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Chemical structures, bioactivities and molecular mechanisms of citrus polymethoxyflavones

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ABSTRACT

Citrus polymethoxyflavones (PMFs) and hydroxylated PMFs demonstrate potent bioactivities in regulating cytoactivity and organ function by modulating signaling cascade, gene transcription and protein activity. Studies have documented a wide variety of pharmacological activities of citrus PMFs in cell culture and animal models. In this review, we summarized the chemical structures of citrus PMFs, presented current knowledge of their physiological properties as well as various bioactivities, such as regulation of metabolic disorder, anti-inflammation, neuro-protection, anti-cancer, anti-microbial. The underlying molecular mechanisms of these activities by citrus PMFs were also discussed. Collectively, though further research is needed in mutual effect, safety and clinical trials, citrus PMFs still have great potential to develop as therapeutic agents or dietary supplements in future decades.

1. Introduction

In recent decades, there has been a growing interest in dietary bioactive compounds protecting or treating various diseases without undesirable effects. These compounds are defined as phytochemical substances since they are found in daily ingested fruits and vegetables. Among these phytochemicals, flavonoids are widely recognized for their anti-inflammatory and antioxidant properties. Citrus flavonoids are polyphenolic compounds specifically derived from citrus fruits or plants, such as oranges, mandarins, grapefruit, lemons, bergamots and limes, which play an unignorable role in regulating physical health. Epidemiological studies have shown that citrus flavonoids possess significant biological functions such as anti-cardiovascular diseases, anti-cancer and anti-inflammation. Generally, citrus flavonoids are composed of three major subgroups including flavanones, flavone glycosides and polymethoxyflavones (PMFs). PMFs are one type of flavone compounds with several methoxyl groups, which exhibited wide range of physiological and pharmacological bioactivities.

PMFs are identified in seeds, leaves, juice, stems and peels, particularly in the flavedo and the peel of citrus. Citrus peels such as orange peel or tangeretin, are usually regarded as by-products in commerce, but they have been used as traditional medicine for relieving stomach upset, cough, skin inflammation, muscle pain, and ringworm infections, as well as for lowering blood pressure in some regions of the world (Li et al., 2009). Recently, intensive pharmacological and mechanistic studies on citrus PMFs have been carried out to explore their therapeutic potential. To date, the bioactivities of citrus PMFs have included regulation of metabolic disorder, anti-atherosclerosis, anti-inflammation, neuroprotection, anti-cancer, anti-microbial and anti-oxidation. The anti-cardiovascular diseases, anti-cancer and neuroprotection activities of citrus PMFs have received considerable attention. An increasing number of articles and citations in the past few years also have indicated a surge of interest in pharmacological research into citrus PMFs.

Although several reviews cover many important facets (e.g., metabolism, bioavailability and cancer chemopreventive effects) of citrus flavonoids, including PMFs and hydroxylated PMFs, some significant aspects of the therapeutic potential of citrus PMFs, such as anti

Abbreviations: ACC, acetyl-coA carboxylase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; BaP, benzo[*a*]pyrene; C/EBP, CCAAT/enhancer-binding protein; CDK, cyclin-dependent protein kinase; COX, cyclo-oxygenase; DMBA, dimethylbenz[*a*]anthracene; ERK, extracellular signal–related kinase; FAS, fatty acid synthase; Glut, glucose transporter; GPx, glutathione peroxidase; GSH, glutathione; HFD, high-fat diet; HMF, heptamethoxylflavone; iNOS, inducible NO synthase; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDR, multidrug resistance; MIC, minimal inhibitory concentration; ox-LDL, oxidized low-density-lipoprotein; PGE_2, prostaglandin E_2; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PMFs, polymethoxyflavones; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SAMP8, senescence accelerated mouse prone 8; SOD, superoxide dismutase; SR-A, scavenger receptor A; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor kappa B; VSMC, vascular smooth muscle cell

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Table 1
The citrus PMFs reported in literatures.

	Chemical name	Species	References
1	3′,4′-dimethoxyflavone	*Citrus Jeju native*	Yongdug, Weonjun, Kyungsoo, Youjin, and Soohyun (2009)
2	3′,4′-dihydroxy-7,5′-dimethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing, Zhao, Zhang, and Li (2017)
3	5,6-dihydroxy-7,4′-dimethoxyflavone	*Fructus aurantii*	Yang, Chen, Bao-Jin, Zhang, and Yan (2008)
4	5,7,4′-trihydroxy-6,8-dimethoxyflavone	*Citrus sudachi*	Tsukayama, Sasaki, Yamamoto, Kawamura, and Ichikawa (2010)
5	5,7,4′-trihydroxy-6,3′-dimethoxyflavone	*Citrus hassaku*	Uckoo, Jayaprakasha, and Patil (2012)
6	3,5,6-trihydroxy-7,4′-dimethoxyflavone	*Citrus medica* L.	He and Ling (1985)
7	3,5,7,4′-tetrahydroxy-8,3′-dimethoxyflavone	*Citrus unshiu*	Chkhikvishvili, Kurkin, and Pervykh (1994)
8	5,7,3′,4′-tetrahydroxy-6,8-dimethoxyflavone	*Citrus sudachi*	Nakasugi, Nakashima, and Komai (2000)
9	5,7, 4′-trimethoxyflavone	*Citrus rutaceae*	Mizuno, Iinuma, Ohara, Tanaka, and Iwamasa (1991)
10	3-hydroxy-5,7,8-trimethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
11	5-hydroxy-6,7,4′ -trimethoxyflavone	*Citrus sinensis*	Uckoo et al. (2012)
12	5-hydroxy-7,3′,4′-trimethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
13	4′-hydroxy-5, 6, 7-trimethoxyflavone	*Citrus aurantium* L.	Ding, Xiong, Zhou, Deng, and Deng (2015)
14	5,4′-dihydroxy-6,7,8-trimethoxyflavone	*Citrus reticulata* (mandarin)	Pinkas, Lavie, and Chorin (1968)
15	3,5,6-trihydroxy-7,3′,4′-trimethoxyflavone	*Citrus medica* L.	He and Ling (1985)
16	5,7,4′-trihydroxy-6,8,3′-trimethoxyflavone	*Citrus sudachi*	Nakasugi et al. (2000)
17	3,6,7,4′-tetramethoxyflavone	*Citrus hallabong* (hybrid)	Han, Kim, Lee, Mok, and Lee (2010)
19	5,6,7,4′-tetramethoxyflavone	*Citrus sinensis* L.	Uckoo et al. (2012)
20	5,7,8,4′-tetramethoxyflavone	*Citrus reticulata* blanco cv.ponkan (M.Uckoo et al., 2012)	Uckoo et al. (2012)
21	5,6,7,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
22	5,6,7,4′-tetramethoxyflavanone	*Citrus sinensis*	Li, Lo, and Ho (2006)
23	5,7,8,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
24	5,7,3′,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
25	6,7,8,4′-tetramethoxyflavone	*Citrus unshiu*	Shin, Nam, Yoon, Han, and Seo (2012)
26	7,8,3′,4′-tetramethoxyflavone	*Citrus Jeju native*	Yongdug et al. (2009)
27	3-hydroxy-5,6,7,4′-tetramethoxyflavone	*Citrus sinensis*	Li et al. (2006)
28	5-hydroxy-3,7,3′,4′-tetramethoxyflavone	*Citrus miaray*	Uckoo, Jayaprakasha, Vikram, and Patil (2015)
29	5-hydroxy-6, 7, 3′, 4′-tetramethoxyflavone	*Citrus aurantium*	Ding et al. (2015)
30	5-hydroxy-7,8,3′,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
31	5-hydroxy-6,7,8,4′-tetramethoxyflavone	*Fructus aurantii*	Yang et al. (2008)
32	5-hydroxy-3,6,7,8-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
33	6 -hydroxyl-5,7,8,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
34	7-hydroxy-5,6,8,4′-tetramethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
35	7-hydroxy-5,6,3′,4′-tetramethoxyflavone	*Citrus reticulata*	Mizuno et al. (1987)
36	5,4′-hydroxy-6,7,8,3′-tetramethoxyflavone	*Citrus reticulata* (mandarin),	Pinkas et al. (1968)
37	5,7-dihydroxy-6,8,3′,4′-tetramethoxyflavone	*Citrus medica* L.	He and Ling (1985)
38	7,4′-dihydroxy-5,6,8,3′-tetramethoxyflavone	*Citrus deliciosa Ten.*	Eldomiaty, Abdelaal, and Elshafae (1997)
39	5,8-dihydroxy-3,7,3′,4′-tetramethoxyflavone	*Citrus miaray*	Uckoo et al. (2015)
40	3,5,6,8,4′-pentamethoxyflavone	*Citrus reticulata Blanco cuv.*	Abdel Alim, El-Hamouly, Aboutabl, and Hetta (1998)
41	3,5,7,3′,4′-pentamethoxyflavone	*Citrus miaray*	Uckoo et al. (2015)
42	3,6,7,8,4′-pentamethoxyflavone	*Citrus sinensis*	Uckoo et al. (2012)
43	5,6,7,8,4′-pentamethoxyflavone	*Citrus sinensis*	Uckoo et al. (2012)
44	5,6,7,3′,4′-pentamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
45	5,6,7,3′,4′-pentamethoxyflavonone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
46	5,7,8,3′,4′-pentamethoxyflavone	*Citrus sinensis*	Uckoo et al. (2012)
47	6,7,8,3′,4′-pentamethoxyflavone	*Citrus reticulata blanco cv.ponkan*	Uckoo et al. (2012)
48	6,7,8,3′,4′-pentamethoxyflavonone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
49	5,6,7,8,4′-pentamethoxyflavone	*Citrus sinensis Citrus unshiu*	Uckoo et al. (2012)
50	2′-hydroxy-3,4,4′,5′,6′-pentamethoxychalcone	*Citrus sinensis*	Uckoo et al. (2012)
51	3-hydroxy-5,6,7,8,4′-pentamethoxyflavone	*Citrus sinensis Osbeck*	Li et al. (2006)
52	3′-hydroxy-5,6,7,8, 4′-pentamethoxyflavone	*Citrus changshan-huyou*	Zhao, Ye, and Zhu (2009)
53	5-hydroxy-3,7,8,3′,4′ -pentamethoxyflavone	*Citrus sinensis Osbeck*	Uckoo et al. (2012)
54	5-hydroxy-6,7,8,3′,4′-pentamethoxyflavanone	*Citrus sinensis*	Li et al. (2006)
55	5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone	*Citrus sinensis*	Li et al. (2006)
56	5-hydroxy-6,7,3′,4′,5′-pentamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
57	6-hydroxy-5,7,8,3′,4′-pentamethoxyflavanone	*Citrus jambhiri*	Hamdan et al. (2011)
58	7-hydroxy-5,6,8,3′,4′-pentamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
59	8-hydroxy-3,4′,5,6,7-pentamethoxyflavone	*Citrus aurantifolia.*	Johann et al. (2007)
60	4′-hydroxy-5,6,7,8,3′-pentamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
61	3,5,6,7,3′,4′-hexamethoxyflavone	Commercially citrus peel extract	Wang, Li, Stephen, Robert, and Ho (2008)
62	3,5,6,7,8,4′-hexamethoxyflavone	*Citrus sinensis* L.	Uckoo et al. (2012)
63	3,5,7,8,2′,5′-hexamethoxyflavone	*Citrus reticulata Blanco*	Wen et al. (2016)
64	3,6,7,8,2′,5′-hexamethoxyflavone	*Citrus unshiu*	Shin et al. (2012)
65	3,5,6,8,3′,4′-hexamethoxyflavone	*Citrus hassaku*	Uckoo et al. (2012)
66	3,5,7,8,3′,4′-hexamethoxyflavone	*Citrus hassaku*	Uckoo et al. (2012)
67	5,6,7,8,3′,4′-hexamethoxyflavanone	*Citrus miaray*	Uckoo et al. (2015)
68	5,6,7,3′,4′,5′-hexamethoxy flavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
69	5,7,8,3′,4′,5′-hexamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)
70	2′-hydroxy-3,4,3′,4′,5′,6′-hexamethoxychalcone	*Citrus sinensis*	Li et al. (2006)
71	3-hydroxy-5,6,7,8,3′,4′-hexamethoxyflavone	*Citrus aurantium*	Ding et al. (2015)
72	5-hydroxy-3,6,7,8,3′,4′ -hexamethoxyflavone	*Citrus kinokuniHort. ex Tanaka*	Uckoo et al. (2012)
73	5-hydroxy-6,7,8,3′,4′,5′-hexamethoxyflavone	*Citrus reticulata; Citrus sinensis*	Xing et al. (2017)

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