



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

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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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. The polyphenols 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. Celery, chamomile, *Ginkgo biloba*, mint, red paper 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 may play a significant role for industrialists and scientists working in this field.

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

ABBREVIATIONS

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

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 study suggested that plant-based diets, high in vegetables and fruits, protect against cancer malignancies [3]. Flavonoids are natural substances that belong to a group of secondary metabolites of herbs with a polyphenolic structure built in vegetables, fruits, and some beverages [4-6]. Flavonoids are low molecular weight compounds. Polyphenols are secondary plant metabolism chemical substances that can accumulate in various plant organs, including leaves, fruits, roots, and stems. So, Flavonoids have several biological activities as a vast group of bioactive compounds used to manage cancers [7-8]. This review highlighted the chemistry of flavonoids, their synthesis and applications in tumour management, and future perspectives.

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. Flavonoids 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 omnipresent secondary metabolites with various functions in plant physiology and ecology. P-coumaroyl CoA formed from phenylalanine using PAL is the substrate of two enzymes leading to flavonoids or phenylpropanoid compounds. Another, chalcone synthase (CHS), catalyzes p-coumaroyl CoA and three malonyl CoA molecules into naringenin chalcone. Subsequently, it is converted into naringenin by chalcone isomerase (CHI). Flavanone 3-hydroxylase (F3H), flavonol synthase (FLS), and (F3'H) catalyze the formation of different types of flavonol, like quercetin and kaempferol. Downstream, anthocyanidin synthase (ANS) catalyzes the formation of anthocyanins, such as cyanidin and pelargonidin. The schematic flow chart of the synthesis of flavonoids are depicted in Fig. 1 [13].

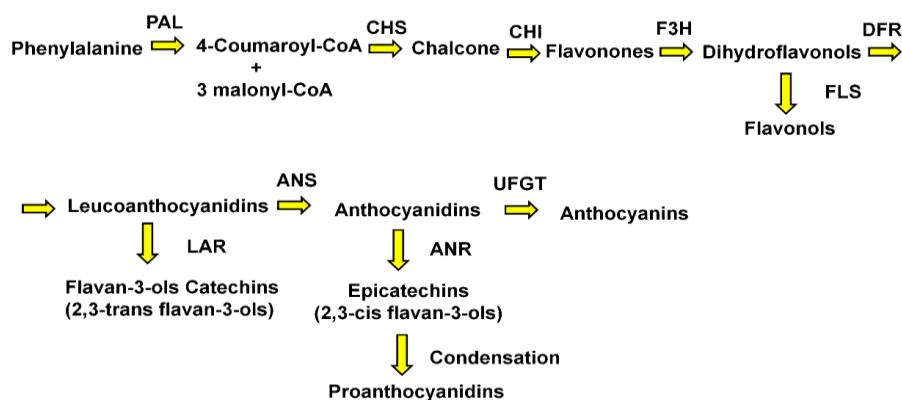


Fig. 1. Schematic flow chart of biosynthesis of flavonoid.

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 Apigenin Chrysin	-OH -OH -OH	-OH -OH -OH	-OH -H -H	-OH -OH -H
Flavonoles		Galangin Kaempferol Quercetin	-OH -OH -OH	-OH -OH -OH	-H -H -OH	-H -OH -OH
Flavanones		Hesperetin Naringenin	-OH -OH	-OH -OH	-OH -H	-OCH ₃ -OH
Flavanonol		Taxifolin	-OH	-OH	-OH	-OH
Isoflavones		Daidzein Genistein	-OH -OH	-H -OH	-H -H	-OH -OH
Flavan-3-ols		Catechin Epicatechin	-OH -OH	-OH -OH	-OH -OH	-OH -OH

5. CANCER CHARACTERISTICS

The apoptosis (a process of programmed cell death), metastatic (spreading), proliferative (growth of cells), mutation (a permanent change in an organism), alteration in metabolism, immune resistance and inflammation characteristics of cancers cells contribute to tumor development and discriminate from normal healthy cells are shown in Fig. 2 [15,16].

5.1 Mechanism of Action of Cancer Cells

Carcinogenesis is a complex and multi-step process that results in various molecular and

cellular changes. Finally, chemoprevention becomes simpler. In the initiation step, the first phase of exposure of the carcinogenic agent and interaction with cells, particularly DNA. In the promotion step, the second phase lasts for a little longer than the previous one; aberrant cells survive, reproduce, and form a cluster of preneoplastic cells. In the final step of progression, carcinogenesis involves the gradual transformation of premalignant cells into neoplastic cells, increased invasiveness, metastatic potential, and the formation of new blood vessels (angiogenesis) shown in Fig. 3 [17,18].

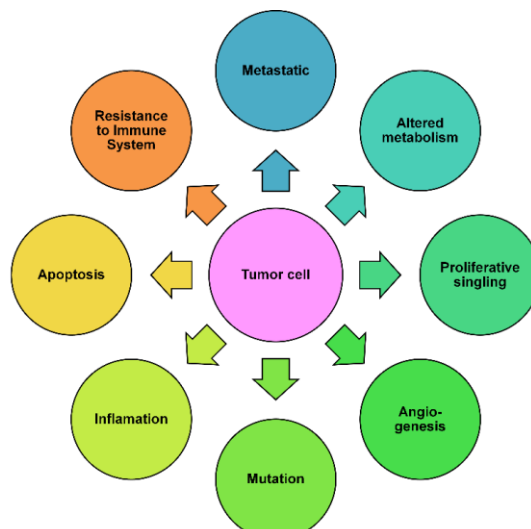


Fig. 2. Characteristics of Tumor cells.

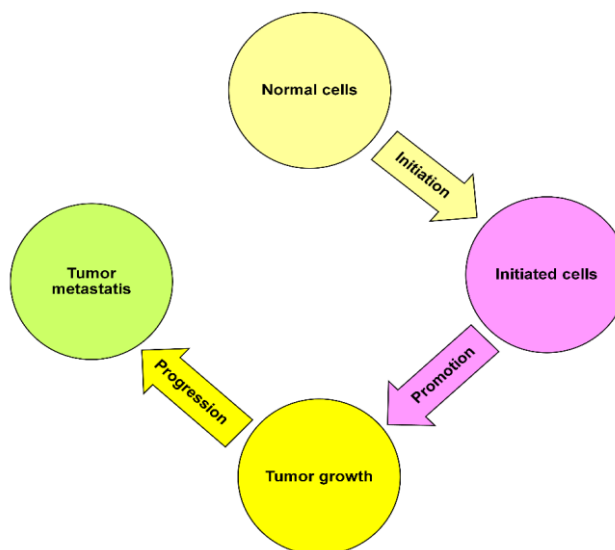


Fig. 3. Mechanism of action of Cancer cells

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 *in-vitro* 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].

6.1. 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]. Challenges of cancer chemoprevention of flavonoids are summarized in Table 3 [33].

6.2 Plant-Based Nanotherapeutic for Cancer

Plant's metabolites have immense potential, organic compounds, referred to as secondary metabolites such as 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 [34-44]. Applications of nanotherapeutics used for cancer management are described in Table 4 [45-73].

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]

Table 3. Challenges in flavonoids in cancer chemoprevention development

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

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		<i>In-vitro</i> model	Du145 cells	Prostate cancer	Induce apoptosis and decrease cell viability [50]

Flavonoids	Nanomaterial Type	Study Type	Cell	Cancer type	Mechanism of action
Quercetin	CSLIPO	<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]
	PEG	Mice model	A549	Lung carcinoma	Antitumor activity in the A549 [53]
	phosphatidylethanolamine	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]
	PLGA-TMX				
	Poly (ethylene glycol)	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]	
Genistein	M-PLGA-TPGS	Mice model	HepG2 cells	Liver cancer	Apoptotic effect [57] pAKT, p-PI3K, DNMT3B and MCL-1 effectively downregulated, anti-proliferative effect non-small cell [58]
	GMLHN (Genistein-miRNA29b-loaded hybrid nanoparticles)	In vitro model	A549 cells	Lung cancer	
	Silibinin	TPGS-b-PCL	Mice model	(HeLa cells)	
PTX-SB-Dex-DOCA		Mice model	A549 cells	Lung carcinoma	
Apigenin	PVA-Eudragit	<i>In-vitro</i> model	KB cells	Oral carcinoma	Inhibition of apoptosis [61]
	AEEA-PEG-PCL	Mice model	4T1 cells	Breast cancer	Angiogenesis suppression [62]
	PEG	<i>In-vitro</i>	MCF 10A	Breast cancer	Cytotoxic effect [63]
	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 hepatoblastoma)	Hepatocellular carcinoma	Inhibit cancer cells [65]

Flavonoids	Nanomaterial Type	Study Type	Cell	Cancer type	Mechanism of action
Naringenin	Chitosan	<i>In-vitro</i>	cell line) and Huh-7 cells A549 cells)	Lung carcinoma	Antioxidant and anticancer activity [66]
Luteolin	Silk fibroin nanoparticles Fa-PEG-PCL	<i>In-vitro</i> Mice model	HeLa cells GL261 cells	Cervical cancer Glioblastoma	Anticancer potential [67] Inhibition of cell growth and apoptosis [68]
Kaempferol	PLA-PEG Gold PEO-PPO-PEO, PLGA	Animal model (mice) <i>In-vitro</i> <i>In-vitro</i>	H292, Tu212 cells A549 A2780/CP70 and OVCAR-3 (A549 cells)	Head and neck carcinoma Lung cancer Ovarian carcinoma	Inhibit tumour growth [69] Cytotoxic effect [70] Selective inhibition of cancer cell viability [71]
Myricetin	SLNs solid lipid nanoparticles	<i>In-vitro</i>		Lung carcinoma	Induce cell growth [72]
Fisetin	HAS (human serum albumin)	<i>In-vitro</i>	MCF-7 cells	Breast carcinoma	Cytotoxic effect [73]

Table 5. List of patents and cancer management from Herbals

Benefit	Patent number	Publication date	Inventor
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 Crysine 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]	US20060189680A1	2006-08-24	Bing-Hua Jiang, Jing Fang
Flavone derivatives act as an antagonist or TNF- α inhibitors [77]	US20060105967A1	2006-05-18	Li-Wei Hsu, Su-Chen Chang, Chen-Hsiang Shen, Yuan-Xiu Liao, Kuo-Sheng Chuang

Benefit	Patent number	Publication date	Inventor
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]	US20030119816A1	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

Brand name	Manufacturer	Dosage form	MRP
Luteolin complex	Swanson	Capsule	1029
Luteolin complex powder	Lutimax	Powder	\$69.95
Apiginin	Swanson ultra	Capsule	IDR297,895
Chrysin	Mrm	Capsule	3100
Quercetin	Healthvit	Capsule	499
Kaemferol	Purebulk	Powder	\$13.75
Galangal root complex	Green organic supplement	Powder	\$18.98
Herceptin	Roche	Liquid	1.11 lakh
Geinstein soy complex	Soy life	Tablet	\$59.48
Isoflavone with genistein	Douglas laboratories	Capsule	\$38

6.3 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.

7. 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 anticancer effects against various cancer and result in novel cancer chemoprevention. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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