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Phytochemical components and biological activities of *Artemisia argyi*

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ABSTRACT

Artemisia argyi Lévl. et Vant. (*A. argyi*) is a region-specific plant of northern temperate zones, especially in Asia. There is a long history of using *A. argyi* not only as an edible plant, but as dietary function material in East Asia. It has been found in *A. argyi* that there is a broad spectrum of nutrients comprising proteins, dietary fiber, essential amino acids, polyunsaturated fatty acids, minerals, and multiple plant bioactives such as essential oil (EO), flavonoids, coumarins, organic acids, and polysaccharides. Both *in vitro* and *in vivo* studies revealed that *A. argyi* phytochemicals afford various health promoting potential, including antioxidant, anti-cancer, anti-inflammatory, immunomodulatory, neuroprotective, anticoagulant, and anti-osteoporotic activities, as well as antimicrobial and insecticidal properties. Herein, we provide a comprehensive review of the nutrients and the health benefits of *A. argyi*, with an emphasis of the characteristic components, and a perspective of future needs in research and development of *A. argyi*.

1. Introduction

Medicinal plants are nature's gift to human beings to help them battle against various ailments since thousands of years ago. Now with the globalization of pursuing improved quality of life, there is actually a general rising tendency in demand for dietary function plants in the world (Kotnis, Patel, Menon, & Sane, 2004). A report from the World Health Organization (WHO) disclosed that almost 80% of the world's population relies on nonconventional drug-treatment, particularly of medicinal herb, in their primary healthcare (Chan, 2003). However, although great progress is being made in uncovering the chemistry and bioactivities of functional food plants, their exact biological functions and regulation mechanisms largely remain to be elucidated.

Artemisia argyi (*A. argyi*) is known in Chinese as "Aicao" and in Japanese as "Gaiyou". It is a perennial herb or small shrub, with thick and intense aromas. *Artemisia* belongs to the Asteraceae family that comprises over 500 species (Abad, Bedoya, Apaza, & Bermejo, 2012). Among which, *A. argyi* is a dominant species mainly found in northern temperate regions, especially in Asia, Europe and North America (Bora & Sharma, 2011). As a traditional medicinal and edible plant, ancient Chinese commonly pick the buds and leafs of *A. argyi* before and after the Tomb-sweeping Day (April 5th, the Memorial day in China), consumed as an infusion or other forms of food supplement. Besides, the dried leaves of *A. argyi* are often used, in China, as a flavoring and colorant for the Chinese dish Qingtuan (He, 2004). More importantly, *A. argyi* exhibits pleiotropic bioactivities and is traditionally used in folk medicine to control dysmenorrhea, abdominal pain, and inflammation (Chinese Pharmacopoeia Commission, 2015). To explain these traditional indications, the chemical composition of *A. argyi* was investigated as the foundation of mechanism exploration. As of today, a wide range of dietary phytochemicals including essential oils (Abad et al., 2012), flavonoids (Han et al., 2017), organic acids (Han et al., 2017), terpenes (Yoshikawa, Shimada, Matsuda, Yamahara, & Murakami, 1996), polysaccharides (Zhang, Shi et al., 2018), and coumarins (Yoshikawa et al., 1996) have been identified in *A. argyi*. Several of these characteristic components have been investigated by modern science to confer health benefits, such as antioxidant (Kim, Shin et al., 2015), anti-tumor (Seo et al., 2003), anti-inflammatory (Yun et al.,

Abbreviations: *A. argyi*, *Artemisia argyi*; EO, essential oil; AAL, *Artemisia argyi* leaves; FW, fresh weight; DW, dried weight; EAA/TAA, essential amino acids/total amino acids; *A. princeps*, *Artemisia princeps* Pamp; HD, hydro-distillation; SPME, solid-phase microextraction; AAEO, *Artemisia argyi* essential oil; MFs, methoxyflavones; ALL, *Artemisiae Lavandulaefoliae* leaves; 3,5-diCQA, 3,5-dicaffeoylquinic acid

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Table 1
Nutrient composition of *A. argyi* leaves.[a]

Type	Content	Type	Content
Protein	22.0 mg/g FW[b]	**Vitamin**	
Total lipid	24.7 mg/g FW		
Dietary fiber	39.9 mg/g FW	Vitamin C, total ascorbic acid	2.09 mg/g DW
Total carbohydrates	52.3 mg/g FW		
Total phenolics	0.75 mg/g DW[c]	**Free amino acids**	
Minerals		Essential amino acids	3.71 mg/g DW
Potassium (K)	74.22 mg/100 g FW	Nonessential amino acids	2.42 mg/g DW
Calcium (Ca)	14.74 mg/100 g FW	Total free amino acids	6.13 mg/g DW
Magnesium (Mg)	36.64 mg/100 g FW	**Fatty acids**	
Zinc (Zn)	0.89 mg/100 g FW		
Copper (Cu)	0.13 mg/100 g FW	Saturated fatty acids	40.8%[d]
Manganese (Mn)	0.76 mg/100 g FW	Monounsaturated fatty acids	7.1%[d]
Iron (Fe)	3.15 mg/100 g FW	Polyunsaturated fatty acids	52.1%[d]

[a] Adapted from the studies of Kim, Shin et al. (2015) and Huang and Li (2014).
[b] FW, fresh weight.
[c] DW, dry weight.
[d] The quantified result of fatty acids is showed as a relative percentage (% of the internal standard).

2016), anticoagulant (Lv, Li, & Zhang, 2018), and anti-osteoporotic activities (Kim, Lee et al., 2015), as well as neuroprotection (Zeng, Wang, Dong, Jiang, & Tu, 2014) and immunomodulation among others (Zhang, Shi et al., 2018).

However, a systematic summary of biologically active ingredients of *A. argyi* and their pharmaceutical potential is still vacant. This review, after a presentation of the nutritional constituents, will focus on the current progress regarding the phytochemistry and bioactivities of *A. argyi*. It is expected that this review will encourage further research on *A. argyi*, thereby contributing to open avenues for scientific applications of *A. argyi* as a dietary plant with multiple health benefits.

2. Nutrients

A. argyi, particularly its aerial part, is widely consumed as a traditional food and a popular tea in East Asia, basically owing to the fact that it is rich in protein, lipid, dietary fiber, phenolic compounds, minerals, vitamin C, and essential amino acids (Table 1). As the fundamental material of life, saccharides keep supplying the body with energy and stamina. For instance, one g of fresh *A. argyi* leaves (AAL) have 52.3 mg of carbohydrates, doubling that of *Emilia sonchifolia* (21.3 mg/g of fresh weight, FW) (Huang & Li, 2014). Dietary fiber is inversely related to body weight by suppressing energy intake through increasing satiety, and thus is effective to battle with obesity (Dahl & Stewart, 2015; Zhang, Pagoto et al., 2018). Moreover, dietary fiber has been proven to be advantageous in preventing type 2 diabetes, cardiovascular diseases, and colorectal cancer (McGuire, 2016). The amount of crude fiber in the fresh AAL is 39.9 mg/g, which is roughly a third of that in fiber-rich oat (Manthey, Hareland, & Huseby, 1999).

The protein content and total free amino acids (TAAs) in AAL is 22.0 mg/g of fresh weight (FW) (Huang & Li, 2014) and 6.13 mg/g of dried weight (DW) (Kim, Shin et al., 2015), respectively. A total of 14 amino acids, including 6 essential amino acids (EAAs) for human body, were found in *A. argyi*. The ratio of essential amino acids/total amino acids (EAA/TAA) is 60.0% (Kim, Shin et al., 2015), which is significantly higher than that of some protein-rich animal foods like eggs (46.2%), milk (44%), and fishes (40.7%) (Jiang & Nie, 2015). FAO and WHO recommend that a food with the value of EAA/TAA beyond 40% is an ideal protein source (Zhong, Ding, Li, Wu, & Lv, 2012). Based on this principle, *A. argyi* could be considered as a high plant protein resource. γ-Aminobutyric acid is a natural non-protein amino acid with great therapeutic potential in neurological disorders and mental illnesses, because it acts as the major inhibitory neurotransmitter in the central nervous system (Awapara, Landua, Fuerst, & Seale, 1950; Zhu et al., 2018). The level of γ-aminobutyric acid reached 12.60 mg/100 g DW in *A. argyi*, which was approximately 3.8-fold higher than that in another congener *Artemisia princeps* Pamp (*A. princeps*) (Kim, Shin et al., 2015).

Polyunsaturated fatty acids (PUFAs) is the major fraction of fatty acids in *A. argyi*, representing around 52.1%, and followed by saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) (40.8% and 7.1%, respectively) (Table 1). A total of nine fatty acids, ranging from C16 to C24, were detected in dried samples. Among which, linolenic acid (C18:3), with a relative percentage of 36.36%, is the most abundant fatty acids in AAL. And then are palmitic acid (C16:0) and linoleic acid (C18:2), accounting for 18.82% and 15.73%, respectively (Kim, Shin et al., 2015). C18:2 and C18:3 could not be produced endogenously, but both are necessary fatty acids for our body since they are indispensable in infants' growth and development, health promotion, and disease prevention (Farvid et al., 2014; Whelan, 2008).

Total phenolic compounds in *A. argyi* is 0.75 mg/g DW, whereas the amount in *A. princeps* is only about half (0.49 mg/g DW). Moreover, high amounts of vitamin C are found in *A. argyi* (2.09 mg/g DW), which is comparable to that of vitamin C-rich foods such as oranges, kiwifruits, tomatoes, and broccoli (Eitenmiller, Ye, & Landen, 2008; Phillips et al., 2010). Generally, the antioxidant activity is positively associated with the contents of phenolics and vitamin C (Ben-Nasr, Aazza, Mnif, & Miguel Mda, 2015; Zheleva-Dimitrova, 2013). Given that, *A. argyi* is found to be promising in free radicals scavenging (Han et al., 2017). Additionally, *A. argyi* is an outstanding source of minerals, particularly of potassium, as high as 74.22 mg/100 g FW. It is then followed by magnesium (36.64 mg/100 g FW) and calcium (14.74 mg/100 g FW), and other essential minerals for health maintenance like iron, zinc, manganese, and copper (Huang & Li, 2014; Jankowska, Rutkowski, & Debska-Slizien, 2017).

3. Characteristic components

The chemical compositions in *A. argyi* can be classified according to their boiling temperatures into volatile essential oil (EO) and non-volatile compounds, the later mainly comprising flavonoids, organic acids, polysaccharides, coumarins, and larger terpenoids.

3.1. Essential oil (EO)

EO represents a large family, in which members are almost characterized by volatile and semi-volatile compounds, usually with a low molecular weight. It is generally formed as the secondary metabolite by aromatic plants. The chemical composition of EO can be categorized by their biosynthetic pathways as terpenes and their oxygenated

derivatives (such as alcohols, ethers, aldehydes, ketones, and esters), and some aromatic and aliphatic compounds (Abad et al., 2012). EO is traditionally obtained by steam or hydro-distillation (HD) (Chen, Zhang, Chao, & Liu, 2017; Ge et al., 2016; Huang, Wang, Yih, Chang, & Chang, 2012; Zhang et al., 2014). Recently, relatively new techniques, including solid-phase microextraction (SPME) (Li, Mao, Deng, & Zhang, 2008), supercritical fluid extraction (SFE) (Guan, Li, Yan, & Huang, 2006), and microwave-assisted extraction (MAE) (Lu, Zhou, Zhang, & Ren, 2018), have been developed and applied to collect these volatile constituents. EO is reported to perform well in alleviating oxidative damage (Campelo-Felix et al., 2017; Mojtahed Zadeh Asl, Niakousari, Hashemi Gahruie, Saharkhiz, & Mousavi Khaneghah, 2018), inflammation (Ehrnhofer-Ressler et al., 2013; Yun et al., 2016), infection (Guan et al., 2006; Loziene et al., 2018; Shi et al., 2017), cancer (Castro et al., 2018; Poma et al., 2018), and neurodegeneration (Zhu et al., 2017).

A. argyi is a rich source of EO (AAEO), approximately 1.13% (w/w) (Ge et al., 2016). Indeed, the strong and aromatic odours of *A. argyi* are mostly attributed to a high concentration of EO. AAEO comprises abundant terpenoids, alcohols, ethers, ketones, and a comparatively minor amount of aldehydes, esters, organic acids, and aromatic compounds (Table 2, see Supporting information-Table S1 for their chemical structures). With the help of gas chromatography-mass spectrometry (GC–MS), a total of 33 compounds were initially identified in AAEO, and eucalyptol was most plentiful, accounting for 23.66% (Huang et al., 2012). However, the amount of eucalyptol, also known as 1,8-cineole, was quantified to 33.4% in another study (Chen et al., 2017). By comparing the phytochemicals of AAEO from eight different areas, locality was considered as a factor affecting the quality of AAEO (Pan, Xu, & Ji, 1992). Besides, AAEO respectively collected by HD and SFE exhibited different chemical composition (Guan et al., 2006). Furthermore, we noticed that eucalyptol content accounted respectively for 9.00–33.42% and 2.56–22.03% of AAEO from leaves and aerial parts, but this value dropped to 2.02–3.58% when flower-heads was used as the samples (Table 2). The same happened with (−)-borneol, camphor, caryophyllene, germacrene D, linalool, and bornyl acetate. Based on these studies, we can make clear that the quality and yield of AAEO may be influenced by the raw material origin, extraction technology and selection of plant parts. Interestingly, Liu et al. recently shed light on this question via comparing the expression pattern of genes involved in terpenoid biosynthesis in *A. argyi* leaf, root and stem tissues (Liu et al., 2018). Results presented that there was significant variance in the expression levels of numerous genes regulating terpenoid synthesis among different plant parts.

3.2. Flavonoids

A variety of flavonoids, including flavones, flavonols, flavononols, and chalcones were found in *A. argyi*, especially in the leaves part (Table 3, see supporting information-Table S2 for their extraction and analytical methods). Methoxyflavones (MFs) is a general term for flavones bearing one or more methoxylated substituents on their basic skeleton of benzo-γ-pyrone (C6-C3-C6) with a carbonyl group at the C_4 position (Liu, Xu, Cheng, Yao, & Pan, 2012). MFs has been reported to be involved in preventing against oxidative damage, inflammation, allergy, and tumor (Li, Lo, & Ho, 2006; Middleton, Kandaswami, & Theoharides, 2000; Wang et al., 2018). Jaceosidin and eupatilin represent by far the most studied MFs in *A. argyi*. Based on fingerprint analysis and quantitative detection of multicomponents, 10 components were quantified in 16 AAL samples and 9 *Artemisiae Lavandulaefoliae* leaves (ALL), respectively (Guo et al., 2018). Results showed that the contents of jaceosidin and eupatilin were 0.26–0.69 mg/g and 0.46–1.22 mg/g in AAL, and 0.05–0.11 mg/g and 0.09–0.21 mg/g in ALL, respectively. The remarkable variance in content of both flavones can be considered as a reference to identify and evaluate the quality of *A. argyi*. Apart from jaceosidin and eupatilin, five other MFs were separated from AAL in another study, including centaureidin, casticin, hispidulin, 5,7,4′,5′-tetrahydroxy-6,3′-dimethoxyflavone, and 5,7,3′,5′-tetrahydroxy-6,4′-dimethoxyflavone (Han et al., 2017). Additionally, chrysoeriol, acacetin, and ladanein were also reported in *A. argyi* (Nakasugi, Nakashima, & Komai, 2000; Seo et al., 2003).

In addition to multiple flavones, some flavonols, flavanones and flavononols were also isolated and identified in *A. argyi*. Their structures are similar but slightly differ in C_2, C_3, and C_4 positions. Compared to flavones, flavonols have a hydroxy group at C_3, while flavanones are saturated with a single bond between C_2 and C_3. Not only are saturated between C_2 and C_3, flavononols also bear a hydroxyl at C_3 in comparison with flavones. Querctin and its glycosylated derivatives quercetin 3-*O*-glucoside (isoquercetin), and kaempferol, as well as rutin, were the chief fraction of flavonols found in *A. argyi* (Han et al., 2017; Li, Zhou, Yang, & Meng, 2018). Besides, three flavanones including naringenin, homoeriodictyol, and 5,7,3′,4′-tetrahydroxyflavone, and one flavononol 2,3-dihydroisorhamnetin, were purified from AAL via preparative high performance liquid chromatography (HPLC) (Lee et al., 2018). Chalcone, featured by C6-C3-C6 skeleton, is a subclass of flavones as well. Eriodictyol chalcone was currently the only chalcone reported in *A. argyi* (Han et al., 2017). In the future, bioactivities of flavonoids remain to be further investigated to provide insights into the structure-activity relationships.

3.3. Organic acids

A. argyi contains a wide range of phenolic acids, mainly represented by hydroxybenzoic acids and hydroxycinnamic acids, and some other organic acids (Table 4). Among hydroxycinnamic acids, caffeic acid and its derivatives were the primary components. By establishing HPLC fingerprints, the contents of 3,4-dicaffeoylquinic acid (3,4-diCQA), 3,5-dicaffeoylquinic acid (3,5-diCQA), and 4,5-dicaffeoylquinic acid (4,5-diCQA) in AAL were quantified as 0.78–6.07 mg/g, 3.12–16.63 mg/g, and 1.94–5.51 mg/g, respectively (Guo et al., 2018). However, the levels of these three dicaffeoylquinic acids in ALL were respectively as low as 0.42 mg/g, 6.59 mg/g, and 1.65 mg/g, which can be used to discriminate between *A. argy* and *Artemisiae Lavandulaefoliae* (Guo et al., 2018). In addition, multiplex PCR was developed as a feasible method to distinguish *A. argyi* from other *Artemisia* species (Doh & Oh, 2012).

Actually, hydroxybenzoic acids and hydroxycinnamic acids belong to phenolic acids, which are a large group of phytochemicals in the plant tissues. Phenolic acids are generally produced from phenylalanine and tyrosine via the shikimic acid pathway (Herrmann, 1995). Phenolic acids, coupled with flavonoids, are involved in attracting insects for pollination, natural defences against harmful insects and microorganisms, and even controlling plant hormones (Khanam, Oba, Yanase, & Murakami, 2012). Of note, phenolic acids existed in the dietary plants, such as leafy vegetables and edible flowers, are presented as the significant antioxidant components (Kaisoon, Siriamornpun, Weerapreeyakul, & Meeso, 2011; Khanam et al., 2012). And in *A. argyi*, phenolic acids were conformed to play an important role in the free radical scavenging action (Han et al., 2017). However, because of the electron-withdrawing properties of the carboxylate group, benzoic acids has a negative effect on the H-donating capacity of the hydroxy benzoates (Rice-Evans, Miller, & Paganga, 1996). As such, hydroxylated cinnamates are more active than its benzoate counterparts.

As see from Table 4, most of the organic acids were finally detected by using ethyl acetate (EA) as the extraction solvent. For example, it was identified in EA fraction that there were 12 phenolic acids and 5 other organic acids (Han et al., 2017), as well as 3 fatty acids, including 13-oxo-9(*Z*),11(*E*)-octadecadienoic acid (0.44 mg/100 g), 13-oxo-9(*E*),11(*E*)-octadecadienoic acid (0.13 mg/100 g), and 9-oxo-10(*E*),12(*E*)-octadecadienoic acid (0.10 mg/100 g) (Yoshikawa et al., 1996). Besides in EA, caffeic acid and its derivatives were also obtained in *n*-butanol (*n*Bu) or water (W) (Han et al., 2017). However,

Table 2
Major essential oil components (> 1.00%) found in *A. argyi*.

Compound	Amount (%)[a]	Plant part	Extraction & Analysis	Reference
Alcohols				
Cyclohexanol	3.00	Leaf	HDE; GC–MS	Chen et al. (2017)
3-Hexen-1-ol	1.33	Flower	SPME and HDE; GC–MS	Li et al. (2008)
1-Octen-3-ol	1.02–1.28	Leaf	HDE; GC–MS	Chen et al. (2017)
Artemisia alcohol	31.48	Leaf	HDE; GC–MS	Pan et al. (1992)
	42.28	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
Yomogi alcohol	22.87	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
(−)-Borneol	4.34–12.77	Leaf	HDE; GC–MS	Chen et al. (2017)
	1.01	Aerial part	HDE followed by SGCCT; GC–MS	Zhang et al. (2014)
	1.05–1.38	Flower	SPME and HDE; GC–MS	Li et al. (2008)
	3.33–4.66	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
(−)-Terpinen-4-ol	1.30–4.00	Leaf	HDE; GC–MS	Chen et al. (2017)
	4.03	Aerial part	HDE followed by SGCCT; GC–MS	Zhang et al. (2014)
	3.81–5.48	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
α-Terpineol	1.05–2.10	Leaf	HDE; GC–MS	Chen et al. (2017)
	2.80	Aerial part	HDE followed by SGCCT; GC–MS	Zhang et al. (2014)
	2.69–4.70	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Sabinenehydrate	1.19–1.61	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
(−)-Menthol	1.19	Leaf		Huang et al. (2012)
Spathulenol	9.14–10.3	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Juniper camphor	8.34–8.74	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Longiborneol	2.67	Leaf		Huang et al. (2012)
Ethers				
Eucalyptol	9.00–33.42	Leaf	HDE; GC–MS	Chen et al. (2017)
	2.56–22.03	Aerial part	HDE followed by SGCCT, and then PTLC; GC–MS	Zhang et al. (2014)
	2.02–3.58	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Linalool	3.31	Leaf	HDE; GC–MS	Huang et al. (2012)
	1.39	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
Eugenol	1.03	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
	1.61–3.10	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Exo-2-hydroxycineole	1.53	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Caryophylleneoxide	1.23–1.59	Leaf	HDE; GC–MS	Pan et al. (1992)
	5.00–6.51	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Isoaromadendrene epoxide	1.90–2.00	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Aldehydes				
3-Hexenal	4.28	Flower	SPME and HDE; GC–MS	Li et al. (2008)
2-Hexenal	2.43	Flower	SPME and HDE; GC–MS	Li et al. (2008)
n-Caproaldehyde	1.99	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Ketones				
Menthone	4.18	Leaf	HDE; GC–MS	Huang et al. (2012)
(−)-α-Thujone	12.92–16.21	Leaf	HDE; GC–MS	Chen et al. (2017)
Camphor	1.53–24.97	Leaf	HDE; GC–MS	Chen et al. (2017)
	5.45	Aerial part	HDE followed by SGCCT, and then PTLC; GC–MS	Zhang et al. (2014)
	1.30–3.49	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
trans-Carveol	1.46	Leaf	HDE; GC–MS	Pan et al. (1992)
	2.09	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
(+)-β-Thujone	1.04–2.37	Leaf	HDE; GC–MS	Chen et al. (2017)
Artemisia ketone	1.20	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Corymbolone	1.06–1.07	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Monoterpenes				
Limonene	12.22–19.79	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Myrcene	9.35–16.44	Flower	SPME and HDE; GC–MS	Li et al. (2008)
β-Pinene	5.62	Leaf	HDE; GC–MS	Huang et al. (2012)
	14.53	Aerial part	HDE followed by SGCCT, and then PTLC; GC–MS	Zhang et al. (2014)
α-Pinene	4.06–9.09	Flower	SPME and HDE; GC–MS	Li et al. (2008)
α-Terpinolene	4.79	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
Carene	4.64	Leaf	HDE; GC–MS	Huang et al. (2012)
	1.05–1.38	Flower	SPME and HDE; GC–MS	Li et al. (2008)
α-Phellandrene	1.08–3.28	Flower	SPME and HDE; GC–MS	Li et al. (2008)
(+)-Dipentene	2.03	Leaf	HDE; GC–MS	Chen et al. (2017)
γ-Terpinene	1.39–1.44	Leaf	HDE; GC–MS	Chen et al. (2017)
Sabinene	1.12	Leaf	HDE; GC–MS	Pan et al. (1992)
	1.08	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Chamazulene	2.05	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Sesquiterpenes				
Caryophyllene	1.43–10.19	Leavf	HDE; GC–MS	Chen et al. (2017)
	6.77–9.24	Aerial part	HDE followed by SGCCT, and then PTLC; GC–MS	Zhang et al. (2014)
	2.34–2.76	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Germacrene D	5.32	Aerial part	HDE followed by SGCCT; GC–MS	Zhang et al. (2014)
	18.48–28.73	Flower	SPME and HDE; GC–MS	Li et al. (2008)
	1.48	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Farnesene	3.01	Aerial part	HDE followed by SGCCT; GC–MS	Zhang et al. (2014)

(*continued on next page*)

Table 2 (*continued*)

Compound	Amount (%)[a]	Plant part	Extraction & Analysis	Reference
α-Cubebene	1.53–2.85	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
β-Cubebene	1.29	Leaf	HDE; GC–MS	Huang et al. (2012)
	2.33	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
Humulene	1.40	Leaf	HDE; GC–MS	Huang et al. (2012)
α-Gurjunene	1.08	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Aromatic compounds				
o-Cymene	1.26–5.01	Leaf	HDE; GC–MS	Chen et al. (2017)
α-Curcumene	1.38	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Cuparene	1.10	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Esters				
Methyl propionate	3.47	Aerial part	HDE; GC–MS	Kim, Shin et al. (2015)
Bergamiol	3.91	Leaf	HDE; GC–MS	Huang et al. (2012)
Bornyl acetate	3.62	Leaf	HDE; GC–MS	Huang et al. (2012)
	1.24–1.92	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Methyl hinokiate	2.16	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Cedryl acetate	2.28	Leaf	HDE; GC–MS	Huang et al. (2012)
Ethyl palmitate	6.09	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Ethyl oleate	1.77	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Ethyl linoleate	1.61	Flower-head	SCFE and HDE; GC–MS	Guan et al. (2006)
Organic acids				
Hexadecanoic acid	3.52	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Oleic acid	1.07	Flower	SPME and HDE; GC–MS	Li et al. (2008)
Stearic acid	1.01	Flower	SPME and HDE; GC–MS	Li et al. (2008)

Abbreviations: HDE, hydro-distillation extraction; SPME, solid-phase microextraction; SGCCT, silica-gel column chromatography; SCFE, supercritical CO_2 fluid extraction; PTLC, preparative thin layer chromatography; GC–MS, gas chromatography-mass spectrometry.

[a] Amount of each content is represented as a relative area (% of the total peak area) from GC–MS analysis of corresponding EO sample.

neochlorogenic acids and chlorogenic acids were currently found only in 75% aqueous methanol (75% MeOH) fraction (Guo et al., 2018).

3.4. Other bioactive compounds

Besides flavonoids and organic acids, other representative constituents identified in the nonvolatile extraction of *A. argyi* were illustrated in Fig. 1. In contrast to the terpenoids in AAEO, nonvolatile terpenes in *A. argyi* were characterized by a higher molecular weight but a lower content, like sesquiterpenoid dimers and triterpenes. In an effort to search for novel bioactive polymeric terpenes, four sesquiterpenoid dimers were isolated from AAL with the help of LC-MS, Artemisian A, B, C, and D (Fig. 1), with a yield of 4 ppm, 3 ppm, 26 ppm, and 4 ppm, respectively (Xue et al., 2017). Artemisians A–D were two pairs of hetero sesquiterpenoid dimers linked in head-to-head (Artemisian A and C) and head-to-tail (Artemisian B and D) formation by units I/II and I/III, respectively (Fig. 1B). They were confirmed to show anti-proliferative activities against a panel of cancer cell lines (Xue et al., 2017). Indeed, dimeric guaianolides is one of the most common form of sesquiterpenoid dimers in *Artemisia* species. They have been endowed with diversified health-care functions, including anti-inflammation (Jin et al., 2004; Wen et al., 2010), anti-cancer (Lee et al., 2003, 1998, 2002), and anti-HIV-1 protease (Ma, Nakamura, Hattori, Zhu, & Komatsu, 2000). Arteminolides A-D (Fig. 1), four guaianolide dimers, were purified from the aerial parts of *A. argyi* via successive separation with silica gel flash column, C-18 column, Sephadex LH-20 column, and preparative HPLC (Lee et al., 2002). They were demonstrated as novel farnesyl protein transferase (FPTase) inhibitors, and may be promising chemotherapeutic agents against *ras*-mutated human cancers. 8-Acetylarteminolide and artanomaloide were two dimeric guaianolides lately identified in *A. argyi* (Shin, Ryu et al., 2017). With regard to isotanciloide and dehydromatricarin, both of them were detected as sesquiterpenes (Li et al., 2018; Shin, Ryu et al., 2017). In addition, another two sesquiterpenes, clovandiol and caryophyllene oxide, and two sesquiterpene ketones mocartenone and moxartenolide, were separated from AAL, together with five triterpenes, gult-5-en-3β-yl acetate, dammara-20,24-dien-3β-yl acetate, cycloartenyl acetate, cycloart-23-ene-3β,25-diol, and cycloart-23-ene-3β,25-diol monoacetate (Yoshikawa et al., 1996). Interestingly, it was found in AAL that there was an unusual sesquiterpene-monoterpene lactone, isoartemisolide (0.3 ppm) (Fig. 1), with outstanding neuroprotective and NO inhibitory effects (Wang et al., 2013; Zeng et al., 2014).

Polysaccharides are polymers of single sugar monomers linked by glycosidic bonds. A water-soluble polysaccharide (FAAP-02A) with a molecular weight of 5.17 kDa, was isolated and characterized in *A. argyi* (Bao, Yuan, Wang, Liu, & Lan, 2013). It is mainly composed of *N*-acetyl-D-glucosamine, glucose, mannose, galactose, rhamnose, arabinose, xylose and ribose. It has been demonstrated that FAAP-02 can not only arrest tumor growth *in vivo*, but also restore the immunity suppressed by the transplanted tumor, according to relevant research findings. Furthermore, total polysaccharides was recently extracted from *A. argyi* and its immunomodulatory confirmed (Zhang, Shi et al., 2018).

In addition, several coumarins were purified from AAL (Adams, Efferth, & Bauer, 2006). Among which, scopoletin and isoscopoletin (Fig. 1) were discovered to effectively postpone cancer progression. In the near future, more phytochemicals will be separated and identified from *A. argyi* to further benefit human health.

4. Biological activities

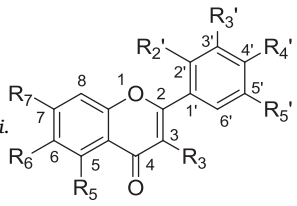
Both *in vitro* and *in vivo* studies have been performed to investigate the health promoting properties of *A. argyi*, including prevention of oxidative damage, cancer, inflammation, osteoporosis, and immunomodulatory and neuroprotective activities (Fig. 2). The main bioactive components of *A. argyi* and their underlying modes of actions were reviewed in detail in Table 5. However, the detailed mechanisms of how *A. argyi* phytochemicals benefit human health still lack enough attention. A summary of current findings is presented below.

4.1. Antioxidant activity

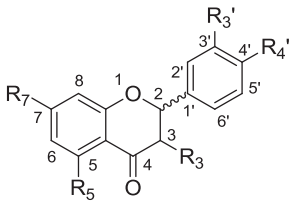
Phenolics are a family of compounds characterized by having at least one aromatic ring with one or more hydroxyl groups attached (Crozier, Jaganath, & Clifford, 2009), which are the most abundant secondary metabolites found in the plant kindom (Lorrain, Ky, Pechamat, & Teissedre, 2013). It was reported that the antioxidant

Table 3

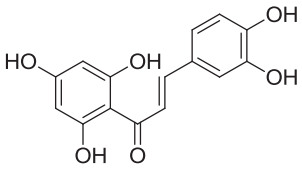
Major flavonoids identified in *A. argyi*.



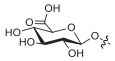
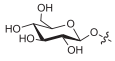
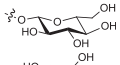
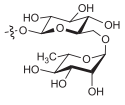
Flavone OR **Flavonol**



Flavanone OR **Flavononol**



Chalcone

Compound	Structure								Content (ppm)	Reference
	R_3	R_5	R_6	R_7	$R_{2'}$	$R_{3'}$	$R_{4'}$	$R_{5'}$		
Flavones										
Jaceosidin	H	OH	OCH_3	OH	H	OCH_3	OH	H	113–122	Nakasugi et al. (2000)
Eupatilin	H	OH	OCH_3	OH	H	OCH_3	OCH_3	H	26–226	Nakasugi et al. (2000)
Luteolin	H	OH	H	OH	H	OH	OH	H	NA[a]	Han et al. (2017)
Apigenin	H	OH	H	OH	H	H	OH	H	26	Li et al. (2018)
Nepetin	H	OH	OCH_3	OH	H	OH	OH	H	3	Yoshikawa et al. (1996)
5,7,4′-Trihydroxyflavone	H	OH	H	OH	H	H	OH	H	3	Lee et al. (2018)
Chrysoeriol	H	OH	H	OH	H	OCH_3	OH	H	0.5	Nakasugi et al. (2000)
Acacetin	H	OH	H	OH	H	H	OCH_3	H	0.7	Lee et al. (2018)
Hispidulin	H	OH	OCH_3	OH	H	H	OH	H	4	Han et al. (2017)
Eupafolin	H	OH	OCH_3	OH	H	OH	OH	H	12	Lee et al. (2018)
3′-Methoxy-apigenin	H	OH	H	OH	H	OCH_3	OH	H	1	Lee et al. (2018)
Ladanein	H	OH	OH	OCH_3	H	H	OCH_3	H	4	Seo et al. (2003)
3′,4′-Dimethoxyluteolin	H	OH	H	OH	H	OCH_3	OCH_3	H	1	Lee et al. (2018)
5,6,4′-Trihydroxy-7,3′-dimethoxyflavone	H	OH	H	OCH_3	H	OCH_3	OH	H	18	Seo et al. (2003)
5,7,4′,5′-Tetrahydroxy-6,3′-dimethoxyflavone	H	OH	OCH_3	OH	H	OCH_3	OH	OH	NA	Han et al. (2017)
5,7,3′,5′-Tetrahydroxy-6,4′-dimethoxyflavone	H	OH	OCH_3	OH	H	OH	OCH_3	OH	NA	Han et al. (2017)
5,6,2′,4′-Tetrahydroxy-7,5′-dimethoxyflavone	H	OH	OH	OCH_3	OH	H	OH	OCH_3	0.4	Lv et al. (2018)
Centaureidin	OCH_3	OH	OCH_3	OH	H	OH	OCH_3	H	NA	Shin, Ryu et al. (2017)
3,6,3′-Trimethoxy-5,7,4′-trihydroxyflavone	OCH_3	OH	OCH_3	OH	H	OCH_3	OH	H	4	Lee et al. (2018)
5,6-Dihydroxy-7,3′,4′-trimethoxyflavone	H	OH	OH	OCH_3	H	OCH_3	OCH_3	H	38	Seo et al. (2003)
5,7,3′-Trihydroxy-6,4′,5′-trimethoxyflavone	H	OH	OCH_3	OH	H	OH	OCH_3	OCH_3	6	Seo et al. (2003)
Casticin	OCH_3	OH	OCH_3	OCH_3	H	OH	OCH_3	H	NA	Shin, Ryu et al. (2017)
Bonanzin	OCH_3	OH	OCH_3	OH	H	OCH_3	OCH_3	H	0.8	Lee et al. (2018)
Chrysosplenetin	OCH_3	OH	OCH_3	OH	H	OCH_3	OCH_3	H	3	Lee et al. (2018)
3′-*O*-Methyl-eupatorin	H	OH	OCH_3	OCH_3	H	OCH_3	OCH_3	H	1	Lee et al. (2018)
5-Hydroxy-6,7,3′,4′-tetramethoxyflavone	H,	OH	OCH_3	OCH_3	H	OCH_3	OCH_3	H	2	Seo et al. (2003)
Artemetin	OCH_3	OH	OCH_3	OCH_3	H	OCH_3	OCH_3	H	2	Lee et al. (2018)
Luteolin-7-glucuronic acid	H	OH	H		H	OH	OH	H	NA	Han et al. (2017)
Eupatilin 7-*O*-*β*-D-glucopyranoside	H	OH	OCH_3		H	OCH_3	OCH_3	H	1	Lv et al. (2018)
Flavonols										
Quercetin	OH	OH	H	OH	H	OH	OH	H	1	Li et al. (2018)
Kaempferol	OH	OH	H	OH	H	H	OH	H	21	Li et al. (2018)
3,5,7,4′-Tetrahydroxyflavone	OH	OH	H	OH	H	H	OH	H	1	Lee et al. (2018)
Isorhamnetin	OH	OH	H	OH	H	OCH_3	OH	H	NA	Shin, Ryu et al. (2017)
Methyl quercetin									NA	Han et al. (2017)
Eupatolitin	OH	OH	OCH_3	OCH_3	H	H	OH	OH	NA	Han et al. (2017)
Apicin	OH	OH	OCH_3	OCH_3	H	OH	H	OCH_3	1	Lee et al. (2018)
Isoquercetin		OH	H	OH	H	OH	OH	H	NA	Han et al. (2017)
Rutin		OH	H	OH	H	H	OH	OH	NA	Han et al. (2017)
Flavanones										
Naringenin	H	OH	–	OH	–	H	OH	–	7	Li et al. (2018)
Homoeriodictyol	H	OH	–	OH	–	OCH_3	OH	–	3	Lee et al. (2018)
5,7,3′,4′-Tetrahydroxyflavone	H	OH	–	OH	–	OH	OH	–	10	Lee et al. (2018)
Flavononol										
2,3-Dihydroisorhamnetin	OH	OH	–	OH	–	OCH_3	OH	–	2	Lee et al. (2018)
Chalcone										
Eriodictyol chalcone	–	–	–	–	–	–	–	–	NA	Han et al. (2017)

[a] NA, not available.

Table 4
Major organic acids characterized in *A. argyi*.

Compound	Content	Extraction Solvents	Extraction & Analysis	Reference
Hydroxybenzoic acids				
Protocatechuic acid	NA[a]	EA[b], *n*Bu[c]	SE; UPLC-MS	Han et al. (2017)
Salicylic alcohol-dihexoside	NA	EA, *n*Bu	SE; UPLC-MS	Han et al. (2017)
Hydroxycinnamic acids				
Neochlorogenic acids	0.43–2.59 mg/g	75% MeOH[d]	SE; UPLC	Guo et al. (2018)
Chlorogenic acids	0.78–10.88 mg/g	75% MeOH	SE; UPLC	Guo et al. (2018)
trans-o-Coumaric acid	2.09 mg/100 g	EA	SE follwed by thrice SGCCT; TLC, IR, ^{1}H NMR, ^{13}C NMR	Yoshikawa et al. (1996)
4-Caffeoylquinic acid	NA	EA, *n*Bu, W[e]	SE; UPLC-MS	Han et al. (2017)
5-Caffeoylquinic acid	NA	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
Caffeic acid	NA	EA, *n*Bu	SE; UPLC-MS	Han et al. (2017)
5-Feruoyl quinic acid	NA	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
1,3-Dicaffeoylquinic acid	NA	MeOH[f]	SE; UPLC-MS	Shin, Ryu et al. (2017)
1,4-Dicaffeoylquinic acid	NA	MeOH	SE; UPLC-MS	Shin, Ryu et al. (2017)
3,4-Dicaffeoylquinic acid	0.78–6.07 mg/g	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
3,5-Dicaffeoylquinic acid	3.12–16.63 mg/g	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
4,5-Dicaffeoylquinic acid	1.94–5.51 mg/g	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
3-Caffeoyl-5-feruoyl-quinic acid	NA	EA, *n*Bu	SE; UPLC-MS	Han et al. (2017)
3,4,5-Tricaffeoylquinic acid	NA	EA, *n*Bu	SE; UPLC-MS	Han et al. (2017)
Other organic acids				
Quinic acid	NA	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
Hydroxyjasmonic acid-*O*-sulphate	NA	EA, *n*Bu	SE; UPLC-MS	Han et al. (2017)
Hydroxyjasmonic acid hexose	NA	EA, *n*Bu, W	SE; UPLC-MS	Han et al. (2017)
Azelaic acid	NA	EA	SE; UPLC-MS	Han et al. (2017)
13-Oxo-9(*Z*),11(*E*)-octadecadienoic acid	0.44 mg/100 g	EA	SE follwed by twice SGCCT, and then HPLC; EI-MS, UV, IR, ^{1}H NMR, ^{13}C NMR	Yoshikawa et al. (1996)
13-Oxo-9(*E*),11(*E*)-octadecadienoic acid	0.13 mg/100 g	EA	SE follwed by twice SGCCT, and then HPLC; EI-MS, UV, IR, ^{1}H NMR, ^{13}C NMR	Yoshikawa et al. (1996)
9-Oxo-10(*E*),12(*E*)-octadecadienoic acid	0.10 mg/100 g	EA	SE follwed by twice SGCCT, and then HPLC; EI-MS, UV, IR, ^{1}H NMR, ^{13}C NMR	Yoshikawa et al. (1996)
9,12,13-Trihydroxy octadecadienoic acid	NA	EA	SE; UPLC-MS	Han et al. (2017)
9,12,13-Trihydroxy octadecenoic acid	NA	EA	SE; UPLC-MS	Han et al. (2017)

Abbreviations: SE, solvent extraction; UPLC, ultra-performance liquid chromatography; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry; SGCCT, silica-gel column chromatography; TLC, thin layer chromatography; IR, infrared absorption spectroscopy; UV, ultraviolet spectrophotometry; ^{1}H NMR, proton nuclear magnetic resonance spectrum; ^{13}C NMR, carbon-13 nuclear magnetic resonance spectroscopy.

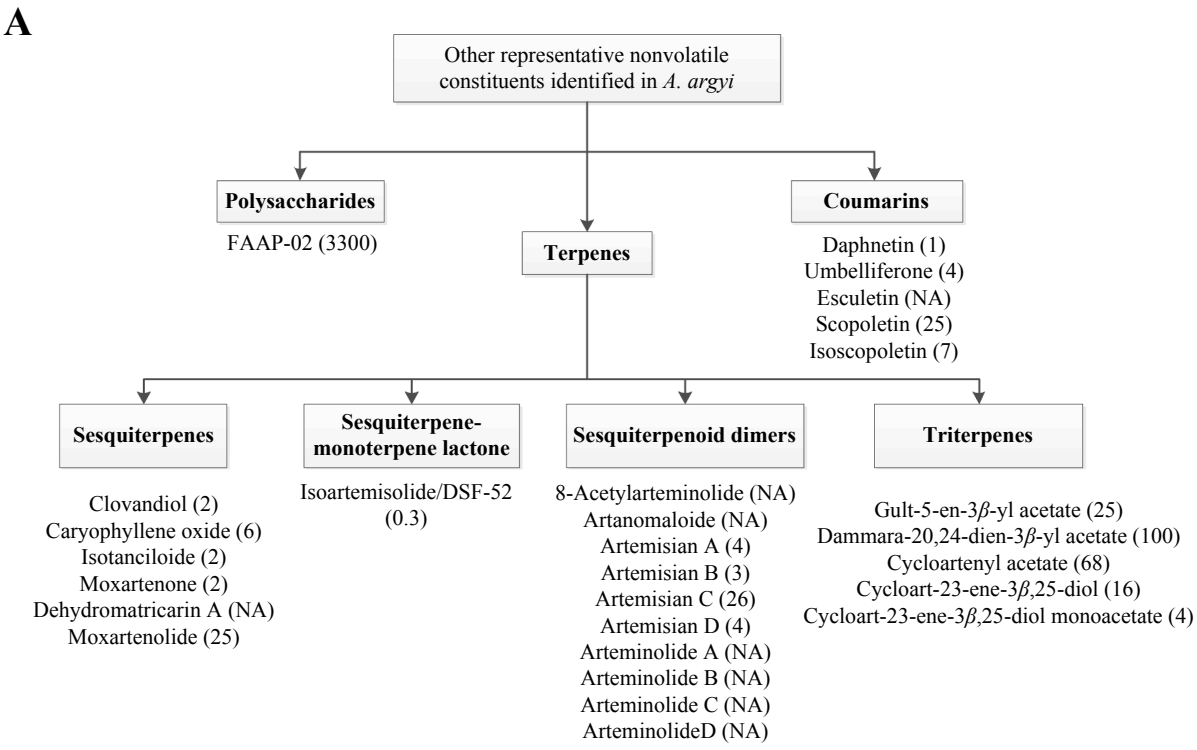
[a] NA, not available. Compounds were respectively detected.
[b] EA (ethyl acetate) fraction.
[c] *n*Bu (*n*-butanol) fraction.
[d] 75% MeOH (75% aqueous methanol) fraction.
[e] W (water) fraction.
[f] MeOH (methanol) fraction.

protection of apple, similar to that of many other dietary plants, may be due largely to the presence of phenolics, rather than vitamin C, vitamin E, or β-carotene (Eberhardt, Lee, & Liu, 2000; Tsao, Yang, Young, & Zhu, 2003).

Actually, free radicals in the biological system are highly reactive and have the capacity to attack membrane lipids, producing carbon radicals, which in turn react with oxygen to give peroxy radicals. These may further attack adjacent fatty acids to release new carbon radicals (Verma & Pratap, 2010). Thus, a single radical may damage many molecules and lead to a lipid peroxidation chain reaction. Phenolic compounds generally contain hydrophobic (non-polar) as well as hydrophilic (polar) fragments, and can establish intense interactions with membrane bilayers (Oteiza, Erlejman, Verstraeten, Keen, & Fraga, 2005). On one hand, the non-polar fragment of the molecule embeds into the hydrophobic interior of the lipid bilayers, and affords chain-breaking antioxidant activity. On the other hand, the hydrophilic fragment of phenolics can form hydrogen bonds with the polar head groups of the lipids, reducing access by deleterious molecules, and thus protect membranes from lipid peroxidation. Furthermore, these interactions further induce the changes in physical characteristic of membranes, and results in a reduction of the rate of oxidation of membrane lipids and proteins (Verma & Pratap, 2010). In addition, phenolics can effectively scavenge reactive oxygen species (ROS) via multiple channels, including H-atom transfer, electron transfer, metal-ions chelation and detoxifying enzymes activation (Brown, Khodr, Hider, & Rice-Evans, 1998; Meng, Xin, Li, & Cai, 2007; Nijveldt et al., 2001; Riceevans, Miller, & Paganga, 1997).

To investigate the correlation between the phytochemicals in *A. argyi* and their antioxidant capacity, five fractions with different content of phenolics were prepared from *A. argyi* by successively extracting with 70% methanol, water, *n*-hexane, ethyl acetate, and *n*-butanol, to yield corresponding extracts, namely, crude extract (CE), water fraction (WF), *n*-hexane fraction (*n*HexF), ethyl acetate fraction (EAF), and *n*-butanol fraction (*n*BuF) (Han et al., 2017). Their antioxidant abilities were determined through DPPH, ABTS, and O_2^- free radicals scavenging assays and ferric-reducing antioxidant power (FRAP) assay. Among the five fractions, EAF possessed the highest total phenolics content (TPC, 225.04 mg/g fraction gallic acid) and total flavonoids content (TFC, 487.40 mg/g fraction rutin), showing the strongest antioxidant activity *in vitro*. Both TPC and TFC were in a decreased order in sequence of *n*BuF, CE, WF, and *n*HexF. The antioxidant capacity of these five fractions followed the same trend with TPC and TFC, as EAF > *n*BuF > CE > WF > *n*HexF. Thus, a significant positive correlation was established between the antioxidant capacity of *A. argyi* and its TPC and TFC. The proposition was further corroborated by a study of comparing the antioxidant potential of two *Artemisia* species with different total phenolic contents (Kim, Shin et al., 2015).

Eupatilin (Table 3) is a specific polymethoxyflavones (PMFs) found in *Artemisia* species. Its protective effects against H_2O_2-induced oxidative injury was estimated in feline esophageal epithelial cells (EECs)



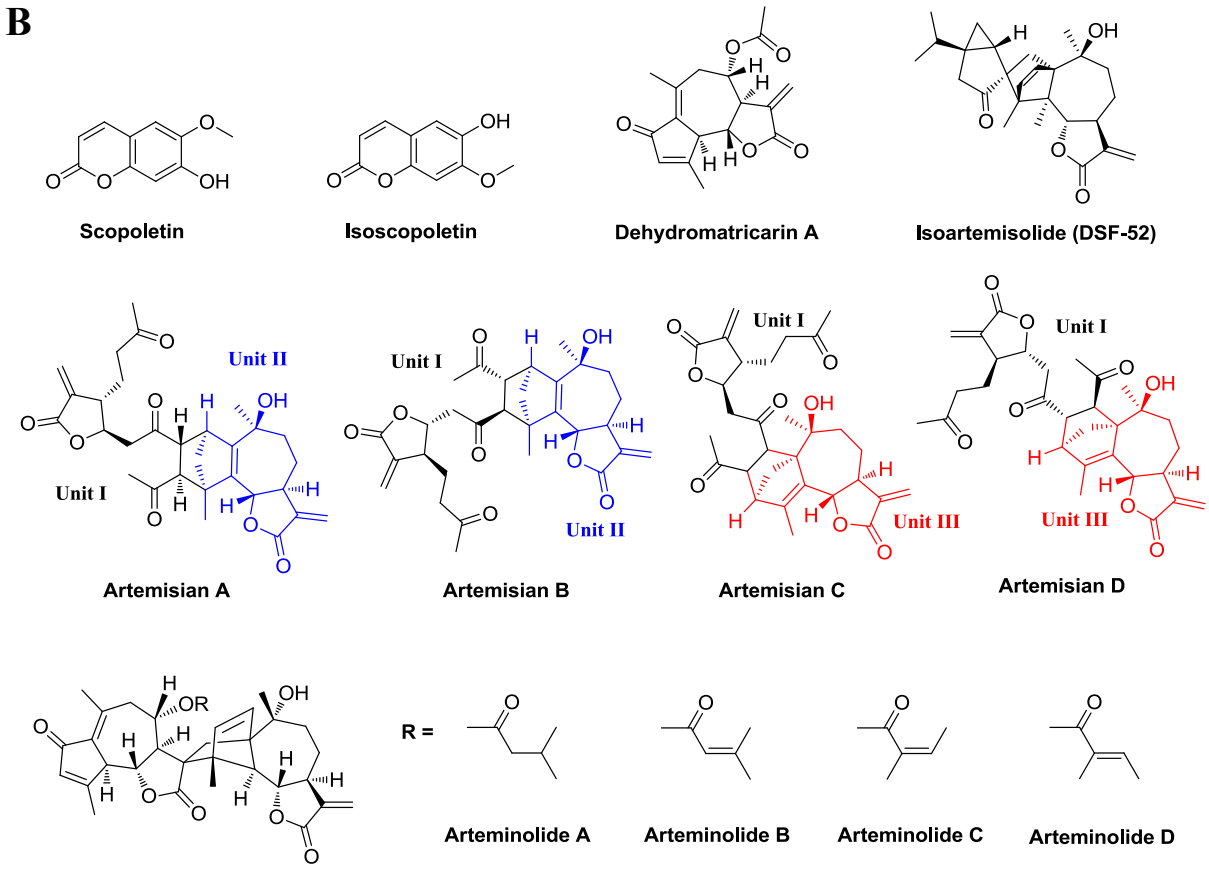


Fig. 1. Other representative compounds isolated in the nonvolatile extraction of *A. argyi* except for flavonoids and organic acids. (A) Overlay of the classification of the main nonvolatile comonents. Parentheses mark a yield (ppm) of the corresponding compound. 'NA' indicates the yield value was not available. (B) Chemical structures of ten terpenes, dehydromatricarin A, isoartemisolide/DSF-52, Artemisian A, B, C, and D, and Arteminolide A, B, C, and D, and two coumarins, scopoletin and isoscopoletin.

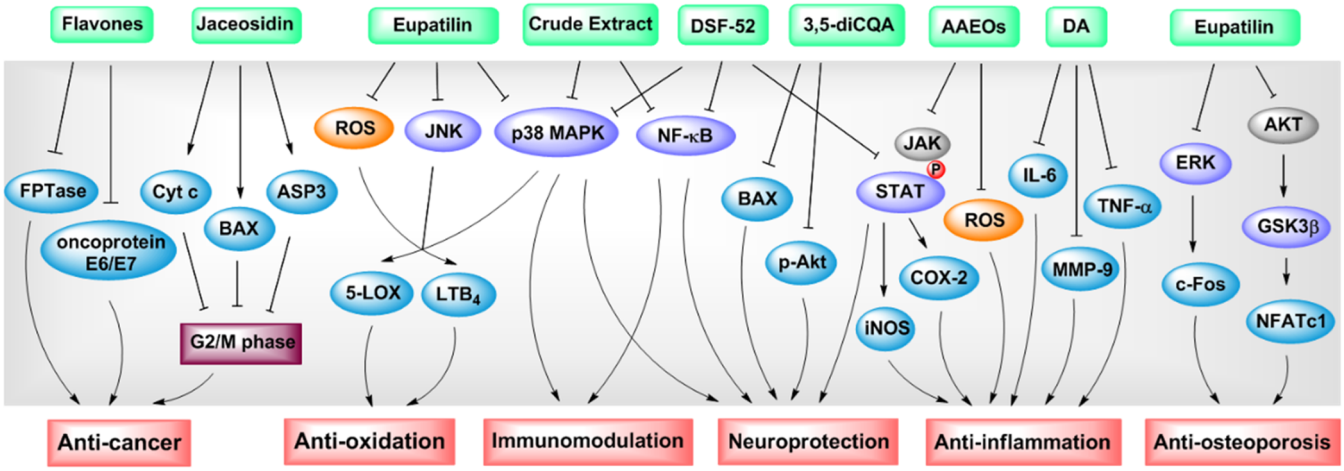


Fig. 2. Schematic representation of the main molecular mechanisms of *A. argyi* phytochemicals on human health.

(Lim, Park, Nam, Nguyen, & Sohn, 2012). Results indicated eupatilin worked in a dose-dependent manner, and can rescue EECs viability from 40% to 65% at a concentration of 150 μM. The mechanism may involve down-regulation of 5-lipoxygenase (5-LOX) expression and suppression of leukotriene B_4 (LTB_4) production by inactivating p38 MAPK and JNK signaling pathways. For instance, the high levels of 5-LOX, LTB_4, and p38 MAPK phosphorylation triggered by H_2O_2 were respectively reduced 10%, 50%, 21% when pretreating EECs with 150 μM eupatillin for 12 h. In addition, the expression of p-JNK in EECs under H_2O_2 was diminished as well after eupitalin preadaption.

The antioxidant effect of AAEO was evaluated by determining its radicals scavenging potential, reducing power, and metal-ion chelating ability (Huang et al., 2012). AAEO exhibited antioxidant potential *in vitro*, especially prominent metal-ion chelating activity. At a concentration of 0.1 mg/mL, AAEO chelated 95.63% of Fe^{2+}, which was comparable to the typical chelator EDTA. Moreover, AAEO performed well in inhibiting melanin synthesis in B16F10 melanoma cells (Huang et al., 2012). These results suggested AAEO could be applied into skin care products as a natural antioxidant.

4.2. Anti-cancer activity

Numerous researchers focused on the antagonistic effects of *A. argyi* phytochemicals against the onset and exacerbation of cancer. In a side by side study, *A. argyi* was found to exhibit almost the strongest *in vitro* anti-proliferative effect among 12 different Chinese medicinal herbs. And, more remarkably, the suppression of the aqueous extract of *A. argyi* on cancer cells was 2–7 folds stronger than on normal human epithelial cells huMEC, hinting that *A. argyi* may selectively destroy cancer cells (Shoemaker, Hamilton, Dairkee, Cohen, & Campbell, 2005).

Jaceosidin (Table 3) is an abundant flavone in *A. argyi*. It was reported that jaceosidin selectively inhibited the growth of immortalized cell lines containing human papillomavirus 16 (HPV16), like SiHa and CaSki, in a dose-dependent manner. The anti-cancer property may be connected with the inhibitory effects on interactions between oncoproteins (E6, E7) and tumor suppressor proteins (p53, pRb), which resulted in the recovery of the functions of tumor suppressors. However, little or no inhibition was observed in the HPV negative HaCaT and HPV18 positive HeLa cells. These findings suggested jaceosidin may be a potential candidate for the treatment of HPV16-associated diseases, such as cervical cancer and anal cancer (Lee et al., 2005). In another research, the viability of U87 glioblastoma cell was observed to dramatically drop to 42.4% and 56.7%, respectively, after a treatment with 100 μM jaceosidin for 24 h and 48 h. The growth inhibitory result was suggeted to attribute to cell cycle arrest and apoptosis induction. Furthermore, the apoptosis-promoting property may be related to G2/M phase arrest, production of ROS, upregulation of p53 and Bax, diminishment of mitochondrial membrane potential, release of cytochrome *c*, and activation of caspase 3. Thus, jaceosidin may exert the apoptosis inducing effect in U87 cells via mitochondrial-caspase-3-dependent pathway (Khan et al., 2012). Together with jaceosidin, three other flavones eupatilin, apigenin, and chrysoeriol were purified and assessed their anti-mutant activities (Nakasugi et al., 2000). Results suggested that the anti-mutation function of the four flavones may be achieved by suppressing the mutagenicity of 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2) in a direct way, or by inhibiting its metabolic activation.

Coumarins are a representative components in *A. argyi*. In a research to screen out the natural anti-proliferative components, two coumarin structures scopoletin and isoscopoletin (Fig. 1) were isolated from AAL based on an activity-guided strategy (Adams et al., 2006). Both scopoletin and isoscopoletin exhibited outstanding repressive effects on human CCRF-CEM leukaemia cells, with an IC_{50} value of 2.6 μM and 4.0 μM, respectively. Of note, multidrug resistant subline CEM/ADR5000 was not observed to display cross-resistance to these two small molecules since both IC_{50} values were all 1.6 μM. For comparison, degrees of resistance to the widely used cytostatic drugs paclitaxel, vincristine, and doxorubicin were estimated to be 200-, 613-, and 1036-fold, respectively (Adams et al., 2006). Thus, although scopoletin and isoscopoletin are simple coumarins, they might be potential candidates as the lead compounds for the development of anti-cancer drugs.

By employing Sarcoma 180 (S180) tumor-bearing mice as a model, Bao et al. evaluated the antitumor activity of FAAP-02, a polysaccharide purified from *A. argyi* (Bao et al., 2013). Results revealed that FAAP-02 inhibited transplanted tumor growth in a dose-dependent manner, and endowed a longer survival time to the tumor-bearing mice than the positive control 5-FU, a typical chemotherapeutic drug. Immunostimulation was subsequently proposed to explain the anti-carcinogenic action of FAAP-02, as FAAP-02 significantly increased the levels of IL-2, IL-6, IL-12, and TNF-α, and the expression of splenic CD4 + and CD8 + T lymphocytes.

FPTase plays a critical role in the post-translation modification of Ras proteins, an expression product of oncogene c-Ras. When the farnesylation of Ras proteins is blocked, their oncogenic activity is abolished. Thus, developing PFTase inhibitors has become an attractive area for cancer treatment (Adjei et al., 2000). In this regard, six flavones were isolated as PFTase inhibitors from the aerial parts of *A. argyi*, and their 50% inhibitory concentrations were determined as 25–200 μg/mL (Seo et al., 2003). The following cytotoxicity assay disclosed that 5,6-dihydroxy-7,3′,4′-trimethoxyflavone and 5,6,4′-trihydroxy-7,3′-dimethoxyflavone (Table 3) effectively inhibited the proliferation of a

Table 5
The main bioactive components of *A. argyi* and their underlying modes of actions.

Bioactive Component	Bioactivities	Experimental Model	Resulting Effect	Comments	Refence
Flavonoids					
Eupitalin	Antioxidant	H_2O_2-induced oxidant damage in feline esophageal epithelial cells	↑cell viability; ↓5-LOX expression; ↓LTB_4 production; ↓p38 MAPK and JNK activation (*In vitro*)	dose-independent (25–150 μM); no cytotoxicity until 200 μM	Lim et al. (2012)
	Anti-osteoporosis	human bone marrow cells (BMCs), mouse BMCs; lipopolysaccharide-induced osteoporosis mice, ovariectomy-induced osteoporosis mice	↓NFATc1 transcription; ↓polymerization actin ring formation; ↓human osteoclasts differentiation; ↑mature osteoclasts fibrosis (*In vitro*) ↓ bone resorption caused by ovariectomy or inflammation (*In vivo*)	BMCs were treated with 50 μM eupitalin for 1 h. Mice were orally administrated with 10 mg/kg eupatilin for 4 weeks	Kim, Lee et al. (2015)
	Antimutagen	*S. typhimurium* TA98 strain, *S. typhimurium* TA100 strain	↓mutagenicity triggered by Trp-P-2, Trp-P-1, IQ, MeIQ, MeIQx, $MeA_{\alpha}C$, AFB_1 and 2-AA in *S. typhimurium* TA98, and by AFB_1 and 2-AA in *S. typhimurium* TA100 (*In vivo*)	With a dose of 100 μM, the inhibition on mutation caused by Trp-P-2 was 74.8% in *S. typhimurium* TA98	Nakasugi et al. (2000)
	PPARα agonist	CV-1 cells	↑PPARα activation (EC_{50} = 41.9 μM); →transcriptional activations of PPARγ, PPARδ and RXRα (*In vitro*)	selective and dose-dependent	Choi et al. (2015)
Jaceosidin	Anti-cancer	recombinant proteins E6, E7, and pRb; HPV (+) (SiHa and CaSki) and HPV (-) (C33A) cell lines	↓binding between HPV E6 and p53; ↓binding between HPV E7 and pRb; ↓HPV16 (+) cells growth;→growth of HPV (−) and HPV18 (+) cells (*In vitro*)	specific and dose-dependent	Lee et al. (2005)
	Anti-cancer	U87 glioblastoma cell line	↓cell viability; ↑cell cycle arrest at G2/M phase; ↑apoptosis; ↑ROS production; ↓mitochondrial membrane potential; ↑apoptosis regulatory proteins expression (p53, Bax, cytochrome *c*, and caspase 3) (*In vitro*)	time- and dose-dependent	Khan et al. (2012)
	Antimutagen	*S. typhimurium* TA98 strain, *S. typhimurium* TA100 strain	↓mutagenicity triggered by Trp-P-2, Trp-P-1, IQ, MeIQ, MeIQx, $MeA_{\alpha}C$, AFB_1 and 2-AA in *S. typhimurium* TA98, and by AFB_1 and 2-AA in *S. typhimurium* TA100 (*In vitro*)	With a dose of 100 μM, the inhibition on mutation caused by Trp-P-2 was 83.1% in *S. typhimurium* TA98	Nakasugi et al. (2000)
5,6-dihydroxy-7,3′,4′-trimethoxyflavone (a) 5,6,4′-trihydroxy-7,3′-dimethoxyflavone (b)	Anti-tumor	Tumor cell lines SW620 (colon), A549 (lung), PC-3 (prostate), LOX-IMVI (melanoma), HCT15 (colon); SW620 tumor-bearing nude mice	↓FPTase activity, IC_{50} = 25 μg/mL (a), 63 μg/mL (b); ↓cell growth, GI_{50} = 4.9–19.3 μM (a), 2.6–11 μM (b); (*In vitro*) ↓ tumor volumn by 44.6% (a) and 14.6% (b); ↓tumor weight (a); →body weight (*In vivo*)	dose-dependent for FPTase inhibition; Mice were intraperitoneally infused with 60 mg/kg per day for 22 days	Seo et al. (2003)
7-*O*-β-D-glucopyranoside (c) 5,6,2′,4′-tetrahydroxy-7,5′-dimethoxyflavone (d)	Anticoagulant	white rabbits plasma	↑thrombin time (c); ↑prothrombin time (d) (*In vitro*)	dose–effect relationship, 20–50 mM (c); effective concentration, 40–50 mM (d)	Lv et al. (2018)
Dimeric sesquiterpenoids					
Artemisian A-D	Anti-proliferation	human breast (MDA-MB-468, MDA-MB-231, MCF-7) and colon (HCT-116) cancer cell lines	↓proliferation, IC_{50} = 3.21–24.55 μM; ↑cell cycle arrest at G2/M phase (Artemisian B) (*In vitro*)	dose-dependent (Artemisian B)	Xue et al. (2017)
Arteminolide A-D	Anti-cancer	FPTase enzyme; H-*ras*-transformed NIH3T3 cells	↓FPTase activity, IC_{50} = 0.76–1.1 μM (*Enzyme assay*)↓ cell growth, GI_{50} = 1.5 mM (Arteminolide C); ↓H-*ras* processing (*In vitro*)		Lee et al. (2002)
Isoartemisolide/DSF-52	Neuroprotection	LPS-activated BV-2 microglia cells	↓NO production, IC_{50} = 4.00 μM; ↓inflammatory mediators expression; ↓ROS production; ↓NF-κB, JNK/p38 MAPKs, and JAK2/STAT3 signaling pathways; →ERK phosphorylation (*In vitro*)	dose-dependent (2.5–10 μM)	Zeng et al. (2014) and Wang et al. (2013)
Organic acids					
3,5-dicaffeoylquinic acid	Neuroprotection	trimethyltin-induced cognition-deficient mice	↓neuronal apoptosis; ↑ACh level; ↓AChE activity; ↓apoptotic signaling molecules (p-Akt, BAX, and p-tau) (*In vivo*)	orally fed 5, 10 mg/kg of body weight once a day for 3 weeks	Kang et al. (2016)
Coumarins					
Scopoletin (e) Isoscopoletin (f)	Anti-proliferation	human CCFR-CEM leukaemia cell line, multidrug-resistant CEM/ADR5000 cell	↓CCFR-CEM cell proliferation, IC_{50} = 2.6 μM (e), 4.0 μM (f); ↓CEM/ADR5000 cell proliferation, IC_{50} = 1.6 μM (e), 1.6 μM (f) (*In vitro*)	CEM/ADR5000 cells exhibited no cross-resistance to (e) or (f) in contrast to positive controls paclitaxel, vincristine, and doxorubicin	Adams et al. (2006)
AAEO					

(*continued on next page*)

Table 5 (*continued*)

Bioactive Component	Bioactivities	Experimental Model	Resulting Effect	Comments	Refence
	Antioxidant		Scavenging DPPH and ABTS by 92.79% and 91.41% at a dose of 0.450 mg/mL; reducing Fe^{3+} by 21.26% and chelating metal-ion by 95.63% at dose of 0.1 mg/mL (*Chemical assay*)	dose-dependent	Huang et al. (2012)
	Anti-inflammation	LPS-induced RAW264.7 mouse macrophages; TPA-induced ear edema mice	↓proinflammatory mediators and ROS; ↓cytokines production; ↓JAK/STATs activation (*In vitro*) ↓ ear skin thickness; ↓mouse ear edema (*In vivo*)	dose-dependent, (10–270 μg/mL for cells, 83–750 mg/kg for mice)	Chen et al. (2017)
	Anti-inflammation	dimethyl benzene-induced ear swelling mice, carrageenan-induced paw oedema mice	↓ear swelling; ↓paw oedema (*In vivo*)	showing better absorption bioavailability and pharmacological effects via skin administration than oral gavage	Ge et al. (2016)
	Anticoagulant	Ice water bath induced acute blood stasis mice	↓blood viscosity of low, medium and high shear rates (*In vivo*)	skin administration dosage, 0.125–0.50 mL/kg	Ge et al. (2016)
	Antimicrobial	*Candida albicans* SC5314	↑intracellular ROS; ↓mitochondrial membrane potential; ↑ apoptosis ratio	MIC 0.5 mL/L, dose-dependent	Shi et al. (2017)
		Staphylococcus aureus strain, *Escherichia coli* strain	bacterial inhibition rate over 98% and 80% kept for 0 and 60 days; ↓bioactivity with increasing storage time (*In vitro*)	showing better solubility, stability and bioactivity after being loaded as microcapsules	Hu et al. (2013)

Abbreviations: ↑, increase compared to control;↓, decrease or inhibition compared to control; →, no change compared to control; 5-LOX, 5-lipoxygenase; LTB_4, leukotriene B_4; NFATc1, nuclear factor of activated T cells c1; Trp-P-2, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole; Trp-P-1, 3-amino-1,4-dimethyl-5*H*-pyrido-[4, 3-*b*]indole; IQ, 2-amino-3-methylimidazo[4,5-*f*]quinolone; MeIQ, 2-amino-3,4-dimethylimidazo-[4,5-*f*]quinolone; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; $MeA_\alpha C$ and 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole; AFB_1, aflatoxin B_1; 2-AA, 2-aminoanthracene; PPAR, peroxisome proliferators-activated receptor; RXR, retinoid X receptor; HPV, human papillomavirus; ROS, reactive oxygen species; ACh, acetylcholines; AChE, acetylcholinesterase; EC_{50}, median effect concentration; IC_{50}, inhibitory concentration for 50% of the samples; GI_{50}, growth inhibition concentration for 50% of the samples; MIC, minimum inhibitory concentration.

panel of human tumor cell lines comprising colon SW620 and HCT15, lung A549, prostate PC-3, and melanoma LOX-IMVI, with GI_{50} values ranging from 2.6 μM to 19.3 μM. Further diet feeding study with nude mice demonstrated that continuously consuming these two flavones at a dose of 60 mg/kg for 22 days, the tumor volume could be reduced by 44.6% and 14.6%, respectively. Almost simultaneously, three dimeric guaianolides (Arteminolides A-D, Fig. 1) were identified in AAL as new FPTase inhibitors, with IC_{50} values of 0.76–1.1 μM (Lee et al., 2002). In H-*ras*-transformed NIH3T3 cells, Arteminolide C was found to significantly inhibit the H-*ras* processing and cell growth with an IC_{50} of 1.5 μM (Lee et al., 2002). Interestingly, these FPTase inhibitors more strongly suppressed the growth of transformed cells than normal cells. Arteminolides were thus suggested as promising FPTase inhibitors and could be used to treat *ras*-mutated human cancers or other relevant cancers. Recently, four dimeric sesquiterpenoids (Artemisians A-D, Fig. 1) were purified and confirmed the anti-carcinogenic effect *in vitro* (Xue et al., 2017). Among of which, Artemisian B dose-dependently increased the apoptosis rate in MDA-MB-468 cell line and exhibited better activity than the positive control oxaliplatin at a dose of 5 μM. Cell cycle arrest was considered as an important way for Artemisian B to suppress the tumor cell proliferation. However, FPTase inhibition was not mentioned in the study to explain the anti-proliferation mechanism.

4.3. Immunomodulation and anti-inflammation activity

Multiple phytochemicals in *A. argyi* have been demonstrated to act as general immune system stimulators to enhance host defense responses through regulating the secretion of cytokines and antibodies, as well as enhancing the function of natural killer cells, T and B lymphocytes and so on. For instance, a recent study disclosed the total polysaccharides extracted from *A. argyi* increased the levels of immunoglobulins (IgM and IgG), cytokines (IL-1β, IL-6 and TNF-α), as well as nitric oxide *in vitro*, suggesting the immunomodulation property of *A. argyi* polysaccharides (Zhang, Shi et al., 2018). Besides polysaccharides, the crude extract of AAL was found as well to exhibit the adjusting effects on the immune system of a mice model with atopic dermatitis-like lesions (Han et al., 2016). As reported, the AAL extract ameliorated the symptoms of atopic dermatitis by suppressing Lyn, Syk, MAPKs, PI3K/Akt and IκBα/NF-κB pathways, but not TLR4/NF-κB pathway. Furthermore, a dietary supplementation with broiler chickens demonstrated that consumption of 1000 mg/kg of *A. argyi* aqueous extract per day was sufficient to relieve the immune stress imposed by lipopolysaccharide (Zhang et al., 2017).

The release of various immune mediators and the activation of macrophages are regulated by proinflammatory cytokines, such as TNF-α and IFN-γ, through oxidation of L-arginine by related NADP-dependent enzyme (Kovalovsky, Refojo, Holsboer, & Arzt, 2000; Oswald & James, 1996). Anti-inflammatory activity was observed in medicinal plant *Alchornea glandulosa* as a result of an inhibition of the production of immune mediators like H_2O_2 and NO, as well as TNF-α (Lopes, Calvo, Vilegas, & Carlos, 2005). With regard to *A. argyi*, a new study showed that AAEO dose-dependently down-regulated the gene expression of inflammatory mediator iNOS and COX-2 and suppressed the release of cytokines IFN-β, IL-6, TNF-α and MCP-1 in LPS-induced RAW264.7 macrophages (Chen et al., 2017). Also, *in vivo* anti-inflammatory effect was further approved by histologic and immunohistochemical analysis in a TPA-induced mouse ear edema model. AAEO suppressed inflammatory responses probably by down-regulating JAK/STATs signaling pathway, as well as by scavenging ROS (Chen et al., 2017). By building ear swelling model and paw oedema model in rats, another *in vivo* evidence was provided to support the anti-inflammatory function of AAEO (Ge et al., 2016).

With respect to inflammatory skin disease, *Artemisia* leaf was proposed as a potential therapeutic agent, for it can restrain inflammatory mediator release and reduce inflammatory cytokine production not

only *in vitro* but also *in vivo* (Yun et al., 2016). Interestingly, AAEO was reported to afford better bioavailability and anti-inflammatory effect through skin administration than by oral gavage, which may be attributed to the better skin permeability of EO than gastrointestinal absorption (Ge et al., 2016).

Besides crude extract, dehydromatricarin A (DA, Fig. 1) was also identified as an active component of *A. argyi* not only against ovalbumin-induced allergic asthma (Shin, Ryu et al., 2017) but also against lipopolysaccharide-induced acute lung injury (Shin, Park et al., 2017). This may be explained, at least in part, by the fact that DA suppressed gene expression of matrix metalloproteinases-9 (MMP-9) and some pro-inflammatory cytokines, such as TNF-α and IL-6. In addition, *A. argyi* was reported to protect mice from gastric mucosal injury induced by ethanol, through ameliorating inflammatory responses and alleviating oxidative damage (Li et al., 2018).

4.4. Neuroprotective activity

In an effort to improve trimethyltin-induced cognitive dysfunction, 3,5-diCQA purified from *A. argyi* was discovered to exhibit ameliorating function on mice with learning and memory deficits (Kang et al., 2016). Brain tissues analysis on the model mice revealed that acetylcholine (ACh) levels increased upon administration of 3,5-diCQA, whereas the activity of acetylcholinesterase (AChE) decreased. Furthermore, 3,5-diCQA inhibited an increase in malondialdehyde content as well as oxidized glutathione ratio, and a decline of superoxide dismutase level. This study suggested that 3,5-diCQA prevented neuronal apoptosis by maintaining mitochondrial activities and repressing apoptotic signaling molecules such as p-Akt, BAX, and p-tau (Ser 404) (Kang et al., 2016). Another study indicated that *A. argyi* fermented by *Monascus purpureus* significantly protected neurons of dysmnesia mice from H_2O_2-induced neurotoxicity through alleviating mitochondrial injury, as well as cellular membrane damage (Kang et al., 2017). Further UPLC-Q-TOF/MS analysis revealed that quinic acid and its caffeic acid derivatives, and chlorogenic acid, were the main effective phytochemicals affording the neuroprotective activity of the *A. argyi* fermention (Kang et al., 2017).

DSF-52 (Fig. 1), a novel sesquiterpene dimer compound purified from *A. argyi*, was found to relieve microglia-mediated neuroinflammation by down-regulating NF-κB, JNK/p38 MAPKs and JAK2/STAT3 signaling pathways (Zeng et al., 2014). This result hinted that DSF-52 might be used to protect neurons in inflammation-mediated neurodegenerative diseases.

4.5. Anticoagulant activity

As early as 1992, *β*-sitosterol was isolated from *A. argyi* for the first time, together with a known compound 2-(3,4-dimethoxyphenyl)-6-methoxy-4-oxo-4*H*-chromene-5,7-dicarboxylic acid, and both were demonstrated to inhibit platelet aggregation (Zhong & Cui, 1992). Recently, Lv et al. tested the *in vitro* anticoagulation activities of two newly purified flavonoids, eupatilin 7-*O*-*β*-D-glucopyranoside and 5,6,2′,4′-tetrahydroxy-7,5′-dimethoxyflavone (Table 3) (Lv et al., 2018). Results indicated that both compounds retarded blood clotting through extending thrombin time (TT) and prothrombin time (PT), respectively. By establishing the acute blood stasis rats model via ice water bath, the anticoagulant property of AAEO was confirmed *in vivo* since AAEO decreased the blood viscosity of low, medium and high shear rates at a skin administration dosage of 0.125–0.50 mL/kg. Furthermore, this action was reported to be related to the ability of reducing the erythrocyte aggregation (Ge et al., 2016).

4.6. Other biological effects

In addition to above summarized medicinal uses, antimicrobial and insecticidal properties are also reported as the important biological activities of *A. argyi*, particularly its volatile components. Using *Candida albicans* SC5314, AAEO was discovered to exerted its antibacterial effect by facilitating intracellular ROS accumulation and mitochondria damage (Shi et al., 2017). In another study, AAEO was found to promote tissue repair of oral ulcer, and the effect was related to its antibacterial activity (Yin et al., 2017). Interestingly, *A. argyi* oil (AAO) was endowed a dramatically improved solubility, stability and bioactivity, when being prepared as AAO-loaded microcapsules (Hu, Yang, Ning, Wang, & Tong, 2013; Nauman & Colin, 2018). The bacterial inhibition rate of AAO-loaded microcapsules against *S. aureus* and *E. coli* maintained as high as 83% even after storage for 60 days. Thus, AAO-loaded microcapsules might be developed as a long-term antimicrobial agent. With regard to insecticidal activity, AAEO was found to exhibit strong contact toxicity and mild fumigant toxicity against *L. serricorne* adults, with a LD_{50} value of 6.42 μg/adult and 8.04 mg/L air, respectively (Zhang et al., 2014). Huang et al. stated that *A. argyi* had 100% anthelmintic efficacy against *Dactylogyrus intermedius* (Monogenea) in goldfish at a dose of 300 mg/L after 48 h of exposure (Huang et al., 2013). Anti-giardia assay showed that the ester derivatives of 3,5-diCQA were effective in killing *G. lamblia* (Zhang et al., 2012). These results indicated that *A. argyi* is promising to be developed as a natural antimicrobial and insecticide.

Anti-osteoporosis activity was recently presented as a health promoting benefit of *A. argyi*. For example, eupatilin (Table 3) was domostrated as an effective versatile therapeutic intervention for osteoporosis (Kim, Lee et al., 2015). On one hand, eupatilin exhibited an inhibitory effect on the differentiation of multinucleated cells *in vitro* by suppressing the transcription of nuclear factor of activated T cells c1 (NFATc1), as well as by constraining the formation of polymerization actin ring. On the other hand, eupatilin induced mature osteoclasts to fibroblast-like cells, but apoptosis was not observed, through a shrunken cytoplasm and accumulation of multi-nuclei. Moreover, eupatilin was demonstrated to effectively attenuate bone resorption *in vivo* based on both different mice osteoporosis models induced by lipopolysaccharide and ovariectomy, respectively. However, this was the only research of anti-osteoporotic effect ever reported of *A. argyi*.

In addition, eupatilin treatment was reported to induce PPARα activation in a dose-dependent manner and the EC_{50} value was estimated to be 41.9 μM. No or little transcriptional activation, however, was observed on PPARγ, PPARδ or RXRα. As such, eupatilin was presented as a selective peroxisome proliferator-activated receptor alpha (PPARα) agonist, which may be beneficial to the treatment of some metabolic diseases (Choi, Jung, & Kim, 2015).

5. Perspectives

In summary, *A. argyi* is a potential health-promoting food and has been widely used as a dietary supplementation in Asia, due to the fact that it contains multiple nutrients and functional constituents. EO represents a large group of bioactive phytochemicals of *A. argyi*, such as terpenes, alcohols, ethers, ketones, and organic acids among others. However, the composition of AAEO may differ quite a bit not only due to the cultivars, but also the selection of plant parts, detection methods, and growing conditions. Flavonoids, especially eupatilin and jaceosidin, are representative nonvolatile bioactives of *A. argyi*, displaying various pharmacology activities, including anti-cancer, antioxidant, anticoagulant, and anti-osteoporosis effects. In addition, organic acids, terpenes, polysaccharides, and coumarins were also found in *A. argyi*. Of note, dimeric sesquiterpenoid structures were demonstrated to have prominent tumor suppression and neuroprotection potentials.

Although the chemistry and bioactivities of *A. argyi* had been well investigated, the molecular mechanism by which these phytochemicals exert influence on human health is largely unresolved. To date, there is little information regarding the metabolomics of phytochemicals such as terpenoids and phenolics. Furthermore, the healing properties of *A. argyi* are still mostly maintained by cultural preferences and traditional practices, and previous functional studies are limited to *in vitro* or in

animal level, while data from clinical trials are almost blank.

To fill these gaps, future researches may dig into the underlying action mechanism of active ingredients of *A. argyi*, such as determination of involved signaling pathway, molecular targets, and drug-receptor binding modes. These are critical for further structural modification of the lead compound to increase its specificity and affinity. Another thing could not be neglected for dietary phytochemicals is their limited bioactivity (Aqil, Munagala, Jeyabalan, & Vadhanam, 2013; Karakaya, 2004; Yin, Lin, Mong, & Lin, 2012). Considering that, the health promoting effects of bioactives are warranted to be confirmed in human subjects or at least animal *in vivo* models. Certain methods like analogs (Walle, 2011), nanotechnology (Wang et al., 2014), microcapsules (Hu et al., 2013) and enhanced delivery systems (Nauman & Colin, 2018) may be employed to improve the bioavailability if necessary. In addition, continued efforts will be needed to investigate the pharmacokinetics, as well as the metabolites of phtytochemicals formed *in vivo*. The pharmacokinetics data also helps to facilitate the rational optimization of natural phytochemicals to increase therapeutic effects and reduce toxicities.

Given the above, there are still some areas in which we need a lot more study before we can fully understand the real potential of *A. argyi*. It is hoped that this review will inspire further reaearches to provide more scientific evidences for future application of *A. argyi* as a such as dietary supplements or functional ingredients in medical foods.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical statement

This review did not include any human subjects and animal experiments.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2018.11.029.

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