Bioactive Compounds and Biological Activities of Tuber Fleeceflower Root (*Polygonum multiflorum* Thunb.)

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Contents

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H. N. Murthy et al. (eds.), *Bioactive Compounds in the Storage Organs of Plants*, Reference Series in Phytochemistry, https://doi.org/10.1007/978-3-031-44746-4_47

Abstract

Polygonum multiflorum Thunb. is an important medicinal plant in North America and East and Southeast Asia. Its tuberous roots contain numerous bioactive compounds, including anthraquinones, stilbenes, tannin, and phospholipids with pharmaceutical properties, and were used as a traditional folk for a thousand years. The root extracts of this herb, as well as isolated compounds, have been demonstrated to possess several medicinal properties which have been widely employed such as coronary heart disease, hyperlipidemia, neurosis, other diseases, etc. In this chapter, we presented the nutritional status, chemical compounds isolated from tuberous roots, and pharmacological properties of this medicinal plant.

Keywords

Biological activities · Pharmacology · Phytochemicals · *Polygonum multiflorum*

1 Introduction

Polygonum multiflorum Thunb. (PM) belongs to the Polygonaceae family and is commonly known as "Fo-ti" in North America, "Heshouwu" in China, "Jeok-Hasuo" in Korea, and "Hà thủ ô đỏ" in Vietnam; it is also popular as tuber fleeceflower root or Chinese knotweed (Fig. 1) [1, 2]. The tuberous roots of this plant are usually harvested from 3- to 4-year-old plants and are used in the preparation of medicine after drying [2, 3]. Numerous studies have demonstrated that the root extracts of this herb contain an array of bioactive compounds, such as anthraquinones, stilbenes glycoside, phenolics, phospholipids, etc. with pharmaceutical properties [4–7]. To date, more than 170 compounds in PM have been identified [5, 7].

In traditional Chinese medicine (TCM), the root extract of PM was used as a tonic to strengthen liver and kidney functions, life longevity, hair dye, and detoxify the body [3, 8]. In traditional Korean medicine (TKM), PM has been cleared to treat the liver, kidney, blood, and hemorrhoids [9]. On the other hand, it has been widely utilized in blood pressure lowering and potential ability to reduce arteriosclerosis, cardioprotection, nerve strengthening, etc. [9–11]. Besides that, the root extract of PM showed potent antioxidant activities, antiaging, antidiabetic, anticancer, anti-inflammatory, and antimicrobial [2, 7]. Especially, the usefulness of PM has been demonstrated in curing Alzheimer's and Parkinson's disease in recent studies [2, 5]. Although PM-based products have been used for thousands of years and were considered to be safe for human consumption [2, 12, 13], long-term usage of PM products may cause liver and kidney toxicity [5, 7]. This chapter presents botanical details, nutritional status, chemical compounds, pharmacological properties, and toxicity of this medicinal plant.

Fig. 1 *Polygonum multiflorum* collected in Da Nang City, Viet Nam. (**a**) the aerial portion of the plant; (**b**) the underground part and tuberous roots; (**c**) roots and rhizome part; (**d**) estimated 100-year-old tuber (collected in Chungbuk province, Korea); (**e**) crude tuberous root slices; (**f**) process tuberous root slices. Scale bar: 5 cm

2 Botanical Details

PM is widely distributed around the globe and is used in many herbal drugs. It was found in North America and East and Southeast Asia like Korea, China, Japan, and Viet Nam, where it has long been known as a traditional medicinal plant [9, 14]. PM is a herbaceous perennial vine plant, with a maximum height of 3–4 m (Fig. 1a). This plant has dark-brown, hypertrophic undergrowth tuberous root with 5–15 cm in length and 3–10 cm in diameter (Fig. 1b–f) [2, 9]. The ovate or heart-shaped leaves are 3–7 cm long and 2–5 cm broad (Fig. 1a). Inflorescences are dense panicles bearing small flowers; fruits are small bearing achenes [5–7, 14]. PM grows in warm and humid places with temperatures of 16 to 21 °C and 70–80% humidity. They can be cultivated in farmlands or the edge of the forest and harvested after 3–4 years in autumn and winter while the leaf turns yellow [7, 9, 15].

In TKM and TCM, many parts of PM such as stem, root, rhizome, leaves, and tuberous roots were used as oriental medicine (Fig. 1b–f) [14, 16–18]. It was used alone or in combination with other remedies in traditional medicine. Among them, the tuberous roots were mainly important for their medicinal value (Fig. 1) [7, 15].

Table 1 Nutritional benefits of *Polygonum multiflorum*

Components	References
Starch	[12, 19, 20]
Phospholipids	
Squalene	[15]
Lecithin	[15, 21]
Lipositol	[15, 21]
Phosphatidic	[15, 21]
Ethyl oleate	[15, 21]
Octadecanoic acid methyl ester	[15, 21]
Octadecanoic acid ethyl ester	[15, 21]
Carbohydrate compounds	
Polysaccharides	[19]
D-glucose	[15, 21]
D-fructose	[15, 21]
Sucrose	[15, 21]
Fatty acid	[22]
Amino acid	[22]

3 Nutritional Benefits

PM is not only well-known in traditional medicine but is also used as a popular functional food and dietary supplement [19]. The tuberous root was rich in nutrients including carbohydrates and starch (Table 1); which were more than 40% (in weight) of starch and non-starch polysaccharide, and approximately 45% starch was observed [9, 19, 20]. In addition, the crude root of PM also contains monosaccharides such as D-glucose and D-fructose [15, 21]. Sucrose, the disaccharide, has also been detected. The content of D-glucose gradually increased, but D-fructose, sucrose, and the total sugars contents are reduced in 16 h of processing [15, 21]. Phospholipids, such as lecithin, lipositol, and phostidic acid, were also obtained in the root of PM with content of approximately 0.15–0.30%. Fatty acids, free amino acids, and essential amino acids were also recorded in PM root processing [22]. In addition, PM is a unique medicinal plant that shows completely different chemical components and concentrations in the crude and processed roots [2, 6]; two major processing methods were recorded in the early literature namely "the black bean processing method" and "steaming method" [2, 6].

4 Bioactive Compounds

PM's crude root and processing root extract contain more than 170 compounds. Phenolics, anthraquinones, and stilbene glycosides are the three main types of effective compounds [6, 7, 18].

4.1 Anthraquinones

Anthraquinones compounds that were mainly isolated from PM were emodin, physcion, and their derivatives (Table 2; Figs. 2 and 3). Various compounds such as rhein, chrysophanol, and 2-methoxy-6-acethyl-7-methyliuglone were also reported (Table 2; Fig. 2).

Table 2 Anthraquinones isolated from *Polygonum multiflorum* (Thunb.)

Compounds	References
Emodin	[2, 5, 23–27]
Aloe-emodin	[24, 28]
Rhein	[24, 26, 28]
Chrysophanol	[23, 24, 28]
Physcion	[1, 2, 4, 24, 25, 27–29]
Emodin-8-O-β-D-glucopyranoside	[28, 30]
Physcion-8-O-β-D-glucopyranoside	[28, 30]
Physcion-8-O-(6′ -O-acetyl)-β-D-glucopyranoside	[31]
Emodin-8-O-(6′ -O-acetyl)- β-D-glucopyranoside	[32]
2-Methoxy-6-acethyl-7-methyliuglone	[33, 34]

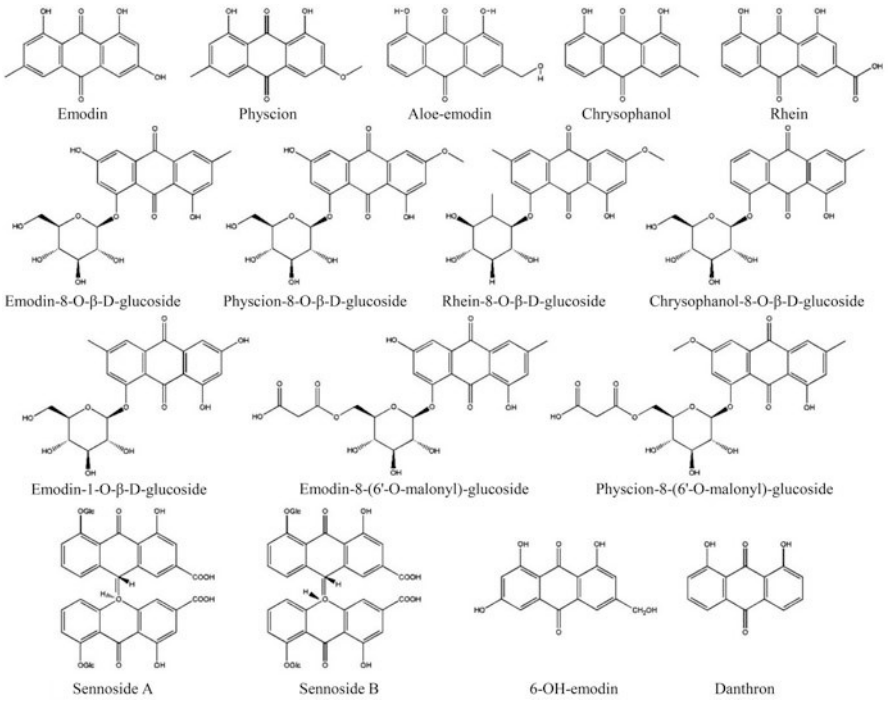

Fig. 2 Anthraquinones isolated from *Polygonum multiflorum* roots [2]

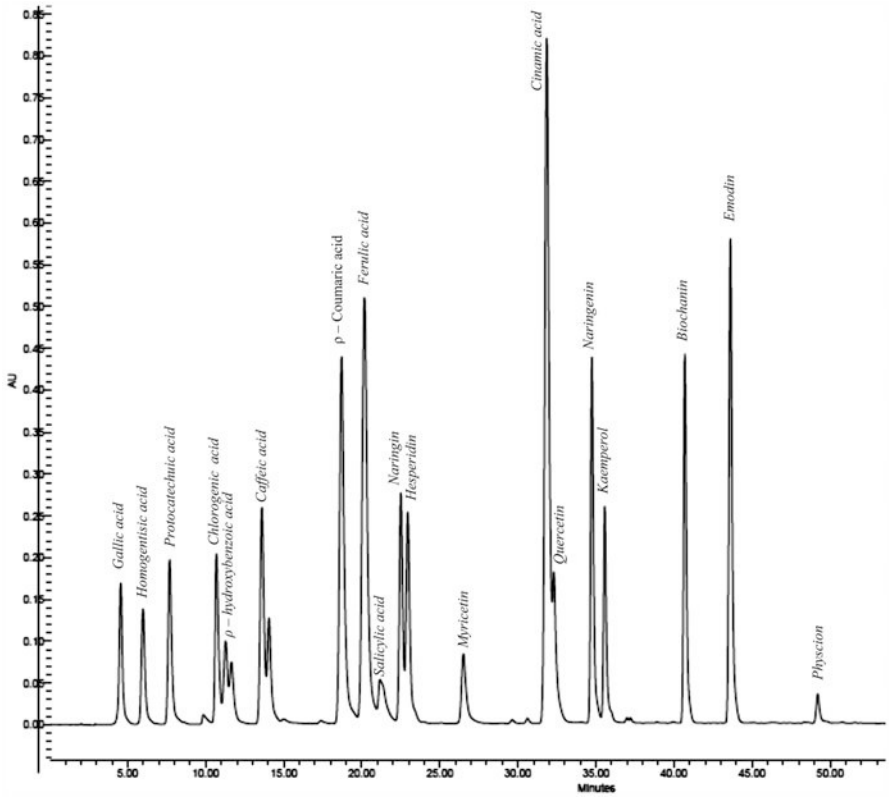

Fig. 3 Chromatogram of the standard mix of some bioactive compounds isolated from *Polygonum multiflorum* by HPLC

4.2 Stilbene Glycoside

Stilbenes glycoside was reported to be the chief constituent of PM. 2,3,5, 4′-tetrahydroxystilbene-2-O-β-D-glucopyranoside (TSG) was reported as the most important compound isolated from the root, which numerous pharmacological effects (Table 3; Fig. 4) [2, 5–7]. Rhaponiticin, polydatin, resveratrol, and cis-TSG were also major stilbenes isolated from roots of PM (Table 3, Fig. 4) [2, 5–7]. In addition, various compound belonging to the stilbenes group was also recorded (Table 3, Fig. 4).

4.3 Phenolic Compounds

Phenolic compounds are the most abundant secondary metabolites in plants, especially medicinal plants, with more than 8000 structures ranging from sample molecules (phenolic acids) to highly polymerize substances (tannins) [6, 27]. PM root extracts were characterized for the content of various phenolic compounds. Flavonoids are reportedly the major compound in PM. Catechin, epicatechin, hypericin,

Table 3 Stilbene glycosides isolated from *Polygonum multiflorum* (Thunb.)

Compounds	References
2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucopyranoside (TSG)	[2, 5–7]
2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-(2″-O-monogalloyl esters)-glucopyranoside	[35]
2,3,5,4′ -Tetrahydroxystilbene-2-O-β-D-(3″-O-monogalloyl esters)-glucopyranoside	[35]
2,3,5,4′-Tetrahydroxystilbene-2,3-di-O-β-D-glucopyranoside	[36]
Polygonumosides A-D	[37]
Polygonumosides E	[38]
2,3,5,4′-Tetrahydroxystilbene-2-O-(2″-O-p-hydroxybenzoyl)β -D-glucoside (TSG)	[38]
Rhaponiticin	[4, 5]
Polydatin	[5, 26, 39]
Multiflorumiside A-G	[40, 41]
Multiflorumiside H-L	[40, 41]
Polygonibene A	[37, 40]
Polygonibene B	[37, 40]
Polygonibene B-2a (deglucoslated)	[37, 40]
Polygonibene C	[37, 40]
Polygonibene C-3a (deglucoslated)	[37, 40]
Polygonibene D-G	[37, 40]
Resveratrol	[5, 6, 39]

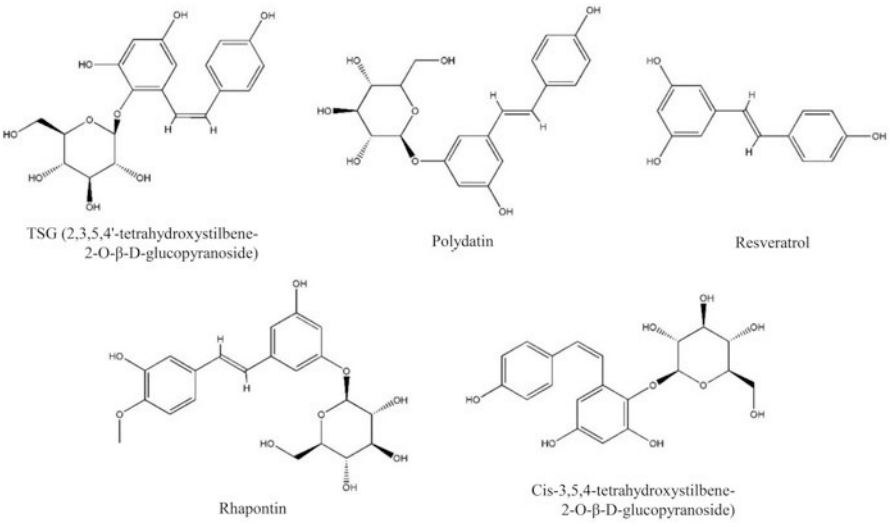

Fig. 4 Stilbenes isolated from *Polygonum multiflorum* roots [2]

quercetin, kaempferol, etc. were observed as the major flavonoid compounds in PM (Table 4, Figs. 3 and 5). Besides, various phenolic groups such as hydroxycinnamic acids and hydroxybenzoic acids have also been reported (Table 4).

Table 4 Phenolic compounds isolated from *Polygonum multiflorum* (Thunb.)

Compounds	References
Flavonoids	
Myricetin	[1, 2, 27, 42, 43]
Quercetin	[1, 2, 27, 42, 43]
Kaempferol	[1, 2, 27, 42, 43]
Catechin	[26–28, 30]
Epicatechin	[26, 28, 30, 44]
Polygonflavanol A	[28, 45, 46]
3-O-Galloyl-(−)-catechin	[35]
Tricin	[33, 39]
Hydroxycinnamic acid	
Chlorogenic acid	[2, 27, 42, 43]
Caffeic acid	[27, 28, 42, 43]
ρ-Coumaric acid	[27, 28, 42, 43]
Ferulic acid	[27, 28, 42, 43]
Cinnamic acid	[27, 28, 42, 43]
Hydroxybenzoic acid	
Gallic acid	[27, 28, 30]
Protocatechuic acid	[27, 28, 42, 43]
ρ-Hydroxybenzoic acid	[27, 28, 42, 43]
Salicylic acid	[2, 28, 42, 43]
Other phenolic compounds	
Hesperidin	[27, 28, 42, 43]
Naringenin	[27, 28, 42, 43]
Biochanin	[27, 28, 42, 43]
Proanthocyanidin	[28, 30]

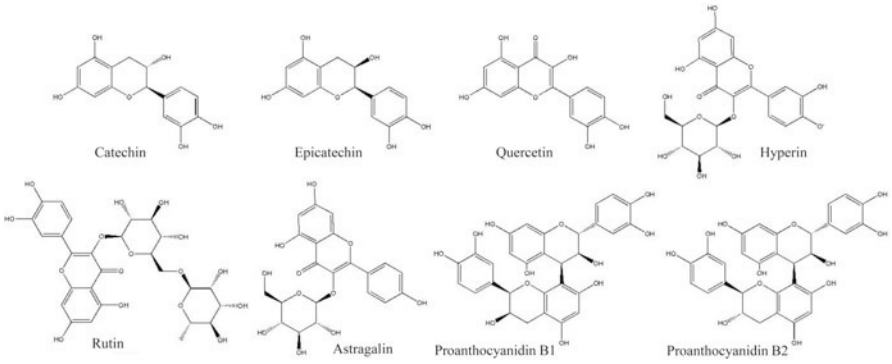

Fig. 5 Flavonoids isolated from *Polygonum multiflorum* roots [2]

Table 5 Other compounds isolated from PM *Polygonum multiflorum*

Compounds	References
Chromone	
2,5-Dimethyl-7-hydroxychromone (chromenone)	[38]
2-(2-Hydroxylpropyl)-5-methylchromenone-7-O-β-D-glucopyranoside	[38]
Trycin-7-O-β-D-glucopyranoside	[38]
Quinine	
7-Acetyl-6-methyl-2,3,8-trihydroxy-1,4-naphthoquinone	[47]
Emodin-1-β-D-glucopyranosyl	[47, 48]
Xanthone glycoside	
Thunberginol C 6-O-β-D-glucopyranoside (polygonimitin D)	[48]
Alkaloid	
Trans-N-caffeoyltyramine	[48]
Hypaphorine	[30]
Tanin	[2, 4, 7, 46]

4.4 Other Compounds

In addition to the three main groups, PM contains numerous other compounds such as chromone, quinine, xanthone glycoside, alkaloid, and tannin (Table 5).

5 Biological Activities

5.1 Antioxidant Activities

Free radicals are molecules containing at least one unpaired electron which can react with the other molecules to induce different types of diseases. The free radicals are released in the living system as by-products during biological oxidation processes. To reduce the negative effect of free radicals, huge natural agents were screened to eliminate them. The genus *Polygonum* with over 300 species, distributed mostly in temperate areas, is an important genus of traditional herbal values [49, 50]. Different important phytochemical compounds were isolated from *Polygonum* species such as phenolcarboxylic acids, flavonoids, anthraquinones, and stilbenes [35, 51], and some of them show free radical scavenging activity.

PM is a valuable herb in traditional medicine. In the early 1980s, Nonaka et al. [35] isolated two novel stilbene glycoside gallates and proanthocyanidins from PM by chromatography. Later on, Kimura et al. [52], for the first time, determined the function of stilbenes from PM in reducing lipid peroxides, which are damaged lipids due to the release of free radicals from oxidative stress and accumulation. The study showed that 2, 3, 5, 4′-tetrahydroxy stilbene-2-O-β-D-glucoside has positive effects in controlling lipid peroxides. More importantly, these agents could inhibit lipid peroxides by artificial induction. Similarly, the water extract of PM also protects mitochondria from lipid peroxides. However, the active

components of the plant have not been determined yet [53]. Thus, the primary data about the antioxidant activity of PM is suggestive of the need for increased focus on the isolation and purification of potentially bioactive compounds. Indeed, Siu et al. [53] suggested that the total water extract of PM root can scavenge oxidants [53]. Moreover, the fraction of the extract indicated that antioxidant components were presented in the ethyl acetate, not in hexane or butanol fractions. However, in this period, it was very rare information about pure compounds of PM involved in antioxidant activity. Later on, ethyl acetate was used to extract the total crude of PM and the crude was fractionated into two fractions, of which the anthraquinone-containing fraction showed a promising effect on inhibiting lactate hydrogenase leakage, whereas the non-anthraquinone-containing fraction had no effect [11]. Similarly, Chen et al. [54] extracted cut-dried root of PM in 95% EtOH and fraction in water, ethyl acetate, and hexane. The authors suggested that only the ethyl acetate fraction showed strong radical scavenging potential. Moreover, they also separated some components in the ethyl acetate fraction and found three compounds that have strong antioxidant activity, including gallic acid, catechin, and 2,3,5,4′-tetrahydroxystilbene 2-O-β-D-glucopyranoside. The study of Lv et al. [55] was the first time to identify pure components of the fraction that can scavenge oxidants. Another study focused on the extraction of dried PM root in water, at different concentrations of EtOH at 65 °C, while crude extract was fed to experimental mice to determine antioxidant activity [53]. The results indicated that the crude water extract was better than the EtOH extract in reducing the accumulation of active peroxide in the hippocampus of treated mice. This leads to protecting the hippocampus from free radicals. Stilbene glycosides are important active compounds of PM, the antioxidant activity of the components in reducing lipid peroxides has been identified and determined so far [52, 54], among the stilbene 2,3,5,4′-tetrahydroxystilbene 2-O-β-D-glucopyranoside has been reported as a potential free radical scavenging. Previously, the pure 2,3,5,4′-tetrahydroxystilbene 2-O-β-D-glucopyranoside was isolated from ethyl acetate fraction from PM root by chromatography (CC) on silica gel [54], and this stilbene was later isolated, purified by polycaprolactam chromatography and was structurally analyzed by high-performance liquid chromatography-mass spectrometry (HPLC-MS) and Nuclear Magnetic Resonance (NMR) [55]. The result suggested that 2,3,5,4′-tetrahydroxystilbene 2-O-β-D-glucopyranoside was the major stilbene in PM root and the pure 2,3,5,4′-tetrahydroxystilbene 2-O-β-D-glucopyranoside strongly scavenged free radical, such as DPPH, hydroxyl, superoxide anion, as well as inhibited lipid peroxide [55]. An interesting research using water extract of PM to defend against the damage induced by ultraviolet B irradiation was conducted [56]. In the research, Hwang et al. [56] showed that 2 weeks of repeated topical application of the water extract of PM on hairless mice after exposure to ultraviolet B irradiation enhanced recovery, during which the extract played an important role in maintaining the activity of SOD1 (Cu, Zn superoxide dismutase), inhibited lipid peroxides and scavenged the free radicals. Hence, PM extract contains different antioxidant compounds that should be used in antioxidant therapy.

5.2 Anticancer Activities

There are different bioactive compounds that have been isolated from PM so far, however, anthraquinones played an important role in the anticancer effect (Table 6). Anthraquinones in PM, including rhein, emodin, chrysophanol, and physcion and some glycosides anthraquinones, were isolated by HPLC, of which emodin and physcion were important anthraquinones in cancer treatment [1, 5, 57] (Table 6). Several cellular pathways have been proposed involving the mechanism of action of anthraquinones against cancer, particularly in apoptosis induction; cell cycle arrest; cancer cell migration, invasion, and metastasis inhibition [5, 57]. Bioactive compounds generally can induce apoptosis through two main pathways mediated by death receptors or mitochondria apoptosomes [5, 58, 59]. In PM, emodin and its derivatives (emodin-8-O-β-D-glucoside, aloe-emodin), chrysophanol, physcion and its glucoside-driven (physcion-8-O-β-D-glucoside), and rhein play an important role in cancer apoptosis [57]. Emodin was the most studied for cancer treatment among others, and it induced apoptosis in various cancer cell types and animal models via different pathways (Table 6) [6, 60, 61]. Anticancer mechanisms of action of emodin were proposed to be direct/indirect, targeting mitochondria to induce apoptosis, and regulating the signaling pathway to repress tumor migration, invasion, metastasis, and angiogenesis such as GF-β signaling [62–64]; Wnt/β-catenin and VEGFR2-AKT-ERK1/2 signaling [65, 66], upregulating miR-34a (tumor-suppressing miR) expression, suppressing AKT, ERK1/2, SMAD2, and SMAD4, or upregulating PI3K/Akt signaling pathways [61, 67]. Recently, several groups tried to incorporate emodin with nanoparticles to enhance anticancer activity [68, 69]. Importantly, the versatile function of emodin in cancer treatment in vitro and in vivo has been summarized in different papers [60, 62].

Some other derivatives of emodin also play an important role in anticancer, of which some of the derivatives were generated by modifying emodin structure [69], or added amino acid sequences to emodin [70], or isolating new emodin-related compounds such as β-DHA-emodin [71] and aloe-emodin [72]. Notably, most emodin-derivatives show better anticancer activity than emodin [62, 68–71], particularly, aloe-emodin, considered a potential agent to repress cancer cells proliferation and metastasis, induce cellular apoptosis, and act as an anticarcinogen by multiple signaling pathways [72, 73]. To date, various human cancer cell types were suppressed by aloe-emodin including bladder cancer, cervical cancer, colorectal cancer, gastric carcinoma, pharyngeal squamous cell carcinoma, transformed glial cell line, malignant glioma, monoblastic leukemia cells, lung nonsmall cell carcinoma, hepatoma, nasopharyngeal carcinoma, neuroblastoma, oral cancer, and ovarian carcinoma [73, 74]. Moreover, rhein, chrysophanol, and physcion also have anticancer effects [75, 76].

5.3 Antiaging Activities

Many previous studies investigated that one of the main effects of PM is antiaging, given that it can be used to treat Alzheimer's and Parkinson's disease [5–7, 88]. TSG

Table 6 Anticancer activities of emodin isolated from *Polygonum multiflorum*

Cancer types	Model	Treatment method	Results	Mechanism	References
Anaplastic thyroid	8505c, SW1736 cells (thyroid cancer)	Incubate cells with different emodin concentrations and evaluate cell migration and VEGF expression	Emodin represses angiogenesis; reduces migration	Emodin inhibits TRAF6/HIF-1α/VEGF and TRAF6/CD147/MMP9 signaling pathways	[77]
	Male Balb/c nude mice tumor xenograft	Artificially induce tumor by 8505c, SW1736 cells and orally administer with emodin once a day for 28 days	Emodin suppresses angiogenesis and metastasis		
Breast	MDA-MB-231; MDA-MB-453 cells (breast cancer)	Incubate cells with different emodin concentration and evaluates cell proliferation/apoptosis	Emodin inhibits MDA MB-231;MDA-MB-453 breast cancer cells proliferation and metastasis	Emodin inhibits the secretion of cc-chemokine ligand 5 from adipocytes leading to inhibits epithelial-mesenchymal transition and metastasis breast cancer	[78]
	Female Balb/C nude mice tumor xenograft	Artificially induce tumor in female Balb/C nude mice with breast cancer cells and treat emodin orally once a day for 21 days	Emodin inhibits MDA MB-231; MDA-MB-453 growth and metastasis in vivo		
	MCF7	Incubate MCF7 cells with different emodin concentrations to evaluate cell proliferation/apoptosis	Emodin inhibits MCF-7 proliferation and apoptosis	Emodin activation of the AhR-CYP1A1 signaling pathway to inhibit breast cancer	[79]
Colon	HCT116 and SW480 (colon cancer)	Incubate cells with different emodin concentrations	Emodin inhibits colon cancer proliferation and induces apoptosis	Emodin regulates cell cycles and apoptosis by inhibiting fatty acid synthase	[80]
	$Apc^{Min/þ}$ (intestinal cancer mouse), AOM/DSS	Treat genetic intestinal cancer mice or chemically induced colorectal cancer with emodin	Emodin inhibits the onset of genetic or chemically induce colon cancer	Emodin reduces tumor associated macrophages and could be a potential antagonist	[81]

	(chemically induced cancer mouse)	by oral gavage 3 times/week for 12 weeks		of the P2X7 receptor that affects proinflammatory cells activation	
	DLD-1, COLO-20 (colon cancer)	Incubate cells with different emodin concentrations	Emodin reduces cancer cell viability, induces apoptosis	Emodin downregulates MAPK/JNK, PI3K/AKT, NF-κβ, and STAT signaling pathways and disrupts the outer membrane potential of cancer cells	[82]
Lung	LLC (Lewis lung carcinoma) cell	For making allograft		Emodin suppresses neutrophils to prevent hypercoagulation and lung carcinogenesis	[83]
	Urethane-induced lung carcinogenesis in ICR mice	Intragastric administration emodin for 4, 7, 17 weeks	Emodin inhibits hypercoagulation and lung carcinogenesis induced by urethane		
	ICR mice allograft	Artificially induce tumor in ICR mice with lung cancer cells and intragastric administration emodin interval a week in 3 weeks	Emodin suppresses tumor growth in LLC-induced allograft		
	A549, H1299 (non-small cell lung cancer)	Incubate cells with different emodin concentrations	Emodin induces apoptosis	Emodin inhibits ERstress and activates of tribbles homolog 3/nuclear factor-κB signaling	[84]
	BALB/c nu/nu nude mice xenograft	Artificially induce tumor in BALB/c nu/nu nude mice and intraperitoneally injected emodin every day for 28 days	Emodin suppresses tumor growth in BALB/c nu/nu nude mice xenograft		
	A549 (non-small cell lung cancer)	Treat A549 with different emodin concentration	Emodin inhibits cell proliferation, migration, and epithelial-mesenchymal transition	Emodin blunted ATP/UTP-induced increase of [Ca2+]; inhibit activation of NF-κB	[85]

(continued)

Table 6 (continued)

Cancer types	Model	Treatment method	Results	Mechanism	References
Liver	HepG2 (human hepatocellular carcinoma)	Treat HepG2 with different emodin concentration	Emodin inhibits cell proliferation	Emodin induces downregulation of LPAR6 (lysophosphatidic acid receptor 6), C5 (complement C5), SSTR5 (somatostatin receptor type 5), GPR68 (ovarian cancer G-protein coupled receptor 1), and P2RY4 (P2Y purinoceptor 4), those are upregulated in different cancer	[86]
	Bel-7402 (human hepatocellular carcinoma)	Treat Bel-7402 with different emodin concentration	Emodin inhibits cell proliferation and induces intrinsic apoptosis	Emodin induces apoptosis in hepatocellular carcinoma cells by SREBP1-dependent and SREBP1-independent manner	[67, 70]
	SMMC-7721 (hepatocellular carcinoma)	Treat SMMC-7721 with different emodin concentration	Emodin inhibits SMMC-7721 proliferation and induces apoptosis	Emodin inhibits SMMC-7721 proliferation and induces apoptosis in vitro and in vivo through MAPK and PI3K/AKT signaling pathways	[86]
	Male BALB/c-nu nude mice	Artificially induce tumor in male BALB/c-nu nude mice and intraperitoneally injected emodin every day for 14 days	Emodin inhibits the growth of SMMC 7721 in nude mice		
	HepG2 (human hepatocellular carcinoma)	Treat HepG2 with different emodin concentrations and evaluate cell viability, proliferation, cell cycle, migration, and invasion	Emodin induces loss of cell viability, reduces proliferation, induces cell cycles arrest, and inhibits migration and invasion	Emodin induces autophagy and suppresses the PI3K/AKT/mTOR and Wnt/β-catenin pathways	[87]

isolated from PM tuberous roots have demonstrated an able effect to treat those diseases through inhibition of acetylcholinesterase (AChE), neuroprotection, and cognitive [5–7, 88]). On the other hand, Yang et al. [89] reported that ethanolic extract of PM to SPFC57BL/6 male mice not only reduction of the activity of malondialdehyde and alanine aminotransferase but also promoted the activity of the enzymes SOD and GSH-Px in aging mice. In addition, TGS isolated from PM should be developed as a potential antiaging drug [90].

5.4 Other Biological Activities

The root extract of PM has numerous biological activities such as depicted antifungal, antibacterial, and antiviral activities [1, 5–7]. In addition, hair growth and hair coloring, antilipidemic, anti-inflammatory, antitumor, neuroprotection, hepatoprotection, and immunomodulation are the other pharmacological effect of PM [5–7, 28, 90]. More detailed studies have also reported pharmacological activities of isolated compounds from PM such as anti-high cholesterol levels, antiatherosclerosis, antilipidemic, liver protection, and antifibrosis. PM has been used for the treatment of many diseases, such as coronary heart, hyperlipidemia, and neurosis, as well as diseases commonly associated with aging [91].

6 Toxicity

PM-based products are supposed to be safe for humans; however, recent researches show toxicity related to long-time use of PM products. Liver and kidney toxicity were the major reports**.** The crude material was more toxic than the processed root. Yang et al. [92] observed that the extract of PM with 70% ethanol considerably shows higher liver toxicity than other solvent extracts (such as water, acetone, and methanol) in Zebrafish. Anthraquinones, anthrones, and naphthols were also mentioned to induce severe liver damage while stilbenes didn't show apparent toxicity [92]. Hepatotoxicity and kidney toxicity in PM related to long-term use and overdose have been summarized by several studies [5–7]. Direct effects of the drug on liver cells or through the generation of toxic reactive metabolites (RMs) using cytochrome P450 enzymes were reported as the two mechanisms causing liver toxicity [6, 7]. There are also other possibly disordered mechanism pathways of hepatotoxicity of PM namely oxidative phosphorylation and TCA cycle pathway, bile acid excretion pathway, different metabolic pathways, genetic polymorphisms, etc.

7 Conclusions

PM is one of the most famous herbal medicinal plants. PM and its processed products have been widely used in oriental medicine to treat numerous diseases. In addition, many cosmetics and functional food products use PM for numerous health

benefits, leading to its introduction to the market. On the other hand, some studies have documented the hepatotoxicity of PM in recent years; however, the mechanisms of the toxicity are still unknown. There are several reviews summarizing the details of the chemical analysis, biological activities, pharmacology, and toxicity of PM [2, 5–7]. Nevertheless, the following aspects still require more investigation.

PM-based products were initially prepared along with other herbs in folk medicine; therefore, it is necessary to investigate the pharmacological effects and toxicity of PM in combination with other herbs. Also, many studies suggest that the toxicity of PM-based drugs in human health was due to long-term usage, higher dose levels, and long-term delivery. So, determining the dose and time of PM treatment is required. Moreover, the biosynthetic pathway for the synthesis of anthraquinones and stilbenes should be studied and explored. In addition, the interaction of different bioactive compounds such as TSG with physcion and emodin needs to be evaluated.

Acknowledgments This research is funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 106.01-2021.34.

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