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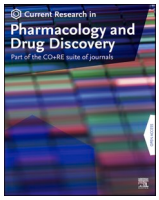

Flavonoids as promising molecules in the cancer therapy: An insight

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ABSTRACT

Cancer continues to increase global morbidity and mortality rates. Despite substantial progress in the development of various chemically synthesized anti-cancer drugs, the poor prognosis of the disease still remains a big challenge. The most common drawback of conventional cancer therapies is the emergence of drug resistance eventually leading to the discontinuation of chemotherapy. Moreover, advanced target-specific therapies including immunotherapy and stem cell therapy are expensive enough and are unaffordable for most patients in poorer nations. Therefore, alternative and cheaper therapeutic strategies are needed to complement the current cancer treatment approaches. Phytochemicals are bioactive compounds produced naturally by plants and have great potential in human health and disease. These compounds possess antiproliferative, anti-oxidant, and immunomodulatory properties. Among the phytochemicals, flavonoids are very effective in treating a wide range of diseases from cardiovascular diseases and immunological disorders to cancer. They scavenge reactive oxygen species (ROS), inhibit cancer metastasis, modulate the immune system and induce apoptotic or autophagic cell death in cancers. This review will discuss the potential of various phytochemicals particularly flavonoids in attempts to target various cancers.

1. Introduction

Cancer is an important public health issue that affects both developed and developing countries. In 2018, over 18.1 million new cancer cases were reported worldwide, and the number is expected to rise by 23.6 million year-wise by 2030 (Bray et al., 2018). Cancer involves abnormal or uncontrolled growth of cells with the potential to metastasize and invade other parts of the body. At the cellular level, there are significant changes in global gene expression in cancers. Among the several forms of cancer, lung cancer is the most frequent cancer followed by breast cancer (Sung et al., 2021). Cancer treatment includes chemotherapy, surgery, immunotherapy, radiotherapy, and stem cell transformation or combination therapy. The type, stage and location of the cancer determine the treatment method regimen to be adopted. These include effective cytostatic and cytotoxic medications used alone or in combination with other cancer treatments (Vinogradov and Wei, 2012a). But these medications have the propensity to cause serious side effects ranging from hair loss, bone marrow suppression, gastrointestinal lesions and neurologic dysfunction to cardiotoxicity (Patra et al., 2014) (Mukherjee and Patra, 2016). Furthermore, a large number of patients besides showing a poor prognosis exhibit multidrug resistance through mutations, caused by overexpression of various proteins including ABCA4 & ABCA12 or efflux proteins like P-gp (p-glycoproteins) and MDR-1 (multiple drug resistance). Therefore, the search for new anticancer agents which are devoid of hazardous side effects is becoming an attractive area of research in cancer biology. Several plants and herbs have been discovered to possess anticancer potential, thereby increasing the scope of plant-derived compounds as an alternative to synthetic drugs (Desai et al., 2008). A large number of phytochemicals have been isolated from plants and tested for their potential in the anticancer therapeutics (Choudhari et al., 2020).

2. Phytochemicals in cancer therapy: a novel approach

The target-oriented cancer therapies have undoubtedly improved the life span of cancer patients. However, the treatment of advanced-stage

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metastatic cancers still remains a big challenge. The search for safe and effective drugs continues with the aim to enhance the anti-cancer treatment efficacy at a lower cost.

Currently, chemoprevention or treatment approaches for cancer using plant-derived compounds are gaining momentum. Many acute and chronic illnesses are being treated with plant-based drugs (Give two or more examples and their references). The intake of certain fruits has proven to decrease the risk of cancer incidences. Despite the use of plant-based compounds in cancer therapy, the scientific basis of the molecular mechanism of action of these plant-based therapies is not completely understood. Recent developments in drug discovery with the help of advanced experimental and molecular biology tools enable researchers to explore the potential of these phytochemicals in the treatment and prevention of cancer, inflammatory diseases and cardiovascular abnormalities.

Plants and their bioactive components have been used in clinical practice for centuries (Aung et al., 2017). So far, around 250,000 plant species have been identified and only 10% of these have been studied in various diseases. Phytoconstituents mainly the secondary metabolites in different parts of the plant viz roots, leaves, bark, stem, fruits, and seeds etc have shown several pharmacological properties (Cragg et al., 2006) (Khan, 2014) (Singh et al., 2016) (Vinogradov and Wei, 2012b) (Patra et al., 2014) (Mukherjee and Patra, 2016) (Ali et al., 2020). Several plant-derived products like alkaloids, saponins, flavonoids, terpenes, and glycosides are known for their effectiveness in cancer chemoprevention. This anticancer effect is thought to be due to their inhibitory action on various cellular metabolic enzymes and proteins such as topoisomerases, cyclooxygenases and kinases. Their effectiveness is also linked to the activation of certain DNA repair mechanisms or signalling pathways such as phosphatidylinositol 3-kinase and mammalian target of rapamycin (mTOR) or stimulating the formation of protective enzymes such as caspases (Fig. 1). Table 1 provides information about bioactive constituents (from plants) in treating varied cancer types. The potential of these bioactive molecules to induce the expression and the activity of catalase (CAT), glutathione peroxidase, and superoxide dismutase (SOD) further strengthens their role as potential chemopreventive agents for cancer (Ighodaro and Akinloye, 2018) (Clere et al., 2011) (Qiu et al., 2018) (Rauf et al., 2018) (Cook, 2018) (Sak, 2014).

3. Flavonoids in cancer therapy

Flavonoids are a class of polyphenolic secondary metabolites primarily found in vegetables, tea, soybeans, fruits, and grains (Wen et al., 2020). They are typically comprised of aromatic rings that define their structural backbone. Their structure and class, degree of hydroxylation and polymerization, conjugations, and other substitutions determine their chemical nature. While individual compounds within a flavonoid class differ in the pattern of substitution on rings A and B, various classes of flavonoids differ in the level of oxidation and pattern of substitution in ring C (Fig. 3). The biological activities of flavonoid classes are correlated to their structure. The flavan nucleus, the position, number and type of substitution affect their free-radical scavenging and chelating activities (Wang et al., 2018).

Evidence-based data suggest that flavonoids can be effective in treating a wide range of diseases, including cancer, cardiovascular diseases, and immunological disorders (Nabavi et al.). They inhibit cellular proliferation and induce apoptotic and autophagic cell death. They are also reported to cause necrosis, cell cycle arrest, inhibit cellular migration, invasion, & tumour angiogenesis, thus having a potential role in the reversal or inhibition of chemo-resistance or by modulating ROS-scavenging enzyme activities (Zhang et al., 2018a) In addition to this, they have the ability to scavenge free radicals, minimise oxidative stress and control cellular metabolism (Fig. 2) (Rodríguez-Garcí et al., 2019) (Yahfoufi et al., 2018) (Chirumbolo et al., 2018) (Abotaleb et al., 2018) (Perez-Vizcaino and Fraga, 2018) (Gorlach et al., 2015). Significantly, flavonoids serve as eco-friendly and cost effective compounds.

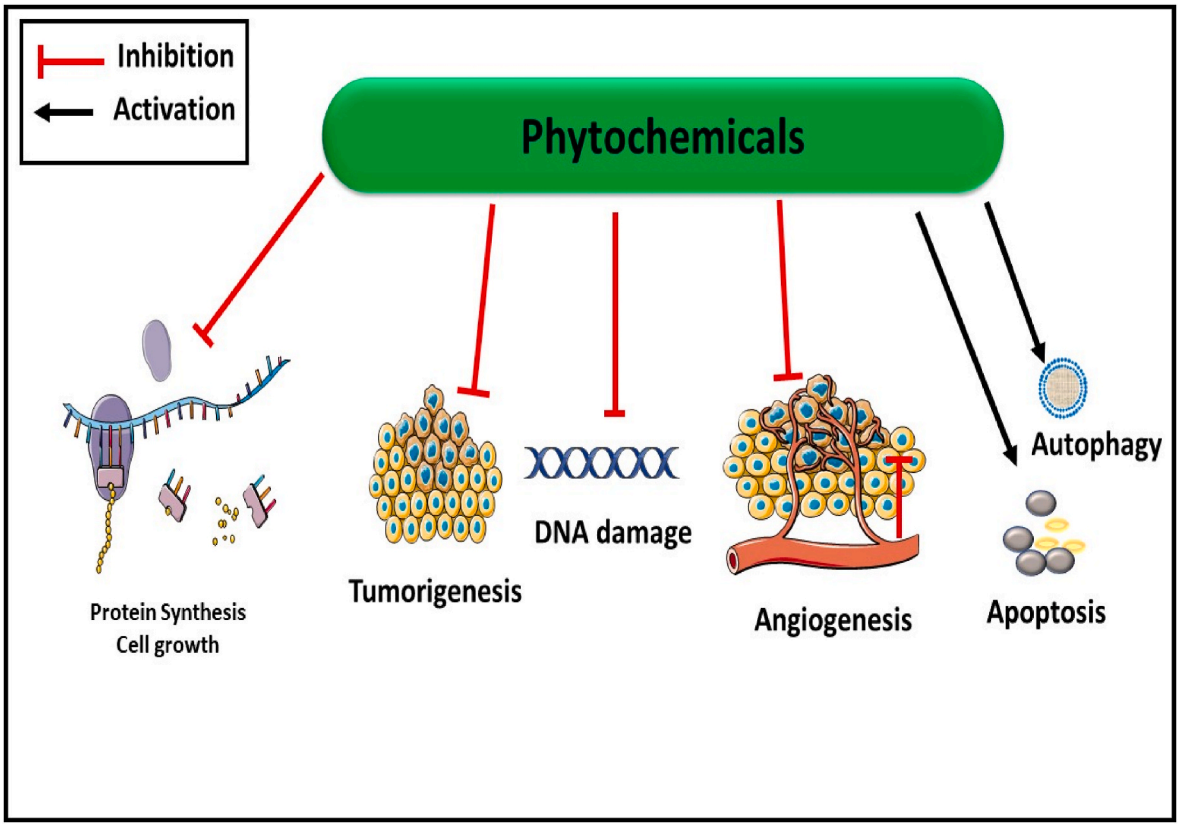

Fig. 1. Showing various anticancer mechanisms of phytochemicals.

Table 1
List of plants and their bioactive constituents in various types of cancers.

Plant name	Family	Phytochemicals	Type of cancer	Reference
Artemisiaannua	*Asteraceae*	Artemisinin Artemisinin	Breast cancer, Liver, and pancreatic cancer	Efferth (2017)
Camellia sinesis	*Theaceae*	EGCG, Epigallocatechin	Breast, skin, lung, prostate and bladder cancer	Iqbal et al. (2017)
Ginkgo biloba	*Ginkgoaceae*	Ginkgetin, ginkgolide A & B	Liver, prostate, Hepatocarcinoma and colon cancers	XIONG et al. (2016)
Solanum nigrum	*Solanaceae*	Solasonine, solamargine	Skin, breast, and Lung cancer	Al Sinani et al. (2016)
Ziziphus spinacristi	*Rhamnaceae*	Doxorubicin, rutin and quercetin	Breast cancer, and lung cancer	Jaradat et al. (2016)
Glycyrrhiza glabra	*Leguminosae*	Licochalcone, and Licochalcone-A	Kidney, stomach, breast and prostate cancer	Zhang et al. (2016)
Psoralea corylifolia	*Leguminosae*	Psoralidin	Prostate and stomach cancers	Pahari et al. (2016)
Xanthium strumarium	*Asteraceae*	Xanthium	Lymphocyte leukemia cancer	Thangapazham et al. (2016)
Tulsi (Ocimum sanctum Linn)	*Lamiaceae*	Vicenin, orientin and eugenol	Fibrosarcoma, and female breast cancer	Chakraborty (2016)
Withaniasomnifera (ashwagandha)	*Solanaceae*	Withaferin D, and Withaferin A	Breast, prostate, cervical and colon, cancer	Lee and Choi (2016)
Ginger (zingiber officinale)	*Zingiberaceae*	Gingerol	Urinary, colon, cervix, liver, and ovary cancers	Rastogi et al. (2015)
Capsicum annuum	*Solanaceae*	Luteolin	Colorectal cancer	Osman et al. (2015)
Podophyllum Peltatum	*Podophyllaceae*	Podophyllotoxin	Non-small cell lung carcinoma	Choi et al. (2015)
Vitis vinifera	*Vilaceae*	Procyanidins	Colon cancer	Cheah et al. (2014)
Aloe vera	*Asphodelaceae*	Emodin and alexin B	Stomach cancer	Shalabi et al. (2015)
Crocus sativus	*Liliaceae*	Crocetin	Lung and Hippocampal cancers	(Bakshi et al., 2009)
Allium sativum	*Amaryllidaceae*	Allylmercaptocysteine, allicin	Cervical and lymphoma cancers	Karmakar et al. (2011)
Ginkgo biloba	*Ginkgoaceae*	Bilobalide	Human colon cancer	Suzuki et al. (2004)
Cannabis sativa	*Cannabaceae*	Cannabinoid	Colorectal, female breast, prostate, and lung cancers	Appendino et al. (2011)
Saffron crocus	*Iridaceae*	Saffron	Pancreatic, lung, and liver cancers	Ververidis et al. (2007)
Crocus sativa	*Iridaceae*	Crocetin, safranal, Picrocrocin, crocin	Oral and sarcoma cancers	Hoshyar and Mollaei (2017)
Zingiber officinale	*Zingiberaceae*	Gingerol	Ovarian and colon cancers	Rastogi et al. (2015)
Zingiber officinale	*Zingiberaceae*	6-Shogaol	Ovarian cancer	Ghasemzadeh et al. (2015)

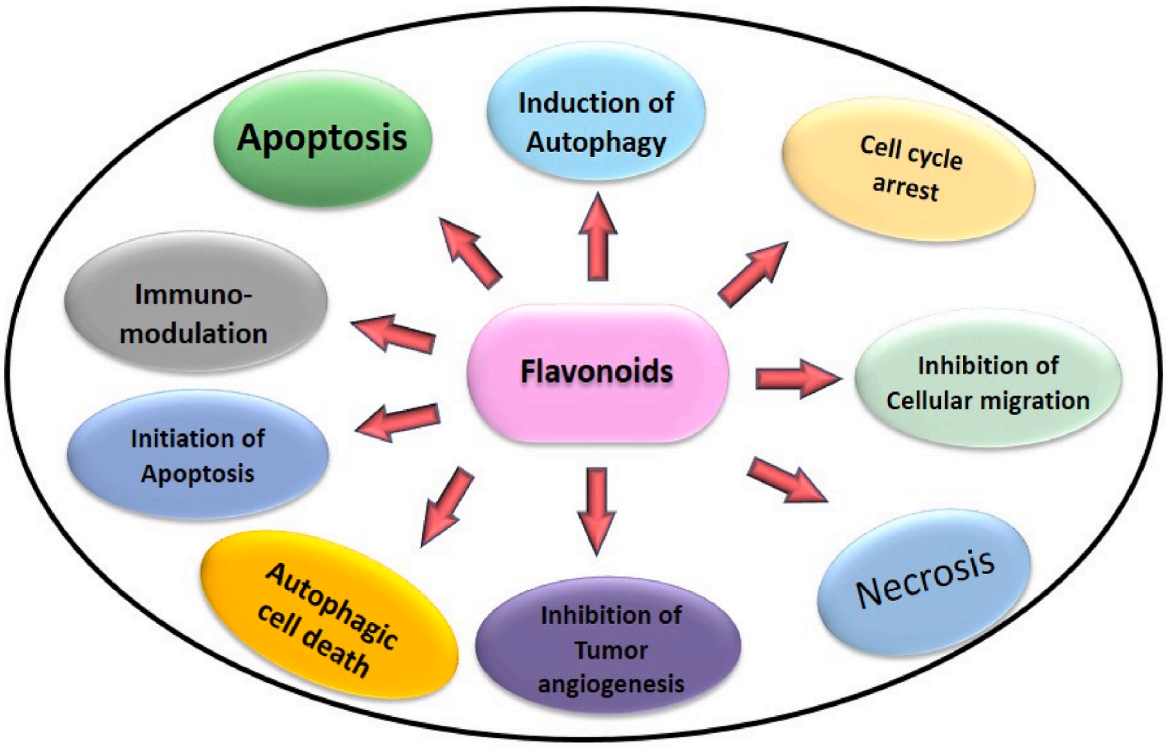

Fig. 2. Illustrating different mechanistic basis of the anticancer potential of flavonoids.

Furthermore, large number of flavonoids have proven to be safe and effective (Liskova et al., 2020a). Structure of some of the flavoniods discussed in this review are mentioned below (see Fig. 4).

3.1. Flavonoids and oxidative stress

One of the most significant and naturally occurring mutagenic substances in the human body are the reactive oxygen species (ROS), which can lead to genetic instability in the cells and is one of the reasons for the

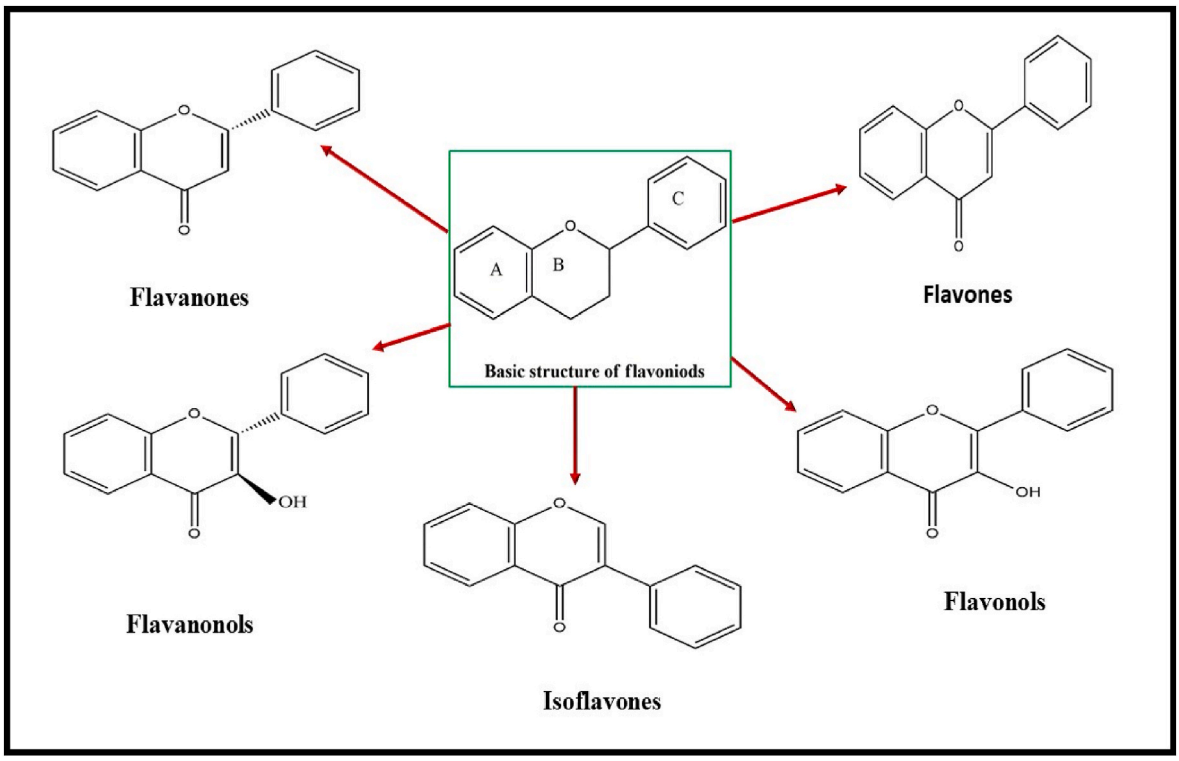

Fig. 3. Showing basic structure and different classes of flavonoids.

transforming normal cells into tumorous cells (Perillo et al., 2020). The cancer cells have the ability to counter the metabolic changes or alterations caused by the oxidative stress due to the fact that these cells switch over to the Warburg effect (using glycolysis instead of normal phosphorylation to generate adenosine monophosphate, ATP) for survival (Liberti and Locasale, 2016).

Flavonoids can directly chelate metal ions and scavenge ROS, owing to the presence of free phenolic hydroxyl groups that help in stabilizing the free radicals (Youn et al., 2006) (Fraga et al., 2010). Their antioxidant and pro-oxidant activities enhance their anticancer activities (Oliveira-Marques et al., 2009). Suppression of pro-oxidant enzymes, stimulation of antioxidant and phase II detoxification enzyme synthesis, and activation of antioxidant enzymes are some of the features of flavonoids that qualify them as anticancer drugs (Valko et al., 2007). The number and pattern of flavonoid hydroxyl groups impact the scavenging ability (Pietta, 2000).

Naringenin, a naturally occurring flavanone is found in a variety of citrus fruits. It works against cancer by promoting choriocarcinoma cells (JAR and JEG 3) to produce reactive oxygen species (ROS) (Park et al., 2018). It also initiates apoptotic cascade in human epidermoid carcinoma, A431 cells (Ahamad et al., 2014). In PC3 and LCNaP prostate cancer cell lines, Naringenin suppresses the migration, proliferation and induces apoptosis. It reduces ROS generation and enhances the activity of glutathione, catalase, and superoxidase dismutase (SOD) chronic in various diseases especially in cancer (Zaidun et al., 2018). Another isoflavone, genistein has been shown to arrest the cell cycle in the G2/M phase and inhibit ROS-dependent apoptosis in breast cancer (Kaushik et al., 2019). Hesperidin, the flavone present in lemons and sweet oranges induces apoptosis in oesophageal and gall bladder carcinoma (Pandey et al., 2019). Apoptosis has also been promoted in MCF-7 breast cancer cells by daidzein, a naturally occurring flavonoid present in soya beans (Jin et al., 2010).

3.2. Chemoprotective effect via initiation of apoptosis

Flavonoids target apoptotic signalling cascade by various mechanisms including intrinsic and extrinsic pathways as depicted in Fig. 5 (Kopustinskiene et al., 2020). The study conducted by Hong-Wei Zhang and colleagues demonstrated that isorhamnetin, genkwanin, and acacetin isolated from *Tephroseris kirilowii* induce apoptosis by reducing the levels of bcl-2 and bcl-xL and increasing the levels of p-53 gene in MDA-MB-231 cells (Zhang et al., 2018a). These findings suggest that an increase in p53 levels and bcl-2 and bcl-xL downregulation might be involved in flavonoid-induced apoptosis in breast cancer cells. This study further demonstrated the inhibition of cell proliferation through induction of apoptosis due to a reduction in the expression of PARP1 and an increase in caspase-3 level in MCF-7 breast cancer cells (Zhang et al., 2018a). Naringenin has been shown to induce apoptosis via increased expression of caspases-3, p53, and Bax proteins and downregulation of anti-apoptotic proteins Bcl-2 and survivin in SGC-7901 cells (Bao et al., 2016) (Zhang et al., 2016). It is involved in the induction of extrinsic apoptotic pathway through overexpression of TNF-family proteins (Abotaleb et al., 2018). Another flavonone, hesperetin induces apoptosis by inhibiting the NF-κB signalling cascade and reducing Bcl-2 transcription and translation in prostate cancer (Sambantham et al., 2013). Daidzein, a plant-derived phytoestrogen, induces apoptosis by up-regulation of BAK and downregulation of various anti-apoptotic proteins in the SK-Hep-1 cell line (Park et al., 2013). Table 2 describes various flavonoids involved in modulating cellular apoptosis.

3.3. Immunomodulation

Immune system plays a key role in protecting an organism from cancer and various life-threatening infections. Immunity is primarily mediated by macrophages, and B and T lymphocytes. B cells are in charge of producing antibodies that can bind to pathogens and mark them so that phagocytes can recognise and scavenge them. (Pérez-Cano and Castell, 2016). T cytotoxic and T helper cells are able to kill the tumour cells directly and secrete cytokines and mediators respectively (Ding et al., 2018). They have been found to directly modulate and differentiate cells that are involved in immune response (Ding et al., 2018) (Pérez-Cano and Castell, 2016). Flavonoids exert

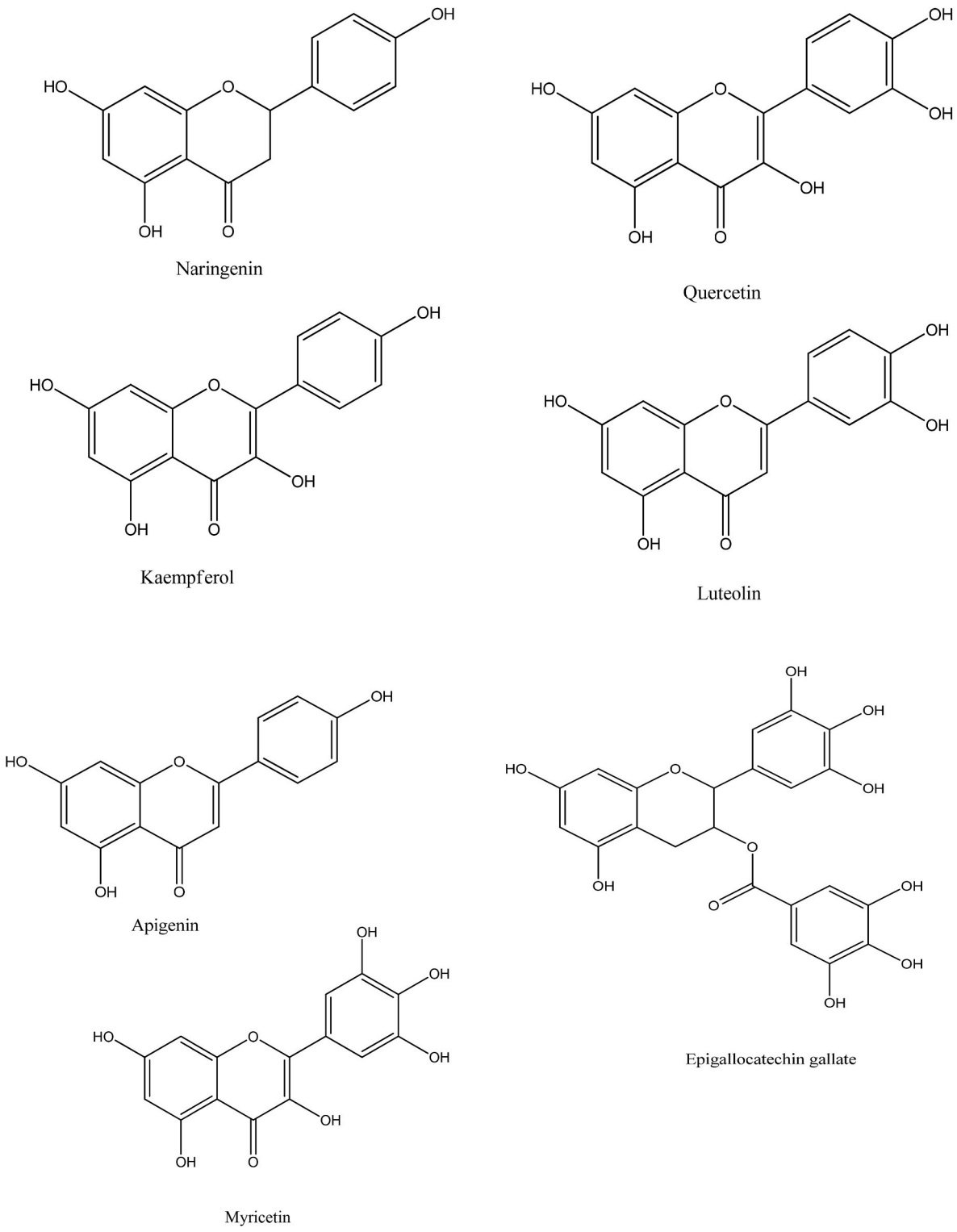

Fig. 4. Structures of some of the flavonoids discussed in this review.

anti-inflammatory action by the suppression of chemokine, pro-inflammatory transcription factors, COX-2, and cytokines (Gupta et al., 2018) (Yahfoufi et al., 2018) (Chirumbolo et al., 2018). Flavonoids also inhibit mammalian target of rapamycin (mTOR), thereby reducing T effector differentiation and inducing T regulatory cells (Hosseinzade et al., 2019). To sum up, flavonoids have immunomodulatory effects on the immune system.

The treatment of the mouse bone marrow-derived dendritic cells (DCs) with Quercetin decreases the expression levels of MHC class II and pro-inflammatory chemokine/cytokines, which in turn inhibits the LPS-induced activation of DCs. It also decreases the endocytosis of DCs and the LPS-induced DC migration (Sun et al., 2015). In a study with mice as the experimental model tevaluated the anti-asthmatic potential of quercetin. It was found that treatment of mice (with induced asthma) with quercetin resulted in a significant reduction in the production of specific immunoglobin E (sIgE) and modulation in the expression of Th2

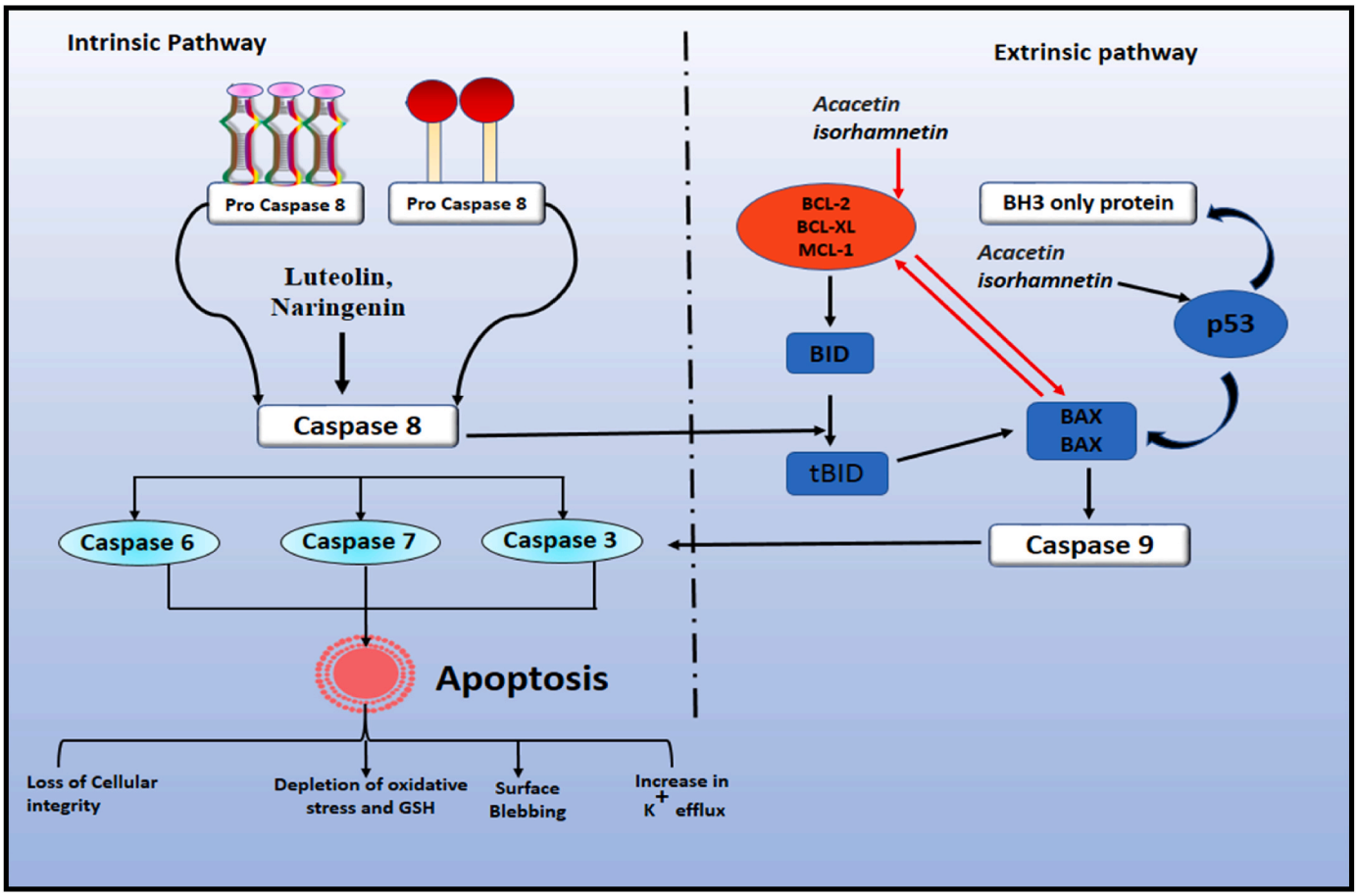

Fig. 5. Graphic representation of the intrinsic and extrinsic mechanistic pathways of apoptosis.

Table 2
Shows some of the flavonoids involved in inhibiting cancer malignancies by modulating apoptosis.

Classification	Compound	Mechanism of action for biological activity	Ref.
Flavones	Apigenin	It has shown to increase anticancer activity via JAK-STAT and Wnt/Catenin signalling pathway	Ozbey et al. (2019)
	Luteolin	It induces autophagy and initiates apoptosis in MCF-7, ANA-1 and ACS gastric cells via akt, JNK and p38 signalling cascade. Initiation of apoptosis is shown by decreasing Bcl-2 & Beclin-1 and increasing caspases-3 & 8.	(Liao et al., 2018)
	Tangeritin	It cases cell cycle arrest via Cyp1A1 and Cyp1B1 mediated metabolism as seen in MCF-7 and MDA-MB-468 breast cancer cell lines.	Surichan et al. (2018)
Flavonols	Quercetin	It decreases cancer mortality via cell cycle inhibition and initiation of apoptosis.	Hirpara et al. (2009) Sethi et al. (2023)
	kaempferol	Help in initiation of apoptosis and induction of autophagy via increase in expression of miR-340 micro RNA in (Colon) HCT-116, HCT15, SW480 and A549 human lung cancer cell lines.	Han et al. (2018)
	Myricetin	Inhibits metastasis via inhibition of cell migration as seen in prostate cancer.	Ye et al. (2018) Kumar et al. (2023)
	Galangin	Decreased cellular proliferation by initiation of apoptosis via PI3K/akt/mTOR signalling pathway in human kidney (A498) cancer cell line.	(Zhu et al.)
Flavononones	Hesperetin	Initiated apoptosis in H522 lung cancer cells	Elango et al. (2018)
	Naringenin	Decreased cancer metastasis via voltage gated sodium channels and initiated both early and late apoptosis in prostate cancer	Gumushan Aktas and Akgun (2018)
Flavonols	Taxifolin	Decreased carcinogenesis through mTOR/PTEN axis and CYP1B1 mediated cancer	Haque et al. (2018)
Flavans	Epigallocatecatechingallate (EGCG)	Increased chemoprevention and apoptosis through Abl/Bcrmediated p38-JAK2/STAT3/Akt and MAPK/JNK pathways in chronic myeloid leukemia and Glioblastoma cancer cells respectively	Grube et al. (2018)
	EGCG, catechin	Decreased cancer growth through programmed cell death	Xiao et al. (2019)
Anthocyanidins	Cyanidin	Decreased angiogenesis in MCF-7 cells through STAT3/VEGF signalling pathway	Ma and Ning (2019)
	Delphinidin	Increased initiation of apoptosis and induction of autophagy in HER2 positive MDA-MB-453 cancer cells	Chen et al. (2018)
Isoflavonoids	Genistein	Increased apoptosis and decreased cellular proliferation in human laryngeal Mcl-1 and EP3 expressing melanoma cancer cells respectively	Ma et al. (2018)

cytokines including xzcIL-4 and 5 (Gupta et al., 2016). Furthermore, Quercetin and Naringenin have been reported to reduce the mRNA expression of liver IL-4, bcl-2, and p53 in a diethylnitrosamine/2-acetylaminofluorene-induced hepatocarcinogenesis rat models (Ahmed et al., 2019; Hazafa et al., 2020).

In MDA-MR-231 cell line, Naringenin has been shown to inhibit the

migration of cells via apoptosis by inhibiting the caspase-3 and caspase-9 pathway (Zhao et al., 2019). It is also thought to inhibit the invasion and migration of glioblastoma cells due to the inhibition of p38 and ERK activities (Chen et al., 2019).

Apigenin, 40,5,7-trihydroxyflavone, is a common dietary flavonoid mostly found in many vegetables, fruits and herbs such as celery, wheat, onion and chamomile tea (Lefort and Blay, 2013) (Shukla and Gupta, 2010). It has antioxidant, anti-proliferative, anti-inflammatory and anticancer properties (Liu et al., 2017a). Its anticancer effect is seen by the induction of apoptosis via the activation of pentose phosphate pathway-mediated NADPH generation in HepG2 cells. It has been shown to reduce the viability, migration and adhesion of cancer cells (Wang et al., 2017). Cardenas and colleagues in their study reported that apigenin significantly modulated NF-κB activity in the lungs (Cardenas et al., 2016). Another study showed that lower colonic damage scores and colonic weight/length ratio were reduced with the administration of apigenin in colitis using rats as an experimental model (Wang et al., 2017). Furthermore, it has been shown that a combination of apigenin with quercetin and Luteolin could protect pancreatic beta-cell injuries by cytokines during inflammation (Kim et al., 2007). Apigenin has also shown inhibition of mast cell secretion (Yao et al., 2020). Thus, apigenin has got immense potential to be considered a modulator of the immune system.

Luteolin (3′,4′,5,7-tetrahydroxyflavone) and its glycosylated form luteolin-7-glucoside (L7G) are among the most common flavonoids present in a vast spectrum of plants. Apart from its antioxidant and anticancer activities, Luteolin has shown anti-allergic and anti-inflammatory potential as well (Arts and Hollman, 2005) (Maron, 2004) (Mennen et al., 2004). Treatment of asthma by luteolin using rats as experiment model resulted in a reduction in the neutrophil count, total cell count, eosinophil count, and levels of IL-4 (Nazari et al., 2013) (Kanazawa et al., 2006) (Si et al., 2014) (Jang et al., 2010). In a study aimed at examining the biological effect of luteolin on experimental autoimmune thyroiditis (EAT) using mice as an experimental model, it was found that luteolin decreased the follicle destruction and lymphocytic infiltration in thyroid glands, inhibited the interferon-γ-induced increase in cyclooxygenase-2 production and secretion of tumour necrosis factor-α (TNF-α) (Xia et al., 2016). Luteolin is also a potential inhibitor of mast cell-derived histamine (Verbeek et al., 2004).

All this data suggests that these flavonoids (naringenin, quercetin, apigenin, and luteolin) may have a role in immune system modulation. However, extensive studies are required to understand their molecular mechanisms of action.

3.4. Modulation of autophagy

Autophagy is referred as a conservative catabolic process involved in maintaining normal cellular haemostasis and physiology under stressful conditions (Cooper, 2018). It combats carcinogenic infectious, degenerative and other toxic agents for maintaining the homeostasis and regulation of healthy living processes in the body; hence, its dysregulation is known to cause a number of human disorders e.g. cancer (Mizushima, 2007) (Yang and Klionsky, 2010) (Lee et al., 2018). Depending on the type of cancer, the relationship between the changes associated with autophagy and cancer therapy to tumour development is complicated (Mathew et al., 2007). It has a different role in normal and tumour cells, however, in cancer, it has a dual role, from tumour promotion to tumour suppression (Salminen et al., 2013). When autophagy exceeds the threshold limit for cell survival, ACD (autophagic cell death) occurs. ACD is considered a novel approach to treating cancer in apoptosis defective cells, commonly known as type II programmed cell death.

Flavonoids show anticancer properties by impairing various signalling cascades like MAPK, PI3K/Akt/mTOR, Wnt/β-catenin and AMPK. Thus, they play a prominent role in inducing excessive autophagy or flux in cancer which is responsible for ACD (Pang et al., 2021).

Several flavonoids like Apigenin, Vitexin, isovitexin, Baicalein, Chrysin, Quercetin, Naringin, galangin, EGCG, xanthoangelol, kaempferol, hydroxysafflor yellow A, flavokawain B, and liquiritin have been reported to induce autophagic cell death *in-vitro* and *in-vivo*. Kaempferol and apigenin isolated from the plant *Tephroseris kirilowii Turcz. Holub* induce autophagy by interrupting PI3K/AKT/mTOR/p70S6K/ULK signalling pathway (Zhang et al., 2018b). Kaempferol has also been reported to induce excessive autophagy through the up-regulation of miR-340 leading to the inhibition of PTEN/PI3K/Akt signalling pathway in lung cancer (Han et al., 2018). Beclin-1, which is the main regulator of autophagy in the nucleation step is reported to be down-regulated by a polyphenolic flavone, luteolin when used in a 100 μM concentration in PC12 cells (derived from a pheochromocytoma of the rat adrenal medulla) (Ashrafizadeh et al., 2020). Kwon et al. found that luteolin interferes with the elongation step of autophagy by downregulating LC3 protein (Kwon et al., 2017). Quercetin, a flavonol has been found to inhibit cellular migration and invasion through induction of autophagic and apoptotic cell death both *in-vitro* (120 μM) and *in-vivo* (50–200 mg/kg) (Li et al., 2016). Naringin has been found to induce autophagy in human gastric adenocarcinoma (AGS) cell line, by the formation of autophagosomes and cytoplasmic vacuoles by down-regulating PI3K/Akt/mTOR cascade (RAHA et al., 2015).

Moreover, one of the key mechanisms responsible for relapse and chemo-resistance in cancer is cytoprotective autophagy (Musial et al., 2021). Flavonoids are reported to induce cytoprotective autophagy which compromises their anticancer potential (Almatroodi et al., 2021). Thus combining small interfering-RNA (siRNA)-mediated autophagy inhibition and autophagy inhibitors with flavonoids like quercetin might potentiate their anticancer action (Liu et al., 2017b) (Kim et al., 2013).

These studies indicate that flavonoids possess significant potential for the treatment of cancer by influencing autophagy (Fig. 6). However, in-depth preclinical and clinical studies are needed to fully understand their mechanisms.

3.5. Flavonoids in cancer metastasis

Metastasis is one of the major complications that hamper the successful treatment of cancer. The development of metastasis involves the spread of cancerous cells from the main tumour, which results in the invasion of target tissues and organs and the emergence of secondary lesions. Anticancer therapy has several challenges, such as the development of chemotherapeutic resistance and subsequent recurrence of the disease with possible metastasis. However, flavonoids have been found as a useful strategy for enhancing the effectiveness of standard medical treatments. These effects are mediated by the regulation of key signalling pathways involved in the migration and invasion of cancer cells as well as the progression of metastatic disease, including regulatory molecules that play a role in the complex process of metastatic spread such as MMPs, uPA/uPAR, TGF-β, and other regulators of the epithelial-mesenchymal transition (Liskova et al., 2020b). In addition, a variety of flavonoids have been shown to be safe and have few negative effects when taken over an extended period. To improve their potential for application in future targeted prevention and therapy of cancer in high-risk patients with aggressive cancer states with metastatic potential, the anticancer properties of flavonoids, which target all phases of carcinogenesis including metastatic progression, may be incorporated into clinical cancer research studies.

Quercetin inhibits AKT and prevents metastasis by blocking the AKT/MMP-9 pathway and downregulating MMP-9. The administration of DTX/Qu-loaded PP-HA/NPs eventually results in the downregulation of p-AKT and MMP-9, which contribute towards the inhibition of cell migration and invasion. It also leads to an improvement of the drug accumulation in the tumour and lungs, thus, suggesting it has the potential to treat of metastasized breast cancer (Lu et al., 2018). Similarly, the interaction of EGCG and gemcitabine has shown a reduction in migration, invasion, and proliferation of MIA PaCa-2 and Panc-1

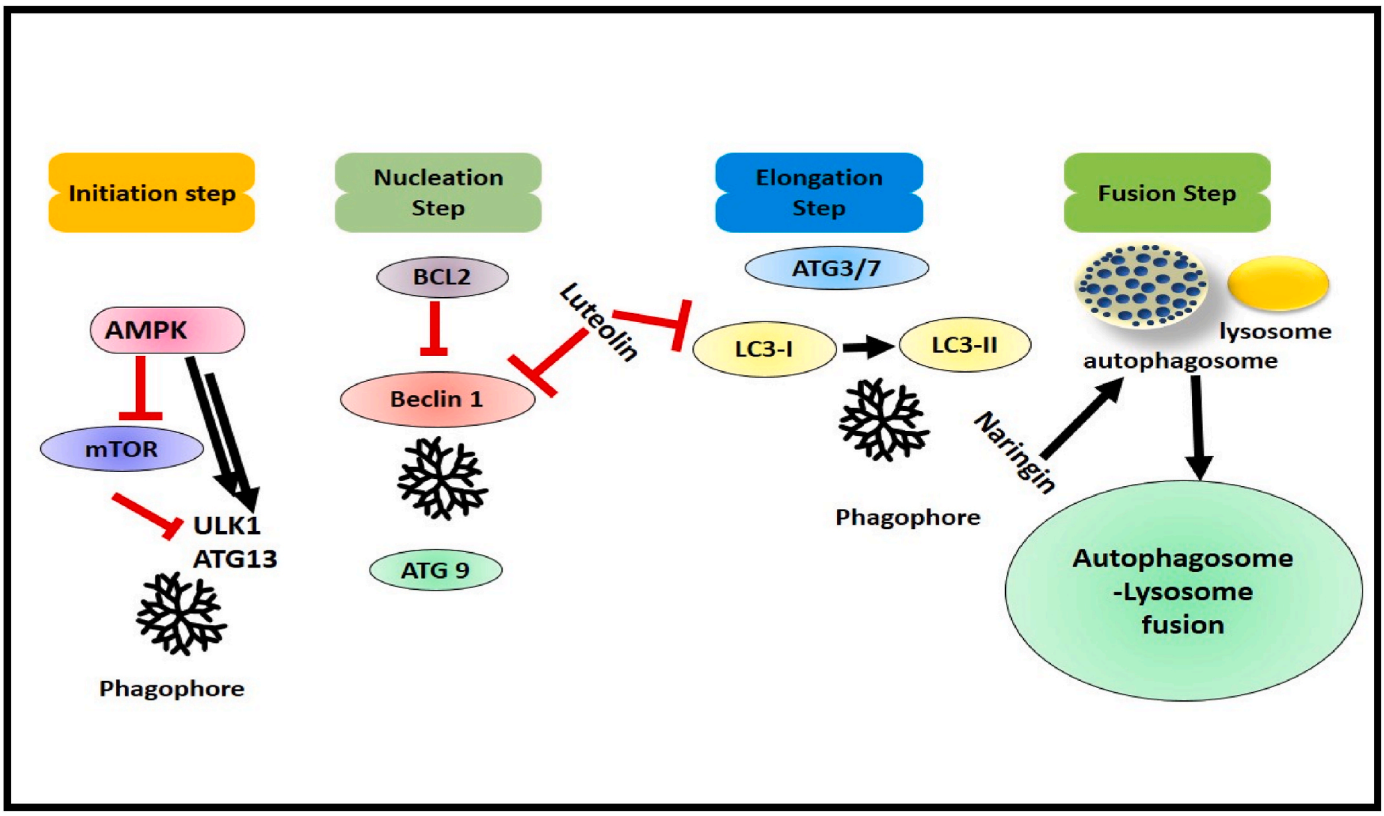

Fig. 6. Illustrates the role of flavonoids involved in various steps of autophagy.

pancreatic cancer cells by altering EMT markers and blocking the Akt pathway (Wei and HackmanWangMackenzie, 2019). Cyanidin has shown improvement in oxaliplatin's sensitivity in hepatic cellular cancer cell lines by decreasing migration and reversing alterations in EMT indicators brought on by oxaliplatin via PDK1-PI3K/AKT signalling (Li et al., 2019). Chrysin has shown inhibition of the growth of cancer cells via the induction of apoptosis and cell cycle arrest in the G2/M phase of B16F10 melanoma cells (Sassi et al., 2018). Table 3 shows different flavoniods downregulating or inhibiting the expression of metastatic protein molecules in various cancers.

Table 3
Show different flavonoids downregulating/inhibiting the expression of metastatic protein molecules in various cancers.

Flavonoid	Type of cancer	Inhibits or decrease the expression of metastatic protein molecules	reference
Luteolin	Colorectal, Breast, Glioblastoma	MMP9/2,β-catenin, SNAIL1/2	Rocchetti et al. (2023)
Apigenin	Prostate, lung, osteosarcoma, &prostate	MMP2/7/9, GSK3β, β-catenin, AXIN	Yadav et al. (2023)
Quercetin	Breast, prostate, colon, ovarian, & lung	VEGF, MMP9, Nf-κB	Duan et al. (2023)
Cardamonin	Breast	GSK3β, VEGF	Arzi et al. (2022)
Resveratrol	Colorectal	MMP9/13, Nf-κB	Lu et al. (2021)
Curcumin	Melanoma	Nf-κB	Chacko and Jacob (2022)
Chalcone	Colon	STAT3	Asati et al. (2022)
Baicalein	Breast	GSK3β	Sun et al. (2023)

4. Effect of flavonoids on different signalling pathways in cancer

4.1. NF-κB pathway

NF-κB plays a critical role in genesis of cancer due to its role inflammatory microenvironment (Yang et al., 2023). Studies have shown that inflammation promotes the development of cancer and metastasis. In response to internal or external stimuli, inflammatory response is mediated in the body through the release of inflammatory markers such as IL-1,6, and 10, TNF-α (Tumour Necrosis Factor α), NF-κB, NO (Nitric Oxide), iNOS (inducible Nitric Oxide Synthase), and COX (Cyclo-oxygenase) (Pereira et al., 2012). Among these mediators, NF-κB pathway is overexpressed in number of cancers, such as lung, breast, and leukemia cancers, which results in the development and poor prognosis of tumours (Mirzaei et al., 2022). NF-κB is also involved in the growth of cancer due to its role in proliferation of cancer cells and suppression of apoptosis (Pavitra et al., 2023). Ample evidence supports the role of flavonoids affecting NF-κB in on or other way some of them are discussed below.

In a study conducted by Shukula *et* al have demonstrated that apigenin inhibited the proliferation of cancer cells through inactivation of NF-κB signalling. It reduced tumour size and inhibited metastasis, and downregulates the expression of genes associated with apoptosis, and angiogenesis when administered in TRAMP-mice (Shukla et al., 2015).

In another study conducted by Jiangqiong Yu *et* al have demonstrated that apigenin and apigenin diester, apigenin-7,4′-O-dioctanoate inhibited the lipopolysaccharide (acrolien) induced inflammation by downregulation of NF-κB signalling pathway in human umbilical vein endothelial cells (HUVEC) (Yu et al., 2022).

In an *in-vivo* study using mice as an experimental model, apigenin inhibited the inflammation and other cellular processes by reducing the activity of NF-κB signalling pathway (Abid et al., 2022).

Apigenin also reduces or overcomes the renal toxicity by cisplatin treatment by NF-κB signalling pathway. This was seen when apigenin

was co-administered with cisplatin in male BALB/c mice (He et al., 2016) (Nozhat et al., 2021).

Another flavonoid, quercetin have shown to inhibit NF-κB signalling in human colon cancer to augment the initiation of apoptosis (Zhang et al., 2015).

In an in-vivo and in-vitro study conducted by Heba and Collegues demonstrated that combination of 50% of IC50 values of quercetin and sulfamethoxazole combination significantly decreased the protein expression of NF-κB in MCF-7 cell line (Sahyon et al., 2022).

Similarly another flavonoid, kaempferol have shown to inhibited the expression of NF-kB through (tumour necrosis factor receptor (TNFR)-associated factor 6) TRAF6 and (interleukin-1 receptor-associated kinase 2) IRAK2 downregulation (dos Santos et al., 2023).

4.2. PI3K/AKT/mTOR pathway

The serine–threonine protein kinase known as mammalian target of rapamycin or mechanistic target of rapamycin (mTOR) plays a crucial role in regulating cellular metabolism, growth, cell proliferation, survival, and gene expression. Recent studies have shown that over 70% of malignancies exhibit hyper activated mTOR pathways (Mir et al., 2023). In recent years, several mTOR inhibitors have been developed with the aim of treating different cancers.

Several natural compounds have shown to influence this critical pathway in one or other way to regulate various cellular processes like proliferation, growth, survival, apoptosis and autophagy.

Granato et al., in their study have demonstrated that quercetin, a naturally occurring flavonoid have significantly decreased c-Myc expression and inhibited PI3K/AKT/mTOR signalling in EBV-negative burkitt's lymphoma cells (Granato et al., 2016). Treatment of quercetin in human colorectal cancer (HCC) has potentially shown cytotoxic effects by downregulated the AKT/mTOR pathway through decrease in phosphorylated levels of p-mTOR, and p-AKT (Wu et al., 2019).

Another polyphenolic compound, apigenin has shown to inhibit the proliferation, migration, suppression of Warburg effect and stem cell like characteristic of osteosarcoma cell (SOSP-9607) when given in a concentration of 10,20, and 40 μM for 24 h (Shi et al., 2022).

Similarly, myricetin has shown to induce apoptosis and inhibit angiogenesis by inhibiting the phosphorylation of PI3K, PKD1, AKT, mTOR and its residues in a dose dependent manner in human umbical vascular endothelial (HUVEC) cells (Kim, 2017).

In a study conducted by Hongyun Cheng and Collegues, have observed that human colorectal cancer cells, SW620 and HCT116 when treated with 6–12 μg/ml of naringin showed significant decrease in the expression levels of phosphorylated levels of p-mTOR, p-AKT, p-PI3K, and mTOR. However, no decrease in the mRNA expression levels of p-mTOR, p-AKT, p-PI3K, and mTOR was seen (Cheng et al., 2020).

Similarly, another flavonoid luteolin have shown significant anticancer effect by inducing apoptosis and inhabiting AKT/mTOR signalling pathway in cervical cancer cells (Raina et al., 2021).

These studies prove that flavonoids modulate PI3K/AKT/mTOR signalling pathway in one or another way in different type of cancer and have the potential to be used alone or in combination with other class of drugs in anticancer therapeutics.

5. Challenges with the use of flavonoids as anticancer agents

Despite the numerous positive effects associated with flavonoids, their limited ability to be absorbed by the body has raised apprehension about their use in cancer therapy (Kopustinskiene et al., 2020). Flavonoids have the ability to interact with various nutrients, which ultimately leads to an increase or decrease in their levels in systemic circulation and their bioavailability for pharmacological or physiological action (Jakobek, 2015). In general, the majority of flavonoids undergo processes such as glucuronidation, methylation, and sulfation within the small intestine and liver (Teng et al., 2023).

While flavonoids demonstrate bioactivity in various *in vitro* systems, their effectiveness *in vivo* relies heavily on their bioavailability. This can be well understood by the example of two flavonoids, anthocyanins and daidzin whose relative urinary excretion is 0.3%, and 43%, explaining their varying bioavailability (Landete, 2012).

The form and source can affect the bioavailability of flavonoids to a large extent. The aglycone form of genistein has higher bioavailability than its glycoside form (Aboushanab et al., 2023).

It can reduce further when it comes to flavonoids that have intricate structures and higher molecular weight (Srivastava and Raghuwanshi, 2021) (Scalbert et al., 2002).

The bioavailability of some flavonoid compounds is also influenced by their interaction with the gut microbiota (Baky et al., 2022). A notable portion of the flavonoids consumed is not absorbed in the small intestine. Instead, it reaches to the large intestines where they are broken down simpler phenolic acids by gut microbiota (Baky et al., 2022) (Xiong et al., 2023). These acids are then absorbed into the bloodstream. These breakdown products exhibit potential biological activities and health benefits associated with flavonoids, despite the fact that the parent compounds themselves are mainly not absorbed in the small intestine (Xiong et al., 2023).

Therefore, it is crucial to enhance their bioavailability in order to achieve desired health and treatment benefits. Several approaches have been explored to improve bioavailability, including the use of absorption enhancers to enhance intestinal absorption, the development of novel delivery systems, improving metabolic stability, and shifting the site of absorption from the large intestine to the small intestine (Tiwari and Mishra, 2023) (Sengupta et al., 2023) (Teng et al., 2023).

Besides several flavonoids such as quercetin, catechins can lead to iron deficiency as they serve as iron chelators forming complexes with iron (Duda-Chodak and Tarko, 2023). They also have the property of deactivating various digestive enzymes which may cause problems with digestion, examples include quercetin, and Hesperedin) (Zhu et al., 2020). Ample evidence also suggests that some of the flavonoids such as apigenin, kaempferol interact with gut microbiota producing undesirable effects (Santhiravel et al., 2022). Some studies suggest that some flavonoids can even effect DNA and can cause genotoxicity (Duda--Chodak and Tarko, 2023). Thus Understanding the interactions between polyphenolic compounds and medical conditions or with other drugs is crucial, particularly in individuals with narrow therapeutic ranges.

6. Flavonoids and nanoparticles, a novel approach

As mentioned above, flavonoids like quercetin, apigenin, naringenin, kaempferol, myricetin etc have tremendous potential in treating different cancers by influencing various signalling pathways. However, due to their low bioavailability, and low solubility, poor absorption and fast metabolism as discussed above have led to the unsatisfactory results in treating different cancers. In recent times, there has been a growing interest in using nanotechnology to address these challenges and has emerged as a promising solution (Mir et al., 2022). A majority of these formulations are now progressing towards clinical testing (Hua et al., 2018).

In a study conducted by Siddiqui and colleagues, demonstrated that polylactic acid-polyethylene glycol (PLA-PEG) with encapsulated epigallocatechin-3-gallate (EGCG) nanoparticles were 10 times more effective in 22Rr1 prostate cancer than a free EGCG (Siddiqui et al., 2009).

Similarly, quercetin nano particles have shown more efficacy against MCF-7, T1 breast cancer, Lung cancer, B16F10 melanoma, ovarian cancer, and hepatocellular cancer cells than free quercetin (Chiu et al., 2012) (Yeh et al., 2014) (Yeh et al., 2012) (Tang et al., 2019) (Pandey et al., 2018).

Effect of Apigenin against a range of cancers is low because of it low bioavailability and low solubility. Recent studies have revealed the importance of novel nanomaterials that play a role in improving the

solubility and bioavailability of apigenin by developing solid dispersions using mesoporous silica nanoparticles (Huang et al., 2019).

Flavonoids have recently gained importance because of their potential as anticancer agents. However due to low solubility, poor absorption, and rapid metabolism their use as anticancer agents have been low. The application of nanotechnology has addressed these challenges, by enhancing the bioavailability of flavonoids. Both *in vitro* and *in vivo* studies have demonstrated the potential of flavonoid nanoparticles in cancer treatment, with most of studies undergoing preclinical testing (Dobrzynska et al., 2020).

7. Flavonoids in clinical settings

Several clinical trials are undergoing, completed or approved against various cancers. These clinical trials are aimed at understanding the deep mechanisms related to safety and efficacy. Tait and colleagues in their phase II clinical trial demonstrated that EGCG administered orally once a day is safe, effective and well tolerated in patients with chronic lymphocytic leukemia (Shanafelt et al., 2009).

Another clinical trial evaluating the effect of fisetin in a group of 37 colorectal cancer patients, accordingly patients were dived into two groups (fisetin group (n = 18), and placebo group (n = 19)). Before and after the fisetin supplementation adjuvant to chemotherapy several parameters were evaluated like IL-8, IL-10, high sensitivity C-reactive protein, matrix metalloproteinase (MMP-7 & 9). It was observed that hs-CRP, and IL-8 was significantly reduced in fisetin treated group (Farsad-Naeimi et al., 2018).

Number of other clinical trials are either completed or ongoing which are aimed at investigating the potential of flavonoids or flavonoid nanoparticles against cancer therapeutic. Table 4 summarizes some of the clinical trial involving various flavonoids.

8. Conclusion

As the mortality with cancer is increasing around the globe. So is the resistance to currently available synthetic drugs developing at an alarming pace. All this has necessitated an urgent need to find and develop newer drugs. Phytochemicals provide a promising and effective research area in this context. Since plant-based drugs have always been an important source for the discovery of new therapeutic agents, they could provide an alternative approach to treat cancers and overcome the challenges faced by the current therapies, viz higher toxicities, multi-drug resistance, and higher cost. Thousands of medicinal plants have been studied for anticancer effectiveness, but only a small proportion have reached in-vitro and in-vivo studies and very few to clinical trials. Various classes of bioactive compounds derived from plants in general and flavonoids, in particular, have shown their ability in reducing oxidative stress and modulating immune response. Flavoniods have shown strong potential in the initiation of apoptotic, and autophagic cell death and inhibit cancer metastasis by modulating different signalling pathways. However, there are some challenges with the use of these agents like bioavailability, drug-drug interactions, which need to be addressed by using various advanced techniques like nanotechnology. Therefore, studying their detailed mechanism of action could pave the way for the development of cancer chemo-preventive drugs.

Author's contribution

SAM: performed literature survey and drafted the content, wrote the manuscript, conceived the idea and edited the manuscript, revised the manuscript. LH: performed literature survey and drafted the content, wrote the manuscript. TA: wrote the manuscript. NN: wrote the manuscript. JAM: wrote the manuscript. GNB: conceptualization and supervision. AD: editing and supervision.

Table 4
Summary of clinical trials involving flavonoids against various cancers.

Flavonoid	Type of cancer	Number of participants	Phase of the study	Reference
Apigenin	Colorectal cancer	382	Phase II	Ponte et al. (2021)
Quercetin	Prostate cancer	31	Phase I	Ponte et al. (2021)
Hesperidin	Breast cancer	40	NA	Ávila-Gá et al. (2019)
Daidzein	Prostate cancer	43	Phase II	Ponte et al. (2021)
Polyphenon E	Chronic lymphocytic leukemia	78	Phase II	Shanafelt et al. (2013)
Flavopiridol	Acute myeloid	165	Phase II	Zeidner et al. (2015)

Ethics statement

No institutional or national ethical committee approval was required for this study.

Declaration of competing interest

Authors declare no competent interest.

Data availability

No data was used for the research described in the article.

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