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Flavonoid derivatives as anticancer moiety and its effect on cancer cell lines: an updated review

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Abstract: Cancer is now considered the number one leading cause of premature death in industrialized countries. Chemotherapy drugs are quite expensive and cause multiple side effects. Natural products have been studied in depth for their potential as anticancer agents because of their remarkable chemical variability. Among the various natural metabolites, flavonoids are secondary metabolites that are extensively present in nature, have potent anti-cancer properties, have few adverse effects, and also show synergistic benefits. Numerous laboratories are diligently investigating the chemistry and biology of novel flavonoid derivatives due to the demand for and worth of these drugs. In this review, we summarized clinical trials of various flavonoids, molecular pathways against various cancer cell lines, and recent updates on the anticancer activity of flavonoid derivatives against various cancer cells synthesized by various methods, more studies are needed to develop the following mentioned flavonoid derivatives as an anticancer drug.

Keywords: flavonoids; cancer; chemotherapy; molecular targets

INTRODUCTION

A significant global issue in terms of human health is cancer. There are many different types of cancer, and each one is associated with an increase in the number of cells in the body. One element of the mechanisms that lead to cancer is cell proliferation and it is distinct from other tumors because of its ability to invade surrounding healthy tissues. The WHO reports that in 2020, there were 2.30 million new instances of breast cancer, 2.20 million cases of lung cancer, 1.90 million cases of colon and rectal cancer, 1.40 million cases of prostate cancer, 1.25 million cases of skin cancer, and 1.08 million cases of stomach cancer.[1–3] Anticancer therapies involve several methods, such as surgery, chemotherapy, and radiation, perhaps individually or in combination. However, side effects and

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multidrug resistance are two major obstacles to successful cancer treatment because this condition is a complicated issue, and it has been challenging to discover new medicines to combat it.[4] Cancer drug sales are forecast to reach $223.21 billion in 2022, up from $199.95 billion in 2021, at a compound annual growth rate (CAGR) of 11.6%. Multiple laboratories are extensively investigating the chemistry and biology of novel anticancer agents due to the demand for and value of these drugs. Cytotoxic drugs, many of which are of natural origin, are currently the pillars of anticancer chemotherapy.

Natural products can be used as important sources for the development of new active molecules that might be used as leads or scaffolds to create novel, highly effective medicines with increased biological activity. Drugs that are obtained from natural sources show better anticancer activities with minimal side effects.[5] Among the various plant metabolites, flavonoids are plants' most significant low molecular weight secondary metabolites. These metabolites have a large number of polyphenolic chemicals, including benzopyran with a substituted keto group on the pyran ring. The configuration, substitution of a hydroxy group, and the number of the hydroxyl group on a parent moiety primarily affect the pharmacokinetics and pharmacological activity. There is a need to examine the relationship between structure and function since flavonoids are directly linked to human dietary components and health.[6,7] Today, flavonoids are considered a significant ingredient in a wide range of nutraceutical, pharmacological, therapeutic, and cosmetic uses. This is explained by their ability to affect important cellular enzyme activity in addition to their antitumor, anti-inflammatory, antifungal, anti-aging, antiviral, antiallergic, and antioxidant activities.[8] Flavanols, anthocyanidins, isoflavones, flavones, flavanones, and flavanonols are the subclasses of flavonoids.[9]

Anti-cancer drugs containing flavonoid moiety from the natural source showed minimal side effects and exhibited synergistic activity. As anticancer drugs without undesirable side effects, quercetin, wogonin, kaempferol, silibinin, and apigenin are all recognized.[10] Luteolin showed synergistic activity with cisplatin against ovarian cancer. Quercetin with doxorubicin exhibited a synergistic effect against neuroblastoma and anaplastic osteosarcoma cell lines, quercetin with cisplatin against human mesothelioma cancer cell lines, and quercetin with temodar (temozolomide) against human astrocytoma cell line.[11]

For the last decade, researchers have mainly focused on synthesizing flavonoid derivatives. In this present review, we have summarized the clinical trials of flavonoids, mode of action, molecular targets for some important flavonoids against various cancer cells, and results of the anticancer activity of different flavonoid derivatives synthesized by the various synthetic method in the past 4 years i.e., between the years 2019-2022, and describe their potential against various cancer cell lines.

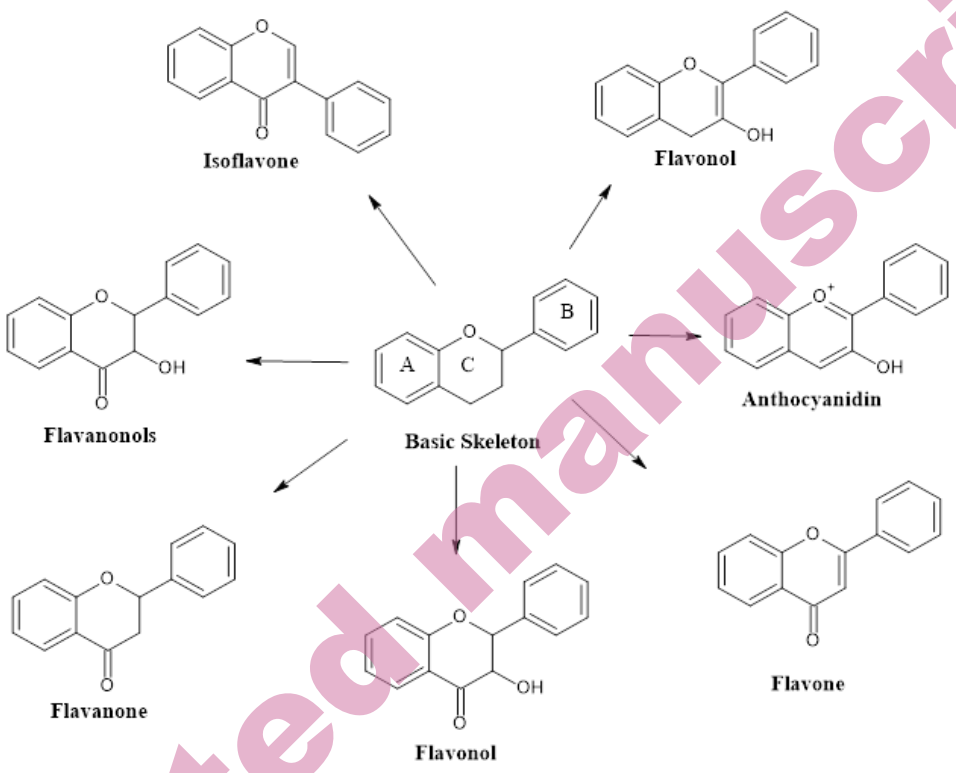


Fig 1: The basic skeleton of Flavonoids and their subclasses

Mode of action of flavonoids in chemotherapy:

Flavonoids are believed to be bioactive, safe, and widely available molecules and it shows a wide variety of anticancer activity through various mechanism of action like cell cycle arrest, mutagen inhibition, antiproliferation, inducing programmed cell death, inhibits the formation of new blood vessels (angiogenesis), antioxidation, modulates ROS-scavenging enzyme activities, and reversal of multidrug resistance or a combination of these mechanisms. Followed by one of the significant drawbacks of anti-cancer agents is the cancer cells' susceptibility to or resistance to chemotherapeutics therapies. Flavonoids like kaempferol, quercetin, or morin, exert potent activity to modulate cancer cell chemoresistance and increase the efficacy of chemotherapy by increased programmed cell death or apoptosis and induced cell cycle arrest in both chemo-resistant and sensitive cancer cells.[12–15]

Clinical trials of flavonoid derivatives:

Clinical trials were undertaken on 64 individuals (18-65years) by Zwicker JI *et al.*, (2015-2019) for 56 days to investigate the effectiveness of the drug Isoquercetin (3-O-glucoside of quercetin) at two doses (500mg for 28 patients and

1000mg for 28 patients) in preventing venous thrombosis (blood clots) in individuals suffering from pancreatic and colorectal cancer by targeting protein disulfide isomerase (PDI). A thiol isomerase called protein disulfide isomerase (PDI), is released by vascular cells and is essential for thrombus development. At 500mg, constipation affected one patient, diarrhea affected four patients, hyponatremia affected one patient, epistaxis affects one patient, and nausea affected two patients. At 1000mg, only one patient was affected by gastrointestinal reflux.[16]

Clinical trials were performed by the University of Minnesota to determine the effectiveness of purple grape juice (rich in flavonoids) in improving vascular health in pediatric cancer survivors to determine the effect of purple color grape juice on endothelial function and biomarkers of vascular and systemic oxidative stress. Twenty-four individuals between the ages of 10 and 30 volunteered in the clinical studies.[17]

The University of Hohenheim, in collaboration with University Hospital Tuebingen and Quercegen Pharmaceuticals, conducted clinical trials to examine the efficiency of genistein (isoflavonoid) and quercetin (flavonoid), polyphenolic phytochemicals in comparison with placebo on the rate of increase in prostate-specific antigen (PSA). Analyzing malondialdehyde and protein carbonyl as markers of oxidative status as well as assessing the prevalence of prostate cancer are the secondary goals.[18]

The effectiveness of quercetin in preventing and treating chemotherapy-induced oral mucositis in blood cancer patients was investigated by Pegah Mosannen Mozafari of Mashhad University of Medical Sciences. They give 250 mg of quercetin capsules to 10 patients in the case group and give a placebo to 10 patients in the control group containing lactose. To determine the onset and severity of oral mucositis, patients underwent examinations every other day.[19]

Fenugreek seeds contain high concentrations of saponins and flavonoids, which are known to reduce blood lipid levels and improve insulin sensitivity. With the main goal of evaluating the decrease in ovarian volume and a decrease in the number of ovarian cysts, Dr. Amrita Sarkari Jaipuriar, MS, and Garg Hospital, Goalghar conducted a clinical trial to examine the effectiveness of fenugreek seeds extract in patients with polycystic ovary syndrome.[20]

Clinical trials were conducted by Philip Diaz of Ohio State University to determine whether green tea (rich in flavonoids), may reduce the chance of developing certain cancers. The primary and secondary objective of this clinical trial is to determine the free radical scavenging and measuring NF-kappaB-inducing kinase by giving 4 cups of green tea for 6 weeks to patients.[21]

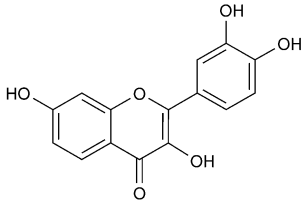
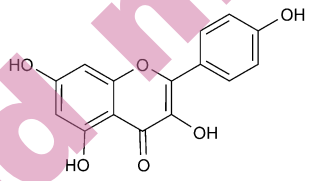
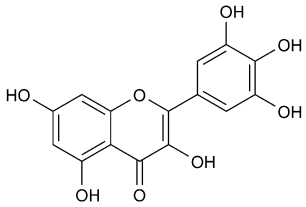
Brigham, Joann E, Manson M D, and Women's Hospital conducted clinical trials by giving 2 cocoa extract capsules (containing 500mg of flavanols, 80 mg of epicatechin, and 50mg of theobromine) as a dietary supplement to evaluate

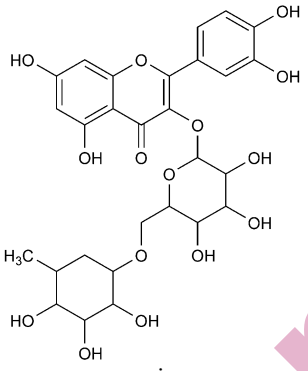
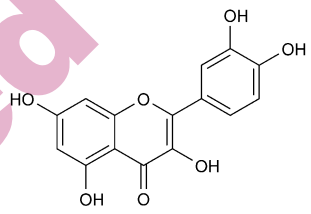
whether cocoa extract decreases the risk of cardiovascular diseases and cancer by reviewing the various reports like pathology, surgical, operative, and diagnostic review of both inpatients and outpatients.[22] The results of the above-mentioned clinical trials were summarized in Table No. 1, in that some of them not disclosed their results of clinical trials.

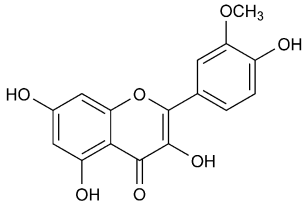
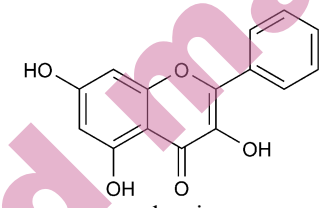
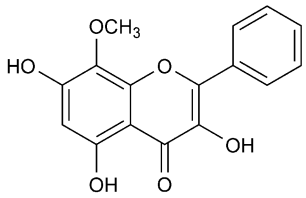
Table 1: Clinical Trials data of Flavonoids:

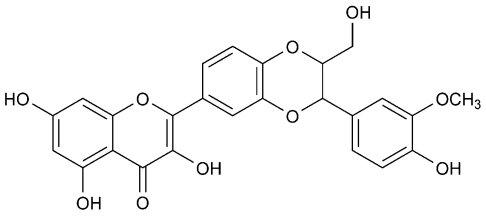
Drugs/NCT No.	Target	Results
Isoquercetin/ NCT02195232	Protein disulfide isomerase (PDI)	D-dimer plasma concentration (Decrease, Median value= -21.9%/p=0.0002). ↑No venous thromboembolism events. Protein disulfide isomerase (PDI) inhibitory activity (37% at 500mg & 73.3% at 1000mg). ↓ Platelet-dependent thrombin generation (Median value = -31.1% at 500mg & -57.2% at 1000mg). ↓Circulation of soluble platelet selectin at 1000mg.
Purple Grape juice & Apple juice/NCT01043939	Endothelial function and biomarkers of vascular and systemic oxidative stress (oxidized low-density lipoprotein, Myeloperoxidase, High Sensitivity C-Reactive Protein.	Enhances the antioxidant activity Reduces the oxidation of low-density lipoprotein Improves vasodilation
Quercetin and Genistein/ NCT01538316	Prostate-specific antigen (PSA)	No results
Quercetin Tablets/ NCT01732393	Chemotherapy Induced Oral Mucositis	No results
Furocyst (Fenugreek seed extract)/ NCT02789488	Reduction in ovary volume	No results
Green Tea/ NCT01162642	Scavenging of free radicals and NF-kappaB-inducing kinase	No results
Cocoa extract/ NCT02422745	Cardiovascular events and Invasive cancer	No results

Table 2: List of Various Molecular Targeted pathways for Flavonoids Against Various Cancer Cell Lines:

Flavonoids	
	 quercetin
Cancer Cell Lines	MCF-7, CNE2, HK1, HL-60, HPB-ALL, and SCC-9 cancer cell lines
Targeted Molecular Pathway	Extracellular signal-regulated kinase (ERK), Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR), Mitochondrial and Caspase Cascade Pathways.
IC_{50} Values	MCF-7=28 µM, HK1= 24 µM, HPB-ALL=18 µM
References	23
	 kaempferol
Cancer Cell Lines	PANC-1 and MIA PaCa-2 cancer cell lines.
Targeted Molecular Pathway	Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR) signaling pathway
Cancer Cell Lines	PANC-1 =78.75 µM and MIA PaCa-2 =79.07 µM
References	24
	 myricetin
Cancer Cell Lines	DU145, PC3, HCT-15, HT-29, A549, OVCAR-3, T24, PaCa-2, Panc1, SKOV3, MCF-7 and HepG2 cell lines.
Targeted Molecular Pathway	Nuclear factor kappa B (NF-κB), Nuclear factor erythroid 2–related factor 2 (Nrf2), Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR), Janus kinase/signal transducers and activators of transcription (JAK/STAT), and canonical Wnt (Wnt/β-catenin) pathways.
Cancer Cell Lines	HT-29=47.6µM, and MCF-7=50µM
References	27

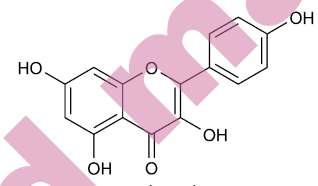
	 rutin
Cancer Cell Lines	MCF-7, MDA-MB-231, A549, HT-29, SW480 cancer cell lines.
Targeted Molecular Pathway	Nuclear factor kappa B (NF-κB), Nuclear factor erythroid 2–related factor 2 (Nrf2), Extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK), and p38 mitogen-activated protein kinases (p38 MAPK) pathways.
Cancer Cell Lines	MDA-MB-231=40 µM, HT-29=46 µM, and SW480= 54 µM.
`References	25,26
	 luteolin
Cancer Cell Lines	HCT15, MV4-11, CO115, and MCF-7 cancer cell lines.
Targeted Molecular Pathway	Nuclear factor kappa B (NF-κB), Reactive oxygen species (ROS), canonical Wnt (Wnt/β-catenin), DNA Topoisomerases and Heat shock protein 90, E-cadherin, Mammalian target of rapamycin (mTOR), Integrin β1 and focal adhesion kinase, Phosphoinositide-3-kinase (P13K) pathways.
Cancer Cell Lines	HCT15=68 µM, MV4-11= 58 µM, CO115=66 µM, and MCF-7=36 µM
`References	28

	 isorhamnetin
Cancer Cell Lines	BT474, BT-549, MDA-MB-231, PANC-1, MCF7, T47D, and MDA-MB-468 cancer cell lines.
Targeted Molecular Pathway	Mitochondria-dependent intrinsic, Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR), Mitogen-activated protein kinase (MAPK) pathways.
Cancer Cell Lines	BT474=10 µM, BT-549=10 µM, MB-231=16 µM, PANC-1= 26.5µM.
`References	29–31
	 galangin
Cancer Cell Lines	MCF-7, T47D, Hs578T, AMN-3, CP70, OVAC-3, HeLa, TU212, HEP-2, hct-15, HT-29, A549, B16F10, Eca9760 TE-1 cancer cell lines.
Targeted Molecular Pathway	Activated protein kinase (AMPK), Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR), Poly (ADP-Ribose) Polymerase-1 pathways.
Cancer Cell Lines	MCF-7=20 µM, T47D=24 µM, Hs578T=11 µM, OVAC-3=34.5 µM, HeLa=50 µM, TU212=10 µM.
`References	32
	 wogonin
Cancer Cell Lines	SW-480, A549, HCT-116, BT-549, and MCF-7 cancer cell lines.
Targeted Molecular Pathway	Mitogen-activated protein kinase 1 (MEK1), Nuclear factor kappa B (NF-κB), Peroxisome proliferator-activated receptor gamma (PPAR-γ), and Tumor necrosis factor-α (TNF- α) pathways.
Cancer Cell Lines	SW480=47.8 µM, HCT-116=44.6 µM, BT-549=36 µM.
`References	33



silibinin

Cancer Cell Lines	MCF-7, H460, HCC827, NCI-H1975, A549, and NCI-H1299 cancer cell lines.
Targeted Molecular Pathway	Epidermal growth factor receptor (EGFR/LOX) pathways.
Cancer Cell Lines	NCI-H1975=96.56 µM, MCF-7= 46µM, H460=50.5 µM, H1975=48 µM
`References	34

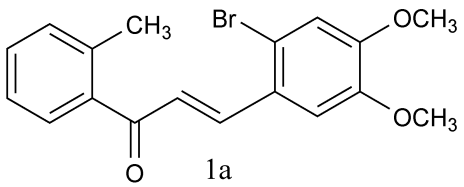


apigenin

Cancer Cell Lines	SW480, A375, A549, BT-474, MDA-MB-231, DLD1, A2780, DU145, and C8161, cancer cell lines.
Targeted Molecular Pathway	Janus kinase/signal transducers and activators of transcription (JAK/STAT), Mitogen-activated protein kinase/ extracellular-signal-regulated kinase (MAPK/ERK), canonical Wnt (Wnt/β-catenin), Nuclear factor kappa B (NF-κB), Phosphoinositide 3 kinase target of rapamycin (PI3K/Akt/mTOR) pathways.
Cancer Cell Lines	MDA-MB-231=35.15 µM, and A549=79.8 µM,
`References	35

Flavonoid derivatives as anticancer moiety:

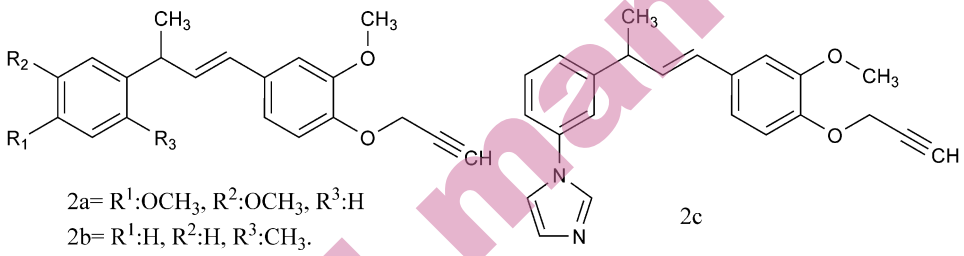
Fikroh RA *et al.*, (2020) synthesized the (2E)-3-(2-bromo-4,5-dimethoxy phenyl)-1-(2-methyl phenyl) propanone by the Claisen-Schmidt condensation reaction of 2-bromo-4,5-dimethoxybenzaldehyde and 2- hydroxy acetophenone with a good yield of 78%. The chalcone derivative, 1a (Fig 1) showed moderated action on breast cancer cell lines (MCF-7) at IC_{50} of 42.19 µg/ml.[36]



1a

Fig 2: (2E)-3-(2-bromo-4,5-dimethoxyphenyl)-1-(2-methylphenyl) propanone.

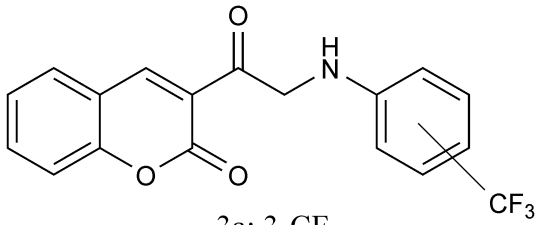
Ngameni B *et al.*, (2021) synthesized the novel series of O-substituted chalcone moieties containing various groups like allyl-, propargyl- or prenyl-substituent at different positions on both rings by the Claisen-Schmidt condensation of O-allyl, and O-propargyl vanillin and substituted aromatic ketones. Compounds 2a showed antitumor action against HCT116 p53 colon adenocarcinoma cells, 2b against CCRF-CEM cells and MDA-MB-231-BCRP breast adenocarcinoma cells, and 2c against HCT116 p53 cells and HCT116 p53 human colon lung cancer cells (Fig 3). All these compounds showed activity at IC_{50} values below 1 µM.[37]



2a= R^1:OCH_3, R^2:OCH_3, R^3:H
2b= R^1:H, R^2:H, R^3:CH_3.

Fig 3: O-propargylchalcone derivatives (2a & 2b) and O-propargylated chalcone (2c).

Pangal A *et al.*, (2022) synthesized the chromen-2-one compounds by grinding of coumarin, trifluoro substituted anilines, and potassium carbonate under solvent-free conditions. Compounds 3a and 3c showed good anticancer activity against HeLa cell lines at ≤10µg/ml. Components 3a and 3b (Fig 4) showed moderate anticancer activity at a lower concentration against HeLa and MCF-7 cell lines.[38]

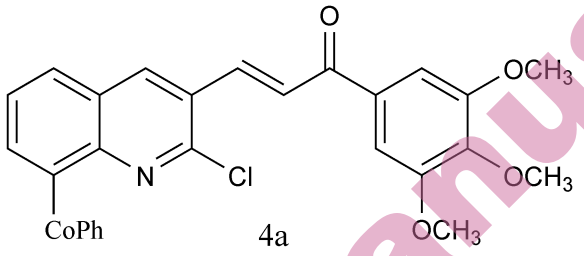


3a: 3-CF_3
3b: 3,5-CF_3
3c: 2-CF_3

Fig 4: 3-(2-(substituted-(trifluoromethyl) phenylamino) acetyl)-2H-chromen-2-one derivatives

Mirzaei S *et al.*, (2020) synthesized the hybrids of quinoline and chalcones as tubulin inhibitors. Compound 4a (Fig 5) showed good antiproliferative activity at LD_{50} of 22.4 µM against four human cancer cell lines like A2780 (human ovarian

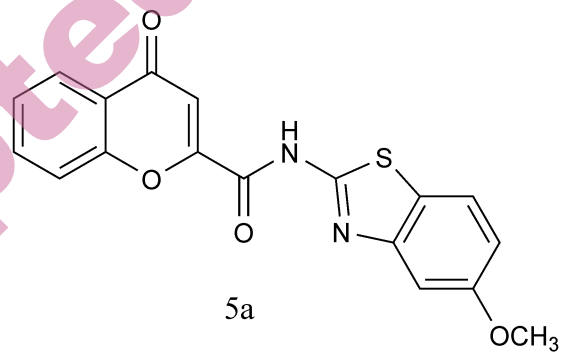
cancer cell lines), A2780/RCIS (Cisplatin resistant human ovarian cancer cell lines), MCF-7 (human breast cancer cell lines), and MCF-7/MX (Mitoxantrone resistant human breast cancer cell lines) and normal Huvec cancer cell lines by causing cell cycle arrest at the G2/M phase.[39]



4a

Fig 5: Benzoyl-2-chloroquinolin-3-yl (E)-3-(1,3,4,5-trimethoxyphenyl) propanone.

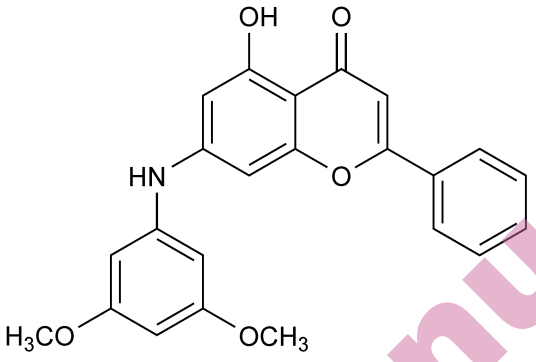
Wang *et al.*, (2022) synthesized the chromone-2- aminothiazole scaffolds as novel CK2 inhibitors. Compound 5a (Fig 6) showed better activity against CK2 cells at IC_{50} value of 0.08 µM and exhibited more potent anticancer activity against HL-60 tumor cells at IC_{50} value of 0.25 µM by inhibiting the downstream of casein kinase II, including α-catenin/Akt pathway and PARP/Survivin pathway.[40]



5a

Fig 6: N-(5-methoxy-1,3-benzothiazol-2-yl)-4-oxo-4H-1-benzopyran-2-carboxamide

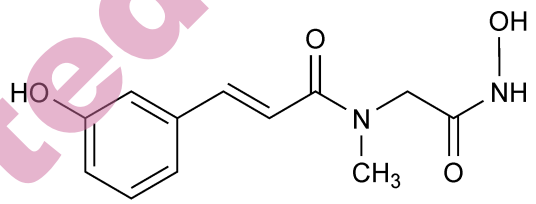
Mayer *et al.*, (2020) reported the synthesis of novel 7-aminochrysin derivatives by alkylated with N-phenylchloroacetamides at the 7th position. Compound 6a (Fig 7) anticancer activity against MCF7 (GI_{50}=30nM) cell line of breast cancer and on the HCT-15 cell line of colon cancer cell line (GI_{50}=60nM) at a nanomolar concentration.[41]



6a

Fig 7: 7-(3,5-dimethoxyanilino)-5-hydroxy-2-phenyl-4H-1-benzopyranone

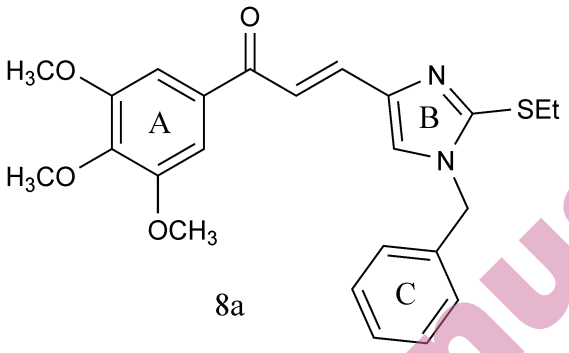
Parvinder Kaur *et al.*, (2022) synthesized a new series of cinnamic acid derivatives by reacting 2-chloro-N-hydroxy acetamide and cinnamic acid amide. Compound 7a (Fig 8) showed potent activity against lung cancer cell lines (A-549) at an IC_{50} value of 10.36 µM among all synthesized derivatives.[42]



7a

Fig 8: (2E)-N-Methyl-N-((hydroxycarbamoyl)methyl)-3-(3-hydroxyphenyl)prop-2-enamide

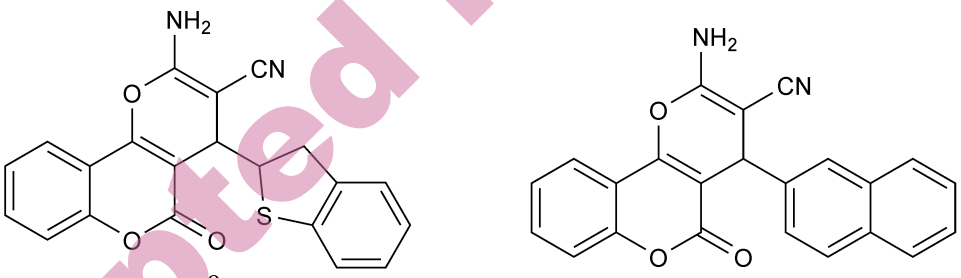
Rahimzadeh Oskuei S *et al.*, (2021) synthesized the novel imidazole-chalcone moities as inhibitors of tubulin polymerization and as an anticancer agent. In that series of derivatives, compound 8a (Fig 9) showed a better cytotoxicity effect against adenocarcinoma human alveolar basal epithelial cells (A549), human breast cancer cells (MCF-7), mitoxantrone resistant human breast cancer cells (MCF-7/MX), and human hepatocellular carcinoma cells (HEPG2) at IC_{50} value ranging from 7.05 to 63.43 µM.[43]



8a

Fig 9: (E)-3-(1-benzyl-2-(ethylthio)-1H-imidazol-4-yl)-1-(3,4,5-trimethoxyphenyl)propenone

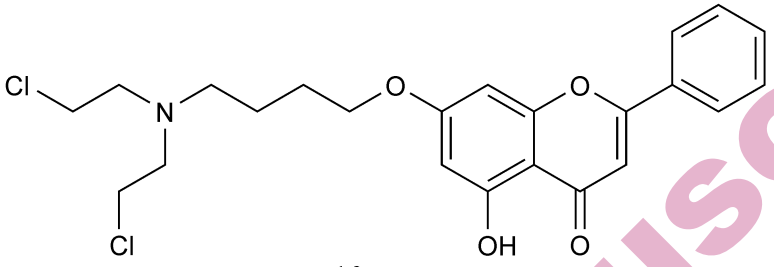
Sarkate AP *et al.*, (2021) reported the one pot synthesis of new series of flavonoid derivatives with different heterocyclic moieties. Compound 9a and 9b showed moderate anticancer activity by inhibiting the enzyme topoisomerase II with IC_{50} values of 10.28 and 12.38 µM against cancer cell lines.[44]



9a 9b

Fig 10: Substituted 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-c]chromene-3-carbonitrile

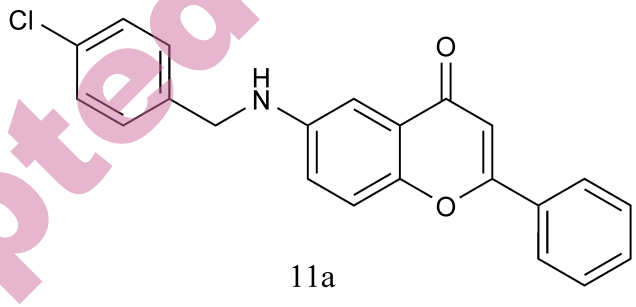
Yan X *et al.*, (2020) reported synthesizing new genistein and chrysin nitrogen mustard derivatives according to the principle of combination and hybridization. In this series, compound 10a (Fig 11) showed better cytotoxic activity against HeLa cancer cell line (IC_{50}=1.43 µM), PC-3 cancer cell lines (IC_{50}=2.32µM), DU145 cancer cell lines (IC_{50}=2.91µM), MCF-7 cancer cell lines (IC_{50}=4.90µM), which were more than 4 times higher than melphalan.[45]



10a

Fig 11: 7-[3-[bis(2-chloroethyl)amino]propoxy]-5-hydroxy-2-phenyl-4H-chromenone

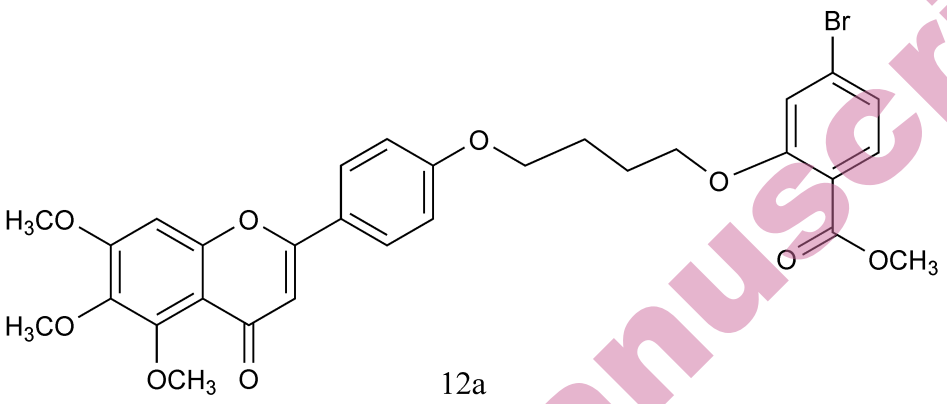
Thorat NM *et al.*, (2021) synthesized the N-benzyl derivatives of 6-aminofavone by using the multi-step synthetic procedure like methylation, Friedel–Craft acylation and in situ demethylation, Bekar–Venkataraman rearrangement, Buchwald coupling reaction, these reactions were employed in different steps for different starting materials as a potent novel anticancer moities. In this series, compound 11a (Fig 12) showed high potent topoisomerase II enzyme inhibition activity at IC_{50} value of 12.10 µM.[46]



11a

Fig 12: 6-{(4-chlorophenyl)methyl]amino}-2-phenyl-4H-1-benzopyranone

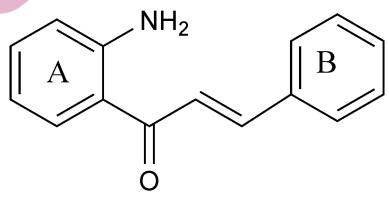
Liu R *et al.*, (2020) designed and synthesized the novel 5,6,7-Trimethoxy flavonoid salicylate moieties by combining 3 different moieties like trimethoxyphenyl, Flavonoid, and Salicylic acid based on the principle of combination. In these derivatives, compound 12a exhibits better anticancer activity against HGC-27 cells and MGC-803 cells with IC_{50} values of 10.20 ± 6.90 µM and 17.20 ± 3.04 µM, respectively.[47]



12a

Fig 13: 5-Bromo-2-{3-[4-(5,6,7-trimethoxy-4-oxo-4H-chromen-2-yl)-phenoxy] -propoxy -benzoate of methyl acid

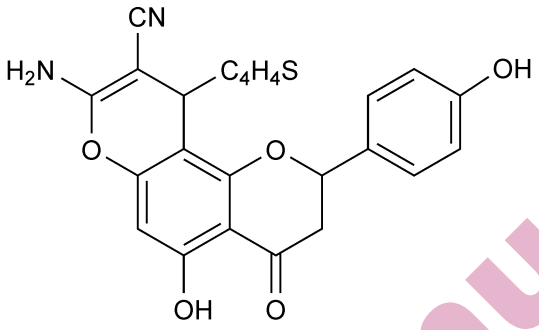
Kozłowska J *et al.*, (2019) synthesized the novel derivatives of aminochalcones by using classical Claisen-Schmidt reaction of substituted aminoacetophenone with aromatic aldehydes. In this series of aminochalcones derivatives, compound 13a (Fig 14) showed better anticancer activity against different human colon carcinoma cell lines at low IC_{50} values i.e., HT-29 (IC_{50}=1.43µmL^{-1}), LS180 (IC_{50}=2.06µmL^{-1}) LoVo (IC_{50}=1.56µmL^{-1}), LoVo/DX (IC_{50}=1.43µmL^{-1}), and COS7 (IC_{50}=26.4µmL^{-1}).[48]



13a

Fig 14: (2E)-1-(2-aminophenyl)-3-phenylpropanone

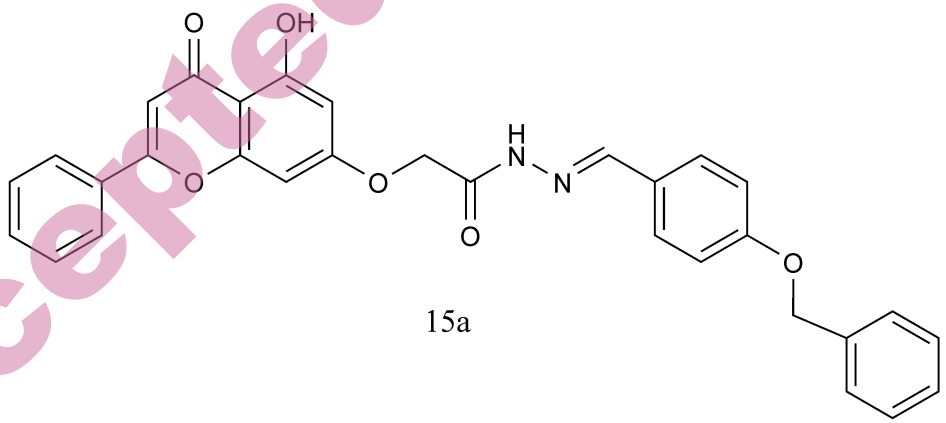
Assirey *et al.*, (2020) synthesized the 4′, 5, 7-trihydroxy-flavanone through knoevenagal condensation of an aldehyde, followed by an intramolecular Michael addition reaction. Compound 14a (Fig 15) exhibited potent anticancer activity against HCT-116, HepG-2, MCF-7, and A-549 tumor cell lines with IC_{50} values at 1.08, 2.42, 2.04, & 1.39 µg/mL respectively.[49]



14a

Fig 15: 8-amino-10-(thiophene)-5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-3,4-dihydro-2H-10H-pyrano[2,3-f] chromene-9-carbonitrile

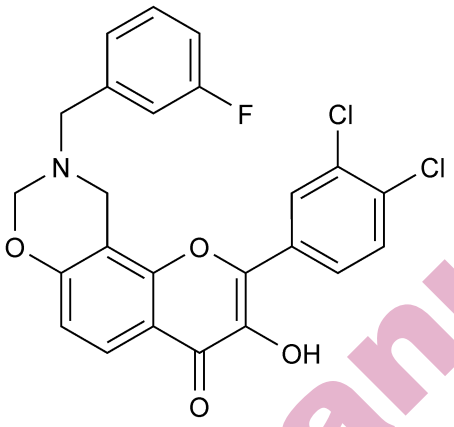
Al-Oudat BA *et al.*, (2019) designed and synthesized the derivatives of chrysin bearing the N′-alkylidene/arylideneacetohydrazide core by the reaction of hydrazide with different aldehydes. Compound 15a (Fig 16) with 4-benzyloxy substituent showed good antitumor activity against MDA-MB-231 and MCF-7 cell lines with IC_{50} values of 3.3 µM, and 4.2 µM respectively.[50]



15a

Fig 16: N-(4-(benzyloxy)benzylidene)-2-((5- hydroxy-4-oxo-2-phenyl-4H-chromen-7-yl) oxy)acetohydrazide

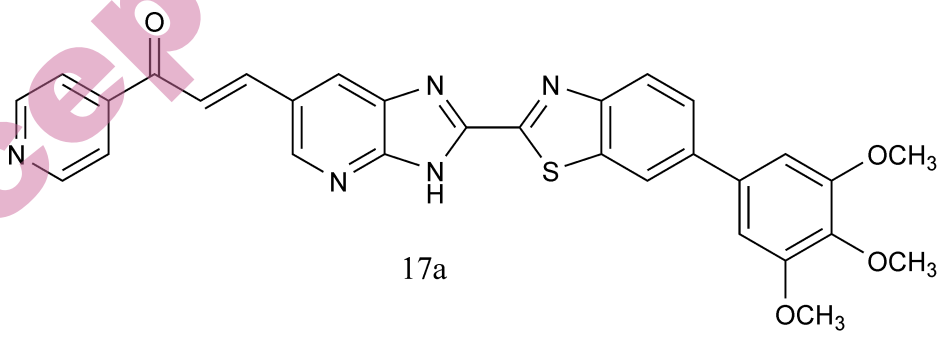
Hou *et al.*, (2021) designed and synthesized the novel derivatives of icaritin as inhibitors of putative DEPTOR by multi-step reaction. Compound 16a (Fig 17) exhibited a good antimultiple myeloma activity with an IC_{50} of 1.09 µM for Human multiple myeloma cell lines (RPMI 8226), induced RPMI 8226 apoptosis, and acts by blocking S phase of the cell cycle.[51]



16a

Fig 17: 2-(3,4-Dichlorophenyl)-9-(3-fluorobenzyl)-3-hydroxy-9,10-dihydro-4H,8H-chromeno[8,7-e]-[1,3]-oxazin-4-one

Kumar *et al.*, (2021) synthesized the chalcone derivatives incorporated benzothiazole-imidazopyridine by employing various reactions like the Suzuki-cross coupling reaction and Claisen-Schmidt condensation reaction. Compound 17a (Fig 18) showed potent cytotoxic activity against Human prostate cancer cell line (PC3), Human lung cancer cell line (A549), Human breast cancer cell line (MCF-7), and Human prostate cancer cell line (DU-145) at IC_{50} value of 0.03, 0.01, 0.12, and 0.17 µM.[52]

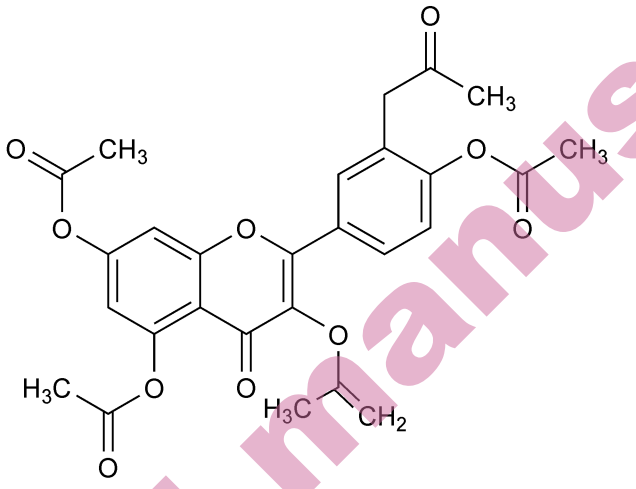


17a

Fig 18: 3-(2-(6-(3,4,5-Trimethoxyphenyl)benzo[d]thiazol-2-yl)−3H-imidazo[4,5-b]pyridin-6-yl)−1-(pyridin-4-yl)propanone

Silva *et al.*, (2021) designed and synthesized the acetylated derivative of quercetin by acetylation of quercetin with acetic anhydride in the presence of pyridine. Compound 18a (Fig 19) exhibited a better cytotoxicity activity against

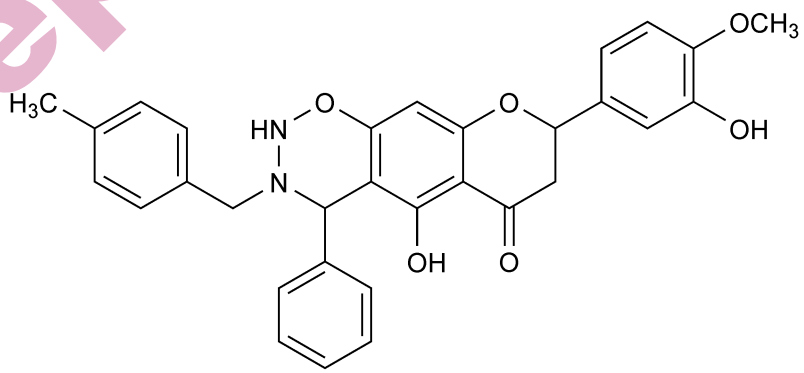
hepatocellular cells (HepG2) and promyelocytic leukemia (HL-60) cell lines with IC_{50} values of 53.9 and 33.6 µM respectively.[53]



18a

Fig 19: Quercetin pentaacetate

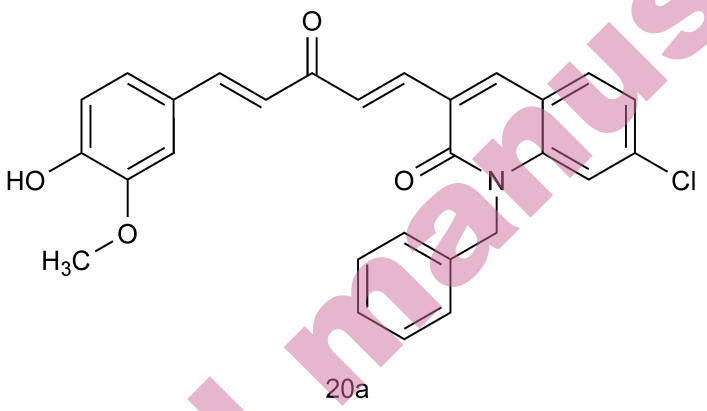
Zhong G *et al.*, (2022) synthesized the novel hesperetin derivatives by the electrophilic substitution reaction in methanol at 40^{O}C at the C-6 position. Compound 19a (Fig 20) showed better antiproliferative effect on Breast cancer cell lines (MCF-7), Human liver cancer cell lines (HepG2), and Cervical carcinoma cell lines (HeLa) at IC_{50} value of 5.3, 8.8, and 8.6 µM respectively.[54]



19a

Fig 20: Hesperetin derivative

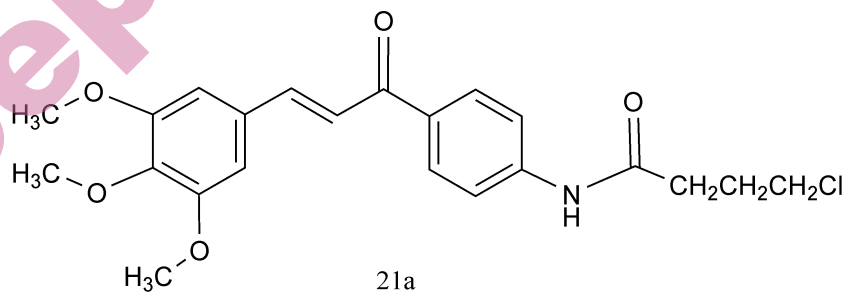
Insuasty *et al.*, (2021) synthesized a novel symmetrical and unsymmetrical quinoline-based bis-chalcone series by Claisen-Schmidt condensation reaction. Among the synthesized derivatives, compound 20a (Fig 21) showed potent anticancer action against the different carcinoma cell lines like HCT-116 and HT29 with a GI_{50} value ranging from 0.16-5.45 µM.[55]



20a

Figure 21: Benzyl-7-chloro-3-((1E,4E)-5-(4-hydroxy-3-methoxyphenyl)-3- oxopenta-1,4-dien-1-yl)quinolin-2(1H)-one

Lu *et al.*, (2020) prepared a novel amino chalcone derivatives as antiproliferative agents. Among the synthesized compounds, compound 21a (Fig 22) showed potent anticancer activity against MCF-7, HCT-116, and MGC-803 tumor cell lines with IC_{50} values of 2.54 µM, 1.83 µM, and 1.52 µM respectively.[56]



21a

Figure 22: 4-Chloro-N-(4-(3-oxo-3,4,5-trimethoxyphenyl) propenyl)phenyl butanamide

CONCLUSION

World Health Organization (WHO) expressed worry about the rising cancer incidence and it has been expected to continue with the number of new cancer cases. Anticancer drugs cause numerous side effects and it also affects various healthy organs and tissues. Flavonoids are secondary metabolites and this is unique

lead compound to design and for developing of potent anticancer drugs, particularly in chemotherapy. We summarized the results of clinical trials of flavonoids and highlighted the synthesized flavonoid derivatives which showed better cytotoxic activity at lower concentrations against various cancer cells, it helps the researchers in future to develop flavonoid derivatives as anticancer drugs by carrying out further clinical studies. Further, need to understand key enzymes related to neoplastic cells and metastasis in-vitro and in-vivo process and it helps in providing novel potent flavonoid derivatives for fighting cancer.

Conflict of Interest: The authors confirm that the contents of this article present no conflicts of interest.

ИЗВОД

ДЕРИВАТИ ФЛАВОНОИДА КАО АНТИКАНЦЕРСКЕ ГРУПА ЈЕДИЊЕЊА И ЊИХОВ ЕФЕКАТ НА ЋЕЛИЈСКЕ ЛИНИЈЕ КАНЦЕРА: АЖУРИРАНИ ПРЕГЛЕД

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Данас, канцер се сматра примарним узроком преране смрти у индустријализованим земљама. Хемотерапије лековима су скупе и изазивају вишеструке споредне ефекте. Природни производи су детаљно испитани због њиховог великог потенцијала као антиканцерских агенаса због њихове хемијске разноликости. Између многих природних метаболита, флавоноиди су секундарни метаболити широко распрострањени у природи, који имају значајна анти-канцерска својства, мало штетних ефеката, и показују синергистички користан утицај. Велики број истраживачких група марљиво истражује хемијске и биолошке особине нових деривата флавоноида због потреба за овим једињењима. У овој ревији, сумирали смо резултате клиничких испитивања различитих флавоноида, ефекат на различите ћелијске линије канцера и нове резултате активности флавоноида, синтетисаних различитим поступцима, према ћелијама канцера. Нова изучавања су неопходна за даљи развој нових деривата флавоноида као антиканцерских лекова.

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