

# **Green Approaches of Flavonoids in Cancer: Chemistry, Applications, Management, Healthcare and Future Perspectives**

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## **ABSTRACT**

In epidemiologic research, a cancer preventive benefit from plant-derived meals has been discovered with unusual consistency. However, identifying individual components responsible for this effect has been difficult. Many phytochemicals have been found to have biological activity, and they may work together to prevent cancer. Cancer is a significant public health concern in both developed and developing countries. Several plants synthesized anticancer agents like taxol, irinotecan, camptothecin, topotecan, and vinblastine, vincristine, etoposide being used in clinical trials. In addition, Flavopiridol, roscovitine, combretastatin A-4, betulinic acid, and silvestrol are promising anticancer compounds. Flavonoids in vegetables, fruits, roots, and stems have demonstrated a wide range of anticancer properties, including modulating ROS, scavenging enzyme activities, participating in cell cycle arrest inducing apoptosis autophagy, and suppressing growth of tumour cell and invasiveness. This review highlighted flavonoids, cancer cell mechanism of action, applications in tumour management, and future perspectives. This review will play a significant role for industrialists and scientists working in this field.

**Keywords:** *Cancer, health concern, plant, anti-cancer drugs, flavonoids, reactive oxygen species.*

## **1. INTRODUCTION**

Cancer chemoprevention, which involves using dietary, natural, or synthetic substances that can suppress, prevent or reverse carcinogenic progression, has become a popular technique for combating the growing number of cancer cases worldwide [1]. Polyphenols are found in about 8000 different chemicals, further grouped into ten different types. In addition, flavonoids are plant metabolites in over 4000 other types [2]. A recent expert panel found that the scientific evidence suggesting plant-based diets, mainly those high in vegetables and fruits, protect against cancer malignancies [3]. Flavonoids are a natural substance that belongs to a group of secondary metabolites of herbs with a polyphenolic structure build in vegetables,, fruits, and some beverages [4-6]. Flavonoids are a low molecular weight compound. Polyphenols are secondary plant metabolism chemical substances that can accumulate in various plant organs, including leaves, fruits, roots, and stems. They have several biological activities as a vast group of bioactive compounds [7-8].

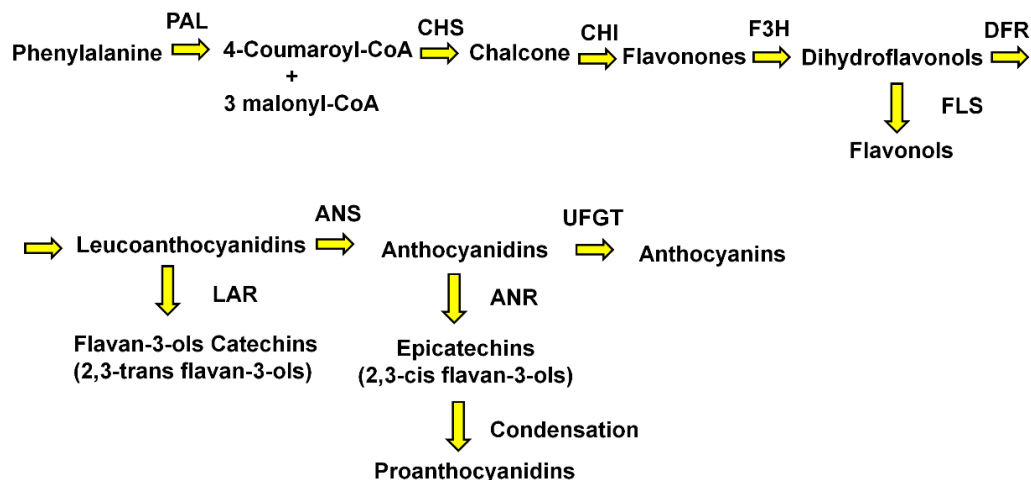
## **2. CHEMISTRY OF FLAVONOIDS**

Flavonoids have a fifteen-carbon structure consisting of two benzene rings joined by a heterocyclic pyran ring. Flavones (such as flavone, apigenin, and luteolin), flavonols (such as quercetin, kaempferol, myricetin, and fisetin), flavanones (such as flavanone, hesperetin, and naringenin), and other flavonoids [9]. Flavonoids are phytonutrients that belong to the

polyphenol class. Polyphenols have long been employed in traditional Chinese and Ayurvedic medicine [10]. Aglycones, glycosides, and methylated derivatives are all types of flavonoids. Flavonoid aglycones (flavonoids without linked sugar) are found in various structural configurations in plants. The basic chemical structure of flavonoid is a diphenyl propane skeleton with fifteen carbon atoms in its core nucleus: two six-membered rings joined by a three-carbon unit that may or may not be a component of a third ring [11-12].

### 3. SYNTHESIS OF FLAVONOIDS

Flavonoids are secondary metabolic products of plants and synthesized from phenylalanine. The schematic flow chart of the synthesis of flavonoids are depicted in Pic. 1 [13].



Pic. 1. Schematic flow chart of biosynthesis of flavonoid.

### 4. FLAVONOIDS CLASSIFICATION

Flavonoids are classified and discussed in Table 1 [14].

Table 1. Classification of Flavonoids.

Types	Structures	Examples	R1	R2	R3	R4
Flavones		Luteolin	-OH	-OH	-OH	-OH
		Apigenin	-OH	-OH	-H	-OH
		Chrysin	-OH	-OH	-H	-H
Flavanones		Galangin	-OH	-OH	-H	-H
		Kaempferol	-OH	-OH	-H	-OH
		Quercetin	-OH	-OH	-OH	-OH
Flavanones		Hesperetin	-OH	-OH	-OH	-OCH <sub>3</sub>

		Naringenin	-OH	-OH	-H	-OH
Flavanonol		Taxifolin	-OH	-OH	-OH	-OH
Isoflavones		Daidzein	-OH	-H	-H	-OH
		Genistein	-OH	-OH	-H	-OH
Flavan-3-ols		Catechin	-OH	-OH	-OH	-OH
		Epicatechin	-OH	-OH	-OH	-OH

## 5. CANCER CHARACTERISTICS

Characteristics of cancers like apoptosis, metastatic, proliferative, and inflammation for targeting tumors are discussed in Fig. 1 [15,16].

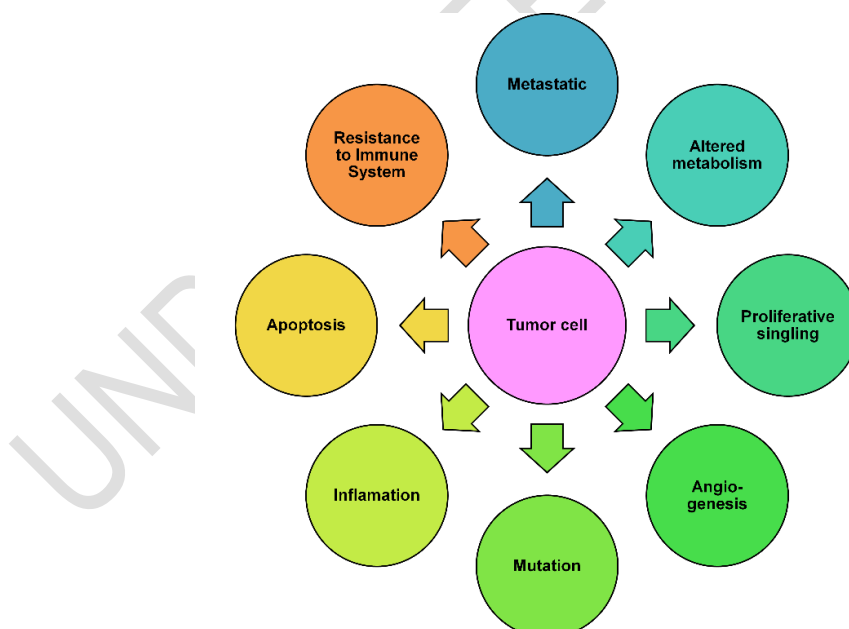


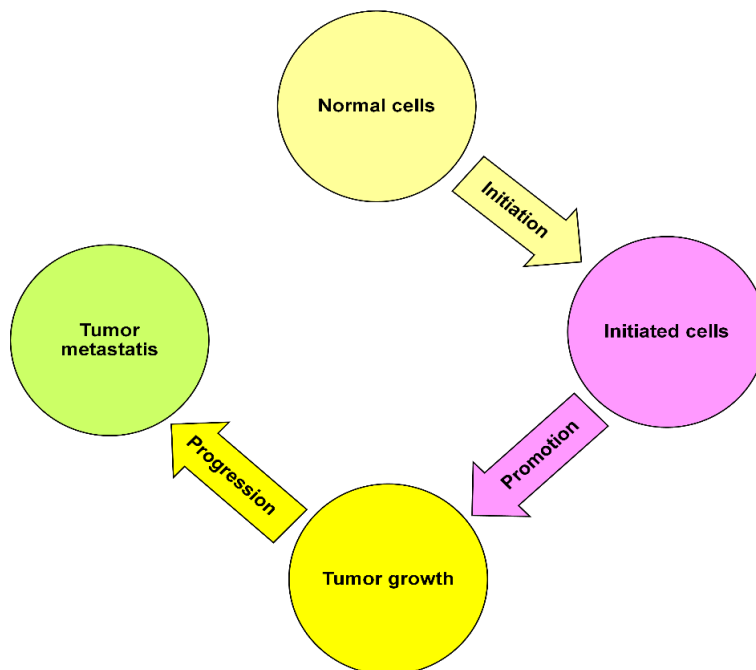
Fig. 1. Characteristics of Tumor cells.

### 5.1 Mechanism of action of Cancer cells

**5.1.1 Initiation:** First phase of the carcinogenic agent's exposure and interaction with cells, particularly DNA.

**5.1.2 Promotion:** This stage lasts a little longer than the previous one; aberrant cells survive, reproduce, and form a cluster of preneoplastic cells.

**5.1.3 Progression:** At the final stage of carcinogenesis involves the gradual transformation of premalignant cells into neoplastic cells, an increase in invasiveness, metastatic potential, and the formation of new blood vessels (angiogenesis), as seen in Fig. 2 [17,18].



**Fig. 2. Mechanism of action of Cancer cells**

A phenolic nucleus (structural unit) that promotes non-covalent interactions at molecular level with proteins. Vander wall and electrostatic interactions are responsible for interactions and suppressed growth of cancer cells. The aromatic ring (non-polar polarizable) in the former can generate significant dispersion contacts with amino acid residues (non-polar), followed by the subsequently release of water. In contrast, H-bonding is an essential electrostatic interaction in the latter type. Flavonoid–protein redox reactions and oxidative covalent coupling can occur due to one- or two-electron flavonoid oxidation caused by autooxidation, reactive oxygen species scavenging, or enzymatic oxidation [19, 20].

## 6. FLAVONOIDS FOR CANCER MANAGEMENT

Flavonoids play a significant role in combating oxidative stress by generating free radical scavengers. Flavonoids inhibit glycoproteins. Multidrug resistance (MDR) and Pin formed (PIN) are responsible for auxin cell to cell movement. In addition to this, flavonoids also regulate IAA oxidase activity dependent on chemical structure. Furthermore, transcriptional regulators modulate protein activity involving cell growth [14]. Flavonoids are found in plants and act as antimicrobials, antioxidants, insect repellents, and several studies suggested that the free scavenger effect is responsible for cancer management [21]. The role of flavonoids involved in the treatment of various cancer discussed in Table 2 [22-32].

**Table 2. Role of flavonoids in treatment of various cancer.**

Flavonoid	Cancer	Cell Line
Flavanones, Curcumin, Quercetin, EGC, Chalcones, EGCG, Isoflavones, Genistein	Oral carcinoma	SCC-25, HSC-2, HSG [22]
Luteolin, Chrysin, Apigenin, Genistein, Kaempferol, Biochanin A	Thyroid carcinoma	NPA, WRO, ARO [23]
Quercetin, Kaempferol, Luteolin, Genistein, Apigenin, Myricetin, Silymarin, Epicatechin, Catechin	Prostate carcinoma	DU145, PC3, LNCaP [24,25]
Myricetin, Chalcones Quercetin, Apigenin	Leukemia	HL-60, Jurkat, K562 [26,27]
Genistein, Daidzein, Luteolin, Flavanones, Quercetin	Breast carcinoma	MCF-7 [28]
Quercetin, Flavone,	Lung cancer	haGo-K-1, SW900, SK-LU1, H661, A549, H441 [29]
Chalcones	B16 mouse melanoma	4A5 [30]
Anthocyanin, Quercetin, Genistein, Flavone	Colon cancer	HT-29, Caco-2, IEC-6, HCT-15 [31,32]

## 7. CHALLENGES FOR CHEMOPREVENTION AND SOLUTION WITH FLAVONOIDS

Flavonoids process various chemoprevention challenges due to isolation, drug interaction, and purification problems that can be overcome by adopting novel and optimized technology to improve anti-cancer effects. [14,21,33-37]. Challenges of cancer chemoprevention of flavonoids are summarized in Table 3 [37].

**Table 3. Challenges in flavonoids in cancer chemoprevention development.**

Flavonoid challenges	Solutions
<b>Isolation &amp; purification:</b> <ul style="list-style-type: none"> <li>• High cost</li> <li>• Plant source extinction</li> <li>• Low predictability</li> <li>• Low yield</li> <li>• Multistep procedure</li> </ul>	<b>Isolation &amp; purification:</b> <ul style="list-style-type: none"> <li>• Novel technology</li> <li>• Fermentation and metabolic</li> <li>• Optimization technique</li> </ul>
<b>Epidemiological:</b> <ul style="list-style-type: none"> <li>• High study cost</li> <li>• Long time activity</li> <li>• Population heterogeneity</li> </ul>	
<b>Pharmacokinetics:</b> <ul style="list-style-type: none"> <li>• Drug interaction</li> <li>• Extensive metabolism</li> <li>• Low stability</li> <li>• Microflora interaction</li> </ul>	<b>Pharmacokinetics:</b> <ul style="list-style-type: none"> <li>• ABC transporter inhibitor</li> <li>• Flavonoid piperine formulation</li> <li>• Flavonoid glycoside</li> </ul>

## 8. PLANT-BASED NANOTHERAPEUTICS FOR CANCER

Plant's metabolites have immense potential and produce many organic compounds, referred to as secondary metabolites. Flavonoids like kaempferol, silibinin, apigenin, and quercetin are effective against various tumors. However, flavonoids have solubility and absorption problems that nanocarriers can overcome. Nanotherapeutics of flavonoids like polymeric nanoparticles, nano-capsules, and solid nanoparticles are useful for cancer therapy. The

anticancer effects are associated with antiproliferation, metastatic, and apoptosis. Nanotherapeutics of flavonoids support cancer therapy and thereby reduce systemic toxicity of anticancer drugs [38-44]. Applications of nanotherapeutics used for cancer management are described in Table 4 [45-73].

**Table 4. Applications of nanotherapeutics in cancer treatment**

Flavonoids	Nanomaterial Type	Study Type	Cell	Cancer type	Mechanism of action
Epigallocatechin-3-gallate	PLA-PEG	Animal model (mice)	22Rr1	Prostate cancer	Show 10-fold dosage advantage for inhibiting pro-apoptosis and angiogenesis [45]
	Chitosan	Mice model	928 cells	Melanoma	Induction of apoptosis [46]
		Mice model	22Rr1 cells	Prostate carcinoma	Inhibited growth of carcinoma [47]
	FU-PEG	Animal model (mice)	MKN45-Luc cells	Gastric cancer	Suppress tumour growth [48]
	Chitin loaded-honokiol	Animal model (mice)	HepG2 cell	Liver carcinoma	Reduced cancer cell in G2/M phase and potential of mitochondrial membrane [49]
	Maltodextrin carbohydrate & Gum Arabic matrix CSLIPO	<i>In-vitro</i> model	Du145 cells	Prostate cancer	Induce apoptosis and decrease cell viability [50]
		<i>In-vitro</i> model	(22Rr1 cell)	Prostate cancer	Inhibit cancer cells [51]
EGCG-nano ethosomes	Animal model (mice)	A375 human melanoma	Melanoma cancer	Suppress tumour growth [52]	
Quercetin	PEG phosphatidylethanolamine PLGA-TMX	Mice model	A549	Lung carcinoma	Antitumor activity in the A549 [53]
	PLGA-TMX	Animal model (rat)	MMP-2/-9 in MCF-7 cells	Breast carcinoma	Regulated the tumour angiogenesis after p.o. administration and concentration of markers became normalized [54]
		Mice model	B16F10 melanoma cells	Melanoma cancer	Suppress tumour growth [55]
	TPP-PEG Triphenylphosphine quercetin nanoparticles poly (ethylene glycol)	Mice model	HepG2, MCF-7, & A459 cells	Mitochondria	Targeted tumour therapy [56]
	M-PLGA-TPGS	Mice model	HepG2 cells	Liver cancer	Apoptotic effect [57]

	GMLHN (Genistein-miRNA29b-loaded hybrid nanoparticles)	In vitro model	A549 cells	Lung cancer	pAKT, p-PI3K, DNMT3B and MCL-1 effectively downregulated, anti-proliferative effect non-small cell [58]
Genistein	TPGS-b-PCL	Mice model	(HeLa cells)	Cervical carcinoma	Suppress tumour growth [59]
Silibinin	PTX-SB-Dex-DOCA	Mice model	A549 cells	Lung carcinoma	Suppress tumour growth [60]
	PVA-Eudragit	<i>In-vitro</i> model	KB cells	Oral carcinoma	Inhibition of apoptosis [61]
Apigenin	AEEA-PEG-PCL	Mice model	4T1 cells	Breast cancer	Angiogenesis suppression [62]
	PEG	<i>In-vitro</i>	MCF 10A	Breast cancer	Cytotoxic effect [63]
Apigenin	PLGA	Mice model	A375 cells	Skin cancer	Proliferative activity of markers of enhanced generation of ROS and influenced mitochondrial apoptosis [64]
		Animal model (rats)	Hep G2 (human hepatoblastom a cell line) and Huh-7 cells	Hepatocellular carcinoma	Inhibit cancer cells [65]
Naringenin	Chitosan	<i>In-vitro</i>	A549 cells)	Lung carcinoma	Antioxidant and anticancer activity [66]
	Silk fibroin nanoparticles	<i>In-vitro</i>	HeLa cells	Cervical cancer	Anticancer potential [67]
Luteolin	Fa-PEG-PCL	Mice model	GL261 cells	Glioblastoma	Inhibition of cell growth and apoptosis [68]
	PLA-PEG	Animal model (mice)	H292, Tu212 cells	Head and neck carcinoma	Inhibit tumour growth [69]
Kaempferol	Gold	<i>In-vitro</i>	A549	Lung cancer	Cytotoxic effect [70]
	PEO-PPO-PEO, PLGA	<i>In-vitro</i>	A2780/CP70 and OVCAR-3	Ovarian carcinoma	Selective inhibition of cancer cell viability [71]
Myricetin	SLNs solid lipid nanoparticles	<i>In-vitro</i>	(A549 cells)	Lung carcinoma	Induce cell growth [72]
Fisetin	HAS (human serum albumin)	<i>In-vitro</i>	MCF-7 cells	Breast carcinoma	Cytotoxic effect [73]

## 9. HERBAL ARRAY: FUTURE TRENDS FOR CANCER MANAGEMENT

Flavonoids in recent times received much attention due to a variety of potential beneficial effects. *In-vitro* and *in-vivo* studies improve human health by adding flavonoids to diet. Herbal serves as a way forward to manage cancer and results in the growth and development of industries. Herbal formulation effectively targets cancer cells with reduced

systemic toxicity and trends in developing the future for newer anticancer agents [34-36]. The list of patents and Herbal marketed formulation of anticancer agents for improving health are illustrated in Table 5 [74-83] and Table 6 [84-93].

**Table 5. List of patents and cancer management from Herbals.**

<b>Benefit</b>	<b>Patent number</b>	<b>Publication date</b>	<b>Inventor</b>
Polymethoxyflavones directly suppress the growth of cancer cells without apoptosis of cancer [74]	Wo2008035208	2008-03-27	Morley, Karen Koropatnick, James Guthrie, Najla
Administration of Apigenin, Luteolin, Diosmetin, and Crysins used in the treatment of colon carcinoma [75]	WO2001058410A2	2001-08-16	Thomas Walle Perry V. Halushka
Apigenin employed for cancer treatment and as chemotherapy in combination with pharmacotherapeutics [76]	US20060189680A 1	2006-08-24	Bing-Hua Jiang, Jing Fang
Flavone derivatives act as an antagonist or TNF- $\alpha$ inhibitors [77]	US20060105967A 1	2006-05-18	Li-Wei Hsu, Su-Chen Chang, Chen-Hsiang Shen, Yuan-Xiu Liao, Kuo-Sheng Chuang
Treatment of cancer by combination therapy using flavonoids [78]	US7510830B2	2009-03-31	Bruce Charles Baguley, Lai-Ming Ching, Martin Philpott
Composition contains DMXAA or related compound used as anticancer [79]	US7585893B2	2009-09-08	Bruce Charles Baguley, Lai-Ming Ching, Philip Kestell, Liangli Zhao
Preparation of flavones derivatives use as medicines [80]	US20030119816A 1	2003-06-26	Jean-Luc Haesslein, Dominique Lefrancois, Eric Uridat, Jidong Zhang
Composition for treatment and prevention of breast cancer [81]	US6300367B1	2001-10-09	Richard B. Taylor, E. C. Henley
Legume plant extracts used for the treatment of cancer [82]	US6004558A	1999-12-21	Michael Joseph Thurn, Li Jiu Huang
Uses of flavanone compound [83]	US7256214B2	2007-08-14	Shigenori Kumazawa, Tsutomu Nakayama, Kayoko Shimoi, Takaki Goto, Syuichi Fukumoto, Tsutomu Arakaki

**Table 6. Herbal marketed formulation of flavonoids for cancer management.**

<b>Brand name</b>	<b>Manufacturer</b>	<b>Dosage form</b>	<b>MRP</b>
Luteolin complex [84]	Swanson	Capsule	1029
Luteolin complex powder [85]	Lutimax	Powder	\$69.95
Apigenin [86]	Swanson ultra	Capsule	IDR297,895
Chrysin [87]	Mrm	Capsule	3100
Quercetin [88]	Healthvit	Capsule	499
Kaemferol [89]	Purebulk	Powder	\$13.75
Galangal root complex [90]	Green organic supplement	Powder	\$18.98
Herceptin [91]	Roche	Liquid	1.11 lakh

Geinstein soy complex [92]	Soy life	Tablet	\$59.48
Isoflavone with genistein [93]	Douglas laboratories	Capsule	\$38

## CONCLUSION

Flavonoids are natural remedies that have existed since ancient times due to their positive effects in reducing inflammation, supporting and restoring normal cell functioning. Flavonoids possess a wide range of anticancer effects and result in novel cancer chemoprevention and mechanism of action. Flavonoids cause cell arrest and suppress the proliferation and growth of tumour cells. Intake of flavonoids-rich herbs improves gut flora, reduces chances of cancer, modulates the immune response, and results in health management. That promotes a promising future of flavonoids in cancer therapy and management of site-specific cancer delivery. Furthermore, flavonoids serve as a potential compound for further studies in generating newer leads for growing herbal industries and promoting health by reducing systemic toxicity and side effects.

## COMPETING INTERESTS DISCLAIMER

Authors have no competing and conflict of interest.

## ABBREVIATIONS

PAL: Phenylalanine ammonia lyase; DFR: Dihydroflavonol reductase; FLS: Flavonol synthase; CHS: Chalcone synthase; CHI: Chalcone isomerase; ANS: Anthocyanin synthase; UFGT: UDP-glucose: flavonoid 3-O-glucosyltransferase; LAR: Leucoanthocyanidin reductase; F3H: Flavonone 3-hydroxylase; ANR: Anthocyanidin reductase; FU-PEG: Fucose-chitosan/polyethylene glycol-chitosan /gelatin; PLGA-TMX: Poly(lactic co-glycolic acid); TPP-PEG: Triphenylphosphine quercetin nanoparticles poly(ethylene glycol); CSLIPO: Chitosan-coated nanoliposomes; PAKT: Phosphorylated protein kinase, strain AK, Thymoma; p-PI3K: Phosphorylated phosphoinositide 3-kinase; DNMT3B: DNA (cytosine-5)-methyltransferase 3 beta; and MCL 1: Myeloid Cell Leukemia Sequence 1.

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