Review

An overview of flavonoids from *Sophora flavescens* (kushen) with some emphasis on the anticancer properties of kurarinone and sophoraflavanone G

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Abstract: In this overview, the current knowledge of the constituents of flavonoids isolated from the roots of *Sophora flavescens* (kushen) is updated. Flavonoids consist of several classes, such as flavanones, flavonols, chalcones, isoflavones, biflavonoids, flavanols, and flavones. The most common compounds are kurarinone (KRN), sophoraflavanone G (SFG), 2′-methoxykurarinone, kuraridine, isoxanthohumol, and formononetin. KRN and SFG are two major flavanones with more vital anticancer properties than other flavonoids. From the literature, the cytotoxic values of KRN and SFG are variable and depend on the type of cancer cells tested. The anticancer activities of these two flavonoids involve different molecular mechanisms. Clinical trials are needed before anticancer drugs from KRN and SFG can be developed.

Keywords: Kushen; Flavanones; Cytotoxicity; Molecular mechanisms

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Contents

1. Introduction

The genus *Sophora* of the family Fabaceae consists of ~70 species widespread in tropical and temperate zones[1]. In China, 21 species have been recorded, of which nine are endemic, and one has been introduced.

Of these, 15 species have been used in traditional Chinese medicine (TCM)[2,3]. They include *S. flavescens*, *S. tonkinensis*, *S. subprostrata*, *S. alopecuroides*, *S. japonica*, *S. viciifolia*, and *S. pachycarpa.* More than 300 compounds have been isolated from *Sophora* species, and major compounds are quinolizidine alkaloids and prenylated flavonoids[2,4]. Flavonoids with prenylated groups are generally more lipophilic, conferring their more potent bioactivities[5].

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Pharmacological properties of *Sophora* species include antioxidant, anticancer, antimicrobial, antiviral, anti-inflammatory, antidiabetic, anti-osteoporosis, antiallergic, antipyretic, anti-diarrheal, cardioprotective, and neuroprotective[2–4] activities.

Sophora flavescens Aiton (syn. *S. angustifolia*) is distributed in East Asia (China, Korea, and Japan), including some European countries[6]. The plant is a deciduous herb 1−2 m tall[1,6]. Roots of *S. flavescens* are cylindrical in shape, 10–30 cm in length, 1–6 cm in diameter, and externally greyish-brown in color. Leaves are pinnately compound bearing 13–25 leaflets. Flowers are borne on racemes and have yellowish-white corolla with many calyces. Fruits are 5–12 cm long with an apex and long beak. They are elongated pods, slightly beaded, and do not dehisce on maturing, each bearing 1–5 brownish seeds[1,5]. In China, three varieties of *S. flavescens* (var. *flavescens*, *kronei*, and *galegoides*) have been identified[1], and the species is widespread in Shanxi, Hubei, Henan, Hebei, and Guizhou[6,7]. Photographs of the flowers, roots, and fruits of *S. flavescens* are shown in Figure 1.

The root of *S. flavescens* (kushen) is a TCM with a strong, bitter taste and cold properties[6,7]. Kushen is traditionally used to treat fevers, diarrhea, eczema, jaundice, vaginal itching, gastrointestinal hemorrhage, inflammatory disorders, ulcers, and skin burns. Scientific evidence has affirmed the anticancer, anti-inflammatory, antimicrobial, and cardioprotective properties of kushen[6–8].

The two main compounds found in kushen are alkaloids and flavonoids[9]. Quinolizidine alkaloids are dominant[9,10], with matrine and oxymatrine comprising ~20% of total alkaloids[11,12]. The contents of matrine and oxymatrine have been reported to be 0.56 and 4.41 mg/g using HPLC[13], and 0.71 and 4.26 mg/g using capillary electrophoresis[14], respectively. Matrine is a tetracyclic alkaloid having four fused-benzene rings, quinolizidine and pyridine nuclei, and nitrogen atoms at C1 and C16[9]. Oxymatrine has quinolizidine and pyridine nuclei and an oxygen atom attached to the nitrogen atom at C1. Other alkaloids from the roots of *S. flavescens* include allomatrine, isomatrine, sophocarpine, sophoramine, and sophoridine[15]. Another primary class of compounds found in kushen includes flavonoids, with kurarinone (KRN) being the most dominant[11,12]. The total content of alkaloids and flavonoids is 3.3% and 1.5%, respectively. Other compounds include quinones, triterpenes, xanthones, fatty acids, and essential oils. Recently, pterocarpans and arylbenzofurans have also been isolated[16,17].

Figure 1. *Sophora flavescens* flowers (left), slices of dried roots (middle), and fruits (right).

Flavonoids represent the largest family of phenolic metabolites from plants, with more than 9000 compounds reported[18]. They are found in most herbs, fruits, and vegetables[19]. The basic skeleton, along with various classes and molecular structures of flavonoids, has been widely reviewed, including lesser-known flavonoids, such as diosmetin, tamarixetin[20], acacetin, and chrysoeriol[21]. The chemical structure of flavonoids consists of two benzene rings A and B, which are joined by a heterocyclic pyran ring C, forming the benzo-pyrone (C6-C3-C6) moiety[22,23]. The majority of the flavonoids have ring B linked in position 2 to ring C, and they can be further divided into classes, such as flavones, flavonols, flavanones, and flavanols. Flavones have a C2–C3 double bond and a 4-carbonyl group but lack the C3 hydroxyl group at ring C. Flavonols possess all three functional moieties. Flavanones lack the C2–C3 double bond, while flavanols lack the C2–C3 double bond and the 4-carbonyl group[19,24]. In nature, flavonoids are found as aglycones, glycosides, and methylated derivatives. Flavonoids in which the ring B is linked at positions 3 and 4 to the ring C are called isoflavones[19]. Chalcones are α,β-unsaturated ketones bearing two aromatic rings A and B and are precursors of flavonoids[25]. Biflavonoids are flavonoids with two identical or non-identical C6-C3-C6 moieties.

In this overview, the current knowledge of the constituents of flavonoids isolated from the roots of *S. flavescens* (kushen) is updated. With the emphasis on the chemistry and pharmacological properties of KRN and sophoraflavanone G (SFG), the pharmacological properties of these two flavanones are focused on their anticancer activities.

2. Constituents of flavonoids

A review of the isoprenoid flavonoids from the roots of *S. flavescens* recorded 25 flavanones, 11 flavonols, eight flavanols, eight chalcones, two bioflavonoids, and one isoflavone[7]. In this review, flavonoids of *S. flavescens* reported from 1970−2021 are 42 flavanones, 31 flavonols, 12 chalcones, 12 isoflavones, nine biflavonoids, seven flavanols, and three flavones (Table 1). The most common flavanones are KRN[13], SFG[11], and 2′-methoxykurarinone[9]. Kuraridine[10] and isoxanthohumol[8] are the most common chalcones, while formononetin[6] is the most common isoflavone.

Table 1. Flavonoids isolated from the roots of *Sophora flavescens* (kushen).

Sub-class (total)	Compound name	Reference
Flavanones (42)	Alopecurone G	[26]
	7,4′-Dihydroxy-5-methoxy-8-flavanone	[26, 27]
	8-[2-(3-Hydroxyisopropyl)-5-methyl-4- hexenyl]-2′-methoxy-5,7,4′-trihydroxyflavanone	[28]
	7-Hydroxy-5-methoxy-8-prenylflavanone	[28]
	8-(3-Hydroxymethyl-2-butenyl)-5,7,2’,4’-tetrahydroxy-flavanone	[29]
	6″-Hydroxynorkurarinone-7-*O*-β-D-galactoside	[30]
	Isokurarinone (Leachianone A)	[27, 31−35]
	Kosamol R	[27]
	Kurarinol	[31, 34−37]
	Kurarinone	[26, 27, 32−36, 38−43]
	Kushenols A, B, E, K, P–W	[26, 27, 34, 35, 38, 43−49]
	Leachianones A, G	[26, 35, 39, 41, 50]
	7-Methoxy-4″,5″-dihydroxynorkurarinone	[30]
	2′-Methoxykurarinone	[26, 32, 34−36, 38, 39, 43, 51]
	5′-Methylsophoraflavanone B	[51]
	Neokurarinol (Kosamol Q)	[27, 31, 35]
	Norkurarinol	[31, 34, 35, 38, 43]
	Sophoflavanones A, B, G, H	[35, 52, 53]
	Sophoraflavanones B, K–N	[28, 33, 34, 39, 48, 50]
	Sophoraflavanone G (Norkurarinone, Kushenol F, Vexibinol)	[26, 27, 33, 35, 36, 38, 40−44, 55]
	Sophoranones A, B	[54]
	3,7,4′-Trihydroxy-5-methoxy-8-prenylflavanone	[29, 51]

Table 1. Continued.

Sub-class (total)	Compound name	Reference
Flavonols (31)	Flavenochromanes A–C	[35, 56]
	Isoanhydroicaritin	[35, 33, 57]
	Isoquercitrin	[42]
	Kaempferol	[35, 43]
	Kushenols C (X), G, K−M, Z	[27, 34, 35, 43, 44, 47−50, 58]
	8-Lavandulykaempferol	[35, 36, 59]
	8-Lavandulyl-5,7,4′-trihydroxyflavonol	[35, 41]
	5-Methoxy-7,4′-dihydroxy-8-lavandulylflavonol	[35, 37]
	Myricetin	[52]
	Naringenin	[35, 49]
	Noranhydroicaritin	[26, 35, 43, 49, 57]
	Quercetin	[35, 42, 49]
	8-Prenylnaringenin	[26]
	Rutin	[46, 42]
	Sophoraflavenochromane G	[37]
	Sophoflavescenol	[35, 43, 49, 60]
	Sophoflavanones A, B, G, H	[32, 49, 54]
	Sophoranodichromanes A–C	[61]
Chalcones (12)	Cyclokuraridin	[50]
	Demethylkuraridin	[34]
	Demethylxanthohumol	[34]
	2′-Hydroxyisoxanthohumol	[41, 43]
	Isokuraridin	[34]
	Isoliquiritigenin	[49]
	Isoxanthohumol	[27, 34, 35, 38, 40, 41, 43, 57]
	Kuraridin (Kuraridine)	[26, 34−36, 38, 40, 43, 49, 51, 53]
	Kuraridinol	[27, 34, 35, 49]
	Kushenol D	[27, 34, 44]
	2-Methoxy-2′,4′,4,6-tetrahydroxy-5-lavanduly dihydrochalcone	[37]
	Xanthohumol	[27, 35, 43, 49, 57]
Isoflavones (12)	Biochanin A	[35, 42, 49]
	Calycosin	[49]
	Calycosin-7-glucoside	[42]
	Daidzein	[42]
	Daidzin	[42]
	3′,7-Dihydroxy-4′-methoxyisoflavone	[27]
	Formononetin	[27, 35, 38, 39, 41, 49]
	Genistein	[49]
	Kushenol	[27, 35, 46]
	Maakiain	[36, 39, 41, 42]
	Trifolirhizin	[42, 43]
	Trifolirhizin-6′-monoacetate	[41, 43]
Biflavonoids (9)	Sophobiflavonoids A–H, CE	[49, 62]
Flavanols (7)	Kurarinols A, B	[49]
	Kushenols H, I (N), Y	[27, 36, 43, 45, 49, 51]
	2′-Methoxykushenol I	[37]
	Sophoraflavanonol A	[37]
Flavones (3)	5,4′-Dihydroxyflavone	[49]
	Luteolin	[42, 49]
	Luteoloside	[42]

Other names: Sophoraflavanone G (Norkurarinone, Kushenol F, Vexibinol); Kushenol C (Kushenol X); Kuraridin (Kuraridine); Kushenol I (Kushenol N).

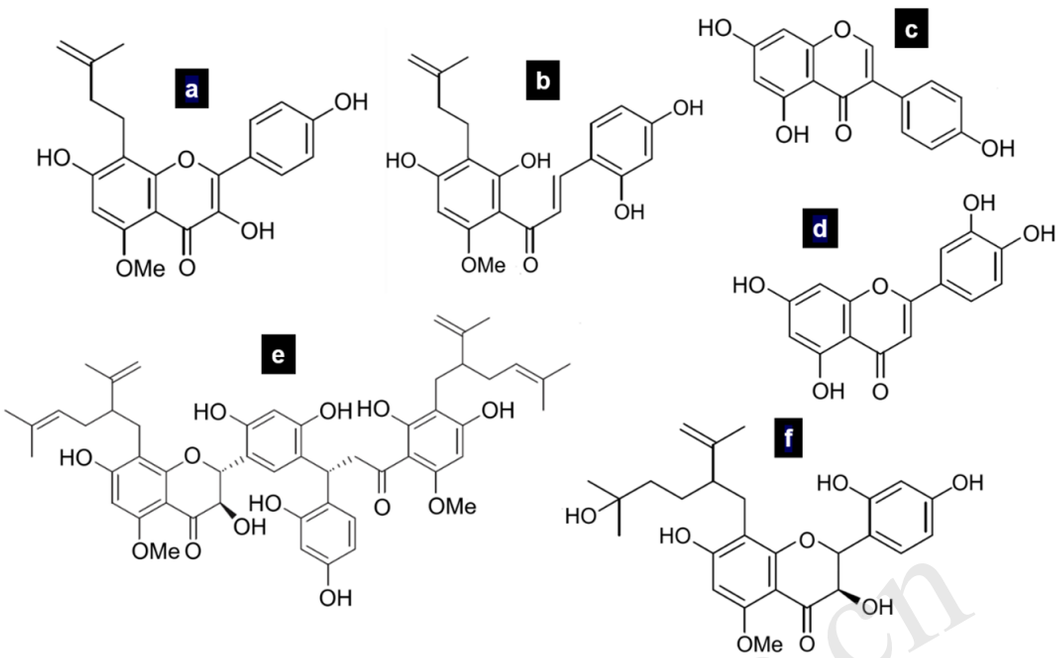

Figure 2. Chemical structures of sophoflavescenol (**a**), kuraridin (**b**), genistein (**c**), luteolin (**d**), sophobiflavonoid E (**e**), and kushenol H (**f**), representing flavonols, chalcones, isoflavones, flavones, biflavonoids, and flavanols in the roots of *Sophora flavescens*, respectively.

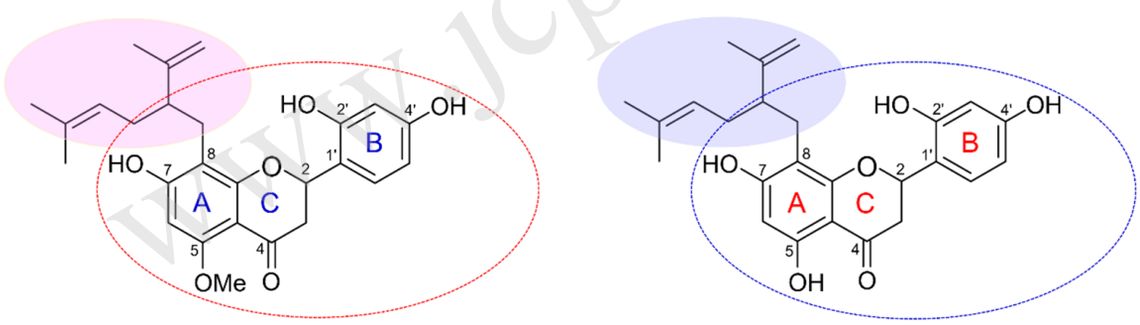

Figure 3. The chemical structures of KRN (left) and SFG (right), showing the highlighted lavandulyl moiety at C8, and the encircled naringenin moiety of rings A–C.

Figure 2 shows the chemical structures of sophoflavescenol (**a**), kuraridin (**b**), genistein (**c**), luteolin (**d**), sophobiflavonoid E (**e**), and kushenol H (**f**), representing the various sub-classes of flavonoids found in the roots of *S. flavescens*, and they are flavonols, chalcones, isoflavones, flavones, biflavonoids, and flavanols, respectively. The chemical structures of KRN and SFG, the two major compounds emphasized in this review, are shown in Figure 3.

3. Chemistry

3.1. KRN

KRN is a lavandulyl flavanone that contains a lavandulyl group at C8, and a methoxy group is attached to an oxygen atom at C5[63]. KRN possesses three hydroxyl (-OH) groups in its flavanone skeleton. It has a molecular formula of $C_{26}H_{30}O_6$ and a molecular weight of 438.5 g/mol. KRN was first isolated from

the roots of *S. flavescens* when the plant was previously named as *S. angustifolia*[57]. In a study on the contents of flavonoids in different plant parts of *S. flavescens*[42], the content of KRN (9274 μg/g) is the highest in the root, followed by the leaf (783 μg/g).

3.2. SFG

SFG is also known as norkurarinone, kushenol F, and vexibinol. SFG is a lavandulyl flavanone, and its chemical structure consists of four -OH groups at C5, C7, C2′, and C4′ in its flavanone skeleton. Its molecular formula is $C_{25}H_{28}O_6$, and its molecular weight is 424.5 g/mol. It is a tetrahydroxyflavanone having a naringenin moiety that bears a -OH group at C2′ and C4′ as well as a lavandulyl group at C8. SFG was first isolated from the roots of *S. flavescens*[64]. The content of SFG is 2252 μg/g in the root and 61 μg/g in the leaf[42].

4. Anticancer activities

4.1. Cytotoxicity

Early studies have reported on the potent cytotoxic activity of KRN. The IC_{50} value was 18.5 μM when tested against HL-60 human myeloid leukemia cells[65]. KRN displays growth inhibition towards human MCF-7/6 breast cancer cells with an IC_{50} value of 22.2 μM[66,67]. Subsequently, KRN was found to be cytotoxic towards A549 and NCI-H1975 lung cancer cells with IC_{50} values of 6.2 and 21.6 μg/mL and non-cytotoxic towards BEAS-2B lung epithelial cells with IC_{50} values of 58.2 μg/mL, respectively[68].

The cytotoxicity of 15 flavonoids from kushen has been tested using a panel of five cancer cell lines[69]. Against A549 lung, SK-OV-3 ovary, SK-MEL-2 skin, XF498 central nervous system (CNS), and HCT-15 colon cancer cells, the cytotoxicity of KRN with the methylated -OH group at the C5 position was slightly weaker than SFG without the methylated -OH group at the C5 position (Fig. 3). The values of KRN were 9.0, 9.4, 6.4, 5.9, and 8.6 μg/mL, while those of SFG were 6.4, 7.9, 3.9, 5.8, and 5.7 μg/mL, respectively[69].

The cytotoxicity of KRN and SFG was compared using a panel of 18 types of cancer cell lines[11]. Against HeLa cervical, PC-3 prostate, A549 lung, AGS gastric, and Eca-109 esophageal cancer cells, cytotoxicity of KRN was 2.0, 6.6, 8.1, 9.3, and 9.6 μg/mL, respectively. Cytotoxicity of SFG was 6.5, 7.7, 7.7, and 7.9 μg/mL against AGS gastric, A549 lung, DU-145 prostate, and Bel-7402 hepatic cancer cells, respectively. Against HeLa cervical cancer cells, the cytotoxicity of SFG (12 μg/mL) was much weaker than KRN (2.0 μg/mL). Against prostate cancer cells, the cytotoxicity of SFG (7.7 μg/mL) was much stronger than KRN (14 μg/mL) against DU-145, while SFG was non-cytotoxic compared to the cytotoxicity of KRN (6.6 μg/mL) against PC-3 cells. Results show that the comparative cytotoxic values of these two flavonoids are variable and depend on the type of cancer cells tested.

Earlier results showed that SFG exhibits stronger cytotoxicity than KRN when tested with HL-60 myeloid leukemia cells and HepG2 liver cancer cells[65,70]. Their IC_{50} values were 12.5, 13.3, 18.5, and 36.2 μM, respectively. The cytotoxicity of SFG was 0.78. 2.14, and 1.57 μg/mL against A549 lung, K562 lymphoma, and HeLa cervical human cancer cells, respectively[64].

Besides KRN and SFG, other flavonoids, such as flavenochromane C, show potent cytotoxic activity against A549 lung, 1A9 ovarian, KB nasopharynx, KB-Vin drug-resistant KB, and MCF-7 breast cancer cell lines with IC_{50} values 1.0, 1.2, 1.3, 1.7, and 3.6 μM, respectively[56]. Flavenochromane B (3.2−6.9 μM) is slightly less potent, while flavenochromane A (13.9−16.1 μM) is not active.

4.2. Molecular mechanisms

In a recent review on the chemopreventive and other pharmacological potentials of KRN[63], it is highlighted that KRN possesses anticancer activities against various cancer cells involving different molecular mechanisms. Lung, gastric, cervical, colorectal, and prostate cancer cells are susceptible to KRN (Table 2). Apoptosis of cancer cells is induced by modulating molecular targets, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), nuclear factor-κB (NF-κB), B-cell lymphoma 2 (Bcl2), matrix metalloproteinases (MMPs), and caspases[71−73]. Studies on the molecular mechanisms show that KRN possesses anticancer activity by promoting activating transcription factor 4 (ATF4)[74], modulating signal transducer and activator of transcription 3 (STAT3), cellular FLICE-inhibitory protein (c-FLIP), and Akt pathways[68,75], and degrading K-RAS *via* WD40-repeat protein 76 (WDR76)[76].

SFG inhibits the growth of oral, lung, and breast cancer cells, including leukemia cells (Table 2). Molecular mechanisms of SFG involve activation of caspase 3 and cleavage of poly (ADP-ribose) polymerase (PARP)[77], modulation of STAT proteins[78], and activation of (MAPK) pathway[79,80]. Recently, the reversal of ATP-binding cassette G2 (ABCG2)-mediated multidrug resistance by SFG in patients with lung cancer has been reported[81].

Table 2. Anticancer activities of KRN, SFG, and other flavonoids.

Flavonoid	Cancer cell line, cancer type, anticancer effect, and anticancer mechanism	Reference
Kurarinone	Attenuation of ERK/RSK2-driven NF-κB expression and proliferation of breast cancer cells.	[67]
	Induced apoptosis in A549 lung cancer cells *in vitro* and *in vivo* by repressing the activity of ER and Akt pathways.	[68]
	Down-regulated Bcl-2, and up-regulated caspases -8 and -3 in H460 lung cancer xenograft mice.	[71]
	Promoted TRAIL-induced apoptosis in HeLa cells by inhibiting NF-κB-dependent cFLIP expression.	[72]
	Induced apoptosis in H1600 lung cancer cells *via* multiple mechanisms, and suppressed cell migration and invasion by suppressing the expression of EMT-related proteins and MMPs.	[73]
	Activated ATF4 and cytostatic effects through PERK phosphorylation in PC3 prostate and HeLa cervical cancer cells.	[74]
	Enhanced TRAIL-induced apoptosis in SGC7901 gastric cancer cells *via* down-regulation of Mcl-1 and c-FLIP as well as inhibition of STAT3 signaling.	[75]
	Induced p53-independent G0/G1 cell cycle arrest by degradation of K-RAS *via* WDR76 (a tumour repressor) in human colorectal cancer cells.	[76]
Sophoraflavanone G	Exerted antiproliferative activity towards KB oral carcinoma cells by promoting apoptosis *via* activation of caspase 3 and PARP.	[77]
	Inhibited proliferation and induced apoptosis of cancer cells by targeting upstream signalling of STAT proteins.	[78]
	Induced apoptosis in HL-60 leukaemia cells by activation of the MAPK pathway.	[79]
	Induced apoptosis in MDA-MB-231 triple negative breast cancer cells *via* suppression of MAPK pathway.	[80]
	Reversed ABCG2-mediated multidrug resistance in in patients with lung cancer.	[81]
DMAI	Showed antitumor activities in U87MG glioblastoma cells *via* inhibition of cell proliferation, migration, and invasion.	[82]
Kuraridin + norkurarinone	Mixture significantly induced apoptosis and inhibited the proliferation of SGC-7901 gastric cancer cells *via* mitochondrial apoptotic pathway.	[83]
Kurarinol	Induced apoptosis of liver cancer cells through suppression of cellular STAT3 signaling.	[84]
Kushenol Z	Mediated the antiproliferative activity in A549 and NCI-H226 lung cancer cells by inhibiting the mTOR pathway *via* the inhibition of cAMP-PDE and Akt.	[85]
Leachianone A	Possessed potent cytotoxic activity against HepG2 hepatoma cells with an IC_{50} value of 3.4 μg/mL, induction of apoptosis involved extrinsic and intrinsic pathways.	[86]
Sophoflavescenol	Inhibited the growth of HL-60 leukaemia cells with an IC_{50} value of 12.5 μg/mL, induction of apoptosis involved activation of caspase-3.	[87]
Trifolirhizin	Exerted significant antiproliferation (50% growth inhibition) at 100 and 250 μM against A2780 ovarian and H23 lung cancer cells, respectively.	[88]

Abbreviations: ABCG2 = ATP-binding cassette G2, ATF4 = activating transcription factor 4, Bcl-2 = B-cell lymphoma 2, c-FLIP = cellular FLICE-inhibitory protein, DMAI = desmethylanhydroicaritin, EMT = epithelial-mesenchymal transition, ER = endoplasmic reticulum, ERK = extracellular signal-regulated protein, MAPK = mitogen-activated protein kinase, MMPs = matrix metalloproteinases, mTOR = mechanistic target of rapamycin, NF-κB = nuclear factor-κB, PARP = poly (ADP-ribose) polymerase, PDE = phosphodiesterase, PERK = PKR-like endoplasmic reticulum kinase, RSK2 = ribosomal S6 kinase 2 kinase, STAT = signal transducer and activator of transcription, TRAIL = tumor necrosis factor-related apoptosis inducing ligand, and WDR76 = WD40-repeat protein 76.

5. Conclusions

From the literature, the cytotoxic values of KRN and SFG are variable and depend on the type of cancer cells tested. The anticancer activities of these two flavonoids involve different molecular mechanisms. Lung, gastric, cervical, colorectal, and prostate cancer cells are susceptible to KRN. Apoptosis in cancer cells is induced by modulating molecular targets, such as TRAIL, NF-κB, Bcl2, MMPs, and caspases. Studies on the molecular mechanisms show that KRN possesses anticancer activities by promoting ATF4, modulating STAT3, c-FLIP, and Akt pathways, and degrading K-RAS *via* WDR76. SFG inhibits the growth of oral, lung, and breast cancer cells, including leukemia cells. Molecular mechanisms of SFG involve activation of caspase 3 and cleavage of poly (ADP-ribose) polymerase (PARP), modulation of STAT proteins, and activation of (MAPK) pathway. Recently, the reversal of ATP-binding cassette G2 (ABCG2)-mediated multidrug resistance by SFG in patients with lung cancer has been reported. The prospects of developing anticancer drugs from KRN and SFG as individual compounds or in combination are promising and should only proceed after sufficient clinical trials have been conducted.

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