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Fallopia japonica: Bioactive Secondary Metabolites and Molecular Mode of Anticancer

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Abstract

Traditional medicinal plants are a large source of natural anticancer compounds that might serve as leads for the development of novel drugs. In recent years, the scientific community in the Western world has recognized the potential of natural products, used in Traditional Chinese Medicine (TCM). Since ancient times Japanese knotweed (*Fallopia japonica*), has been utilized in many TCM herbal preparations as anti-cancer agent. *F. japonica* (FJ) is known to produce a series of bioactive secondary metabolites, including anthraquinones, stilbens, tannins, lignans, anthocyanins, phenethyl alcohols, sterols, and essential oils. Resveratrol (a stilben) and emodin (an anthraquinone) are the major active ingredients of FJ. The anticancer activity of both compounds has various molecular modes of action and mechanisms through their ability to modulate the proliferation, apoptosis, cell cycle, growth factors, protein kinase C (PKC), NF-kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) signaling cascades. This review presents an overview of the secondary metabolites of *F. japonica* and anticancer activities of the extract and main active principles, resveratrol and emodin. The possible molecular targets and potential chemopreventive effects are discussed.

Keywords: *Fallopia japonica*; Traditional Chinese Medicine (TCM); Resveratrol; Emodin; Chemopreventive

Introduction

Traditional Chinese medicine (TCM, Zhong-Yi), has a long history of use, with extensive literature and clinical applications covering thousands of years [1,2]. It has been widely accepted that TCM has evolved over the millennia, with a battery of herbal materials to preserve health, as well as treat and prevent illnesses [3,4]. Over the past decades, TCM has been an area of intensive research aiming at developing new drugs for the ever-evolving diseases afflicting mankind [5]. Because the development of new chemical drugs remains time consuming, capital-intensive and risky (i.e., a low rate of success), much more effort has been put into TCM for drug discovery. Now, TCM is a growing means of drug development in China. In 2007, China collected 3563 extracts, 64,715 compositions, and 5000 single compounds from 3000 Chinese herbs, together with about 130 kinds of chemical drugs obtained from either TCM ingredients or their derivatives [6].

Fallopia japonica (Syn. *F. japonica* Houtt.) is a member of the Polygonaceae family (buckwheat). It is known as Japanese knotweed Pleuropteris zuccarinii, *P. japonicum* Meissn, Ronse Decraene (Syn. *Reynoutria japonica* Houtt.), and Polygonum zuccarinii Small [7,8]. The English names for Japanese knotweed include, Huzhang, fleeceflower, Hancock's curse, elephant ears, donkey rhubarb, sally rhubarb, American bamboo, Japanese bamboo, and Mexican bamboo (though it is not actually a bamboo). Huzhang root extract is a TCM treatment. It is also known as, He Shou Wu, which is used as a blood tonic (herbal preparation). Japanese Knotweed is considered an invasive pest and is a commercial source of resveratrol.

Fallopia japonica (FJ) is a large perennial plant, native to eastern Asia in Japan, China and Korea, this species grows in vast areas throughout the northeastern USA into Canada and Europe, and it was introduced from Japan into the UK in the 19th century [9].

Historically, in 1777, Houttuyn as Reynoutria japonica described Japanese knotweed. Japanese knotweed stems have distinct raised nodes (appearance of bamboo). Stems are a reddish color and have a maximum height of 3–4 m (per growing season). The young stems have a flavor similar to mild rhubarb [10]. In some locations, semi-cultivated Japanese knotweed has been used for food production. Such populations can be controlled to prevent the invasion of sensitive wetland areas and driving out of the native vegetation. Morphological, leaves rang from triangular to heart-shaped, and are 7–14 cm long and 5–12 cm broad, and an entire margin [10]. The flowers are an attractive white color (July–August), and are considered an important source of nectar for honeybees; they yield a nice monofloral honey (bamboo honey, USA) (Figure 1) [11]. Knotweed flowers are mainly male sterile as reported in the UK and North America [12]. Japanese knotweed rhizomes with a distinctive orange interior can extend more than 15–20 m in length and 2 m in depth [10,13]. *Fallopia japonica* is highly able to produce series bioactive secondary metabolites including anthraquinones, stilbens, tannins, lignans, anthocyanins, phenethyl alcohols, sterols, and essential oils. Interestingly, resveratrol concentration in *F. japonica* is much higher than that reported in red wine, thus it is an important commercial source of resveratrol, and its scientific name is used in supplement labels. *F. japonica* also produces emodin. Emodin is used in traditional Chinese herbal medicine as a quality-control index for *F. japonica*. It has a wide range of pharmacological activities such as anti-bacterial [14], anti-inflammatory [15] immunosuppressive [16], and antitumor activity [17]. In addition, our LC-MS data suggests that the quantity of emodin from total contents of methanolic extract of *F. japonica* is about 30%. The medicinal importance of rhizomes of *Fallopia* spp., have been reported, related to resveratrol and emodin

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Figure 1: Photographs (clockwise from left to right) of Japanese knotweed (*Fallopia japonica*, Sieb. & Zucc.) invasive growth in riparian habitat inflorescence fruit, stem, and rhizomes.

[18]. This review presents an overview of the chemical composition of *F. japonica* and anticancer activity of the extract and main active principles resveratrol and emodin. We highlight the possible molecular targets of their chemopreventive effect, and consider this herb and its active metabolites as novel dietary chemopreventive agents.

The use of *Fallopia japonica* in traditional medicine

Traditionally, *F. japonica* has been used in China, Korea, Taiwan, and Japan. The extract from the roots of *F. japonica* has been used in TCM as a natural laxative, and occasionally as food. It has been recorded that emodin has a mild laxative effect in doses of 20-50 mg per day. *F. japonica* is a concentrated source of emodin, and is used as a nutritional supplement to regulate the bowels motility.

Therapeutically, the aerial parts, dried root, and rhizome of *F. japonica* are often used as analgesic, antipyretic, diuretic, and antitussive agents. It can also be used for the treatment of chronic bronchitis, infectious hepatitis, diarrhea, cancer, gallstone, hypertension, atherosclerosis, menoxenia, hyperlipidemia, leucorrhoea, pruritus vulvae of the dampness-heat type, mycotic trichomoniasis, bacterial vaginitis, dysmenorrhea, trauma with blood stasis, snake bites, skin burns, osteomyelitis and allergic inflammatory diseases [19-24]. Methanolic extract of the roots of *F. japonica*, is used to maintain oral health in Korea, it is shown to reduce the viability of *Streptococcus mutans* and *Streptococcus sobrinus*; and inhibit sucrose-dependent adherence, glucan formation, and glycolytic acid production [25].

Bioactive secondary metabolites of *Fallopia japonica*

Many chemical components have been reported from this plant (Table 1 and Figure 2). The roots of *F. japonica* has been reported to contain a large number of stilbens, frequently found as glycosides and sulfates, including resveratrol (trans-3,5,4'–trihydroxystilbene) (1), hydroxyresveratrol (2) resveratroloside (3), piceid (polydatin) (4), piceatannol or astringinin (5), piceatannol glucoside (6), trans-resveratrol derivatives (7-13) and cis-resveratrol derivatives (14-18) [9,26-28]. Anthraquinones, including emodin and its derivatives (19-21), anthraglycosides A (22) and B (23), physcion (24), chrysophanol (25), rhein (26), fallacinol (27), citreorosein (28), questin (29) and questinol (30), are important chemical constituents of the rhizome [18, 29-31]. Additionally, phenol glycosides: Quercetin and its glycosides (31-36), kaempferol-3-O-α-L-rhamnoside (37) and apigenin derivatives (38, 39) are found in its roots [32,33]. Furthermore, (−)-epicatechin-5-O-β-D-glucopyranoside (40) [34], (+)-catechin (41) and its glucoside (42) [35], cyanidin (43) [36], (−)-lyoniresinol-2a-sulfate (44) and (+)-isolaricireinol-2a-sulfate (45), 1-(3',5'-dihydroxyphenyl)-2-(4"-hydroxyphenyl)-ethane-1,2-diol (44), gallic acid and derivative (47, 48), tryptophan (49), 2,6-dihydroxybenzoic acid (50), tachioside (51), isotachioside (52) [35,37], 2-methoxy-6-acetyl-7-methyljuglone (53), protocatechuic acid (54), 2,5-dimethyl-7-hydroxy chromone (55), torachrysone-8-O-β-D-glucoside (56), 7-hydroxy-4-methoxy-5-methylcoumarine (57), 1-(3-O-β-D-glucopyranosyl-4,5-dihydroxyphenyl)-ethanone (58) [18], 5,7-dimethoxyphthalide (59) [38], and chlorogenic acid (60) [39] have been identified in *F. japonica* root. A total of 18 volatile compounds were identified in the extract of *F. japonica* leaves. The major volatile compounds found in the extract of *F. japonica* leaves are 2-hexenal (61), 3-hexen-1-ol (62), n-hexanal, 1-penten-3-ol and 2-penten-1-ol [40-47].

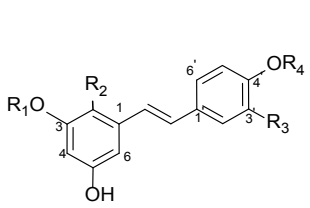
General biological and pharmacological activities of extracts

Pharmacological studies have evaluated several aspects of FJ extract including antioxidant [48], anti-inflammatory activities. FJ has ability to inhibit NF-κB and neutrophil infiltration animal models of edema [49]. Water extracts and essential oil of FJ inhibited growth of several strains of MO and prevented the induction of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) by lipopolysaccharide (LPS) [40].

F. japonica increases the burn's healing through their ability to enhancing the immune system in a dose-dependent manner [50]. Administration of *F. japonica*, the neutrophil levels, and neutrophilic adhesive rates remained normal in severely burned animals [51]. Moreover, *F. japonica* treatment maintained normal levels of TNF and adhesive leukocytes in burned rats [52]. Treatment of burn shock animals with *F. japonica* isolated substance leads to enhance the cardiac and microcirculatory functions (cardiac output, cardiac index, and stroke volume index) and decreases in the number of leukocytes [52-55].

Additionally, the EtOH extract of *F. japonica* possess antiviral activity against HBV [56], inhibiting several kinds of virus, which highly express the surface antigen of HBV (HBsAg) [57] and inhibit bacterial DNA primase [58].

Furthermore, *F. japonica* extracts protected the gastric mucosa from the harmful effect stress ulcers and decreased the gastric secretion [59]. *In vitro* and *in vivo*, the tannins of *F. japonica* decreased the activities of the digestive enzymes (trypsin, amylase, and lipase) [60,61]. *F. japonica* extracts inhibit acyl-co enzyme A–cholesterol acyltransferase activity [23]. *F. japonica* suppressed the activity of the CNS in mice [59]. Finally, the alcohol extract and compounds of *F. japonica* possess potent estrogenic activities [45,62].



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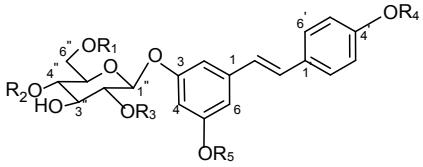

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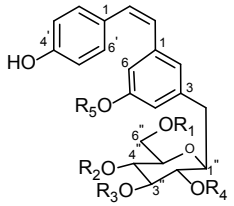

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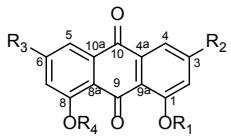

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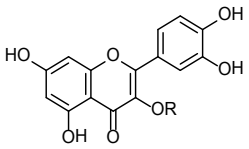

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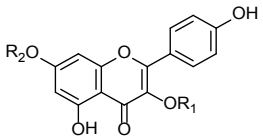

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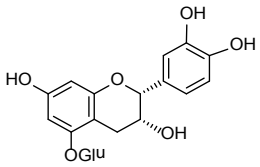

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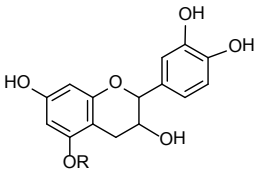

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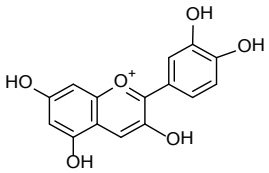

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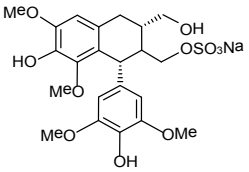

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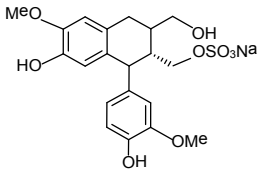

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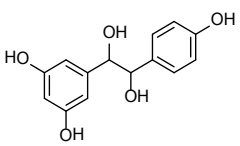

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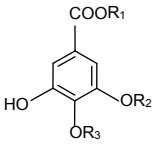

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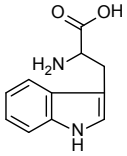

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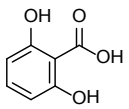

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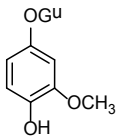

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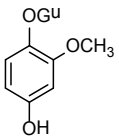

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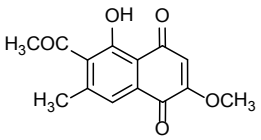

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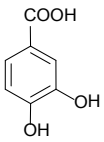

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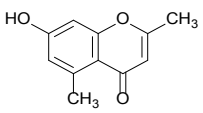

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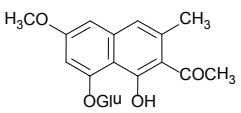

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Figure 2: Chemical structures of isolated and identified substances from *Fallopia japonica*.

S. No.	Compounds	Reference
1	Resveratrol (trans-3,5,4'–tetrahydroxystilbene): R_1=H, R_2=H, R_3=H R_4=H	[26,41]
2	Hydroxyresveratrol (trans-2,3,5,4'–tetrahydroxystilbene):R_1=H, R_2=OH, R_3=H, R_4=H	[28,42]
3	Resveratroloside: R_1=H, R_2=H, R_3=H, R_4=Glu	[26]
4	Piceid (polydatin): R_1=Glu, R_2=H, R_3=H, R_4=H	[26]
5	Piceatannol or Astringinin (trans-3,4,3',5'-tetrahydroxystilbene): R_1=H, R_2=H, R_3=OH, R_4=H	[28,42]
6	Piceatannol glucoside: R_1=H, R_2=H, R_3=OH, R_4=Glu	[9]
7	Sodium and potassium *trans*-resveratrol-3-*O*-β-D-glucopyranoside-6''-sulfate: R1=SO3M, R2=H, R3=H, R4=H, R5=H	[27]
8	Sodium and potassium *trans*-resveratrol-3-*O*-β-D-glucopyranoside-4''-sulfate: R_1=H, R_2=SO_3M, R_3=H, R_4=H, R_5=H	[27]
9	Sodium and potassium *trans*-resveratrol-3-*O*-β-D-glucopyranoside-2''-sulfate: R_1=H, R_2=H, R_3=SO_3M, R_4=H, R_5=H	[27]
10	Sodium and potassium *trans*-resveratrol-3-*O*-β-D-glucopyranoside-4'-sulfate: R_1=H, R_2=H, R_3=H, R_4=SO_3M, R_5=H	[27]
11	Sodium and potassium *trans*-resveratrol-3-*O*-β-D-glucopyranoside-5-sulfate: R_1=H, R_2=H, R_3=H, R_4=H, R_5=SO_3M, M=K^+ or Na^+	[27]
12	2''-O-Galloylpiceid: R_1=H, R_2=H, R_3=3,4,5-trihydroxybenzoyl, R_4=H, R_5=H	[43]
13	6''-O-Galloylpiceid: R_1=3,4,5-trihydroxybenzoyl, R_2=H, R_3=H, R_4=H, R_5=H	[43]
14	Sodium and potassium *cis*-resveratrol-3-*O*-β-D-glucopyranoside-6''-sulfate: R_1=SO_3M, R_2=H, R_3=H, R_4=H, R_5=H	[27]
15	Sodium and potassium *cis*-resveratrol-3-*O*-β-D-glucopyranoside-4''-sulfate: R_1=H, R_2=SO_3M, R_3=H, R_4=H, R_5=H	[27]
16	Sodium and potassium *cis*-resveratrol-3-*O*-β-D-glucopyranoside-3''-sulfate: R_1=H, R_2=H, R_3=SO_3M, R_4=H, R_5=H	[27]
17	Sodium and potassium *cis*-resveratrol-3-*O*-β-D-glucopyranoside-2''-sulfate: R_1=H, R_2=H, R_3=H, R_4=SO_3M, R_5=H	[27]
18	Sodium and potassium *cis*-resveratrol-3-*O*-β-D-glucopyranoside-5-sulfate: R_1=H, R_2=H, R_3=H, R_4=H, R_5=SO_3M, M=K^+ or Na^+	[27]
19	Emodin: R_1=H, R_2=CH_3, R_3=OH, R_4=H	[44]
20	Emodin-8-*O*-β-D-glucopyranoside: R_1=H, R_2=CH_3, R_3=OH, R_4=Glu	[44]
21	Emodin-8-*O*-β-D-(6'-*O*-malonyl)-glucoside: R_1=H, R_2=CH_3, R_3=OH, R_4=(6'-*O*-malonyl)-Glu	[33]
22	Anthraglycosides B: R_1=Glu, R_2=CH_3, R_3=OH, R_4=H	[45]
23	Anthraglycosides A: R_1=Glu, R_2=CH_3, R_3=OCH_3, R_4=H	[29]
24	Physcion: R_1=H, R_2=CH_3, R_3=OCH_3, R_4=H	[44]
25	Chrysophanol: R_1=H, R_2=CH_3, R_3=H, R_4=H	[46]
26	Rhein: R_1=H, R_2=COOH, R_3=H, R_4=H	[33]
27	Fallacinol: R_1=H, R_2=CH_2OH, R_3=OCH_3, R_4=H	[18]
28	Citreorosein: R_1=H, R_2=CH_2OH, R_3=OH, R_4=H	[18]
29	Questin: R_1=H, R_2=CH_3, R_3=OH, R_4=CH_3	[18]
30	Questinol: R_1=H, R_2=CH_2OH, R_3=OH, R_4=CH_3	[18]
31	Hyperin: R=3-*O*-β-D-Gal	[33]
32	Avicularin: R=3-*O*-α-L-Ara	[33]
33	Reynoutrin: R=3-*O*-Xyl	[33]
34	Isoquercitrin (quercetin-3-glucoside): R=3-*O*-β-D-Glu	[33]
35	Quercetin-3-glucuronide: R=3-*O*-β-D-Glc	[33]
36	Quercitrin (quercetin-3-rhamnoside): R=3-*O*-α-L-Rha	[33]
37	Kaempferol-3-*O*-α-L-rhamnoside: R_1=*O*-Rha, R_2=H	[33]
38	Apiin (apigenin-7-*O*-[-β-D-Apiofuranosyl-(1→2)-β-D-glucopyranoside]): R1=H, R2=Apio-(1→2)-Glu	[33]
39	Apigenin-7-*O*-β-D-glucoside: R_1=H, R_2=Glu	[33]
40	(−)-Epicatechin-5-*O*-β-D-glucopyranoside	[47]
41	(+)-Catechin: R=H	[35,47]
42	(+)-Catechin-5-*O*-β-D-glucopyranoside: R=Glu	[35]
43	Cyanidin (3,3',4',5,7-pentahydroxyflavylium)	[36]
44	Sodium (−)-lyoniresinol-2a-sulfate	[35]
45	Sodium (+)-isolaricireinol-2a-sulfate	[35]
46	1-(3',5'-Dihydroxyphenyl)-2-(4''-hydroxyphenyl)-ethane-1,2-diol	[35]
47	Sodium 3,4-dihydroxy-5-methoxybenzoic acid methyl ester-4-sulfate: R_1=Me, R_2=Me, R_3=SO_3Na	[35]
48	Gallic acid: R_1=H, R_2=H, R_3=H	[35]
49	Tryptophan	[35]
50	2,6-Dihydroxybenzoic acid	[35]
51	Tachioside	[37,47]
52	Isotachioside	[37,47]
53	2-Methoxy-6-acetyl-7-methyljuglone	[18]
54	Protocatechuic acid	[18]
55	2,5-Dimethyl-7-hydroxy chromone	[18]
56	Torachrysone-8-O-β-D-glucoside	[18]
57	7-Hydroxy-4-methoxy-5-methylcoumarine	[18]
58	1-(3-O-β-D-Glucopyranosyl-4,5-dihydroxyphenyl)-ethanone	[35]
59	5,7-Dimethoxyphthalide	[37,47]
60	Chlorogenic acid	[37,47]

61	The major volatile compound 2-hexenal (74.27%) and	[40]
62	3-hexen-1-ol (8.11%)	[40]

Table 1: Names of isolated and identified substances from *Fallopia japonica*.

Anticancer and Chemopreventive Properties

Several environmental carcinogens, inflammatory agents, and tumor promoters activated tumorigenesis process. These carcinogens are known to modulate the transcription factors (e.g., NF-κB, AP-1, p53), anti-apoptotic proteins (e.g., Bcl-2, Bcl-XL, Mcl-2), proapoptotic proteins (e.g., caspases, PARP), protein kinases (e.g., IκK, EGFR, HER2, JNK, MAPK), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), cell adhesion molecules, ABC-transporters proteins (e.g., MDR1, BCRP, MRP), metabolic enzymes (e.g., CYP1A1, CYP3A4, GST), COX-2, and growth factor signaling pathways [63]. The use of traditional medicine plants is widespread and provides a large source of natural anticancer compounds that might serve as leads for the development of novel drugs. Therefore, there is much interest from investigations of natural anticancer and bioactive compounds for preservation of traditional medicines. The use of naturally occurring products has been a major focus for a long period due to their potential chemotherapeutic activity. Extract of *F. japonica* is used in nutraceutical products because its resveratrol and emodin content. Both compounds have shown antitumor, antimetastatic, chemopreventive, chemical carcinogenesis-inhibitive, oncogene signal transduction-inhibitive and immunomodulating properties. Extensive pharmacological studies have shown that resveratrol and emodin contribute to the traditional efficacy of *F. japonica*. The molecular targets of chemopreventive activity of resveratrol and emodin are summarized in Figure 3.

Inhibition of cancer cell growth

The extracts of *F. japonica* inhibited proliferation and induced apoptosis of many cancer cells for example on 0.2 mg/mL concentration in human lung cancer (A549 and H1650) cell lines [64] but not cytotoxic effect on the normal human liver cells [65]. Additionally, methanolic extract of *F. japonica* was highly effective in multiple oral cancer cell lines due to its inhibitory effect on cell proliferation in KB, HEp-2, and YD-15 cells. Sp 1 protein is an important target of anticancer drugs development because its expression is very high in several cancer cell lines and solid tumor. *F. japonica* induced apoptosis, and reduced the expression level of Sp1 protein (transcriptional level) in HEp-2 and YD-15 cells and decreased Sp1 promoter activity [66-70]. Furthermore, ethyle acetate extract and its fractions exhibited anti-proliferative activities in KB cells differentially more than aqueous extract, dependent on the amount of emodin [71]. However, it has been reported that methanolic extract of *F. japonica* increases cell proliferation in breast cancer cell lines MCF-7 (at 30 and 100 μg/mL) because its estrogenic activity [45].

Resveratrol, a stilbene contained in *F. japonica* extract, has been reported as a biologically active compound. Resveratrol exhibited anti-proliferative effects through various molecular mechanisms on different cancer cells [72-78]. These anti-proliferative effects of resveratrol is mainly because its interaction with replication enzymes e.g. DNA polymerase and ribonucleotide reductase (by scavenge the essential tyrosyl radical) [79,80]. Resveratrol also possesses inhibitory effects on each stages of carcinogenesis process (initiation, promotion, and progression [81].

Since the clinical use of two anthraquinones, mitoxantrone and daunorubicin, for cancer treatment began 25 years ago, anthraquinones and anthraquinone derivatives, such as emodin from *F. japonica*, have been reported to possess anticancer activity [82,83]. These anthraquinones are usually potent inhibitors of topoisomerase II in DNA, and some also induce apoptosis in cancer cells [84]. Anthraquinones target DNA damage by mutation, their intercalation action usually leads to frame-shift mutations. This mutation leads to change in the amino acid sequence of a protein, influences promoters, and other regulatory sequences in gene code, resulting in cell death [85,86]. Emodin has been reported to inhibit proliferation in breast, lung, cervical, colorectal, and prostate cancers cells *in vitro* [87-91]. Emodin has been reported to exhibit anti-proliferative effects in lung, breast and pancreatic cancer and sensitize these cells to chemotherapeutic agents mainly by inhibiting HER-2/neu overexpression [92-96]. Relevant to its antiproliferative effects, emodin is also known to inhibit tyrosine phosphorylation of protein tyrosine kinases, p56lck and HER-2/neu [44]. Emodin also displays an over 25-fold differential cytotoxicity against ras transformed bronchial epithelial cells to the normal human bronchial epithelial cells [90]. By studying the SAR of emodin and comparing its activity to another anthraquiniones found that the C1 and C3 position of emodin structure is important for anti-tumor function (Figure 2) [97].

However, emodin evokes less or no cytotoxic effect in several normal cells, including: HBL-100 cells derived from normal human breast tissue, human fibroblast like lung WI-38 cells, and three primary cultured normal rat cells [98]. These data suggest that cancer cells more sensitive to emodin-induced cytotoxicity than normal cells. Emodin's specificity towards malignant cells might be due to its targeting on some oncogene signaling transductions, which are constitutively active or amplified in cancer cells. We demonstrated the potential of cytotoxic effect of FJ extract related to emodin, which showed significant cytotoxicity more than resveratrol or polydatin on five different cell lines including MDR and sensitive cells.

Inhibition of cytochrome P450 and other metabolic enzymes (anti-initiation or anti-xenobiotic effects)

The function of most cytochrome P450 superfamily (CYP) enzymes is to catalyze the oxidation of organic substances. The substrates of CYP enzymes include metabolic intermediates such as lipids and steroidal hormones, as well as xenobiotic substances such as drugs and other toxic chemicals like those found in smoking and gasoline. CYPs are the major metabolic enzymes involved in drug bioactivation or detoxification, representing for ~75% of the total metabolism. They are catalyzed by cytochromes P450 is a monooxygenase reaction. For example, monoxygenase (cytochromes P450 1A1, 1A2 and 1B1) can insert one oxygen atom into an organic substrate (RH) while the other oxygen is reduced [99]. Inhibiting the monooxygenation reaction is the molecular target of anticancer activity of natural plant SMs.

F. japonica antimutagenicity is believed to cause the inhibitory action of resveratrol, and emodin on CYP1A1. Resveratrol, by very different mechanisms of action displays numerous properties. However, its anti-initiation effects are related to its anti-xenobiotic abilities through Phase I cytochromes and Phase II detoxifying enzymes (Figure 4). The aryl hydrocarbon receptor (AhR) is modulated the carcinogen activation pathway by activation of CYP1A1 and CYP1A2 enzymes in microsomes. Different carcinogens are targeted by certain CYP: The classic hydrocarbon carcinogen; 7,12-dimethyl-benz(a)anthracene (DMBA) is activated by CYP1A1, CYP1A2, and CYP1B1 enzymes. For

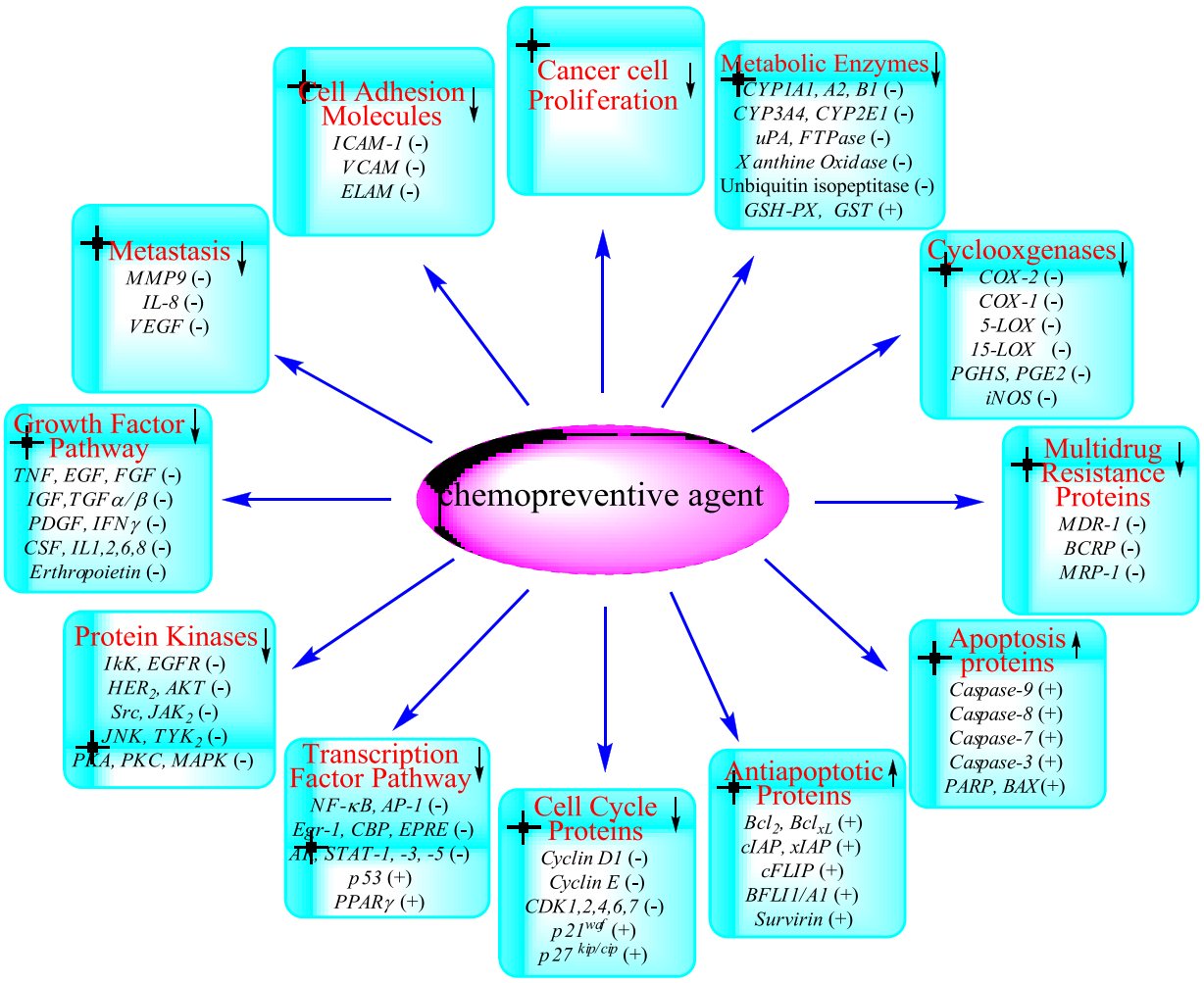

Figure 3: The major's chemopreventive targets of resveratrol and emodin.

example, tobacco smoke is a core problem in at least eight different kinds of cancer because it contains high amounts of aryl hydrocarbon and dioxin receptor (AhR) ligands such as anthracenes and benzo(a) pyrene (BaP) [100]. The mutagenesis caused by peroxidative strand breakage or covalent adduct formation of DNA is considered a major mechanism in tobacco-related carcinogenesis. Adduct formation is essentially caused by monooxygenases, which catalyzed oxidation of tobacco smoke compounds (inert molecules) e.g. BaP into diol-epoxy derivatives (highly mutagenic) (Figure 4). Consequently, free radicals responsible for oxidative DNA damage are released [101]. BaP itself is an agonistic ligand of the AhR, the principal inducer of CYP1A transcription.

Resveratrol is a competitive antagonist for AhR and blocks the conversion of the AhR forms (cytosolic ligand bound ◊ nuclear DNA-binding) resulting in inhibition of AhR-mediated transactivation of CYP genes. In addition, resveratrol inhibit the interaction between AhR and the transcriptional complex and subsequent free radical production, leading to cellular and DNA damage [102-104]. Resveratrol is also directly inhibited CYP1A1 and CYP1A2 human liver cells in dose dependent manner [105,106]. Moreover, resveratrol is inhibitor of CYP3A4 (irreversible) and of CYP2E1 (noncompetitive reversible) [106]. It has been demonstrated that the inhibitory effects of resveratrol on substrate-oxidation reaction that catalyzed by CYP3A4 and CYP3A5 is depend on the time and NADPH concentration [107,108].

Chen et al. reported that the resveratrol has therapeutically effect on hypercholesterolaemia. They demonstrated significant decreasing in the level of all parameters of lipid profile in mice that fed with a hypercholesterolaemic diet and resveratrol (200 mg/kg/day) for 8 weeks [109]. The underlying mechanism of the anti-dyslipidaemic effect of resveratrol is the ability of resveratrol to modulate the enzyme expression and activity of cholesterol 7a-hydroxylase (CYP7A1). CYP7A1 has an important role in conversion of cholesterol into 7-ahydroxycholesterol and subsequently eliminated from plasma and excreted as cholic acid in bile [109].

The anti-inflammatory role of resveratrol in humans via down-regulating proinflammatory conditions or by inhibiting LDL oxidation need more studies. Previously studies were designed in triple-blind, randomised, placebo-controlled trial in 75 patients consuming resveratrol-enriched grape extract, grape extract alone, or placebo for at least 6 months. Resveratrol-enriched grape extract induced a significant decrease in the low-density lipoprotein (LDL) cholesterol, apoB, oxidised LDL and oxidized LDL/apoB ratio compared

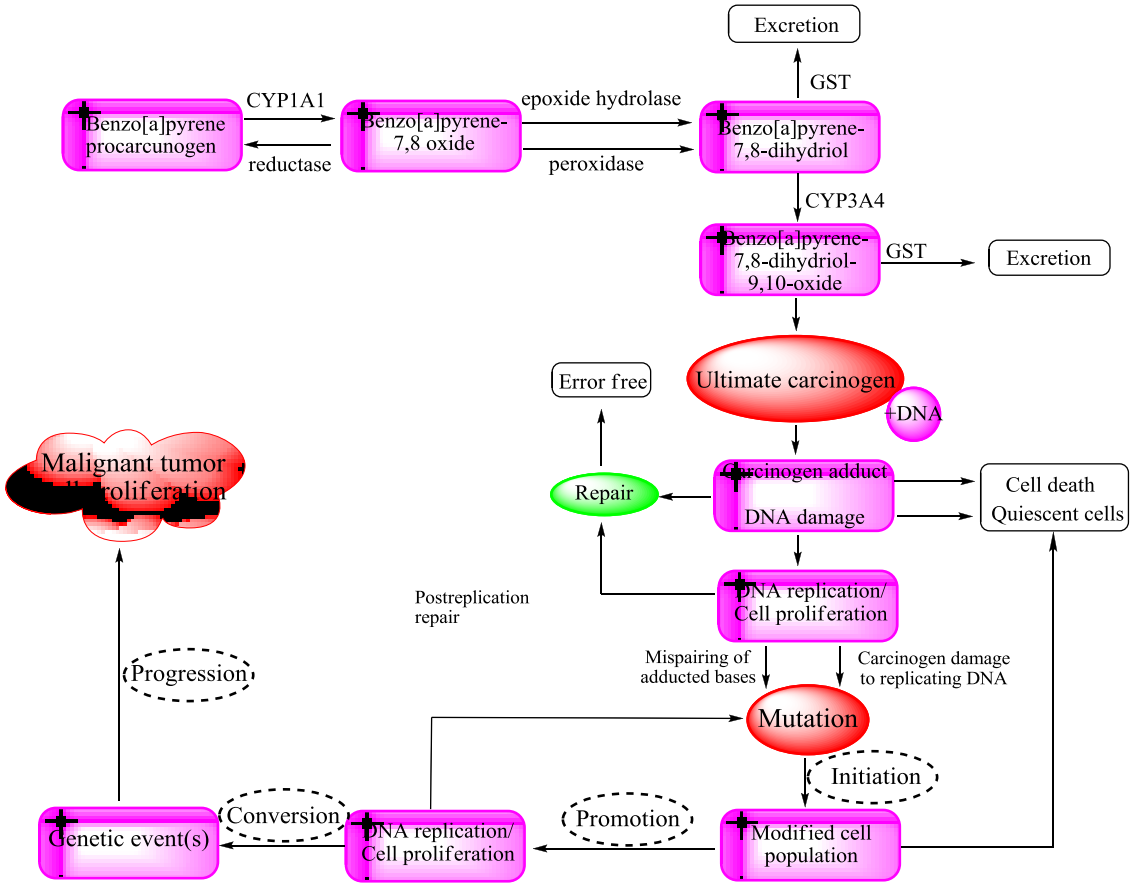

Figure 4: Metabolism of benzo[a]pyrene procarcinogenes (smoking) by action of metabolic enzymes; CYP1A1, CYP3A4 and GST. FJ active SMs, resveratrol and emodin have inhibitory effects on CYPs and enhance the GST activity; thus through stopping this initiation step of carcinogen metabolism there is a chemopreventive effect (Adapted from Wang and Samet [102]).

with placebo and grape extract groups [110,111] Considering the homogenous consumption of statins by all individuals enrolled in the three groups, these data revealed impressive results: Resveratrol reduces hypercholesterolaemia, and, more importantly, it reduces the overall burden of oxidation of lipids and thus can be safely administrating in the primary prevention of cardiovascular disease in association with statins [112].

Emodin can also suppress the mutagenicity of carcinogens that are metabolically activated by this enzyme, like heterocyclic amines (food carcinogens) i.g indole type (Trp-P-2), quinoline type (2-amino-3-methylimidazo[4,5-f] quinoline) and the pyridine type (2-amino-1-methyle-6-phenylimidazo[4,5-b]pyridine) [113]. This may means that the chemical structure of emodin is responsible for the destroying effects on CYP1A1 and CYP1A3 protein [114]. In addition, emodin produced oxidative stress, which resulted in extreme down-regulation of CYP protein expression as reported in previous studies. Anthraquinone inhibited incorporation of amino acids to protein in mouse neoplastic cells [115,116].

Moreover, emodin effect on rat liver microsomes exhibits phosphorylation CYP1A1 protein (inactive) and inhibition of monooxygenase activity (CYP1A1-dependent) [117,118]. Therefore, the direct interaction of hydroxyanthraquinone and CYPs leads to inhibition of monooxygenase activity (Figure 4). However, Wang et al. reported that emodin has the ability to induce CYP1A1 and CYP1B1 in human lung cancer cells at both gene (mRNA) and protein levels [119]. Binding of the emodin to an aryl hydrocarbon (Ah) receptor, a transcriptional factor of CYP1A1 and CYP1B1 genes are the possible mechanism involved [120]. Emodin also increases monooxygenase activities by benzo[a]pyrene and 7-ethoxyresorufin, which are substrates of CYP1A1 and CYP1B1 [121,122]. We demonstrated that *F. japonica*, and its active SMs; resveratrol, emodin, and polydatin significantly inhibit CYP3A4 in dose dependent manner and suppress gene expression (data unpublished), suggesting the predominately *F. japonica* extract inhibition of CYP3A4 related to resveratrol effect as CYP3A4 inhibitor.

Glutathione-S-transferase (GST) is a phase II metabolic enzyme. It is involved in carcinogenesis and resistance of cancer cells to oxidative stress and chemotherapeutic drugs. *In vitro* and *in vivo*, resveratrol has been shown to induce phase II of metabolism; detoxification enzymes mainly UDP-glucuronosyltransferase (UGT), glutathione-S-transferase (GST), and quinone reductase activities through modulation of the mitogen-activated protein kinase (MAPK) pathway [123,124]. It is capable of metabolically detoxifying drug/carcinogens, thus Phase II metabolic enzymes exert antimutagenic action [125]. On the other hand, emodin decreases TNF-α and TPA-induced GSTP1-1 gene expression through inhibiting NF-κB and AP-1 binding onto GSTP1-1 promoter in K562 and U937 leukemia cells [126]. This could

contribute to a reduction of incidences of glutathione-related drug resistance in human cancers.

Inhibition of COX-2 (anti-promotion effects)

Cyclooxygenase (COX) is an enzyme that is responsible for the formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin, and thromboxane. Lipooxygenase (LOX) enzyme is responsible for formation of leukotrines. The inflammation process is mainly related to the activities of COX-2 and lipooxygenase (LOX) enzymes. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs (e.g aspirin and ibuprofen), target inhibition of COX. The ability of resveratrol to inhibit the NF-κB pathway (IκB kinase inhibition) is linked to its chemopreventive activity [127]. The transcription nuclear factor kappa B (NF-κB) and activated protein-1 (AP-1) regulate the action of these enzymes. These compounds enhance tumor growth by acting on cell proliferation, angiogenesis, and immunosuppression (Figure 5). Cyclooxygenases inhibitors are considered valuable therapeutic agents against cancer [128]. Resveratrol has a chemopreventive effect on various cancer models unrelated to AhR activation and xenobiotic metabolism. Resveratrol inhibits the constitutive cyclooxygenase-1 (COX-1) but not the inducible COX-2 and inhibits COX-2 activity as well as COX-2 gene expression, which is important in promoting tumorigenesis [129-131]. Down regulation of the COX-2 gene is resulting in the inhibition of protein kinase C (PKC) [129].

Recent, emodin studies show potent dose dependent inhibition of COX-2 and NO• through its direct inhibition of iNOS enzyme activity, and suppression of iNOS protein without affecting macrophage viability and causing 65–68% reduction of oedema volume at 40 mg/kg [132,133]. In addition, emodin is a potent inhibitor of LPS-induced NO production and iNOS gene expression. The mechanisms of inhibition of iNOS by emodin is inhibited NF-κB activation [134]. Moreover, expression of iNOS and the COX-2 protein was inhibited by emodin in LPS-activated RAW 264.7 cells, and PGE2 production was reduced [135]. These results indicate that emodin can prevent the initiation stage of cancer through its ability to inhibition of COX-2 and inflammatory mediators (Figure 5).

Inhibition of multidrug resistance proteins

Multidrug resistance is the phenomenon of tumor resistance to chemically and functionally unrelated anticancer drugs, and is the one of the most formidable challenges in the field of cancer chemotherapy. The first mediator of MDR to be characterized at the molecular level was P-glycoprotein (P-gp/MDR1 or ABCB1), and there were many ATP-binding cassette (ABC) proteins including MRP1, and BCRP involved in MDR [136,137]. ABC-transporters mediate resistance to different classes of chemotherapeutic drugs including: vinblastine, vincristine, daunorubicin, doxorubicn, colchicine, paclitaxel, and etoposide, by actively extruding the drugs from the cells to lower the intracellular concentrations. Actually, there are few studies dealing with modulation of MDR with *F. japonica* and its active metabolites. Recent studies reported that, resveratrol has inhibitory effects on P-gp efflux function and increased the accumulation of P-gp substrates (rhodamine 123 and daunorubicin) in a concentration-dependent in KB-C2 cells [138]. In addition, resveratrol down-regulated Bcl-2 and MDR1 genes and hence synergistically enhance the cytotoxic

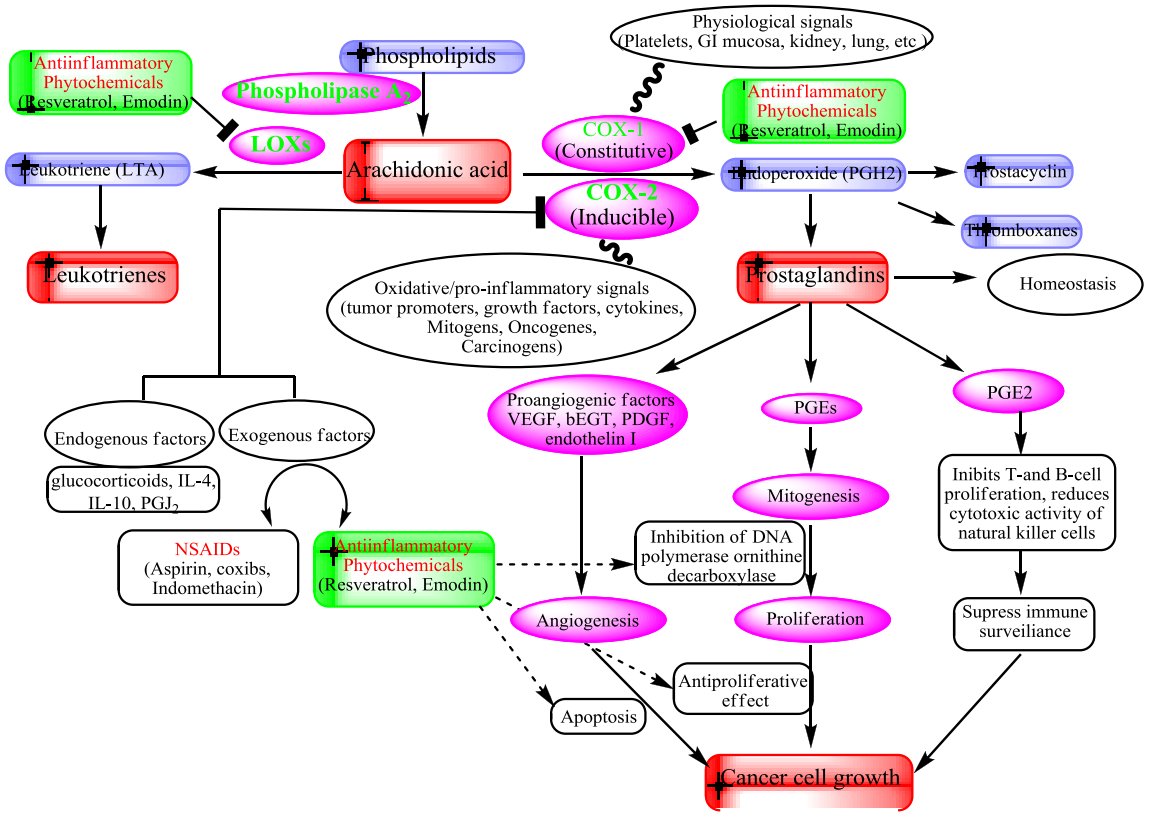

Figure 5: *Fallopia japonica* active SMs, resveratrol and emodin effects on steps of eicosanoids biosynthesis.

effect of combined chemotherapeutic agents leading to overcome the multidrug-resistant of KBv200 cells. Resveratrol can reverse multidrug resistance in KBv200 cells. The potential mechanism may be by inhibiting the multidrug-resistant gene expressions and/or promoting cell apoptosis [139].

Resveratrol also induced apoptotic death in doxorubicin-resistant AML cells, and it was shown to inhibit the efflux function and expression of an MRP1 gene [140]. Moreover, resveratrol can enhance the sensitivity of CNE2 cells to chemotherapeutic drugs under hypoxia. The potential mechanism is partly attributed to inhibiting the gene expressions of HIF-1 alpha, MDR1 and MRP1 [141].

On the other hand, co-treatment with emodin could remarkably enhance chemosensitivity of SGC996 cells when compared to cisplatin, carboplatin or oxaliplatin treatment alone. The mechanisms may be attributed to reduction of glutathione levels, and downregulation of multidrug resistance-related protein 1 (MRP1) expression in SGC996 cells. Furthermore, *in vivo* experiments on mice show that emodin/cisplatin co-treatment decreased the tumor size by increasing apoptosis and down regulating MRP1 expression [142]. In addition, emodin/cisplatin co-treatment increases ROS level and enhanced sensitivity of resistance cells, as compared to cisplatin-only treatment with little effect on normal cells. Emodin/cisplatin co-treatment inhibited the tumor growth *in vivo* by down regulated MDR1 expression and increased drug accumulation [143].

We evaluated the effect of *F. japonica* and its active principle resveratrol, emodin, and polydatin on MDR colon and leukemia cell lines and we found that the tested substance and extract show significant inhibition of efflux function and down regulation of MDR1, MRP1, and BCRP genes. Moreover, the effect of co-treatment of the MDR cell lines with FJ extract, or its active compounds with doxorubicin, remarkably enhance the chemosenstivity of resistance cells, especially leukemia cell lines.

Induction of apoptosis (anti-progression effects)

Apoptosis is a programed cell death, which is a fundamental process in the developmental and homeostatic maintenance of complex biological systems. A disregulation or failure of normal apoptotic processes will contribute to transformation of cells and provide a growth advantage to cancer cells. Apoptosis is characterized by cell shrinkage, chromatin condensation, DNA fragmentation, and the activation of specific cysteine proteases known as caspases. There are two pathways mediated by caspase-3; extrinsic pathway (receptor- and caspase-8–mediated) and the intrinsic pathway (mitochondrial release of cytochrome c and activation of caspase-9) [144]. Apoptosis and necrosis are distinguished by the initiation of cell death from the outside and inside the cell (mitochondria), respectively [145].

Many studies has concerned the apoptotic effect of *F. japonica* and its active SMs. Lin et al. reported that A549 cells treated with *F. japonica* extracts showed chromatin condensation, nuclear fragmentation, and vacuolization of cytoplasm. In addition, FJ methanolic extract induced apoptosis by PARP cleavage and the activation of caspase 3 (64). *Ex vivo* and *in vivo* studies have confirmed the apoptotic effect of resveratrol [146]. In numerous cell types, resveratrol has been observed inducing apoptosis through different pathways (Figure 6) [147-149].

Anti-leukemic activity in mice and human cell lines of resveratrol by inducing apoptosis [150] however, resveratrol has not any apoptotic effects on normal cell even at higher concentrations [151,152]. Resveratrol has been shown to induce apoptosis by activating death receptors (Fas and TNF) pathways [147,148,153]. This extrinsic pathway activates intracellular caspases (effectors mediators), thus the apoptotic effects of resveratrol cytotoxicity block by caspase inhibitors.

On the other hand, apoptosis could be a potential general mechanism, providing a mechanistic basis for the antiproliferative and anti-neoplastic effects of emodin (Figure 6). A number of studies have demonstrated that emodin is capable of inducing apoptotic cell death in various cancer cells through both mechanisms [94,154-157]. Emodin is activated the caspase-3 cascade independent or dependent on ROS [158]. Emodin (quinone structure) is highly redox active molecules can form semiquinone radicals and reactive oxygen species (superoxide anion radical, hydrogen peroxide, and hydroxyl radical). The generation of ROS may contribute to mitochondrial damage, reduction of mitochondrial transmembrane potential, release of cytochrome c and Smac, and subsequent caspase activation and apoptosis [159].

Suppression of anti-apoptotic proteins

The therapeutic value of chemotherapeutic agents is largely dependent on their ability to trigger the anti-apoptotic molecules. The Bcl-2 protein family contains anti-apoptotic (Bcl-2, Bcl-XL, and Mcl-1) and proapoptotic (Bax, Bak) proteins and they are well-characterized regulators of apoptosis. *F. japonica* active SM; resveratrol and emodin, trigger Bcl-2 and Bax modulation, mitochondrial dysfunction, mitochondrial cytochome c release, caspase activation and consequently leads to apoptosis (Figure 6) [149,155,156,160-163].

Direct caspase inhibitors are participants in different survival signaling pathways, the inhibitors of apoptosis protein (IAP) family such as XIAP (X-linked inhibitor of apoptosis) and surviving are important to the control of drug resistance and cell proliferation in different cancer types [164-166]. *F. japonica* methanolic extract, resveratrol, and emodin decreased expression of XIAP and survivin mRNA, protein, and its transactivation, suggesting that *F. japonica* inhibits survivin expression through the down-regulation of Sp1 to induce apoptosis in several cancer cells [71,167]. Surprisingly, survivin expression induced by gemcitabine could be inhibited when combined with emodin treatment [93]. Its downstream target, surviving, mediates apoptoitc cell death, indicating that the inhibitory effects of *F. japonica* and its franctions on oral cancer cell proliferation are due to emodin in *F. japonica* [71].

Cell Cycle Arrest

The cell cycle, or cell-division cycle, is a series of events that takes place in a cell leading to its division and duplication (replication). In eukaryotes, the cell cycle can be divided into two brief periods: interphase (during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA) and the mitosis (M) phase (during which the cell splits itself into two distinct cells, often called "daughter cells"). The cell cycle consists of four distinct phases: G1 phase, S phase (synthesis), G2 phase (collectively known as interphase) and M phase (mitosis). Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G0 phase. A dysregulation of the cell cycle components may lead to tumor formation. Cells contain various pathways designed to protect them from the genomic instability, or toxicity that can result when their DNA is damaged. Checkpoint proteins that control the normal passage of cells through the cell cycle play a pivotal role in this response. There are several cell cycle

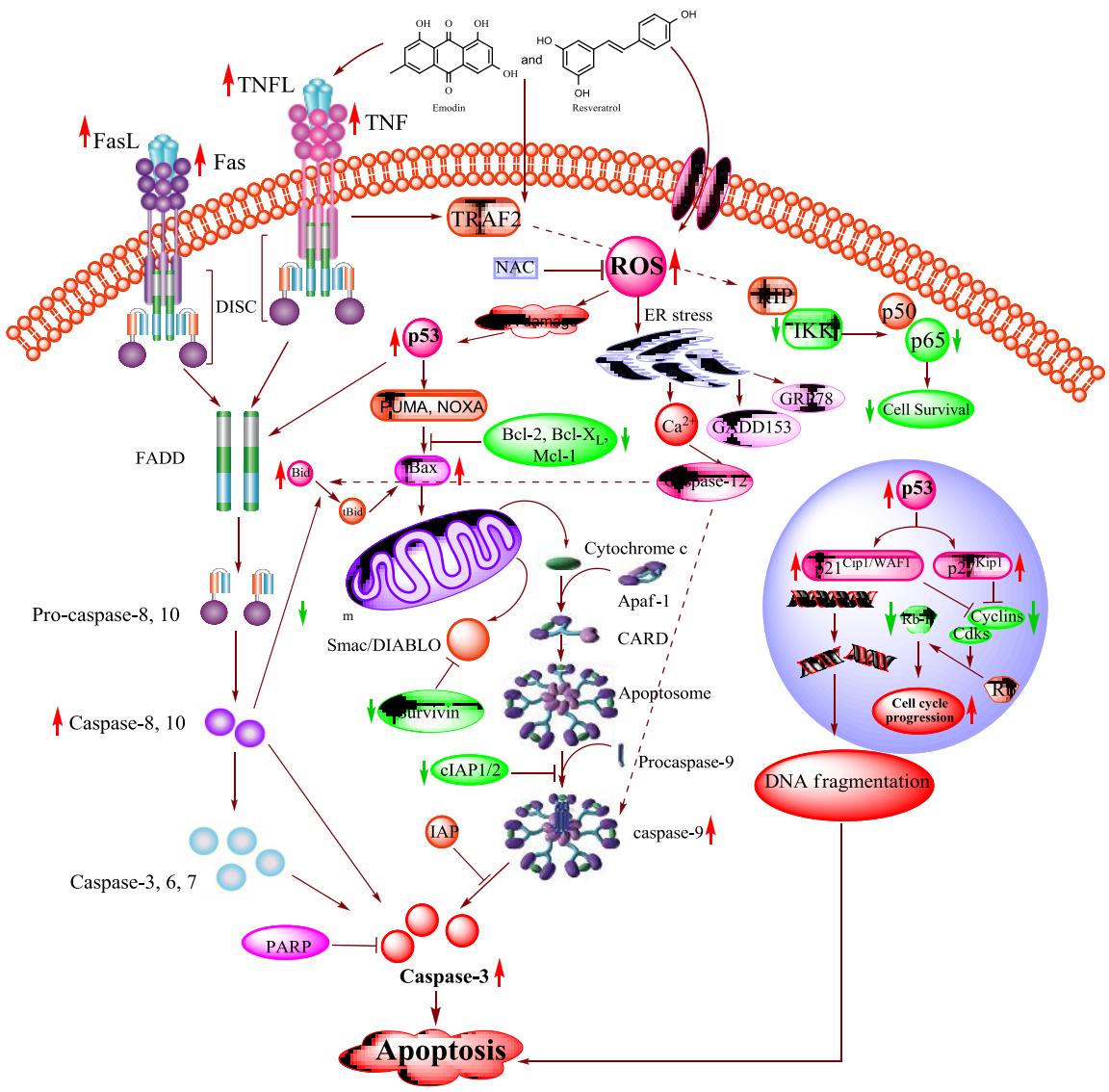

Figure 6: FJ active SMs; resveratrol and emodin induced apoptosis in cancer cells either via a receptor-mediated pathway regulated apoptosis genes expression. FJ active SMs; resveratrol and emodin regulated cell-cycle genes (cyclins, Cdks, and p53). Extrinsic pathway (independently of p53), the ligands (TNFL and FasL) activate the pro-apoptotic receptors (TNF and Fas) leads to the recruitment of the adaptor Fas-associated death domain (FADD) and initiator procaspases 8 and 10 to rapidly form the death-inducing signaling complex (DISC). Procaspase 8 and 10 are self-cleaved, and activated caspase 8 and 10 activate the effector caspases 3, 6, and 7, thus triggering apoptosis. The down regulation of antiapoptotic proteins (Bcl-x_L and Mcl-1) plus significant upregualtion of proapoptotic (Bax, Apaf-1, Bid and tBid. tBid) are other effective target.

checkpoints, which are used by the cell to monitor and regulate the progress of the cell cycle [168]. The two main checkpoints are the G1/S checkpoint (rate-limiting step and restriction point) and the G2/M checkpoint [169]. Tumor cells frequently loose checkpoint controls and this facilitates the development of the tumor [170]. Thus, one of the important approaches for cancer chemotherapy is to regulate cell-cycle progression [169].

Resveratrol produces a differentiation of human promyelocytic cells (HL-60 line) and decreases tumor growth in rat models [146,171]. The effect of resveratrol on cell cycle arrest (G2/M transition and G0/G1 phase) gradually decreases the anti-apoptotic oncoprotein Bcl-2 expression and subsequently undergoes apoptosis [172,173]. In addition, resveratrol induces antiproliferation and arrests the S phase at low concentrations (30-60 μM), but high concentrations do not induce S phase accumulation in human histiocytic lymphoma U937 cells. Removal of resveratrol from the culture medium stimulates U937 cells to reenter the cell cycle synchronously, as judged by the expression patterns of cyclin E, A and by fluorescent activated cell sorting analysis [174]. This data demonstrates that resveratrol causes S phase arrest and reversible cell cycle arrest. Thus, resveratrol provides an important new cell cycle blocker as well as a cancer chemopreventive agent. Hsieh et al. found that resveratrol suppress of cell growth through cell cycle arrest at S- and G2-phases [72,175].

On the other hand, the effect of the main FJ anthraquinone, emodin, on the G2/M cell cycle has been demonstrated on various cancer cells, including v-ras-transformed and hepatoma cells [90,98]. Elevations of p53 and p21 expression were suggested as a common mechanism involved in this induced G2/M cell-cycle arrest [98]. Similarly, G1/S

cell-cycle arrest was found in human breast, colon carcinoma cells upon treatment with emodin [88,176].

G2/M phase arrest was observed with increased protein levels in the cell cycle regulatory genes; cyclin A, cyclin B, Chk2, Cdk2, and P27 and decreased protein levels in Cdc25c and P21 in hepatoma cells; Huh7, Hep3B, and HepG2 after time courses of emodin treatment [177]. Furthermore, treatment of cancer cells with various concentrations of emodin led to cell cycle arrest at G0/G1 and G2/M increased the Bax, p21, and Chk2 expression but inhibited Bcl-2, cyclin B1 and Cdc2 [163].

Apoptosis in HL-60 cells was efficiently induced by emodin in a dose dependent manner and cells were arrested at G0/G1. The expressions of Akt, p-Akt, IκB-α, p- IκB-α, p65, p-p65, mTOR and p-mTOR in Akt signal pathway was downregulated after emodin treatment [178]. However, G0/G1 phase cell population increased and G2/M phase cells decreased in HL-60/ADR cells after treatment with emodin [179].

Transcription factor pathway

The transcription factor is a protein that binds to specific DNA sequences, thereby controlling the transcription of genetic information from DNA to mRNA [180]. Transcription factors perform this function alone, or with other proteins in a complex, by promoting (as an activator), or blocking (as a repressor) the recruitment of RNA polymerase to specific genes [181]. Many transcription factors, especially some that are oncogenes or tumor suppressors, help regulate the cell cycle. Due to their important roles in development, intercellular signaling, and cell cycle, some human diseases have been associated with mutations in transcription factors [182]. Many transcription factors are either tumor suppressors or oncogenes, and, thus, mutations or aberrant regulations of them is associated with cancer.

NF-κB transcription factors

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA. Conversely, the modulation of NF-κB has been impact role in cancer development. Active form of NF-κB increase the expression of genes that responsible on cell proliferation, cell survival and prevent apoptosis. Apoptosis is increased by deficiency in NF-κB expression due to its regulates the anti-apoptotic genes and caspases [183].

In cancer cells there is NF-κB in active form because mutations in genes encoding the NF-κB transcription factors themselves or in IκB genes that control NF-κB activity. Inhibition of NF-κB in tumor cells leads to prevent the proliferation and stop the cell resistance to the anti-tumor agents. Thus, NF-κB has much interest in drug discovery research as a target for anti-cancer agents [184]. Block of NF-κB is considered as an important target for many natural products that have been discovered to use as anti-oxidants, anti-cancer, and anti-inflammatory agents [185]. Thus, NF-κB is considered as one of the main molecular targets of chemopreventive phytochemicals (Figure 7), as a transcription factor involved in multiple cellular processes, including cytokine gene expression, cellular adhesion, apoptosis, and metastasis [186]. Free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, g-radiation, ultraviolet (UV) light, and X-rays, activate NF-κB. In nucleus, active NF-κB induces >200 genes that have a role in suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance, and inflammation.

Resveratrol and emodin mediate the anti-inflammatory, cell growth modulatory and anticarcinogenic effects may be by block any one or more steps in the NF-κB signaling pathway, such as the signals that activate the NF-κB signaling cascade, translocation of NF-κB into the nucleus, DNA binding of the dimers, or interactions with the basal transcriptional machinery [187,188]. Resveratrol suppressed TNF-induced phosphorylation of the p65 subunit, induced oncogenic H-Ras that blockaded of IκB kinase activity, and blocked the expression of mRNA-encoding monocyte chemoattractant protein-1 of NF-κB and NF-κB-dependent reporter gene transcription [127,188-190]. Therefore, the NF-κB suppression that targeted by resveratrol is essential for induction the cell cycle arrest and apoptosis in cancer cells.

Emodin has similar immunosuppressive and anti-inflammatory effects. Many researchers are interested in how emodin may regulate NF-κB signaling pathways. Kumar et al. reported that emodin inhibits NF-κB activation induced by TNF. This inhibition is not due to its chemical modification of NF-κB subunits, but its suppressive effect of degradation of IκB, an inhibitory subunit of NF-κB molecules [159]. In addition, down-regulation of IκK-γ, which is essential in phosphorylating IκB-α by emodin treatment lead to subsequently inhibit NF-κB [191]. Protein tyrosine kinases (PTK), reactive oxygen species, proteases IκKs, RIP, NIK, TRAF-2 play a critical role in regulating NF-κB activation [192]. Moreover, there is a positive association between cellular ROS and cytotoxic efficacy of anti-cancer drugs, and NF-κB is involved in this relationship [193-195].

On the other hand, manipulation of cellular redox state and NF-κB activation may initiate a novel approach to improving chemotherapeutic efficacy [196,197]. TNF-induced NF-κB activation, IκB degradation, ROS generation, mitochondrial- and caspase-dependent apoptosis pathways are mediated by treatment of human cancer cells by emodin [20,155,156,159]. Emodin inhibiting AP-1 and NF-κB signaling pathways lead to suppressing MMP-9 expression and inhibits the invasiveness of cancer [198].

Tumor Suppressor Gene p53

Tumor suppressor gene p53 is an important molecule in the process of apoptosis and cell cycle arrest. Many tumor cells evade apoptosis and cell-cycle arrest via mutation of p53. In response to stress stimuli, such as DNA damage, p53 is stabilized, which leads to its nuclear translocation and transactivation of many target genes (e.g., p21, Bax, CD95). In certain cells, activation of p53 leads to activation of p21 (tumor suppressor gene) which inhibits the cyclin-cdk complex, cell cycle arrest (G1 phase) and apoptosis (Figure 7).

There are many studies reported the role of p53 in resveratrol-induced apoptosis [199-201]. Resveratrol increased expression of p53 and suppression of cell progression through the S- and G2-phases of the cell cycle [175].

In addition, resveratrol modulate the cell cycle regulating genes (e.g. cyclins, Cdks, p53, and hyperphosphorylated Rb) leads to a reversible cell arrest (S phase) of the vascular smooth muscle cell (VSMC) [202]. Narayanan et al. reported that resveratrol down-regulated PSA, androgen receptor (AR) co-activator ARA 24, and NF-κB p65 in androgen sensitive prostate cancer cells (LNCaP). The down-regulation of these genes related with activation of p53-responsive genes (e.g. PIG 7, p21 Cip1/WAF1, p300/CBP, and Apaf-1) [75,200].

On the other hand, the modulation of p53 and p21 pathway is the underlining mechanism of anti-proliferative effects of emodin [203]. In addition, emodin induced accumulation of p53 in HepG2/C3A cells with a resultant increase in p21 expression and cell cycle arrest [98]. This action might be through emodin's inhibitory effect on the

COP9 signalosome (CSN) associated kinases CK2 and PKD [204,205]. CSN is a multimeric protein kinases complex associated with CK2 and PKD, which can be phosphorylate p53, and subsequently degrade by the Ub/26S proteasome system [206]. Moreover, there is a positive association between cellular ROS and cytotoxic efficacy of anti-cancer drugs [194,195].

Reactive oxygen species that initiated the ATM-p53-Bax signaling pathway considered as mode of emodin action to induce apoptosis in human lung adenocarcinoma A549 cells [94]. Furthermore, Emodin increased the protein levels of p53 as response to reactive oxygen species (ROS) production in a dose-dependent manner [207]. In addition, the change in the expression of p53 pathway is associated with IGF-2 pathway leads to apoptosis in BCap-37 cells that treated [208]. Emodin induced apoptosis in the C6, HepG2/C3A, prostate LNCaP, and vascular smooth muscle cells by decreased the expression of AR and PSA, increased of Bax/Bcl-2 ratio, and increased the expression of p53, p21, Fas, caspase-3 and -9 [98,209,210].

Suppression Protein Kinases

A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). Phosphorylation usually results in a functional change of the target protein (substrate) by changing enzyme activity, cellular location, or association with other proteins. The human genome contains about 500 protein kinase genes and they constitute about 2% of all human genes. Up to 30% of all human proteins may be modified by kinase activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction [211].

The human protein kinase family is divided into the following groups: AGC kinases (e.g., PKA, PKC and PKG protein kinases); the calcium/calmodulin-dependent protein kinases (CAMK); CK1- the casein kinase 1 group (CMGC) (e.g., CDK, MAPK, GSK3 and CLK kinases); the homologs of yeast Sterile 7, Sterile 11, and Sterile 20 kinases (STE); the tyrosine kinases (TK); and the tyrosine-kinase like group of kinases (TKL) [211]. The MAPK pathway has received increasing attention as a target molecule for cancer. In addition, Rb and the E2F transcription factors regulate cell cycle (G1/S-phase). Tumor suppressor protein p16 is a member of the cyclin-dependent kinase 4 (CDK4 or INK4) inhibitor protein families (Figure 7). It functionally competes with cyclin-D for association with cyclin-dependent kinase 4/6 (CDK4/6) and keeping CDK4/6 inactive. The cyclin-D/CDK4 complex is known to phosphorylate the retinoblastoma (Rb) protein at mid-G1 phase, which is thought to be a critical step in the progression through G1 into S-phase of the cell cycle [212]. The Rb-E2F/DP pathway is an important contributor to resveratrol-mediated cell cycle arrest and apoptosis [213]. It has been reported that resveratrol inhibits phosphorylation of Rb, down-regulation of expression of E2F transcription factors, and induces of the Cdk inhibitor (p21Cip1/WAF1) resulted in cell cycle arrest (S-phase and G1/S-phase) in cancer cells [190,213]. Furthermore, in hormone-insensitive DU145 prostate cancer cells, resveratrol modulated mitogen-activated protein kinase [MAPK, extracellular signal-regulated kinase 1/2 (ERK1/2)], and stimulated c-fos and c-jun expression [214].

Emodin was found to act similarly to antiestrogens, capable of inhibiting estrogen-stimulated growth and DNA synthesis, and the phosphorylation of Rb protein [96]. In addition, there is high synergy of As/IFN-α with emodin treatment with regard to the inhibition of proliferation and induction of cell death of HTLV-I–transformed T cells. There is a potent antiproliferative effect on tumor cells, which was linked to the accumulation of hypophosphorylated Rb and G0/G1 arrest. Emodin reduces the level of phosphorylated Rb and induces G1 cell-cycle arrest in HTLV-I–transformed cells [157].

Protein kinase CKII has essential role in cell proliferation, transformation, and differentiation process [215,216]. Unlike most of the Ser/Thr protein kinases, whose substrates contain consensus sequences generally determined by basic and prolyl residues, substrates of CKII share unique phosphoacceptor sites specified by clusters of acidic residues [215,216]. Yim et al., reported that emodin is specific inhibitor of CKII. They unexpectedly found that emodin acts as a competitive inhibitor of CKII with respect to ATP, with an IC50 value of 2 mM [217].

Structurally, emodin fit to penetrate and coupling with the active site of CKIIa, block the ATP binding as well as it close the hydrophobic pocket between the N-terminal and the C-terminal lobes. This leads to its inhibition of the binding of the natural co-substrates of CKII, in a competitive manner [218]. The importance of hydroxyl group 3 in anchoring emodin with CKII through polar interactions is further proven by the observation that the two analogues of emodin, 1,8-dihydroxy-anthraquinone and chrysophanic acid, both lacking this group, did not show obvious inhibitory effect on CKII activity [219].

In addition to protein kinase CKII, emodin also shows an inhibitory effect on some other kinases. Among them, emodin acts as a modest inhibitor of PKC [217,220]. The mitogen-activated protein kinase (MAPK) signaling pathways play a central role in regulating cell proliferation, apoptosis, and migration [221]. The MAPK members consist of three major classes; the c-jun N-terminal kinases (JNKs), the extracellular signal-regulated proteins kinase (ERKs) and p38 (Figure 7) [198,222].

Growth factors pathway

Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Some of the growth factors implicated in carcinogenesis are: epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors (TGF)-α and -β, erythropoietin (Epo), insulin-like growth factor (IGF), interleukin (IL)-1, 2, 6, 8, tumor necrosis factor (TNF), interferon-γ (INF-γ) and colony-stimulating factors (CSFs) (Figure 7) [223]. Resveratrol modulates growth factors (e.g. EGF, TGF-α, TGF-β, and FJ) lead to decrease in cell migration, adhesion, and stop the cell proliferation in much cancer cell line [224-228]. Furthermore, resveratrol exhibited activation of mitogen-activated protein kinase [MAPK, extracellular signal-regulated kinase 1/2 (ERK1/2)], nuclear translocation of Ser15-phosphorylated p53, and p53-dependent apoptosis and stimulated c-fos and c-jun expression in hormone-insensitive DU145 prostate cancer cells.

On the other hand, emodin decreased the level of LIGHT-induced generation of ROS, as well as the expression of CCR1, CCR2, and ICAM-1 and the production of IL-8, MCP-1, TNF-alpha, IL-6, IκB-alpha, and the phosphorylation of the p38 MAPK [229]. In addition, emodin induces gene expression profiling changes in p53, JAK2/STAT3, and IGF-2 pathways lead to mitochondrial induction of apoptosis in myeloma and BCap-37 cells [208,230].

In vitro, emodin stimulated VEGF-α, inhibited basic fibroblast growth factor-induced proliferation and migration dose-dependently in human umbilical vein endothelial cells (HUVECs). It suppress cyclin D1 and E expression (G0/G1 arrest) and retinoblastoma protein

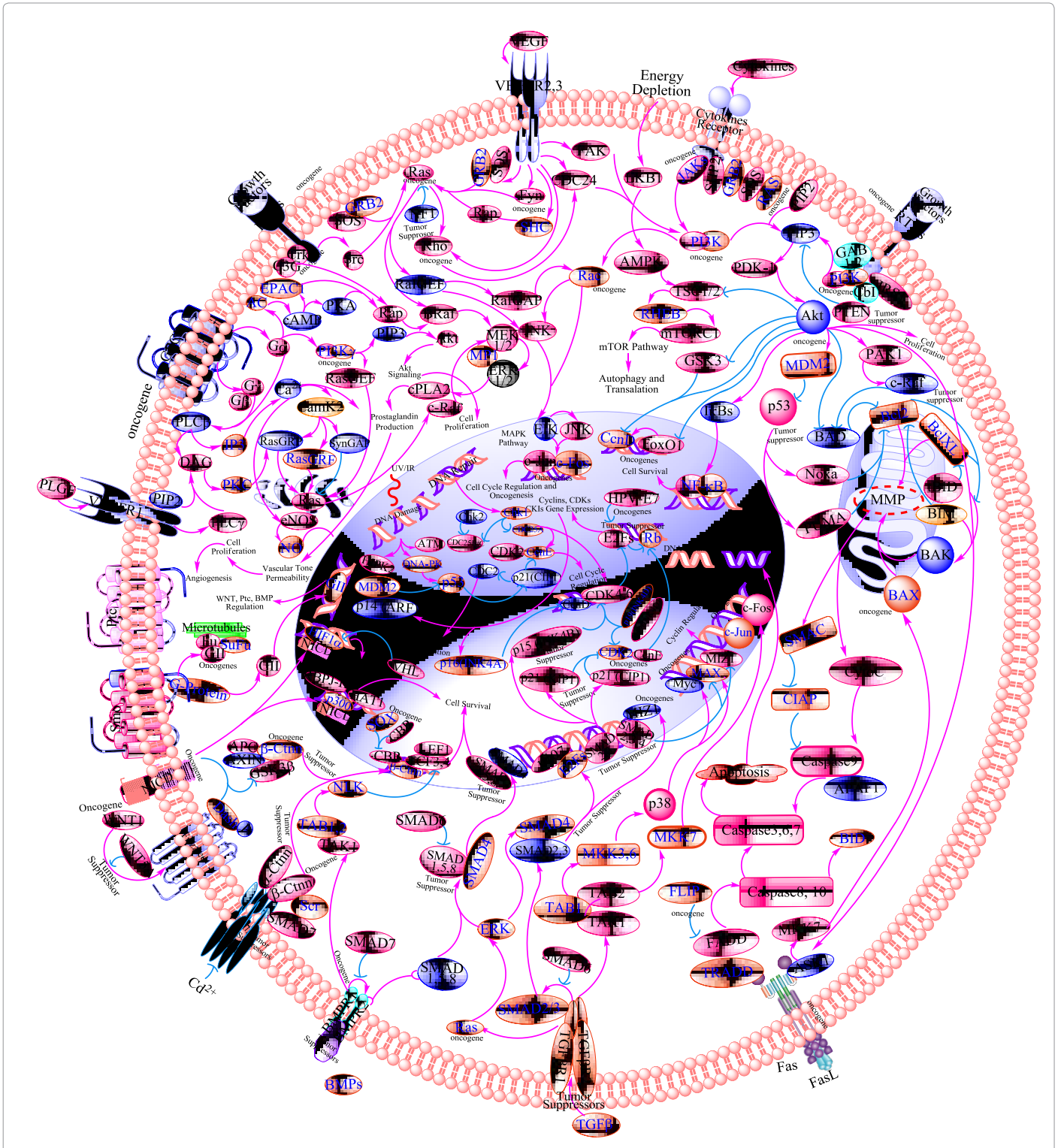

Figure 7: Overview of the molecular mechanisms pathway involved in cancer.

phosphorylation inhibits proliferation, migration of HUVECs (231). *In vivo*, emodin strongly suppresses VEGF-α-induced angiogenesis through inhibition of phosphorylation of KDR/Flk-1 of the Matrigel plug in mice [231]. In addition, inhibition of phosphatidylinositol 3-kinase (PI3K) is considered as molecular target of emodin that leads to inhibition of EGF-induced migration in various human cancer cell lines [232]. In addition, treatment of EC cell with emodin inhibits expression of ICAM-1, ELAM-1, and VCAM-1 [159].

Anti-metastasis

The high mortality rates associated with cancer are caused by the metastatic spread of tumor cells from the original site. There are at least four inter-related biological events required for tumor metastasis: Angiogenesis, cell adhesion, cell invasion (extracellular matrix degradation and cell migration), and cell proliferation. Angiogenesis is a process of blood vessel formation, it is plays an important role in cell growth. Tumor angiogenesis actually starts with cancerous tumor cells releasing molecules that send signals to surrounding normal host tissue. These signaling upregulated different genes in the host tissue that, in turn, make proteins to encourage growth of new blood vessels. More than a dozen different proteins (e.g., FGF, EGF, GC-SF, IL-8, PDEGF, TGFα, TNF, VEGF), as well as several smaller molecules (e.g., adenosine, PGE), have been identified as angiogenic factors released by tumors as signals for angiogenesis. Among these molecules, VEGF and βFGF appear to be the most important for sustaining tumor growth (Figure 7). VEGF and βFGF are produced by many kinds of cancer cells and by certain types of normal cells. Chemopreventive phytochemicals; resveratrol, and emodin have been found to target these pathways [233].

Resveratrol effects on angiogenesis have been studied [175,233-243]. Lin et al. reported that resveratrol suppressed the angiogenesis process that induced by VEGF in human umbilical vein endothelial cells [238]. Resveratrol suppressed of MMP-9 mRNA expression and PMA-mediated activation of JNK and PKC-α [234]. Bruder et al. reported the disruption of ROS dependent Src kinase activation is the underlying mechanism of the inhibition of VEGF-induced angiogenesis by resveratrol [237]. Resveratrol upregulated tissue type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) gene transcription in endothelial cells [239,240].

Similarly, one critical aspect of the anti-cancer activity of emodin is its inhibitory effect on cancer metastasis. Emodin potentially interferes with tumor metastasis progression at several pivotal points. Cell surface adhesion proteins (ICAM-1, VCAM-1, and ELAM-1) that regulated by NF-κB are inhibited by emodin [159,244]. The cholesterol content in membrane of cancer cells is higher than normal cells. Emodin decrease cholesterol content in cell membrane and disrupt the lipid rafts-associated integrin-signaling pathway [245]. Emodin inhibits EGF-induced cell migration in various cancer cells [232]. Emodin inhibits the PI3K-mediated Cdc42 and Rac1 activation and suppresses the p21-activated kinase (PAK) complex [232]. Similar to resveratrol, emodin inhibits MMP-9, AP-1 and NF-κB signaling pathways resulting in inhibit the invasiveness cancer cells [198,246-248].

Conclusion

From above mention studies that described in this review, we can conclude the traditional use of *Fallopia japonica* in many anticancer formulas relates to its ability to produce active SMs, especially resveratrol and emodin. *F. japonica* active SMs, resveratrol and emodin, have great potential in the prevention and therapy of a wide variety of tumors. *F. japonica* active SMs, resveratrol and emodin have antiproliferative effects through the induction of apoptosis in various cell lines: leukemia and breast, prostate, colon, pancreas, hepatic carcinomas. Lastly, resveratrol and emodin have potential for treating inflammatory disorders other than cancer; through their action as antiinflammatory, they can effect in different molecular targets, which are involved in chemotherapy approaches. To conclude, *F. japonica* should be considered for used in cancer therapy due to its SMs multifactoral effect; large scales clinical studies of the extract should be encouraged.

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