Cancer Cell International

REVIEW

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Medicinal plants: nutritional, immunological and therapeutic role in treating cancer-related malnutrition: a comprehensive review

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Abstract

Cancer is the second leading cause of death globally, following microbial infection, with an estimated 16 million deaths projected by 2040. However, natural resources can potentially treat up to 60% of cancer cases. Various cancers, including those affecting the breast, prostate, stomach, colon, lung, liver, kidney, bone, skin, and blood, have strong dietary connections regarding their occurrence and prevention. Cancer and its treatments, particularly chemotherapy, are closely associated with malnutrition in humans. The adverse effects of medical therapies and the disease itself often prevent patients with cancer from meeting their nutritional needs through regular food intake. The etiology of malnutrition in patients with cancer is complex and multifactorial, influenced by the type and location of cancer, disease stage, side effects of treatment, economic status, functional capacity, symptoms impacting nutrition, fasting requirements, inadequate dietary therapy, and awareness of the clinical staff regarding the role of dietary habits in diagnosis, treatment, and quality of life. Although there have been advances in drug-targeted therapies, they remain unelucidated, and therefore, this review aims to elucidate the relationship between cancer, chemical treatments, and malnutrition. In addition, it highlights the significant role of medicinal plants in treating various cancers and mitigating the adverse side effects of chemotherapy, offering a comprehensive understanding of their nutritional, immunological, and therapeutic benefits.

Keywords Cancer, Chemotherapy, Clinical nutrition, Dietary intake, Drugs, Medicinal herbs

Introduction

Cancer is a multi-disease characterized by the uncontrolled proliferation of somatic cells, which can spread to other organs and cause metastasis [1]. Although cell growth, differentiation, and death processes are tightly programmed, some cells, particularly those with somatic and epigenetic mutations, may evade regulation and grow uncontrollably [2, 3]. A neoplasm is a type of uncontrolled, abnormal growth that can be benign, limited to the original tissue, or malignant, invading other tissues and generating secondary tumors [1, 2, 4].

Cancer is a ubiquitous disease affecting all organisms in the metazoans of life regardless of body size and lifespan [4, 5]. Cancers can affect broad vertebrates and some invertebrate species, such as the basal metazoan *Hydra* and zebrafish, indicating that the principles of

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tumorigenesis are prevalent in all species [5, 6]. Cancer risk varies between species; data from captive wild animal autopsies indicate that the incidence rates of neoplasms in mammals, reptiles, and birds are 2.75%, 2.19%, and 1.89%, respectively [7]. Furthermore, data on adult zoo mammals imply that carnivorous, particularly mammal-consuming animals, are more prone to tumors than herbivorous mammals [5]. Cancer progression is primarily attributed to oncogenic mutations in tumor suppressor genes in somatic cells [8].

A previous study by Peto [9] suggested that animals with large bodies and long lives are at a higher risk of developing cancers, as their cells are susceptible to increased cell divisions, resulting in the introduction of additional somatic mutations [9]. However, this association is not observed across species; for example, some animals, such as long-lived whales and elephants, have a lower rate of cancer incidence than predicted [10]. Peto's paradox suggests that the incidence of cancers is comparable among animals such as elephants, whales, and mice [10, 11].

A recent study by Vincze et al. [5] showed that the mortality rate of cancers relies on body mass and life expectancy, which is empirical proof of Peto's paradox [12]. Peto's paradox implies that certain species may have already developed anticancer mechanisms through natural selection. Therefore, comparative oncology research can prioritize anticancer strategies [12].

Cancer is characterized by the invasion and metastasis of cells anywhere in the body. The top six cancer types, according to sex, account for more than 50% of new cancer diagnoses and deaths worldwide [13]. The cancer incidence rates from a total of 11.7% estimated cases in 2020 were as follows: breast (11.7%), lung (11.4%), colorectal (10.0%), prostate (7.3%), stomach (5.6%), and liver cancers (4.7%) [13]. Figure 1 displays the most typical locations where cancer can form in the human body.

In Sweden, the mortality rates of lung, colorectal, liver, stomach, and breast cancers were reported to be 18, 9.4, 8.3, 7.7, and 6.9%, respectively [13]. The incidence rates of prostate and breast cancers have increased among males and females. In 2020, the incidence of cancer in males was highest for prostate cancer (32.5%), followed by colorectal cancer (10.5%), bladder cancer (6.6%), lung cancer (6.4%), and melanoma of the skin (6.4%). The incidence of cancer in females during the same year was highest for breast cancer (26.2%), followed by colorectal cancer (11.2%), lung cancer (8.4%), skin melanoma (7.4%), and corpus uteri cancer (5.1%) [13].

The 5-year survival rates for prostate, skin, breast, lung, liver, esophagus, and pancreatic cancers are 98, 93, 90, 22, 20, and 11%, respectively [14]. However, the incidence and mortality rates related to cancer are increasing every day worldwide [15]. If the cancer is localized in the original tissue and has not invaded other tissues in the body, it should be surgically removed [16]. It is impossible to treat metastatic cancer because it spreads to other tissues and organs. During metastasis, detached cancer cells travel from the primary site to distant organs, developing secondary growth and metastatic lesions [16, 17].

The most targeted organs for cancer differ between men and women [18]. The incidence rate of bone cancer, followed by liver and lung cancer, is higher in men, whereas liver cancer, followed by bone and lung cancer, is more common in women [18, 19]. Cancer metastasis is the leading cause of the high mortality rate (90%) associated with solid tumors [20].

Traditional medicine has long relied on medicinal herbs to prevent and treat disease. Currently, chemical treatments are not the only option for combating cancer; herbal medicine is a widely available, safe, and nontoxic alternative [21–29]. The current review assessed the influence of anticancer therapies on malnutrition prevalence, body structure, dietary intake, and biological measurements of blood nutrients. Additionally, the role of medicinal herbs in treating different types of cancer and improving the general health of treated patients was evaluated.

Malnutrition and the progression of cancer

With advancements in cancer therapy, cancer survival rates are rising. The cancer continuum encompasses diagnosis, treatment, recovery, post-recovery living, and, for specific individuals, palliative care [30]. Patients have various nutritional needs and difficulties at every stage. Surgery, radiation, and chemotherapy are the three primary treatment modalities that affect metabolism and dietary needs. They also change standard eating patterns and harm how the body breaks down, absorbs, and uses food.

Malnutrition affects the majority of cancer patients receiving therapy, which lowers their reaction to the medication and necessitates lowering the dosage or possibly stopping it altogether [31]. The overarching goals of nutritional support during active cancer treatment are to avoid or rectify nutrient deficiencies, preserve skeletal muscle mass and strength, enhance immunological response, reduce nutrition impact symptoms (NIS), and optimize quality of life [32].

Malnutrition prevalence in cancer patients receiving chemotherapy

Unlike malnutrition caused by starvation, cancer-related malnutrition is characterized by reduced food consumption due to the disease and treatment-induced NIS and metabolic alterations, including increased resting

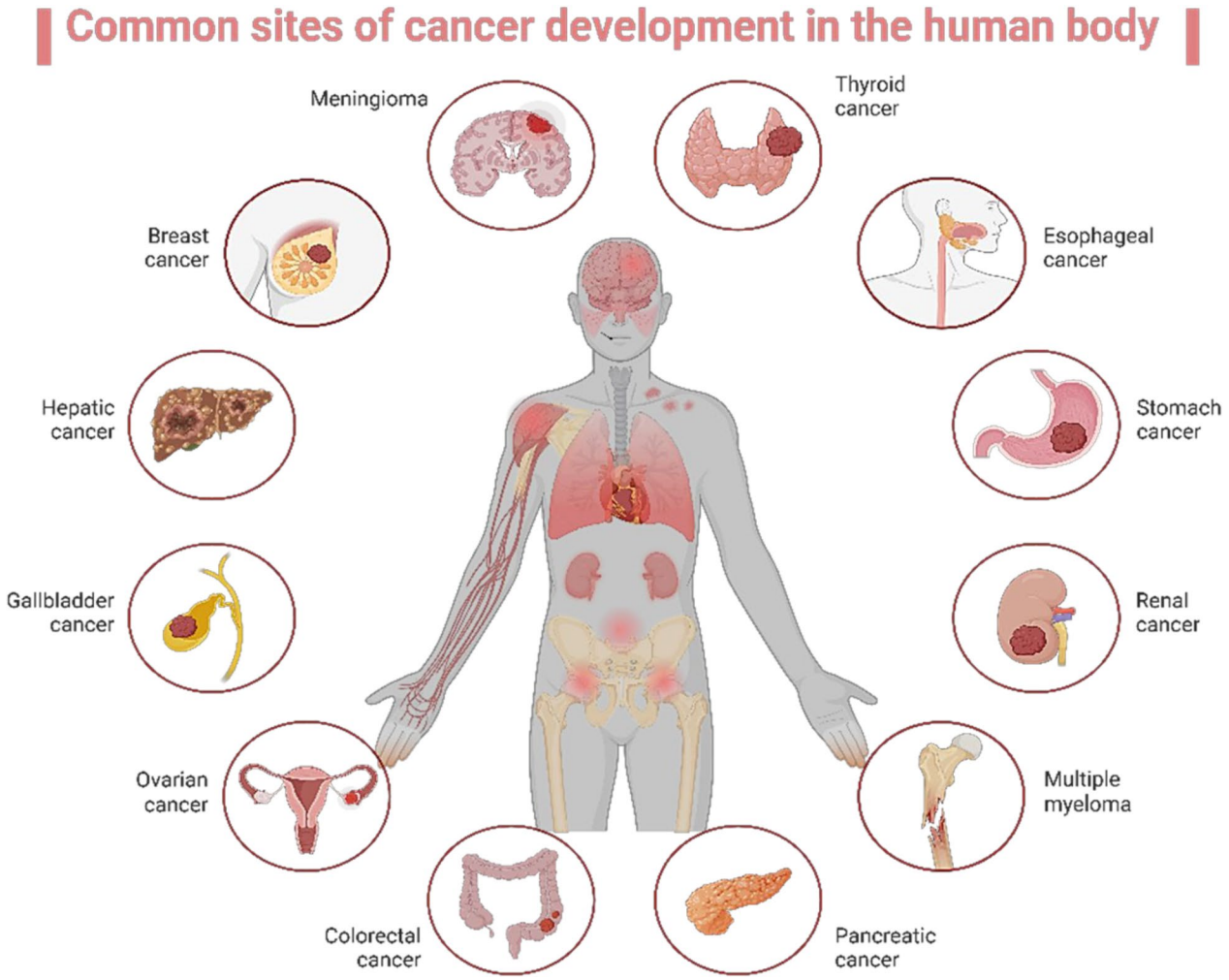

Fig. 1 Common sites of cancer development in the human body

metabolic rates, insulin resistance, and exacerbated muscle loss due to systemic inflammation [33]. Patients identified for cancer therapy exhibited a considerable prevalence of malnutrition at the time of diagnosis. Cancer treatment exacerbates pre-existing nutritional issues by increasing the incidence of malnutrition from 40 to 98% post-therapy [34, 35]

The absence of widely recognized criteria for malnutrition in the context of cancer contributes to the wide variation in the standards for evaluating nutritional status, including nutritional screening and assessment instruments, which may result in incorrect categorization [36]. Nutritional screening and assessment are two completely separate procedures. Nutritional assessment facilitates nutrition diagnosis, whereas nutritional screening evaluates risk markers to identify those at risk. A screening tool must be brief and have the proper specificity and sensitivity [36].

The malnutrition universal screening tool, micro nutritional assessment (MNA) short form updated, and nutrition risk screening 2002 (NRS-2002) are among the most used screening instruments [36]. Various techniques, including global subjective assessment (SGA), patient-generated subjective global assessment (PG-SGA), and MNA, have been used in clinical practice and research for nutritional evaluation [37].

During cancer therapy, nutritional status diminishes despite the methods used to measure malnutrition. In one research, all patients with acute leukemia were moderately malnourished at baseline, but 97% of patients were diagnosed with severe malnutrition (PG-SGA score of $\geq$9) after receiving chemical therapy, which exacerbated their nutritional status [38]. Comparably, another

research found that 30% of patients with progressive head and neck malignancies (PG-SGA B or C) were malnourished upon diagnosis; 95% of cases were classified as malnourished during chemotherapy and radiation treatment [39]. Malnutrition was present in 38% of elderly patients with gastrointestinal cancer at the first visit, but it sharply rose to 46% after a single chemotherapy session [40]. MNA, the recommended instrument for evaluating the nutritional state of older people, was used to assess the nutritional status in this research [40].

Two studies found that the proportion of patients who were likely to suffer from malnutrition significantly increased when the NRS-2002 tool was used for patients with colon cancer and mixed malignancies [41, 42]. Both investigations documented a substantial rise in malnourished patients after therapy using a serum albumin level of less than 35 g/L and a body mass index of less than 18.5 kg/m^2 as markers. These studies' primary drawback was that they failed to account for confounding variables such as age, disorder stage, tumor location, and treatment methods that affect cancer patients' nutritional condition. Compared to younger patients, older patients (over 65) are more vulnerable to nutritional problems [41]. Patients with head and neck cancer are more likely than those with other cancers to suffer from malnutrition [43].

The association between dietary changes during cancer therapy and patient outcomes is poorly established [44]. Clinical outcomes related to nutritional status were evaluated in most trials at a single point in time, usually upon diagnosis and before treatment initiation. In order to lower morbidity and mortality, some studies have combined nutritional assistance with early-stage cancer therapy [45]. Nutritional screening and assessment of at-risk patients should commence immediately upon cancer diagnosis to prevent treatment-related malnutrition and improve oncological outcomes, accompanied by simultaneous nutritional management and oncologic therapy [45].

According to our current knowledge of the pathophysiology of malnutrition associated with cancer, malnutrition symptoms such as metabolic disturbances, systemic inflammation, and changes in body composition should be included in nutritional assessments [46]. These elements have been excluded from the tools currently in use. Therefore, it is necessary to establish a complete instrument to evaluate malnutrition utilizing both objective (muscular mass, physical performance, and degree of systemic inflammatory response) and subjective (patients' NIS score, weight history, and nutritional intake) evaluations. Figure 2 illustrates the prevalence of malnutrition in cancer patients undergoing treatment.

Effect of cancer treatment on the human body

The dietary condition, illness progression, chemotherapy, and patient response to treatment all influence long-term alterations in body structure [39]. These conditions depend on the nature of the human body, the type of cancer, and the drug used [47]. Nonetheless, research has shown that short-term changes in body composition, mainly skeletal and muscular mass, are associated with cancer treatment and persist during survival [47]. Several trials have shown that anticancer treatment significantly reduces lean or skeletal muscle mass [39, 47, 48]. Skeletal muscle changes as anticancer therapy side effects are receiving more attention due to the importance of the link between oncological outcomes and muscle loss during cancer treatment [48].

However, further research is needed to understand the full extent of these effects and to identify any confounding factors. Notably, it has been noted that the rate of muscle loss after cancer therapy is ten times greater than the 1% annual rate of normal aging [49]. In one study, individuals who had non-Hodgkin lymphoma undergoing chemotherapy had a reduction in lean mass. However, no significant changes were seen [49]. Nonetheless, two investigations indicated that cancer patients exhibited increased skeletal and lean muscle mass [50, 51]. Frenzel et al. [50] assessed lean body mass using bioelectrical impedance analysis (BIA), which weakly correlates with skeletal muscle mass in an oncology context [52]. Because BIA measures body water content to determine lean mass, individuals who have changed hydration status during BIA may have overstated their fat-free mass (FFM). Moreover, lean mass is the term used to describe organ expansion in people with advanced cancer [53].

Unexpectedly, Heus et al. [51] found that therapy resulted in a record-breaking rise in skeletal muscle mass. Notably, individuals who got the targeted drug selumetinib in a trial by Prado et al. [54] showed more muscle mass than those in the group receiving conventional treatment. When assessing the nutritional status of cancer patients, the European Society for Clinical Nutrition and Metabolism (ESPEN) now strongly emphasizes measuring muscle mass [46]. Muscle tissue contains almost 60% of the protein in the human body, making it a vital protein reserve. In many anticancer therapies, dose-limiting injury is linked to decreased muscle mass [54].

By accelerating the loss of muscle mass, cancer treatments, especially chemotherapy, may also damage the body's structure [55]. By inhibiting key muscle synthesis pathways (including PI3K/AKT/mTOR), cancer treatments like sorafenib cause muscular atrophy [55]. In individuals with sarcoma or melanoma, biopsies performed both before and after treatment with doxorubicin

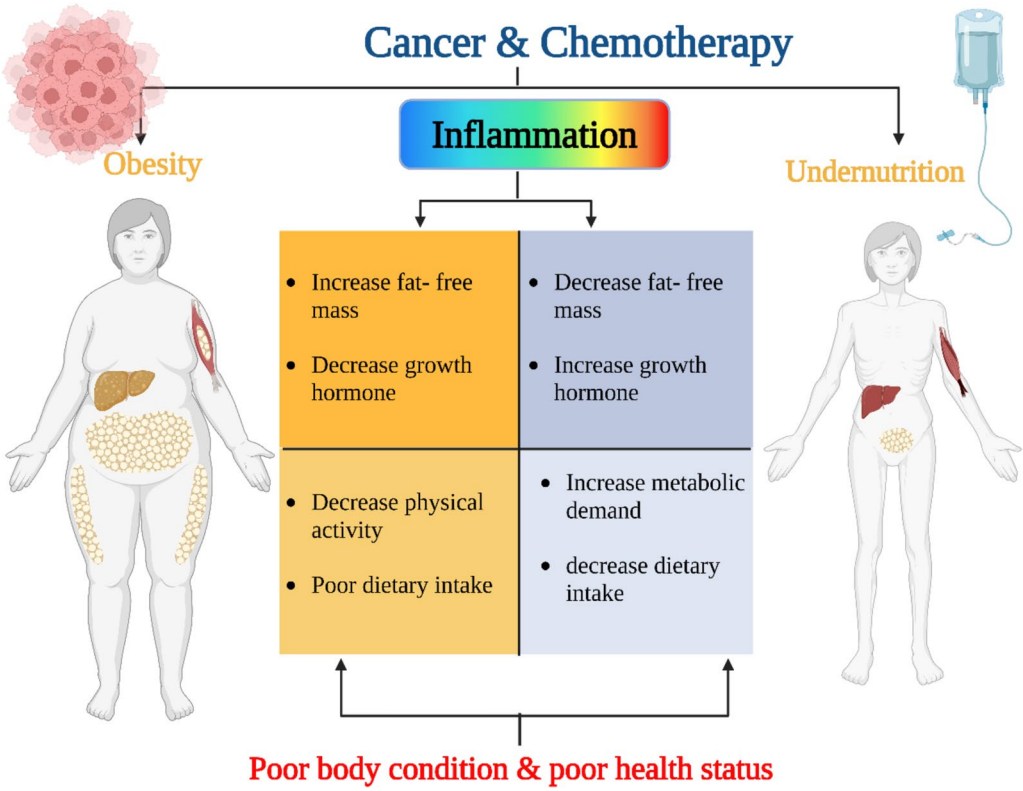

Fig. 2 Malnutrition in cancer patients undergoing chemotherapy

or melphalan showed significant reductions in myofiber size along with mitochondrial dysfunction [56].

During chemotherapy, corticosteroids may affect the body composition of cancer patients and cause muscle loss in addition to chemotherapeutic drugs and physical inactivity [57]. According to preclinical research, cisplatin may cause muscular atrophy when treating mice by activating the NF-κB signaling pathway in mouse muscles and myotube cells. The nature and treatment of the cancer are the main factors influencing the short-term development of fat accumulation after anticancer therapy [58]. During and after anticancer therapy, few investigations found that fat mass decreased [58, 59]. Further research has shown that after anticancer therapy, fat mass either rose or remained unchanged [39, 60, 61].

Previous studies indicate that chemotherapeutic agents such as doxorubicin and cisplatin facilitate lipolysis and suppress de novo lipogenesis, leading to fat reduction [62]. Nevertheless, elevated fat levels are principally responsible for weight gain linked to adjuvant chemotherapy for breast cancer [63]. The reduced activity of brown adipose tissue following chemotherapy has been linked to fat accumulation [64] and decreased survival [65]. Esophageal cancer patients with surgical complications saw reduced loss of lean mass compared to individuals in similar situations without complications [66]. Compared to patients receiving cytotoxic chemotherapy, those receiving targeted treatments seemed to have a considerable increase in muscle mass or a reduction in the loss of skeletal muscle; regardless of the kind of treatment, adipose tissue diminished in both groups [47].

Compared to conventional cytotoxic chemotherapy, targeted molecular treatment is less harmful and more successful for some cancer types [67]. Consequently, alterations in body structure after cancer treatment may be sex-dependent since male patients often have a more dramatic drop in muscle mass than female patients, and variances in toxic side effects during therapy may be associated with skeletal muscle loss [61]. Tang et al. [68] assessed how radiation affected body composition based on the kind of cancer [68].

One study found a decrease in lean mass in patients with head and neck cancer and those with abdominal or pelvic cancer but no discernible changes in lean mass in patients with breast or lung cancer [68]. Patients with breast or chest cancer showed a considerable decrease in fat mass. The impact of several cofactors, including sex, age, cancer type, treatment mode, and comorbidities (such as diabetes), on changes in body composition

throughout therapy has not received much attention in research [68]. Future studies should focus on evaluating and statistically correcting these important confounding factors to understand how they affect the association between body composition changes and cancer therapy [53].

It is important to note that cancer patients' weight and body mass index are ineffective indicators of their nutritional health [53]. Therefore, it is essential to use a technique that differentiates between various FFM components and regional adipose tissue due to the exponential growth in the size of the liver and spleen, hepatic metastases, and concomitant muscle loss with or without fat loss along with the progression of the disease [53]. This emphasizes the importance of using appropriate techniques to assess body composition in cancer patients, ensuring precision in medical practice [53].

For the diagnosis and staging of cancer, imaging methods like computed tomography and magnetic resonance imaging are often used [69]. These methods, which identify reductions in muscle mass and local fat stores, are becoming increasingly popular for assessing cancer patients' body composition. However, the relationship between changes in body composition during cancer therapy and clinical health outcomes is not well understood. Reduced muscle mass following treatment was independently linked to survival in metastatic colorectal malignancies [69]. Numerous avenues for investigation exist with the purpose of quantifying the oncologically relevant longitudinal changes in body composition that occur during cancer treatment. Various effects of cancer and its treatment on body weight are illustrated in Fig. 3.

Influence of anticancer therapy on food intake

NIS, which is defined as any obstruction to oral food intake, is often brought on by cancer therapy [70, 71]. Patients with head and neck cancer have the highest prevalence of NIS, which commonly occurs in oncology settings [72]. Modifications in taste and smell, nausea, mucositis, discomfort, constipation, or dyspnea are all part of NIS [71]. NIS rates are more significant when chemotherapy and radiation are administered together than when any treatment is used alone [73]. The association between NIS and weight loss in cancer patients has been shown in earlier research [74].

Alterations in NIS-induced dietary patterns may disrupt the quality of food intake [71]. According to an assessment of the NIS, symptoms including dysphagia, mucositis, and anorexia were essential indicators of decreased oral nutritional intake in patients with head and neck cancers. Nonetheless, there is insufficient evidence concerning standard dietary patterns and food selections during cancer therapy. Most research examined dietary selections at a singular moment during

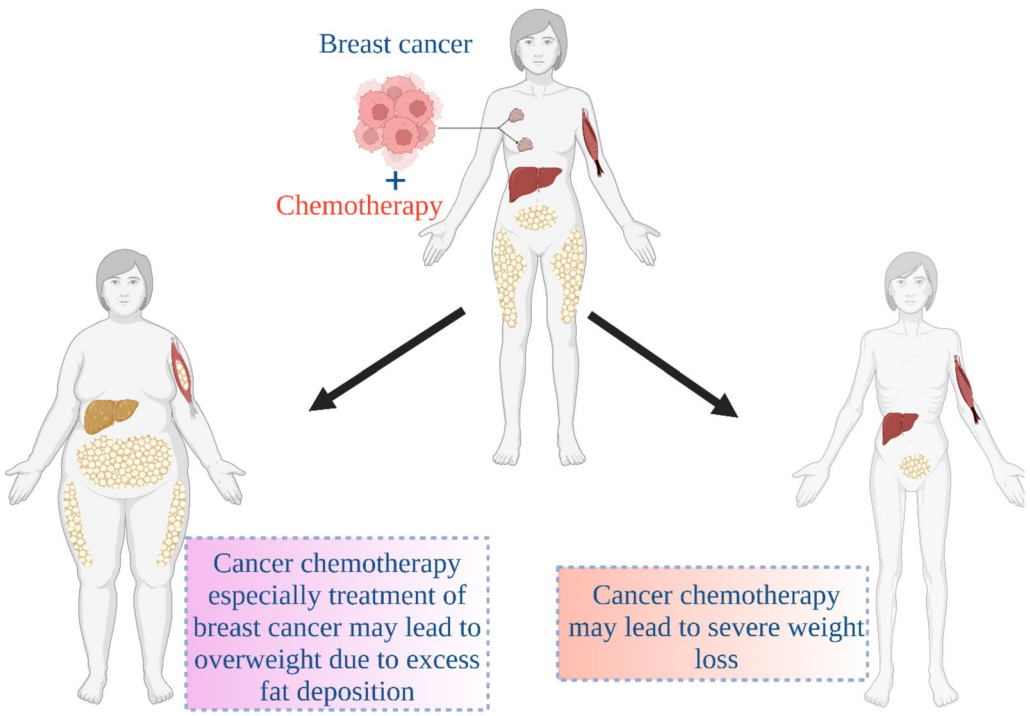

Fig. 3 Different influences of cancer and cancer treatment on body weight

diagnosis or along the cancer trajectory, irrespective of treatment status; only a few studies assessed modifications during cancer therapy [71]. The Brazilian Healthy Eating Index Revised (BHEI-R) was used in a cohort study to evaluate the dietary quality of women with breast cancer both during and after chemotherapy [75]. The findings demonstrated that most patients' diet quality declined after chemotherapy due to substantially reduced consumption of fruits, vegetables, and legumes throughout treatment [75].

Data regarding food selections is essential for formulating dietary guidance aligned with individual preferences [76]. The assessment of dietary acceptance among patients with hematological tumors during chemotherapy revealed that some food items, including meat, rice, pasta, beans, vegetable soup, and salad, were refused more frequently, but all patients accepted milk and sweets [76]. Changes during cancer treatment may hamper adequate dietary intake. Patients with hematological cancers who received chemotherapy showed an elevated deficiency of calories, protein, iron, calcium, magnesium, phosphorus, niacin, thiamin, riboflavin, vitamin B6, zinc, and vitamin C [77].

A study evaluating 3-day food records in 47 patients with head and neck cancer during and post-therapy indicated a reduction in overall energy intake from baseline after treatment, followed by a significant increase in energy intake during follow-up [78]. Individuals undergoing chemoradiotherapy exhibited the lowest caloric intake throughout treatment, roughly 1000 kcal/day fewer than those receiving alternative treatment modalities. Patients with the lowest caloric consumption exhibited the most substantial weight reduction (about 10%) from baseline to treatment; nevertheless, during the follow-up phase, weight persisted in declining despite an elevation in caloric intake [78]. Patients undergoing cancer treatment may experience a catabolic condition characterized by decreased energy expenditure due to chemotherapy, which may explain why they lose weight gradually after treatment [79].

Typically, chemotherapy correlates with diminished nutritional intake; yet, three investigations indicated no alterations in the dietary consumption of patients undergoing cancer treatment [39, 80, 81]. A prospective research including 63 individuals with acute leukemia demonstrated a significant decrease in macronutrient and micronutrient consumption throughout chemotherapy treatments [38]. In prior studies [39, 81], all patients received dietary counseling and nutritional support from the moment of diagnosis as a component of their regular care. This may partially explain their capacity to sustain dietary consumption during active therapy. The dietary intake evaluated during the follow-up period (one month post-therapy) reportedly increased but may not accurately represent food consumption throughout cancer treatment [79].

Moreover, nutritional consumption during cancer therapy may be affected by the specific treatment and kind of cancer [82]. Patients diagnosed with breast cancer and melanoma exhibited heightened dietary consumption; however, the food intake of individuals with non-small-cell lung cancer remained unchanged throughout therapy [82]. The intensity of NIS, encompassing modifications in taste and smell, appetite reduction, and sensations of satiety, is most pronounced during the opening days of chemotherapy, especially within the first week of each cycle [83].

Dietary consumption varied according to the chemotherapy cycle, with the least intake occurring on the initial day of treatment and the highest intake preceding the subsequent chemotherapy cycle [84]. Given the variations in food intake at different treatment time points, supplementary studies assessing dietary intake should delineate the time point of dietary evaluation in their study protocols [84].

Variations in dietary consumption throughout anticancer treatment are diverse due to the specific effects of different cancer types and treatments on the burden of nutritional intake and dietary habits, alongside the utilization of varying evaluation time points in multiple studies [78]. Insufficient information exists concerning the impact of dietary intake during cancer therapy on treatment-related toxicities and oncological outcomes [80]. Patients with head and neck cancer who consumed higher caloric and protein intake (> 35 kcal/kg and > 1.5 g protein/kg body weight) experienced significantly less weight and lean mass loss compared to those with lower dietary intake throughout treatment [78, 80].

Moreover, in individuals with progressing tumor conditions receiving chemotherapy, reduced protein intake was associated with about a twofold heightened risk of treatment-related tiredness and mortality [85]. Evidence indicates that all efforts should be used to guarantee sufficient nutritional intake in cancer patients. Qualitative or quantitative measures must be employed to promptly identify and mitigate inadequate dietary intake. Research on the nutritional consumption of cancer patients indicates various potential dietary modifications [85].

Impact of anticancer treatment on nutrition levels

Inadequate dietary intake by patients undergoing tumor therapy may lead to nutritional depletion in serum and tissues [46]. Cancer patients whose daily energy consumption is less than 60% of their dietary needs for over 7–10 days have insufficient macronutrients and micronutrients. Furthermore, patients

undergoing chemotherapy or radiotherapy may experience impaired absorption of micronutrients due to gastrointestinal symptoms and mucositis [86]. Furthermore, metabolic changes and inflammatory responses triggered by antineoplastic drugs may modify micronutrient needs [46]. Consequently, while research on dietary shortages arising from anticancer treatment is few, patients undergoing tumor therapies may probably encounter deficits. ESPEN, a preeminent expert on oncology nutrition, has recognized the comprehension of micronutrient needs in cancer patients as a significant knowledge deficiency [46].

Single-instance micronutrient assessments may not accurately represent long-term status and could result in underestimating or overestimating adequacy [87]. Limited research has evaluated micronutrient status at a singular time point along the cancer trajectory; hence, data regarding treatment-induced abnormalities and the subsequent recovery of micronutrient status post-treatment is deficient [87]. Some cohort studies evaluated plasma or serum nutrition levels during cancer treatment at a minimum of two-time intervals [87–89]. While the spectrum of deficits in cancer patients may be extensive, these investigations exclusively evaluated the levels of selenium, water-soluble vitamins (C, B6, B12, and folate), and fat-soluble vitamins (A, D, and E). Patients with breast cancers had a reduced serum selenium concentration post-radiotherapy compared to levels at diagnosis [87].

Selenium is a vital trace element in numerous crucial endogenous antioxidant mechanisms. Anticancer medication may worsen vitamin C insufficiency, especially in individuals with advanced malignancies [88]. Chen et al. [89] observed a substantial reduction in plasma vitamin C levels during cisplatin treatment. Reduced plasma vitamin C levels correlate with increased C-reactive protein and albumin concentrations, as well as diminished survival durations. Research indicates that vitamin C amplifies the cytostatic properties of certain chemotherapeutic drugs while mitigating their adverse effects [90].

Vitamin D insufficiency manifests in patients with tumors after chemotherapy [91–93]. A retrospective study of 315 colorectal cancer patients indicated that those undergoing chemotherapy were four times more likely to experience severe vitamin D insufficiency compared to non-chemotherapy patients [93, 94]. Reduced serum vitamin D levels are a risk factor for sarcopenia in elderly individuals [95]. Reduced serum 25OHD levels after chemotherapy may be partially attributed to lifestyle modifications, including restricted dietary vitamin D intake and diminished outdoor exercise, leading to decreased solar exposure.

Furthermore, chemotherapy may facilitate the activation of CYP3A4 or other metabolizing enzymes, converting 25OHD into inactive metabolites, including 24 and 25OHD [94]. Nonetheless, there exists a considerable deficiency of information on the potential impact of vitamin D levels on muscle conditions in cancer patients. Besides its effects on muscular health, little evidence indicates that vitamin D insufficiency may influence chemotherapy-induced toxicity, survival, and prognosis in cancer; nevertheless, contradictory results have been documented [86].

Vitamins A and E are fat-soluble vitamins possessing antioxidant characteristics essential for numerous physiological activities. Some studies indicated a notable decrease in vitamin E levels following cancer treatment [91, 96]; however, plasma vitamin E levels returned to baseline six months post-treatment [91]. Vitamin A levels were reduced in individuals with acute myeloid leukemia following chemotherapy [91]; however, two more trials reported no alterations in plasma vitamin A levels post-treatment [91, 96].

The efficacy of chemotherapy and radiotherapy is predominantly contingent upon the generation of reactive oxygen species (ROS) and, consequently, on heightened oxidative stress [97]. Furthermore, the deleterious consequences of chemotherapy and radiotherapy, including cardiotoxicity and nephrotoxicity, result from excessive ROS production in healthy tissues [98]. Enzymatic antioxidants, like superoxide dismutase (SOD) and glutathione (GSH), along with nonenzymatic antioxidants such as antioxidant vitamins, reduce excessive ROS. Vitamins C, E, and beta-carotene serve multiple functions in antioxidant protection. This outcome indicates diminished levels of antioxidant micronutrients during cancer therapy and elevated amounts of oxidative stress indicators [97, 98].

Cancer treatment causes deficiencies in micronutrients with antioxidant activities, including reduced immune function [99] and an increased risk of treatment-induced toxicities. Patients with head and neck cancer treated with radiotherapy who had greater plasma beta-carotene levels had considerably less severe acute side effects and decreased local recurrence rates [100]. Further research is needed to evaluate the micronutrient status of cancer outcomes and treatment-induced toxicities.

Nutrition interventions

Early nutritional support and metabolic interventions are undertaken to maintain or improve dietary consumption, modulate metabolic abnormalities, maintain skeletal muscle mass and physical function, reduce the risks of treatment-induced toxicities and treatment discontinuation, and enhance the quality of life [45]. Taking into consideration the information presented above, it would appear that all cancer patients who are undergoing

treatment for cancer are required to undergo nutritional screening before beginning therapy. This screening is intended to identify the presence or danger of malnutrition and to establish the most effective treatment for nutritional support [45]. They are based on a recent study that was conducted on patients who were receiving chemoradiotherapy for esophageal cancer. The study discovered that beginning nutritional support before the treatment increased the patient's chances of survival. The findings of this study highlight the significance of beginning nutritional intervention and conducting evaluations at an early stage [45].

Unfortunately, there is a dearth of information regarding the ideal time to begin providing nutritional support [101]. Providing nutritional counseling by a healthcare expert is the initial stage in providing nutrition assistance [102]. This step aims to enhance the patient's food intake by offering nutritional guidance and changing their eating habits to be effective over time [101, 102]. As a result of the fact that food and eating play a crucial part in social integration, which may influence a patient's quality of life, it is essential to consider ways to improve the eating experience [102]. When treating patients with greater calorie and protein requirements, it is preferable to consider their desire for foods that have been enhanced or fortified to improve their nutritional status. Patients with cancer who are unable to fulfill their dietary requirements through the consumption of food are advised to take oral nutritional supplements (ONS). On the other hand, patients undergoing oncological treatment typically have a low level of compliance with ONS consumption [101, 102].

The capacity to consume sufficient food over a long period is crucial to the success of ONS. Baldwin et al. [103] demonstrated that only 19% of patients reported taking all prescription oral neurostimulants (ONS) for high-energy conditions by week 6. Compliance with these ONS began to decline after week 1. Regarding older patients, the primary determinant of long-term compliance and effective usage of ONS was its palatability [104].

Many elements can influence supplement palatability, including color, flavor, texture, and taste [105]. Furthermore, cancer patients frequently have changes in their sense of smell and taste, which can lead to anorexia and potentially impact their ability to adhere to oral nutritional supplements over the long run. The failure to consider food's social and cultural contexts is another factor contributing to poor compliance with ONS [105]. ONS doesn't consider the cultural and social norms around food and eating and doesn't offer much sensory enjoyment. Nutritional therapies during cancer therapy lack evidence of their effectiveness. Overall, body weight was positively affected by oral nutritional interventions during oncological treatment, according to a systematic review that evaluated their nutritional and clinical efficacy [105].

Nutrition counseling and high-energy density oral nutritional supplements did not yield a substantial positive effect on body weight [105]. Nonetheless, subsequent subgroup analysis revealed that this effect was confined to high-protein and n-3 PUFA-enriched ONS interventions, underscoring the need to address metabolic alterations in cancer patients [105, 106]. The failure to achieve calorie and protein objectives due to inadequate compliance may partially elucidate the absence of a notable impact on body weight [105]. Enhancing compliance strategies will augment the effectiveness of nutritional therapies. For instance, sensory preferences differ among individuals; therefore, offering ONS and fortified meals that align with the patient's sensory preferences can improve adherence to interventions and nutritional outcomes [106]. Moreover, the ability to sample supplements and choose the favored option can enhance adherence.

One further strategy to boost compliance is to use items with a higher concentration and reduce consumption amounts [54]. With flexible meal planning, patients with severe NIS can reduce their food intake on therapy days while still meeting their nutritional requirements between treatment cycles. Dietary therapies may impact cancer patients less due to metabolic abnormalities (such as systemic inflammation, insulin resistance, anabolic resistance, and muscle loss). There is an increase in protein turnover, catabolism, and muscle loss when there are metabolic anomalies. Loss of muscle mass in tumor patients predicts treatment-induced side effects and survival rates independently of other factors [54].

The most effective method for alleviating muscle wasting and malnutrition in a cancer setting is to provide adequate energy as well as high quantities of high-quality proteins and essential amino acids (overcoming anabolic resistance) and nutrients to modulate the inflammatory reaction, such as n-3 polyunsaturated fatty acids [107, 108]. The ESPEN recommendations recommend a protein intake of 1–1.5 g/kg/day, and n-3 polyunsaturated fatty acids should be provided to patients undergoing oncological treatment [46]. Because cancer-related malnutrition is a syndrome that derives from a combination of factors, a single nutritional intervention on its own is not adequate to treat the condition [109]. A multimodal approach that incorporates NIS management might be beneficial to patients. This approach would involve both anabolic and anticatabolic medicines. It is necessary to conduct additional research to improve the effectiveness of the nutritional intervention. This can be accomplished by identifying the risk of malnutrition at an early stage, determining the optimal timing and duration of the

intervention, enhancing compliance with nutritional support, and investigating the ideal anabolic and anti-inflammatory components [109].

Role of medicinal herbs in cancer treatment and improving the general health conditions of treated patients

According to the WHO, cancer is a disease that is characterized by excessive cell growth and has a high mortality rate—nearly 10 million fatalities in 2020 [110]. The uncontrolled growth of cancer cells results from changes in the molecular mechanisms of genes during normal cell growth [111]. Traditional and highly contemporary methods, including chemotherapy, radiation therapy, and surgery, are used to treat cancer; however, each method has certain drawbacks [111–115]. Alternative therapeutic options are required due to the increased incidence of cancer worldwide. Herbal therapy offers a convenient alternative to conventional cancer treatment [116].

Plants are essential in the combat against many cancer cell lines, including those found in the breast, stomach, colon, oral cavity, lung, liver, cervix, and blood systems [117]. Many plants were chosen for their solid anticancer chemicals based on predetermined criteria. The secondary metabolites in plant extracts inhibited cancer cells via DNA destruction and activated apoptosis-inducing enzymes [117, 118]. Since ancient times, people have used natural plants to treat and prevent various diseases [118]. Herbal medicine is a safe, nontoxic, and widely accessible cancer therapy source compared to chemical therapeutics. Because of their diverse characteristics, medicinal plants are thought to neutralize the effects of diseases on the body and improve body performance. Table 1 and Fig. 4 summarize the most used medicinal plants, their modes of action, and their therapeutic effects. Figure 5 illustrates the anticancer mechanism of medicinal plants, depicting the molecular pathway involved.

According to Kanwal et al. [21], active phytochemicals, including quercetin, digitoxingenin, α-tocopherol, oleandrin, adigoside, ursolic acid, and odorosides, extracted from *Nerium oleander* have antiviral, anti-inflammatory, and anticancer activities. Oleandrin exerts anticancer effects by targeting the NF-κB, MAPK, and PI3K/Akt signaling cascades in cancer cells [21]. It activates the release of cytochrome c and caspase enzymes, which drive the death of cancer cells. Furthermore, oleandrin may be used as a chemosensitizer to enhance the sensitivity of cancer cells toward chemotherapeutic drugs. Salehi et al. [22] reported the liposomal codelivery system as a significant technology in cancer treatment. Liposomes are natural products from phospholipids and cholesterol and are used to deliver chemotherapy drugs, including doxorubicin, paclitaxel, mitoxantrone, and irinotecan.

Nanoparticles have a range of characteristics based on liposomes, such as multifunctionality, controlled permeability, controlled biodistribution, as well as targeting and specificity. Liposome-entrapped cytosine arabinoside increases the survival rate in vivo compared with the drug alone. Furthermore, liposome nanoparticles loaded with the drug have cationic amphiphiles, which enhance the stability and efficiency of the drug, increase its long-circulating time, and enhance its accumulation in cancer cells [22].

The genus *Lavandula* contains lavender oils that have antimicrobial properties. It is used for flavor or to preserve food and for medical therapy with antispasmodic, antiseptic, analgesic, antimicrobial, and antiviral properties [23]. Antiviral activity is not limited to synthetic pharmaceuticals; medicinal plants also contain phytochemicals employed as antiviral agents in the Covid-SARS-CoV-2 pandemic [24–26]. Rehman et al. [24] analyzed natural products, such as phenolic compounds, flavonoids, steroids, and coumarins, by molecular docking in vitro to evaluate their activity against SARS-CoV-2. Glycyrrhizin and its metabolite 18-β-glycyrrhetinic demonstrated significant binding affinities for MPro, helicase, RdRp, spike, and E-channel proteins. Alternatively, the flavonoid baicalin effectively bound to PLpro and RdRp viral proteins and inhibited viral propagation.

Achillea is another medicinal plant containing a wide variety of volatile and nonvolatile secondary metabolites, including terpenes, polyphenols, and flavonoids [27]. The genus *Achillea* treats spasmodic gastrointestinal and hepatobiliary disorders, hemorrhages, rheumatic pain, wounds, and pneumonia. *Achillea* also has vigorous antioxidative and potent antiproliferative and anticancer activities in vitro and in vivo [27]. It is used as a food preserver due to its antibacterial activity against many pathogens. Osthole, an active plant-derived coumarin extracted from *Cnidium monnieri,* exhibits diverse pharmacological properties, including anticancer, antioxidant, antihyperglycemic, neuroprotective, and antiplatelet activities. It exerts anticancer effects by modulating various apoptosis-related proteins, cell cycle regulators, protein kinases, transcriptional factors, cytokines, and growth receptors in cancer cells [28].

Zafar et al. [28] observed that osthole inhibits cancer cell metastasis by arresting the cancer cell cycle and inducing programmed cell death. Tahir et al. [29] reported the presence of secondary metabolites, such as terpenoids, ketones, coumarins, pentacyclic, furocoumarin, flavonols, flavonoids, sterols, esters, carbohydrates, carboxylic acid, and polycyclic aromatic hydrocarbons, in *Ficus benghalensis*. Several in vitro and in vivo studies have demonstrated that *F. benghalensis* possesses antioxidant, anti-inflammatory,

Table 1 The most commonly used medicinal plants in cancer treatment and their mechanisms of action

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Olive (*Olea europae*)	Leaves, and fruits	Oleic acid, oleuropein, acidic triterpenes, pinoresinol, oleanolic acid, and maslinic acid	Oleuropein and oleanolic acid suppressed cancer cell growth by inhibiting the signaling cascade of Akt/mTOR, resulting in protein synthesis in cancer cells and cell death	Breast, and colon cancers	[119]
Greater burdock (*Arctium lappa*)	Seeds, roots, fruits, and leaves	Lappaol, and arctigenin	These active compounds induced intrinsic apoptosis by losing mitochondrial ΔΨm inducing caspase cascade	Malignant melanoma, lymphoma and cancers of the pancreas, breast, ovary, esophagus, bladder, bile duct and the bone, lung, cervix, prostate cancer, leukemia, and hepatic cancer	[120, 121]
Neem (*Azadirachta indica*)	Leaves, and flowers	Liminoids, and nimbolide	Suppressed the expression of VEGF and phosphoinositol PI3K/Akt pathways and cell cycle arrest in the G2/M phase	Breast, stomach, lung, prostate, skin cancer, colon cancer, prostate cancer, malignant lymphoma, malignant melanoma, and leukemia	[122]
Damask rose (*Rosa damascene*)	Petals	Phenolic compounds such as gallic acid, catechin, and epicatechin	Showed antioxidant impacts and DNA protection	Lung, cervix, and breast cancers	[123]
Asafoetida—Devil's Dung (*Ferula assafoetida*)	Shoots, and resins	Coumarin compounds especially sesquicoumarins, sulfur-containing compounds, and b-sitosterol, and oleic acid	Induced the expression levels of caspase cascade, resulting in DNA fragmentation and cancer cell death	HepG2 cancer	[124]
Black cumin (*Nigella sativa*)	Seeds	Thymoquinone, and dinitroquinone	Induced the expression of apoptotic marker BAX, decreased the expression level of the anti-apoptotic marker Bcl-2 and suppressed the signaling pathway of AKT/PI3K, resulting in cancer cell death	Colon, prostate, breast, and pancreatic cancer	[125]
Thyme (*Thymus vulgaris*)	Shoots	Thymol, and carvacrol	Triggered the expression level of BAX and suppressed the expression level of Bcl-2, inducing apoptosis and cell death	Prostate, and head cancers	[126]
Mediterranean thyme (*Thymbra spicata*)	Shoots	Thymol, and carvacrol	Showed antioxidant activity in lung cancer by suppressing the enzymes producing reactive oxygen species, lipid peroxidation, and protecting DNA from damage and cancer incident	Lung cancer	[126, 127]
Aelijaan (*Taverniera spartea*)	Shoots	Isoflavonoid compounds, and saponins	Induced the p53 pathway and decreased the expression levels of the signaling pathway of PI3K/AKT, resulting in cancer cell death	Breast, and prostate cancers	[128]

Table 1 (continued)

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Harmel (*Peganum harmala*)	Seeds	Alkaloids	Induced the caspase cascades, especially caspase 3 and 9, and decreased the expression levels of signaling PI3K/mTOR, resulting in cancer cell	Breast, and cervix cancers	[129]
Heartsease (*Viola tricolor*)	Shoots	Flavonoids especially rutin and quercetin	It decreased the signaling effect of the PI3K/AKT pathway, inhibiting the expression of mTOR and cancer cell death	Cervix, breast, colon, lung, and prostate cancers	[130]
Tea plant (*Camellia sinensis*)	Leaves	Epicatechin, epigallocatechin, epigallocatechin gallate, and epigallocatechin3-gallate	Induced caspase cascade, BAX, and p53 tumor suppressor gene, resulting in cancer cell death. Epigallocatechin gallate also induced autophagy by increasing the expression level of LC3 II and degrading p62 in mesothelioma cells, resulting in cancer cell death	Lung, bladder, skin, prostate, and breast cancers	[131]
Ginger (*Zingiber officinale*)	Rhizomes	Flavonoids especially kaempferol, catechin, fisetin, and quercetin	Induced the expression levels of caspase cascade including 3,9,7, pro-apoptotic marker BAX, and p21 protein and suppressing the expression of anti-apoptotic marker Bcl2 and the signaling pathway of PI3K/AKT resulting in cancer cell death	Ovary, cervix, colon, hepatic and urinary cancers	[132]
Shiitake (*Lentinus edodes*)	Fruiting bodies	Lentinan, terpenoids, and steroids	Induced the expression level of p21, BAX, and caspase 3 and 9 and suppressed the expression level of Bcl2, resulting in cancer cell death and cell cycle arrest in the G0/G1 phase	Lung carcinoma, and colon cancers	[133]
Buckwheat (*Fagopyrum esculentum*)	Seeds	Amygdalin, rutin, buckwheat inhibitor-1 protein	Decreased the signaling effect of the PI3K/AKT and Bcl-2 pathway and induced the BAX, caspase 3, resulting in cancer cell death	Pancreatic cancer cell, and T-acute lymphoblastic leukemia (T-ALL) cells	[134, 135]
Bottle gourd (*Lagenaria siceraria*)	Shoots, and fruits	Vitamins B group and C, saponins, and cucurbitacin	Enhanced apoptosis and autophagy by inhibiting Akt/mTORC1 signaling, p38 protein, and inhibiting the ERK 1/2 (extracellular signal-regulated kinase) signaling pathway	MDA-MB-231, and SKBR3- MCF-7 cancers	[136]

Table 1 (continued)

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Black samson echinacea (*Echinacea angustifolia*)	Whole plant	Arabinogalactan	Induced apoptosis and cell cycle arrest at the G_0/G_1 phase via altering the function of mitochondria, inducing the mitochondrial oxidative stress resulting in activated MAPK signaling pathway, apoptosis, and cancer cell death	Carcinoma of the esophagus and colon	[137]
Chinese cinnamon (*Cinnamomum cassia*)	Bark	Coumarin	Increased the expression level of BAX and caspase cascade, including 3,7 and 9, and decreased the expression levels of Bcl-2, resulting in apoptosis and cancer cell death	Promyelocytic leukemia, hepatic, prostate, and breast cancers	[138]
Marijuana (*Cannabis sativa*)	Leaves	Cannabinoids, and stereoisomers of cannabidiol	Showed anti-tumor effect by modulating key cell-signaling pathways	Breast, brain, lung, pancreas, prostate, and colorectal cancers	[140]
Bladder cherry (*Physalis alkekengi*)	Fruits	Physalins	Decreased signal transducer and activator of transcription 3 (STAT3), the regulator of cell survival inducing the caspase 3,9, p53, BAX expression and decreasing the Bcl2, and AKT/PI3K signaling pathway resulting in cancer cell death and cell cycle arrest	MCF-7, MDA-MB-231, and cervix cancers	[141]
Wormwood (*Artemisia absinthium* L.)	Roots, and shoots	Artemisinin, quercetin, isorhamnetin, limonene, myrecene, linalool, a-pinene, b-pinene, and artesunate	Induced BAX pro-apoptotic marker, signaling caspases including 3 and 9 and increased the expression levels of LC3- II, resulting in apoptosis and autophagy, respectively	Colorectal, leukemia, HeLa, HT-29, MCF7, HepG2 hepatoma, ovarian, cervical, pancreatic cancer, and embryonal rhabdomyosarcoma	[142]
Garlic (*Allium sativum* L.)	Fruits	Allicin, and ajoene	Suppressed the expression of cyclin B, resulting in inducing the expression of p21, and tumor suppressor gene p53, resulting in cell cycle arrest at the G_2/M phase	MCF7, HCC-70, Caco2, HepG2, A549, and cervix cancers	[143]
Galbanum (*Ferula gummosa*)	Shoots	Sesquiterpenes, and coumarins	Induced expression of apoptotic marker-related cellular death (Bax), caspase cascade such as caspase 3,9 and suppressed the expression of (Bcl-2) resulting in cancer cell death	Breast, colon, bladder, pancreatic, prostate, cervical, brain, liver, blood, ovarium, bone, endometrial, oral, lung, eye, stomach, and kidney cancers	[144]
Coriander (*Coriandrum sativum*)	Roots, and leaves	Beta-carotene, quercetin, and rutin	Showed antioxidant activity by suppressing the enzymes producing reactive oxygen species, lipid peroxidation, and protecting DNA from damage and cancer incidents against breast cancer	Breast cancer	[145]

Table 1 (continued)

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Allheal, bloodwort (*Achillea wilhelmsii*)	Shoots	Phenolic compounds Mainly flavonoids and monoterpenes like 1,8- cineole and a-pinene	Induced the expression of caspase cascade and downregulate cycle dependence on kinase 1 (CDK 1), resulting in cell death and arrest of the cell cycle at the G2/M phase	Non-small cell lung carcinoma, colon cancer, ovarian cancer cell lines, and hepatocellular liver carcinoma cell lines	[146]
Turmeric (*Curcuma longa*)	Rhizomes	Curcumin	Caused the distribution of the potential of the mitochondria, induced the expression of the tumor necrosis factor (TNF), and reduced the expression levels of survival and anti-apoptotic markers, including STAT3 and Bcl-2, respectively	Leukemia, glioblastoma, colon, lung, breast, prostate, cervix, and larynx cancers	[147]
Grey mangrove (*Avicennia marina*)	Leaves	Flavonoids particularly naphthoquinone compounds like 3 chlorodeoxylapachol	Showed antioxidant impacts, and stimulation of apoptosis	Breast, larynx cancer, leukemia, and colon, liver, and cervix cancers	[149, 150, 154, 155]
Cress (*Lepidium sativum*)	Shoots	Vitamins A, B, C and E, isothiocyanate, linolenic acid, and glucosinolates	Showed apoptosis, necrosis, antioxidant impacts, and cell cycle arrest	Breast, hepatocellular carcinoma, and chronic myeloid leukemia	[159]
Pennyroyal, squaw Mint (*Mentha pulegium*)	Shoots	Pulegone, menthone, piperitone, limonene, iso menthone, and octen-3-ol	Showed initiation of apoptosis	Leukemia cells, melanoma, and breast cancer	[163]
Birch (*Betula alba*)	Leaves	Betulinic acid	Killed tumor cells, caused antiproliferative impact, lowered cancer cell motility, and stimulated apoptotic cell death. It also decreased bcl2 and cyclin D1 genes expression and elevates bax gene expression	Breast, ovarian, cervical, gastric, colorectal, lung, liver, prostate, leukemia, thyroid, pancreatic, and lung cancers	[165, 166]
European mistletoe (*Viscum album*)	Sprouts, and fruits	Lectins like viscumin, and phenolic compounds like gallic acid	Stimulated apoptosis by activation of caspase cascades and showed anti-angiogenesis activity	Gliomas, breast, lung, colon, and oral cancers,	[171, 172, 174]
Cardusmarianus (*Silybum marianum*)	Seeds	Flavonoids particularly silymarin	Showed antioxidant impacts, cell cycle arrest, apoptosis induction, chemosensitivity, and chemoprotective activity	Prostate, colon, gastric, breast, lung, liver, ovarian, and pharynx cancers	[179, 182]
Mountain ebony (*Bauhinia variegate*)	Flowers, leaves, stems, and barks	Cyanidinglucoside, malvidin glucoside, peonidin glucoside, and kaempferolgalactoside	Showed antioxidant activity, promotes apoptosis, and showed hepatoprotective activity	Leukemia, cervical, liver, breast, and larynx cancers	[186, 187, 189]
Saffron crocus (*Crocus sativus* L.)	Stigmas	Phenolic compounds Particularly quercetin, crocetin, crocin, picrocrocin, and safranal	Prevented cancer cell proliferation, inhibited DNA synthesis, and promoted apoptosis	Leukemia, breast, ovarian, colorectal, gastric, and prostate cancers	[197, 198, 201]

Table 1 (continued)

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Bisnaga (*Ammi visnaga*)	Shoots	γ-Pyrones, coumarins, Khellin, visnagin, ammiol, khellol, dihydropyranocoumarin glucoside xanthotoxin, ammoidin, bergapten, and psoralene	Induced apoptosis, and the production of reactive oxygen species	Cervical, breast, and liver cancers	[209, 210, 212]
Fenugreek (*Trigonella Foenum-graceum*)	Shoots	Flavonoids and alkaloids such as gingerol, cedrene, zingerone, vanillin, and eugenol; saponins, tannins, phenols, and a plethora of phenolic compounds	Showed antioxidant effects, cell cycle arrest, and induction of apoptosis, targeting STAT-3	Hepatocellular carcinoma, breast, lymphoma, pancreatic, bladder, and prostate cancers	[214, 216, 217]
Tulsi (*Ocimum sanctum*)	Leaves	Eugenol, orientin, cirsilineol, Ursolic acid cirsimaritin, Caryophyllene, camphor, eucalyptol, alpha-bisabolene, and beta-bisabolene	Antioxidants induced apoptosis, p53, and Bax, inhibited Bcl-2, E2F1 blocked the supply of oxygen and nutrients to the cancer cells and killed them by starving	Leukemia, breast cancer, lung carcinoma, cervical, gastric, colon, colorectal, skin, and prostate cancers	[221, 223, 231]
Cape bush-willow (*Combretum caffrum*)	Barks, kernels, and fruits	Combretastatin	Hindered blood supply to the cancer and inhibits proliferation, growth, showed tumor necrosis, cell arrest, and antioxidant activity	Leukemia, colon, and lung cancers	[234, 236]
licorice (*Glycyrrhiza glabra*)	Roots	18α-glycyrrhizic, 18 β -glycyrrhizic, saponins–licorice saponin K2/H2, licorice saponin B2, licorice saponin G2/yunganoside K2, apiosides (liquiritin apioside, isoliquiritin apioside, licuraside), and 8-cyclized isoprenyl isoflavanes	Prevented cancer cell proliferation (bcl-2 phosphorylation), caused morphological changes in cancer cells and initiation of apoptosis. Alleviated conventual therapy adverse effects, antioxidant, anti-inflammatory	Prostate, breast, lung, gastric and renal cancers, colon, acute myeloid leukemia, and melanoma	[238–240] [245, 246, 253]
Yew (*Taxus baccata* L)	Leaves	Taxol, paclitaxel, and cabazitaxel-larotaxel	Antioxidant-induced apoptosis, decreased resistance through the down-regulation of cell cycle arrest	Breast, lung, liver, and colon cancers	[111, 114, 256, 296]
Nothapodytes tree (*Nothapodytes foetida*)	Barks, and heartwoods	Acetylcamptothecin, camptothecin, scopolectin, and camptothecin	Prevented DNA topoisomerase found in cancerous cells and halts the mutation and growth of the cancer cells	Uterine, breast, cervical, ovarian, colorectal, and small lung cell cancers	[259]
Flax (*Linum usitatissimum*)	Seeds	Lignans	Caused apoptosis and induction of caspase 3,8, and 9, angiogenesis. Showed antioxidant and anti-inflammatory activity	Colon, and lung cancers	[260–262] [265]
True indigo (*Indigofera tinctoria*)	Leaves	Flavonoids, saponins, tannins, phenols, and anthraquinone	Showed antioxidant and cytotoxic impacts, cell cycle G0/G1 phase arrest, and apoptosis	Lung cancer	[267]
Soybean (*Glycine max*)	Leaves, and seeds	Genistein, and daidzein	Showed antioxidant and anti-inflammatory activities and induced apoptosis	Lung, and colon cancers	[268]

Table 1 (continued)

Plant	Plant part	Active ingredients	Mode of action	Cancer type	References
Kew tree (*Ginkgo biloba*)	Leaves, and seeds	Ginkgetin, and ginkgolides A and B	Showed antioxidant, anti-angiogenic activities, stimulated apoptosis Bax/Bcl-2, and stimulated autophagy through altering mTOR/p70S6k	Breast, and liver cancers	[271, 272]
Elliptic yellowwood (Ochrosia elliptica)	Leaves	Ellipticine, and 9-methoxy ellipticine	Modulated cell cycle by Cdc2, induction of apoptosis by MAPKs, AIF, cytochrome C, caspase, Bcl-2, showed anti-inflammatory and antioxidant capacity	Breast cancer	[273, 274, 278]
Kutki (*Picrorrhiza kurroa*)	Whole plant	Picrosides-I, II and III, and kutkoside	Lowered levels of lipid peroxidases and hydroperoxides, free radical producing agents, and facilitated the recovery of a powerful antioxidant in the hepatic tissues	Hepatic cancer, sarcoma, papilloma	[282, 283]
Suma (*Pfaffia paniculata*)	Roots	Presents cytotoxic substances	Caused degeneration of cytoplasmic components and profound morphological and nuclear alterations of cancer cells	Estrogen-positive breast cancer	[284, 285]
Ginseng (*Panax ginseng*)	Roots	Flavonoids, polysaccharides, polyacetylenes, ginsenoside such as Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1	Promoted apoptosis, BAX, via caspase-3, caspase-9, p21, and p53, inhibition of Bcl-2	Breast, cervical, bladder, thyroid, ovaries, larynx, pancreas, esophagus, and gastric cancers	[290, 292]
Oregano (*Origanum vulgare*)	Whole plant	Rosmarinic acid	Antioxidant, anti-inflammatory, modulated cell lipid peroxidation, induced apoptosis via rising BAX levels, and decreased BCL_2 expression	Prostate, colon, and stomach cancers	[299]
Snake-needle grass (*Oldenlandia diffusa*)	Stem barks, leaves, and fruit peel	Ursolic acid, and oleanolic acid	Showed typical cytotoxic impact on cancer cells by stimulating apoptosis, antioxidant, anti-inflammatory, and inducing autophagy	Leukemia, ovary, lung, fibrosarcoma uterus, gastric, hepatic, colon, rectum, and brain cancers	[301, 305–307]
Amygdalin *Prunus dulcis*	Seeds	Hydrocyanic acid, and benzaldehyde	Induced the expression of Nrf-2, Restored the liver function parameters, improved the drug's effect (Sorafenib), increased the number of dead cancer cells, and decreased the cancer volume	Liver cancer	[312]
Alpinia officinarum	Rhizomes	Diarylheptanoids	Promoted Caspase-8, p53, and reduced MMP-9, IL-6, and VEGF	Hepatocellular carcinoma	[311]

antibacterial, antidiabetic, anticancer, immunomodulatory, anthelmintic, antiangiogenic, and anticancer activities [29].

Olea europae contains compounds and secondary metabolites—including oleuropein, oleanolic acid, and polyphenols—that exhibit anticancer effects against breast and colon cancer [119]. Oleuropein and oleanolic acid suppress cancer cell growth by inhibiting the signaling cascade of Akt/mTOR, resulting in protein synthesis in cancer cells and cell death. In addition, these compounds bind to G protein-coupled estrogen receptor and induce the expression levels of proapoptotic Bax protein and suppress the expression levels of Bcl-2 (antiapoptotic protein), inducing cancer cell death. Oleuropein and its secondary metabolites increase the protein expression of p21, inducing cell cycle arrest [119].

Arctium lappa L. contains lappaol and arctigenin that exert potent anticancer effects against several types of cancers, including malignant melanoma, leukemia, and cancers of the breast, cervix, bladder, bone, esophagus, lung, ovaries, and prostate [120]. These active compounds induce intrinsic apoptosis via loss of mitochondrial $\Delta\Psi_m$, which activates a caspase cascade [121]. This process involves an increase in the activity of caspase-3–7 and pro-caspase-9, which induces the expression of caspase-9 and results in DNA fragmentation within cancer cells [121].

Azadirachta indica contains limonoid and nimbolide, which have potent anticancer effects against breast, stomach, lung, prostate, skin, colon, and prostate cancer, as well as malignant melanoma and leukemia. These active compounds induce cancer cell death by inhibiting the Akt/mTOR signaling cascade, inhibiting protein synthesis in cancer cells and cell death, and arresting the cancer cell cycle in the G2/M phase [122].

Petals of *Rosa damascenes* contain phenolic compounds such as gallic acid, catechin, and epicatechin that exert antioxidant effects in lung, cervical, and breast cancers by inhibiting the enzymes that produce scavenging ROS, chelating free metal ions, suppressing lipid peroxidation, and protecting DNA from damage [123].

Ferula assafoetida contains coumarin compounds that exert anticancer effects against HepG-2 cancer by increasing the expression levels of the caspase cascade, resulting in DNA fragmentation and cancer cell death [124]. *Nigella sativa,* which contains thymoquinone and dinitroquinone compounds, also induces the caspase cascade (caspase 3 and 9) and cancer cell death in colon, lung, renal, cervical, skin, prostate, breast, and pancreatic cancers [125]. Additionally, thymoquinone and dinitroquinone compounds induce the expression of the apoptotic marker BAX, decreasing the expression level of the antiapoptotic marker Bcl-2 and suppressing the signaling pathway of AKT/PI3K, resulting in cancer cell death [125].

Thymus vulgaris and *Thymbra spicata* contain thymol and carvacrol compounds that exert anticancer effects against prostate, head, and neck cancers by elevating the expression level of BAX and suppressing that of Bcl-2, inducing apoptosis and cell death [126]. Thymol and carvacrol compounds also suppress the PI3K/protein kinase B signaling pathway, resulting in cell death. Furthermore, these compounds exert antioxidant activities in lung cancer by reducing ROS production and lipid peroxidation while protecting DNA from damage [127].

Taverniera spartea contains isoflavonoid and saponin compounds that exert anticancer effects against breast and prostate cancers by inducing the p53 pathway and modulating the PI3K/AKT signaling pathway, resulting in cancer cell death [128]. *Peganum Harmala* contains alkaloid compounds that exert anticancer effects against breast and cervical cancers by inducing the caspase cascades, especially caspase 3 and 9, and decreasing the expression levels of signaling PI3K/mTOR, resulting in cancer cell death [129].

Viola tricolor contains flavonoids—primarily rutin and quercetin—that act against breast, colon, lung, and prostate cancers by modulating the signaling effect of the PI3K/AKT pathway, resulting in the inhibition of the expression of mTOR and cancer cell death [130]. These compounds also exert antioxidant activity against ROS by inhibiting the enzymes producing ROS.

Camellia sinensis contains epicatechin, epigallocatechin, epigallocatechin gallate, and epigallocatechin-3-gallate (EGCG) compounds, which exert anticancer effects against lung, bladder, skin, prostate, and breast cancers by inducing the caspase cascade, BAX, and p53 tumor suppressor gene, resulting in cancer cell death [131]. EGCG, the major catechin found in green tea, also induces autophagy by increasing the expression level of LC3 II and degrading p62 in mesothelioma cells, resulting in cancer cell death [131].

Zingiber officinale contains flavonoids, especially kaempferol, catechin, fisetin, and quercetin, which exert anticancer effects against ovarian, cervical, colon, hepatic, and urinary cancers by inducing apoptosis and cell cycle arrest at the G2/M phase [132]. These compounds induce the expression levels of components in the caspase cascade, including caspase 3, 9, and 7, the proapoptotic marker BAX, and the p21 protein, and suppress the expression of the antiapoptotic marker Bcl2 and the PI3K/AKT signaling pathway, resulting in cancer cell death [132].

Lentinus edodes contains lentinan, terpenoids, and steroids that exert anticancer effects against lung

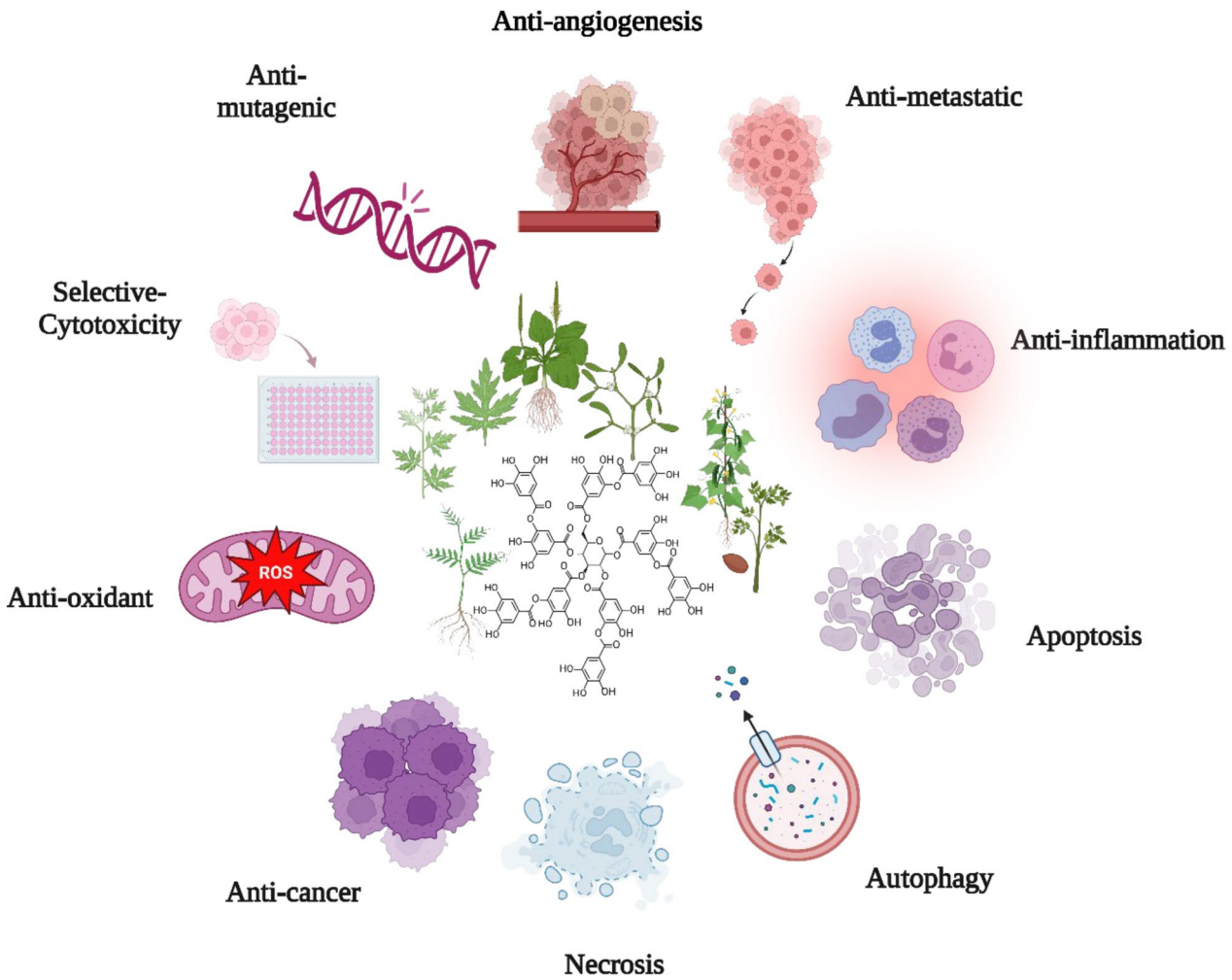

Fig. 4 Mechanism of action of medicinal plants in cancer treatment

carcinoma and colon cancers by inducing the expression levels of p21, BAX, and caspase 3 and 9 and suppressing that of Bcl2, resulting in cancer cell death and cell cycle arrest in the G_0/G_1 phase [133]. *Fagopyrum esculentum* contains amygdalin, rutin, and buckwheat inhibitor-1 protein, which exert anticancer effects against pancreatic cancer and T-acute lymphoblastic leukemia (T-ALL) cells by decreasing the signaling effect of the PI3K/AKT and Bcl-2 pathways and inducing the expression levels of BAX and caspase-3, resulting in cancer cell death [134, 135].

Lagenaria siceraria, which contains vitamins (B group and C), saponins, and cucurbitacin, exerts anticancer effects against breast cancer cells, including MDA-MB-231 and SKBR3- MCF-7 cells, by enhancing apoptosis and autophagy via inhibition of the Akt/mTORC1 and ERK 1/2 (extracellular signal-regulated kinase) signaling pathways and the p38 protein [136]. *Echinacea angustifolia* contains arabinogalactan, which exerts its effects against esophageal and colon cancers by inducing apoptosis and cell cycle arrest at the G_0/G_1 phase [137]. This compound alters the function of mitochondria, inducing mitochondrial oxidative stress, resulting in the activation of the MAPK signaling pathway, apoptosis, and cancer cell death [137].

Cinnamomum cassia contains a coumarin compound that exerts anticancer effects against prostate, renal, hepatic, prostate, and breast cancers, as well as leukemia by increasing the expression levels of BAX and caspase 3, 7, and 9 and decreasing the expression level of Bcl-2, resulting in apoptosis and cancer cell death [138, 139].

Cannabis sativa contains cannabinoids and stereoisomers of cannabidiol that exert potential anticancer effects against breast, brain, lung, pancreas, prostate, and colorectal cancers by activating the JNK-AP1 and NF-κB signaling pathways, resulting in apoptosis and cancer cell death [140].

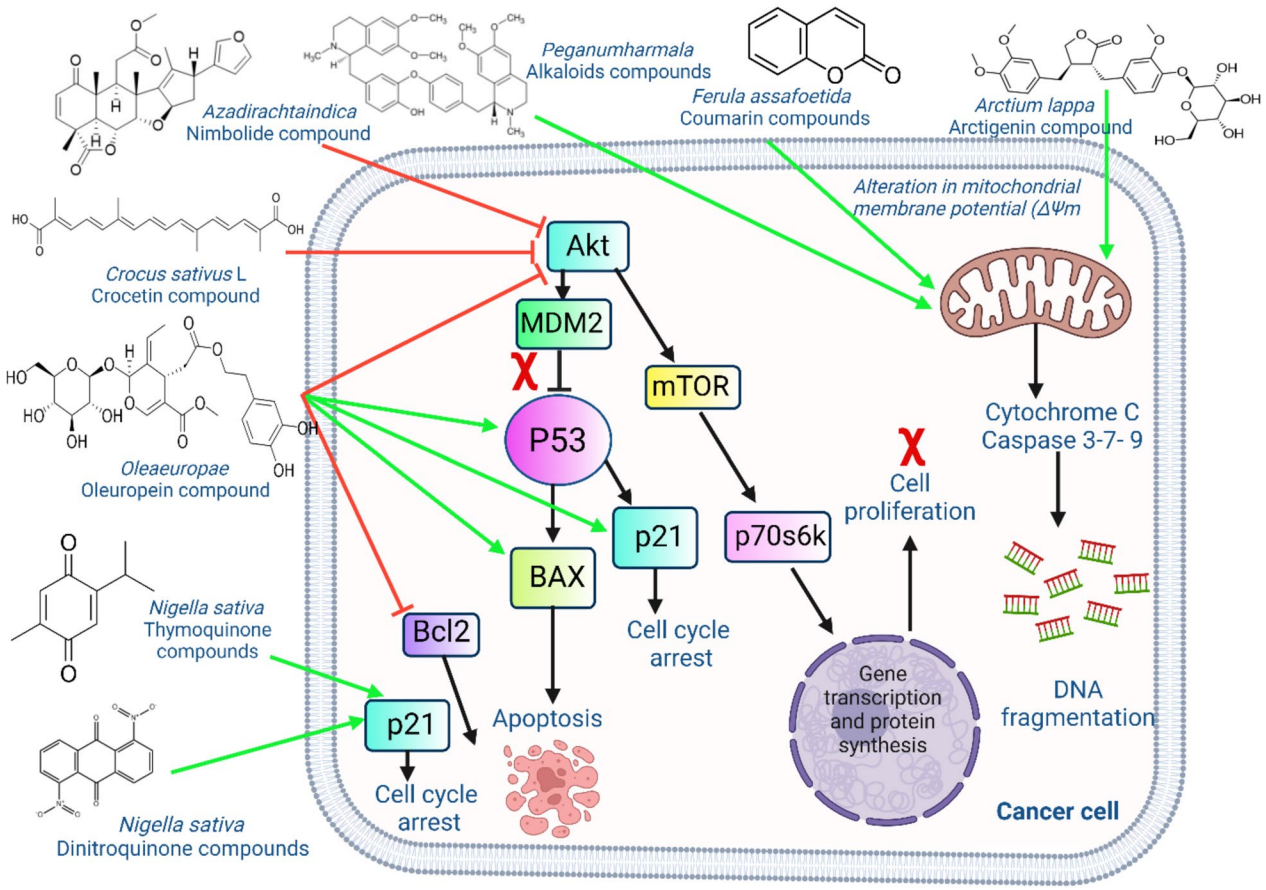

Fig. 5 The molecular pathway involved in the anticancer mechanisms of medicinal plants

Physalis alkekengi contains physalis, which exerts potent anticancer activity against cervical cancer by decreasing signal transducer and activator of transcription 3 (STAT3). This cell survival regulator induces the expression of caspase 3 and 9, p53, and BAX and decreases Bcl2 expression and the AKT/PI3K signaling pathway, resulting in cancer cell death and cell cycle arrest [141].

Artemisia absinthium L. contains artemisinin, quercetin, isorhamnetin, limonene, myrcene, linalool, a-pinene, b-pinene, and artesunate that have anticancer effects against colorectal cancer, leukemia, HeLa, HT-29, MCF7, HepG2 cells, hepatoma, ovarian cancer, cervical cancer, pancreatic cancer, and embryonal rhabdomyosarcoma by increasing the expression levels of BAX, caspase 3 and 9 and LC3-II, resulting in apoptosis and autophagy [142].

Allium sativum L. contains allicin and ajoene compounds that induce anticancer effects against MCF7, HCC-70, Caco2, HepG2, and A549 cells and cervical cancer by suppressing the expression of cyclin B and inducing the expression of p21 and p53, resulting in cell cycle arrest at the G_2/M phase [143]. *Ferula gummosa* contains sesquiterpenes and coumarin compounds that exert anticancer effects against breast, colon, bladder, pancreatic, prostate, cervical, brain, liver, blood, ovarium, bone, endometrial, oral, lung, eye, stomach, and kidney cancers by inducing the expression of apoptotic markers related to cellular death (Bax) and the caspase cascade (caspase 3 and 9) and suppressing the expression of (Bcl-2) resulting in cancer cell death [144].

Coriandrum sativum contains beta-carotene, quercetin, and rutin that exert antioxidant activity by suppressing the enzymes that produce ROS species, cause lipid peroxidation, and protect DNA from damage [145]. *Achillea wilhelmsii* contains phenolic compounds, comprising mainly flavonoids and monoterpenes like 1, 8-cineole and a-pinene that exert anticancer effects against non–small-cell lung carcinoma, colon cancer, ovarian cancer cell lines, and hepatocellular liver carcinoma cell lines by inducing the expression of the caspase cascade and downregulating the cycle dependence on kinase 1 (CDK 1), resulting in cell death and arresting the cell cycle at G_2/M phase [146].

Curcuma longa contains a curcumin compound that shows anticancer effects against leukemia, glioblastoma, colon, lung, breast, prostate, cervical, and larynx cancers [147]. Curcumin has phenolic and β-diketone functional groups, which helps it to be an antioxidant and free radical scavenger. Curcumin enhances the activities of SOD, catalase (CAT), and glutathione peroxidase (GPX). Curcumin's ability to penetrate mitochondria safeguards against oxidative damage and prevents mitochondrial dysfunction [148]. It induces the expression of tumor necrosis factor (TNF-α) and causes a reduction in the expression levels of survival and antiapoptotic markers, STAT3 and Bcl-2, respectively. Curcumin induces the expression of BAX and p53 proteins, resulting in apoptosis and cancer cell death [147].

Gray mangrove (*Avicennia marina*) includes a variety of bioactive compounds, such as flavonoids, steroids, polysaccharides, iridoids, and naphthoquinones, which showed antitumor activity in different models, including breast, larynx, lung, cervix, leukemia, colon, and liver cancer in a dose-dependent manner by promoting apoptosis [149]. The favorable roles could be attributed to lupeol's capacity to inhibit BCL-2 expression in Hep3B cells by contributing to apoptosis; however, the effects of BAX were not observed [150].

A. marina could be formulated at the nanoscale and has been functional in alleviating adverse chemotherapeutic effects and improving the treatment results [149]. Naphthalene derivatives of *A. marina* showed substantial antiproliferative and moderate cytotoxic effects [151]. Two flavones, luteolin 7-O-methyl ether 3′-O-β-D-glucoside, possess cytotoxic potential against BT-20 cells, and the terpenoid content exhibits similar cytotoxic effects [152, 153]. In the context of nano-applications, silver nanoparticles derived from *A. marina* exhibit cytotoxic activity on lung cells via the ROS-dependent apoptosis machinery, recruiting both p53-dependent and -independent caspases [154, 155].

Cress (*Lepidium sativum)* contains plant phytosterols and their derivatives with robust antioxidant and anti-inflammatory capacity exhibiting protective roles against cancers [156]. It can promote apoptosis and necrosis in breast cancer cells (MCF-7); however, apoptosis was not linked to caspase 3 [157] and may be attributed to the interaction with effector caspases such as caspase 6 or 7 [158]. Moreover, the n-hexane extract of *L. sativum* was significantly potent against hepatocellular carcinoma cell lines, accompanied by attenuation of epidermal growth factor receptor and BCL2 and elevated SMAD3, BAX, and P53 levels [159]. Furthermore, *L. sativum* has an anticancer effect against chronic myeloid leukemia [159].

Mentha pulegium significantly affected the cytotoxicity effect in leukemia cells [160]. The plant contains several bioactive compounds, such as mentone, piperine, limonene, isomenthone, and Octaan-3-ol [161]. The inhibitory effects of *M. pulegium* was attributed to its flavonoid content [162]. Interestingly, solid lipid nanoparticles, including *M. pulegium*, exerted an impact on human melanoma and breast cancer cells [163].

The favorable effects of birch (*Betula alba*) in the context of cancer have been linked to a naturally occurring triterpene called betulin and its underlying molecular consequences [164]. This compound assists in combating inflammation, predominantly by regulating nuclear factor-κB (NF-κB), which influences the survival, proliferation, angiogenesis, metastasis, and differentiation signaling cascade of cancer cells [164], and has proven highly useful in reducing inflammation and mitigating adverse effects during therapy [165]. In addition, birch blocks the COX-2-mediated NF-κB pathway and controls inflammation and carcinogenesis [165, 166].

Betulin-mediated cascades can tackle cancer progression and enhance therapy modalities for several carcinomas, including breast, ovarian, cervical, gastric, colorectal, lung, liver, and prostate cancers, via nuclear factor erythroid2-related factor 2 (Nrf2) [167]. The inhibition of MAPK hinders the attenuation of antioxidant enzymes and enhances the cell's oxidative power [168]. Betulin induces the release of cytochrome c from mitochondria and mobilizes Bak and Bax, which can inhibit the growth of various carcinomas [169]. Furthermore, it plays a role in leukemia, thyroid, pancreatic, and lung cancers by attenuating the genetic expression levels of Bcl2 and cyclin D1 and increasing that of BAX [170].

The *Viscum album* (mistletoe extract) contains a spectrum of glycoproteins or mistletoe lectins and viscotoxin, as well as secondary metabolites such as alkaloids, polysaccharides, and amino acids. It exerts significant cytotoxicity in numerous human cancer cell lines, including leukemia and lymphoma. However, it acts against breast cancer and glioma in vitro [171] and against murine tumors, Lewis lung carcinoma, colon adenocarcinoma, and mammary adenocarcinoma in vivo [172]. In addition, it has shown apoptotic potential through mitochondrial pathways with significant apoptosis induction in the human leukemic cell line MOLT [173]. Interestingly, *V. album* was reported to impact significantly the survival of oral melanoma patients [171, 174]. Furthermore, a synergetic effect between mebendazole and malignant gliomas was observed in dogs [175]. The mistletoe boosts immunity, enhances the patient's health and quality of life, and attenuates the adverse effects of conventional therapies [176].

Silybum marianum (milk thistle) is used to extract silymarin, which contains many similar flavonolignan bioactive compounds, such as silibinin [177]. Silymarin is well-known for protecting the liver with a significant impact against different carcinomas, including those of the prostate, colon, gastric, breast, lung, liver, ovary, and pharynx [178], with substantial impact as an antimetastatic and anti-inflammatory agent [179]. Silymarin is a framework of xenobiotics and metabolizing enzymes that tackle the adverse effects of chemotherapy on normal cells and preserve organ health by reducing the toxic load [180]. In addition, it can suppress and inhibit organic anion transporters and ATP-binding cassettes, two players involved in the chemoresistance and cellular export of pharmaceutics and toxins [181].

It showed apoptotic properties by promoting phosphorylated (p)-JNK, Bax, and p-p38, in addition to cleaved poly-ADP-ribose polymerase (PARP) [182]. Conversely, it suppresses Bcl-2 and p-ERK1/2 expression, which are distinguished features that make silymarin a great candidate for anticancer trials, as reported in gastric cancer. As the main component of silymarin, silibinin has a beneficial effect against bladder, lung, colorectal, and prostate cancers by attenuating growth and invasiveness [183]. Silibinin provokes apoptosis through a mitochondrial-mediated pathway [184], promotes cell arrest in the G2/M phase in gastric cell lines, and attenuates the p-STAT3 level, consequently tackling proliferation, survival, angiogenesis, and invasion while promoting apoptosis [177]. Silibinin suppresses survivin, cyclinB1, Bcl-xL, and CDK1 and induces caspase 9, indicating its robustness as an apoptotic factor and cell cycle arrest modulator [185].

Bauhinia variegate includes terpenoids, flavonoids, tannins, saponins, reducing sugars, steroids, and cardiac glycosides [186, 187], and compounds derived from leaves, stem bark, and flower that are well-known for their hepatoprotective, antioxidant, and anticancer potential [188]. *B. variegate* var. *candida* stem cells possess cytotoxic and antimetastatic activity against human cervical cancer cells (HeLa cells). The efficacy is attributed to the inhibitory effect on metalloproteinases, particularly MMP-2 and MMP-9, which are highly invasive and expressed in association with cervical cancer [189, 190]. Additionally, palmitic acid shows selective cytotoxicity to human leukemic cells, but no cytotoxicity to normal HDF cells [191]. *B. variegate* can induce apoptosis by upregulating the level of TNFR-1, which interacts with FADD proteins and recruits caspase 8, leading to extrinsic cell death via caspase 3 [189].

Conversely, *B. variegate* played a protective role against melanoma in skin cancer mouse models and tackling angiogenesis [188]. *B. variegata* restored the capacity of antioxidant enzymes and GSH levels altered by cancer-related changes. This property *of B. variegata* is beneficial against human epithelial larynx and breast cancer cell lines. Moreover, it has also shown hepatoprotective effects against DEN-induced liver cancers in rat models [192]. Scavenging these radicals ameliorates cancer progression and improves the subjects' health. Furthermore, *B. variegata* flowers have been shown to induce chemopreventive activity against DMBA-induced skin papillomagenesis [193].

Crocus sativus L. (saffron) and its bioactive compounds, crocin, crocetin, and safranal, have potential anticancer activity [194]. The administration of saffron prevents DMBA-induced oral squamous cell carcinomas and skin papilloma [195, 196]. Saffron ethanol extract was reported to promote apoptosis in breast cancer cells (MCF-7), activating caspases, increasing Bax expression, significantly suppressing VEGF levels, and consequently inhibiting cell proliferation and angiogenesis [197, 198]. Similarly, in MCF-7, crocin has been shown to potentially disrupt the mitochondrial membrane, leading to the release of cytochrome c, which directs cells toward apoptosis and attenuates proliferation [199].

In one study, crocin participated in cell arrest in the G0/G1 phase, causing an increase in the levels of p53, Fas/APO-1, and caspase 3, which resulted in apoptosis among ovarian cancer cells (HO-8910) [200]. Crocin also suppressed cell proliferation in gastric and colorectal cancers through p53-dependent or -independent machinery [201]. In contrast, crocetin has proven beneficial in suppressing the invasion and proliferation of lung adenocarcinoma cells by attenuating Bcl-2 and promoting p53 and Bax [202]. Similarly, crocetin promoted apoptosis in colon and leukemia cells through p21 activation and cell cycle arrest in the S-phase [203, 204].

Saffron exhibited a synergistic impact with chemotherapy against cancer among patients with liver metastasis [205]. In addition, combining trans sodium crocetinate (TSC) with radiotherapy promoted the survival of patients with glioblastoma [206].

Ammi visnaga (Bisnaga) bioactive compounds include γ-pyrones and coumarins and their sub-molecules [207]; the γ-pyrones include khellin, visnagin, 5,7-dihydroxy-2-methyl-γ-pyrone-7-O-glucoside, and picolin (III), and vesnarinone, while the coumarins include dihydrofuranocoumarin glucoside, visnadin, amidin, and dihydrosamidin [208]. *A. visnaga* exerts hepatoprotective effects by inducing apoptosis through modulation of the mitochondrial membrane potential, alterations in Bax and Bcl2 expression, and upregulation of caspase-3 [209, 210].

Moreover, the ethanolic extract of *A. visnaga* exhibited a significant cytotoxic and apoptotic impact on human

liver cancer cell lines (HuH-7) and inhibitory effects on HeLa (cervical cancer) and breast cancer (MCF7) cell lines [211]. However, *A. visnaga* was reported to increase oxidative stress and GSH levels by reducing SOD and CAT [212]. Additionally, khellin and visnagin have demonstrated cytotoxic potency against the HepG2 cell line [213].

Fenugreek (*Trigonella foenum-graceum*), which contains valuable bioactive compounds, such as alkaloids, saponins, tannins, phenols, and many phenolic compounds, exhibited oxidant scavenging capacity and moderated cytotoxic activity against HepG2 [214]. Interestingly, fenugreek-rich food significantly decreased the incidence of colon cancer and lipid peroxidation in liver cancer-induced rats, promoting antioxidant activities in the organ [215]. Fenugreek also showed protective effects against breast cancer by inducing apoptosis and exerting a cytotoxic effect on T-cell lymphoma [216, 217].

Furthermore, the extract was cytotoxic to prostate and pancreatic cell lines with substantial selectivity [218]. It targets STAT3-regulated genes, which attenuate proliferation and sensitize the apoptotic potential of chemotherapy regimens. In addition, the extract causes cell cycle arrest at the G2/M phase, leading to productive inhibitory roles on the growth of the breast, pancreatic, and prostate [214]. Fenugreek extract and its active constituents work efficiently in preventive/therapeutic protocols to improve health status [214].

Ocimum sanctum, commonly named the queen of herbs, has a high eugenol content in addition to ursolic acid, apigenin, caryophyllene, carvacrol, cirsimaritin, estragole, linalool, oleanolic acid, and rosmarinic acid [219]. However, the general anticancer activity of *O. sanctum* has been attributed to eugenol [220]. Additionally, neo-lignans, saponin, tannins, sterols, cerebrosides, triterpenoids, and alkaloids are commonly found in *O. sanctum* with well-discussed anticancer and antioxidant potential due to their ability to elevate p53, Bax, and BH3-interacting domain death agonist (Bid), as shown in a breast cancer study using *O. sanctum* essential oil (OSEO) [221].

Eugenol, the key player in the context of cancer, showed a synergetic impact when added to conventional treatments to alleviate adverse effects on normal cells [222]. Additionally, eugenol can enhance the overall antioxidant power by increasing the levels of SOD1, CAT, Gpx1, and GST and attenuating inflammation (via inhibition of nuclear factor-kappa B [NF-κB]) [223]. Eugenol was profoundly beneficial in leukemia, melanoma, lung carcinoma, and cervical, gastric, colon, colorectal, skin, and prostate cancers [224]. It can induce apoptosis through ROS production and modulation of the MMP [225]. Eugenol also mediates cell cycle arrest at the S-phase, as shown in lung cancer cells, with the capacity to induce necrosis and boost the cytotoxic effects of cisplatin and doxorubicin in colon cancer [226, 227].

Additionally, it promotes apoptosis by altering Bcl-2, as observed in a gastric cancer cell line [228], with the attenuation of E2F1 and antiapoptotic regulators [229]. Eugenol attenuates cell migration by altering the epithelial-mesenchymal transition (EMT) protein effectors addressed in HeLa cancer cells [230]. Similar results were obtained from ursolic acid, another component of *O. sanctum,* which decreased Bcl-2 levels and triggered apoptosis [231]. In another study, rosmarinic acid modulated the expression of EMT-associated proteins and reduced tumor invasion [232].

Combretum caffrum includes several bioactive compounds, including combretastatin, with numerous activities, such as antioxidant, anti-inflammatory, inhibition of cell proliferation, and limiting of the tumor vasculature in colon cancer, resulting in tumor necrosis [233]. In leukemia and other cell lines, it causes cell cycle arrest in the G2/M phase, with subsequent cell death unrelated to apoptosis [234]. Combining combretastatin with tubulins near the colchicine locus can suppress angiogenesis in cancer tissues [235].

Combretastatin can inhibit the proliferation of non-small-cell lung carcinoma cells due to its ability to disrupt the microtubule assembly [236]. Interstingly, the nano-drug of combretastatin was significantly more robust than the conventional administration in terms of attenuating angiogenesis [237]. The nano-drug combretastatin A4 nano-drug (CA4-NPs) promoted CXCR4, which was linked to cancer metastasis; combining it with plerixafor substantially inhibited tumor growth and metastasis.

Glycyrrhiza glabra possesses highly valuable bioactive compounds, such as 18 α-glycyrrhizic, 18 β-glycyrrhizic, saponins–licorice saponin K2/H_2, licorice saponin B2, licorice saponin G2/yunganoside K2, apioside (liquiritin apioside, isoliquiritin apioside, licuraside), and 8-cyclized isoprenyl isoflavone [238–240]. Licorice and its derivatives exhibit significant anti-inflammatory and antioxidant capacities, which aid in alleviating the adverse effects of radiotherapeutic and chemotherapeutic agents and improving the quality of life of patients with prostate, breast, lung, gastric, renal, and colon cancers and those with acute myeloid leukemia and melanoma [241–243]. In addition, it has also shown neuroprotective, chemosensitivity, pain relief, anti-anxiety, and anti-depression properties [241].

Reducing inflammation and allergy could prevent the adverse toxic effects on the liver [244]. Licorice significantly alleviated the consequences of radiotherapy in oral and head and neck cancers [245, 246]. The alleviation of the adverse effects of chemotherapy was attributed to

glycyrrhizin's capacity to suppress inflammatory regulators and oxidative stress, down-regulate NF-κB and Nrf2, and enhance chemosensitivity via the nitric oxide regulator [247].

Licorice demonstrated a nephroprotective effect following cisplatin administration by attenuating HMGB1 and tackling resistance via the inhibition of MRP2, MRP3, MRP4, and MRP5 [248, 249]. Furthermore, it induced apoptosis by altering the Bax/Bcl-2 ratio and activating caspase 3 [250]. Licorice showed G0/G1 cell cycle arrest via attenuation of the CDK4-Cyclin D1 complex, alleviating proliferation through increased antigen presentation and enhanced CD8 + T invasion [251]. Licorice flavonoids significantly impacted oral squamous cell carcinoma by provoking the mitochondrial apoptotic pathway [252]. Furthermore, attenuation via the PI3K/AKT pathways could suppress the proliferation of lung cancer cells [253].

Taxus baccata includes numerous bioactive compounds, such as taxol (paclitaxel), baccatin, lignans, and flavonoids [254]. It demonstrated a significant antioxidant potential because of the phenolic and flavonoid content in the extract [255]. Paclitaxel showed significant anticancer effects against breast cancer cells by inducing apoptosis, enhancing the responsiveness toward chemotherapy, and suppressing TRG1, which has been linked to chemoresistance via altered drug efflux machinery during treatment [111, 114, 256]. Furthermore, the extract of *T. baccata* was shown to promote apoptosis in colon and breast cell lines [255].

Nothapodytes foetida is recognized for its richness in camptothecin (CPT), a water-immiscible terpenoid indole alkaloid that can substantially suppress DNA topoisomerase I, a crucial enzyme for modulating the topology of DNA by releasing/relaxing DNA supercoiling during DNA replication [257]. CPT derivatives showed significant actions against various carcinomas, such as gastric, uterine, cervical, ovarian, colorectal, and small lung cell cancers [258]. ZBH-ZM-06 is another derivative of CPT that showed antitumor effects against several cancer cell lines by promoting apoptosis via caspase 3 and poly (ADP-ribose) polymerase (PARP) activation; additionally, it induced G2/M phase arrest in treated cancer cells [259].

Linum usitatissimum is considered a valuable herb due to its contents, which include phenols, alpha-linolenic acid (omega-3), linoleic acid, oleic acid, lignins, vitamin B, and flavonoids that possess robust radical scavenging, anti-inflammatory, and antiangiogenic activities, in addition to promoting apoptosis; these properties were attributed to modulation of the apoptotic genes, such as caspase3, 8, and 9 to substantially low levels in various cancers [260–262]. In addition, *L. usitatissimum* can decrease the risk of prostate and colon cancers by acting synergistically with chemotherapeutics [263]. *L. usitatissimum* extract promoted Bax and Bad expression in LS174T and COLO205 [264] and exhibited anticancer activities against the lung cancer cell line PC-14, linked to its robust antioxidant activity [265].

Indigofera tinctoria includes crucial bioactive compounds, such as flavonoids, saponins, tannins, steroidal terpenes, phenols, and anthraquinone, implying potent antioxidant power [266]. The leaf extract attenuated the proliferation of the lung cancer cell line A-549 and suppressed the cell cycle in the G0/G1 phase [267]. Interestingly, the flavonoid content of the methanolic extract caused a significant induction of apoptosis [267].

Glycine max includes a variety of valuable compounds, such as isoflavone, which substantially affects health and quality of life; it also contains malonyl-genistin and genistin. The phenol content of the plant exhibits antioxidant capacity in a dose-dependent manner [268]. Furthermore, it is reported to exhibit anti-inflammatory activities with inhibitory actions on LPS-induced inflammation, NO production, and PGE2. The extract demonstrated antiproliferative activities against colon and lung cancer cell lines by attenuating colony formation and promoting apoptosis [268].

Ginkgo biloba (maidenhair tree) possesses several flavonoid compounds, such as lignin, quercetin, kaempferol, and isorhamnetin, in addition to terpenoids, such as ginkgolide (A, B, C, and J) [269]. It has a significant therapeutic impact attributed to its antioxidant, antiangiogenic, and gene-modulatory actions [270]. The polysaccharides derived from the extract also alter cell cycle progression by elevating the G2-M cells and inducing apoptosis in hepatoma cells. The extract has been linked to increased (CYP) 1B1 that subsequently suppressed the proliferation of breast cancer cells [271].

In a previous study, the exocarp extract of *G. biloba* increased the Bax/Bcl-2 ratio in Lewis lung carcinoma cells, accompanied by an increase in the mobility of Bax/Bcl-2 to the mitochondria along with the release of cytochrome C, which induced the caspases and resulted in apoptosis. In addition, it plays a significant role in stimulating autophagy through AMPK-induced inactivation of mTOR/p70S6k [272].

Ochrosia elliptica was mainly studied for its ellipticine content, which was found to exhibit cell cycle arrest activity and induction of the apoptotic pathways; the MCF7 and MDA-MB-231 cell lines were also profoundly inhibited [273, 274]. Ellipticine was found to modulate the levels of cyclin B1 and Cdc2 and phosphorylation of Cdc2, which altered the cell cycles of MCF-7 cells in human mammary adenocarcinoma [275]. It promotes ROS production and subsequent DNA damage

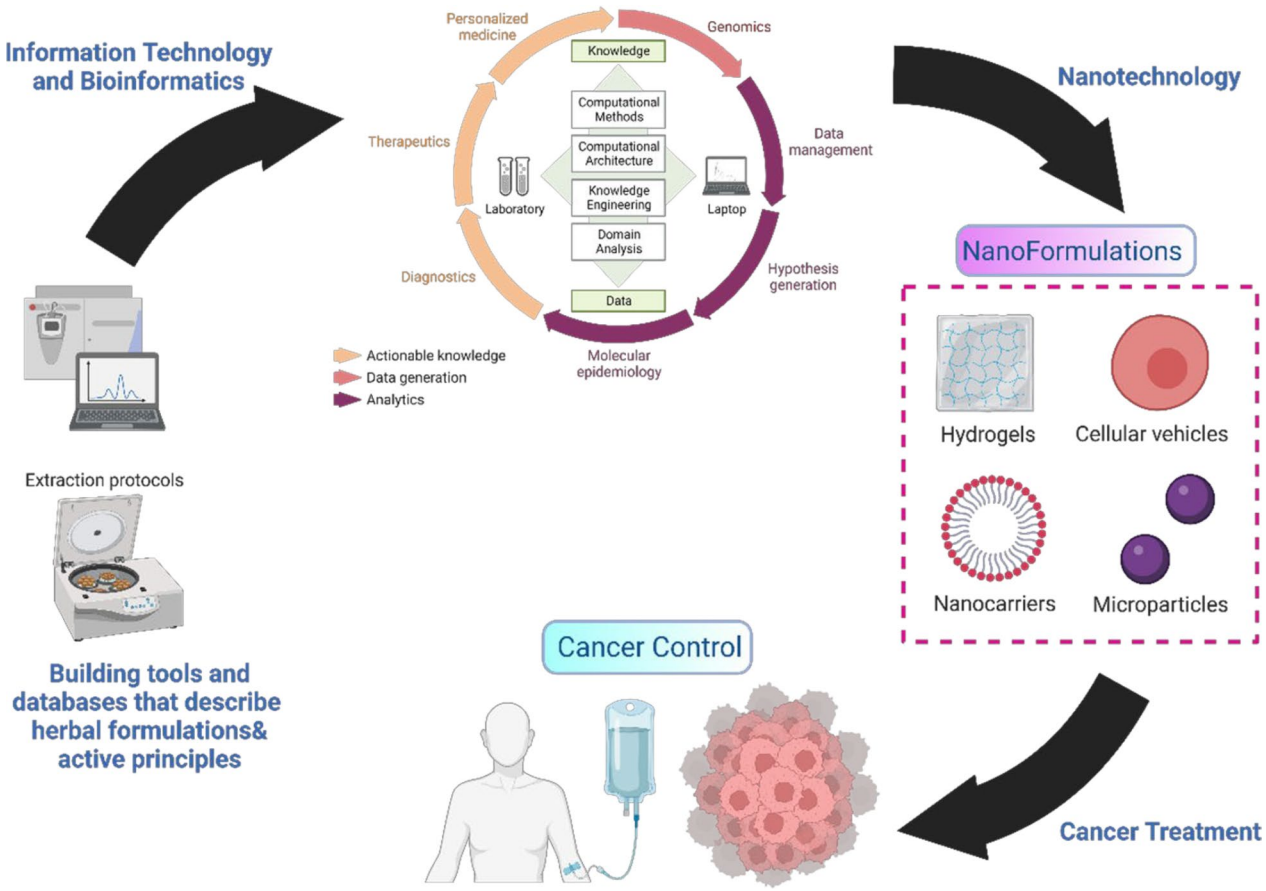

Fig. 6 Advanced approaches for cancer control using medicinal plants

by activating MAPKs, cytochrome C, apoptosis-inducing factor, caspases, and the non-dependent apoptosis machinery [276]. Moreover, ellipticine can modulate Bcl-2 [277].

O. elliptica consists of lupeol and lupeol acetate in addition to uvaol, rutin, 8-methoxy, and 9- 9-methoxy ellipticine. Lupane and ursane work as multitarget agents that can alleviate cancer management through different approaches [278]. Moreover, it possesses β-sitosterol glucoside and ursolic acid [279] and exerts an anti-inflammatory effect by blocking histamine and the COX-selective drug machinery and attenuating PGE2, tumor necrosis factor-α, and serotonin production. This effect was attributed to a combination of several phytochemicals, such as pentacyclic triterpenes, lupeol, lupeol acetate, β-sitosterol glucoside, and alkaloids [279, 280].

Picrorrhiza kurroa contains bioactive compounds such as picrosides-I, II, III, IV, rutoside, apocynin, catechol, and rosin. It is generally studied based on its standard picroliv content, which is a mixture of picroside I and rutoside or picroside II [281]. Picroliv showed anticancer activity against sarcoma and papilloma in BALB/c mice [282]. *P. kurroa* exhibited an inhibitory action against liver cancer via N-nitroso diethylamine (NDEA) and by inhibiting topoisomerase I and II [283].

Pfaffia paniculata consists of saponins, pfaffia acid; saponins pfaffosides A, C, D, E, and F; that was accompanied by cytotoxic action as well as attenuation of growth of melanoma B-16, HeLa S-3 and Lewis lung carcinoma cells in vitro that was attributed to saponins and pfaffia acid [284]. The extract also reduced oxidative stress by decreasing the IL-1β, INF-γ, TNF-α, and IL-6 levels [285].

Panax ginseng includes numerous compounds such as polysaccharides, flavonoids, volatile oils, amino acids, and vitamins; however, its anticancer, anti-inflammatory, and antioxidant capacities are attributed to ginsenoside [286]. *P. ginseng* includes different types of ginsenoside, such as Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1 [287]. Rg1, for instance, can act as an antiproliferative agent by inhibiting c-myc and c-fos and attenuating nucleophosmin [288]. *P. ginseng* and its metabolites can sensitize cisplatin and induce apoptosis via caspase 3 and 9, p21, and p53 in lung cancer [289]. Moreover, it inhibits the proliferation and elevation of ROS-meditated endoplasmic reticulum stress-dependent apoptosis with a favorable impact on reducing metastasis [290].

Similar outputs were obtained with apoptosis induction in addition to EMT and proliferation attenuation in breast cancer cells accompanied by the elevation of C-cadherin and the reduction of N-cadherin, vimentin, FN, and p-Akt [291]. In colon cancer, *P. ginseng* promoted arrest in the G1 phase and suppressed cancer invasion and tumor metastasis by downregulating the levels of pY-STAT3, p-JAK2, MMP-1, MMP-2, and MMP-9 [292]. Moreover, *P. ginseng* reduce IL-8 level that limits inflammation [293]. In prostate cancer, apoptosis was elevated by increasing PPAR-δ and decreasing p-STAT3 [294]. In gastric cancer, apoptosis was elevated and proliferation was inhibited by increasing Bax and IκBα levels and decreasing p-mTOR and p-PKB levels [295]. Ginseng supplementation has been shown to improve the quality of life of patients with cancer [296].

Oregano (*Origanum vulgare*) essential oil includes thymol, ρ-cymene, γ-terpinene, and carvacrol [297]. It inhibits metastasis and proliferation [298] and suppresses lipogenesis and cholesterol biosynthesis in cancer cells, altering the crosstalk between lipid metabolism and cancer [297]. The downregulation of lipid metabolism in prostate cancer, such as HMGCR, FASN, and SREPB1, enhanced proliferation and metastasis [299]. Additionally, oregano essential oil extract exhibits antioxidant and anticancer potency. The extract caused a decrease in growth, an increase in cell death, and an increase in the oxidized form of glutathione. It induced apoptosis in cancer cells through intrinsic or extrinsic machinery, with high selectivity [300]. Furthermore, oregano essential oil promoted BAX (BCL2 associated X) and caspase 3, which was beneficial in prostate cancer [299].

Oldenlandia diffusa consists of ursolic acid and oleanolic acid, along with asperuloside (IG1), E-6-O-p-coumaroyl mannoside methyl ester (IG2), and E-6-O-p-coumaroyl mannoside methyl ester-10-methyl ether (IG3) [301]. *O. diffusa* has demonstrated the ability to fight and prevent cancers [302]. In addition, it has anti-inflammatory and antioxidant properties and can induce apoptosis [303]. The methanol extracts significantly attenuated cell viability in two types of ovarian cancer cell lines: the cisplatin-sensitive A2780 and the cisplatin-resistant A2780cis cells [304]. However, the water extract affected only the A2780 cells [301].

Epigenetic profiling of resistant A2780cis cells revealed an elevation in the epigenetic marker lysine demethylase 1B (KDM1B), which was efficiently inhibited by the methanolic extract of *O. diffusa*. This was associated with the mechanism by which *O. diffusa* induced cell demise in the resistant cells [301]. *O. diffusa* substantially facilitated apoptosis, demonstrated antiproliferative properties, and reduced the migration of hepatocellular carcinoma cells. The induction of apoptosis was attributed to caspase 3 [301].

Furthermore, *O. diffusa* extract attenuated several mediators of metastasis, such as CXCR1, CXCR2, and CXCR4. Interestingly, survival in the *O. diffusa*-administered groups revealed a therapeutic impact compared to that in the control group [301]. Oleanolic and ursolic acids have an anticancer impact on fibrosarcoma, liver, gastric, and colon cancer cells [305–307]. In addition, the flavonoid content of the extract increases autophagy in hepatocellular carcinoma cells by promoting endoplasmic reticulum stress and activating the PERK-eIF2α-ATF4 signaling pathway [308].

Alpinia officinarum contains diarylheptanoid, which possesses potency against inflammation, oxidative stress, and bacteria [309]. The anti-inflammatory robustness was attributed to the inhibitory effect of diarylheptanoid on TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β) [310]. A combination of diarylheptanoid and sorafenib attenuated the growth of HepG2 cells, with favorable effects on liver function and oxidative stress. In comparison to the control groups, the hepatocellular carcinoma group's hepatic expression of CASP8 and p53 was dramatically downregulated, whereas that of MMP-9, IL-6, and VEGF was significantly upregulated [311]. Advanced methods for controlling cancer with medicinal plants are shown in Fig. 6.

Conclusion

Careful investigations of numerous plants revealed that medicinal herbs have great anticancer potential. The mechanisms underlying some significant antitumor effects of plants are systematically highlighted in this review. Signaling pathways are regulated to inhibit cancer growth, and several studies have shown that enzymes that limiting cancer growth can be suppressed. Nonetheless, additional studies involving various plants, their active components, and the processes that underlie the anticancer benefits are warranted. Moreover, additional research must be conducted to investigate the effects of contemporary technological advances on human health to enhance the effectiveness of anticancer medicinal herbs.

Acknowledgements

The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for supporting this work through Large Research Project under grant number RGP2/265/45.

Author contributions

All authors were equal contributors in writing this review article. All of them read and approved the final manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 15 January 2024 Accepted: 28 February 2025
Published online: 16 July 2025

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