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Flavonoid Nanoparticles: Revolutionizing Cancer Treatment Strategies

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Abstract

Flavonoids, a widely distributed class of polyphenolic chemicals found in nature, have recently emerged as significant anticancer agents. Regrettably, the anticancer potential of dietary flavonoids is inadequate due to their limited solubility, absorption, and fast metabolism. Nanocarriers promote the body's ability to absorb flavonoids and utilize them. This review aims to assess studies regarding the potential therapeutic benefits of flavonoid nanoparticles. In an examination of English-language publications released on June 30, 2020, a search was conducted using CINAHL Plus, Cochrane, PubMed (including MEDLINE), and other relevant databases. Preclinical research is now where most studies are looking into flavonoid nanoparticles' potential as anticancer agents by data from the Web of Science. A549 and MCF-7 breast cancer cells are the main subjects of this study. The cancer cells discussed are carcinoma cells, lung cancer cells, and HepG2 tumor cells. Moreover, flavonoid nanoparticles can augment cancer treatments' effectiveness by bolstering their anti-tumor characteristics. Reducing the negative impacts of drugs on the body's physiological systems

Keywords: *Anticancer Agents, Anti-Tumor Effects, Flavonoid Nanoparticles, Nan carriers, Preclinical Research.*

Introduction

In almost every part of the plant, flavonoids are the most common and widely distributed class of plant compounds. There is still a class of substances that can be divided into numerous subfamilies, including isoflavones, flavones, flavanols, and flavanones [1]. Flavonoids are considered a dietary component that improves human well-being [2]. Its health-promoting qualities are attributed to the chemical's associations with an anti-oxidant [3], anti-inflammatory characteristics [4], and anticancer activities [5]. The centre of attention is still on flavonoids' ability to fight cancer. The occurrence of flavonoids has been comprehensively documented in numerous research studies, including It contains the following compounds: kaempferol, naringenin, silibinin, quercetin, genistein, apigenin, and epigallocatechin-3-gallate. Highly successful in treating different kinds of cancer. Unfortunately, there is not enough evidence to support the application of flavonoids in the treatment of cancer because of their inability to dissolve effectively [2], inadequate absorption [6], and fast disintegration in the body [7]. There is a chance that this topic will be connected to modern nanotechnology. Unfortunately, due to their insufficient

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solubility [2], insufficient absorption [6], and quick metabolism [7], flavonoids have not been suitably used in cancer therapy. Contemporary nanotechnology shows significant potential for improving the transportation and effectiveness of flavonoids. Through the utilization of nanocarriers, we may significantly enhance the bioavailability of these advantageous substances. Recent research has emphasized the capacity of flavonoid nanoparticles to provide significant anti-cancer characteristics, as demonstrated by trials on both cell cultures and live animal models [8-11]. The study encompasses a diverse range of tumor cell lines, including the A549 lung tumor cells, B16F10 cells from melanoma, MCF-7 carcinoma of the breast cells, HepG2 malignancies of the liver cells, and CT26 cells from colorectal cancer. Various cutting-edge flavonoid nanocarriers are presently employed in cancer therapy, including nanoparticles made of polymers, nano-capsules, gold metallic nanoparticles, and solid lipid carriers [12-16]. This research aims to evaluate the body of knowledge on flavonoid nanoparticles' ability to fight cancer. Focusing on the English language literature published until June 30, 2020, the analysis uses large databases like Web of Science, CINAHL Plus, PubMed (including MEDLINE), and Cochrane. The search method utilized Medical Subject Headings (MESH) phrases and pertinent keywords. The user's search keywords focused on "flavonoid nanoparticles" and their applications in cancer therapy, including "flavonoid-infused nanomaterials" and the anticancer efficacy of these nanoparticles.

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), a key component of green tea, shows promise for cancer management but faces challenges such as low oral absorption and potential hepatotoxicity [17-20]. Nanoparticles encapsulating EGCG, such as PLA-PEG nanoparticles, have significantly improved efficacy and reduced toxicity. Studies show these nanoparticles enhance EGCG's effectiveness against various cancers, including prostate, breast, and liver [21]. Gold nanoparticles combined with EGCG also show potential, especially in imaging and radiation sensitivity [22-26]. Additionally, chitosan-based EGCG and EGCG-loaded folic acid poly(ethylene) nanoliposomes have shown promise in targeting cancer cells and inducing apoptosis [27-31]. Combining EGCG with advanced nanoparticles, such as chitin-loaded honokiol, is being explored to enhance anticancer effects further [32-34]. These innovations could improve EGCG's therapeutic impact and reduce side effects. Table 1 illustrates the therapeutic effect of preventing cancer cell growth in the existence of epigallocatechin-3-gallate nanoparticles.

Table 1: The Anti-Cancer Effects of Epigallocatechin-3-gallate (EGCG) Nanoparticles In Laboratory And *in vivo* Experiments

Type of nanomaterials	**CANCER CLASS/INFLUENCE**	**Type of Study**	**Reference**
Gum-arabic and maltodextrin carbohydrate matrix	CARCINOMA PROSTATE Apoptosis is the process that lowers the overall viability of Du145 cells and induces programmed cell death.	In vitro methods	[27]
Gold	MELANOMA Inhibition of tumor growth in B16F10 cells	Mice are used as the animal model	[26]
PLA-PEG	A dose differential of more than ten times is needed to produce	mice as the animal model	[21]

	the proapoptotic and angiogenesis-inhibiting effects of CARCINOMA OF THE PROSTATE. impact on the 22Rr1 cells		
EGCG-based nanoelectrodes	MELANOMA inhibition of A375 human melanoma cell tumor growth.	Model animal (mice)	[33]
Chitosan	CARCINOMA PROSTATE 22Rr1 cells exhibit growth suppression of cancer cells.	Mice are used as the animal model	[30]
Nanoliposomes coated with chitosan (CSLIPO)	BREAST MALIGNANCE In MCF-7 cells, anti-proliferative and proapoptotic effects were observed.	Model in vitro	[8]

Quercetin

Quercetin (QT), a vegetable flavonoid, inhibits tumor cell growth and arrests the cell cycle in lymphoid tissue [35]. Due to its poor solubility and absorption, nanoparticles have been employed to enhance its properties. Studies show that quercetin-loaded nanoparticles, including those made of poly (lactic-co-glycolic acid) (PLGA), PLA, and PEG, improve their solubility, stability, and circulation time [47]. PEG nanoparticles, for instance, have shown superior anticancer efficacy against various cancer cells, including A549 lung, MCF-7 breast, and B16F10 melanoma [9, 36, 37]. PEG-liposomal nanoparticles also reduced ovarian cancer angiogenesis [49]. Quercetin encapsulated in PLGA nanoparticles has effectively treated liver and breast cancers, enhancing inflammatory markers and liver function [42, 45]. Combined with gold or other carriers, quercetin nanoparticles have also demonstrated anticancer properties across several cancer types [43]. Quercetin nanoparticles may be used to treat cancer, according to in vivo research (Table 2).

Table 2: Quercetin (QT) nanoparticles' anticancer properties in living things

Kind of Nanomaterials	**Type/Effect of Cancer**	**Types of Study**	**Reference**
PLGA-TPGS loaded with QT (QPTN) succinate of poly-(dl-lactic-co-glycolic acid)-D-α-tocopherol polyethylene glycol	LIVER CANCER inhibits the growth of HCa-F and HepG2 cell tumors	Rats as the model animal	[46, 47]
Peptonidylethanolamine, or PEG	LUNG CANCER A549 lung cancer cells exhibit anticancer activity.	Mice are used as the animal model	[41, 44, 45]
Poly(ethylene glycol) quercetin nanoparticles TPP-PEG triphenylphosphine	HepG2, A459, and MCF-7 cells used in mitochondrial-targeted tumor therapy	Animal model (mice)	[36]
Poly(ethylene glycol) or PEG	MELANOMA (B16F10 melanoma cells) suppression of tumor growth	Animal model (mice)	[48]

Polymeric micelles that are freeze-dried	The effect of cytotoxicity on C6 glioma cells in GLIOMA	Model animal (mice)	[40]
Polyethylene glycol-liposomal, or PEG-liposomal	Induction of apoptosis and prevention of angiogenesis in OVARIAN CANCER	Animal model (mice)	[49]
GPSLN Gelu Pearl with nanoparticles of Precirol ATO 5	MELANOMA reduced lung colonization and enhanced anti-metastatic activity against B16F10 melanoma cells	Animal model (mice)	[53, 54]
Poly (lactic-co-glycolic acid) nanoparticles of rutin, or RT-PLGA	CARCINOMA HEPATOCELLULAR reduced the incidence of hepatic nodules, necrosis formation, inflammatory cell infiltration, inflammation of blood vessels, and cell swelling	Animal model (rats)	[45]
PLA (dl-lactide-co-glycolide) polymer	Limited development of hepatocarcinogenesis in HEPATOCELLULAR CARCINOMA	Animal model (rats)	[43]
Polyethylene glycol 1,2-distearoyl-sn-glycero3-phosphoethanolamine N-methoxy is known as DSPE-MPEG.	CANCER IN THE PROSTATE The stimulation of apoptosis by human androgen-independent PC-3 cells boosted the effectiveness of chemotherapy by enhancing the accumulation of drugs at the tumor site.	Model animal (mice)	[50]
PVP poly (vinyl pyrrolidone)	Antioxidant characteristics and efficient photothermal cancer-killing in breast cancer Four T1 cells	Animal model (mice	[38, 39]
Monomethoxy poly (ethylene glycol)-poly(ε-caprolactone) is MPEG-PCL.	OVARIAN CANCER: Suppression of the mitochondrial apoptotic pathway during the cell's formation. The A2780S	Animal model (mice)	[51]
	In CT26 cells, COLORECTAL CANCER increased apoptosis activation and cell proliferation suppression.	Animal model(mice)	[11]

Nanoparticles of poly (lactic-co-glycolic acid)	CARCINOMA HEPATOCELLULAR Liver mitochondrial membrane defense against cancer inhibits the expression of cytochrome C in living things.	Rats as the model animal	[42]
SPC-CHOL cholesterol and phosphatidylcholine from soybeans	CERVICAL CANCER The in vivo inhibitory effect of U14 cells and the antitumor activity of HeLa cells	Animal model (mice	[40, 41]
MPEG-PLA poly(ethylene glycol) methoxy-poly(lactide)	BREAST CANCER: T1 cells from breast cancer limit the formation of tumors	Model animal (mice)	[52]
Gold-PLA Making poly (dl-lactide-co-glycolide) nanoparticles with gold and quercetin.	CARCINOMA HEPATOCELLULAR decrease of the AP-2β/telomerase reverse transcriptase hTERT, inhibition of the NF-κB/cyclooxygenase 2 COX-2 and Akt/ERK1/2 signalling pathways, and deactivation of the caspase/Cyto-c pathway	Animal model (mice)	[53]

Genistein

Among the many plants that contain the isoflavonoid genistein are lupins, fava beans, and soybeans [55, 56]. Studies have demonstrated the positive benefits of genistein nanoparticles for anti-tumor lines. The limited oral bioavailability, quick metabolism, and poor water solubility of genistein restrict its clinical use [57]. TPGS-b-PCL (d-tocopheryl polyethylene glycol 1000 succinate-poly (caprolactone)) loaded with genistein was more cytotoxic and suppressed the proliferation of HeLa cervical tumor cells than PCL nanoparticles supplied with genistein [58]. However, M-PLGA-TPGS (poly (d, l-lactide-co-glycolide)-d-tocopheryl polyethylene glycol 1000 succinate) loaded with genistein showed a linear apoptotic impact on HepG2 liver cancer cells [12]. Unfortunately, using nanoparticles has been shown to improve the bioavailability of genistein and cause considerable harm to normal cells. The anticancer potential of different genistein-loaded nanoparticles was investigated through in vitro research. Mainly, HT29 colon cancer cells were used to test PEGylated silica hybrid nanomaterials, A549 lung cancer cells were used to test genistein-miRNA-29b-loaded hybrid nanoparticles (GMLHN), and hematopoietic cancer cells were used to test genistein carboxymethylated chitosan nanoparticles (Fe3O4-CMC). The study focused on apoptosis and autophagy [59–61]. Although pure genistein is hindered by low water solubility, limited bioavailability, and instability, the nanoparticle formulations have shown stability, making them suitable for application in anticancer therapy [62]. Table 3 is a compilation of papers investigating the usefulness of genistein nanoparticles in fighting cancer.

Table 3: The anticancer effects of genistein nanoparticles in both laboratory and in vivo experiments

Kind of Nanomaterials	Type and Impact of Cancers	Type of Study	Reference
Carboxymethylated chitosan, or Fe3O4-CMC	CANCER HAEMATOPOIETIC Significant inhibition of hematopoietic cancer cells' ability to proliferate	Model in vitro	[62]
TPGS-b-PCL	CERVICAL CANCER Suppression of tumor formation in HeLa cells.	Model animal (mice)	[58]
PEGylated hybrid nanoparticles of silica	COLON CANCER The amounts of endogenous antioxidant enzymes and H_2O_2 production in the cells of HT29 were changed, which led to the concurrent activation of autophagy and apoptosis.	In vitro model	[59]
GMLHN (hybrid nanoparticles loaded with gelatin, miRNA, and 29b)	LUNG CANCER Thymoma strain AK contains the protein kinase known as phosphorylated protein kinase B (pAKT). Inositide that has been phosphorylated-PI3K (phosphoinositide 3-kinase), DNAbeta-methyltransferase of the cytosine-5 The function of the gene DNMT3B in the growth and development of myeloid cells in Leukemia's first sequence, or MCL 1, is efficiently repressed. The anti-proliferative impact on non-small cells has been noted. Cells from pulmonary cancer A549	In vitro model	[61]
M-PLGA-TPGS	CANCER OF THE LIVER causes HepG2 cells to undergo apoptosis.	Model animal (mice)	[12]

Silibinin

The milk thistle seed contains silibinin [63]. Research indicates that silibinin may have antineoplastic effects on various malignancies by encouraging the cell cycle and preventing proliferation [64, 104]. Nevertheless, Because of its hydrophobic properties, silibinin has low solubility in water and a restricted capacity to pass past intestinal epithelial cells. To overcome these challenges, lipid-polymer hybrid nanoparticles modified with grain germ agglutinin have been coated with PEG, PVA, and poly-N-(2-hydroxypropyl) methacrylamide (p HPMA) to increase the effect of silibinin [65]. TPGS and phosphatidylcholine were utilized to create lipid nanoparticles loaded with silibinin. The nanoparticles were generated using a thin-film hydration approach [66]. Silibinin had strong anticancer properties on oral carcinoma cells when encapsulated in PVA-Eudragit nanoparticles [67]. Furthermore, another investigation revealed that using MCF 10A breast cancer cells in a lab setting, the cytotoxic characteristics of silibinin were encapsulated in PEG nanoparticles [68]. Limited solubility and insufficient dissolution of free silibinin result in limited oral bioavailability. This publication [69] by Sahibzada et al. describes two methods for

silibinin nanoparticle production: APSP (anti-solvent precipitation using a syringe pump) and EPN (evaporative precipitation of nanosuspension). These methods make silibinin more soluble and a viable oral drug option for cancer treatment. Huo et al. demonstrated the considerable effects of mixing paclitaxel (PTX) and silibinin in dextran-deoxycholic acid (Dex-DOCA) nanoparticles to efficiently accumulate in tumor areas by passive targeting and reduce tumor development in mice by improving intra-tumoral penetration [70]. According to a separate study [71], silibinin in combination with IPI-549 nanoparticles (AEAA-PEG-PCL, aminoethylanisamide-polyethylene glycol-polycaprolactone) inhibited 4T1 breast cancer cells and significantly altered the tumor microenvironment. Studies utilizing the wheat germ agglutinin-modified lipid-polymer nanoparticles that are hybrid loaded with the silibinin and cryptotanshinone (S/C-p W) and coated in poly-N-(2-hydroxypropyl) methacrylamide (p HPMA) also showed the anti-metastatic qualities of silibinin. These nanoparticles effectively prevented metastasis in the lungs and curbed tumor growth in 4T1 tumor-bearing mice [72]. Table 4 summarizes studies on silibinin nanoparticles' potential in vivo and in vitro anticancer effects.

Table 4. Demonstrates how silibinin Nanoparticles Work Against Cancer in Laboratory and Living Organism Studies

Sort of Nanomaterial	Type/Effect of Cancer	Study type	Reference
SB-Dex-DOCA-PTX	LUNG CANCER inhibits the development of A549 cell tumors	Model animal (mice)	[70]
PVA-Eudragit	Suppression of KB cell apoptosis by ORAL CARCINOMA	Model in vitro	[67]
S/C-pW microcapsules	BREASTCANCER's anti-metastasis effect	Model animal (mice)	[72]
PEG	The effect of cytotoxicity on MCF 10A in BREAST CANCER	In vitro model	[68]
AEAA-PEG-PCL	BREAST CANCER 4T1 cells inhibit angiogenesis	Model animal (mice)	[71]

Apigenin

Many kinds of fruits and vegetables, particularly berries, contain apigenin. This flavonoid controls the signaling pathways that lead to skin cancer and hepatocellular carcinoma. Because free apigenin is poorly soluble in lipids and water, its therapeutic benefits in cancer therapy are very small [73]. These days, PLGA nanoparticles are typically employed to increase the bioavailability of flavonoids. A study by Das et al. found that apigenin loaded in PLGA nanoparticles had a suppressive impact on A475 skin cancer cells. The fact that these nanoparticles prevented UV light-induced photodegradation is noteworthy [74]. Recent work used mesoporous silica particles to create solid dispersions of newly created nanomaterials that improve apigenin’s solubility and absorption [76]. Table 5 presents specific information regarding the effectiveness of apigenin nanoparticles in combating cancer.

Table 5: The Anticancer Effects of Apigenin Nanoparticles in Live Organisms

Different types of nanomaterials	Type and Impact of Cancer	Study Category	Reference
MSN mesoporous silica nanoparticles	better dissolution, solubility, and absorption after being taken by mouth	Rats as the model animal	[76]
PLGA	SKIN CANCER A375 cells had less of specific signs of proliferative activity, which led to more ROS production and apoptosis caused by mitochondria.	Rats as the model animal	[74]
	HEPATOCELLULAR CARCINOMA the suppressive impact on Huh-7 and HepG2 cancer cells.	Animal model (rats)	[75]

Naringenin

Naringenin, found in tomatoes, bergamot, and citrus fruits, is known for its anticancer properties due to its anti-inflammatory and antioxidant effects [77]. However, its effectiveness is limited by poor solubility and bioavailability [78]. Nanoparticles containing naringenin have shown promise in treating various cancers, including oral squamous cell carcinoma [79], colorectal cancer [81], and lung cancer [80]. Nanoparticle formulations, such as PVA-EE and Eudragit 500, have improved naringenin's efficacy and tumor prevention in oral applications [79]. In vitro studies have shown that naringenin-loaded chitosan nanoparticles are effective against A549 lung cancer cells without harming healthy cells [80]. Additionally, naringenin in Soluthin-maltodextrin nanoparticles has been effective in reducing colorectal cancer cell proliferation [32, 33]. Silk fibroin nanoparticles have also demonstrated promising anticancer effects against HeLa cells in cervical cancer [78]. Table 5 illustrates the naringenin nanoparticles prevent cancer in living beings.

Table 6: The Way that Naringenin Nanoparticles Prevent Cancer in Living Beings [103]

Types of Nanomaterial	Type/Effect of Cancer	Type of Study	Reference
Nanoparticles of silk fibroin	The antitumor potential of HeLa cells in cervical cancer	within a vitro model	[78]
Edragit 500 (polyvinyl alcohol)-PVA	Action of CARCINOMA ORAL SQUAMOUS CELL on tumors	Model animal (hamster)	[79]
NPs in NRG-EE100(Eudragit 100)	In colon-26 cells harboring BALB/c mice, COLORECTAL CANCER increased oral bioavailability and tumor suppression.	Rats as the model animal	[83]

Chitosan	Anticancer and antioxidant characteristics are present in A549 cells, which are used in lung cancer research.	Model in vitro	[80]
Eudragit	Anti-lipid peroxidative activity, anti-proliferative effect, antioxidant potential, prevention of tumor development, reduction of the degree of histological lesions, ORAL SQUAMOUS CELLCARCINOMA	A model animal (hamster)	[82]
Maltodextrin and solutehin	In BALB/c mice carrying colon-26 cells, COLORECTAL CANCER improved oral bioavailability and tumor suppression.	Rats as the model animal	[81]

Luteolin

Many different plant species contain luteolin, including fruits, vegetables, and medicinal plants [84, 106]. It triggers programmed cell death and hinders cancer cells' movement, invasion, and formation of new blood vessels [85]. Because of its hydrophobic form, it exhibits limited ability to dissolve in water, inadequate ability to distribute throughout the body, and low effectiveness. To enhance or optimize. Researchers recently looked into the effects of luteolin in addition to nanoparticles such as folic acid-PEG-PCL and PLA-PEG [86]. A laboratory experiment demonstrated that nano-luteolin, which originates from luteolin and possesses hydrophobic characteristics, was encapsulated within water-soluble polymers. This formulation inhibited the H292 cell line's ability to proliferate, which is a lung cancer cell type. The Tu212 cell line, which comprises squamous cell carcinoma of the head and neck (SCCHN), is also mentioned in the text [86]. Research has documented these as among the most prevalent types of cancer globally [87–89]. Furthermore, a study conducted in living organisms employing a tumor xenograft in the mouse model experiment showed that nano-luteolin effectively suppressed the growth of the tumor. Comparing the growth rate of unencapsulated luteolin with that of squamous cell carcinoma of the head and neck (SCCHN), a comparative value of 86 was achieved. Wu et al.'s study showed that the substance known as Fa-PEG-PCL is made up of luteolin encased in a framework made of poly (ethylene glycol) modified by folic acid (caprolactone). The development of GL261 cells in glioblastoma multiforme was stimulated by nano-micelles [90]. Furthermore, the safety evaluation of nanoparticles administered to the mice under study revealed no apparent adverse reactions [90]. Because of despite the hydrophobic nature of luteolin [91] and its limited biocompatibility [90], additional research is still needed. To boost its potential to be absorbed and utilized by the body (Table 7).

Table 7: Demonstrates how Luteolin Nanoparticles Prevent Cancer in Living Organisms

Kind of Nanomaterial	**Cancer Type and Impact**	**Study Category**	**Reference**
PEG-PCL Fa	GLIOBLASTOMA The GL261 cells were killed and their proliferation was	Model animal (mice)	[90]

	inhibited by the multiforme therapy.		
PLA-PEG	HEAD AND NECK CANCER, LUNG CANCER halting the development of Tu212 and H292 cell cancers	Model animal (mice)	[86]

Kaempferol

Kaempferol, found in apples, strawberries, broccoli, spinach, and herbal remedies, has anticancer properties but suffers from poor systemic dispersion and absorption [92, 93]. Nanoparticles, including chitosan, gold, and PLGA, can enhance kaempferol's efficacy in cancer therapy. Kaempferol inhibits ribosomal S6 kinase (RSK) and phosphatidylinositol-3-kinase (PI3K), leading to cell cycle arrest [94]. Nanoparticles containing kaempferol have been shown to slow cancer growth, particularly in ovarian cancer cells (A2780/CP70 and OVCAR-3) [93] and rat glioma cells (C6) [95]. Studies indicate that kaempferol-loaded PEO-PPO-PEO nanoparticles are more effective against ovarian cancer cells than PLGA nanoparticles. Additionally, a mucoadhesive chitosan nanoemulsion (MNE) containing kaempferol has shown potential in reducing glioma cell viability [95]. Gold nanoparticles combined with kaempferol have been more hazardous to A549 lung cancer cells compared to normal cells [96]. Table 8 shows the anticancer effects of kaempferol nanoparticles in laboratory investigations.

Table 8: The Anticancer Effects of Kaempferol Nanoparticles in Laboratory Investigations.

Kind of Nanomaterial	Cancer Type and Impact	Study Category	Reference
Gold	LUNG CANCER: A549 lung cancer cells are killed by lung cancer	In vivo prototype	[96]
PEO-PPO-PEO and PLGA	The growth of OVARIAN CANCER cells is resisted both firmly and specifically. The cell lines A2780/CP70 and OVCAR-3 are those of ovarian cancer.	Model in vitro	[93]
Chitosan	Brain cancer - activation of apoptosis in the C6 rat glioma cell line.	Within a vitro model	[95, 96]

Additional Flavonoids (Fisetin and Myricetin)

Many fruits and vegetables contain fisetin, including apples, strawberries, grapes, persimmons, and onions [97]. When fisetin was added to human serum albumin nanoparticles, the particles showed antitumor effects on MCF-7 breast cancer cells in a lab setting [96]. In vivo studies on fisetin nanoparticles with 4T1 breast cancer cells and in vitro tests on fisetin formulations indicated that PLA nanoparticles also demonstrated anticancer effects on HCT116 colon cancer cells [95]. Solid lipid nanoparticles, composed of phosphate and Gelucire, were encapsulated with myricetin using an in vitro process. Both fisetin and myricetin-containing nanoparticles exhibited anticancer properties. Recent research highlights the potential of flavonoids in cancer treatment, which are polyphenolic compounds abundant in nature. However, their anticancer potential is limited by solubility and metabolism issues. Nanotechnology has improved the bioavailability and efficacy of flavonoids, showing promise in preclinical

cancer research targeting various cell types. Table 9 shows the anticancer effects of Fisetin and Myricetin nanoparticles in laboratory investigations.

Table 9. Research on the Anti-cancer Effects of Myricetin and Fisetin Nanoparticles both in vivo and *in vitro*

Flavonoid	Type of Nanomaterial	Kind and Impact of Cancer	Study Category	Reference
Fisetin	Albumin (human serum)	BREAST MALIGNANCE induces MCF-7 cells to become cytotoxic.	Model in vitro	[96]
	PLA	COLON CANCER and BREAST CANCER The chemical demonstrated its ability to eradicate tumors in two tests: one conducted in a lab using HCT116 colon cancer cells and the other using a real-world xenograft 4T1 breast cancer model.	Rats as an animal model and in vitro	[97]

Conclusion

Flavonoid-based nanoparticles represent a promising advancement in cancer therapy, addressing the limitations of traditional dietary flavonoids, such as poor solubility, limited absorption, and rapid metabolism. The preclinical studies highlighted in this review demonstrate the potential of these nanocarriers to enhance the bioavailability and therapeutic efficacy of flavonoids, particularly against carcinoma, lung cancer, and HepG2 tumor cells. By improving the anti-tumour characteristics of flavonoids and reducing the adverse effects associated with conventional treatments, flavonoid nanoparticles offer a novel and potentially effective strategy for cancer management. However, further clinical investigations are necessary to elucidate their safety and efficacy fully and to pave the way for their integration into mainstream cancer therapy.

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Authors Contribution

Hashvitha P. and Subhashini K authored the manuscript, with Sheshan A. contributing to the review. Lokeshvar R. and Velmurugan R. reviewed and edited the manuscript. All authors are responsible for the content and similarity index and have thoroughly reviewed and approved the final draft.

Conflict of Interest

The authors declare no conflicts of interest.

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