Flavonoids-Apoptotic inducers in cancer therapy

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Abstract

Flavonoids are important class of natural drugs with a potent activity against various diseases like inflammation, ulcers, diabetes, cancer etc. they are well known for their antioxidant activity by scavenging free radicals. Due to the growing negativity to existing cancer therapies using synthetic drugs with side effects and harmful radiations, search for safer alternatives had been a target of study in many researches. Flavonoids came into focus with their properties of inhibition of cellular proliferation, free radical scavenging, autophagy, apoptosis which enables them to fight and prevent cancer effectively. Most of the flavonoids exhibit their anti-cancer ability via prevention of cancer but few of them can be used as safer therapeutic agents while they kill the cancerous cells by induction of apoptosis in various mechanisms like induction of pro-apoptotic mediators, inhibition of anti-apoptotic mediators, inhibition of expression of cancer genes finally resulting in the induction of caspases in extrinsic and intrinsic mechanism. This review focuses on mechanism of inhibition of apoptosis in cancer cells compared to usual process and various pathways triggered and inhibited by the flavonoids to exhibit their apoptotic property which is beneficial in treating cancer.

Keywords: Flavonoids, apoptosis, TNF, Caspases, Flavonols

DOI Number: 10.48047/NQ.2022.20.21.NQ99088 **Neuro Quantology 2022; 20(21): 733-741**

Introduction

Flavonoids are one of the prominent categories of herbal leads especially secondary metabolites with polyphenol nature those are well known as natural antioxidants. These chemical constituents are widely available in fruits, vegetables and natural beverages which are known for their medicinal properties like anticancer, anti-alzheimer's, anti-mutagenic, anti-atherosclerosis etc. Flavonoids have a huge efficacy to modulate critical cellular functions of enzymes [Burak and Imen, 1999].

Flavonoids have a basic 15-carbon chain with phenylpropanoid molecule (Flavan skeleton)-that is formed with two aromatic C6 (A and B) rings linked with a pyran C3 (C) chain. Flavonoids are classified into many major classes based on the chemical structure and unsaturation. Flavonols, flavones, flavanols, flavonones, anthocyanidins and isoflavones are important classes [Durazzo et al., 2019]. Two chromane rings attached to B ring at C2 position in flavonoids and C3 position in isoflavonoids like in Diadzein and Genistein. Saturation in oxidized C ring is characteristic of flavanones that are described as di-hydroflavones. Hesperetin and Naringenin are classic examples of di-hydroflavones [Panche et al., 2016].

Unoxidized C ring with saturation and hydroxyl group at C3 position is common in flavanols is found in catechins of green tea. Epicatechins are stereoisomers that exist in cis and tran forms based on the C2 and C3 atoms. Flavanols conjugates during esterification with gallic acid and forms epicatechin gallate and epigallocatechin gallate [Braicu et al., 2013; Rosen, 2012]. An unsaturated ring at C2-C3 position that is hydroxylated and oxidized at C3 and C4 position respectively is characteristic of flavonols. Quercetin, Kaempferol, Myricetin, Isorhamnetin, Galangin etc are examples of flavonols that has –OH group and is responsible for their activity. Flavonols with absence of

hydroxylation at C3 and =O group at C4 position makes them into flavonone nucleus present in Apigenin, Luteolin, Tangeritin and Chrysin. Afterall 2-phenyl-benzopyrylium flavylium structure is basic nucleus for anthocyanidins type flavonoids. Hydroxylation at C3 and multiple hydroxyl groups in the molecule are important for activity shown by Delphinidin, Pelargonidin, Petunidin, Cyanidin, Malvidin and Peonidin [Abotaleb et al., 2018].

Neoflavonoids have a basic 2-phenyl-4-chromenone skeleton with no hydroxyl groups at C2. Calophyllolide is the first neoflavone that is isolated from Calophyllum inophyllum [Garazd et al., 2003]. Chalcones are a group of flavonoids that has an opening in C ring that are widely found in tomatoes and fruits like strawberries and pears. Arbutin, Chalconaringening and Phloridzin are classic examples.

Cellular Apoptosis

Apoptosis is a process of programmed dying of cells due to age or other metabolic factors that occurs in the body. The apoptosis is induced majorly by 2 ways;

1. Extrinsic pathway occurs outside the cell and is related to tumour necrosis factor (TNF) that signals the trigger of caspase-8 and

2. Intrinsic pathway occurs inside the cell and is related to the mitochondria where in apoptotic proteins causing the activation of caspases 3, 7 and 9 [McArthur and Kile, 2018].

Extrinsic pathways take place with the involvement of ligand (CD-95, CD-95-L, TNF) to the receptors on the surface of sensitive cell membranes. These receptors are known as the prototypes of the death receptors. The activation of caspase-8 is caused by Death inducing signalling complex (DISC) which is a combination of procaspase-8, Flice inhibitory protein (FLIP) and fas associated death domain (FADD). The activated caspase-8 further activates caspase-3 which leads to apoptosis. Other extrinsic ligand is TNF which binds to its receptor TNF-R which has two complexes; complex 1 and complex 2. Complex 1 contains TNF receptor associated death domain (TRADD), receptor interacting protein 1 (RIP1) and telomeric binding factor 2 (TRF-2). Complex 2 contains RIP1, FADD, procaspase-8 and TRADD. Binding to the TNF receptors also activates caspase-8 further activating caspase-3.

Cellular apoptosis is caused and regulated through pro-apoptotic mediators like Bax, Bak and anti-apoptotic regulators like Bcl-2, Mcl-1 and Bcl-x that induce the release of cytochrome C in the mitochondria of the cells. Mitochondria triggers the production of death signals that are need in the extrinsic pathway which link to the intrinsic pathway that activates apoptotic genes corresponding to Bax and Bak. The generation of ROS and stress induction in endoplasmic reticulum, deprivation of the growth factor and radiation are usual causative factors responsible for the release of cytochrome C from mitochondria. Adapter protein apoptotic protease activating factor-1 (Apaf1), pro-caspase-9 and dATP are bound to the cytochrome C causing the formation of apoptosome. They also activate caspase which is an apoptotic mediator by cleaving procaspase-8 and 9 and converting it into active form [Ramos, 2007]. Thus the released caspase 9 activates caspase 3 that triggers the cleavage of apoptotic proteins.

NF-κB is often activated by the inflammation, carcinogens, radiation and free radicals and is helpful in supressing the apoptosis and promotion of cell growth. The NF-κB family of transcription factors are composed of P50, 52, 65, c-Rel and b-Rel which have a common Rel homology gene that is responsible for binding of the DNA that supresses apoptosis and enhance cell proliferation [Ju et al., 2007]. Translocation of NF-κB target genes to the nucleus leads to the activation of NF-κB signalling cascades which result in stimulation of anti-apoptotic proteins like Bcl-2 and Bcl-x and matrix metalloproteinases (MMP).

Generally cancer cells are resistant to the usual apoptosis process. This occurs in many ways like the overexpression of the cancer inducing genes that result in the proliferation of the cancer cells and suppression of Cytochrome P53. Activation of the antiapoptotic proteins like Bcl2 class and inhibition of caspases and pro apoptotic proteins can also be possible mechanisms of prevention of apoptosis in cancer cells [Jan and Chaudhry, 2019].

Apoptotic mechanisms of flavonoids

There are numerous studies that demonstrate and prove the ability of flavonoids to prevent

oxidative stress and related diseases by regulating the cellular metabolism and scavenging free radicals. There has been a substantial evidence of available flavonoids that are potent anti-cancer drugs however the mechanism of anti-cancer activity is not completely elucidated till date. Assertions have been made that the anti-cancer activity of flavonoids might be due to various actions of flavonoids induction of apoptosis, autophagy, suppression of cancer cell proliferation and invasion, free radical scavenging and arrest of the cell division cycle [Chirumbolo et al., 2018].

Flavonoids supresses the mitogen activated protein kinase (MAPK)/epidermal growth factor receptor (EGFR), protein kinase B, Phosphatidyl inositide-3-kinase (PI-3-K) resulting in inhibition of proliferation of the cancer cells. Other anti-proliferative actions include the inhibition of nuclear factor kappa light chain enhancer of activated B cells (NF-κB) [Neagu et al., 2019]. Studies revealed that the flavonoids block the NF-κB signalling pathways by inhibiting the anti-apoptotic factors and also by inhibiting the cellular proliferation [Li et al., 2006; Hastak et al., 2003]. Flavonoids have also exhibited suppression of activator protein (AP-1) and modulation of AP-1 tagetted genes [Shaulian and Karin, 2002]. Most importantly flavonoids stimulate the pathways promoting cell death by signalling the apoptotic cascade.

As per the literature states about the intrinsic and extrinsic pathways of the apoptosis, flavonoids interfere with the receptors, ROS and anti-apoptotic mediators to stimulate apoptosis in cancer cells and also stimulate pro-apoptotic mediators however in both pathways resulting in the stimulation of capsase-3, 6 and 7 as shown in figure 1. A list of flavonoids that were previously researched and proven for their anti-cancer activity in various cell lines was cumulated in the table 1. It also summarizes the mechanisms of tested flavonoids that trigger or inhibit various pathways in which they induce apoptosis in cancer cells.

Table 1: Anti-apoptotic mechanisms of various flavonoids

Name of the Flavonoid	Cell lines	Mechanism of apoptosis	Reference
Apigenin	PC-3 and DU145 cell lines	Induction of Bax overexpression, the downregulation of Bcl-2 and Bcl-xL	Shukla et al., 2014
	ACHN, Caki-1 RCC cell lines	Upregulation of p53	Meng et al., 2017
	T24 cell line	Inactivation of PI3K/Akt signaling pathway; inhibition of Bcl-xL	Shi et al., 2015
	ovarian cancer cells	Inhibition of HIF-1α and VEGF expression	Fang et al., 2005
Baicalein	SCC-4 human tongue cancer cells	Regulation of Ca2+ mediated intrinsic pathway	Chiang et al., 2008
Chrysin	HeLa cells	Stimulation of p38 and NF-κB pathways	Abotaleb et al., 2018
	U937 cell line	Upregulation of caspase 3	Khoo et al., 2010
	HTH 7 and KAT 18 (anaplastic thyroid cancer cell lines)	Elevation in cleaved caspase-3; decrease in cyclin D1, Mcl-1 and XIAP	Phan et al., 2011
	SP6.5 and M17 melanoma cells	Activation of caspases 3 and 9	Xue et al., 2016
Cyanidin	U87 cells	Upregulation of Bax protein expression; downregulation of	Hosseini et al., 2017

		Bcl-2 expression	
Daidzein	MCF-7 cells	Activation of caspase 7 and 9; alteration of Bax/Bcl-2 ratio	Jin et al, 2010
	HCCSK-HEP-1 cell line	Bak upregulation and activation of caspases 3 and 9	Park etal., 2013
Delphinidin	SKOV3 cell line	Suppression of PI3K/Akt and ERK1/2/MAPK signalling pathways	Lim et al., 2017
	NSCLC cell line	Activation of caspases 3 and 9	Pal et al., 2013
Epigallocatechin galate	HFF cells	Regulation of Bax/Bcl-2 ratio, upregulation of p53, p21, caspases-3, and 9, and down regulation of PI3K, Akt, and Bcl-2	Moradzadeh et al., 2017
	HepG2	Induciton of NF-κB activator protein-1 (AP-1) and nuclear transcription factor erythroid 2p45-related factor-2 (Nrf2)	Granado-Serra et al., 2010
Genistein	MCF-7 and 3T3-L1	Supression of Bcl-2, Bcl-xL,	Choi et al, 2014
	C200 and A2780	Inhibition of protein-1 (c-IAP1), Survivin, and NF-κB	Solomon et al., 2008
	HCT-116 and LoVo	Activation of intrinsic signaling apoptotic pathway	Qin et al., 2016
	P Ca cell lines	Apoptosis	Lakshman et al., 2008
	human malignant glioma cell lines	Activation of p53 and 21	Schmidt et al., 2008
	HT-29 colon cancer cells	Elevation in activity of caspase-3	Shafiee et al., 016
Hesperetin	gastric cancer cells	activation of caspases-3 and 9, and suppression of Bax to Bcl-2 ratio	Zhang et al., 2015
	Eca109 cell line	lowering Bax to Bcl-2 ratio	Wu et al., 2016
	HT-29, MCF-7, and MDA-MB-231 cell lines	Activation of ASK1/JNK Pathway	Palit et al., 2015
	H522 cells	Overexpression of TNF; activation of caspase-9, and suppression of P53	Elango et al., 2018
	PC-3 cells	Inhibition the NF-κB signalling pathway; reduction in transcription of Bcl-2	Sambantham et al., 2013
Kaempferol	A2780/CP70, A2780wt and OVCAR-3 cell lines	Activation of caspases 3 and 7, the upregulation of p53, Bax and Bad and the downregulation of Bcl-xL protein	Luo et al., 2010

Luteolin	Lung cancer	blockade of tumor necrosis factor-activated nuclear factor kappa B pathway	Ju et al., 2007
	LNCaP human prostate cancer cells	Repression of AR mRNA and protein expression	Chiu et al., 2008
Naringenin	SGC-7901 cell line	Elevation of p53 expression; suppression of Bcl-2 and survivin	Bao et al., 2016
	aSki and SiHa human cervical cancer cells	Inhibition of PI3K/AKT pathway	Kim et al., 2003
Pelargonidin	HT-29 cells	Activatio Bax, Bid, caspases 3 and 9, and inhibition of expression of Bcl-2 and Bcl-xL	Lopez de Las Hazas et al., 2017
	U2OS cell line	Downregulation of the PI3K/Akt signalling pathway	Chen et al., 2018
Quercetin	MCF-7 cells	upregulation of Bax and caspase-3 and downregulation of Bcl-2	Ranganathan et al., 2015
	PC-3 and LNCaP cells	Regulation of p53 signalling pathway	Wang et al., 2012
	HL-60 cells	Regulation of cascade-modulating COX-2, activation of caspase-3, modulating Bax, Bad, Bcl-2 expression	Niu et al., 2011
	human hepatoma cell line	Regulation of Bcl-2, and inhibition of PI-3-kinase/Akt	Granado-Serrano et al., 2006
	HeLa cells	Induction of intrinsic apoptosis via p53 and NF-κB inhibition	Vidya et al., 2010
Scutellaria baicalensis flavonoids	U14 cervical cancer	Regulation of the expression of Bax and Bcl-2	Peng et al., 2011
Tangeretin	human gastric cancer AGS cells	Activation of caspases 3 and 8	Dong et al., 2014

Conclusion

Researchers around the world revealed the effect of cancer in transforming itself into a dreadful disease with no to less effective and safe treatment options. Out of several anticancer agents available in the markets, most of them pose potential side effects and adverse drug reactions. Flavonoids are natural derived chemicals that have various activities like antioxidant, anti-inflammatory, anti-ulcer etc. However flavonoids present themselves as potential anti-cancer agents acting in different mechanisms like inhibition of cell proliferation, scavenging of free radicals, and prevention of mutations and induction of apoptosis being an important and potent mechanism. So subjective to the previous studies proving the efficacy of flavonoids in induction of cellular apoptosis, researches were targeted to elucidate exact mechanism of action in several pathways and also to synthesize newer flavonoids so as to improve the potency and lower the dose and to meet the supply demand. Evaluative studies to establish a correlation between natural and synthetic flavonoids in terms of their activity, efficacy, toxicity and availability. However natural flavonoids can claim their position as best and economical anti-cancer agents with therapeutic and preventive benefits.

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