Review Article

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

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.*

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].

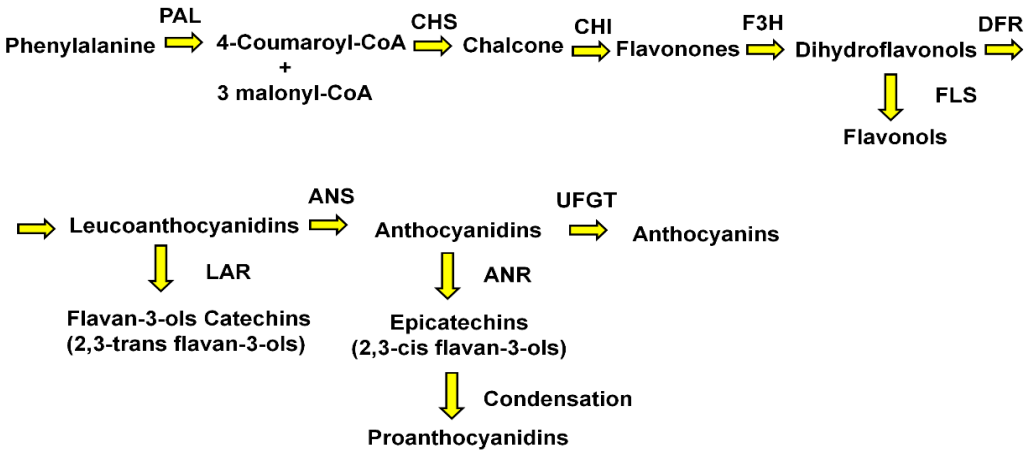
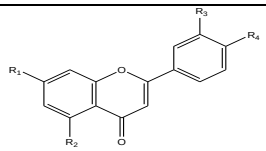
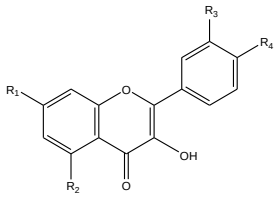
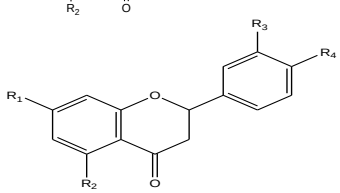
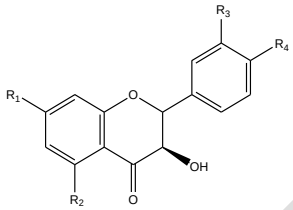
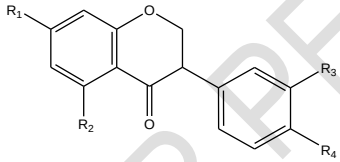
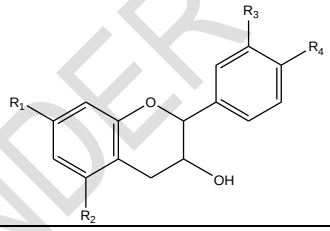


Fig. 1. Schematic flow chart of biosynthesis of flavonoid.

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	-OH	-OH	-OH	-OH
		Apigenin	-OH	-OH	-H	-OH
		Chrysin	-OH	-OH	-H	-H
Flavonoles		Galangin	-OH	-OH	-H	-H
		Kaempferol	-OH	-OH	-H	-OH
		Quercetin	-OH	-OH	-OH	-OH
Flavanones		Hesperetin	-OH	-OH	-OH	$-OCH_3$
		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

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].

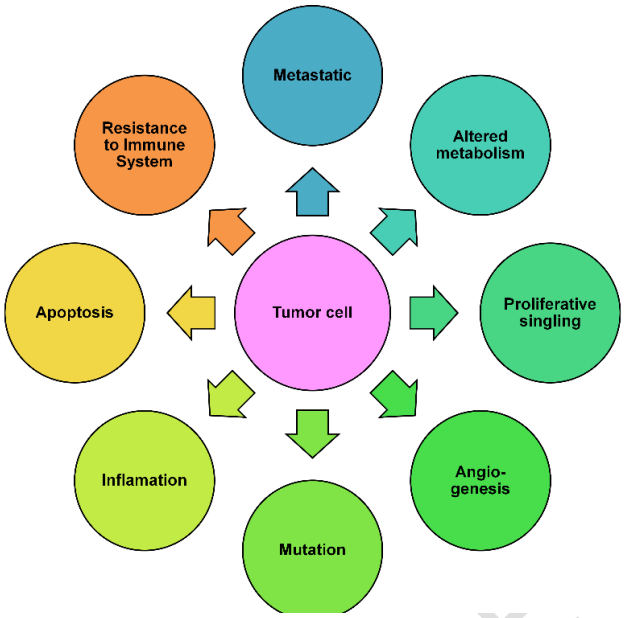


Fig. 2. Characteristics of Tumor cells.

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].

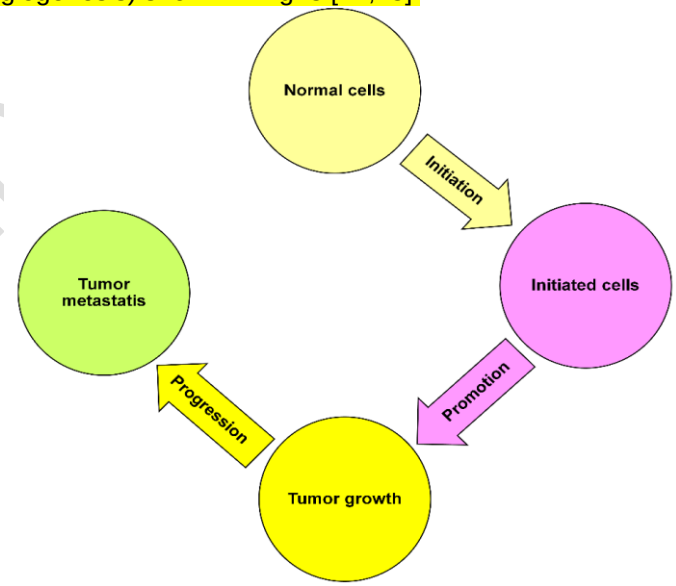


Fig. 3. Mechanism of action of Cancer cells

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 iv-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].

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
Isolation &purification: • High cost • Plant source extinction	**Isolation &purification:** • Novel technology • Fermentation and metabolic

• Low predictability • Low yield • Multistep procedure **Epidemiological**: • High study cost • Long time activity • Population heterogeneity **Pharmacokinetics**: • Drug interaction • Extensive metabolism • Low stability • Microflora interaction	• Optimization technique • Appropriate designing of epidemiological study • High throughput screening technique **Pharmacokinetics**: • ABC transporter inhibitor • Flavonoid piperine formulation • Flavonoid glycoside

8. 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 [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	*In-vitro* model	Du145 cells	Prostate cancer	Induce apoptosis and decrease cell viability [50]
	CSLIPO	*In-vitro* 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 phosphatidyleth	Mice model	A549	Lung carcinoma	Antitumor activity in the A549 [53]

	anolamine				
	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]
	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]
	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	*In-vitro* model	KB cells	Oral carcinoma	Inhibition of apoptosis [61]
	AEAA-PEG-PCL	Mice model	4T1 cells	Breast cancer	Angiogenesis suppression [62]
	PEG	*In-vitro*	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 hepatoblastoma cell line) and Huh-7 cells	Hepatocellular carcinoma	Inhibit cancer cells [65]
Naringenin	Chitosan	*In-vitro*	A549 cells)	Lung carcinoma	Antioxidant and anticancer activity [66]
	Silk fibroin nanoparticles	*In-vitro*	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	*In-vitro*	A549	Lung cancer	Cytotoxic effect [70]
	PEO-PPO-PEO, PLGA	*In-vitro*	A2780/CP70 and OVCAR-3	Ovarian carcinoma	Selective inhibition of cancer cell viability [71]

Myricetin	SLNs solid lipid nanoparticles	*In-vitro*	(A549 cells)	Lung carcinoma	Induce cell growth [72]
Fisetin	HAS (human serum albumin)	*In-vitro*	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.

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 Crysin 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
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

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.

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.

REFERENCES

1. Tsao AS, Kim ES, Hong WK. Chemoprevention of cancer. CA Cancer J Clin. 2004;54(3):150-80.
2. Bravo L. Polyphenols chemistry, dietary sources, metabolism and nutritional significance. Nutr Rev. 1998; 56:317-33
3. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Perspective. 1997

4. Burak M, Imen Y. Flavonoids and their antioxidant properties. Turkiye Klin Tip Bil Derg.1999;19:296–304.
5. Castañeda-Ovando A., Pacheco-Hernández MDL, Páez-Hernández ME, Rodríguez JA, Galán-Vidal CA. Chemical studies of anthocyanins: A review. Food Chem. 2009;113(4):859–871
6. Lee YK, Yuk DY, Lee JW, Lee SY, Ha TY, Oh KW, et al. (-)-Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of beta-amyloid generation and memory deficiency. Brain Res. 2009;1250:164-74.
7. Fernandez SP, Wasowski C, Loscalzo LM, Granger RE, Johnston GAR, Paladini AC, *et al*. Central nervous system depressant action of flavonoid glycosides. Eur J Pharmacol. 2006;539:168-176.
8. Heim KE, Tagliaferro AR, Bobliya DJ. Flavonoids antioxidants: Chemistry, metabolism and structure-activity relationships. J Nutr Biochem. 2002;13:572-584.
9. Middleton EJ. Effect of plant flavonoids on immune and inflammatory cell function. Adv Exp Med Biol. 1998;439:175–182.
10. Karak P. Biological activities of flavonoids: An overview. Int J Pharm Sci Res. 2019;10(4):1567-1574.
11. Harborne JB. The flavonoids- Advances in Research Since 1980. ed 1. London: Chapman and Hall 1988.
12. Middleton E. The flavonoids. Trends Pharmacol Sci. 1984;5:335-338.
13. Zhu Q, Sui S, Lei X, Yang Z, Lu K, Liu G, Liu YG, Li M. Ectopic Expression of the Coleus R2R3 MYB-Type Proanthocyanidin Regulator Gene SsMYB3 Alters the Flower Color in Transgenic Tobacco. PLoS One. 2015;10(10):1-27.
14. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. Sci World J. 2013;29(2013):162750.
15. Neagu M, Constantin C, Popescu ID, Zipeto D, Tzanakakis G, Nikitovic D, *et al.* Inflammation and Metabolism in Cancer Cell-Mitochondria Key Player. Front Oncol. 2019;9:1-15.
16. Lu S, Wang Y. Nonmetabolic functions of metabolic enzymes in cancer development. Cancer Commun. 2018;38(1):1-7.
17. Weinberg RA. Oncogenes and the Molecular Origins of cancer Cold Spring Harbor Laboratory. New York: Cold Spring Harbor; 1989.
18. Pimentel E. Oncogenes. 2nd ed. Florida: CRC Press, 1989.
19. Kurisawa M, Chung JE, Kim YJ, Uyama H, Kobayashi S. Amplification of antioxidant activity and xanthine oxidase inhibition of catechin by enzymatic polymerization. Biomacromolecules. 2003;4(3):469-471.
20. Kim YJ et al. Superoxide anion scavenging and xanthine oxidase inhibition of (þ)-catechin—aldehyde polycondensates. Amplification of the antioxidant property of (þ)-catechin by polycondensation with aldehydes. Biomacromolecules. 2004;5(2):547-552.
21. Panche AN, Diwan AD, Chandra SR. Flavonoids: An overview. J Nutr Sci. 2016;29(5):1-15.
22. Shi YQ, Fukai T, Sakagami H, Chang WJ, Yang PQ, Wang FP, *et al*. Cytotoxic flavonoids with isoprenoid groups from morusmongolica. J Nat Prod. 2001;64:181-188.
23. Preedy VR. Apoptosis. Enfield, N.H: Science Publishers; 2010.
24. Deep G, Agarwal R. Chemopreventive efficacy of silymarin in skin and prostate cancer. Integr Cancer Ther. 2007;6:130-45
25. Knowles LM, Zigrossi DA, Tauber RA, Hightower C, Milner JA. Flavonoids suppress androgen-independent human prostate tumor proliferation. Nutr Cancer. 2000;38:116-122.
26. Wang IK, Lin-Shiau SY, Lin JK. Induction of apoptosis by apigenin and related flavonoids through cytochrome c release and activation of caspase-9 and caspase-3 in leukaemia HL-60 cells. Eur J Cancer.1999;35:1517-1525.

27. Csokay B, Prajda N, Weber G, Olah E. Molecular mechanisms in the antiproliferative action of quercetin. Life Sci.1997;60:2157-2163.
28. Han D, Tachibana H, Yamada K. Inhibition of environmental estrogen induced proliferation of human breast carcinoma MCF-7 cells by flavonoids. In Vitro Cell Dev Biol Anim. 2001;37:275-282.
29. Bai F, Matsui T, Ohtani-Fujita N, Matsukawa Y, Ding Y, Sakai T, *et al*. Promoter activation and following induction of the p21/WAF1 gene by flavone is involved in G1 phase arrest in A549 lung adenocarcinoma cells. FEBS Lett.1998;437:61-64.
30. Iwashita K, Kobori M, Yamaki K, Tsushida T. Flavonoids inhibit cell growth and induce apoptosis in B16 melanoma 4A5 cells. Biosci Biotechnol Biochem. 2000;64:1813-1820.
31. Hakimuddin F, Paliyath G, Meckling K. Selective cytotoxicity of a red grape wine flavonoid fraction against MCF-7 cells. Breast Cancer Res Treat. 2004;85:65-79
32. Kuntz S, Wenzel U, Daniel H. Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. Eur J Nutr.1999;38:133-142.
33. Batra P, Sharma AK. Anti-cancer potential of flavonoids: Recent trends and future perspectives. 3 Biotech. 2013;3(6):439-459.
34. Chahar MK, Sharma N, Dobhal MP, Joshi YC. Flavonoids: A versatile source of anticancer drugs. Pharmacogn Rev. 2011;5(9):1-12.
35. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoni ene J. Flavonoids as anticancer agents. Nutrients. 2020;12(2):1-25.
36. Le Marchand L. Cancer preventive effects of flavonoids-A review. Biomed Pharmacother. 2002;56(6):296-301.
37. https://cancercommun.biomedcentral.com/articles/10.1186/s40880-017-0217-4 Accessed on October 27, 2021.
38. Dobrzynska M, Napierala M, Florek E. Flavonoid nanoparticles: A promising approach for cancer therapy. Biomolecules. 2020;10(9):1-17.
39. Gupta R, Gupta J. Investigation of antimicrobial activity of *euphorbia hirta* Leaves. Int. J. Life Sci. Siddiqui IA, Adhami VM, BharaliDJ, Hafeez BB, Asim M, Khwaja SI, *et al*. Introducing Nanochemoprevention as a Novel Approach for Cancer Control: Proof of Principle with Green Tea Polyphenol Epigallocatechin-3-Gallate. Cancer Res. 2009;69:1712–1716.
40. Siddiqui IA, Bharali DJ, Nihal M, Adhami VM, Khan N, Chamcheu JC, *et al*. Excellent anti-proliferative and pro-apoptotic effects of (−)-epigallocatechin-3-gallate encapsulated in chitosan nanoparticles on human melanoma cell growth both in vitro and in vivo. Nanomed. 2014;10:1619–1626
41. Khan N, Bharali DJ, Adhami VM, Siddiqui IA, Cui H, Shabana SM, *et al*. Oral administration of naturally occurring chitosan-based nanoformulated green tea polyphenol EGCG effectively inhibits prostate cancer cell growth in a xenograft model. Carcinogenesis 2014;35:415–423.
42. Lin YH, Chen ZR, Lai CH, Hsieh CH, Feng CL. Active Targeted Nanoparticles for Oral Administration of Gastric Cancer Therapy. Biomacromolecules 2015;16:3021–3032.
43. Tang P, Sun Q, Yang H, Tang B, Pu H, Li H. Honokiol nanoparticles based on epigallocatechin gallate functionalized chitin to enhance therapeutic effects against liver cancer. Int J Pharm. 2018;545:74–83.
44. Rocha S, Generalov R, Pereira MDC, Peres I, Juzenas P, Coelho MA. Epigallocatechin gallate-loaded polysaccharide nanoparticles for prostate cancer chemoprevention. Nanomed. 2011;6:79–87
45. De Pace RC, Liu X, Sun M, Nie S, Zhang J, Cai Q, Gao W, Pan X, Fan Z, Wang S. Anticancer activities of (-)-epigallocatechin-3-gallate encapsulated nanoliposomes in MCF7 breast cancer cells. J Liposome Res. 2013 Sep;23(3):187-96.

46. Liao B, Ying H, Yu C, Fan Z, Zhang W, Shi J, et al. (−) Epigallocatechin gallate (EGCG)-nanoethosomes as a transdermal delivery system for docetaxel to treat implanted human melanoma cell tumours in mice. Int J Pharm. 2016;512:22–31
47. Tan BJ, Liu Y, Chang KJ, Lim BKW, Chiu GNC. Perorally active nanomicellar formulation of quercetin in the treatment of lung cancer. Int J Nanomed. 2012;7:651-661.
48. Jain AK, Thanki K, Jain S. Co-encapsulation of Tamoxifen and Quercetin in Polymeric Nanoparticles: Implications on Oral Bioavailability, Anti-tumour Efficacy, and Drug-Induced Toxicity. Mol Pharm. 2013;10:3459–3474
49. Dora CL, Costa Silva LF, Mazzarino L, Siqueira JM, Fernandes D, Pacheco LK, Maioral MF, Santos-Silva MC, MuccilloBaisch AL, Assreuy J, *et al*. Oral Delivery of a High Quercetin Payload Nanosized Emulsion: In Vitro and In Vivo Activity Against B16-F10 Melanoma. J Nanosci Nanotechnol. 2016;16:1275-1281.
50. Xing L, Lyu JY, Yang Y, Cui PF, Gu LQ, Qiao JB, *et al*. pH-Responsive de-PEGylated nanoparticles based on triphenylphosphine–quercetin self-assemblies for mitochondria-targeted cancer therapy. Chem Commun. (Camb.) 2017;53:8790-8793.
51. Wu B, Liang Y, Tan Y, Xie C, Shen J, Zhang M, *et al*. Genistein-loaded nanoparticles of star-shaped diblock copolymer mannitol-core PLGA–TPGS for the treatment of liver cancer. Mater Sci Eng C. 2016;59:792-800.
52. Sacko K, Thangavel K, Shoyele SA. Codelivery of Genistein and miRNA-29b to A549 cells using aptamer-hybrid nanoparticle bioconjugates. Nanomaterials 2019;9(7):1-12.
53. Zhang H, Liu G, Zeng X, Wu Y, Yang C, Mei L, *et al*. Fabrication of genistein-loaded biodegradable TPGS-b-PCL nanoparticles for improved therapeutic effects in cervical cancer cells. Int J Nanomed. 2015;10:2461–2473
54. Huo M, Wang H, Zhang Y, Cai H, Zhang P, Li L, *et al*. Co-delivery of silybin and paclitaxel by dextran-based nanoparticles for effective anti-tumour treatment through chemotherapy sensitization and microenvironment modulation. J Control Release. 2020;321:198–210
55. Gohulkumar M, Gurushankar K, Rajendra Prasad N, Krishnakumar N. Enhanced cytotoxicity and apoptosis-induced anticancer effect of silibinin-loaded nanoparticles in oral carcinoma (KB) cells. Mater Sci Eng C. 2014;41:274–282.
56. Jiang M, He K, Qiu T, Sun J, Liu Q, Zhang X, *et al*. Tumour-targeted delivery of silibinin and IPI-549 synergistically inhibit breast cancer by remodeling the microenvironment. Int J Pharm. 2020;581:119239.
57. Sajjadiyan SZ, Ghadernejad H, Milani AT, Mohammadian M, Abdolahpour S, Taslimi S, *et al*. Preparation of silibinin loaded pegylatedniosomal nanoparticles and investigation of its effect on MCF-10A human breast cancer cell line. Der Pharm Lett. 2016;8:70–75.
58. Das S, Das J, Samadder A, Paul A, Khuda-Bukhsh AR. Efficacy of PLGA-loaded apigenin nanoparticles in Benzo[a]pyrene and ultraviolet-B induced skin cancer of mice: Mitochondria mediated apoptotic signalling cascades. Food Chem Toxicol. 2013;62:670–680
59. Bhattacharya S, Mondal L, Mukherjee B, Dutta L, Ehsan I, Debnath MC, *et al*. Apigenin loaded nanoparticle delayed development of hepatocellular carcinoma in rats. Nanomed. 2018;14:1905–1917.
60. Kumar SP, Birundha K, Kaveri K, Devi KTR. Antioxidant studies of chitosan nanoparticles containing naringenin and their cytotoxicity effects in lung cancer cells. Int J Biol Macromol. 2015;78:87–95
61. Fuster MG, Carissimi G, Montalbán MG, Víllora G. Improving Anticancer Therapy with Naringenin-Loaded Silk Fibroin Nanoparticles. Nanomaterials 2020;10(4):1-17.
62. Wu C, Xu Q, Chen X, Liu J. Delivery luteolin with folacin-modified nanoparticle for glioma therapy. Int J Nanomed. 2019;14:7515–7531.

63. Majumdar D, Jung KH, Zhang H, Nannapaneni S, Wang X, Amin ARMR, *et al*. Luteolin Nanoparticle in Chemoprevention: In vitro and in vivo anticancer activity. Cancer Prev Res. 2014;7:65–73.
64. Govindaraju S, Roshini A, Lee M, Yun K. Kaempferol conjugated gold nanoclusters enabled efficient for anticancer therapeutics to A549 lung cancer cells. Int J Nanomed. 2019;14:5147–5157.
65. Luo H, Jiang B, Li B, Li Z, Jiang BH, Chen YC. Kaempferol nanoparticles achieve strong and selective inhibition of ovarian cancer cell viability. Int J Nanomed. 2012;7:3951–3959.
66. Khorsandi L, Mansouri E, Rashno M, Karami MA, Ashtari A. Myricetin Loaded Solid Lipid Nanoparticles Upregulate MLKL and RIPK3 in Human Lung Adenocarcinoma. Int J Pept Res Ther. 2020;26:899–910.
67. Ghosh P, Singha RA, Chaudhury S, Jana SK, Chaudhury K, Dasgupta S. Preparation of albumin-based nanoparticles for delivery of fisetin and evaluation of its cytotoxic activity. Int. J. Biol. Macromol. 2016;86:408–417.
68. Morley K, Koropatnick J, Guthrie N. The use of flavonoids for the inhibition of cellular growth. WO2008035208 (2008). Accessed on October 13, 2021.
69. Walle T, Halushka PVA. Method of treating colon cancer by administering apigenin, luteolin, diosmetin and crysin. WO2001058410 (2001). Accessed on October 13, 2021.
70. Jiang BH, Fang J. Apigenin for chemoprevention, and chemotherapy combined with therapeutic reagents. US20060189680 (2006). Accessed on October 14, 2021.
71. Hsu L, Chang S, Shen C, Liao Y, Chuang K. Flavone derivatives as TNFalpha inhibitors or antagonists. US20060105967 (2006). Accessed on October 14, 2021.
72. Baguley BC, Ching L M, Philpott M. Cancer treatment by combination therapy. US7510830 (2009). Accessed on October 16, 2021.
73. Baguley BC, Ching L, Kestell P, Zhao L. Anti-cancer composition comprising DMXAA or related compound. US7585893 (2009). Accessed on October 16, 2021.
74. Haesslein J, Lefrancois D, Uridat E, Zhang J. Flavone derivatives, preparation method and use as medicines. US20030119816 (2003). Accessed on October 16, 2021.
75. Taylor RB, Henley EC. Composition for and method of preventing or treating breast cancer. US6300367 (2001). Accessed on October 16, 2021.
76. Thurn M J, Huang L J. Methods for treating cancer with legume plant extracts. US6004558 (1999). Accessed on October 16, 2021.
77. Sarkar F, Padhye S. Flavanone Compound and uses thereof. US7256214 (2007). Accessed on October 16, 2021.
78. https://www.desertcart.in/products/70311729-luteolin-complex-100-mg-supplement. Accessed on October 2, 2021.

79. https://www.lutimax.com/shop/powder/luteolin-complex-powder-l-theanine/. Accessed on October 3, 2021.
80. https://www.ubuy.co.id/en/product/gk9z9b2-swanson-apigenin-prostate-health-supplements-nerve-health-glucose-metabolism-50-mg-90-capsules. Accessed on October 2, 2021.
81. https://www.indiamart.com/proddetail/mrm-chrysin-500-dietary-suppliment-23728031830.html. Accessed on October 2, 2021.
82. https://healthvit.com/products/healthvit-quercetin-100mg-natural-bioflavonoid-60-capsules?variant=37103456944320&currency=inr&utm_medium=product_sync&utm_source=google&utm_content=sag_organic&utm_campaign=sag_organic&gclid=cj0kcqjwtrslbhclarisach6rmjfiizmje0yi9m-hj5ufnzb6ono5_orfk9nj-qz3hqcpfzh7snnqewaavqyealw_wcb Accessed on October 4, 2021.
83. https://purebulk.com/products/kaempferol. Accessed on October 6, 2021.
84. https://greenorganicsupplements.com/products/galangal-galangin?variant=37060904222900#&gid=productimages&pid=1 Accessed on October 7, 2021.
85. https://www.indiamart.com/proddetail/herceptin-trastuzumab-440mg-infusion-22625822673.html Accessed on October 14, 2021.
86. https://www.ayurvedicherbsdirect.com/products/genistein-soy-isoflavones-1000mg-240-ct-source-naturals Accessed on October 18, 2021.
87. https://www.douglaslabs.com/isoflavone-250-with-genistein.html Accessed on October 20, 2021.