Rhodomyrtus tomentosa (Aiton.): A review of phytochemistry, pharmacology and industrial applications research progress

Zefeng Zhao, Lei Wu, Jing Xie, Ying Feng, Jiale Tian, Xirui He, Bin Li, Lin Wang, Xianmei Wang, Yongmin Zhang, et al.

Rhodomyrtus tomentosa (Aiton.): a review of phytochemistry, pharmacology and industrial applications research progress

Zefeng Zhao [1], Lei Wu [1], Jing Xie [1], Ying Feng [1], Jiale Tian [1], Xirui He [2], Bin Li [1], Lin Wang [1], Xianmei Wang [1], Yongmin Zhang[1,3], Shaoping Wu [1]*, Xiaohui Zheng [1]

[1] *School of Pharmacy, Key Laboratory of Resource Biology and Biotechnology in Western China (Northwest University), Ministry of Education; Biomedicine Key Laboratory of Shaanxi Province, Northwest University, Xi'an 710069, China;*

[2] *Department of Bioengineering, Zhuhai Campus of Zunyi Medical University, Zhuhai, 519041, China;*

[3] *Sorbonne Université, Institut Parisien de Chimie Moléculaire, CNRS UMR 8232, 4 place Jussieu, 75005 Paris, France.*

** Correspondence: wushaoping@nwu.edu.cn;*

Abstract

Rhodomyrtus tomentosa (Aiton) is a flowering plant native to southern and southeastern Asia. Up to date, 106 chemical constituents have been isolated and identified from *R. tomentosa*. Among these compounds, triterpenoids, flavonoids, phenols and meroterpenoids are the major constituents. Investigations of pharmacological activities of *R. tomentosa* revealed that this edible medicinal herb exhibits a wide range of therapeutic potential including antibacterial, antitumor, anti-inflammatory and antioxidant activities both *in vivo* and *in vitro*. The purpose of this review is to provide an overview of *R. tomentosa* studies until 2019. This article also intends to review advances in the botanical, phytochemical, pharmacological studies and industrial applications of *R. tomentosa*, which will provide a useful bibliography for further investigations and applications of *R. tomentosa* in medicines and foods.

Keywords: *Rhodomyrtus tomentosa*; edible medicinal herb; meroterpenoids; antibacterial; antioxidant; review

Abbreviations: AChE, acetylcholinesterase; AP, activator protein; ATP, adenosine triphosphate; CAMP, cyclic adenosine monophosphate; CAT, catalase; CUPRAC, copper reducing antioxidant capacity; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DW, distilled water; EER, ethanol extract of *R. tomentosa*; ERK1/2, extracellular signal-regulated kinase 1/2; FAK, focal adhesion kinase; GSH, glutathione; GPx, glutathione peroxidase; IL-6, interleukin 6; IRAK, interleukin-1 receptor-associated kinase; iNOS, inducible NO synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MIC, minimum inhibitory concentration; MMP, matrix metalloproteinase; MRSA, methicillin-resistant *Staphylococcus aureus*; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SOD, superoxide dismutase; SsaA, staphylococcal secretory antigen; Syk, spleen tyrosine kinase; TBARS, thio-barbituric acid reactive substances; TCM, traditional Chinese medicine; TLR2, toll-like receptor; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor-β; UV, ultraviolet.

Contents

1. Introduction

Rhodomyrtus tomentosa (Ait.) Hassk. also known as rose myrtle, is a flowering plant in the family Myrtaceae, native to southern and southeastern Asia, from India, east to southern China, the Philippines, and south to Malaysia and Sulawesi. It grows in coasts, natural forest, riparian zones, wetlands, moist and wet forests, bog margins, from sea level up to 2400 m elevation. *R. tomentosa* enjoys sunshine, and is relatively undemanding with regards to soil conditions (Lai et al., 2015). The whole parts of this plant (leaves, roots, buds and fruits) have been used in traditional medicine in Vietnamese, Chinese and Malaysian medicine for a long time. In traditional medicine of Vietnam, the unripe fruits of the plant are utilized to treat diarrhea or dysentery and ripe ones are used to stimulate the immune system. In Traditional Chinese Medicine (TCM), *R. tomentosa* is regarded as a medicinal herbal medicine effective in nourishing the blood system, resisting rheumatism and treating hematemesis, diarrhea, uterine bleeding. Modern pharmacological investigations have proved that ingredients from *R. tomentosa* show a wide range of pharmacological actions including antibacterial, antitumor, anti-inflammatory and antioxidant activities. In Indonesia, the roots and leaves of *R. tomentosa* are used to treat diarrhea, stomachaches and as a tonicafter childbirth, the leaves of *R. tomentosa* are often crushed and used as an external poultice and the tar from *R. tomentosa* wood is used to blacken eyebrows (Description from Florida Foraging database). Most of these effects are consistent with those observed for *R. tomentosa* in traditional uses. The principal components of *R. tomentosa* include triterpenoids, flavonoids, phenols meroterpenoids and microelements. Among these ingredients, rhodomyrtone (**51**) is the most representative compound with multiple potential pharmacology activities, and piceatannol (**71**) is the major and effective phenolic compound of *R. tomentosa* (Lai et al., 2013). Recently, the usable range of *R. tomentosa* is expanding from medicine plant to ornamental plant. Due to the beautiful appearance, *R. tomentosa* has been utilized as a popular ornamental plant in wide regions. Additionally, it has shown promise as fire retardant species for use in fire breaks in the Himalayas. It is a popular ornamental plant in gardens in tropical and subtropical areas, grown for its abundant flowers and sweet, edible fruit. The fruit can be made into pies and jams, or used in salads. In China and Vietnam, the fruits are used to produce a wine, and are also made into jellies, or freshly canned with syrup for human consumption.

Fig. 1. *R. tomentosa*: (A) *R. tomentosa* bushes; (B) *R. tomentosa* immature fruit; (C) *R. tomentosa* flowers; (D) *R. tomentosa* fruits.

To date, there are no authoritative published comprehensive reviews of *R. tomentosa* included in the content of SCI. In this review, we compile the progress on phytochemical studies over the past decades, with all the elucidated structures listed. The biological characterization of the extracts or components isolated from *R. tomentosa* is summarized as well. The purpose of this article is to interpret recent advances on the chemical composition, pharmacology benefits and industrial applications of *R. tomentosa*.

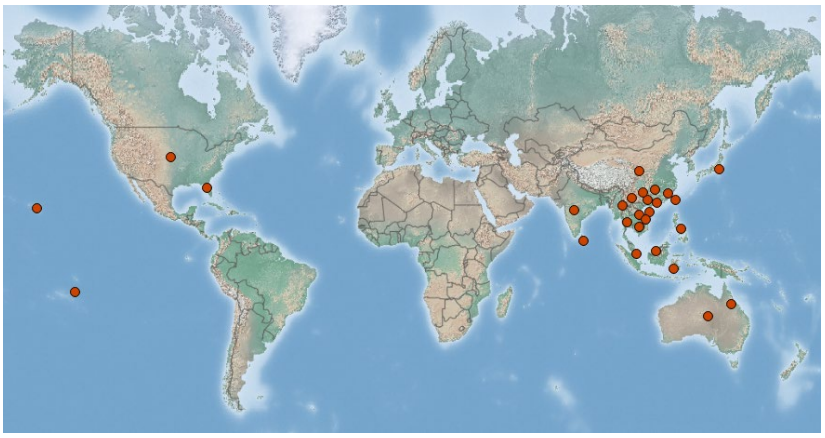

Fig. 2. Distribution of *R. tomentosa* around the world (https://www.cabi.org/isc/datasheet/47297).

2. Botany

R. tomentosa (**Fig. 1**) is a member of Myrtacea family (Lai, T.N.H. et al., 2015). According to "The Plant List" (www.theplantlist.org), *R. tomentosa* is the only accepted name for the plant with relative to other four synonyms including *Cynomyrtus tomentosa* (Aiton) Scriv., *Myrtus canescens* Lour., *Myrtus tomentosa* Aiton and *Rhodomyrtus tomentosa var. tomentosa*.

R. tomentosa is about 1-2 m high of evergreen shrub. It often has branchlets with grayish tomentose. The leaves of *R. tomentosa* are often opposite and blade elliptic to obovate. The flowers of *R. tomentosa* have 5 hypanthium obovoid sepals with gray tomentose. Obovate petals and red stamens can be also found in the flowers of *R. tomentosa*. *R. tomentosa* fruits are urceolate black berry. The flowering stage ranges from April to May, and the mature fruit phase is typically from July to August (Flora of China Editorial Committee, 2006).

3. Nutritional and physiochemical composition

3.1. Nutritional composition

Nutrient substances including proteins, carbohydrates, lipids, vitamins, minerals dietary fiber, essential oil and trace elements have been proved to be contained in the fruit of *R. tomentosa* (Huang et al., 2010; Lai et al., 2015; Wu et al., 2004). It was reported that the fruits of *R. tomentosa* contain the total protein of 4.00 % distilled water (DW), and the tryptophan was reported to be the main amino acid. High concentration of total dietary fiber (66.56 DW) was also found in the fruits of *R. tomentosa*. The insoluble fibers were the main type of dietary fiber, precisely, cellulose represented up to 50% content of the insoluble fibers, relatively, the soluble dietary fiber contributed 7.60% of the total dietary fiber content. Compared with other tropical fruits, the digestible sugar content of *R. tomentosa* fruits was not high (19.96% DW). Moreover, *R. tomentosa* fruits contain a low level of lipids (4.19 DW), in which linoleic and palmitic acids are the most abundant fatty acids with the contents of 75.36% and 10.45% for total fatty acids, respectively. Additionally, trace elements were also proved to be contained in *R. tomentosa*, with high level of potassium (221.76 mg/150 g fruit), calcium (73.65 mg/150 g fruit), manganese (3.23 mg/150 g fruit), iron (1.54 mg/150 g fruit), zinc (0.61 mg/150 g fruit), and copper (0.40 mg/150 g fruit). These results indicated the low-calorie and health-promoting properties of *R. tomentosa.*

3.2. Physiochemical and structural features

The detailed phytochemical and nutritional analyses of *R. tomentosa* have been carried out. Among the constituents isolated from *R. tomentosa*, triterpenoids, flavonoids, phenols and

meroterpenoids are the primary types. All compounds are summarized and compiled in **Table 1**, and their structures have been detailed in **Supplementary material** .

3.2.1. Triterpenoids

R. tomentosa contains multiple triterpenoids. To date, 24 triterpenoid compounds have been isolated from *R. tomentosa* (**1-24**). Among them, most of compounds are pentacyclic triterpenoid sapogenins except for compounds **15, 22** and **23**. β-sitostenone (**15**) and β-stigmasterol (**23**) are lanostane type tetracyclic triterpenoid sapogenins, and laevigatanoside A (**22**) is a pentacyclic triterpenoid saponin. The basic skeleton of the pentacyclic triterpenoid sapogenins could be divided into three types such as ursane, oleanane and lupane. The contents of the triterpenoids are shown in **Table 1** with their specific chemical structures presented in **Fig. S1**.

3.2.2. Flavonoids

Abundant flavonoids (**25-47**) have been isolated from *R. tomentosa*. The details about their chemical scaffolds and substituent groups have been listed in **Fig. S2**. They mainly contain the skeleton of myricetin (**25-28, 39, 42, 44** and **47**), which is characterized in the 3`,4`,5`-trihydroxyl group on the C ring of the flavonoid. The derivatives of anthocyanins (**31-36**), a kind of positively charged flavonoids, are often considered as the valuable natural pigments in plants. The analogues of kaempferol (**29**, **38** and **40**), quercetin (**30** and **43**) also have been isolated from *R. tomentosa*. In addition, other types of flavonoids including laricitrin (**37**), vitexin (**41**), naringenin (**45**) and blumeatin A (**46**) have been separated and identified from *R. tomentosa* as well.

3.2.3. Polyphenols

Phenols are widely distributed in *R. tomentosa*. Approximately 34 kinds of phenols (**48-81**) have been isolated from *R. tomentosa* in total (**Fig. S3**). Among them, simple phenols and phenol acids can be found, such as progallin A (**59)**, gallic acid (**60**), methyl gallate (**67**), resveratrol (**70**) and its analogues, piceatannol (**71**), astringin (**72**) and so on. Moreover, hydrolysable tannins (**48-50** and **73**) with gallic acid unit in the structure of phenol also have been isolated from *R. tomentosa*.

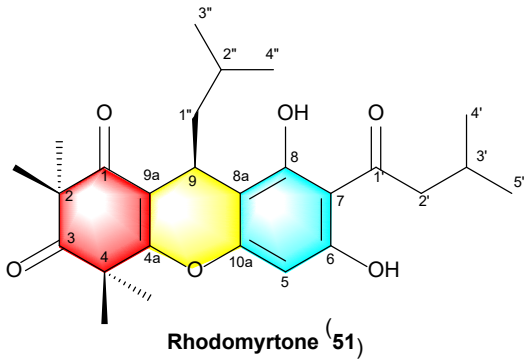

Fig. 3. Structure of rhodomyrtone (**51**).

Rhodomyrtone (**51**) is a typical compound with multiple bioactivities isolated from *R. tomentosa*, the compound **51** can be regarded as the derivative of phloroglucinol (**76**). The multiple bioactive properties of compound **51** have been widely reported including antimicrobial (Saising et al., 2018), antitumor (Chorachoo et al., 2016) and anti-inflammatory (Na-Phatthalung et al., 2018b). The favorable bioactivities are closely related to the unique diastereomeric structure of the skeleton in compound **51**, in which there are several chiral carbons (**Fig. 3**, C2, C4 and C9). Additionally, compound **51** and its derivatives could be obtained by organic synthesis through a series of condensation reactions with the help of the asymmetric catalyst (Tan et al., 2017), with phloroglucinol as the starting material, indicating the possibility of industrial scale production for phloroglucinol.

3.2.4. Meroterpenoids

Meroterpenoids are hybrid natural products partially derived from terpenoid pathways as the prefix "mero-" means "part, partial, and fragment" (Geris and Simpson, 2009). The skeleton of this meroterpenoids is made up of two parts, an alkylated syncarpic acid unit with a terpenoid moiety (Zhang et al., 2017). The structural diversity of mono- or sesquiterpenes instills chemical structures to this type of meroterpenoids. Not only from *R. tomentosa,* but also from other plants of the Myrtaceae family including *Eucalyptus tereticornis* (Liu et al., 2018), *Leptospermum brachyandrum* (Zou et al., 2018) and *Callistemon rigidus* (Cao et al., 2018), meroterpenoids have been isolated and identified. Specially, the chiral carbons are common at the structure of meroterpenoids in *R. tomentosa*, and the isobutyl group can be frequently seen as the terminal group of the compounds (**86-89**, **93-97** and **99-102**). The structures of these distinctive constituents have been crystallized in **Fig. S4**.

Table 1. Chemical constituents isolated from *Rhodomyrtus tomentosa*

NO	Name	Cas	Formula	Ref.
Triterpenoids				
1	Taraxerol	127-22-0	$C_{30}H_{50}O$	Hui et al. (1975)
2	Betulin	473-98-3	$C_{30}H_{50}O_2$	Hui et al. (1975)
3	Lupeol	545-47-1	$C_{30}H_{50}O$	Hui et al. (1975)
4	β-Amyrin	559-70-6	$C_{30}H_{50}O$	Hui et al. (1975)
5	Friedelin	559-74-0	$C_{30}H_{50}O$	Hui et al. (1975)
6	Viminalol	638-95-9	$C_{30}H_{50}O$	Hui et al. (1975)
7	Betulin monoacetate	27570-20-3	$C_{32}H_{52}O_3$	Hui et al. (1975)
8	β-Amyrenonol	38242-02-3	$C_{30}H_{48}O_2$	Hui et al. (1975)
9	(3β,21β)-A'-Neogammacer-22(30)-ene-3,29-diol	62498-82-2	$C_{30}H_{50}O_2$	Hui and Li (1976)
10	3β-Acetoxy-11α,12α-epoxyoleanan-13β,28-olide; 3β-O-Acetyl-11α,12α-epoxyolean-28,13-olide	35738-25-1	$C_{32}H_{48}O_5$	Hui and Li (1976)
11	Oleanan-28-oic acid, 3β,12α, 13β-trihydroxy-, γ-lactone, 3-acetate	62498-83-3	$C_{32}H_{50}O_5$	Hui and Li (1976)
12	Urjinolic acid	465-00-9	$C_{30}H_{48}O_5$	Huang et al. (2010)
13	3-Acetoxy-oleanolic acid	4339-72-4	$C_{32}H_{50}O_4$	Huang et al. (2010)
14	Oleanolic acid	508-02-1	$C_{30}H_{48}O_3$	Hiranrat et al. (2012a)
15	β-Sitostenone	1058-61-3	$C_{29}H_{48}O$	Hiranrat et al. (2012a)
16	3-*p*-(*E*)-Coumaroyloleanolic acid	151334-06-4	$C_{39}H_{54}O_5$	Hiranrat et al. (2012a)
17	Maslinic acid	4373-41-5	$C_{30}H_{48}O_4$	Xiong et al. (2013)
18	(2α,3β,4α)-2,23-Dihydroxy-3-[[(2*E*)-3-(4-hydroxyphenyl)-1-	171864-20-3	$C_{39}H_{54}O_7$	Xiong et al. (2013)

NO	Name	Cas	Formula	Ref.
	oxo-2-propen-1-yl]oxy]olean-12-en-28-oic acid			
19	(2α,3β,4α)-2,3-Dihydroxy-23-[[(2*E*)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]olean-12-en-28-oic acid	207905-07-5	$C_{39}H_{54}O_7$	Xiong et al. (2013)
20	(2α,3β,4α)-2,23-Dihydroxy-3-[[(2*Z*)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]olean-12-en-28-oic acid	412951-23-6	$C_{39}H_{54}O_7$	Xiong et al. (2013)
21	23-Hydroxytormentic acid	105706-08-9	$C_{30}H_{48}O_6$	Zhu et al. (2015)
22	Laevigatanoside A	95262-48-9	$C_{36}H_{58}O_{11}$	Zhu et al. (2015)
23	β-Stigmasterol	83-48-7	$C_{29}H_{48}O$	Zhu et al. (2015)
24	Hederagenin	465-99-6	$C_{30}H_{48}O_4$	Zhang et al. (2016)
Flavonoids				
25	Myricitrin	17912-87-7	$C_{21}H_{20}O_{12}$	Hou et al. (1999)
26	Isomyricitrin	19833-12-6	$C_{21}H_{20}O_{13}$	Hou et al. (1999)
27	Betmidin	35589-22-1	$C_{20}H_{18}O_{12}$	Hou et al. (1999)
28	Combretol	5084-19-5	$C_{20}H_{20}O_8$	Hiranrat and Mahabusarakam (2008)
29	Leucoside	27661-51-4	$C_{26}H_{28}O_{15}$	Phan et al. (2007)
30	Quercetin	117-39-5	$C_{15}H_{10}O_7$	Nguyen et al. (2009)
31	Delphinidin-3-O-glucoside	50986-17-9	$C_{21}H_{21}O_{12}$	Cui et al. (2013)
32	Petunidin-3-O-glucoside	71991-88-3	$C_{22}H_{23}O_{12}$	Cui et al. (2013)
33	Malvidin-3-O-glucoside	18470-06-9	$C_{23}H_{25}O_{12}$	Cui et al. (2013)
34	Pelargonidin-3-glucoside	47684-27-5	$C_{21}H_{21}O_{10}$	Cui et al. (2013)
35	Cyanidin-3-O-glucoside	47705-70-4	$C_{21}H_{21}O_{11}$	Cui et al. (2013)
36	Peonidin 3-β-D-glucoside	68795-37-9	$C_{22}H_{23}O_{11}$	Cui et al. (2013)

NO	Name	Cas	Formula	Ref.
37	Laricitrin	53472-37-0	$C_{16}H_{12}O_8$	Zhu et al. (2015)
38	Kaempferol 3-arabinoside	5041-67-8	$C_{20}H_{18}O_{10}$	Zhu et al. (2015)
39	Myricetin	529-44-2	$C_{15}H_{10}O_8$	Zhu et al. (2015)
40	Kaempferol	520-18-3	$C_{15}H_{10}O_6$	Wu et al. (2015)
41	Vitexin	3681-93-4	$C_{21}H_{20}O_{10}$	Wu et al. (2015)
42	Dihydromyricetin	27200-12-0	$C_{15}H_{12}O_8$	Wu et al. (2015)
43	Quercetin 7,4'-diglucoside	42900-82-3	$C_{27}H_{30}O_{17}$	Wu et al. (2015)
44	Myricetin-3,7,3′-trimethyl ether-5′-O-β-glucopyranoside	2170444-56-9	$C_{24}H_{26}O_{13}$	Liu et al. (2016a)
45	Naringenin	480-41-1	$C_{15}H_{12}O_5$	Liu et al. (2016a)
46	Blumeatin A	70411-27-7	$C_{16}H_{14}O_7$	Liu et al. (2016a)
47	Myricetin-3,7,3'-trimethyl ether	94390-21-3	$C_{18}H_{16}O_8$	Liu et al. (2016a)
Phenols				
48	Castanin	115406-24-1	$C_{34}H_{24}O_{22}$	Liu et al. (1997)
49	Pedunculagin	7045-42-3	$C_{34}H_{24}O_{22}$	Liu et al. (1998)
50	Dibenzo[f,h][1,4]dioxecin, D-glucose deriv.; 2,3-(Hexahydroxydiphenoyl) glucose	36378-47-9	$C_{20}H_{18}O_{12}$	Hou et al. (1999)
51	Rhodomyrtone	468757-69-9	$C_{26}H_{34}O_6$	Dachriyanus et al. (2002)
52	Rhodomyrtosone A	1079988-16-1	$C_{26}H_{32}O_7$	Hiranrat and Mahabusarakam (2008)
53	Rhodomyrtosone B	1079988-17-2	$C_{26}H_{34}O_6$	Hiranrat and Mahabusarakam (2008)
54	Rhodomyrtosone C	1079988-18-3	$C_{41}H_{54}O_8$	Hiranrat and

NO	Name	Cas	Formula	Ref.
				Mahabusarakam (2008)
55	α-Tocopherol	59-02-9	$C_{29}H_{50}O_2$	Hiranrat and Mahabusarakam (2008)
56	3,3',4-Tri-O-methylellagic acid	1617-49-8	$C_{17}H_{12}O_8$	Hiranrat and Mahabusarakam (2008)
57	4,8,9,10-Tetrahydroxy-2,3,7-trimethoxyanthracene 6-O-β-D-glucopyranoside	1152440-38-4	$C_{23}H_{26}O_{13}$	Nguyen et al. (2009)
58	α-L-Mannopyranoside, 3,4,6,8,9,10-hexahydroxy-7-methoxy-2-anthracenyl 6-deoxy-	1152440-40-8	$C_{21}H_{22}O_{12}$	Nguyen et al. (2009)
59	Progallin A	831-61-8	$C_9H_{10}O_5$	Huang et al. (2010)
60	Gallic acid	149-91-7	$C_7H_6O_5$	Huang et al. (2010)
61	1,4,7-Trihydroxy-2-methoxy-6-methyl-9,10-anthracenedione	905459-38-3	$C_{16}H_{12}O_6$	Chen et al. (2011)
62	1,1',3,3',5,5'-Hexahydroxy-7,7'-dimethyl[2,2'-bianthracene]-9,9',10,10'-tetrone	1345719-04-1	$C_{30}H_{18}O_{10}$	Chen et al. (2011)
63	Tomentosone A	1350886-68-8	$C_{41}H_{52}O_9$	Hiranrat et al. (2012b)
64	Tomentosone B	1350886-69-9	$C_{41}H_{52}O_9$	Hiranrat et al. (2012b)
65	1-Hydroxy-2,3,7,8-tetramethoxy[1]benzopyrano[5,4,3-*cde*][1]benzopyran-5,10-dione	1402163-89-6	$C_{18}H_{14}O_9$	Hiranrat et al. (2012a)
66	Rhodomyrtosone I	1402725-98-7	$C_{28}H_{30}O_6$	Hiranrat et al. (2012a)
67	Methyl gallate	99-24-1	$C_8H_8O_5$	Hiranrat et al. (2012a)

NO	Name	Cas	Formula	Ref.
68	4-Hydroxy-3-methoxybenzoic acid	121-34-6	$C_8H_8O_4$	Hiranrat et al. (2012a)
69	1,4-*O*-Diferuloylsecoisolariciresinol	56973-66-1	$C_{40}H_{42}O_{12}$	Hiranrat et al. (2012a)
70	Resveratrol	501-36-0	$C_{14}H_{12}O_3$	Lai et al. (2013)
71	Piceatannol	10083-24-6	$C_{14}H_{12}O_4$	Lai et al. (2013)
72	Astringin	29884-49-9	$C_{20}H_{22}O_9$	Lai et al. (2013)
73	Furosin	81552-37-6	$C_{27}H_{22}O_{19}$	Lai et al. (2013)
74	Tomentosone C	1801847-62-0	$C_{37}H_{46}O_8$	Liu et al. (2016a)
75	Trichocarpin	10590-85-9	$C_{20}H_{22}O_9$	Liu et al. (2016a)
76	Phloroglucinol	108-73-6	$C_6H_6O_3$	Hiranrat et al. (2017)
77	Tomentodione S	2241542-77-6	$C_{28}H_{30}O_6$	Zhang et al. (2018)
78	Tomentodione T	2241542-78-7	$C_{26}H_{34}O_6$	Zhang et al. (2018)
79	Protocatechuic acid	99-50-3	$C_7H_6O_4$	Zhao et al. (2017)
80	Syringic acid	530-57-4	$C_9H_{10}O_5$	Zhao et al. (2017)
81	Ferulaic acid	1135-24-6	$C_{10}H_{10}O_4$	Zhao et al. (2017)
Meroterpenoids				
82	Rhodomyrtosone D	1079988-19-4	$C_{25}H_{32}O_6$	Hiranrat and Mahabusarakam (2008)
83	Endoperoxide G3	33998-54-8	$C_{14}H_{20}O_5$	Hiranrat and Mahabusarakam (2008)
84	6*R*,9*R*-3-Oxo-α-ionol	52210-15-8	$C_{13}H_{20}O_2$	Hiranrat and Mahabusarakam (2008)
85	Rhodomentone A	1982377-64-9	$C_{30}H_{46}O_3$	Hiranrat and Mahabusarakam (2008)
86	Tomentodione A	1983191-58-7	$C_{30}H_{46}O_3$	Hiranrat and Mahabusarakam (2008)
87	Tomentodione B	1983191-59-8	$C_{30}H_{46}O_3$	Hiranrat and

NO	Name	Cas	Formula	Ref.
				Mahabusarakam (2008)
88	Tomentodione C	1983191-60-1	$C_{30}H_{46}O_3$	Hiranrat and Mahabusarakam (2008)
89	Tomentodione D	1983191-61-2	$C_{30}H_{46}O_3$	Hiranrat and Mahabusarakam (2008)
90	Watsonianone A	1416740-73-2	$C_{25}H_{36}O_6$	Zhuang et al. (2017)
91	Watsonianone C	1416740-75-4	$C_{31}H_{38}O_8$	Liu et al. (2016a)
92	Tomentosenol A	2172835-33-3	$C_{25}H_{38}O_3$	Liu et al. (2016a)
93	4R-focifolidione	617706-94-2	$C_{25}H_{38}O_3$	Liu et al. (2016a)
94	4S-focifolidione	617711-01-0	$C_{25}H_{38}O_3$	Liu et al. (2016b)
95	Tomentodione E	2085264-25-9	$C_{30}H_{42}O_3$	Zhang et al. (2017)
96	Tomentodione F	2085264-26-0	$C_{30}H_{42}O_3$	Zhang et al. (2017)
97	Tomentodione G	2085264-27-1	$C_{30}H_{42}O_3$	Zhang et al. (2017)
98	Tomentodione B	1983191-59-8	$C_{30}H_{46}O_3$	Liu et al. (2018)
99	4,6(2*H*,5*H*)-Benzofurandione, 3,7-dihydro-2-hydroxy-5,5,7, 7-tetramethyl-3-(1-methylethyl)-, (2*R*,3*R*)-	2241294-73-3	$C_{15}H_{22}O_4$	Zhang et al. (2018)
100	Tomentodione N	2241542-72-1	$C_{15}H_{22}O_4$	Zhang et al. (2018)
101	Tomentodione O	2241542-73-2	$C_{31}H_{48}O_4$	Zhang et al. (2018)
102	Tomentodione P	2241542-74-3	$C_{31}H_{48}O_4$	Zhang et al. (2018)
103	Tomentodione Q	2241542-75-4	$C_{30}H_{44}O_4$	Zhang et al. (2018)
104	Tomentodione R	2241542-76-5	$C_{30}H_{44}O_4$	Zhang et al. (2018)
105	Rhodomyrtusials A	-	$C_{30}H_{44}O_4$	Qin et al. (2019)
106	Rhodomyrtusials B	-	$C_{30}H_{44}O_4$	Qin et al. (2019)

3. Progress of pharmacological studies on *R. tomentosa*

To date, numerous studies have disclosed the bioacitivities of *R. tomentosa*. The largely effective extractions of constituents possess a variety of pharmacological properties, ranging from

antibacterial, antitumor, anti-inflammatory and antioxidant potencies. Next, these pharmacological studies were discussed one by one in the following paragraphs, and the recapitulative summary was presented in **Table 2**.

Table 2. The pharmaceutical effects of *R. tomentosa*.

Pharmaceutical effects	Part	Extract /compound	Model and effective concentrations	Ref.
Antibacterial effect	Leaf	Ethanol extract	Clinical isolates of *Streptococcus pyogenes* (MIC: 3.91-62.5 μg/mL)	Limsuwan et al. (2012)
	Leaf	95% Ethanol extract	Staphylococcal isolates (MIC: 16-64 μg/mL)	Mordmuang et al. (2015)
	Leaf	95% Ethanol extract	*Streptococcus agalactiae* and *Streptococcus iniae* (MIC: 7.8-62.5 μg/mL)	Na-Phatthalung et al. (2017)
	Leaf	Rhodomyrtone (**51**)	*Staphylococcus aureus* (MIC: 1.83 μg/mL)	Liu et al. (2016)
	Leaf	Tomentosone C (**74**)	*Staphylococcus aureus* (MIC: 3.66 μg/mL)	Liu et al. (2016)
Antitumor activity	Leaf	Rhodomyrtone (**51**)	HeLa cells (IC_{50}: 0.33 μM)	Zhang et al. (2018)
	Leaf	Tomentodione D (**89**)	DLD-1 cells (IC_{50}: 43 μM)	Zhang et al. (2016)
Anti-inflammatory activity	Leaf	Ethanol extract	LPS-induced inflammatory in rainbow trout (10 and 100 μg per fish)	Na-Phatthalung et al. (2018)
Antioxidant activity	Leaf	Methanol fraction	CUPRAC model (EC_{50}: 53.84 μM)	Abd Hamid et al. (2017)
Anti-Alzheimer's	Leaf and	Tomentodione	AChE assay (IC_{50}: 6.6 μM)	Qin et al.

Pharmaceutical effects	Part	Extract /compound	Model and effective concentrations	Ref.
	stem	Q (**103**)		(2019)
	Leaf and	Rhodomyrtusi	AChE assay (IC_{50}: 8.8 μM)	Qin et al.
	stem	als A (**105**)		(2019)
	Leaf and	Rhodomyrtusi	AChE assay (IC_{50}: 6.0 μM)	Qin et al.
	stem	als B (**106**)		(2019)

3.1. Antibacterial effect

Some formulations obtained from *R. tomentosa* have been characterized by antimicrobial and antifungal properties due to the presence of high content of meroterpenoids (Saeloh et al., 2018). As the common secondary metabolites produced by the Myrtaceae (Nicoletti et al., 2018), meroterpenoids have been widely investigated with panorama enlarging, leading to proposing the use of some Myrtaceae plants in soil sanitization as the antibiotic agents (Prosser et al., 2016). Therefore, *R. tomentosa* can be potentially used as biocontrol agent and natural preservative to prevent microbial spoilage as well as to extend the shelf life of food (Salehi et al., 2018).

Crude extracts

Ethanol extract of *R. tomentosa* (EER) displayed antibacterial effect against 47 kinds of clinical isolates of *Streptococcus pyogenes* (minimum inhibitory concentration, MIC: 3.91-62.5 μg/mL) (Limsuwan et al., 2012), meanwhile, weak cytotoxicity was detected at the dosage of 8 times of MIC. EER was demonstrated to play a role in treatment of the staphylococcal bovine mastitis (Mordmuang and Voravuthikunchai, 2015), the tissue damages and inflammatory injuries induced by bacterial infections were also alleviated by *R. tomentosa.* EER also reduced bacterial infection against staphylococcal isolates with minimum inhibitory concentration (MIC) values for 16-64 μg/mL (Mordmuang et al., 2015). The extract dose-dependently promoted the hydrophobicity of bacterial cell surface and reduced the adhesion of the bacterial cells to the tissues. EER as a bio-control agent was proved to inhibit *Listeria monocytogenes* (Odedina et al., 2015). Contacting 30 min with EER (128 μg/mL), stationary phase *L. monocytogenes* cells were rapidly inactivated by greater than 3-log units. EER was reported to decrease numbers of *L. monocytogenes* at different inoculum levels in chicken meat by both rinse and injection

application methods (Odedina et al., 2016). EER solvent markedly decreased the bacterial number of *L. monocytogenes* after 5 min rinse, indicating that *R. tomentosa* could be applied in cooked chicken as a potent bio-additive agent to ensure food safety. In the *Streptococcus agalactiae* and *Streptococcus iniae* infected Nile tilapia model, EER exerted strong antibacterial effect against the fish pathogens in a dose-dependent manner with MICs ranging from 7.8 to 62.5 μg/mL (Na-Phatthalung et al., 2017). In addition, by the induction of H_2O_2, *S. agalactiae* cells pre-treated with EER became more sensitive to oxidative stress, and the mortality of Nile tilapia was reduced by the mediation of EER. EER displayed remarkable reduction in the methicillin-resistant *Staphylococcus aureus* (MRSA) adhesion to human HaCaT keratinocytes (Srisuwan and Voravuthikunchai, 2017). At nontoxic concentration (128 mg/L), EER showed strong antibacterial effect against intracellular MRSA. Moreover, MRSA-induced cytotoxicity was decreased at least 50% by *R. tomentosa.* EER exhibited potential to develop as alternative therapeutic agent against oral candidiasis (Hmoteh et al., 2018). At different dosages, the inhibition of EER against virulence factors of *Candida albicans* can be interpreted as indicating the decrease in adherence ability to surfaces and biofilm forming ability, and the promotion of phagocytosis and killing effect of neutrophils against the organism.

Isolated compounds

Rhodomyrtone (**51**), which was isolated from *R. tomentosa* leaf extract, exhibited significant antibacterial effects on *Streptococcus pyogenes* stain (Limsuwan et al., 2011). Proteomics analyses showed that *S. pyogenes* cultivating with compound **51** obviously altered the cellular and secreted protein related to three metabolic pathways. Additionally, the cells of *S. pyogenes* with compound **51** decreased many virulence factors including the cyclic adenosine monophosphate (CAMP) factor and the glyceraldehyde-3-phosphate dehydrogenase. Compound **51** can be used as an anti-MRSA agent (Visutthi et al., 2011). Extracellular proteins of MRSA treated with compound **51** presented expressive suppression and overexpression, meanwhile, staphylococcal antigenic proteins such as staphylococcal secretory antigen (SsaA) was decreased, indicating that compound **51** disturbed WalK/WalR (YycG/YycF) systems, which is involved in autolysin synthesis related to the cell wall metabolism and biofilm formation. Compound **51** presented significant antibacterial activity by inducing the expression of factors associated with the innate immune

responses in the THP-1 monocytes with MRSA (Srisuwan et al., 2014). Compound **51** caused the upregulation of interleukin 6 (IL-6) and inducible NO synthase (iNOS) in THP-1 monocytes with low doses of heat-killed MRSA, high expression of innate immune response key factors toll-like receptor (TLR2) and CD14 at 106 to 109 cfu/mL heat-killed MRSA and low expression of tumor necrosis factor alpha (TNF-α) with MRSA at high doses, exhibiting immunostimulatory and anti-inflammatory activities. On the other hand, Compound **51** can also activate monocyte by increasing the expression of innate immune receptors to assist in clearing MRSA.

R. tomentosa leaves ethanol extract and compound **51**, serving as a potential agent associated with oral diseases, at different MIC presented the anti-adherence activity against oral microbes including *Staphylococcus aureus* ATCC 25923 and *Streptococcus mutans* (Limsuwan et al., 2014). After *C. albicans* ATCC 90028 was treated for 48 h, it can be found that the inhibition of adhesion of the extract was superior to compound **51.** Compound **51** could be used as a novel anti-acne agent because of its strong inhibition capability on virulence enzymes production, biofilm formation and the destruction of cells mature biofilm in *Propionibacterium acnes* (Wunnoo et al., 2017). After culture medium was supplemented with compound **51** at 1/2 MIC, all the isolates apparently reduced lipolytic regions while only 50% isolates decreased proteolytic effects. The compound at different concentrations also decreased biofilm formation. The isolates treated with compound **51** at 8 MIC (2 mg/mL) distorted bacterial cell structure and their percentage survival was between 39% and 75%. Compound **51** was reported to target bacterial and mammalian cell membranes (Saising et al., 2018). In *Staphylococcus aureus*, compound **51** dissipated the membrane potential rapidly and promoted the release of adenosine triphosphate (ATP) and cytoplasmic proteins, without pole formation. The addition of saturated fatty acids and lipopolysaccharide (LPS) counteracted the antimicrobial effect of compound 5**1**. Compound **51** caused intracellular vesicles to capture various membrane proteins by inducing membrane invagination and remodels membrane by interacting instantaneously with the phospholipid head rather than embedding the lipid bilayer traditionally (Saeloh et al., 2018). Rhodomyrtosone B (**53**) from *Rhodomyrtus tomentosa* leaves presented significant *in vivo* antibacterial activities *via* the interference of bacterial membrane potential and the increase of membrane permeability and showed antibacterial activity by relieving skin ulcer in a murine model *in vitro* (Zhao et al., 2018). Tomentosone C (**74**) and compound **51** isolated from *R. tomentosa* leaves were considered to be

responsible for the antimicrobial effect against gram-positive microbe *Staphylococcus aureus* observed with the *n*-hexane and ethyl acetate-soluble fraction of the ethanol extract with MIC values for 3.66 and 1.83 μg/mL (Liu et al., 2016a), respectively. The Sigma factor B (SigB) which controlled the expression of *Staphylococcus aureus* was also related to the inhibitory effect of compound **51** against the bacterial strain (Mitsuwan et al., 2019), with the development of microbiology (Saeloh et al., 2018), there would be more valuable investigations to prove the potential of active compounds from *R. tomentosa* as antibiotic agents.

3.2. Antitumor activity

In recent years, some studies have found that *R. tomentosa* also exhibits certain antitumor effects on multiple models. Several constituents were isolated and characterized from the leaves of *R. tomentosa* by Zhang and co-workers (Zhang et al., 2018). Among the isolated compounds, compound **51** exerted the most potent antitumor effect on HeLa cells (IC_{50}: 0.33 μM), and showed favorable selectivity between normal cells and tumor cells (IC_{50} for Vero cells: 0.94 μM, selectivity index: 2.85) Chorachoo et al. (2016) reported that compound **51** (2-32 mg/mL) time-dependently inhibited the proliferation of HaCaT keratinocyte cells *in vitro* with no skin irritation observed *in vivo*, suggesting the potential to develop as a natural anti psoriasis agent. After treating for 24, 48, and 72 hours, compound **51** inhibited the test cell strains with the inhibition rate for 13.62-61.61%, 50.59-80.16%, and 61.82-85.34%, respectively. Tayeh et al. (2017) and the collogues found that compound **51** at the subcytotoxic concentrations (0.5 and 1.5 μg/mL) showed pronounced inhibition of cancer metastasis by reducing cell migration, cell adhesive ability and cell invasion on epidermoid carcinoma A431 cells. Further investigation indicated that compound **51** suppressed cell metastasis by reducing matrix metalloproteinase (MMP)-2/9 activities and expression through inhibiting extracellular signal-regulated kinase 1/2 (ERK1/2), p38 and focal adhesion kinase (FAK) signaling pathways *via* nuclear factor-κB (NF-κB) activities. A series of meroterpenoids were isolated from *R. tomentosa* (Zhang et al., 2016). Among them, tomentodione D (**89**) displayed the most potent metastatic inhibitory activity against DLD-1 cells by inhibiting activation of Akt and ERK induced by 12-*O*-tetradecanoylphorbol-13-acetate, ultimately down-regulating the expression levels of MMP-2 and MMP-9.

3.3. Anti-inflammatory activity

R. tomentosa exerted potential in aquaculture to protect fish against inflammatory-related diseases. EER displayed anti-inflammatory activity in rainbow trout model by mediating the expression of immune-related genes (Na-Phatthalung et al., 2018a). In different organs, multiple genes including IL-10, SAA, hepcidin, transforming growth factor-β (TGF-β) and iNOS were influenced by *R. tomentosa.* After combining with LPS, *R. tomentosa* (10 μg per fish) inhibited the levels of pro-inflammatory cytokine IL-1β, IL-8, suggesting the anti-inflammatory activities of *R. tomentosa.* Moreover, *R. tomentosa* decreased the level of cortisol but it did not exert any impact on hematological parameters, pointing out the potential to develop as the anti-stress agent. EER and compound **51** exhibited immunostimulatory and anti-inflammotary activities by inducing the expression of immune-related genes in the model of rainbow trout head kidney macrophages (Na-Phatthalung et al., 2018b). The results demonstrated that EER and compound **51** changed the expression of immune-related genes, including pro-inflammatory cytokines (IL-1β, IL-8, and TNF-α) and anti-inflammatory cytokines (IL-10 and TGF-β). Moreover, after exposure to compound **51** for 4 hours, the expression levels of IL-1β, IL-8 and TNF-α in head kidney macrophages were upregulated, meanwhile, the expression levels of IL-10 and TGF-β were promoted.

Watsonianone A **(90)** isolated from *R. tomentosa* fruits significantly inhibited inflammatory reaction by induction of respiratory-syncytial-virus (RSV) on RAW264.7 macrophages and HEp-2 cells (Zhuang et al., 2017). Compound **90** down-regulated the expression levels of TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) in respiratory syncytial virus (RSV)-infected RAW264.7 cells. Further investigations revealed that compound **90** inhibited activation of nuclear factor *κ*B (NF-*κ*B) pathway via stimulating the thioredoxin system and reducing intracellular reactive oxygen species (ROS) which is closely related to the inflammatory response. The methanol extract of *R. tomentosa* leaves possessed anti-inflammatory effect in the LPS-stimulated macrophages *in vitro* and acute inflammation model *in vivo* (Jeong et al., 2013). The extract inhibited the production of inflammatory mediators (NO and PGE2) in RAW264.7 cells and peritoneal macrophages exposed to LPS in a dose-dependent manner. Moreover, *R. tomentosa* directly targeted activating signaling pathways of NF-*κ*B and activator protein (AP)-1 *via* directly

suppressing their upstream enzymes, including Syk/Src and IRAK1/IRAK4.

3.4. Antioxidant activity

The acetone extract of the *R. tomentosa* leaves exerted antioxidant activity *in vitro* and *in vivo* (Lavanya et al., 2012). The researchers indicated that *R. tomentosa* could notably inhibit lipid peroxidation, increase reducing ability and scavenge free radical dose-dependently *in vitro*. Meanwhile, the *R. tomentosa* extract (0.8 g/kg) effectively prevented the promotion of levels for thio-barbituric acid reactive substances (TBARS) and the reduction of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) induced by CCl_4 in Swiss Albino mice. The *R. tomentosa* fruit was reported to show potential antioxidant effect (Lai et al., 2015). The presence of high amounts of phenolic compounds (49.21 mg gallic acid equivalent/g dry weight) resulted in a high antioxidant capacity (431.17 μmol Trolox equivalent/g dry weight), suggesting a potential to develop as a resource of health-promoting compounds. The antioxidant capacity of different sub-fractions of the *R. tomentosa* extractions was evaluated by radical scavenging assay (2,2-diphenyl-1-picrylhydrazyl, DPPH), copper reducing antioxidant capacity (CUPRAC) and β-carotene bleaching assay (Abd Hamid et al., 2017). The methanol fraction showed the most significant antioxidant activities in DPPH, CUPRAC and β-carotene bleaching with EC_{50} values of 110.25, 53.84 and 58.62 μg/mL, respectively. The strong antioxidant activity was considered to be closely related to the presence of high total flavonoid and total phenolic contents.

3.5. Other activities

Apart from the activities mentioned above, *R. tomentosa* was disclosed to show other activities as well. As for the central nervous system, compound **51** exerted antidepressant effect in preventing source consumption decrease and decreased social behaviors in chronic unpredictable mild stress mice model (Chai et al., 2019). Compound **51** prevented the impairment of spatial memory, reversed dendritic spine density defects, suppressed the promotion of glycogen synthase kinase-3β activity, and reversed the decrease of brain-derived neurotrophic factor and postsynaptic density protein 95. The petroleum ether extract of leaves and stems of *R. tomentosa* exhibited a significant acetylcholinesterase (AChE) inhibition rate (81%, 500 μg/mL) (Qin et al., 2019), and

then active compounds **103**, **105** and **106** were isolated from *R. tomentosa* and evaluated the AChE inhibitory effect, with the favorable IC_{50} values of 6.6, 8.8 and 6.0 μM, respectively.

The aqueous alcoholic (70%) extract of R. tomentosa displayed antiulcer effect (Geetha et al., 2015). The antiulcer effect was proved by the reduction of ulcer index, the promotion of the levels of superoxide dismutase and catalase, and the decrease in lipid peroxidation.

The active compounds **57** and **58** isolated from *R. tomentosa* were disclosed to promote the alkaline phosphatase activity (Nguyen et al., 2009), collagen synthesis, and mineralization of the nodules of MC3T3-E1 osteoblastic cell. The result indicated the potential of *R. tomentosa* to explore as therapeutic agent for osteoporosis.

EER and the active constituent piceatannol (**71**) were reported to suppress against ultraviolet (UV)-induced cytotoxicity in cultured normal human epidermal keratinocytes (Shiratake et al., 2015). The extract and compound **71** decreased the production of UV induced cyclobutane pyrimidine dimers and increased the DNA polymerases cellular enzyme activity, suggesting that the DNA damage stimulated by UV was repaired by the polymerases. This result revealed the potential market value for *R. tomentosa* and the possibility to develop as the skincare products.

4. Toxicity

Investigations on the safety and side effects evaluations for *R. tomentosa* are limited, although this plant has multiple pharmacological activities. It was reported that the cytotoxicity is weak (Zhang et al., 2018). The IC_{50} values of the *R. tomentosa* ethanol extract and the representative compound rhodomyrtone (**51**) were 476 mg/mL and more than 200 mg/mL, respectively, which is approximately 15- and 400-fold higher than their respective MIC90 values, suggesting the safety of *R. tomentosa*.

5. Industrial applications

Developing hopeful active natural products to industrial product with market value is not only a meaningful task, but also a project beneficial to human health. In recent decades, several patents have reported the potential development value of *R. tomentosa*. Based on the record in "Supplement to Compendium of Materia Medica" (Bencao Gangmu Shiyi, Qing dynasty), *R. tomentosa* is considered to be effective in nourishing the blood system, resisting rheumatism and

treating hematemesis, diarrhea, uterine bleeding, thus could be widely used for the treatment of various diseases including anemia, dysentery, rheumatism and hyperlipidemia (Zhang et al., 2018). Nowadays, a modern prescription "Fufang Gangren Pian" has been approved by CFDA (Z20043503) for the treatment of hepatitis and icterus, which is a formula mainly composed of the extract of *R. tomentosa* roots. As mentioned above, *R. tomentosa* exhibits much promise in supporting the blood system with its unique ingredients.

Outside of China, *R. tomentosa* has been widely utilized as well. In Malaysia, the berries of *R. tomentosa* have been used for the treatment of dysentery and the roots and trunk have been used for curing stomach ailments (Ong and Nordiana, 1999). In Thailand, *R. tomentosa* is used as the remedy of antipyretic and antidiarrheal herbal medicine (Chuakul, 2005). Native people in Vietnam have developed as the fermented drink named "Ruou Sim" (Vo and Ngo, 2019). Foodservice industry applications of *R. tomentosa* provide a novel choice for people to select health-care foods such as beverage, wine, noodles, bean curds which contain some constituents from *R. tomentosa* (**Table 2**). According to the abundant content of flavonoids and phenols, *R. tomentosa* exerted potential antioxidant capacity (Lavanya et al., 2012). Likewise, *R. tomentosa* was disclosed to show potential to explore as the skin cosmetic agent, for example, piceatannol (**71**) was demonstrated to be the functional substance for applications in cosmetics (**Table 2**) (JP2012046448A).

When we summarized the research studies about *R. tomentosa*, we found that it is easy to confuse rose myrtle (*R. tomentosa*) and myrtle (*Myrtus communis*) in China because of the same common names of the plants in Chinese (Taojinniang/桃金娘). Currently the industrial applications of myrtle are sophisticated and multiple products have been developed, such as the respiratory medicine Myrtol Standardized and the salable perfume Mirto di Panarea. The essential oil of myrtle is regarded as the functional substance, suggesting that essential oil should be appreciated when industrial applications are possessed.

Table 3. Patents list of products containing constituents from *R. tomentosa* and their claimed pharmacological properties.

Application	Main composition	Pharmacological properties	Publish number
Beverage	*R. tomentosa* leaves and fruits extract	Nourishing the blood system and protect against diarrhea and bleeding	CN103564585A
Solid beverage	*R. tomentosa* fruits extract	Nourishing the blood system and protect against diarrhea and bleeding	CN105942125A
Wine	*R. tomentosa* fruits extract and honey	Nourishing the blood system and protect against diarrhea and bleeding	CN104762157A
Fine dried noodles	*R. tomentosa* fruits powder, Cordyceps powder and flour	Nourishing lung, kidney and blood system	CN104323135A
Dried bean curds	*R. tomentosa* fruits juice, soybeans, *Dioscorea polystachya* powder, *Brassica rapa* powder, Cordyceps powder	Enhancing immunity function	CN106260071A
Body tonifying can	*R. tomentosa* fruits juice, cane juice, grape juice, watermelon juice	Nourishing liver and strengthening stomach, supplementing body needed vitamins and trace elements	CN104757447A
Skin cosmetic agent	*R. tomentosa* aerial part extract	Inhibiting the release of hexosaminidase, the activity of tyrosinase, elastase and cyclic AMP phosphodiesterase	JP2006199678A

Application	Main composition	Pharmacological properties	Publish number
Preventing of wrinkles and skin disorders agent	*R. tomentosa* extract, *Cipadessa baccifera* extract, *Woodfordia fruticosa* extract and *Camellia sinensis* extract	Preventing wrinkles and other skin disorders due to aging, stress and environmental factors without any side effect	WO2008032331A1
UV damage recovery agent	*R. tomentosa* extract	Protecting skin from UV damage	JP2012046448A
Hair growing agent	*R. tomentosa* fruits extract, *Origanum majorana* extract, *Actinidia polygama* extract, *Prunus mume* extract	Promoting the production of bone morphogenetic protein-2 and fibroblast growth factor-18	JP2014185131A

6. Conclusions and perspectives

This review summarized the phytochemistry, pharmacological activities and industrial applications of *R. tomentosa* according to traditional literatures and modern evidences, and it should provide a new milestone for further investigations on its mechanism of bioactivity and the better therapeutic antibacterial agents of rhodomyrtone (**51**) isolated from *R. tomentosa* in the future. Recent reports of *R. tomentosa* predominantly concentrate on the active ingredients from leaves or fruits, but the existing studies are still unclear and insufficient, more investigations about other constituents and other parts of the plant are urgently needed. It is also necessary to combine studies of the biological activity with research on clinical applications that explore the material basis of their efficacy. Although *R. tomentosa* has been widely used as the food and medicinal resource, we are still lacking sufficient safety information and only a small number of toxicity studies have been conducted. Therefore, the further toxicological investigations are also indispensable.

Overall, *R. tomentosa* is a kind of valuable edible medicinal herb resource that is worthy to paying additional attention due to its extensive bioactivities and potential development value in food industry. However, the existing health-related information on *R. tomentosa* is not sufficient, and its clinical value has not been sufficiently explored. A plenty of compounds have been isolated from *R. tomentosa*, but the existing studies of these substances might be only the tip of the iceberg. Hence, systematic phytochemical investigations about *R. tomentosa* and its pharmacological properties, especially its mechanism of bioactivity, to illustrate its ethnomedicinal application, and support further healthcare product development will undoubtedly be the focus of further research. This article should facilitate the development and application of *R. tomentosa*.

Acknowledgments

This work was supported by the 9th Group of Hundred-Talent Program of Shaanxi Province (2017), the Program for Changjiang Scholars and Innovative Research Team in University (No. IRT_15R55), Scientific Research Program Funded by Shaanxi Provincial Education Department (No. 18JK0774), the International Science & Technology Cooperation Program of Shaanxi Province (No. 2019KWZ-001).

References

Abd Hamid, H., Mutazah, R., Yusoff, M. M., Abd Karim, N. A., & Abdull Razis, A. F. (2017). Comparative analysis of antioxidant and antiproliferative activities of *Rhodomyrtus tomentosa* extracts prepared with various solvents. *Food and Chemical Toxicology, 108*(Pt B), 451-457.

Cao, J. Q., Wu, Y., Zhong, Y. L., Li, N. P., Chen, M., Li, M. M., Ye, W. C., & Wang, L. (2018). Antiviral triketone-phloroglucinol-monoterpene adducts from *Callistemon rigidus*. *Chemistry & Biodiversity, 15*(7), e1800172-e1800192.

Chai, H., Liu, B., Zhan, H., Li, X., He, Z., Ye, J., Guo, Q., Chen, J., Zhang, J., & Li, S. (2019). Antidepressant effects of rhodomyrtone in mice with chronic unpredictable mild dtress-induced depression. *The International Journal of Neuropsychopharmacology, 22*(2), 157-164.

Chen, T., Yu, C. G., & Yang, B. L. (2011). Structure elucidation and NMR assignments for two new quinones from fructus rhodomyrti of *Rhodomyrtus tomentosa*. *Chemistry of Natural Compounds, 47*(4), 524-526.

Chorachoo, J., Saeloh, D., Srichana, T., Amnuaikit, T., Musthafa, K. S., Sretrirutchai, S., & Voravuthikunchai, S. P. (2016). Rhodomyrtone as a potential anti-proliferative and apoptosis inducing agent in HaCaT keratinocyte cells. *European Journal of Pharmacology, 772*, 144-151.

Chuakul, W. (2005). Medicinal plants in the Khok Pho District, Pattani Province (Thailand) (Vol. 12).

Cui, C., Zhang, S. M., You, L. J., Ren, J. Y., Luo, W., Chen, W. F., & Zhao, M. M. (2013). Antioxidant capacity of anthocyanins from *Rhodomyrtus tomentosa* (Ait.) and identification of the major anthocyanins. *Food Chemistry, 139*(1-4), 1-8.

Dachriyanus, Salni, Sargent, M. V., Skelton, B. W., Soediro, I., Sutisna, M., White, A. H., & Yulinah, E. (2002). Rhodomyrtone, an antibiotic from *Rhodomyrtus tomentosa*. *Australian Journal of Chemistry, 55*(3), 229-232.

Flora of China Editorial Committee, 2001. Flora of China. Science Press, Beijing, China.

Geetha, K. M., Sridhar, C., & Murugan, V. (2015). Antioxidant and healing effect of aqueous alcoholic extract of *Rhodomyrtus tomentosa* (Ait.) Hassk on chronic gastric ulcers in rats. *Journal of Pharmacy Research*.

Geris, R., & Simpson, T. J. (2009). Meroterpenoids produced by fungi. *Natural Product Reports, 26*(8), 1063-1094.

Hiranrat, A., Chitbankluoi, W., Mahabusarakam, W., Limsuwan, S., & Voravuthikunchai, S. P. (2012). A new flavellagic acid derivative and phloroglucinol from *Rhodomyrtus tomentosa*. *Natural Product Research, 26*(20), 1904-1909.

Hiranrat, A., & Mahabusarakam, W. (2008). New acylphloroglucinols from the leaves of *Rhodomyrtus tomentosa*. *Tetrahedron, 64*(49), 11193-11197.

Hiranrat, A., Mahabusarakam, W., Carroll, A. R., Duffy, S., & Avery, V. M. (2012). Tomentosones A and B, Hexacyclic Phloroglucinol derivatives from the Thai shrub *Rhodomyrtus tomentosa*. *Journal of Organic Chemistry, 77*(1), 680-683.

Hiranrat, W., Hiranrat, A., & Mahabusarakam, W. (2017). Rhodomyrtosones G and H, minor phloroglucinols from the leaves of *Rhodomyrtus tomentosa*. *Phytochemistry Letters, 21*, 25-28.

Hmoteh, J., Musthafa, K. S., & Voravuthikunchai, S. P. (2018). Effects of *Rhodomyrtus tomentosa* extract on virulence factors of Candida albicans and human neutrophil function. *Archives of Oral Biology, 87*, 35-42.

Hou, A., Wu, Y., & Liu, Y. (1999). Flavone glycosides and an ellagitannin from Downy Rose myrtle (*Rhodomyrtus tomentosa*). *Zhongcaoyao, 30*(9), 645-648.

Huang, M., Ya, Q., Chen, H., Tan, X., Liu, H., & Dang, M. (2010). Chemical compositions of *Rhodomyrtus tomentosa*. *Zhongcaoyao, 41*(7), 1079-1080.

Huang, W. Y., Cai, Y. Z., Corke, H., & Sun, M. (2010). Survey of antioxidant capacity and nutritional quality of selected edible and medicinal fruit plants in Hong Kong. *Journal of Food Composition & Analysis, 23*(6), 510-517.

Hui, W. H., & Li, M. M. (1976). Two new triterpenoids from *Rhodomyrtus tomentosa*. *Phytochemistry, 15*(11), 1741-1743.

Hui, W. H., Li, M. M., & Luk, K. (1975). Triterpenoids and steroids from *Rhodomyrtus tomentosa*. *Phytochemistry, 14*(3), 833-834.

Jeong, D., Yang, W. S., Yang, Y., Nam, G., Kim, J. H., Yoon, D. H., Noh, H. J., Lee, S., Kim, T. W., Sung, G. H., & Cho, J. Y. (2013). In vitro and in vivo anti-inflammatory effect of *Rhodomyrtus tomentosa* methanol extract. *Journal of Ethnopharmacology, 146*(1), 205-213.

Lai, T. N. H., Andre, C., Rogez, H., Mignolet, E., Nguyen, T. B. T., & Larondelle, Y. (2015). Nutritional composition and antioxidant properties of the sim fruit (*Rhodomyrtus tomentosa*). *Food Chemistry, 168*, 410-416.

Lai, T. N. H., Herent, M. F., Quetin-Leclercq, J., Nguyen, T. B. T., Rogez, H., Larondelle, Y., & Andre, C. M. (2013). Piceatannol, a potent bioactive stilbene, as major phenolic component in *Rhodomyrtus tomentosa*. *Food Chemistry, 138*(2-3), 1421-1430.

Lavanya, G., Voravuthikunchai, S. P., & Towatana, N. H. (2012). Acetone extract from *Rhodomyrtus tomentosa*: a potent natural antioxidant. *Evidence-Based Complementary and Alternative Medicine, 2012*, 535479-5354886.

Limsuwan, S., Hesseling-Meinders, A., Voravuthikunchai, S. P., van Dijl, J. M., & Kayser, O. (2011). Potential antibiotic and anti-infective effects of rhodomyrtone from *Rhodomyrtus tomentosa* (Aiton) Hassk. on Streptococcus pyogenes as revealed by proteomics. *Phytomedicine, 18*(11), 934-940.

Limsuwan, S., Homlaead, S., Watcharakul, S., Chusri, S., Moosigapong, K., Saising, J., & Voravuthikunchai, S. P. (2014). Inhibition of microbial adhesion to plastic surface and human buccal epithelial cells by *Rhodomyrtus tomentosa* leaf extract. *Archives of Oral Biology,*

59(12), 1256-1265.

Limsuwan, S., Kayser, O., & Voravuthikunchai, S. P. (2012). Antibacterial activity of *Rhodomyrtus tomentosa* (Aiton) Hassk. leaf extract against clinical isolates of *Streptococcus pyogenes*. *Evidence-Based Complementary and Alternative Medicine*, 697183-697188.

Liu, H., Feng, M. Y., Yu, Q., Yan, H., Zeng, Y., Qin, X. J., He, L., & Liu, H. Y. (2018). Formyl phloroglucinol meroterpenoids from *Eucalyptus tereticornis* and their bioactivities. *Tetrahedron, 74*(13), 1540-1545.

Liu, H. X., Tan, H. B., & Qiu, S. X. (2016). Antimicrobial acylphloroglucinols from the leaves of *Rhodomyrtus tomentosa*. *J Asian Nat Prod Res, 18*(6), 535-541.

Liu, H. X., Zhang, W. M., Xu, Z. F., Chen, Y. C., Tan, H. B., & Qiu, S. X. (2016). Isolation, synthesis, and biological activity of tomentosenol A from the leaves of *Rhodomyrtus tomentosa*. *Rsc Advances, 6*(31), 25882-25886.

Liu, J., Song, J. G., Su, J. C., Huang, X. J., Ye, W. C., & Wang, Y. (2018). Tomentodione E, a new sec-pentyl syncarpic acid-based meroterpenoid from the leaves of Rhodomyrtus tomentosa. *J Asian Nat Prod Res, 20*(1), 67-74.

Liu, Y., Hou, A., Ji, C., & Wu, Y. (1998). Isolation and structure of hydrolysable tannins from *Rhodomyrtus tomentosa*. *Tianran Chanwu Yanjiu Yu Kaifa, 10*(1), 14-19.

Liu, Y. Z., Hou, A. J., Ji, C. R., & Wu, Y. J. (1997). A new C-glycosidic hydrolyzable tannin from *Rhodomyrtus tomentosa*. *Chinese Chemical Letters, 8*(1), 39-40.

Mitsuwan, W., Jimenez-Munguia, I., Visutthi, M., Sianglum, W., Jover, A., Barcenilla, F., Garcia, M., Pujol, M., Gasch, O., Dominguez, M. A., Camoez, M., Duenas, C., Ojeda, E., Martinez, J. A., Marco, F., Chaves, F., Lagarde, M., Lopez-Medrano, F., Montejo, J. M., Bereciartua, E., Hernandez, J. L., von Wichmann, M. A., Goenaga, A., Garcia-Arenzana, J. M., Padilla, B., Padilla, C., Cercenado, E., Garcia-Prado, G., Tapiol, J., Horcajada, J. P., Montero, M., Salvado, M., Arnaiz, A., Fernandez, C., Calbo, E., Xercavins, M., Granados, A., Fontanals, D., Pintado, V., Loza, E., Torre-Cisneros, J., Lara, R., Rodriguez-Lopez, F., Natera, C., Blanco, J. R., Olarte, I., Benito, N., Mirelis, B., Murillas, J., Ruiz de Gopegui, E., Espejo, H., Morera, M. A., Rodriguez-Bano, J., Lopez-Cortes, L. E., Pascual, A., Martin, C., Lepe, J. A., Molina, J., Sorde, R., Almirante, B., Larrosa, N., Rodriguez-Ortega, M. J., Voravuthikunchai, S. P., & Grp, R. G. S. (2019). Rhodomyrtone decreases *Staphylococcus aureus* SigB activity during exponentially growing phase and inhibits haemolytic activity within membrane vesicles. *Microbial Pathogenesis, 128*, 112-118.

Mordmuang, A., Shankar, S., Chethanond, U., & Voravuthikunchai, S. P. (2015). Effects of *Rhodomyrtus tomentosa* leaf extract on staphylococcal adhesion and invasion in bovine udder epidermal tissue model. *Nutrients, 7*(10), 8503-8517.

Mordmuang, A., & Voravuthikunchai, S. P. (2015). *Rhodomyrtus tomentosa* (Aiton) Hassk. leaf extract: an alternative approach for the treatment of staphylococcal bovine mastitis. *Research in Veterinary Science, 102*, 242-246.

Na-Phatthalung, P., Chusri, S., Suanyuk, N., & Voravuthikunchai, S. P. (2017). *In vitro* and *in vivo*

assessments of *Rhodomyrtus tomentosa* leaf extract as an alternative anti-streptococcal agent in Nile tilapia (*Oreochromis niloticus* L.). *Journal of Medical Microbiology, 66*(4), 430-439.

Na-Phatthalung, P., Teles, M., Voravuthikunchai, S. P., Tort, L., & Fierro-Castro, C. (2018a). Immune-related gene expression and physiological responses in rainbow trout (*Oncorhynchus mykiss*) after intraperitoneal administration of *Rhodomyrtus tomentosa* leaf extract: A potent phytoimmunostimulant. *Fish & Shellfish Immunology, 77*, 429-437.

Na-Phatthalung, P., Teles, M., Voravuthikunchai, S. P., Tort, L., & Fierro-Castro, C. (2018b). Immunomodulatory effects of *Rhodomyrtus tomentosa* leaf extract and its derivative compound, rhodomyrtone, on head kidney macrophages of rainbow trout (*Oncorhynchus mykiss*). *Fish Physiology and Biochemistry, 44*(2), 543-555.

Nguyen, H. T., Ding, Y., Choi, E. M., Phan, V. K., Chau, V. M., & Kim, Y. H. (2009). New anthracene glycosides from *Rhodomyrtus tomentosa* stimulate osteoblastic differentiation of MC3T3-E1 cells. *Archives of Pharmacal Research, 32*(4), 515-520.

Nicoletti, R., Salvatore, M. M., Ferranti, P., & Andolfi, A. (2018). Structures and bioactive properties of myrtucommulones and related acylphloroglucinols from Myrtaceae. *Molecules, 23*(12), 3370-3397.

Odedina, G. F., Vongkamjan, K., & Voravuthikunchai, S. P. (2015). Potential Bio-Control Agent from *Rhodomyrtus tomentosa* against *Listeria monocytogenes*. *Nutrients, 7*(9), 7451-7468.

Odedina, G. F., Vongkamjan, K., & Voravuthikunchai, S. P. (2016). Use of *Rhodomyrtus tomentosa* ethanolic leaf extract for the bio-control of Listeria monocytogenes post-cooking contamination in cooked chicken meat. *Journal of Food Science and Technology, 53*(12), 4234-4243.

Ong, H. C., & Nordiana, M. (1999). Malay ethno-medico botany in Machang, Kelantan, Malaysia. *Fitoterapia, 70*(5), 502-513.

Phan, M. G., Tran, T. H., Nguyen, T. H. A., & Phan, T. S. (2007). Contribution to the study on polar constituents from the buds of *Rhodomyrtus tomentosa* (Ait.) Hassk. (Myrtaceae). *Tap Chi Hoa Hoc, 45*(6), 749-750.

Prosser, J. A., Woods, R. R., Horswell, J., & Robinson, B. H. (2016). The potential in-situ antimicrobial ability of Myrtaceae plant species on pathogens in soil. *Soil Biology & Biochemistry, 96*, 1-3.

Qin, X.-J., Rauwolf, T. J., Li, P.-P., Liu, H., McNeely, J., Hua, Y., Liu, H.-Y., & Porco, J. A., Jr. (2019). Isolation and synthesis of novel meroterpenoids from *Rhodomyrtus tomentosa*: investigation of a reactive enetrione intermediate. *Angewandte Chemie (International ed. in English), 58*(13), 4291-4296.

Saeloh, D., Tipmanee, V., Jim, K. K., Dekker, M. P., Bitter, W., Voravuthikunchai, S. P., Wenzel, M., & Hamoen, L. W. (2018). The novel antibiotic rhodomyrtone traps membrane proteins in vesicles with increased fluidity. *Plos Pathogens, 14*(2), 1-35.

Saising, J., Nguyen, M. T., Hartner, T., Ebner, P., Bhuyan, A. A., Berscheid, A., Muehlenkamp, M., Schakermann, S., Kumari, N., Maier, M. E., Voravuthikunchai, S. P., Bandow, J., Lang, F.,

Brotz-Oesterhelt, H., & Gotz, F. (2018). Rhodomyrtone (Rom) is a membrane-active compound. *Biochimica Et Biophysica Acta-Biomembranes, 1860*(5), 1114-1124.

Salehi, B., Valussi, M., Jugran, A. K., Martorell, M., Ramírez-Alarcón, K., Stojanović-Radić, Z. Z., Antolak, H., Kręgiel, D., Mileski, K. S., Sharifi-Rad, M., Setzer, W. N., Cádiz-Gurrea, M. d. l. L., Segura-Carretero, A., Şener, B., & Sharifi-Rad, J. (2018). Nepeta species: From farm to food applications and phytotherapy. *Trends in Food Science & Technology, 80*, 104-122.

Shiratake, S., Nakahara, T., Iwahashi, H., Onodera, T., & Mizushina, Y. (2015). Rose myrtle (*Rhodomyrtus tomentosa*) extract and its component, piceatannol, enhance the activity of DNA polymerase and suppress the inflammatory response elicited by UVB-induced DNA damage in skin cells. *Molecular Medicine Reports, 12*(4), 5857-5864.

Srisuwan, S., Tongtawe, P., Srimanote, P., & Voravuthikunchai, S. P. (2014). Rhodomyrtone Modulates Innate Immune Responses of THP-1 Monocytes to Assist in Clearing Methicillin-Resistant *Staphylococcus aureus*. *Plos One, 9*(10), e110321- e110331.

Srisuwan, S., & Voravuthikunchai, S. P. (2017). Rhodomyrtus tomentosa Leaf Extract Inhibits Methicillin-Resistant Staphylococcus aureus Adhesion, Invasion, and Intracellular Survival in Human HaCaT Keratinocytes. *Microbial Drug Resistance, 23*(8), 1002-1012.

Tan, H., Liu, H., Zhao, L., Yuan, Y., Li, B., Jiang, Y., Gong, L., & Qiu, S. (2017). Structure-activity relationships and optimization of acyclic acylphloroglucinol analogues as novel antimicrobial agents. *European Journal of Medicinal Chemistry, 125*, 492-499.

Tayeh, M., Nilwarangoon, S., Mahabusarakum, W., & Watanapokasin, R. (2017). Anti-metastatic effect of rhodomyrtone from *Rhodomyrtus tomentosa* on human skin cancer cells. *International Journal of Oncology, 50*(3), 1035-1043.

Visutthi, M., Srimanote, P., & Voravuthikunchai, S. P. (2011). Responses in the expression of extracellular proteins in methicillin-resistant Staphylococcus aureus treated with rhodomyrtone. *Journal of Microbiology, 49*(6), 956-964.

Vo, T. S., & Ngo, D. H. (2019). The health beneficial properties of *Rhodomyrtus tomentosa* as potential functional food. *Biomolecules, 9*(2), 76-91.

Wu, P. P., Ma, G. Z., Li, N. H., Deng, Q. G., Yin, Y. Y., & Huang, R. Q. (2015). Investigation of *in vitro* and *in vivo* antioxidant activities of flavonoids rich extract from the berries of *Rhodomyrtus tomentosa* (Ait.) Hassk. *Food Chemistry, 173*, 194-202.

Wu X. L., Beecher, G. R., Holden, J. M., Haytowitz, D. B., Gebhardt, S. E., & Prior, R. L. (2004). Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *Journal of Agricultural & Food Chemistry, 52*(12), 4026-4037.

Wunnoo, S., Saising, J., & Voravuthikunchai, S. P. (2017). Rhodomyrtone inhibits lipase production, biofilm formation, and disorganizes established biofilm in *Propionibacterium acnes*. *Anaerobe, 43*, 61-68.

Xiong, J., Huang, Y., Tang, Y., You, M., & Hu, J. (2013). Pentacyclic triterpenoids from the roots of *Rhodomyrtus tomentosa*. *Youji Huaxue, 33*(6), 1304-1308.

Zhang, Y. B., Li, W., Jiang, L., Yang, L., Chen, N. H., Wu, Z. N., Li, Y. L., & Wang, G. C. (2018).

Cytotoxic and anti-inflammatory active phloroglucinol derivatives from *Rhodomyrtus tomentosa*. *Phytochemistry, 153*, 111-119.

Zhang, Y. B., Li, W., Zhang, Z. M., Chen, N. H., Zhang, X. Q., Jiang, J. W., Wang, G. C., & Li, Y. L. (2016). Two new triterpenoids from the roots of *Rhodomyrtus tomentosa*. *Chemistry Letters, 45*(3), 368-370.

Zhang, Y. L., Chen, C., Wang, X. B., Wu, L., Yang, M. H., Luo, J., Zhang, C., Sun, H. B., Luo, J. G., & Kong, L. Y. (2016). Rhodomyrtials A and B, Two meroterpenoids with a triketone-sesquiterpene-triketone skeleton from *Rhodomyrtus tomentosa*: structural elucidation and biomimetic synthesis. *Organic Letters, 18*(16), 4068-4071.

Zhang, Y. L., Zhou, X. W., Wu, L., Wang, X. B., Yang, M. H., Luo, J., Luo, J. G., & Kong, L. Y. (2017). Isolation, structure elucidation, and absolute configuration of syncarpic acid-conjugated terpenoids from *Rhodomyrtus tomentosa*. *Journal of Natural Products, 80*(4), 989-998.

Zhao, L. Y., Liu, H. X., Wang, L., Xu, Z. F., Tan, H. B., & Qiu, S. X. (2018). Rhodomyrtosone B, a membrane-targeting anti-MRSA natural acylgphloroglucinol from *Rhodomyrtus tomentosa*. *Journal of Ethnopharmacology*, 50-57.

Zhu, C. F., Liu, H. X., He, L., Wang, J. G., & Qiu, S. X. (2015). Chemical constituents from leaves of *Rhodomyrtus tomentosa*. *Redai Yaredai Zhiwu Xuebao, 23*(1), 103-108.

Zhuang, L., Chen, L. F., Zhang, Y. B., Liu, Z., Xiao, X. H., Tang, W., Wang, G. C., Song, W. J., Li, Y. L., & Li, M. M. (2017). Watsonianone A from *Rhodomyrtus tomentosa* Fruit Attenuates Respiratory-Syncytial-Virus-Induced Inflammation In Vitro. *Journal of Agricultural and Food Chemistry, 65*(17), 3481-3489.

Zou, Z. X., Tan, G. S., Huang, Q., Sun, H. H., Huo, L. Q., Zhong, W. Q., Zhao, L. Y., Liu, H. X., & Tan, H. B. (2018). Brachyanins A-C, pinene-derived meroterpenoids and phloroglucinol derivative from *Leptospermum brachyandrum*. *Fitoterapia, 130*, 184-189.