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The interplay of exercise and green tea: a new road in cancer therapy

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Abstract

Exercise is one of the most important activities for every individual due to its proven health beneficials. Several investigations have highlighted the advantageous impacts of aerobic exercise, largely attributed to its capacity to enhance the body's capability to defend against threats against oxidative stress. The information currently accessible suggests that adding regular aerobic exercise to a daily routine greatly decreases the chances of developing serious cancer and passing away. An unevenness in the levels of free radicals and the body's antioxidant defenses, made up of enzyme and non-enzyme antioxidants, results in oxidative pressure. Generally, an imbalance in the levels of oxidative stress triggers the creation of harmful reactive oxygen or nitrogen compounds, causing the development or progression of numerous ailments, including cancer. The equilibrium between pro-oxidant and antioxidant substances is a direct indicator of this imbalance. Green tea and its derivatives are rich sources of bioactive substances such as flavonoids and polyphenols which possess antioxidant abilities. Moreover, modulation of epigenetic targets as well as inflammatory pathways including ERK1/2 and NF-κB are other proposed mechanisms for its antioxidant activity. Recent studies demonstrate the promise of green tea as an antioxidant, showing its ability to decrease the likelihood of developing cancer by impacting actions like cell growth, blood vessel formation, and spread of cancer cells. This summary will concentrate on the complex network of different pathways related to physical activity and consumption of green tea. In particular, the focus of this research will be on examining how oxidative stress contributes to health and investigating the potential antioxidant properties of green tea, and the interconnected relationship between exercise and green tea in the treatment of cancer. Elucidation of these different pathways would help scientists for development of better therapeutic targets and further increase of current anticancer agents efficiency.

Keywords Cancer, Exercise, Green tea

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Introduction

Cancer is responsible for a high number of untimely deaths and presents major obstacles in the widespread efforts to improve life expectancy worldwide [1]. Significant results were unveiled in the 2022 update of data by the International Agency for Research on Cancer (IARC). A noteworthy observation is that there were 19.98 million new cases of cancer and 9.74 million cancer-related deaths reported globally [2].

Patients with cancer may undergo feelings of tiredness, sadness, worry, decreased overall well-being, and difficulties with sleeping [3–6].

Cancer therapies often result in numerous adverse effects, causing harm to various bodily systems such as the cardiovascular, endocrine, digestive, immune, nervous, and respiratory systems. Additionally, individuals may experience prolonged systemic symptoms, including fatigue, following treatment, and may even develop lymphedema [7].

It is crucial for individuals with cancer to engage in regular physical exercise [8]. The World Health Organization has categorized physical activity into two main types: aerobic and anaerobic. Furthermore, physical activity can also be divided by its level of intensity, with three distinct levels being recognized. These include light-intensity physical activity, which falls between 1.5 and 3 METs and does not considerably raise heart or respiratory rate (such as slow walking); moderate-intensity physical activity, which ranges from 3 to 6 METs; and vigorous-intensity physical activity, which consists of activities that require more than 6 METs [9].

Physical activity has been demonstrated to be substantially enhance the overall quality of life for cancer patients by boosting their aerobic capacity, positively impacting their mental well-being, reducing the adverse reactions of cancer therapy, exhaustion, and death [3, 4, 8, 10–14]. Moreover, exercise has anti-oxidative effects and could counteract with free radicals such as reactive oxygen species (ROS) and further prevent the body from the damages of these radicals as well as improvement of antioxidant capacity of the body [15]. Also, in patients with malignancies, studies showed that exercise increases telomerase integrity, improves immune response, and enhances therapeutic efficacy as well as reduction of some side effects of chemo- or radiation therapy [16–21]. The appropriate form of physical exercise should be determined based on the specific circumstances of each patient. The way in which a patient reacts to a certain physical activity may differ because of treatment side effects, age-related factors, limitations in mobility, or additional medical conditions [22]. Unless their disruptions are to the extent that it hinders their ability to exercise, individuals should partake in physical activity [23]. In addition, an individual's capacity to handle physical activity may fluctuate throughout an illness due to the inconsistency in the severity of their symptoms [7].

Suggesting more physical activity to individuals battling a serious disease may appear overly taxing or overly simplistic, since it demands the patient to dedicate both time and effort [22].

There are limitations associated with existing treatment methods, such as chemotherapy and radiotherapy, which include cancer cells developing resistance to chemotherapy drugs and negative repercussions resulting from radiotherapy [24, 25].

Throughout different periods, different cultures have encouraged the ingestion of consumable items, particularly those obtained from plants, to heal and prevent sickness. This has led to an understanding of the abilities of certain natural compounds, called phytochemicals, to act as anticancer agents [26, 27]. Nearly half of the currently available cancer treatments have been derived from natural sources [28].

Natural polyphenols are a type of organic compounds that originate from plants and are characterized by having multiple phenol units in their chemical structure (29–31). Multiple research projects have done in regard to polyphenols to explore their potential positive impacts on health, specifically in protecting against diabetes, cardiovascular issues, oxidative stress, neurodegenerative disorders, and the aging process [32]. Polyphenols have the ability to inhibit cancer through a diverse set of mechanisms such as altering signaling pathways, triggering apoptosis, and impeding cell cycle processes resulting in the elimination of cancer cells [31]. Polyphenols control the functions of enzymes that participate in the development and multiplication of tumor cells [33]. Ongoing research has linked natural polyphenols to their ability to prevent cancer due to various characteristics such as inhibiting angiogenesis, preventing metastasis, and interacting with DNA [34, 35].

Flavonoids, phenolic acid, and tannins are among the most important phenolic compounds with wide range of health beneficial effects [36–38]. These polyphenols modulate different cancer related pathways such as inflammatory and oxidative pathways and as mentioned before, eliminate cancer cells [39].

Many athletes advocate for the incorporation of dietary supplements into their regimen, as there is notable proof that they can improve overall physical performance while training [40]. Numerous studies have unequivocally demonstrated the advantageous effect on improving exercise performance of certain compounds particularly quercetin, resveratrol, and grape extract or beetroot juice-derived polyphenolic compounds [40–46]. Moreover, the antioxidant effects of both exercise and antioxidant supplements suggest that they could have synergistic effect against cancer development and progression along with

the increase of cancer treatment efficacy [47, 48]. On the best of our knowledge, there was no review article on the synergistic effects of antioxidant supplements, especially green tea, and exercise. In this review, we provide a comprehensive review about the antioxidant effects of both exercise and polyphenols as well as their anti-cancer activity and their synergistic effects against cancer by discussing about common pathways and subcellular mechanisms they used for modulation of cancer activity and progression. Also, we discussed about how these findings could be used in further studies and trials.

Polyphenol and cancer

Polyphenols are an extensive collection of 10,000 naturally occurring organic compounds present in plants, featuring a uniform framework consisting of a three-part flavan ring and numerous phenol components [49, 50]. Mostly found in an array of fruits, as well as green and black tea leaves, red wine, coffee beans, cocoa beans, and seeds, these natural compounds are highly prevalent [51]. These beneficial substances found in nature are categorized into distinct clusters, comprising of catechins, flavonoids (including flavanols, flavones, and flavanols), catechins, anthocyanins, curcuminoids, isoflavones, chalcones, and phenolic acids (Structures are clearly presented in Fig. 1) [51, 52]. The concept of utilizing polyphenols in the treatment of cancer has been previously explored. Research on the potential anti-cancer properties of various polyphenols was initiated in the later part of the 20th century and has significantly advanced since that time [53, 54]. What sets these agents apart and makes them exceptionally advantageous and intriguing is their ability to combat cancer cells through a multitude of approaches and tackle numerous distinguishing features of cancer (summarized in Fig. 2). This section presents a concise overview of the various ways in which polyphenols can influence the human body. These compounds possess the ability to function as antioxidants by either eliminating harmful free radicals or forming a protective shield against their production (Fig. 2) [49]. The primary harmful particles found within our cells which lead to the damaging process of oxidative stress are known as reactive nitrogen species (RNS) and ROS [55]. The previous process by which polyphenols function is based on the existence of hydroxyl groups bound to a benzene ring, granting the capability to transfer a hydrogen atom or electron to unpaired molecules known as free radicals [56]. The event works to maintain the stability of free radicals, ultimately stopping them from causing harm to the components of cells [56]. The B ring of polyphenols appears to be the primary factor in effectively removing peroxyl, hydroxyl, and peroxynitrite radicals. In contrast, the ability to scavenge these radicals may also be influenced by other structural components found in various types of polyphenols [56]. As an example, Flavonoids, a well-known type of polyphenols, contain a 3-OH group which involves in neutralizing the impact of free radicals [57]. As stated earlier, polyphenols possess the ability to impede the production of RNS and ROS by disrupting the function of the enzymes responsible for their creation.

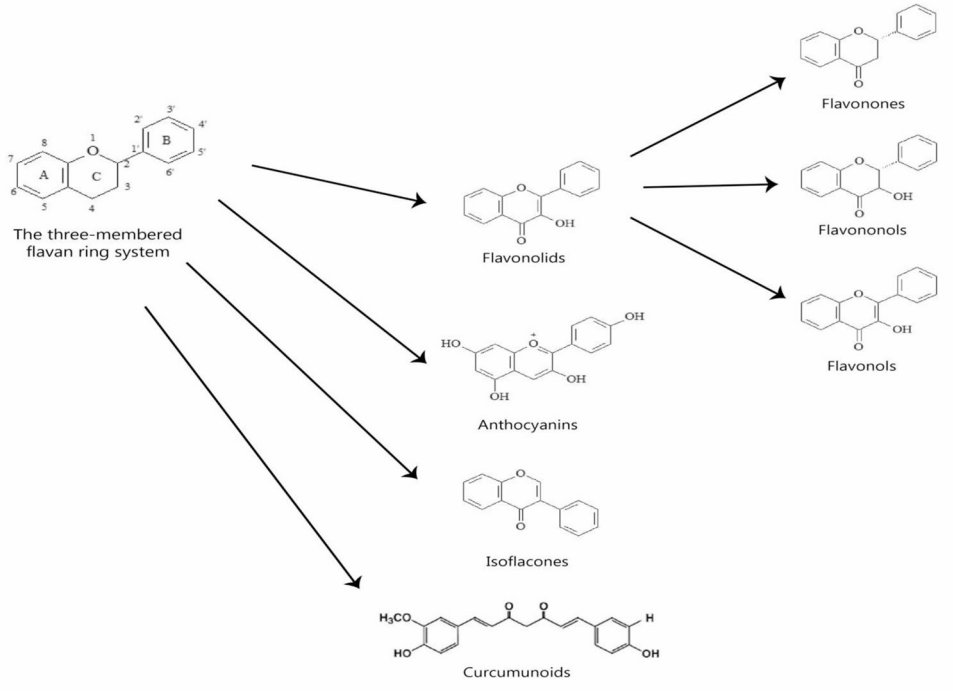

Fig. 1 A visual depiction of various forms of polyphenols. These compounds all share a similar three-membered flavan ring system

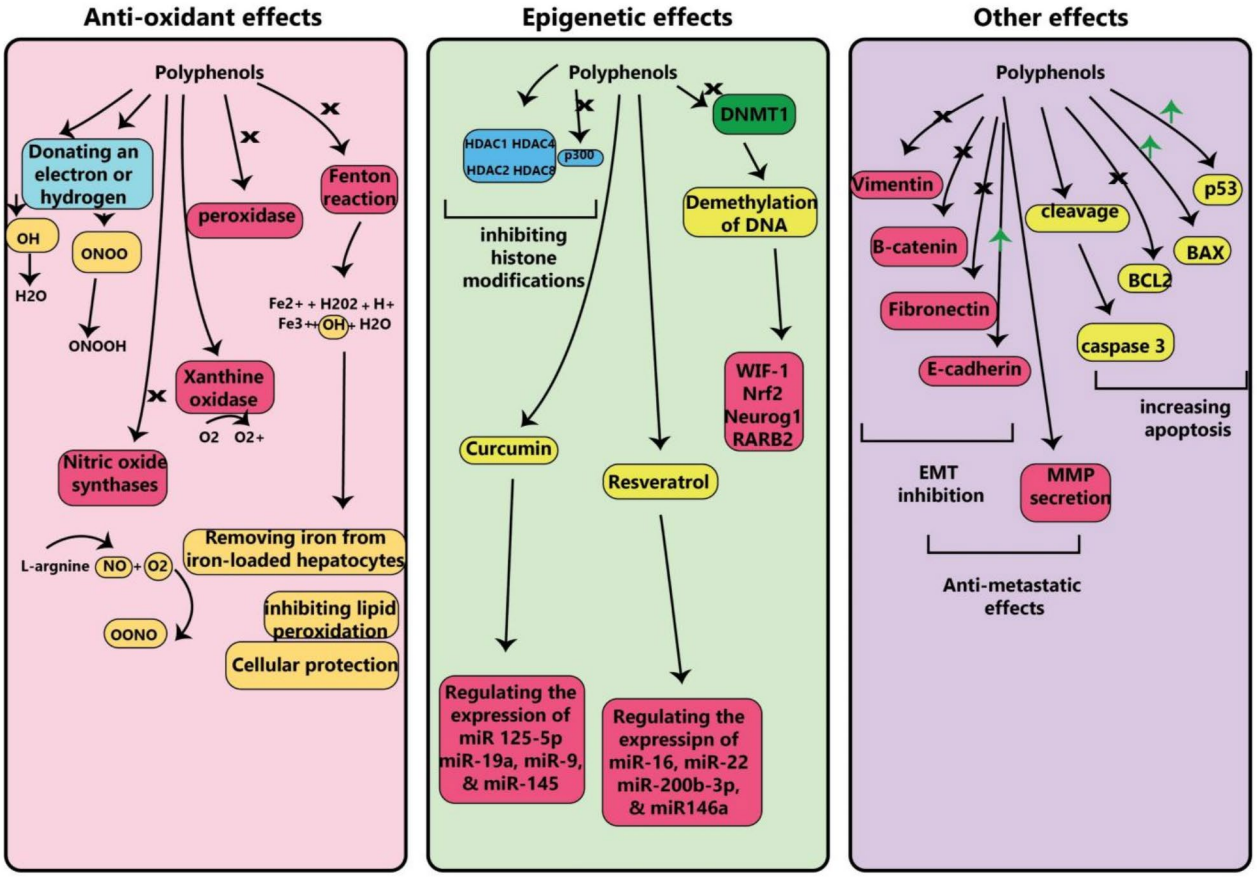

Fig. 2 The polyphenols are known to have numerous anti-cancer benefits, such as pro-apoptotic, anti-metastatic, epigenetic, and anti-oxidant effects

Several enzymes, such as xanthine oxidase (XO), nitric oxide synthases (NOS), and peroxidase, can be influenced by polyphenols through specific interactions. This can ultimately affect their level of activity [58, 59]. Xanthine oxidase plays a crucial role in producing superoxide by converting oxygen molecules [60]. Myricetin, kaempferol, quercetin, and chrysin have been thoroughly studied and found to be effective in hindering the activity of this enzyme due to their polyphenolic nature [61]. NOS is essential in producing nitric oxide in endothelial cells and macrophages, playing a pivotal role in its creation. This reactive molecule is responsible for inducing oxidative stress by elevating the levels of peroxynitrite, resulting in cellular membrane damage [59]. Anthocyanidins, a specific type of polyphenols, can inhibit the production of nitric oxide by NOS, leading to a decrease in the ability to scavenge excess NO [62]. One way in which polyphenols can be impacted by their chelating characteristics is through the reduction of peroxides by metals [63]. The Fenton reaction, also referred to as the mechanism, involves the reduction of H2O2 by Fe2+ions, resulting in the formation of a harmful hydroxyl radical that can damage cells [63, 64]. Polyphenols have the ability to act as chelating agents and create strong complexes with iron, making this an influential process that is dependent on concentration levels [63]. The interaction between various polyphenols and iron leads to multiple effects such as inhibiting the oxidation of lipids, eliminating iron from overloaded liver cells, preventing the Fenton reaction, and providing protection to cells [64–67].

Yu He and colleagues examined 126 individuals and concluded that a daily dose of 1.08 g of curcumin for a period of 10–30 days effectively enhanced the overall well-being of individuals with colorectal cancer. This positive result was attributed to the elevated levels of P53 molecules in the cancerous cells [68]. According to a research study by Cruz-correa, it was found that a daily intake of 1.44 g of curcumin effectively decreases the quantity and dimensions of polyps without causing any major adverse reactions [69].

According to Nguyen et al., the initial clinical experiment focused on resveratrol and cancer involved studying the impact of GP (which contained resveratrol and plant-derived resveratrol) that had been freeze-dried on the Wnt signaling pathway, a critical factor in the development of colon cancer, in both typical colon cancer and

colonic mucosa. After administering GP twice a day for two weeks, which contained 80 g and 0.07 mg of resveratrol, there was a noticeable reduction in Wnt target gene expression in regular tissue, but it did not impact cancerous tissue [70]. This suggests that GP or resveratrol might have a positive role in preventing colon cancer, rather than treating it once it has already developed. The impact of consuming resveratrol at doses of either 0.5–1 g per day for a period of eight days on the level of proliferation marker Ki-67 expression within colorectal tissue was examined by Patel et al. The results showed a 5% reduction in the proliferation of cancerous cells [71]. When administering 5 g/day of SRT501 (a micronized resveratrol formulation) to patients with colorectal cancer and liver metastases for 14 days, there was a notable increase in the presence of cleaved caspase-3 in the liver tissue. This indicates a higher rate of apoptosis in the cancer cells compared to those who received a placebo [72].

A team of researchers conducted a small-scale investigation on the effects of silymarin supplementation in metastatic colorectal cancer (CRC) patients undergoing treatment with FOLFIRI plus bevacizumab as their first-line therapy. The results showed that administering silymarin simultaneously has the potential to effectively decrease toxicities in this patient population [73].

Table 1 lists different polyphenols that show anticancer properties.

In relation to programmed cell death, a considerable amount of substances known as polyphenols possess the ability to cause cells to die by modifying the expression of genes involved in apoptosis. One well-studied polyphenol is curcumin, which triggers apoptosis in cancer cells through multiple mechanisms such as lowering levels of reactive oxygen species within the cell, changing the phosphorylation and activation of a signaling pathway called mitogen-activated protein kinase (MAPK), increasing the influx of calcium ions and activating a signaling pathway involving calcium and calmodulin-dependent protein kinase II (CaMKII), boosting the expression of the PI3K/Akt protein, inducing the expression of a tumor suppressor protein called p53, controlling the activity of molecules known as miRNAs, decreasing the levels of a protein called B-cell lymphoma 2 (BCL2), causing the production of a pro-apoptotic molecule known as BCL-2-associated X protein (BAX), and promoting the cleavage of an enzyme called caspase 3 [68, 74–77]. Resveratrol is a type of polyphenol that has been found to play a positive role in apoptosis, or programmed cell death, in numerous cancer types such as bladder, prostate, breast, lung, glioblastoma, colon, and ovarian

Table 1 Various polyphenols in the cancer therapy

Type of cancer	Polyphenol	Effect	Model	Ref
Breast cancer	Curcumin	Inhibited proliferation	In vitro	[91]
Head and Neck	Curcumin + Phototherapy	ATP synthase inhibition	In vitro, In vivo	[92]
Colorectal cancer	Curcumin	increased p53 molecule expression in tumor cells and consequently speeds up tumor cell apoptosis	Human	[68]
Breast cancer	Quercetin	Serve as a potential adjuvant for immune therapy	In vitro, In vivo	[93]
Hepatocellular carcinoma	Quercetin	Regulated degradation of RhoC level by targeting SMURF2	In vitro	[94]
Non-small cell lung cancer	Quercetin	Induced apoptosis	In vitro, in vivo	[95]
cancer	Resveratrol	Disrupted colorectal cancer metastasis by activating miR-125b-5p/TRAF6 signal pathway	In vitro	[96]
Colon cancer	Resveratrol	inhibited the Wnt pathway	Human	[70]
Colon cancer	Resveratrol	Inhibited cell proliferation	Human	[71]
Colon cancer	Resveratrol	Induced apoptosis	Human	[72]
Colrectal cancer	Silymarin	Reduced toxicities in mCRC patients undergoing first-line FOLFIRI plus bevacizumab	Human	[73]
Glioma	Silymarin	Enhanced the Nrf2/HO-1 pathway	In vitro	[97]
Prostate and cervical cancer	Garlic	Increased apoptosis and autophagy	In vitro	[98]
pancreatic tumor	Acetyl-l-cysteine- loaded niosomes	Increased apoptosis and autophagy	In vivo	[99]
Liver cancer	sorafenib/resveratrol PE-Gylated liposomes	Reduced cell proliferation	In vitro, In vivo	[100]
Osteosarcoma	Kaempferol	Reduced tumor growth inducing apoptosis and autophagy.	In vitro, In vivo	[101]
Colorectal cancer	Silymarin	Inhibited cell proliferation	In vitro, In vivo	[102]
Lung cancer	Kaempferol	An increase in the proportions of three types of immune cells	In vitro, In vivo	[103]
Gastric cancer	Coumarin	Modulated some lncRNAs that are related to anti-tumor response	In vitro	[104]
Prostate cancer	Benzylidene coumarin derivatives	Increased apoptosis and autophagy	In vitro	[105]

cancer [78]. In specific, resveratrol has been found to effectively inhibit the growth and movement of ovarian cancer SKOV3 and A2780 cells. Additionally, it disrupts the process of glycolysis and triggers cell death. Research provides proof that administration of resveratrol leads to decreased activation and expression of mTOR, a kinase downstream of AMPK, while also increasing caspase-3 and AMPK activation and expression. Moreover, experiments on live subjects have demonstrated that resveratrol can impede the development of ovarian cancer and its spread to the liver, as observed in a mouse xenograft model [79]. Metastasis refers to a complex set of simultaneous processes that enable cancerous cells to move away from their original location and spread to different areas of the body, ultimately leading to greater cancer mortality [80]. The process of metastasis is influenced by microenvironmental factors like stromal fibroblasts and immune cells that have an impact on the tumor cells. This process is facilitated by cellular movement, lack of oxygen, epithelial-mesenchymal transition (EMT), and formation of new blood vessels, which are the main mechanisms that aid in the infiltration of cancerous cells [78]. Based on studies, it has been found that the management of metastasis heavily relies on the involvement of matrix metalloproteinases (MMPs), TGF-β, and TP53 [78]. Polyphenols have demonstrated their effectiveness in influencing various stages of this procedure. An example of this is how curcumin impacts the proteins involved in epithelial-mesenchymal transition (EMT), such as vimentin, fibronectin, β-catenin, and E-cadherin, as well as the genes expressed in cancer stem cells, namely Oct4, Nanog, and Sox2. As a result, this reduces the metastatic abilities of cancer cells [81]. Quercetin and its derivatives have proven to be highly efficient in preventing the process of EMT, inhibiting the secretion of MMP, suppressing NF-kappaB levels, and curbing the migration of cancer cells, effectively inhibiting their metastasis [78]. Resveratrol was found to have anti-metastatic effects by reversing EMT through the AKT/GSK-3β/Snail signaling pathway and reducing the levels of MMP-2 and 9, as well as Smad2 and 3 [82]. The initiation, development, and resistance to treatment of tumors originate from disruptions and irregularities in epigenetic processes [83]. Changes to the DNA structure known as DNA methylation, modifications to the proteins called histones, changes in the organization of chromatin or nucleosomes, and regulation of small RNA molecules (miRNA) are all examples of epigenetic modifications that play a role in various aspects of cancer [83]. Curcumin, a type of plant-based compound, is particularly effective in preventing these alterations and aiding in the control of cancer cells. There is a group of enzymes called histone deacetylases (HDACs) that are responsible for silencing certain genes by removing acetyl groups from histones. Curcumin is known to inhibit the activity of HDACs, thereby preventing their gene silencing effects [84]. Curcumin has the ability to block these enzymes and control the growth and death of different types of cancer cells [85]. Curcumin is capable of effectively inhibiting HDAC1, HDAC2, HDAC3, HDAC4, and HDAC8 [86, 87]. One type of enzymes that have been linked to the progression of cancer cells are known as histone acetyltransferases (HATs). One specific enzyme in this class, called p300, has been speculated by certain studies to be suppressed by curcumin in either a direct or indirect way, impacting cancer cell growth and viability [88, 89]. Moreover, curcumin has been found to inhibit the process of DNA methylation in the promoter region of numerous genes involved in cancer, such as Wnt inhibitory factor-1 (WIF-1), Fanconi anemia group F protein (FANCF), nuclear factor erythroid 2-related factor 2 (Nrf2), Neurogenin 1 (Neurog1), and retinoic acid receptor beta 2 (RARβ2). This is achieved by reducing the levels of DNMT1 [78]. Curcumin has been shown to have an impact on several miRNAs involved in various types of cancers such as nasopharyngeal, breast, ovarian, and leukemia. Some of these miRNAs include miR-125-5p, miR-19a, miR-9, and miR-145 [90]. In addition to its effects on miR-200, miR-122-5p, miR-20, and miR-633, resveratrol has the capability to alter other polyphenols as well [78]. Quercetin has been found to affect the regulation of several miRNAs, including miR-16, miR-22, miR-200b-3p, and miR-146a, within cancer cells [78].

Green tea and cancer

Green tea has a palpable impact on inhibiting tumors through its catechin-regulated properties, with ECGC being the most influential (Table 2). The most powerful inhibitory activity is possessed by EGCG, followed by EGC, ECG, and EC. The anti-tumor activity is further enhanced when catechins are combined, leading to a stronger effect than EGCG alone. Based on the findings of Fujiki et al., it has been established that green tea catechins (GTCs) possess a wide range of properties that effectively counteract genetic mutations and inhibit the development of different cancer including breast, esophageal, colorectal, prostate, intestinal, gastric, pulmonary, and liver malignancies. This section will delve into several of these effects in detail [106].

In order to conduct investigations on living organisms, researchers utilized xenograft tumor models which involved the subcutaneous injection of human tumor cells into nude mice. The tumors gradually developed as time goes by, depending on the concentration of cells that were injected. The mice received EGCG in different ways, such as through injections into their peritoneal cavity, through their water or food intake, or through oral gavage. The concentration of catechins in these treatments varied according to the specific design

Table 2 Various studies on anti-tumor effects of green tea

Type of cancer	Green tea formulation	Effects	Model	Ref
Melanoma	EGCG	Induced cell death	In vitro, In vivo	[147]
Prostate cancer	Curcumin + Ginger + GT + chamomile	Increased apoptosis	In Vitro	[148]
	Arctigenin + GT + Quercetin	Highly effective in prostate cancer chemoprevention	In vivo	[149]
	GT + Quercetin	No liver toxicity was observed	Human	[150]
Breast cancer	Curcmin + GT	Inhibited tumor growth	In vitro	[151]
	EGCG	Inhibited tumor growth	In vitro, In vivo	[152]
Lung cancer	Niosomes –EGCG	Increased apoptosis	In vitro	[153]
	GT	Not appear to offer protective benefits against lung cancer at a population level	Human	[154]
Digestive cancer	GT	-	Human	[133]
Colorectal cancer	EGCG	Inhibited cell proliferation	In vitro, In vivo	[155]
	EGCG	Increased apoptosis and autophagy	In vitro	[156]
pancreatic cancer	GT	Repressed the expression of NF-κB	In slico, in vitro	[157]
Head and Neck	EGCG	Epigenetically silenced tumor suppressors to inhibit the growth of HNSCC cells	In vitro	[158]
Liver cancer	GT	An inverse association between cumulative consumption of tea, especially green tea and the risk of primary liver cancer	Human	[159]
Ovarian cancer	EGCG	Targeted intracellular transducing events that regulate the acquisition of an invasive CSC phenotype.	In vitro	[160]
Bladder cancer	EGCG	Inhibited proliferation, increased autophagy	In vitro, In vivo	[161]
Osteosarcoma	EGCG	Reduced the stemness and abate drug-resistance of osteosarcoma cells	In vitro	[162]

of each experiment. Even though the specific amount of GTCs given may differ depending on the type of cancer cells being researched, a relatively unchanging range of EGCG concentrations (5-200 μM) was primarily utilized. It has been shown through various research that GTCs effectively decrease the activity of telomerase in various cell lines, cause cell demise, halt the progression of cell cycles, and have a favorable effect on cell receptors by attaching to receptor tyrosine kinases (RTKs) [107]. GTCs possess the ability to both cancel out and produce reactive oxygen species [108]. GTCs have also shown to have prooxidant properties which have a important function in triggering programmed cell death and hindering the growth of cancer cells [109]. GTCs possess effective demethylating properties and can function as modifiers of epigenetic processes, altering the structure of histones and regulating the transcription of miRNAs. This allows for the epigenetic manipulation of cellular functions and the repression of oncogene expression [110, 111]. Figure 2 provides a broad understanding of the different ways in which GTCs impact and interact with cancer-related mechanisms.

Hepatocellular carcinoma (HCC) is acknowledged as one of the most intense types of cancer across the world, primarily due to its highly aggressive characteristics and its specific location within the liver [112]. Many studies and trials have comprehensively evaluated the effectiveness of green tea catechins in preventing and treating HCC. Currently, it has been established that EGCG can hinder the growth of liver cancer cells by triggering programmed cell death, regulating the process of self-digestion, and functioning as a substance that prevents the development of new blood vessels [113]. Several laboratory experiments have demonstrated that EGCG can restrict the proliferation of human liver cancer cells by obstructing the activation of the tyrosine-kinase receptor insulin-like growth factor 1 receptor (IGF-1R) and triggering apoptosis through the activation of Caspase-9 and −3. EGCG also suppresses the expression of cyclooxygenase-2 (COX-2), lipogenic enzymes and Bcl-2, while stimulating the levels of VEGF and its receptor (VEGFR-2), as well as factors associated with cellular survival like ERK1/2 and NF-κB. Additionally, EGCG stimulates AMPK (adenosine monophosphate-activated protein) and induces an growth in ROS-mediated membrane permeability [114]. GTCs hinder the proliferation of hepatocyte stem cells, activation of AMPK protein within the liver, and control of epigenetic manifestation [113, 115]. Furthermore, by inhibiting the activity of the IGF/IGF1R or VEGF/VEGFR signaling pathway, EGCG effectively hindered the growth of HCC xenografts [116, 117].

An estimated 25% of deaths attributed to cancer are attributed to lung cancer, which surpasses the combined number of deaths from breast, colon, and prostate cancers annually [118]. Several findings are currently accessible regarding the impact of consuming GTCs in preventing chemically induced lung tumors in genetically modified rodents. GTCs have the potential to not only treat or prevent lung cancer, but also to hinder essential protein kinases, regulate molecular communication, and regulate the activation of specific genes including Bcl-2, cyclin D1, p21, Bax, p53, VEGF, Caspase-3-7-9 and COX-2 [119–121], . Lu et al. confirmed that GTCs were better at inhibiting lung cancer growth compared to caffeine in a research project involving 4-(methylnitrosamino)-1-(3-Pyridyl)-1-Butanone (NNK)-induced A/J mice. The mice were fed a liquid diet containing either 0.5% Polyphenon E (which contains 65% EGCG) or 0.044% caffeine for a duration of 52 weeks [122]. Contrary to popular belief, there have been claims that EGCG has the capacity to completely inhibit the process of phosphorylation [122]. In a similar manner, when 50 and 100 μM of EGCG were used to treat H1299 and Lu99, two types of non-small cell lung cancer (NSCLC), it was observed that the spread of lung cancer cells was inhibited. It is possible that this occurred because the process of epithelial-mesenchymal transition (EMT) was suppressed, and the activation of focal Adhesion Kinase (FAK) and matrix metalloproteinases-9 (MMP-9) were suggested as potential reasons for this suppression [123–125]. GCG has been studied across a range of concentrations (0–20 μM) to examine its impact on H1299 cells. It has been observed that EGCG has a high propensity to attach itself to G3BP1, a rat sarcoma-GTPase activating protein and a src Homology-3 domain-binding protein. This interaction causes the synthesis of ROS, which ultimately induces the apoptosis of cancerous cells [126, 127]. Studies using EGCG concentrations ranging from 10 to 100 μM have exhibited noticeable impacts on the development and dissemination of lung cancer by inhibiting various protein receptors, impeding nicotine-induced movement, and altering the differentiation of NSCLC cells [128, 129]. Similarly, administration of EGCG at varying concentrations (ranging from 0 to 120 μM) has been demonstrated to interfere with the levels of telomerase enzyme and the functions of Caspase-3 and −9 in NSCLC treatment [130].

A study aimed to conduct a quantitative examination of the correlation between green tea intake and the likelihood of developing esophageal cancer (EC), considering the contentious findings presented by earlier meta-analyses [131]. The relationship between dosage of green tea and EC risk was summarized using odds ratios (ORs). Fourteen studies with a combined total of 5057 EC cases and 493,332 participants were included. The dose-response analysis revealed a summary odds ratio of 1.00 (95% CI, 0.95–1.04; I2=77%) for every 1 cup per day increase in green tea intake. No evidence of a nonlinear relationship between tea consumption and the risk of EC was found (P=0.71 for nonlinearity). In the category of gender, the collective odds ratio for every 1 cup/d increase in green tea was found to be 1.03 (95% CI, 0.95–1.11, I2=67%) for males and 0.79 (95% CI, 0.68–0.91; I2=0%) for females. Unlike previous research, the latest dose-response analysis indicates that there is no correlation between green tea consumption and the likelihood of developing EC. On the other hand, there is a possibility of a shielding influence of green tea specifically in females. It should be noted that their final findings may have been affected by the restricted number of studies and potential prejudice, including inadequate evaluation of green tea dosage and biased selection of case-control studies. In order to obtain more accurate evidence, it is important to conduct a greater number of larger, well-designed prospective studies, particularly in regards to women and in various regions such as the United States and Europe [131].

Kim and colleagues conducted an umbrella review with the intention of clarifying and establishing the links between tea consumption, specifically green and black tea, and different types of cancer [132]. A total of 64 observational studies (case-control or cohort), representing 154 effect sizes on the incidence of 25 different types of cancer, were analyzed. Of these, 43 (27.9%) showed statistically significant results in 15 different types of cancer. Combining multiple studies focused on a specific type of cancer, a total of 19 outcomes across 11 different types of cancer indicated a notable link with a reduced likelihood of developing gastrointestinal tract organ cancer (including oral, gastric, colorectal, biliary tract, and liver cancer), breast cancer, gynecological cancer (such as endometrial and ovarian cancer), as well as leukemia, lung cancer, and thyroid cancer. Conclusive findings indicated a proven decrease in the likelihood of developing oral cancer in groups that consume tea (OR=0.62; 95% CI: 0.55, 0.72; P value<10−6). There were also hints of a potential link between tea consumption and reduced risks for biliary tract, breast, endometrial, liver, and oral cancer, as seen in the suggestive evidence. Overall, it can be concluded that drinking tea has a positive impact on preventing certain forms of cancer, specifically oral cancer. However, further research must be conducted using proper methods and accounting for potential biases in order to fully understand the extent of tea's beneficial effects [132].

Prior research has revealed that incorporating green tea into one's diet is linked to a decrease in the occurrence of digestive system cancers (DSCs) [133]. The potential correlation observed might potentially be

attributable to outside variables. The findings indicated that there is no evidence to suggest a causal relationship between tea consumption and the risk of digestive system cancers among the European population. The odds ratios (ORs) for esophageal cancer (OR = 1.044, 95% CI 0.992–1.099, $p = 0.096$), stomach cancer (OR = 0.988, 95% CI 0.963–1.014, $p = 0.368$), colorectal cancer (OR = 1.003, 95% CI 0.992–1.015, $p = 0.588$), liver cancer (OR = 0.996, 95% CI 0.960–1.032, $p = 0.808$), and pancreatic cancer (OR = 0.990, 95% CI 0.965–1.015, $p = 0.432$) all had non-significant results. Therefore, it can be concluded that tea intake is not associated with an increased or decreased risk of these types of cancers in the European population. The findings from various techniques such as the MR-Egger regression, MR-PRESSO analysis, and other methods provided additional support for the validity of the conclusion. Likewise, there was no considerable correlation observed between the intake of green tea and the development of DSCs among individuals of East Asian descent. After taking into account smoking and alcohol use ($P > 0.05$), it can be concluded that this connection has no significance. The findings of their research demonstrate that there is no causal link between genetically predicted consumption of green tea and development of DSCs among European and East Asian individuals [133]. In an observational study on women with breast cancer conducted by Inoue and colleagues, they found significant reduction of breast cancer risk among women with low folate intake [134]. In a dose response meta-analysis conducted by Chen and colleagues, they found inverse correlation between consumption of green tea and risk of colorectal cancer development [135]. However, despite the proven effects of green tea extract and polyphenols in vitro and in vivo, some clinical studies did not show any effects for green tea in reduction of cancer development risk [136–138]. Thus, further studies with larger population along with conducting clinical trials would be needed for better clarification of the role of green tea on cancer.

Table 2 provides a comprehensive overview about green tea and its effects on different cancer types.

One of the important aspects of green tea that is often overlooked is its low bioavailability [139]. Green tea polyphenols, especially EGCG, have poor intestinal absorption. Only a small fraction of the catechins is absorbed into the bloodstream, with the majority being excreted in urine. This is because catechins are poorly soluble in water and do not readily cross cell membranes in the gut [139–141]. Once in the bloodstream, green tea polyphenols have a relatively short half-life, which means they are rapidly cleared from the body. This makes it difficult for green tea to exert prolonged effects, even if consumed in large quantities [142, 143].Some of these controversial results about the effects of green tea on different cancers could be explained by the low bioavailability of this agent as discussed above. Recent studies have been conducted to improve bioavailability by different techniques including liposome- and nano-encapsulation as well as nano-formulation of these compounds [144, 145]. As an example, Golpour and colleagues found that green tea mediated silver nanoparticles would not only enhance anti-cancer effects but also reduced the cytotoxic effects of these agents [146].

Figure 3 in brief, GTCs have been found to effectively combat cancer through multiple signaling pathways and molecular targets.

Exercise and cancer

The degree to which physical activity can reduce the likelihood of developing cancer differs depending on the particular type of cancer (Table 3). While no direct link has been established between exercise and cancer risk, studies indicate that adopting healthier lifestyle habits can decrease the likelihood of developing the disease. For instance, regularly engaging in exercise for 3 to 5 h per week can decrease the chances of cancer, with women reaping the most benefits from vigorous activities such as intense household chores and dancing, which have been discovered to be particularly effective in reducing the risk of breast cancer [163]. According to research findings, engaging in physical activity was found to notably diminish the likelihood of developing breast cancer by 15–20% and colorectal cancer by 24% [164]. A study has demonstrated that participating in any form of physical movement or exercise can lessen the chances of developing breast cancer among postmenopausal females and also involve in preventing abnormal function of the autonomic nervous system in individuals diagnosed with breast cancer [165, 166]. Engaging in physical activity results in lifestyle modifications that greatly affect the occurrence of colorectal cancer. After analyzing 126 research studies examined on the effects of exercise on colorectal cancer, it was found that individuals who engage in more physical activity have a 19% lower likelihood of developing the disease compared to those who are less active [167]. After evaluating the findings of 10 cohort and 12 case-control studies on gastric cancer, it was determined that individuals who participated in more vigorous physical exertion were at a reduced risk of 19% for developing the specified condition of disease compared to those who had lower levels of physical activity [168]. Research has shown that being overweight is considered a major risk factor for developing endometrial cancer [169].

Therapies for cancer, including chemotherapy and targeted therapy, can lead to various negative effects such as fatigue, cognitive impairment, depression, reduction in bone and muscle mass, and even detrimental effects on

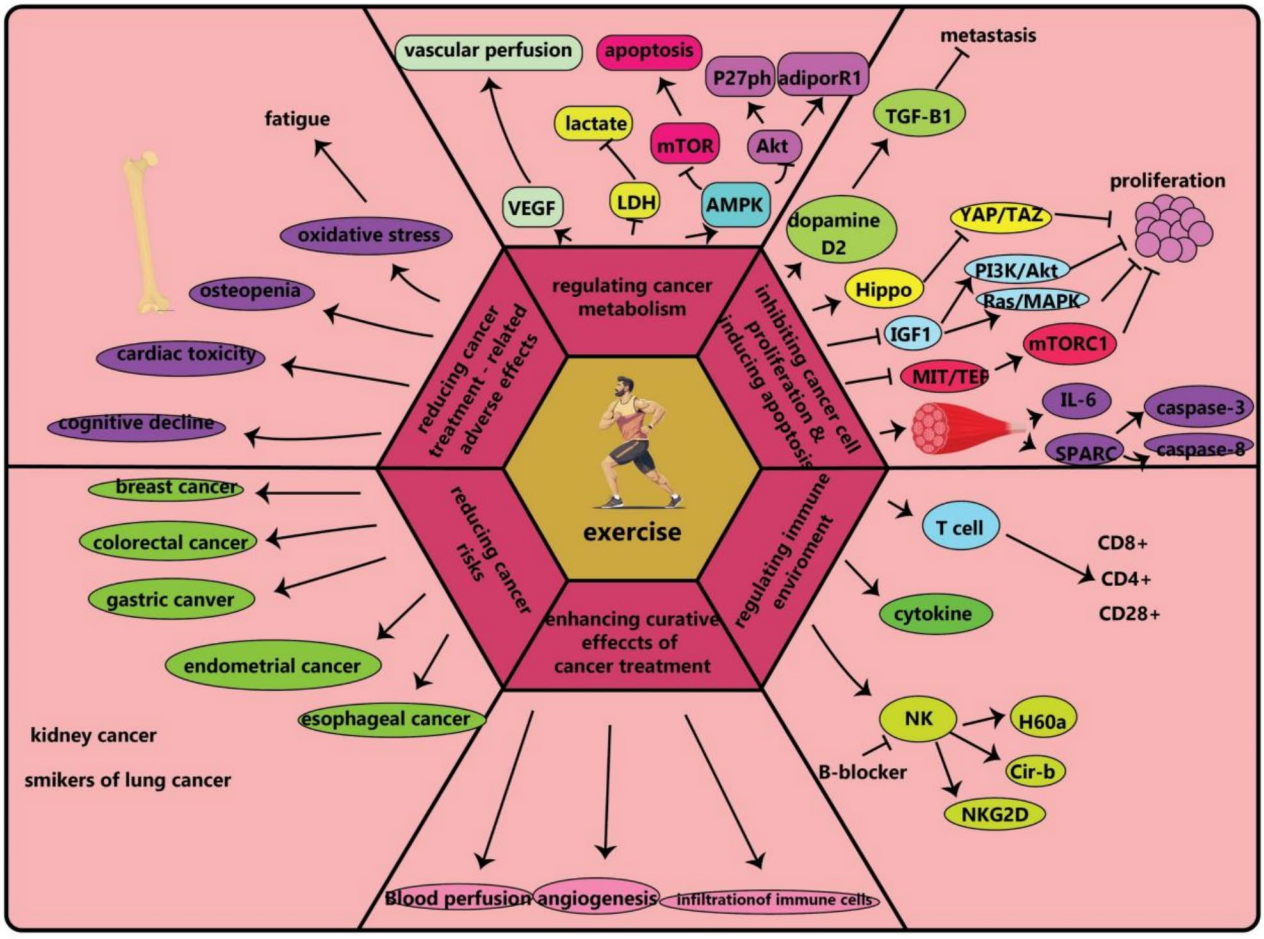

Fig. 3 Physical exercise plays multiple important roles in both preventing and treating cancer. These roles encompass mitigating negative effects associated with cancer treatment, amplifying the effectiveness of cancer treatment, and decreasing the likelihood of developing cancer. These beneficial effects are achieved through various mechanisms including inhibiting the growth of cancer cells, promoting cell death, regulating cancer cell metabolism, and modulating the immune system to create an optimal environment for fighting cancer. adiporR1 = adiponectin receptor 1; Akt = protein kinase B; AMPK = AMP-activated protein kinase; β-blocker = beta-adrenageic receptor block; CD = cluster of differentiation; Clr-b = C-type lectin-related protein B; D2 = dopamine receptor 2; H60a = the minor histocompatibility antigen 60; Hippo = serine/threonine-protein kinase hippo; IGF1 = insulin-like growth factor-1; IL-6 = interleukin 6; LDH = lactate dehydrogenase; MiT-TFE = microphthalmia/transcription factor E; microphthalmia/transcription factor E; mTOR = mammalian target of rapamycin; mTORC1 = mammalian target of rapamycin complex 1; NK = natural killer; NKG2D = natural killer group 2 member D; P27ph = cyclin-dependent kinase inhibitor phosphorylation; PI3K/Akt = phosphatidylinositol 3 kinase/protein kinase B; Ras/MAPK = rat sarcoma/mitogen-activated protein kinase; SPARC = secreted protein acidic and rich in cysteine; T cell = thymus dependent lymphocyte; TGF-β1 = the kinase phosphorylation and transforming growth factor-β1; VEGF = vascular endothelial growth factor; YAP/TAZ ph = phosphorylation of yes-associated protein/transcriptional co-activator with (postsynaptic density-95 (PSD-95), discs-large, zona occludens 1 (ZO-1))PDZ-binding motif

the heart. The negative responses could potentially result in negative impacts on one's quality of life and treatment outcomes. Furthermore, undesirable responses can adverse the difficulty cancer patients experience in adhering to or enduring their treatment, ultimately affecting their overall lifespan. Numerous research has shown that consistently engaging in physical activity can effectively ward off certain negative side effects of treatment. The effect of exercise training on cancer and its corresponding treatment can have an effect on the illness itself, as well as physiological and psychological outcomes [170]. In a comprehensive clinical trial examining the effectiveness of exercise as a form of therapy, 301 breast cancer patients receiving chemotherapy were categorized into separate groups: a high-intensity group (High) performing about 60 min of aerobic exercise, a standard group performing 30 min of aerobics, and a combined group completing 60 min of exercise that included both resistance training and aerobics. The study revealed that the exercise program had significantly greater advantages for the combined group, resulting in significantly better muscle strength compared to the other two groups. In contrast to the standard group, the combined group showed considerable enhancements in endocrine symptoms, whereas the exercise program implemented for the High group had various advantageous impacts on

Table 3 Different studies on exercise and cancer

Type of cancer	Type of Exercise	Duration	Effect	Ref
Breast cancer	Aerobic	150 min/week	Reduced fatigue, improved survival rates	[212]
Colon Cancer	Resistance	3 times/week	Increased muscle mass, improved quality of life	[213]
Prostate Cancer	Aerobic + Resistance	120 min/week	Improved cardiorespiratory fitness	[214]
Lung Cancer	Yoga	60 min/day	Reduced anxiety, improved lung function	[215]
Ovarian cancer	Walking	30 min/day	Enhanced mood, reduced inflammation	[216]
Pancreatic Cancer	Low-Intensity	45 min/day	Improved glucose metabolism	[217]
Bladder Cancer	Swimming	90 min/week	Improved cardiovascular health	[218]
Kidney Cancer	Resistance	2 times/week	Increased strength, reduced depression	[219]
Skin Cancer	Moderate Aerobic	30 min/day	Enhanced skin barrier function, improved mood	[7]
Breast cancer	Dance	3 times/week	Improved flexibility, reduced fatigue	[220]
Leukemia	Light Aerobic	150 min/week	Improved immune function	[221]
Lymphoma	Walking	30 min/day	Reduced pain, improved energy levels	[222]
Multiple Myeloma	Resistance	2 times/week	Increased bone density	[223]
Thyroid Cancer	Aerobic	150 min/week	Improved thyroid function	[224]
Head and Neck Cancer	Yoga	60 min/day	Improved swallowing function, reduced anxiety	[225]
Endometrial Cancer	Moderate Aerobic	90 min/week	Reduced risk of recurrence	[226]
Brain Cancer	Light Aerobic	150 min/week	Enhanced cognitive function, reduced fatigue	[227]
Melanoma	Resistance	3 times/week	Increased muscle strength, reduced stress	[228]
Hodgkin's Lymphoma	Walking	30 min/day	Improved cardiovascular health	[229]
Non-Hodgkin's Lymphoma	Light Aerobic	150 min/week	Better immune response, enhanced affect	[230]
Testicular Cancer	Mixed Modalities	120 min/week	Enhanced overall fitness, reduced anxiety	[231]
Soft Tissue Sarcoma	Light Aerobic	150 min/week	Improved mobility, reduced treatment side-effects	[232]
Oral Cancer	Yoga	60 min/day	Reduced oral pain, improved quality of life	[233]

breast cancer such as ameliorated endocrine symptoms, improved body pain and overall body composition as assessed by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [171]. Patients diagnosed with cancer typically opt for conventional therapies like surgery, radiation, chemotherapy, targeted therapy, and immunotherapy, which have been proven to effectively suppress the progression of the disease. Recent experiments have additionally shown the positive impact of incorporating physical exercise into the treatment regimen, as it not only mitigates the harmful effects of the treatments, but also enhances their efficacy [172].

When it comes to the initial course of action for treating the majority of solid cancers, the most prevalent approach is complete removal of malignant tumors. Research has indicated that engaging in physical exercise can enhance muscle weakness experienced post-surgery by patients, leading to a decrease in both complications and the duration of hospitalization following surgery [173]. The spread and migration of cancer cells during surgery has acknowledged as a significant contributor to a decrease in the effectiveness of the procedure, resulting in metastasis after the surgery and negatively impacting the forecast and chances of survival for patients [174]. Physical activity can enhance the effectiveness of radiotherapy in treating cancer. Studies have revealed that implementing resistance workouts in conjunction with radiotherapy can greatly enhance the strength and density of spinal bones affected by cancer [175]. According to recent studies, radiotherapy has been shown to significantly boost the ability of natural killer (NK) cells to enter and stimulate the immune system. Physical activity training on its own does not have any effect on the staining and genetic expression of NK1.1, killer cell lectin-like receptor K1 (KLRk1), or interleukin-2 receptor β (IL-2Rβ), the levels do rise with an increase in radiotherapy and are further improved when exercise and radiotherapy are combined [176]. The combination of NK cell activation and physical activity yields a beneficial impact on overall systemic circulation. Furthermore, exercise can greatly improve cancer cell death and augment the anti-tumor efficacy of radiotherapy [177]. Having adequate blood perfusion permits the effective transportation of cytotoxic drugs and immune cells to the interior of the body. Engaging in physical activity improves blood perfusion and increases the overall body temperature. Similarly, the precise immune response triggered by immunotherapy must be released in order to function effectively. Studies indicate that the process of hindering the programmed cell death-1 axis could potentially be triggered by a particular immune response that is released to target a specific type of cancer, ultimately resulting in a desired therapeutic outcome [178]. The process of programmed cell death-1 has the ability to enhance the presence of immune cells within cancerous cells and can be effectively controlled through physical activity prior to treatment. Numerous research studies have demonstrated that cancer patients exhibit a

higher likelihood of positive treatment outcomes when there is a swift influx of immune cells during the treatment process [179]. Furthermore, when exercise is combined with chemotherapy, it has significantly extended the period of time in which the growth of breast cancer is delayed. Exercise has proven to decrease the presence of low levels of oxygen, elevate the density of tiny blood vessels, promote better blood flow, and restore a more regular and functional network of blood vessels within the cancerous area [180]. Numerous research studies have consistently provided the positive effects of engaging in physical activities enhancing the healing results of chemotherapy. Research has determined that subjecting pancreatic duct cancer-ridden mice to a forced exercise regimen with 60–70% exertion is more effective in suppressing tumor growth than keeping them inactive. However, this suppressive effect was diminished in mice with a mutated platelet reactive protein 1 gene [181]. The findings suggest that a combination of exercise and chemotherapy can be effective in treating cancer by promoting a return to normal blood vessel function through improved blood flow. This is in contrast to the current use of anti-angiogenic drugs for treating colon cancer. Further research should be conducted to analyze the effects of physical activity on angiogenesis and blood flow. Overall, therapeutic benefits in the context of anti-angiogenic therapy. As shown in Fig. 3, exercise serves various functions in the management of cancer, thus incorporating physical activity into cancer treatment holds immense importance.

Taken all together, most studies suggested the aerobic exercise for different types of the cancer (Table 3) while there are controversies on the best intensity of exercise against cancer as it is varied by the person, its cancer type, the stage of the cancer, and several other factors. But the effects of exercise, regardless of its type, have been proven against cancer.

Numerous research projects have established that physical activity can partially impede the growth of cancer cells. Specifically, the proliferation of 3 negative breast cancer cells was reduced when they were subjected to exercise-induced serum as part of their culture condition [182]. According to the research, the capacity of triple-negative breast cancer cells to form colonies in a soft agar environment was notably decreased [182].

The effect of exercise intensity on suppressing the growth of cancer cells has been a topic of frequent research. Studies using animals have shown that moderate-intensity exercise can effectively curb the proliferation of cancer cells and trigger programmed cell death, thus highlighting the protective advantages of moderate-intensity exercise [183, 184]. The Ki-67 antigen level rises as the intensity of exercise is amplified [185]. Engaging in intense physical activity can demonstrate a harmful impact on the development of cancer [186]. Recent studies have found that low-intensity physical activity does not impede the growth of cancer cells, whereas moderate and high-intensity exercise can. These exercise intensity levels encompass those below the recommended amount for cardiovascular wellbeing (less than 35% of maximum intensity) and also 70% of the maximum intensity recommended for improving cardiovascular health [187, 188].

What is the reason for this suppressive impact? Research has indicated that engaging in moderate swimming can enhance dopamine levels in the prefrontal cortex, serum, and cancerous tissues in mouse models. The binding of dopamine to dopamine receptor 2 (D2) regulates kinase phosphorylation and TGF-β1 through extracellular signal regulation, which in turn suppresses cancer cell growth and prevents the development of lung metastases [189]. The Hippo signal is closely connected to the growth of cancer cells and other fundamental biological functions, serving as the primary mechanism for suppressing the development of cancer [190]. The process of adding a phosphate group can trigger the Hippo signaling pathway and impede the activity of two similar transcription factors: the Yes-Associated Protein and the Transcriptional Co-activator with PDZ-binding Motif. This modification separates YAP/TAZ from the cellular cytoplasm and hinders the expression of target genes involved in promoting cancer cell growth and survival [191]. On the other hand, the Hippo pathway is suppressed by the majority of G-coupled receptor agonists. Furthermore, sudden physical activity triggers the release of catecholamine, which activates the Hippo pathway via the β-adrenergic receptor and ultimately results in the inactivation of YAP/TAZ [190, 192]. The level of catecholamine significantly rose during acute exercise, but returned to its baseline level shortly after exercise ended. The ongoing increase in stress-related factors, such as catecholamine, was linked to the progression of cancer [192]. As a constituent of the group of proteins known as Interleukin 6 (IL-6) superfamily, Leukemia inhibitory factor has been found to play a crucial role in hindering the spread of breast cancer. Its functions as an inhibitor have been linked to the regulation of Hippo and YAP signals [193]. Extensive research has revealed that exercise plays a crucial role in weight management by effectively addressing key factors such as diminishing cancer-related gene activity, bolstering the body's ability to eliminate unstable oxygen molecules, and altering hormone levels associated with cancer development [194].

Extensive research on managing weight through physical activity has revealed that the primary factors responsible for repairing DNA include the suppression of cancer gene expression, increased capacity to eliminate reactive oxygen species, and alterations in hormone levels associated with cancer development. Numerous studies

have demonstrated that exercising to maintain a healthy body weight leads to modifications in hormone levels, which play a favorable role in cellular growth. One such hormone, insulin-like growth factor (IGF), influences cell division and prevents cell death, as well as impacts the multiplication and specialization of cancer cells [195]. Research has demonstrated that among menopausal females, engaging in a 6-month walking regimen results in a substantial decrease in levels of IGF-1 and IGF-3 compared to females who do not partake in exercise [196]. IGF binding protein-3 (IGFBP-3) plays a crucial role in controlling the process of cell division and the functions of insulin-like growth factor (IGF). However, in breast cancer cells, the ability of IGFBP-3 to prevent cell death is impaired [197]. Research has indicated that when mice with skin cancer lose weight, their levels of IGF-1, insulin, and leptin decrease. This results in a reduction of related signaling pathways, such as Ras-MAPK proliferation and AKt-PI3K anti-apoptosis, both of which are known to promote cancerous growth. IGF-1 also targets PKB/Akt and the AMP-activated protein kinase pathway, ultimately leading to the inactivation of cell cycle and suppression of cancer [198]. Research has extensively investigated the impact of physical activity on the growth of cancer in both human subjects and different animal species that possess various types of malignant tumors. Findings have revealed that engaging in exercise can effectively impede the escalation of the microphthalmia/transcription factor E (MiT/TFE) gene in individuals diagnosed with renal cell carcinoma, pancreatic ductal carcinoma, and melanoma. Consequently, the proliferation of cancer cells is successfully suppressed [199]. Physical activity can greatly reduce the growth of cancer cells due to the presence of mammalian target of rapamycin (mTOR) targets, which are found in various parts of the body such as the liver, brain, fat, and skeletal muscle [200]. Physical activity can additionally trigger programmed cell death, known as apoptosis, in cancer cells located within the skeletal muscle. Further processes associated with this phenomenon are outlined below. Research has found that following chemotherapy treatment, mice experience significant muscle wasting, while exercise can effectively hinder this muscle loss by restoring drug-induced autophagy or cell division and restoring proper functioning of the mitochondria [201]. During physical activity, the skeletal muscle generates its own IL-6, leading to a decrease in both the level and creation of TNF-α. At the same time, IL-6 can help relieve cancer-related fatigue [202]. Through studies with mice and individuals suffering from colon cancer, it has been found that engaging in consistent physical activity triggers the skeletal muscles to generate secreted protein acidic and rich in cysteine (SPARC). This in turn leads to enhanced decomposition of caspase-3 and caspase-8, resulting in increased cell apoptosis and a hindrance in the progression of colon cancer [203]. Lactic acid is a crucial byproduct of the glycolysis pathway. In cancer cells, the process of aerobic glycolysis is heightened, resulting in a significant production of lactic acid. This accumulation of lactic acid leads to a decrease in pH levels in the surrounding environment of cancer cells. As a consequence, the immune response is suppressed in cancer patients, hindering the function of T cells and disrupting the output of lactic acid in their metabolic pathway [204]. It is evident that lactate, which acts as a suppressor of T-cell function, plays a significant role in aiding cancer cells to evade detection. The relationship between lactate dehydrogenase (LDH) and the outlook of malignant tumors is widely recognized, with elevated LDH levels often being a negative indicator for cancer patients. Engaging in moderate exercise can alter LDH levels and consequently decrease lactate levels in cells. As a result, this metabolic process works to hinder cancer's anaerobic glycolysis [205].

The AMPK acts as the primary controller of metabolism. It plays a crucial role in maintaining the balance of energy within the body and it has the ability to impede cell growth when there is a lack of resources and metabolic processes [206]. When mice were given a diet high in fat, their physical activity triggered the activation of AMPK and suppressed the Akt signal. This resulted in an upregulation of p27 phosphorylation and adiporR1 protein levels, causing the cells to enter a state of growth inhibition. As a result, the growth of breast cancer cells was reversed [207]. The experiment aimed to use exercise as a method for causing liver cancer in mice and found that exercise caused a decrease in the growth of cancer cells and also lowered the activity of mTOR kinase. This effect was achieved by initiating the phosphorylation of AMPK and its substrate raptor through exercise [208]. Activating AMPK in the body leads to an increase in the production of glucose transporter 4 (GLUT4) and hexokinase 2 (HK2), which are important for processing glucose, and this is made possible through the regulation of histone deacetylase 5 (HDAC5) and cyclic adenosine monophosphate (cAMP) binding element protein [209, 210]. New research has discovered that engaging in regular physical activity can prevent breast cancer by hindering the mTOR signaling pathway. Additionally, this type of physical activity can impede the cancer's metabolic restructuring and decrease levels of glucose and glutamine, leading to the activation of apoptosis [211].

Table 3 provides a comprehensive review about studies conducted on the role of exercise on the cancer.

Green tea and exercise in cancer

The growing amount of data suggests that catechins possess the potential to regulate the effects

of exercise-induced muscle damage, as identified by Haramizu et al. [83] demonstrated that administering catechins for a period of 8 weeks can effectively reduce the decline in muscular strength, muscle damage caused by exercise, and levels of oxidative stress biomarkers (such as LDH, MDA, and CK) in senescence-accelerated mice. Additionally, recent studies have demonstrated that this therapy effectively preserves the GSH/GSSG ratio following downhill running activities. The impact of catechin on improving physical performance has been thoroughly examined in both animal and human subjects. Murase et al. [84] demonstrated that green tea extract drastically raises the amount of time that BALB/c mice can sustain a swimming task before becoming fatigued. Additionally, the impact of the extract on endurance is directly correlated with the dosage given. Besides, these findings have been substantiated by biochemical and indirect calorimetry investigation, indicating that the consumption of green tea extract results in a greater utilization of lipids, demonstrated by increased levels of oxygen consumption, muscle beta-oxidation activity, and fat oxidation. This suggests that the boosted capability for endurance can be attributed to the green tea extract-induced enhancement of lipid utilization and mobilization. These results have been furthered, and recent research demonstrated that treating mice with EGCG can enhance the activation of genes responsible for fat oxidation in mitochondria in muscle tissue of mice fed a high-fat diet [85]. While the primary focus of studies surrounding green tea has been on testing with animals, there exists a significant quantity of data pertaining to humans. Dulloo et al. [86] demonstrated that a concentrated green tea supplement containing high levels of catechins and caffeine enhances the amount of energy expended by individuals on a daily basis. A newer study has also examined the effects of a single dose of green tea extract on physically fit men, who engaged in a 30-minute cycling exercise at a moderate intensity of 60% [87]. The research findings proved that the use of green tea extract effectively enhances the process of burning fat and improves insulin sensitivity during moderate physical activity. Additionally, recent research has further demonstrated that the consumption of EGCG supplements for a brief duration result in heightened levels in grown individuals [88], while Dean et al. [89] After careful consideration and analysis, it was determined that administering EGCG for a period of 6 days has no notable impact on the process of fat oxidation during a 60-minute cycling session at 60% intensity in men who are moderately trained. This was observed in a controlled experiment where 10 subjects with a background in endurance training participated in a randomized and double-blind crossover trial, performing a 2-hour workout at 50% of their maximum power output before and after a 3-week regime of taking green tea extract supplements [90]. The intervention had no impact on measurements related to fat and energy metabolism, such as oxygen consumption, respiratory exchange ratio, and energy use. Additionally, it did not influence markers of inflammation, such as IL-6 and C-reactive protein, or signs of oxidative stress, including thiobarbituric acid-reactive substances and oxidized LDL. However, there was a noticeable decrease in plasma levels of CK. Recently Jowko at al. [91] conducted on a specific group of 16 individuals who are involved in playing soccer. These individuals were given a single dose of 640 mg of green tea catechins and were then subjected to a muscle-endurance test. This experiment involved three sets of bench press and back squat exercises until the participants reached complete fatigue. Prior to and after the exercise, levels of thiobarbituric acid-reacting substances, catechins, uric acid, and CK activity were measured in the plasma. The findings indicated that there was not a palpable shift in these biomarkers after consuming 640 mg of green tea catechins, indicating that this dosage was inadequate in reducing the effects of oxidative stress and muscle damage caused by physical activity. However, those who received green tea catechins were able to complete more repetitions during the test. In conclusion, previous studies suggest that catechins may improve endurance and performance in sedentary individuals, but this may not be the case for physically active individuals and highly trained athletes.

Vahabzadeh et al. conducted a study to investigate the impact of aerobic exercise and hydroalcoholic extract of green tea (HEGT) on N-methyl-N-nitrosourea-induced prostate cancer model, specifically looking at the changes in prostate-specific antigen (PSA), pro-oxidant-antioxidant balance (PAB), and the histopathological score of the cancerous tissue [234]. The researchers developed an experimental rat model for prostate cancer through the manipulation of hormonal levels and the administration of N-Nitroso-N-methylurea (NMU). The rats were then subjected to a schedule of 45 min of aerobic exercise, five days a week for eight weeks, with the addition of 0.1% HEGT. The presence of significant amounts of catechins in the samples was confirmed through the use of GC-MS. The preventive effects of treatments were monitored through the utilization of histological examination, as well as PAB and PSA levels. The prostate weights of rats afflicted with cancer were notably greater than those of the healthy control group (with a p-value lower than 0.05). Additionally, only the PAB of the cancerous rats and those that engaged in aerobic exercise showed a noteworthy increase (with a p-value lower than 0.05). In this study, the mean histological score of cancerous tissue was noticeably decreased in rats who were administered HEGT alone, as well as those who received both HEGT and participated in aerobic exercise. There were

no noticeable discrepancies found in the levels of PSA between the groups (with a P-value greater than 0.05). The outcomes of our study offer concrete evidence, both in a laboratory setting and through examination of tissue samples, demonstrating that green tea extract have an essential part in preventing the development of prostate cancer. To accomplish this, the body's ability to balance pro-oxidants and antioxidants is restored, promoting overall health [234].

In a separate examination, the influence of an 8-week routine of aerobic physical activity and ingestion of green tea extract on the amounts of cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-kB) and P53 in the prostates of rats that were induced with N-methyl-N-nitrosourea to induce prostate cancer evaluated [235]. Sixty Wistar rats of the male gender were separated into six distinct groups: a control group consisting of healthy individuals, a cancer control group (CCt), a group that participated in low to moderate intensity exercise for 45 min a day, five days a week for a time span of eight weeks (CTr), a group that was given 1.34 mL of green tea extract three times a week for eight weeks (CEx), a group that combined the aforementioned cancer training and cancer extract (CTr+CEx), and a sham group. The rats were put to death 48 h after the interventions, and their prostate tissues were separated to determine the amounts of NF-kB, COX-2, and p53. The CCt group showed markedly elevated levels of NF-kB compared to the healthy control group ($P=0.02$), whereas the CTr group displayed lowered levels of NF-kB when compared to the CCt and CEx groups ($P=0.001$ and 0.05, respectively). Moreover, the levels of p53 were significantly lower in the CTr, CEx, and CTr+CEx groups when compared to the CCt group ($P=0.001$, 0.02, and 0.004, respectively). The levels of COX-2 did not show any notable alterations among the groups. This indicates that A blend of extended physical workouts and regular intake of green tea extract has the potential to lower the quantities of NF-kB and p53 in rats suffering from prostate cancer [235].

Physical activity and cancer both impact the growth of blood vessels, which is known as angiogenesis. This process can be seen as a connection between exercise and cancer [236]. New evidence proposes that combining exercise training with plant-based phytochemicals may serve as a beneficial complementary treatment in preventing the advancement of cancer [237]. Training patients with cancer through physical exercise has consistently been approached with caution due to the potential risk of exacerbating metastasis and promoting factors related to the development of angiogenesis [238]. However, studies have conclusively shown that when it comes to suppressing angiogenesis markers in tumor tissue, moderate aerobic exercise training was found to be more effective than high-intensity training [239]. MMPs, are a group of zinc-dependent endo-peptides with pronounced functions in promoting cancer cell invasion, increasing tumor size, and facilitating metastasis. These enzymes have the ability to break down various extracellular matrix proteins without affecting the angiogenesis in tumors [240, 241]. A variety of MMPs, MMP-9 and MMP-2, have the potential to act as a safeguard against cancer, and their increase in activity may involve in eradicating abnormal tumor cells. Studies have shown that endothelial cells possess the ability to selectively express and activate MMPs [242]. Extensive research has determined that the transportation of VEGF into the tumor microenvironment by MMP-9 and its subsequent release from the tumor matrix by MMPs is crucial for inducing the angiogenic switch and promoting angiogenesis [243].

Khosravi et al. research project was conducted to investigate the effects of an eight-week program of aerobic exercise and green tea extract consumption on the levels of MMP-2/-9 and VEGF in the tissues of both healthy and prostate cancer-inflicted rats [244]. In total, 90 wistar rats were split into two primary categories: healthy and cancer. Of the healthy group, there were four divisions - healthy control, healthy AT (received exercise on a treadmill five days a week), healthy GTE (received green tea extract through gavage three times a week for eight weeks), and healthy AT+GTE. Following tumor induction, the cancer group was then separated into five divisions: cancer control, cancer AT, cancer GTE, cancer AT+GTE, and a sham group. According to the findings, the MMP-2 levels were not notably distinct between the healthy and CaCtr groups ($P=0.07$), however the CaAT group exhibited lower levels of MMP-2 comparing the healthy AT group ($P=0.01$). The levels of MMP-9 and VEGF were not significantly different between the healthy and cancer groups ($P=0.23$ and $P=0.08$, respectively). The current research exhibited that engaging in aerobic exercise at a low to moderate intensity and undergoing treatment with a small amount of green tea extract had no impact on the levels of angiogenesis and markers of metastasis. These findings create a path for future investigations to explore tactics for controlling the dispersion of tumors and the development of blood vessels in correlation to physical exercise and the implementation of antioxidants [244].

The occurrence of depression in the general population can be minimized through various lifestyle choices, such as engaging in regular physical activity [245, 246]. It has not been extensively recorded that breast cancer survivors experience these connections. Various research has been conducted to thoroughly analyze and investigate the correlation between engagement in physical exercise and the occurrence of depression in individuals with breast cancer, resulting in contradictory findings [247–251]. Research studies have yielded inconclusive outcomes

and conflicting evidence regarding the impact of lifestyle changes on depression [252–255]. Experimental research has proposed that the consumption of tea and alternative medicines, known as CAMs, could potentially possess characteristics that can alleviate symptoms of depression [256–259]. The relationship between dietary practices and tea consumption and their impact on depression has not been thoroughly examined. Additionally, while the use of CAM (complementary and alternative medicine) is widespread among those who have survived breast cancer, its effects on depression in this population remain largely unexplored [260, 261].

Chen et al. thoroughly investigated the link between lifestyle choices, intake of supplements, and the prevalence of depression among individuals who have survived breast cancer [262]. During the period of April 2002 to December 2006, a population-based investigation was carried out in Shanghai, China. It involved 1,399 females who had been diagnosed with stage 0 to III breast cancer. These women were interviewed in person, 6 and 18 months after their diagnosis. Out of all the women, 26% reported experiencing depressive symptoms and 13% were found to have clinical depression according to the defined criteria. According to the study, women who engaged in a moderate to high level of physical activity (defined as ≥8.3 MET h/week) had a lower risk of developing depression compared to those who did not exercise. After considering multiple elements including population characteristics, medical diagnoses, and initial well-being, the odds of mild depression were decreased by 0.71 (with 95% confidence interval of 0.47 to 1.07) and clinical depression was lowered by 0.56 (with 95% confidence interval of 0.35 to 0.88). The risk of depression was reduced in women who raised their physical activity levels. Those who drank tea regularly, consuming more than 100 g of dried leaves per month, had a significantly lower risk of overall depression (with an odds ratio of 0.39 and a confidence interval of 0.19 to 0.84). There was no palpable link between depression and dietary intake or supplementation. Engaging in regular exercise and regularly consuming tea may be crucial factors in preventing depression in breast cancer survivors [262].

Conclusion

Overall, previous studies have consistently demonstrated that nutraceutical bioactive substances, specifically polyphenols, show promising results in addressing degenerative and long-term diseases such as cancer. These compounds can provide defense against muscle damage and oxidative stress induced by physical exercise due to their potent antioxidant and anti-inflammatory characteristics. Despite extensive research, the potential for polyphenols to enhance exercise performance remains uncertain. Although in vivo and in vitro experiments suggest that polyphenols may improve endurance capacity, numerous human studies have shown contradictory results, failing to demonstrate significant impacts on exercise performance or VO2 max from nutraceuticals like quercetin, catechins, and resveratrol. This inconsistency could arise from variations in study design, including participants' fitness levels. Research involving untrained individuals has yielded more promising outcomes in enhancing endurance ability, though it remains unclear if the disparities are related to initial fitness levels, as indicated by Kressler et al.'s examination of quercetin. While the effects of some polyphenols have been extensively studied, further investigation in human trials is needed to reach a definitive conclusion. Combining physical exercise with polyphenol consumption, like that found in green tea, presents a hopeful solution for enhancing the results of cancer treatment, yet it also presents various obstacles to overcome. Engaging in regular physical activity, such as aerobic, resistance, and flexibility exercises, has been proven to decrease fatigue, increase muscle mass, promote better quality of life, and potentially lower the chances of cancer recurrence in patients. In addition, at the same time, polyphenols, which are active elements present in various foods such as fruits, vegetables, tea, and wine, have the potential to prevent cancer by displaying anti-cancer characteristics like reducing inflammation and providing antioxidant benefits that can hinder the development and spread of tumors. Integrating physical activity with the addition of polyphenolic supplements is known to produce a cooperative outcome, presenting a comprehensive non-intrusive supplementary approach to traditional methods of cancer treatment. Despite its potential benefits, there are numerous obstacles to overcome in order to successfully implement these treatments. The diverse health statuses, levels of physical ability, and adverse reactions to treatment among patients make it more challenging to devise universal exercise plans, requiring personalized approaches instead. Additionally, while the efficacy of polyphenols is supported by preclinical research, their bioavailability, optimal dosages, and long-term safety in cancer patients need further investigation. Ensuring adherence to both exercise programs and dietary polyphenol intake amidst the psychological and physical toll of cancer is another significant challenge. Incorporating these methods into current treatment procedures necessitates collaboration among oncologists, nutrition specialists, physical therapists, and other medical staff, which can be demanding in terms of resources. Practical implementation in clinical settings would likely necessitate multidisciplinary approaches, personalized patient plans, and robust patient education to ensure adherence and maximize benefits. Despite these challenges, the integration of structured exercise programs and dietary

polyphenols such as green tea holds significant promise as a complementary strategy in cancer care, potentially leading to improved outcomes and quality of life for patients. Further clinical trials and research are essential to refine these approaches and fully understand their mechanisms and benefits.

Abbreviations

IARC	International Agency for Research on Cancer
MET	Metabolic Equivalent of Task
ROS	Reactive Oxygen Species
DNA	Deoxyribonucleic Acid
RNS	Reactive Nitrogen Species
XO	Xanthine Oxidase
NOS	Nitric Oxide Synthases
GP	Grape Powder
WNT	Wingless/Integrated
CRC	Colorectal Cancer
EGCG	Epigallocatechin Gallate
EGC	Epigallocatechin
ECG	Epicatechin Gallate
EC	Epicatechin
GTCs	Green Tea Catechins
RTKs	Receptor Tyrosine Kinases
HCC	Hepatocellular Carcinoma
GF-1R	Insulin-like Growth Factor 1 Receptor
COX-2	Cyclooxygenase-2
BCL-2	B-cell Lymphoma 2
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
ERK1/2	Extracellular Signal-Regulated Kinase 1/2
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
AMPK	AMP-Activated Protein Kinase
IGF	Insulin-like Growth Factor
IGF1R	Insulin-like Growth Factor 1 Receptor
Bax	Bcl-2-associated X Protein
EMT	Epithelial-Mesenchymal Transition
FAK	Focal Adhesion Kinase
MMP-9	Matrix Metalloproteinases-9
G3BP1	GTPase-Activating Protein SH3-Domain-Binding Protein 1
NSCLC	Non-Small Cell Lung Cancer
EC	Esophageal Cancer
ORs	Odds Ratios
DSCs	Digestive System Cancers
AgNPs	Silver Nanoparticles
GT	Green Tea
CSC	Cancer Stem Cell
SF-36	36-Item Short-Form Health Survey
NK	Natural Killer
KLRK1	Killer Cell Lectin-Like Receptor K1
IL-2Rβ	Interleukin-2 Receptorβ
LDH	Lactate Dehydrogenase
MDA	Malondialdehyde
CK	Creatine Kinase
GSH/GSSG	Glutathione (Reduced)/Glutathione (Oxidized)
IL-6	Interleukin 6
LDL	Low-Density Lipoprotein
HEGT	Hydroalcoholic Extract of Green Tea
PSA	Prostate-Specific Antigen
PAB	Pro-Oxidant-Antioxidant Balance
NMU	N-Nitroso-N-Methylurea
CCt	Cancer Control Group
CAMs	Complementary and Alternative Medicines
VO2 max	Maximal Oxygen Consumption

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