breast and prostate cancer cell lines. J. Complement. Integr. Med. 2013, 10, 113–122.
18. Shakib, M.-C.R.; Gabrial, S.; Gabrial, G. Beetroot-Carrot Juice Intake either Alone or in Combination with Antileukemic Drug ‘Chlorambucil’ As A Potential Treatment for Chronic Lymphocytic Leukemia. Open Access Maced. J. Med. Sci. 2015, 3, 331–336.
19. Szefler, B.; Czeleń, P.; Szczepanik, A.; Cysewski, P. Does the Affinity of Cisplatin to B-Vitamins Impair the Therapeutic Effect in the Case of Patients with Lung Cancer-consuming Carrot or Beet Juice? Anticancer Agents Med. Chem. 2019, 19, 1775–1783.
20. Pagano, C.; Navarra, G.; Coppola, L.; Avilia, G.; Bifulco, M.; Laezza, C. Cannabinoids: Therapeutic Use in Clinical Practice. Int. J. Mol. Sci. 2022, 23, 63344.

21. Johnson, J.R.; Lossignol, D.; Burnell-Nugent, M.; Fallon, M.T. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J. Pain Symptom. Manag. 2013, 46, 207–218.
22. Johnson, J.R.; Burnell-Nugent, M.; Lossignol, D.; Ganae-Motan, E.D.; Potts, R.; Fallon, M.T. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J. Pain Symptom Manag. 2010, 39, 167–179.
23. Bar-Sela, G.; Vorobeichik, M.; Drawsheh, S.; Omer, A.; Goldberg, V.; Muller, E. The medical necessity for medicinal cannabis: Prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. Evid. Based Complement. Altern. Med. 2013, 2013, 510392.
24. Abrams, D.I.; Guzmán, M. Cannabis in cancer care. Clin. Pharmacol. Ther. 2015, 97, 575–586.
25. Torres, S.; Lorente, M.; Rodríguez-Fornés, F.; Hernández-Tiedra, S.; Salazar, M.; García-Taboada, E.; Barcia, J.; Guzmán, M.; Velasco, G. A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma. Mol. Cancer Ther. 2011, 10, 90–103.
26. Cohen, K.; Abraham, W.A.; Weinstein, A. Positive and Negative Effects of Cannabis and Cannabinoids on Health. Clin. Pharmacol. Ther. 2019, 105, 1139–1147.
27. Khacha-Ananda, S.; Chantawannakul, P.; Tragoolpua, K.; Tragoolpua, Y. Propolis extracts from the northern region of Thailand suppress cancer cell growth through induction of apoptosis pathways. Investig. New Drugs 2016, 34, 707–722.
28. Seyhan, M.F.; Yılmaz, E.; Timirci-Kahraman, Ö.; Saygılı, N.; Kısakesen, H.İ.; Gazioğlu, S.; Gören, A.C.; Eronat, A.P.; Begüm Ceviz, A.; Öztürk, T.; et al. Different propolis samples, phenolic content, and breast cancer cell lines: Variable cytotoxicity ranging from ineffective to potent. IUBMB Life 2018, 71, 619–631.
29. Alizadeh, A.M.; Afrouzan, H.; Dinparast-Djadid, N.; Sawaya, A.C.H.F.; Azizian, S.; Hemmati, H.R.; Mohagheghi, M.A.; Erfani, S. Chemoprotection of MNNG-initiated gastric cancer in rats using Iranian propolis. Arch. Iran. Med. 2015, 18, 18–23.
30. López-Romero, D.; Izquierdo-Vega, J.A.; Morales-González, J.A.; Madrigal-Bujaidar, E.; Chamorro-Cevallos, G.; Sánchez-Gutiérrez, M.; Betanzos-Cabrera, G.; Alvarez-Gonzalez, I.; Morales-González, J.; Madrigal-Santillán, E. Evidence of Some Natural Products with Antigenotoxic Effects. Part 2: Plants, Vegetables, and Natural Resin. Nutrients 2018, 10, 1954.
31. Borawska, M.H.; Naliwajko, S.K.; Moskwa, J.; Markiewicz-Żukowska, R.; Puścion-Jakubik, A.; Soroczyńska, J. Antiproliferative and anti-migration effects of Polish propolis combined with Hypericum perforatum L. on glioblastoma multiforme cell line U87MG. BMC Complement. Altern. Med. 2016, 16, 367.
32. Barroso, P.R.; Lopes-Rocha, R.; Pereira, E.M.F.; Marinho, S.A.; de Miranda, J.L.; Lima, N.L.; Verli, F.D. Effect of propolis on mast cells in wound healing. Inflammopharmacology 2012, 20, 289–294.
33. Münstedt, K.; Männle, H. Using Bee Products for the Prevention and Treatment of Oral Mucositis Induced by Cancer Treatment. Molecules 2019, 24, 3023.
34. Chen, P.; Yu, J.; Chalmers, B.; Drisko, J.; Yang, J.; Li, B.; Chen, Q. Pharmacological ascorbate induces cytotoxicity in prostate cancer cells through ATP depletion and induction of autophagy. Anticancer Drugs 2012, 23, 437–444.
35. Pathi, S.S.; Lei, P.; Sreevalsan, S.; Chadalapaka, G.; Jutooru, I.; Safe, S. Pharmacologic Doses of Ascorbic Acid Repress Specificity Protein (Sp) Transcription Factors and Sp-Regulated Genes in Colon Cancer Cells. Nutr. Cancer 2011, 63, 1133–1142.
36. Du, J.; Martin, S.M.; Levine, M.; Wagner, B.A.; Buettner, G.; Wang, S.-H.; Taghiyev, A.F.; Du, C.; Knudson, C.M.; Cullen, J.J. Mechanisms of Ascorbate-Induced Cytotoxicity in Pancreatic Cancer. Clin. Cancer Res. 2010, 16, 509–520.
37. Takemura, Y.; Satoh, M.; Satoh, K.; Hamada, H.; Sekido, Y.; Kubota, S. High dose of ascorbic acid induces cell death in mesothelioma cells. Biochem. Biophys. Res. Commun. 2010, 394, 249–253.
38. Welsh, J.L.; Wagner, B.A.; Van't Erve, T.J.; Zehr, P.S.; Berg, D.J.; Halfdanarson, T.R.; Yee, N.S.; Bodeker, K.L.; Du, J.; Roberts, L.J., 2nd; et al. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): Results from a phase I clinical trial. Cancer Chemother. Pharmacol. 2013, 71, 765–775.
39. Klimant, E.; Wright, H.; Rubin, D.; Seely, D.; Markman, M. Intravenous vitamin C in the supportive care of cancer patients: A review and rational approach. Curr. Oncol. 2018, 25, 139–148.
40. Böttger, F.; Vallés-Martí, A.; Cahn, L.; Jimenez, C.R. High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. J. Exp. Clin. Cancer Res. 2021, 40, 343.

41. Lo, Y.H.; Mok, K.L. High dose vitamin C induced methemoglobinemia and hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency. Am. J. Emerg. Med. 2020, 38, 2488.e3–2488.e5.
42. Streyczek, J.; Apweiler, M.; Sun, L.; Fiebich, B.L. Turmeric Extract (Curcuma longa) Mediates Anti-Oxidative Effects by Reduction of Nitric Oxide, iNOS Protein-, and mRNA-Synthesis in BV2 Microglial Cells. Molecules 2022, 27, 784.
43. Meng, B.; Li, J.; Cao, H. Antioxidant and anti-inflammatory activities of curcumin on diabetes mellitus and its complications. Curr. Pharm. Des. 2013, 19, 2101–2113.
44. Sreekanth, C.N.; Bava, S.V.; Sreekumar, E.; Anto, R.J. Molecular evidences for the chemosensitizing efficacy of liposomal curcumin in paclitaxel chemotherapy in mouse models of cervical cancer. Oncogene 2011, 30, 3139–3152.
45. Shakibaei, M.; Mobasheri, A.; Lueders, C.; Busch, F.; Shayan, P.; Goel, A. Curcumin Enhances the Effect of Chemotherapy against Colorectal Cancer Cells by Inhibition of NF-κB and Src Protein Kinase Signaling Pathways. PLoS ONE 2013, 8, e57218.
46. Selvendiran, K.; Ahmed, S.; Dayton, A.; Kuppusamy, M.L.; Rivera, B.K.; Kálai, T.; Hideg, K.; Kuppusamy, P. HO-3867, a curcumin analog, sensitizes cisplatin-resistant ovarian carcinoma, leading to therapeutic synergy through STAT3 inhibition. Cancer Biol. Ther. 2011, 12, 837–845.
47. Qiao, Q.; Jiang, Y.; Li, G. Curcumin improves the anti- tumor effect of X-ray irradiation by blocking the NF-kappaB pathway: An in-vitro study of lymphoma. Anticancer Drugs 2012, 23, 597–605.
48. Chang, K.W.; Hung, P.S.; Lin, I.Y.; Hou, C.P.; Chen, L.K.; Tsai, Y.M.; Lin, S.C. Curcumin Upregulates Insulin-Like Growth Factor Binding protein-5 (IGFBP-5) and C/EBPalpha During Oral Cancer Suppression. Int. J. Cancer 2010, 127, 9–20.
49. Perkins, S.; Verschoyle, R.D.; Hill, K.; Parveen, I.; Threadgill, M.D.; Sharma, R.A.; Williams, M.L.; Steward, W.P.; Gescher, A.J. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiol. Biomark. Prev. 2002, 11, 535–540.
50. He, Z.Y.; Shi, C.B.; Wen, H.; Li, F.L.; Wang, B.L.; Wang, J. Up- regulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Investig. 2011, 29, 208–213.
51. Carroll, R.E.; Benya, R.V.; Turgeon, D.K.; Vareed, S.; Neuman, M.; Rodriguez, L.; Kakarala, M.; Carpenter, P.M.; McLaren, C.; Meyskens, F.L., Jr.; et al. Phase IIa Clinical Trial of Curcumin for the Prevention of Colorectal Neoplasia. Cancer Prev. Res. 2011, 4, 354–364.
52. Palatty, P.L.; Azmidah, A.; Rao, S.; Jayachander, D.; Thilakchand, K.R.; Rai, M.P.; Haniadka, R.; Simon, P.; Ravi, R.; Jimmy, R.; et al. Topical application of a sandal wood oil and turmeric based cream prevents radiodermatitis in head and neck cancer patients undergoing external beam radiotherapy: A pilot study. Br. J. Radiol. 2014, 87, 20130490.
53. Ryan, J.L.; Heckler, C.E.; Ling, M.; Katz, A.; Williams, J.P.; Pentland, A.P.; Morrow, G.R. Curcumin for Radiation Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Thirty Breast Cancer Patients. Radiat. Res. 2013, 180, 34–43.
54. Jantan, I.; Raweh, S.M.; Sirat, H.M.; Jamil, S.; Yasin, Y.M.; Jalil, J.; Jamal, J.A. Inhibitory effect of compounds from Zingiberaceae species on human platelet aggregation. Phytomedicine 2008, 15, 306–309.
55. Abushammala, I. Tacrolimus and herbs interactions: A review. Pharmazie 2021, 76, 468–472.
56. Zhang, W.; Lim, L.Y. Effects of spice constituents on P-gly-coprotein-mediated transport and CYP3A4-mediated metabolism in vitro. Drug. Metab. Dispos. 2008, 36, 1283–1290.