

## Review

# Flavonoids: A new generation molecule to stimulate programmed cell deaths in cancer cells.

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Programmed cell death (PCD) is decisive in eliminating affected cells in human cancers, whereas there are increasing cases of cancer-related death due to side effects of modern treatment methods. There is an urge for new methods of growth inhibition and elimination of cancer cells with a lower cytotoxicity to normal cells. Irregularity along PCD pathways plays a crucial role in cancer cell carcinogenesis. Apoptosis is a distinct cell death mechanism occurring in multicellular organisms and also called type one programmed cell death. Autophagy and paraptosis are non-apoptotic PCD occurring in multicellular organisms. Natural compounds are the fundament of pharmacological treatments, and flavonoids are natural polyphenolic compounds which are unique due to their diverse chemical structures and various biological active mechanisms like anticancer, anti-inflammatory, anti-oxidative and much more. This gives an increasing number of studies indicating that some flavonoids from medicinal plants could be promising candidates for new natural anticancer drugs, which attract high interests of academic researchers and advanced users. An understanding of the underlying mechanism of PCD induced by flavonoids in cancer cells is important as it plays a pivotal role in the pathogenesis of many diseases. This systematic review is to report flavonoids and their derivatives as new anticancer candidates to stimulate PCD with a different mechanism based on the pharmacological evidence.

**Key words:** flavonoids, apoptosis, autophagy, paraptosis, cancer cells, caspases

## Introduction

Cancer is being the second leading cause of mortality worldwide, and it is expected to overcome heart diseases as the leading cause of death in few years [1-4]. It is pivotal to understand the detailed mechanisms of advancement in cancer therapy that induce death in cancer cells. One of the most effective cancer therapy methods is induction of programmed cell death (PCD) using various cytotoxic agents to eradicate cancer cells [5-8]. To date, various natural products have been reported to confer anticancer effects by inducing PCD like apoptosis, autophagy, and paraptosis-associated cell death [9-13].

Flavonoids are naturally occurring polyphenolic metabolites which are primarily benzo- $\gamma$ -pyrone (phenyl chromone) derivatives, distributed throughout the plant kingdom and found in a substantial amount in fruits, vegetables, grains, nuts, seeds, tea, and traditional medicinal herbs. These natural compounds constitute more than 4,000 chemically unique and distinct moieties [13, 14]. Flavonoids have been classified according to their molecular structure that consists of two benzene rings joined by a linear three-carbon chain and forms an oxy-

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generated heterocycle (C6-C3-C6), and their large number of derivatives arise from the various combinations of multiple hydroxyl, methoxyl, and O-glycoside group substituents on the basic benzo—pyrone (C6-C3-C6). These excessively diverse group of compounds broadly comprise distinct classes such as flavonols, flavans, proanthocyanidins, anthocyanidins, flavanones, flavones, isoflavones, and neoflavonoids [15, 16] (Fig. 1). Within individual plants, flavonoids occur concentrated in the leaves and flowers but it is in every part of the plant. Flavonoids are edible plant pigments responsible for much of the coloring in nature. It has been estimated that an average daily intake of mixed flavonoids in human beings was in the range of 0.5 to 1 g, expressed as glycosides [17]. Many of the different flavonoids are part of the regular human diet. Although they are nonessential dietary factors, flavonoids are thought to be nutritionally valuable compounds, being the key natural products that provide an essential link between the diet and prevention of chronic disorders. One of the most investigated activities of flavonoids is their contribution to cancer prevention and treatment [14, 18].

The previous studies demonstrated flavonoid extracts, as well as their monomers, have covered a broad spectrum of biological activities like anti-oxidation, anti-inflammation and anticancer. Flavonoids exhibited anti-cancer activity by inducing several PCD mechanisms with lower cytotoxicity in normal cells indicating their cancer-specific cytotoxicity in different cancer cells [13, 19-30]. It is

imperative to understand the molecular mechanisms in which flavonoids triggered the activation of PCD in cancer cells.

### Induction of apoptosis by flavonoids in cancer cells

Apoptosis and necrosis are two distinct cell death mechanisms that occur in multicellular organisms. Apoptosis also called PCDs which play a critical role in hormone-dependent atrophy, metamorphosis, and embryonic development as well as in the maintenance of tissue homeostasis. Apoptosis occurs mainly in two pathways, the extrinsic or death receptor pathway which is triggered by the death receptor-like Fas, a member of the tumor necrosis factor (TNF) receptor superfamily, and intrinsic or mitochondrial pathway that leads to the release of cytochrome-c from the mitochondria. Both the pathways assemble to a common point where caspase-3, an effector caspase of apoptosis, is activated. Activated caspase-3 is responsible for the cleavage of poly (ADP-ribose) polymerase (PARP) that leads to cleavage of several cellular and structural molecules related to DNA regulation and repair (Fig. 2) [6, 8, 31, 32]. Plenty of literature suggests that irregularity along apoptotic pathways plays a crucial role in cancer cell carcinogenesis. Studies have shown that apoptosis can eliminate potentially malignant cells and inhibit tumor progression and hyperplasia [33]. There are several ways in which malignant cells can acquire reduction in apoptosis or apoptosis resistance. The mechanisms by which the evasion of apoptosis occurs broadly by three ways: 1) disrupted balance of pro-apoptotic and anti-apoptotic proteins, 2) reduced caspase function, and 3) impaired death receptor signaling. Targeting pathways which induce cancer cell apoptosis is one of the molecu-

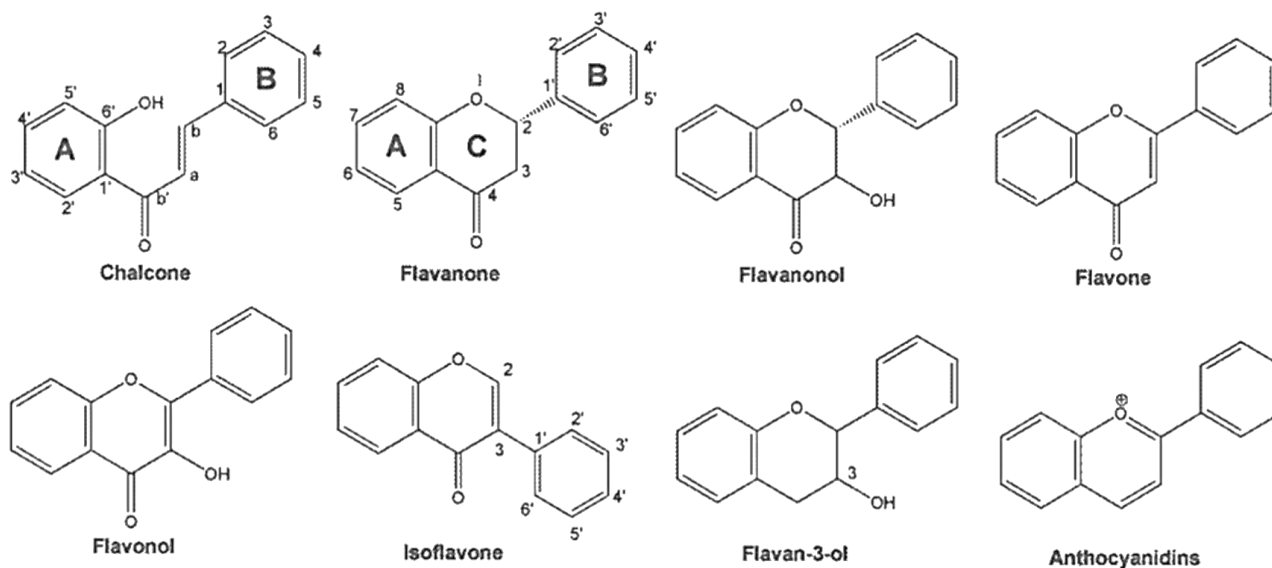


Fig. 1. General structures of representative flavonoids [69].

lar target therapies in a modern era of cancer treatment. Natural products are known to have potential anticancer effects by targeting the multiple cellular signaling pathways like apoptosis. Many studies showed that flavonoid extracts and its monomers have a regulatory effect on cell cycle arrest and apoptosis of cancer cells. Disruption in the balance of anti-apoptotic and pro-apoptotic members of the Bcl-2 family leads to dysregulated apoptosis in the affected cells. Flavonoids have been reported to regulate Bcl-2 family proteins by up-regulating pro-apoptotic protein and by down-regulating anti-apoptotic proteins, leading to apoptosis in several cancer cells [25, 34-39]. The p53 protein, also called tumor protein 53, is

known as tumor suppressor protein. The p53 functions as a transcription factor regulating downstream genes that are important in cell cycle arrest, DNA repair, and apoptosis. Several studies showed that mutation in this gene in several cancer cells leads to resistance to the induction apoptotic cell death of cancer cells [7, 40-42]. Several drugs have been investigated to target p53 via different mechanisms. The flavonoids are such molecules which regulate p53 in several cancer cells and induce cell cycle arrest and apoptosis which helps to inhibit cancer cell growth [43, 44]. The inhibitor of apoptosis proteins (IAPs) are a group of structurally and functionally similar proteins that regulate cytokinesis, signal transduction,

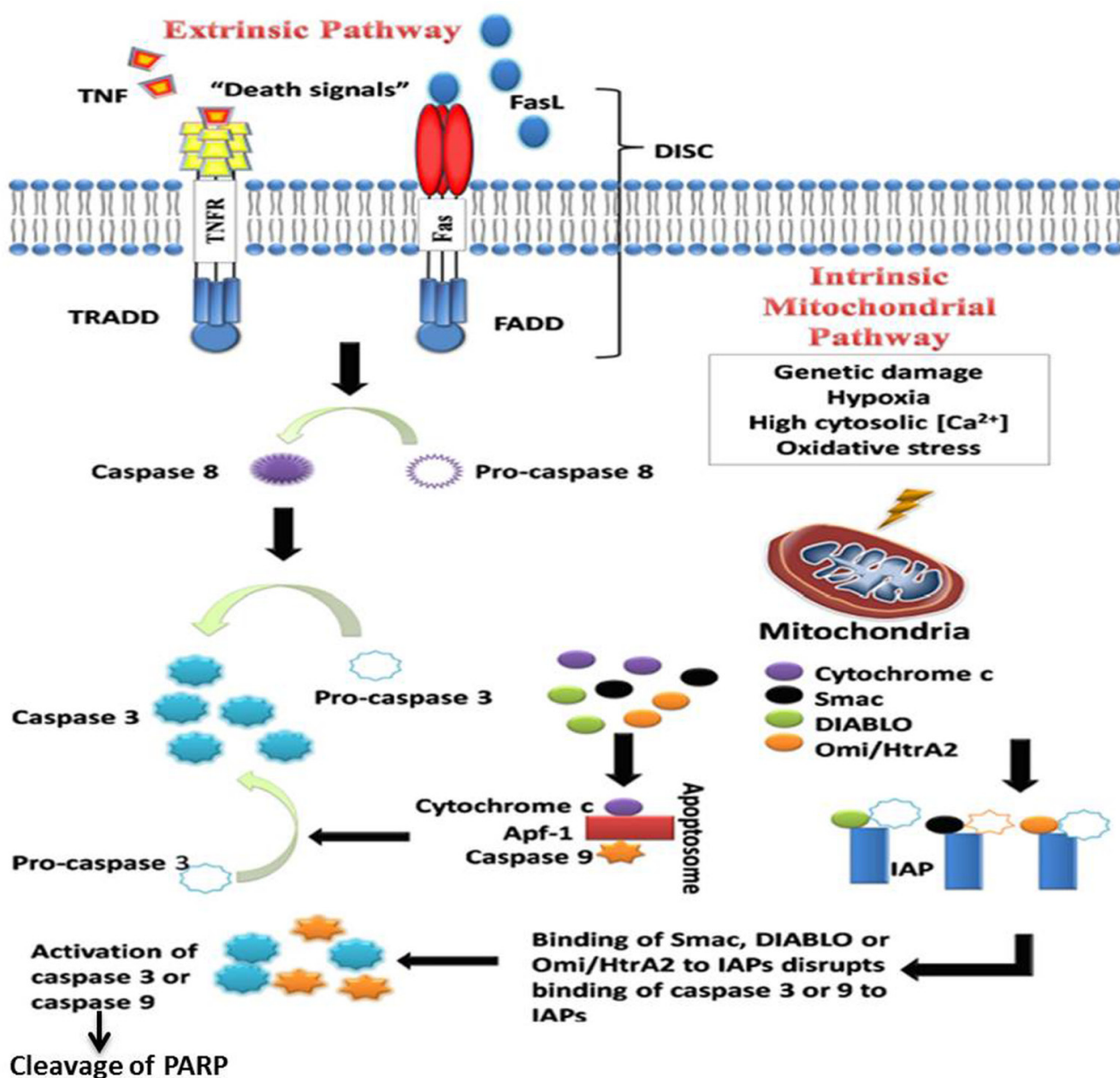


Fig. 2. The intrinsic and extrinsic pathways of apoptosis [70].

and apoptosis. IAPs are subjective inhibitors of caspases, and they can inhibit caspase activity by binding their conserved BIR domains to the active sites of caspases, leading to degradation of active caspases. A distinct amount of studies has shown the dysregulated IAP expression in several cancers [45, 46]. The IAPs are attractive molecular targets to promote apoptosis in cancer cells. Cancer cells treated with flavonoid have down-regulated the expressions of several IAPs and induces both extrinsic and intrinsic pathway of apoptosis in cancer cells [12, 38, 47]. Activation of caspases remains one of the important players in the initiation and execution of apoptosis [8, 29, 31, 48]. Studies have revealed that cancer cells treated with flavonoids induce apoptosis by activating both initiator caspases (e.g. caspase-2, -8, -9 and -10) which are primarily responsible for the initiation of the apoptotic pathway and effector caspases (caspase-3, -6 and -7) which are responsible for the actual cleavage of cellular components during apoptosis [20, 21, 25, 34]. Ligands of the death receptors and death receptors are key players in the extrinsic pathway of apoptosis. These receptors possess a death domain, and when triggered by a death signal, a number of molecules are attracted to the

death domain, resulting in the activation of a signaling cascade. Flavonoid treated cancer cells regulated death ligands and their receptors and induced apoptosis in several cancer cells [29, 34, 49, 50].

### Induction of autophagy by flavonoids in cancer cells

Autophagy is defined as type II PCD which is a ubiquitous physiological process in eukaryotic cells. The most common form of autophagy is known as macroautophagy. Autophagy is characterized by the formation of double-membrane vesicles known as autophagosomes that inundate cytoplasmic constituents including organelles followed by maturation process upon fusion with lysosomes and which finally lead to becoming autolysosomes, which undergoes a cellular degradation led by a lysosomal enzyme in response to stress and starvation. Abundant literature suggests that autophagy promotes cancer cell death in response to various anticancer agents on apoptosis-resistant cells [11, 51, 52]. Several studies have reported that flavonoid induces autophagy cell death by altering key regulators of autophagy-like PI3K/Akt (protein kinase B)/mTOR [22, 28, 30, 53]. Induction of autophagic cell

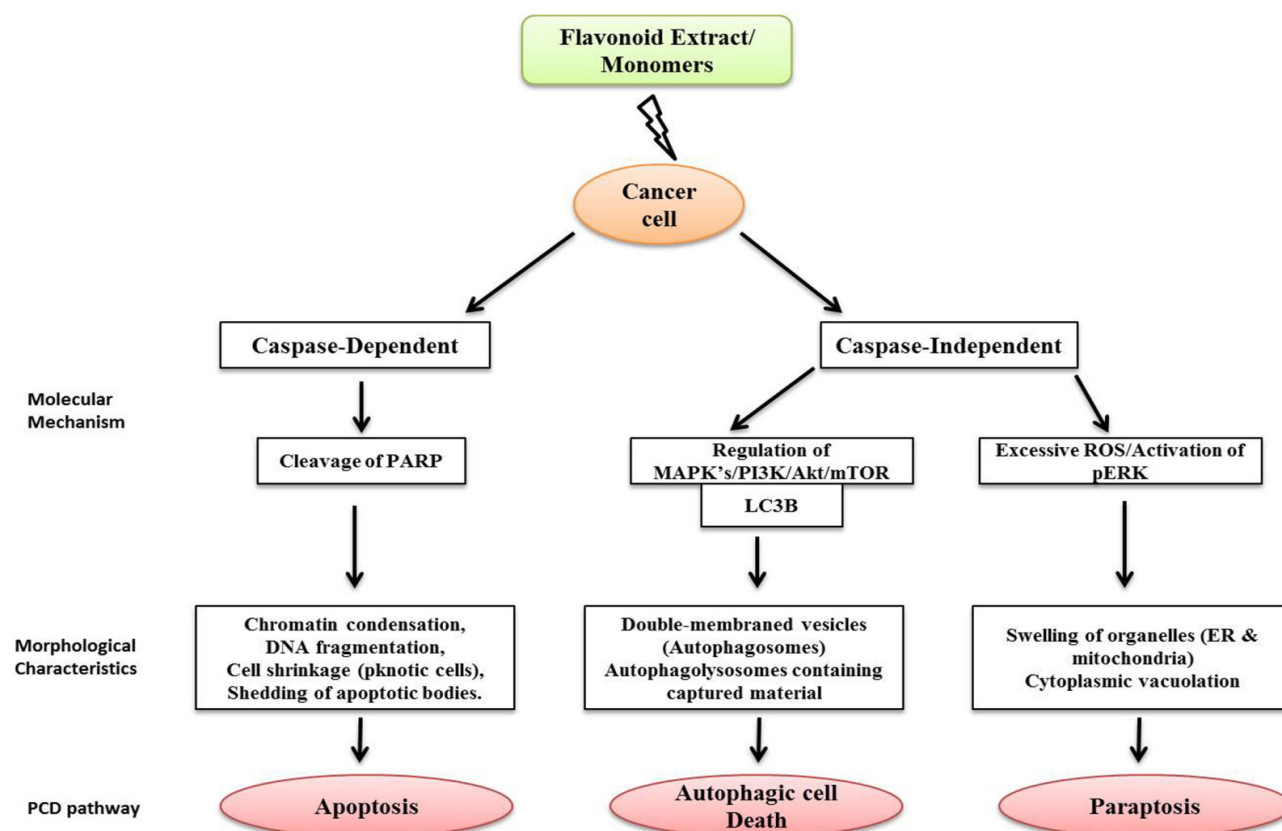


Fig. 3. Comparison of three types of Programmed Cell (PCD) Pathways in cancer cells treated with Flavonoid extracts/ flavonoid monomers.



death by flavonoid in cancer cells could be triggered by mitogen-activated protein kinases (MAPKs) and increase in reactive oxygen species (ROS) of which both play a crucial role in the induction of autophagic cell death in tumor cells [54-57].

### Induction of paraptosis by flavonoids in cancer cells

Cellular resistance to apoptosis in anti-cancer therapies is closely associated with carcinogenesis in many cancers. Studies have shown that failure of apoptosis leads to the trigger of many non-apoptotic cell death mechanisms and may contribute to tumor cell death [58-60]. Paraptosis, a non-apoptotic PCD is characterized by cytoplasmic vacuolization derived from endoplasmic reticulum (ER) and/or mitochondrial swelling, lack of apoptotic morphology, lack of DNA fragment, lack of caspase activation, lack of inhibition by caspase inhibitors (z-VAD.fmk, p35, and XIAP) and Bcl-XL, and lack of poly (ADP-ribose) polymerase (PARP) cleavage [61, 62]. In this type of cell death, the formation of apoptotic bodies, or other characteristics of apoptotic morphology such as chromatin condensation and DNA fragmentation are absent. Paraptosis cell death, that may be induced by the insulin-like growth factor I (IGF-1) receptor, is mediated by MAPKs and triggered by induction of ROS [26, 63-66]. Natural compounds are the fundament of pharmacological treatments, and more than 60% of all anticancer drugs are of natural origins or at least derived from areas present in nature [10, 13, 67]. Natural flavonoids have shown induction of paraptosis through the phosphorylation of ERK1/2 and increase of ROS production and loss of membrane potential which finally lead to paraptotic cell death in cancer cells [27, 68]. Study results revealed that; flavonoid can stimulate an alternative form of apoptosis in apoptotic resistant cancer cells for anti-cancer therapies.

### Conclusions

Cancer in humans caused by continual DNA damage has an increasing global concern of health care for over few decades. The modern treatments like chemotherapy and radiotherapy have their own limitation including cancer resistance against anticancer drugs and side effects due to radiotherapy. Hence, there is a need to develop an effective method to treat the cancer cell growth which is uncontrolled due to modifications of base pairs in DNA without causing damage to normal cells. The studies discussed in this review give an insight that flavonoids can play important beneficial roles in human health and nutritional status. Flavonoids play a crucial role in eliminating cancer cells by inducing cancer specific PCD with lower cytotoxicity, which gives a promising and most realistic chemopreventive approach for malignant disorders. There is a lack of

knowledge about diet–healthy relationships, where flavonoids usually act through multiple pathways, and each flavonoid can have different molecular targets and mechanisms on both cancer and normal cells. Phytochemical combinations may offer greater chemoprevention than administration of single agent alone. It is decisive to find out the optimal concentration of flavonoids from a treatment point of view considering that higher concentrations of flavonoids which may be cytotoxic to normal cells. Due to their versatile nature of cancer-specific cytotoxicity, flavonoids make them attractive agents in anticancer drug discovery (Fig. 3.). However, more studies need to be carried out to construct the mechanism of action of this selective nature of flavonoids in order to understand various epigenetic process which will provide a rational basis for combining specific dietary compounds and enhancing efficacy in the clinical setting.

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