Rhodiola: An Overview of Phytochemistry and Pharmacological Applications

Pushpender Bhardwaj, Garima Bhardwaj, Rinky Raghuvanshi, Mohan Singh Thakur, Raj Kumar, and O. P. Chaurasia

Introduction

Plants, on the planet earth, are one of the most important natural resources available for the human life. They provide oxygen, food, essential pigments, and ornamental and medicinal components that provide support to humans for sustenance of life and combat with the harmful and life-threatening conditions on the planet. There are more than 300–315 species of medicinal plants which have been identified by the various botanists of the world (Sundriyal et al. 2004). The main and foremost use of the plant by humans is in the form of medicines. Since ancient times it has been recognized that there are many plant species which have huge medicinal value and have healing potential against various fatal diseases. Plants like *Azadirachta indica* (Neem), *Ocimum tenuiflorum* (Tulsi), *Mentha arvensis* (Menthol), *Psidium guajava* (guava), *Aleo vera*, *Rheum* sp., *Hypericum* sp., *Rhodiola* sp., etc. were not only used by the ancient people for treatment of diseases like stomachache, headache, paralysis, fever, etc., but in the present day also, they are being used in their raw as well as in the mixture form with other compounds for various human-related abnormalities like high free radical production in the body, inflammation, tumor, etc. (Sikkink 2009) The knowledge to use these plant species is available to us through various Vedas in which they are properly classified and designated for their potential use as medicine. Besides these well-known species of plants, there are many other species which are known for their high medicinal values and are maintained by various local traditional medicinal systems like Ayurveda, Siddha medicine, Unani, and Ancient Iranian medicinal system. All over the world, there are various practitioners who practice the medicinal plants for the treatment. In some African and Asian countries, around 80% of the their population relies on these traditional medicinal systems. Amchi system (sowa-rigpa) is also one of the well-developed medicinal system of

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India. In Amchi system of medicine, they have provided a very deep knowledge of medicinal uses of various plants which are found in the high mountain ranges of Ladakh region of Jammu and Kashmir. There are more than 200 species of plant species like *Rhodiola, Rheum, Podophyllum, Artemisia, Centurea,* etc. from these regions which have extensive application for the treatment against diseases like malaria, cancer, etc. and also show antimicrobial-, anticancer-, anti-inflammatory-, antihypotensive-, and anticholinergic-like activities. In various traditional formulations, these plant species were dried and mixed with the butter and applied as the ointment to relieve pain and swelling (Halldorsson and Grasnytjar 1783) and also being used as a supplement for long journey (Alm 2004). These plants contain a plethora of various classes of bioactive compounds like flavonoids, glycosides, phenylpropanoid, etc., which have a very high value toward the human health (Chaurasia et al. 2007). *Rhodiola* is one of the perennial herbs which belongs to the *Campanulaceae* family and also resembles to the sebum which is known as stonecrops. This genus is made up of about 93 species. It has a few distinguishing characters which includes the series of stamen and has a stout rhizome from which the plant arises. This plant makes a whorl and contain red or yellow color top which includes seeds of plants. *Rhodiola* has adapted to harsh and almost unforgiving climate. These *Rhodiola* species were reported to find in the northern hemisphere in countries like China, Mongolia, Korea, Sakhalin, the Kuriles, Japan, Sweden, Norway, Finland, India, and Pakistan. In China, it is distributed in the northwest and the southwest region, and it is locally known as Hong Jing Tian (Bassa et al. 2016). In India, it is distributed in Jammu and Kashmir region, Himachal Pradesh and Arunachal Pradesh, and almost in complete Himalayan belt. Tibet is one of the places which are rich in its production (Kumar et al. 2010a). *Rhodiola* species are also reported to find in Russia, the United States, and Canada (Lei et al. 2003).

In the Ladakh region of Jammu and Kashmir, *Rhodiola imbricata* and *Rhodiola heterodonta* have a diverse distribution. Out of the five different valleys of Ladakh (Suru, Zanskar, Nubra, Indus, and Changthang), these plants are available in Changthang, Nubra, Zanskar, and Indus valley. The major population of the plant found in the passes such as Khardungla pass (between Indus and Nubra valley), Changla pass (between Nubra and Changthang), Pensi-la pass (between Zanskar and Suru valley), etc. are present in between these valleys; they join these valleys to one another (Chaurasia et al. 2007). Few of the commonly known species of this family are *Rhodiola rosea* (known as roseroot), *Rhodiola imbricata* (recently known as a sanjivani), *Rhodiola heterodonta*, *Rhodiola quadrifida*, etc. All these species were reported to have very high medicinal values like antioxidant, anti-inflammatory, leprosy, antistress, etc. The kind of environment in which these plants grow is very harsh with a low temperature of around −10 °C and at a height of around 4000–5000 m above the sea level. In such hard survival conditions, these plants survive as well as propagate and have successfully adapted to that environment. The key component for their survival in those conditions is the adaptation of these plants and also the kind of compounds these plants produce in their biological mechanism

which are not only helpful to the plants but for human also. Historically, these plants have been used in various traditional medicine systems of India, China, Europe, etc. In the modern world, these plants of *Campanulaceae* genus are extensively used in various formulations and basically include the roots of these plants which contain a very high content of secondary metabolites. The key secondary metabolites which have been reported and extensively studied in these plants are rosin, rosavin, salidroside, etc. The present chapter discusses about the distribution of the plants in various countries, its bioactive compounds, and their bioactivity (Chaurasia et al. 2007).

Distribution of *Rhodiola* Species

Rhodiola rosea

Rhodiola rosea is an inhabitant of subarctic area of the northern hemisphere. It is mainly available in high altitudes over rocks and on Arctic sea cliffs in Europe, Asia, and North America, including Britain, further south in mountains, and China (Zhang et al. 2016). Mountain Altai and south region of foothill Altai, mainly in Ust-Kansky, Ust-Koksinsky, and Charishki regions, the availability of commercial roots and rhizome is in great abundance (Saratikov and Krasnov 2004).

Rhodiola imbricata

Rhodiola imbricata, found in Sinai Himalayas, Nepal, Qinghai, Xizang, and India, is also found in the hilly region of western Himalaya (Kanupriya et al. 2005). The major distribution of *Rhodiola imbricata* is in three different valleys (Zanskar (N33.95 and E76.46), Indus (N34.29 and E77.86), and Changthang (N 34.26 and E 78.14)) of Ladakh region of Trans-Himalayas (Chaurasia et al. 2007).

Rhodiola heterodonta

Rhodiola heterodonta species are endemic to the mountain range of Central Asia and mainly distributed in East Europe and Asia (Grace et al. 2009).

Rhodiola crenulata

The plant *Rhodiola crenulata* is native to the Qinghai-Tibet Plateau and the only original plant, according to the "*Pharmacopoeia of China*" (Chinese Pharmacopoeia Commission 2010). This plant has shown a distribution in Hengduan Mountains Region of China, Tibet, and Yunnan (Lei et al. 2003).

Rhodiola kirilowii

The plant is mainly prevalent in Gansu, Hebei, Qinghai, Shaanxi, Shanxi, Sichuan, Xinjiang, Xizang, and Yunnan (Kazakhstan, Myanmar). In Central Asia it is found in Narynskiy Range, Terskey Alatau, Alayskiy Range, northern China, and Tibet (Maximowicz 2007).

Rhodiola bupleuroides

The plant *R. bupleuroides* is aboriginal to western Tibet Autonomous Region, locally known as "Sheng-Chang Hong Jing Tian" or "Bu-Dan Hong Jing Tian, northwest of Yunnan, and Sichuan (Li et al. 2007). It is also found in Pakistan, Kumaon, Nepal, Sikkim, Bhutan, Myanmar, and SW China, at altitudes of 2750–3700 m (Hooker and Thomson 1998).

Rhodiola dumulosa

Rhodiola dumulosa is a perennial plant species that are found in various regions of China that includes Northern, Northwestern, and Central China. It is distributed as fragmented populations across Northern, Northwestern, and Central China (Hou and Lou 2011).

Rhodiola algida

Rhodiola algida is mainly distributed in the Qinghai Plateau in China (Qi et al. 2015). It is also present in large amount in Tibet. *Rhodiola algida* helps to improve oral mucositis which were induced in breast cancer patients (Loo et al. 2010).

Rhodiola sachalinensis

Rhodiola sachalinensis is a herbaceous plant (perennial) of the Crassulaceae family, predominantly found in the polar region of Arctic and Alpine (Seo et al. 2001) and high rocky mountain areas of East Asian countries (Ohwi 1984).

Rhodiola quadrifida

Rhodiola quadrifida is a grassy plant occurring predominantly in some highland regions of the East Siberia, former USSR *(Altai-Sayan)*, mountainous regions of China (Sichuan), and Mongolia (Hentii, Hangai, Hovsgol, Hovd, and Mongol Altai) (Wiedenfeld et al. 2007).

Rhodiola alsi

The data related to the distribution of this species is not extensively available, but it is only reported to be found in Qinghai-Tibet Plateau of China (Ma et al. 2008).

Chemoprofiling of *Rhodiola* Species

From age-old times, Asia and Europe have been utilizing *Rhodiola* species as medicinal resource which is endemic to the northern hemisphere's subarctic areas. Their usages include valuable functions as adaptogen, anti-inflammatory, and anti-depressant drugs. In the process to establish the therapeutic/pharmacological uses of these plants in modern medicine, the effects of *Rhodiola* sp. have been extensively studied. Out of all the species, *Rhodiola rosea* has been shown to possess greater amount of activities like angiomodulatory, antioxidant, antimicrobial, adaptogenic, antistress, immunomodulatory, and antitumoral effects. From a chemotaxonomical's view, eight compounds which include the phenylpropanoids rosarin, rosavin, and rosin, the phenylethanoids salidroside and tyrosol, the flavonol rhodionin, as well as catechin and gallic acid have been proposed as reference markers (Recio et al. 2016). These are monoterpene alcohols and their glycosides (cyanogenic and aryl glycosides), phenylethanoids and their glycosides, proanthocyanidins, flavonoids and gallic acid derivatives, flavonolignans. In chemical nature of the adaptogens, they are typically tetracyclic triterpenoids/steroids complex or phenolics. Salidroside (p-hydroxyphenethyl-β-D-glucoside), which is a major compound in *Rhodiola*, seems to be accountable for many observed with *Rhodiola* extract's effects (Table 1).

Figure 1 represents the structure of salidroside, rosavin, and rhodionin compounds (Panossian et al. 2010).

Rhodiola rosea

The phenolic compounds included in this species are based on phenylpropanoids and phenylethane derivatives class, such as rosavin, tyrosol, salidroside (rhodioloside), syringin, and triandrin. Few of the reported lignans are eleutherosid E and schisandrin B. Figure 2 represents the structure of important compounds from *Rhodiola rosea* (tyrosol, syringin, rosiridine, ginsinoside, sitoindoside) (Panossian et al. 2010).

Rhodiola imbricata

Rhodiola imbricata contains large amount of bioactive compounds. The Chemoprofile of *Rhodiola imbricata's* root revealed the presence of 63 phyto-chemotypes (Fig. 3), among them, 1-pentacosanol; hexadecanoic acid; 2-hydroxy-

Table 1 Chemical compounds of various *Rhodiola* species

S. No.	Plant	Compound
1.	*Rhodiola rosea*	Salidroside (rhodioloside); rosavin; syringing; triandrin; tyrosol; eleutherosid E and schisandrin B; syringin; rosiridine, ginsenoside; sitoindoside
2	*Rhodiola imbricata*	1-pentacosanol, stigmast-5-en-3-ol, (3β,24S); 1-tetracosanol; 1-hentetracontanol; 9,12,15-octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z); 17-pentatriacontene; bis (2-ethylhexyl) phthalate; 7,8-dimethylbenzocyclooctene; ethyl linoleate; 3-methoxy-5-methylphenol; camphor; methyl tri-butyl ammonium chloride; 1,3-benzenediol, 5-methyl dodecanoic acid, 3-hydroxy; octadecane, 1-chloro; ethanone, 1-(4-hydroxyphenyl); a-tocopherol; d-tocopherol; ascaridole; campesterol; heptadecane, 9 hexyl; 1-hentriacontane; 1-heptacosane; 1-tericosanol; 13-docosen-1-ol; 1,30-triacontanediol; Stigmast-3,5-dien-7-one; stigmastanol; 9,12-octadecadienoic acid(Z,Z)-,2-hydroxy-1-(hydroxymethyl)ethyl ester; 1-tetratetracontane; A-Tocopherol-β-D-mannoside;1-pentatriacontane; bacteriochlorophyll-c-stearyl; 1,3-dimethoxybenzene; a-D- glucopyranoside, O-b-D-glucopyranosyl-(1.fwdarw.3)-b-D-fructofuranosyl; benzene sulfonic acid, 4-amino-3-nitro; cholest-4-ene-3,6-dione; Cis-9- eicosen-1-ol; (4-carboxymethoxy) benzoyl, methanol; oleic acid; hexadecanoic acid, bis(2-ethylhexyl) ester; hexadecanoic acid, methyl ester; bacteriochlorophyll-c-stearyl; eucalyptol; 1-(2,6-dihydroxy-4-methoxyphenyl) ethanone; linalyl isovalerate; 1-chloro-2,4-dimethoxybenzene; Borneol;4-chlorobenezenethiol; thujone; phenol,3,5-dimethoxy acetate; 2,4-bis(1,1dimethylethyl) phenol; b-fenchyl alcohol; 5-pentadecyl −1,3-benzenediol; A-D-glucopyranoside,O-α-D-glucopyranosyl-(1.fwdarw.3)-β-D-fructofuranosyl; 1-pentatricontene; 3,7,11-trimethyl- 1-dodecanol; 1-dodecane; 3-methoxy-5-methyl phenol; di-butyl phthalate; 3,5-dihydroxybenzyl alcohol; 3-methoxy-5-hydroxybenzyl alcohol; orcinol; O-methylorcinol; *p*-hydroxybenzaldehyde; *p*-hydroxyacetophenone, *p*-hydroxybenzyl alcohol; 4-methoxyphenethyl alcohol, 3-hydroxy-5-methylphenyl-β-D-glucopyranoside; Stigmast-4-en-3-one; methoxyphenyl-β-D-glucopyranoside; 2-hydroxymethyl-6-methoxy- β-D-glucopyranoside; 13-tetradecen-1-ol acetate; phenyl- β-D-glucopyranoside,3,5-dimethoxyphenyl- β-D-glucopyranoside, trimethoxyphenyl- β-D-glucopyranoside, 3-hydroxy-2-(3-methyl-2-buten-1-yl)-benzoic acid, 2-(hydroxymethyl(−6-methoxy-3-acetylphenyl- β-D-glucopyranoside, 2-(hydroxymethyl)-6-methoxyphenyl β-D-glucopyranoside; 1-dotriacontane; 2-hydroxy-4-methylphenyl- β-D-glucopyranoside; hexadecanoic acid; benzenemethanol, 3-hydroxy, 5-methoxy
3	*Rhodiola heterodonta*	Salidroside; tyrosol methyl ester; mongrhoside; Rhodiocynanoside A; epigallocatechin gallate; viridoside; epigallocatechin-epigallocatechin-3-O- gallate; Tyrosol; heterodontoside and 3-O-galloyl-epigallocatechin- epigallocatechin-3-O gallate; (−)-EGCG-4β-benzylthioether and (−)- Epigallocatechin-3-O-gallate

(continued)

Table 1 (continued)

S. No.	Plant	Compound
4	*Rhodiola crenulata*	Salidroside; tyrosol; p-hydroxyphenacyl-b-D-glucopyranoside; icariside D2; rutin; lotaustralin; herbacetin-7-methyl ether; rhodiocyanoside A; crenulatin; rhodionin; daucosterol; b-sitosterol; geraniol; gallic acid; creosides I,II, III, IV, V; kenposide A; rhodioloside E; Isopentyl-3-O-β-glucopyranoside; rhodiooctanoside; dihydroconiferin; 4-hydroxypenzyl- β-D-glucopyranoside; triandrin; vimalin; caffeic acid; pollenitin; rhodiosin; kaempferol; 5,7,3′,5′-tetrahydroxydihydroflavone; luteolin; kaempferol-7-O-α-L-rhamnoside; ternatumoside II; crenuloside; (+)-isolarisiresinol; (+)-dihydrodehydrodiconiferyl alcohol; methyl gallate;2-(4-hydroxyphenyl) ethyl 3,4,5-trihydroxybenzoate; Clemastanin A; (7R,8R)-3-methoxy-8′-carboxy-7′-en-3′,7-epoxy-8,4′-oxyneolignan-4,9-diol; (7R,8R)-3-methoxy-8′-carboxy-7′-en-3′,8-epoxy-7,4′-oxyneolignan-4,9-diol; (7β,7′β",8α,8′α′)-3′-methoxy-9-oxo-7,9′,7,9″-diepoxylignan-3,4,4″-triol; icariside D2; rhodiolate; 4′-hydroxyacetophenone (4-HAP) Coniferoside; epicatechin-(4β,8)-epicatechin gallate (B2–3′-*O*-gallate); salidroside and *p*-tyrosol; (3R,5R,8R)-3-O-[α-l-arabinopyranosyl (1 → 6)-β-d-glucopyranosyl]-5-hydroxymegastigma-6,7-dien-9-one; (1R)-1-O-(β-d-glucopyranosyl)-phenylethylene glycol; n-octanol; 2-methyl-3-buten-2-ol; citronellol;,3-methyl-2-buten-1-ol; myteolp; picein and linalool
5	*Rhodiola kirilowii*	Tyrosol; digalloylproprodelphinidin B2 (rhodisin); Arbutin; epigallocatechin gallate; rhodiocyanoside A; fructopyran(1-4)-glycopyranose; lotaustralin; 3,3′- 3,3′-Digalloylprocyanidin B2; epicatechin-3-O-gallate; beta-sitosterol; trans-hydroxycinnamic acid; neryl beta-glucopyranoside; hexyl beta-glucopyranoside; gallic acid; rhodiolgin; isolariciresinol-9-O-beta-glucopyranoside; rhodiooctanoside; sacranoside B; geranyl beta-glucopyranoside
6	*Rhodiola bupleuroides*	Kaempferol-7-O-α-L-rhamnopyranoside; rhodiosin; quercetin; syringic acid; β-sitosterol; rhobupcyanoside; B gallic acid
7	*Rhodiola dumulosa*	β-sitosterol; sexangularetin; β-sitosterol glucoside; herbacetin-7-α-L-rhamnoside; kaempferol; gallic acid; kaempferol-3-O-beta-D-glucopyranoside-7-alpha-O-L-rhamnoside; rutin; kaempferol-7-O-α-L-rhamnoside; quercetin
8	*Rhodiola algida*	Salidroside; tyrosol; diacetylrhodalgin; rhodalgin; acetylrhodalgin; triacetylrhodalgin
9	*Rhodiola sachalinensis*	Salidroside; rhodiocyanosides; sacranosides; kaempferol, cinnamyl alcohol, and daucosterol
10	*Rhodiola qundrifida*	Rhodiacyanosides A and B, glycosides – octyl α-L-arabinopyranosyl (1-6)-β-D-glucopyranoside and gossypetin 7-O-β-D glucopyranosyl (1-3)-α-L-rhamnopyranoside, tricetin; quercetin; kaempferol, p-tyrosol, and rhodioloside

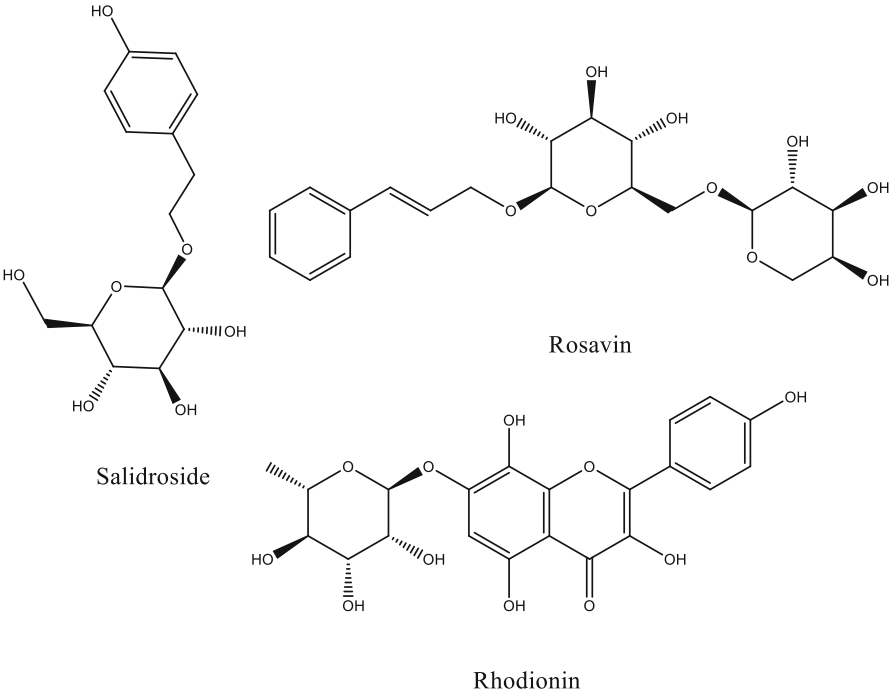


Fig. 1 Structure of salidroside, rosavin, and rhodionin reported by Panossian et al. (2010)

1-(hydroxymethyl)ethyl ester; stigmast-5-en-3-ol, (3β,24S); 1-tetracosanol; 1-hentetracontanol; 9,12,15-octadecatrienoic acid, 2,3-dihydroxypropyl ester,(Z,Z,Z); thujone; 9,12-octadecadienoic acid(Z,Z)-,; 17-pentatriacontene; 13-tetradecen-1-ol acetate; bis(2-ethylhexyl) phthalate; 7,8-dimethylbenzocyclooctene; ethyl linoleate; 3-methoxy-5-methylphenol; camphor; 1,3-dimethoxybenzene; methyl tri-butyl ammonium chloride; 1,3-benzenediol, 5-methyl; 1-heptacosane; benzenemethanol, 3-hydroxy, 5-methoxy; cholest-4-ene-3,6-dione; dodecanoic acid, 3-hydroxy; octadecane, 1-chloro; ethanone, 1-(4-hydroxyphenyl); a-tocopherol; d-tocopherol; campesterol; 1-dotriacontane; heptadecane, 9 hexyl;1-hentriacontane; 1-tericosanol; 13-docosen-1-ol; 1,30-triacontanediol; Stigmast-4-en-3-one; Stigmast-3,5-dien-7-one; stigmastanol; 1-tetratetracontane; 1-pentatriacontane; bacteriochlorophyll-c-stearyl; ascaridole; a-D- glucopyranoside, O-b-D- glucopyranosyl-(1.fwdarw.3)-b-D-fructofuranosyl; benzene sulfonic acid, 4-amino-3-nitro; Cis-9- eicosen-1-ol; (4-carboxymethoxy) benzoyl, methanol; oleic acid; hexadecanoic acid, bis (2-ethylhexyl) ester; hexadecanoic acid, methyl ester; bacteriochlorophyll-c-stearyl; eucalyptol; 1-(2,6-dihydroxy-4-methoxyphenyl) ethanone; linalyl isovalerate; 1-chloro-2,4-dimethoxybenzene; borneol; 4-chloro benzenethiol; phenol,3,5-dimethoxy acetate; 2,4-bis(1,1dimethylethyl) phenol; b-fenchyl alcohol; 5-pentadecyl −1,3-benzenediol; A-D-glucopyranoside,O-α-D-glucopyranosyl-(1.fwdarw.3)-β-D-fructofuranosyl; 1-pentatricontene; 3,7,11-trimethyl- 1-dodecanol; 1-dodecane;

3-methoxy-5-methyl phenol; and di-butyl phthalate were found to be present (Tayade et al. 2013). Figure 4, 3,5-dihydroxybenzyl alcohol; 3-methoxy-5-hydroxybenzyl alcohol; orcinol; O-methylorcinol; *p*-hydroxybenzaldehyde; *p*-hydroxyacetophenone, *p*-hydroxybenzyl alcohol; 4-methoxyphenethyl alcohol, 3-hydroxy-5-methylphenyl-β-D-glucopyranoside, methoxyphenyl-β-D-glucopyranoside,2-hydroxymethyl-6-methoxy-β-D-glucopyranoside, phenyl- β-D-glucopyranoside,3,5-dimethoxyphenyl- β-D-glucopyranoside, trimethoxyphenyl- β-D-glucopyranoside,3-hydroxy-2-(3-methyl-2-buten-1-yl)-benzoic acid, 2-(hydroxymethyl(−6-methoxy-3-acetylphenyl- β-D-glucopyranoside,2-(hydroxymethyl)-6-methoxyphenyl β-D-glucopyranoside,2-hydroxy-4-methylphenyl- β-D-glucopyranoside (Choudhary et al. 2015).

Rhodiola heterodonta

Rhodiola heterodonta contains a wide range of secondary metabolites. Figure 5 represents the structure of tyrosol, viridoside, salidroside, and tyrosol methyl ester. Heterodontoside, mongrhoside, and Rhodiocynanoside A were found in the ethanol extract (Grace et al. 2009). In case of the proanthocyanidins fraction, the class of compounds are epigallocatechin – epigallocatechin-3-O- gallate, epigallocatechin gallate, and 3-O- galloyl-epigallocatechin-epigallocatechin-3-O gallate. Figure 6 shows the chemical compounds reported by Yousef et al. (−)-EGCG-4*β*-benzylthioether and (−)- Epigallocatechin-3-O-gallate (Yousef et al. 2006).

Rhodiola crenulata

This species of *Rhodiola* also contain many medicinally important phytochemicals. A total of around 48 chemical compounds were found which includes 12 flavonoids and their glycosides, 5 flavanols and gallic acid derivatives, 26 alcohols and their glycosides, and 4 organic acids and 1 cyanogenic glycoside (Han et al. 2016). Figure 7 salidroside; tyrosol; p-hydroxyphenacyl-b-D-glucopyranoside; picein; icariside D2; rutin; lotaustralin; rhodiocyanoside A; daucosterol; crenulatin; rhodionin; b-sitosterol; gallic acid; creosides I,II, III, IV, V (Grech-Baran et al. 2015). Figure 8 kenposide A; rhodioloside E; isopentyl-3-O-β-glycopyranoside; rhodiooctanoside; coniferoside; dihydroconiferin; Icariside D2; 4-hydroxybenzyl- β-D-glycopyranoside; triandrin; vimalin; caffeic acid; pollenitin; rhodiosin; kaempferol; clemastanin A (Nakamura et al. 2008). The other various phenolic compounds identified from *R. crenulata* are (Fig. 9) 5,7,3′,5′-tetrahydroxydihydroflavone; luteolin; kaempferol-7-O-α-L-rhamnoside; ternatumoside II; crenuloside; (+)-isolarisiresinol; (+)-dihydrodehydrodiconiferyl alcohol; methyl gallate; (7β,7′β”,8α,8′α′)-3′-methoxy-9-oxo-7,9′,7,9”-diepoxylignan-3,4,4”-triol; (7R,8R)-3-methoxy-8′-carboxy-7′-en-3′,7-epoxy-8,4′-oxyneolignan-4,9-diol; (7R,8R)-3-methoxy-8′-carboxy-7′-en-3′,8-epoxy-7,4′-oxyneolignan-4,9-diol; 2-(4-hydroxyphenyl) ethyl 3,4,5-trihydroxybenzoate; herbacetin-7-methyl ether; and rhodiolate (Zhou et al. 2015). Some different phytochemicals isolated from *R. crenulata* includes 4′-hydroxyacetophenone;

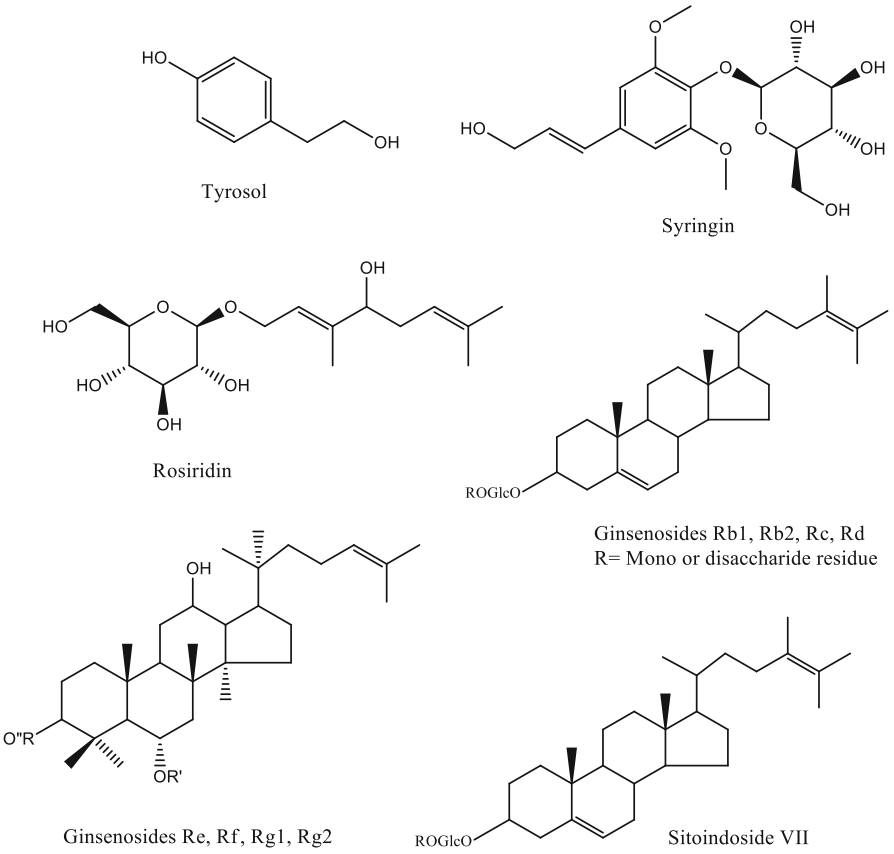


Fig. 2 Structure of some important phenylpropanoids and phenylethane derivatives reported by Panossian et al. (2010)

salidroside; *p*-tyrosol epicatechin-(4β,8)-epicatechin gallate (B2–3′-*O*-gallate) (Fig. 10) (Chu et al. 2014). (1R)-1-O-(β-d-glucopyranosyl)-phenylethylene glycol; (3R,5R,8R)-3-O-[α-l-arabinopyranosyl (1 → 6)-β-d-glucopyranosyl]-5-hydroxymegastigma-6,7-dien-9-one (Fig. 11) (Ma et al. 2008). n-octanol; 3-methyl-2-buten-1-ol ; 2-methyl-3-buten-2-ol; citronellol; myteolp ; Geraniol; and linalool (Fig. 12) (Lei et al. 2003).

Rhodiola kirilowii

The compounds isolated from *R. kirilowii* were arbutin, epigallocatechin gallate, rhodiocyanoside A, fructopyran(1–4)-glycopyranose, and lotaustralin (Fig. 13)

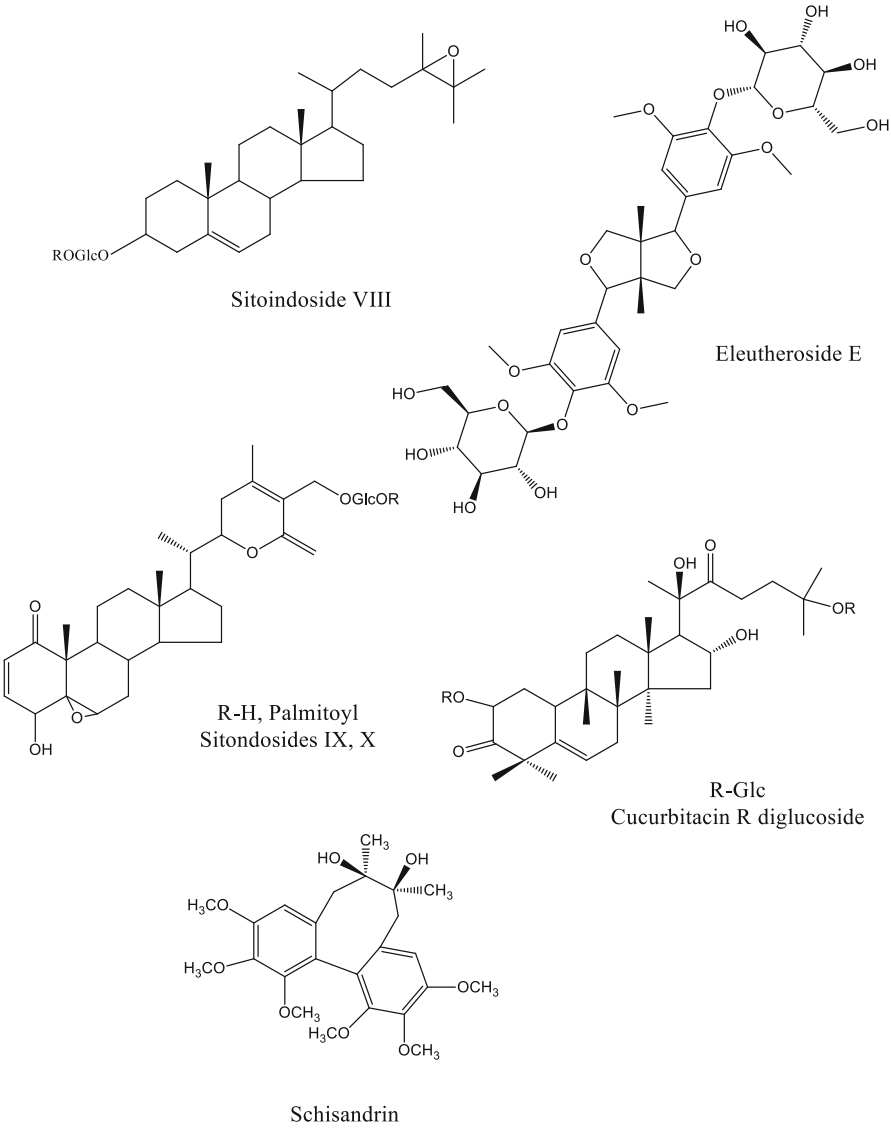


Fig. 2 (continued)

(Wiedenfeld et al. 2007). 3,3′-Digalloylprocyanidin B2; 3,3′-Digalloylproprodelphinidin B2 (Rhodisin); epicatechin-3-O-gallate (Fig. 14) (Wojcik et al. 2009). Beta-sitosterol; trans-hydroxycinnamic acid; geranyl beta-glucopyranoside; neryl beta-glucopyranoside; sacranoside B; hexyl beta-glucopyranoside; tyrosol; gallic acid; rhodiolgin; isolariciresinol-9-O-beta-glucopyranoside; rhodiooctanoside (Fig. 15) (Wong et al. 2008).

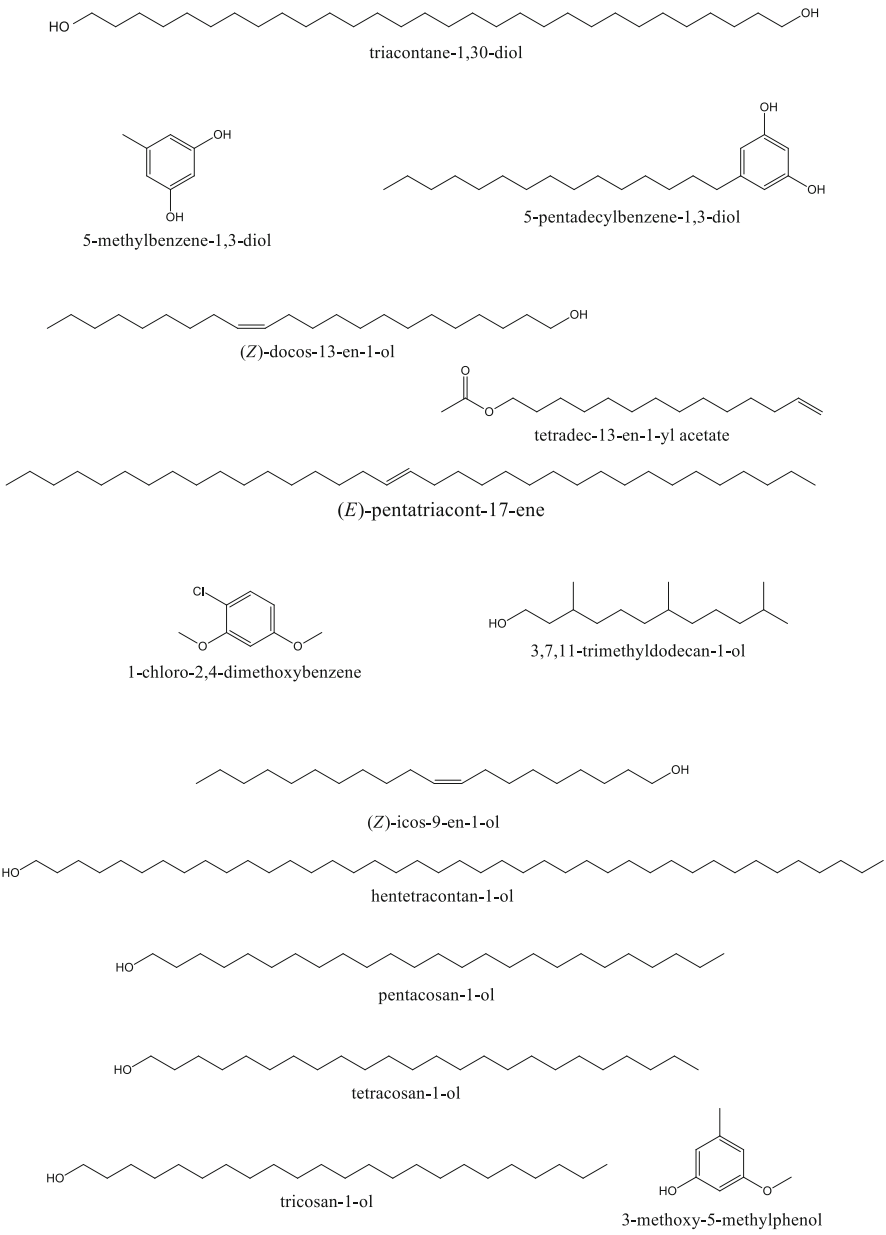
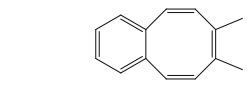
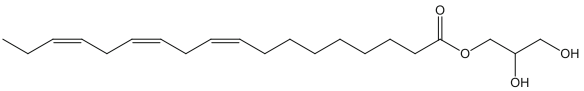


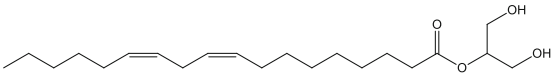
Fig. 3 63 Phyto-chemotypes reported by Tayade et al. (2013)



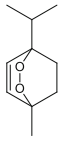
7,8-dimethylbenzocyclooctene



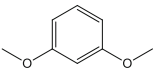
9,12,15-octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)



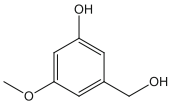
9,12-octadecadienoic
acid (Z,Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester



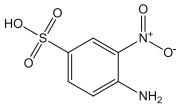
Ascaridole



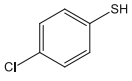
benzene, 1,3-dimethoxy



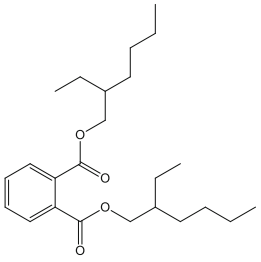
benzenemethanol, 3-hydroxy-5-methoxy



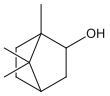
benzene sulfonic acid, 4-amino-3-nitro



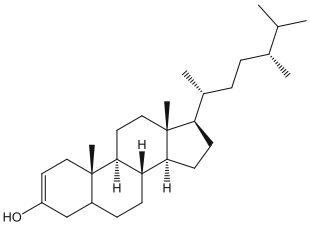
benzenethiol, 4-chloro



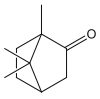
bis(2-ethylhexyl) phthalate



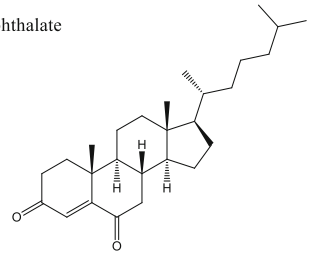
borneol



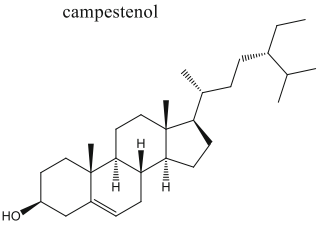
campestenol



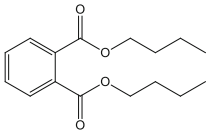
camphor



cholest-4-ene-3,6-dione



stigmast-5-en-3-ol, (3b,24S)



di-butyl phthalate

Fig. 3 (continued)

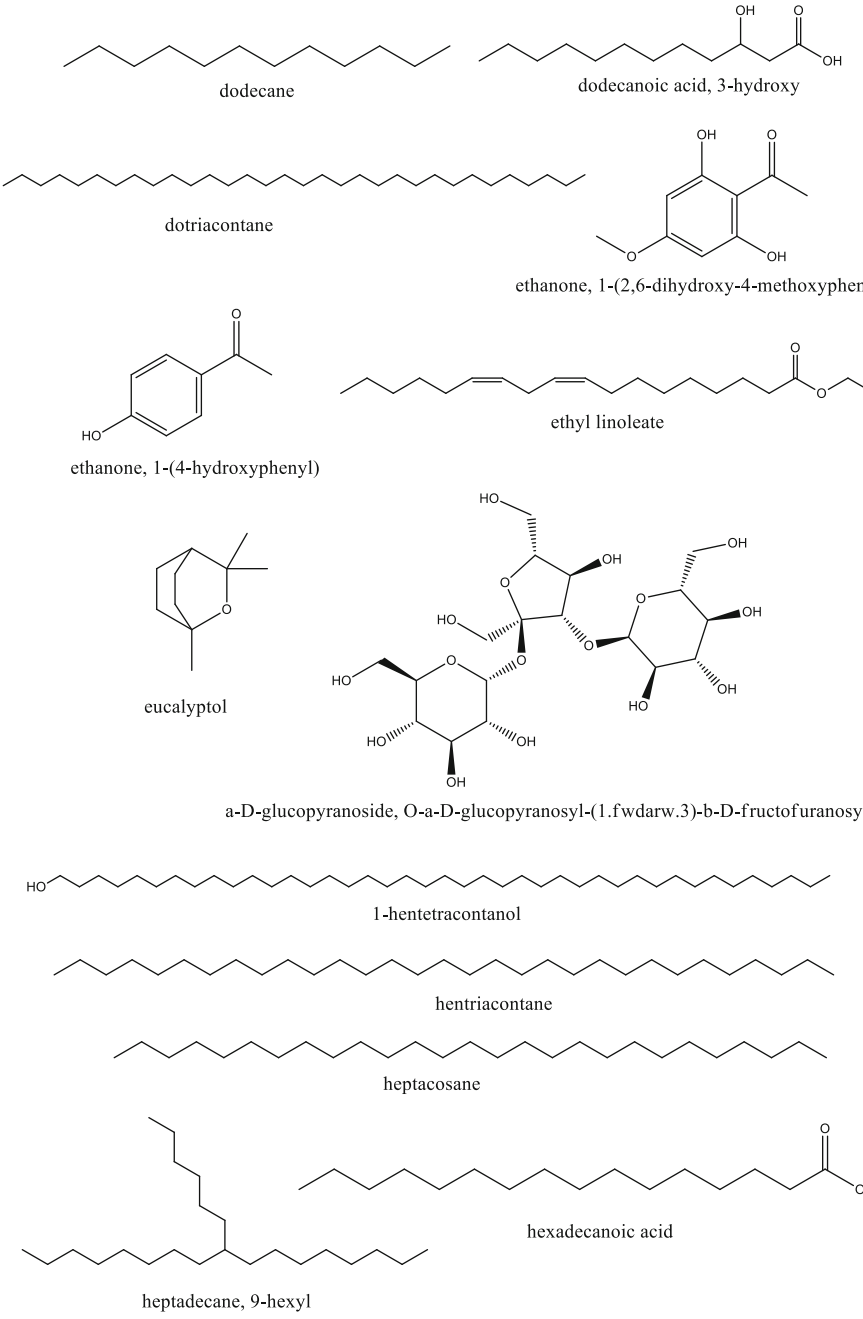


Fig. 3 (continued)

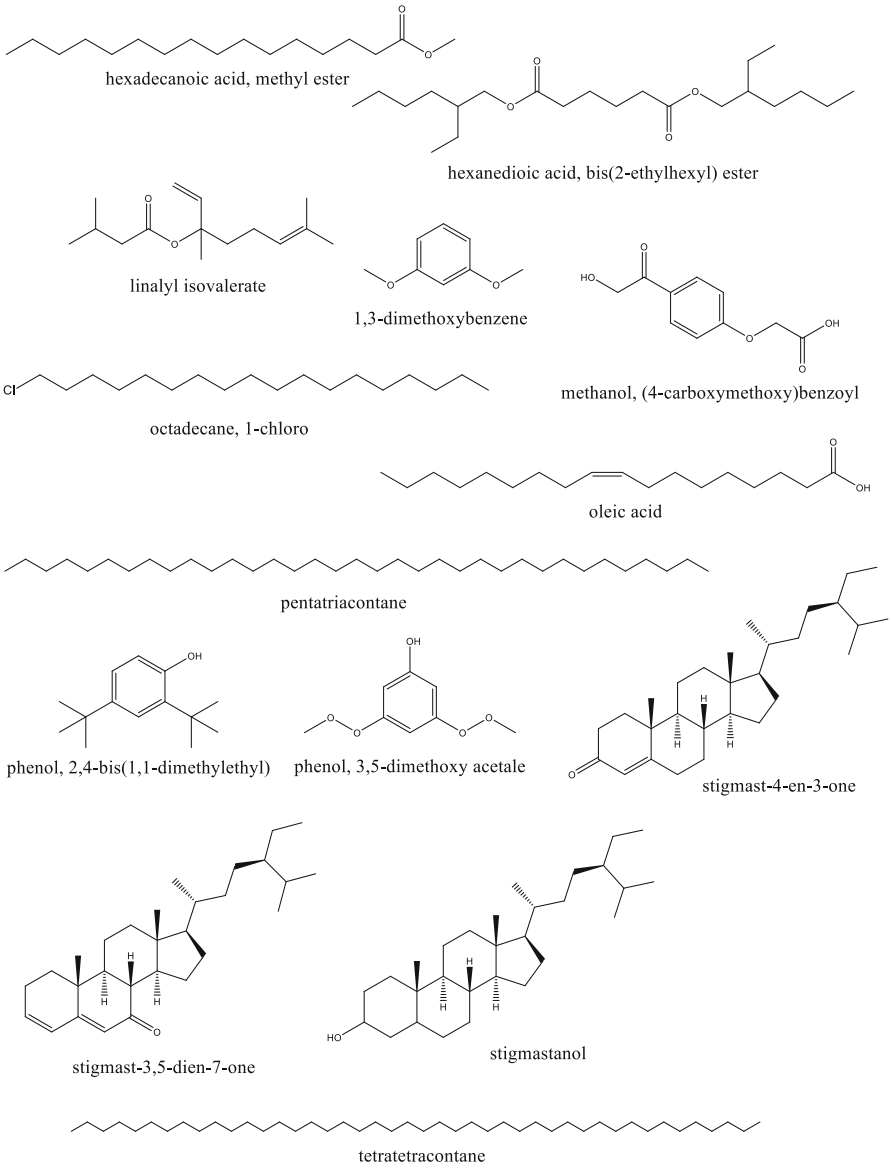


Fig. 3 (continued)

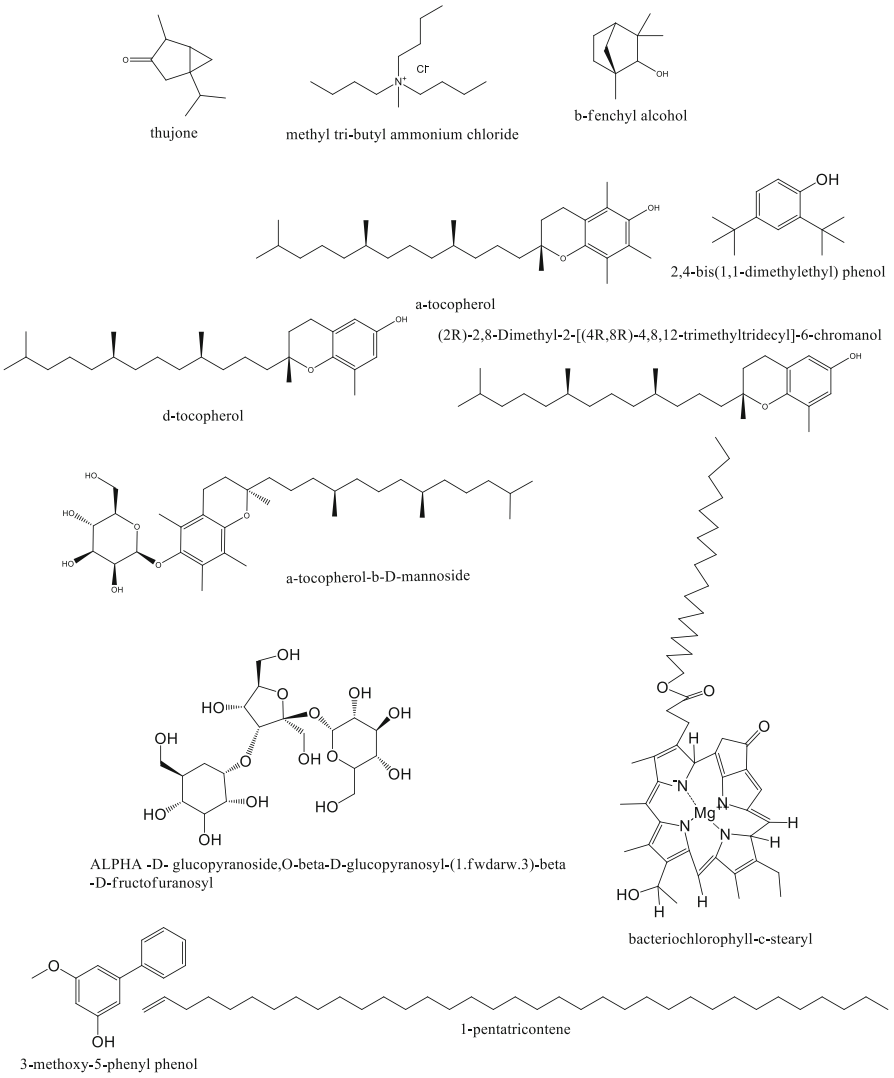


Fig. 3 (continued)

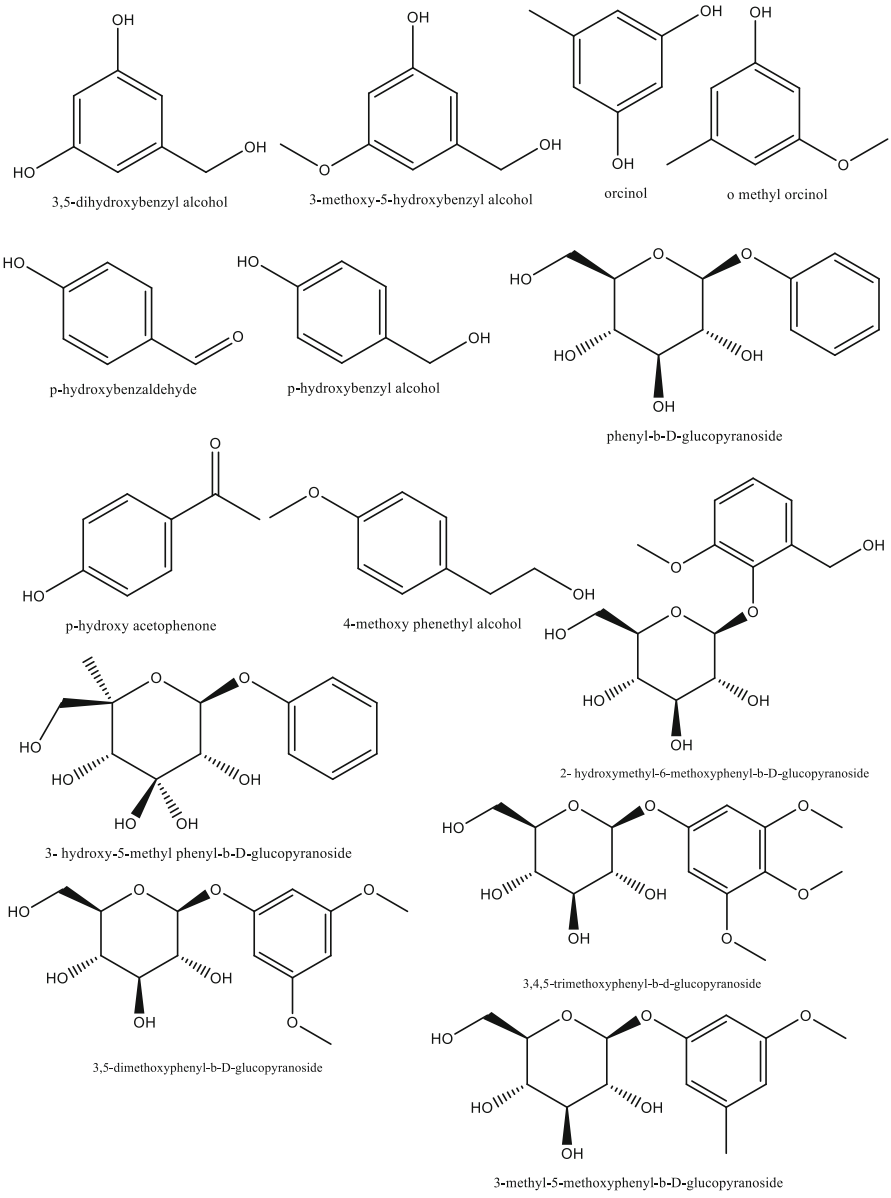


Fig. 4 Phytocomponents reported by Choudhary et al. (2015)

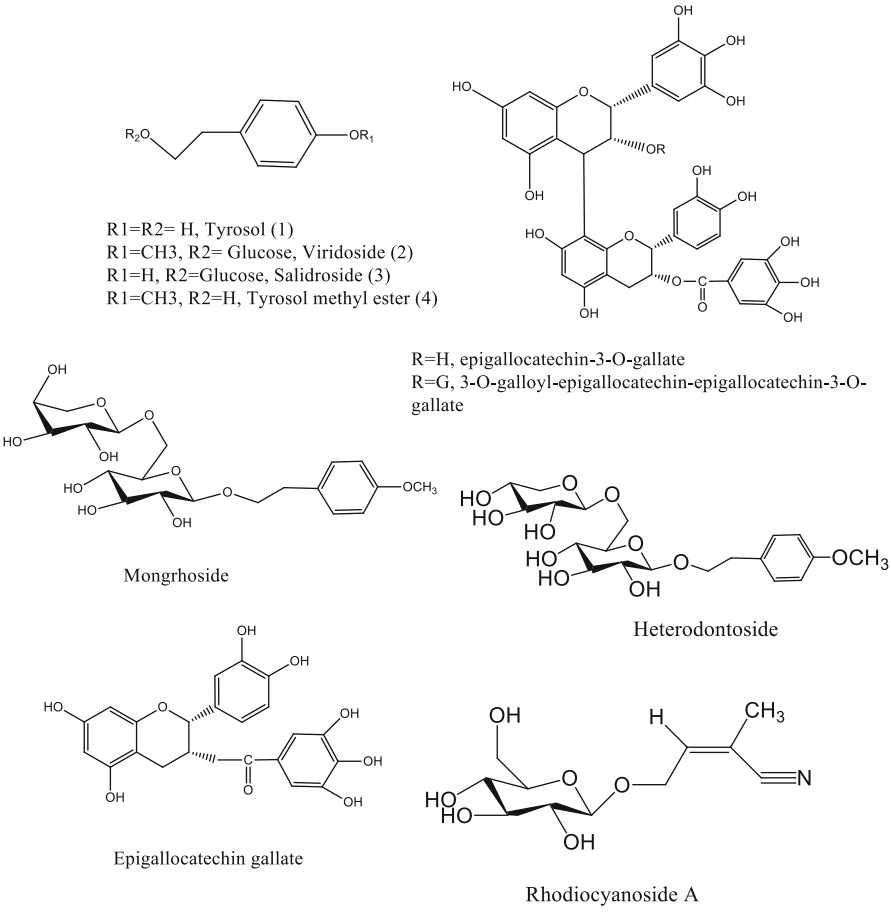


Fig. 5 Phytocomponents reported by Grace et al. (2009)

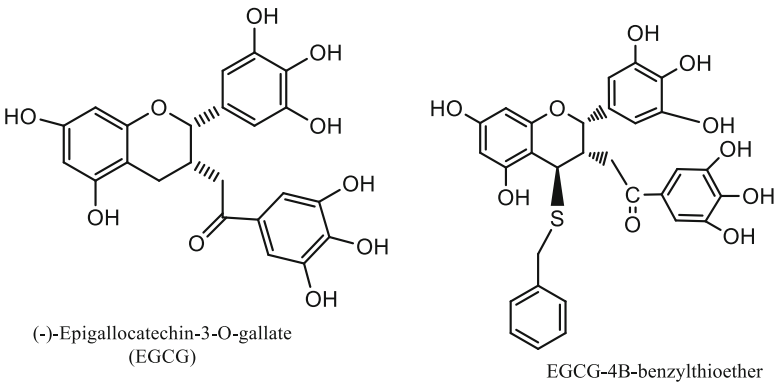


Fig. 6 Phytocomponents reported by Yousef et al. (2006)

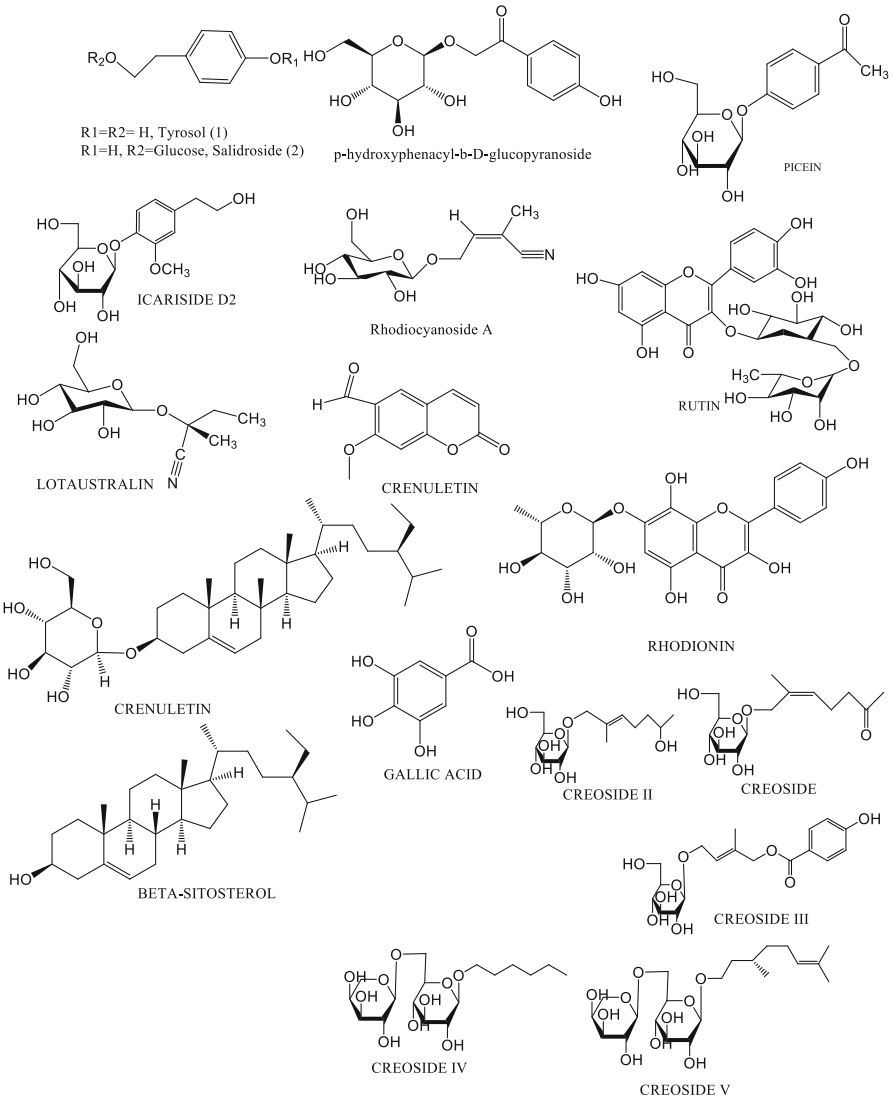


Fig. 7 Phytocomponents reported by Grech-Baran et al. (2015)

Rhodiola bupleuroides

The various compounds isolated from *R. bupleuroides* were gallic acid; kaempferol-7-O-α-L-rhamnopyranoside; rhodiosin; quercetin; syringic acid; and β-sitosterol (Fig. 16) (Li et al. 2007). Rhobupcyanoside B (Fig. 17) (Wang et al. 2016).

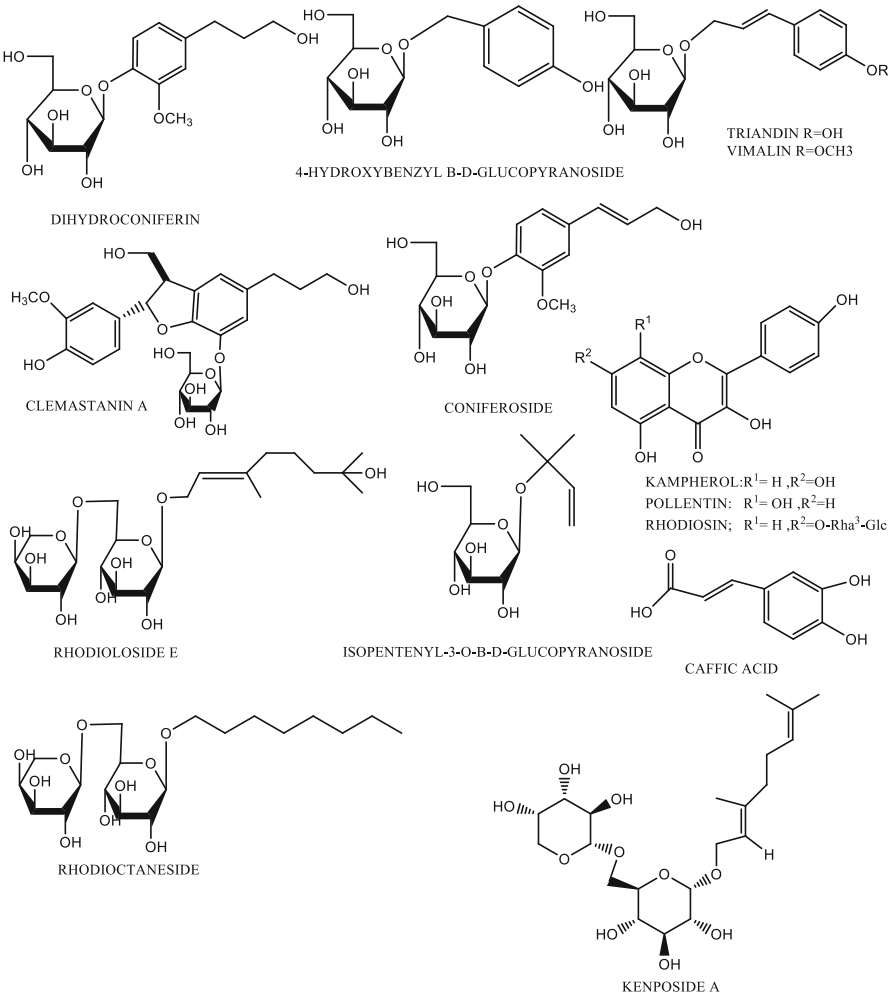


Fig. 8 Phytocomponents reported by Nakamura et al. (2008)

Rhodiola dumulosa

The various bioactive compounds isolated from *Rhodiola dumulosa* were β-sitosterol; sexangularetin; kaempferol-7-O-α-L-rhamnoside; herbacetin-7-α-L-rhamnoside; kaempferol ; and β-sitosterol glucoside (Fig. 18). The compounds which were obtained from this plant for the first time are (Dingqiang et al. 2005) quercetin; gallic acid; (±) -Isolariciresinol-3-alpha-O-beta-D-glucopyranoside; rutin; kaempferol-3-O-beta-D-glucopyranoside-7-alpha-O-L-rhamnoside (Fig. 19) (Liu et al. 2008).

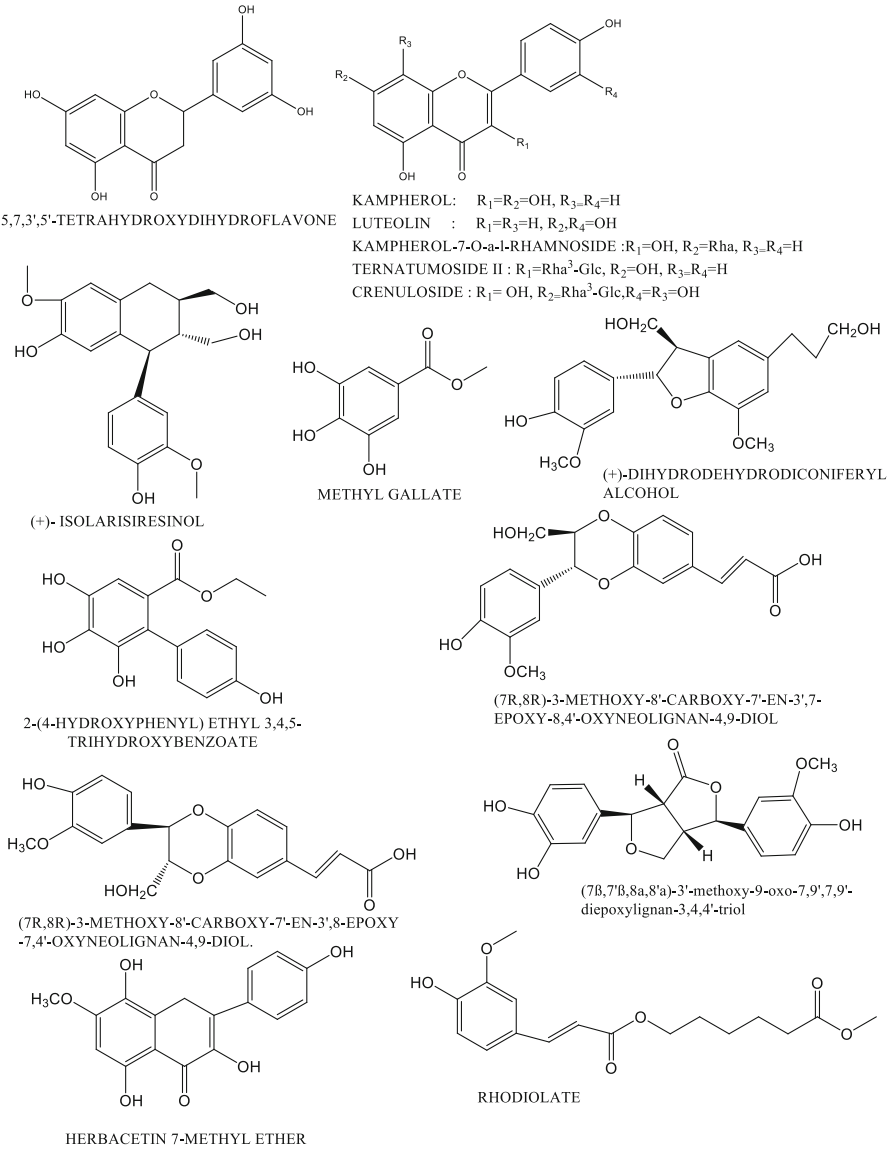


Fig. 9 Phytocomponents reported by Zhou et al. (2015)

Rhodiola algida

The marker compounds found in *Rhodiola algida* were salidroside and tyrosol (Fig. 20) (Lu et al. 2011). The other bioactive compounds reported in *Rhodiola*

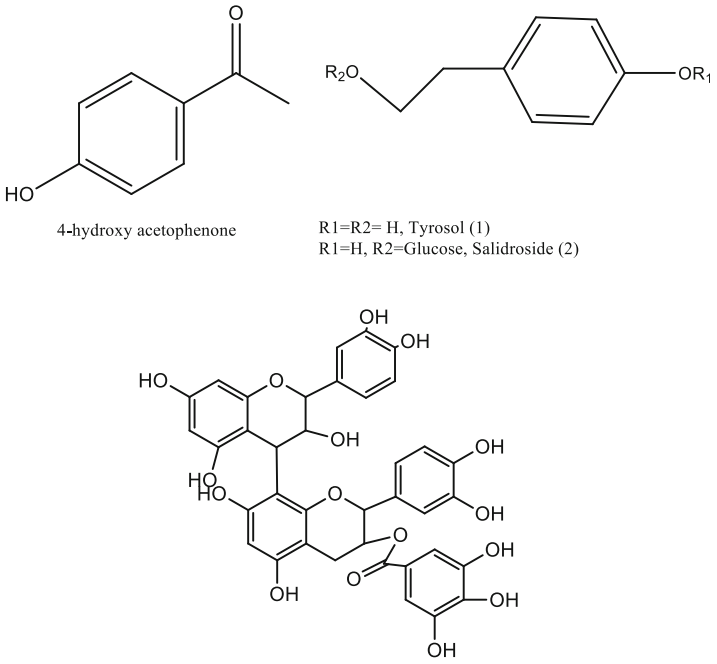


Fig. 10 Phytocomponents reported by Chu et al. (2014)

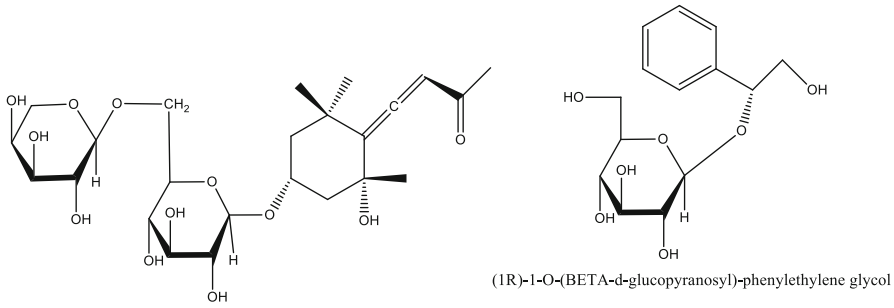


Fig. 11 Phytocomponents reported by Ma et al. (2008)

algida were rhodalgin, acetylrhodalgin, diacetylrhodalgin, and triacetylrhodalgin (Fig. 21) (Pangarova and Zapesochnaya 1975).

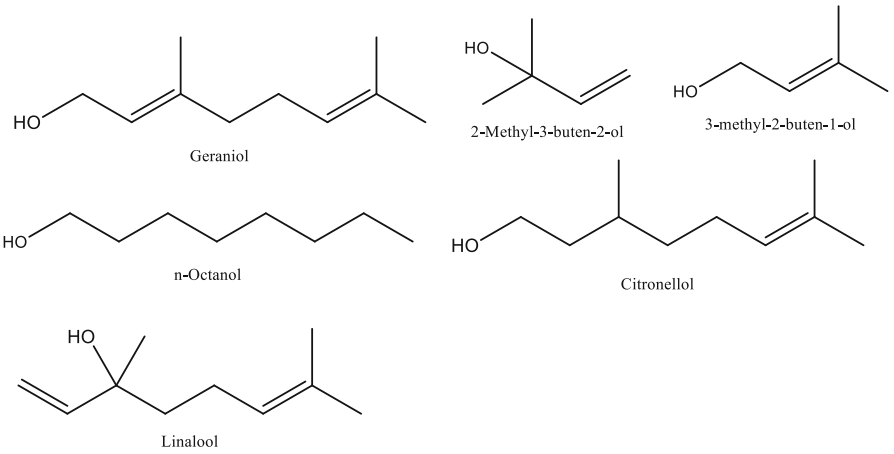


Fig. 12 Phytocomponents reported by Lei et al. (2003)

Rhodiola sachalinensis

The major active constituent of *Rhodiola sachalinensis* is salidroside (Li and Chen 2001). Several other bioactive compounds are glycosides such as rhodiocyanosides (Yoshikawa et al. 1995), sacranosides (Yoshikawa et al. 1997), and phenolic components (Fig. 22) (Lee et al. 2000). Kaempferol, cinnamyl alcohol, and daucosterol (Song et al. 2003).

Rhodiola qundrifida

Rhodiacyanosides A and B; octyl α-L-arabinopyranosyl(1-6)-β-D-glucopyranoside; tricetin and gossypetin 7-O-β-D glucopyranosyl(1-3)-α-L-rhamnopyranoside (Fig. 23) (Yoshikawa et al. 1995), two flavonols (quercetin and kaempferol); p-tyrosol and rhodioloside (Fig. 24) (Troshchenko and Kutikova 1967) were major compounds of this species of *Rhodiola.*

Bioactivity of *Rhodiola* Species

Rhodiola rosea

Antioxidant, adaptogenic, antistress, antimicrobial, immunomodulatory, angiomodulatory, and antitumor effects were the activities reported for *Rhodiola rosea*. *p*-Hydroxyphenethyl-*β*-D-glucoside is one of the major compounds found in *Rhodiola* that is responsible for many of the effects observed with *Rhodiola* extracts (Recio et al. 2016). Salidroside can be used as an effective agent against diabetes due

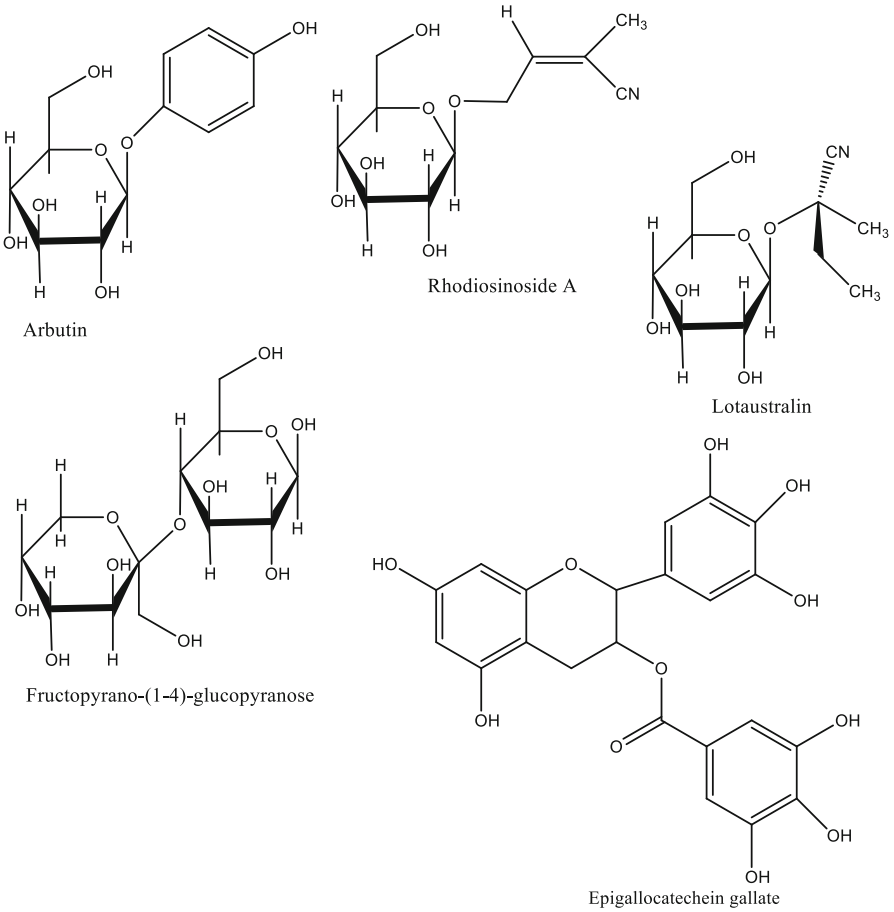


Fig. 13 Phytocomponents reported by Wiedenfeld et al. (2007)

to repression of adipogenesis and inflammation in eWAT and stimulation in hypothalamus of leptin signal transduction (Wang et al. 2016). The compounds from *Rhodiola rosea* showed RRL-induced protective effect on pulmonary fibrosis (PF) in rats. The treated rats had less lung fibrosis and inflammation than those in BLM-treated rats. Significant reduction of MMP-9 and α-SMA expression in the (bleomycin) BLM-induced PF rat mode was found after RRL treatment. Consistently, the expression of matrix TGF-β1 was inhibited significantly, while metalloproteinase-9 increased in the lungs of rats. These results strongly suggest that RRL attenuated BLM-induced fibrotic lung injury in rats (Zhang et al. 2016). The compound salidroside found to have protective effects toward the pulmonary arterial hypertension (PAH) induced chronic hypoxia. It has the potential to inhibit chronic hypoxia-induced pulmonary arterial smooth muscle cells (PASMCs) proliferation and reverse apoptosis resistance via AMPKα1-P53-P27/P21 pathway and via

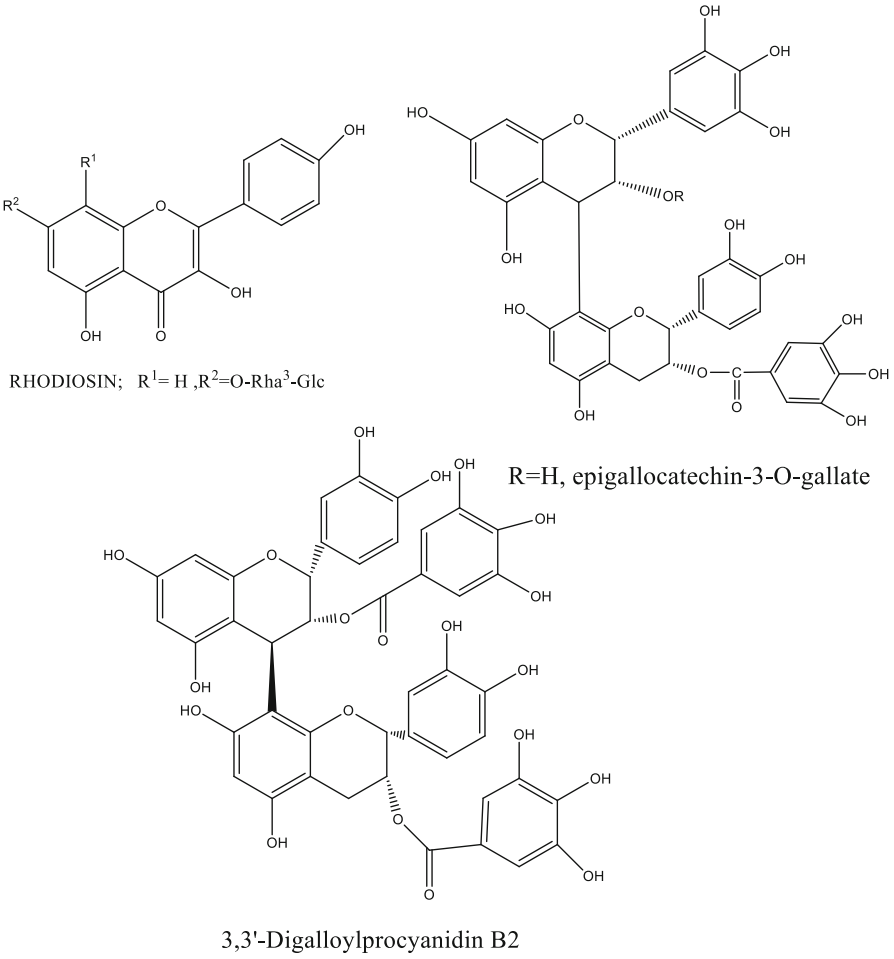


Fig. 14 Phytocomponents reported by Wojcik et al. (2009)

adenosine monophosphate-activated protein kinase (AMPK) α1-P53-Bax/Bcl-2-caspase 9-caspase 3 pathway (Chen et al. 2016). The extracts of *R. rosea* promote the host's immune response showing antitumoral properties, weak and medium-strength mutagens, and protecting tissues against free radicals. Even the *Rhodiola* extracts have the ability to inhibit angiogenesis. Extracts and salidroside stimulated specific and nonspecific immunity in in vivo as well as in vitro. It seems that they ameliorate immunity by enhancing Th1 cytokines without affecting the Th2 profile (Recio et al. 2016). The studies on *R. rosea* indicate that *R. rosea* extract was also characterized by unique pharmacological properties and stimulate positive effect on ATP synthesis in mitochondria of skeletal muscles in rat and stimulated reparative energy processes after intense exercise. *R. rosea* was found to be most effective for stimulating and increasing physical endurance. Treatment with *R. rosea* found to

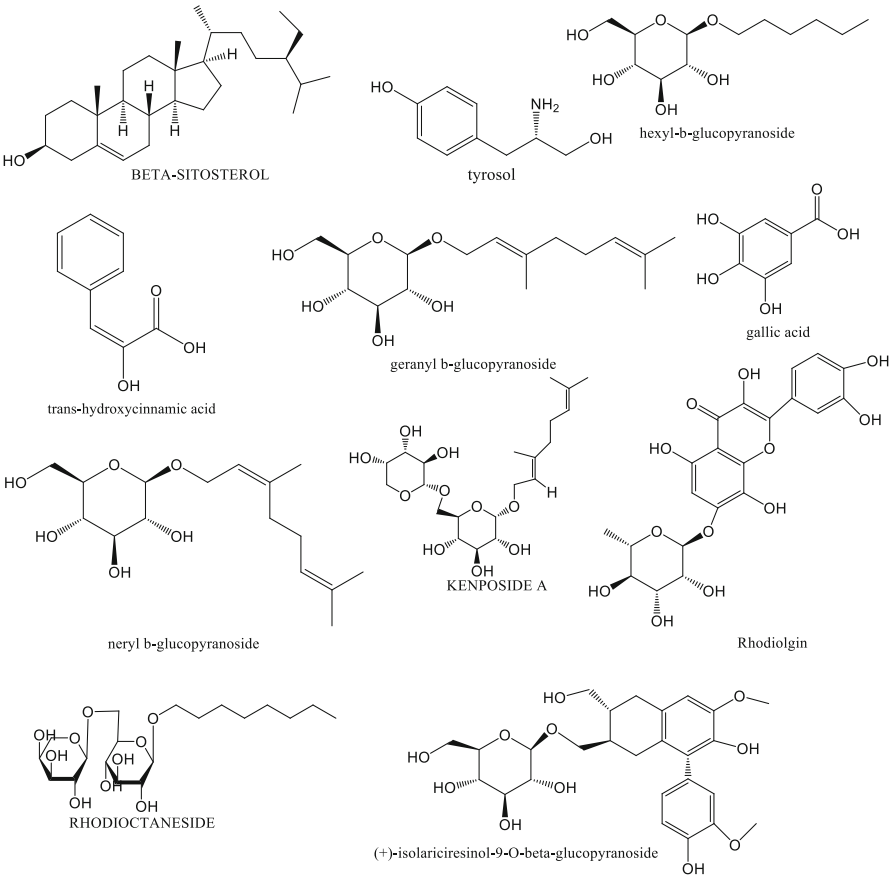


Fig. 15 Phytocomponents reported by Wong et al. (2008)

decrease the ammonia concentration in mouse muscles, thus reducing acidosis (Abidov et al. 2003). Based on numerous studies conducted over recent 35 years, *R. rosea* is recommended as the means of improving strength and endurance and replenishing the energy resources of the body (Seifulla 1999). *R. rosea* acts as an adaptogens by improving the physical endurance of male athletes, reducing blood lactate level, and accelerating recovery after exhausting exercise (Abidov et al. 2003; Azizov and Seifulla 1998; Maimeskulova et al. 1997). Administration of *Rhodiola rosea* (SHR-5) prior to acute stress produce favorable results and helps to prevent stress-induced disruptions in performance (Panossian et al. 2010). *Rhodiola rosea* extract found to have an anti-inflammatory effect and protected muscle tissue during exercise (Abidov et al. 2004). Various preclinical studies revealed the adaptogenic effect of *Rhodiola* root water-alcoholic extract (Abidov et al. 2003; Saratikov 1976; Saratikov et al. 1968; Aksenova et al. 1968; Panossian and Wagner 2005; Jafari et al.

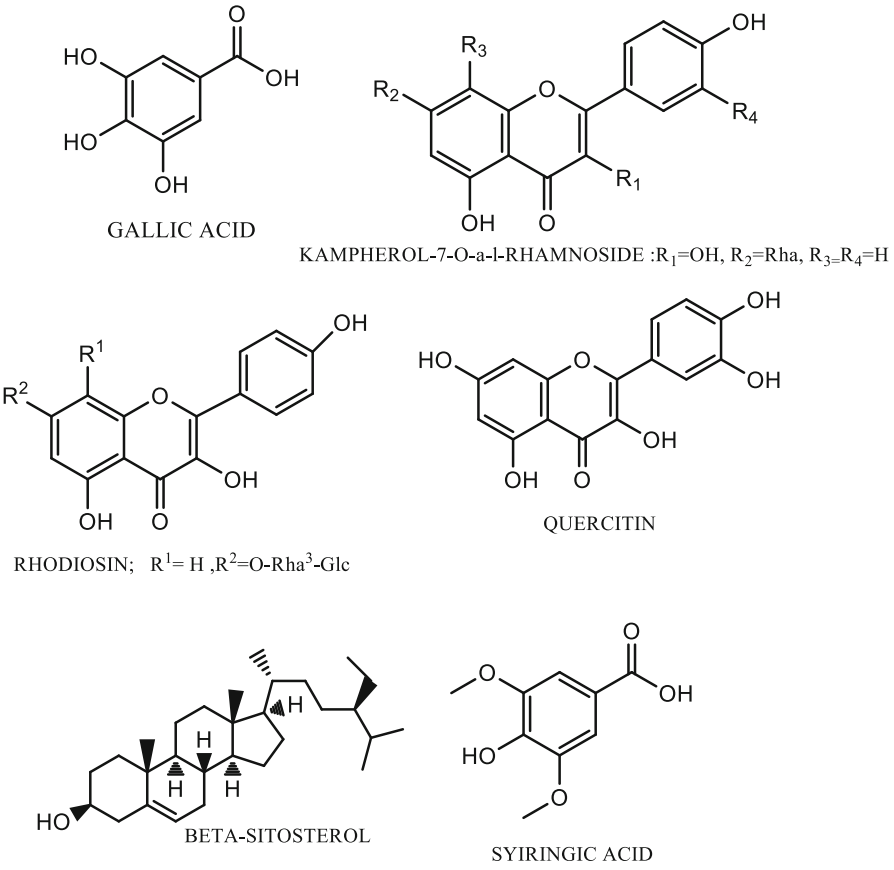
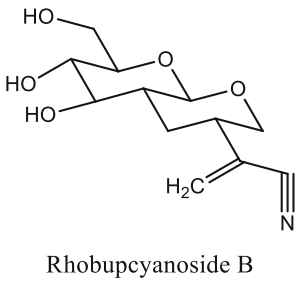


Fig. 16 Phytocomponents reported by Li et al. (2007)

Fig. 17 Phytocomponents reported by Wang et al. (2016)



2007; Perfumi and Mattioli 2007; Mattioli et al. 2008; Diermen et al. 2009; Qin et al. 2008; Siwicki et al. 2007; Wang et al. 2009; Pooja et al. 2009; Bany et al. 2009).

Many studies demonstrated that the regulation of key mediator like molecular chaperones (e.g., Hsp70) (Lishmanov et al. 1996; Prodius et al. 1997; Panossian

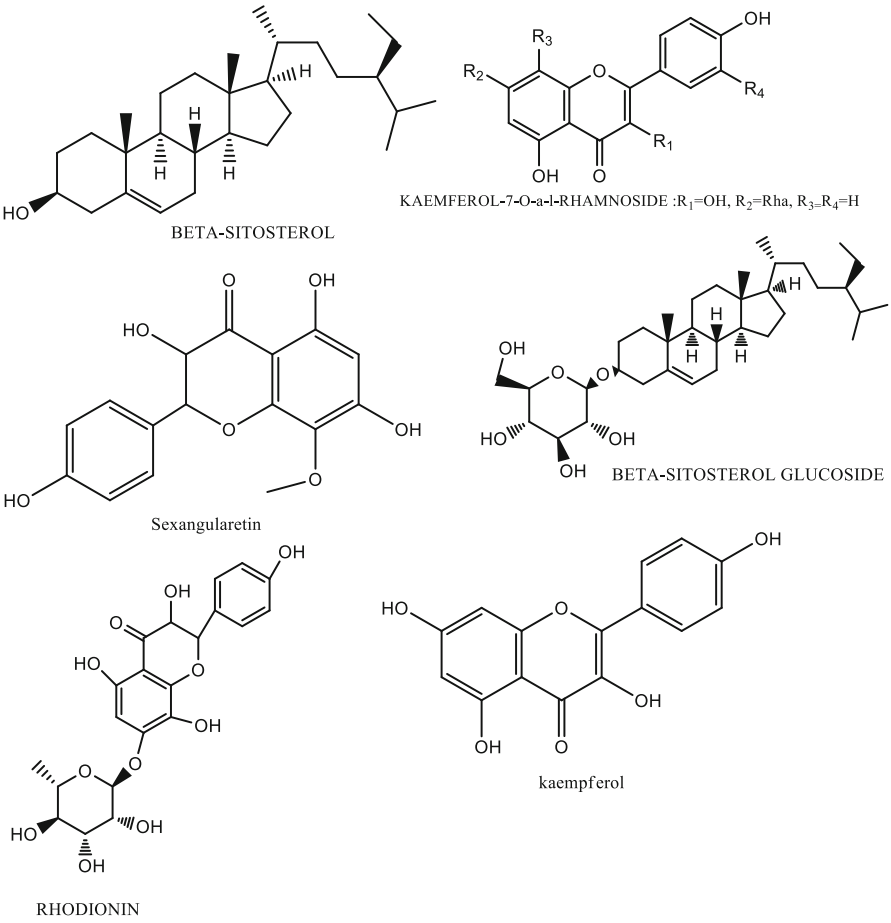


Fig. 18 Phytocomponents reported by Dingqiang et al. (2005)

et al. 2007, 2008, 2009; Wiegant et al. 2008; Olsson et al. 2009), cortisol (Olsson et al. 2009), nitric oxide (Panossian et al. 2007), Forkhead box O (FOXO) transcription factor DAF-16 (Wiegant et al. 2009), stress-activated c-Jun N-terminal protein kinase 1 (JNK1) (Panossian et al. 2007), and beta-endorphin by *Rhodiola rosea* is associated with the stress response (Lishmanov et al. 1987; Maslov et al. 1997; Arora et al. 2005). The studies reveal that the administration of *Rhodiola rosea* promotes a moderate increase in serum immune reactive beta-endorphin in rats under basal conditions which is equivalent to rats adapted to exercise. When *Rhodiola rosea*-treated rats were subjected to a 4 h period of nonspecific stress, the expected elevation in beta-endorphin was either not observed or substantially decreased. Consequently resulting in the characteristic perturbations of the

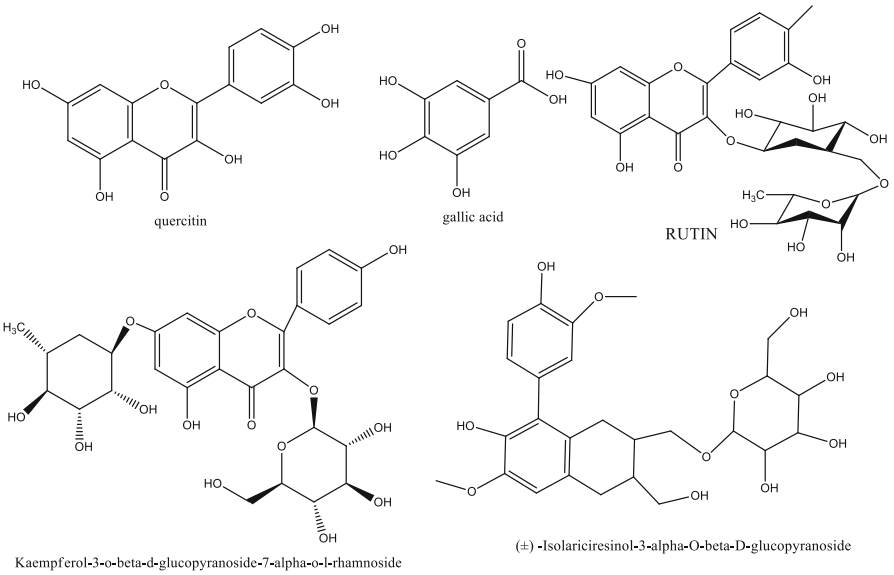
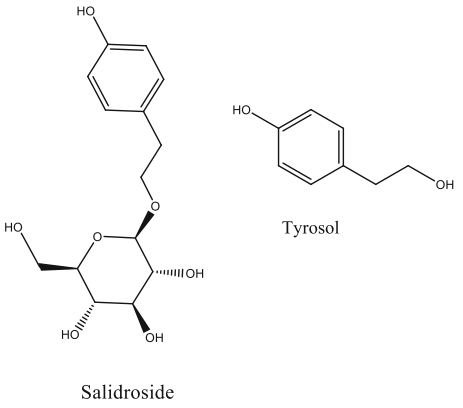


Fig. 19 Phytocomponents reported by Liu et al. (2008)

Fig. 20 Phytocomponents reported by Lu et al. (2011)



hypothalamic-pituitary-adrenal axis was decreased or totally prevented (Lishmanov et al. 1987). *Rhodiola rosea*, with its potential to act as an anticancer agent, might be useful in conjunction with some pharmaceutical antitumor agents, and even supplementation of *Rhodiola rosea* extract inhibits the growth of both tumor types, extended survival times in rats with transplanted solid Ehrlich's adenocarcinoma and metastasizing rat Pliss lymphosarcoma and decreased metastasis to the liver. The studies reveal that the extract also directly suppressed the lung carcinomas (Udintsev and Shakhov 1991). *R. rosea's* protective effect against the antioxidant stress is not totally because of its antioxidant or prooxidant effects (Wiegant et al. 2008;

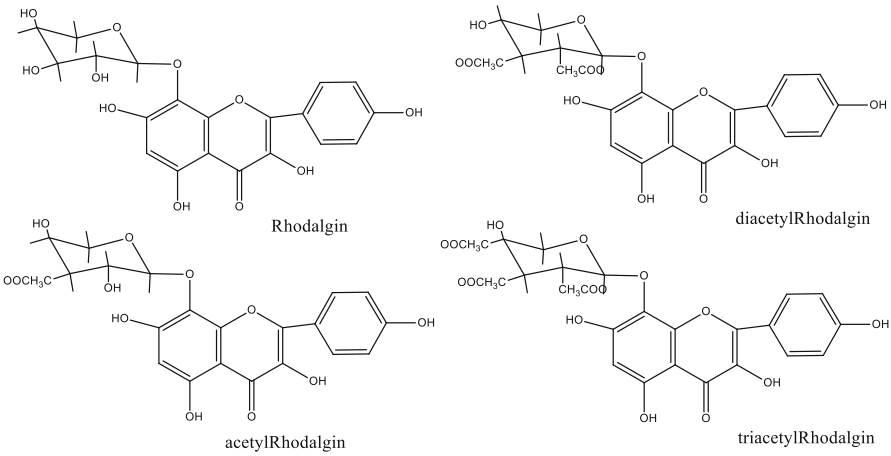


Fig. 21 Phytocomponents reported by Pangarova and Zapesochnaya (1975)

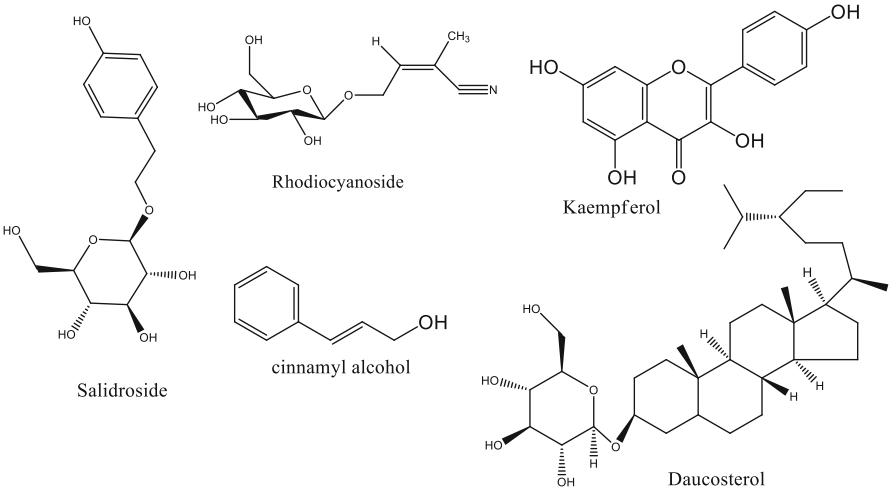


Fig. 22 Phytocomponents reported by Li and Chen (2001), Yoshikawa et al. (1995), Yoshikawa et al. (1997), Lee et al. (2000), Song et al. (2003)

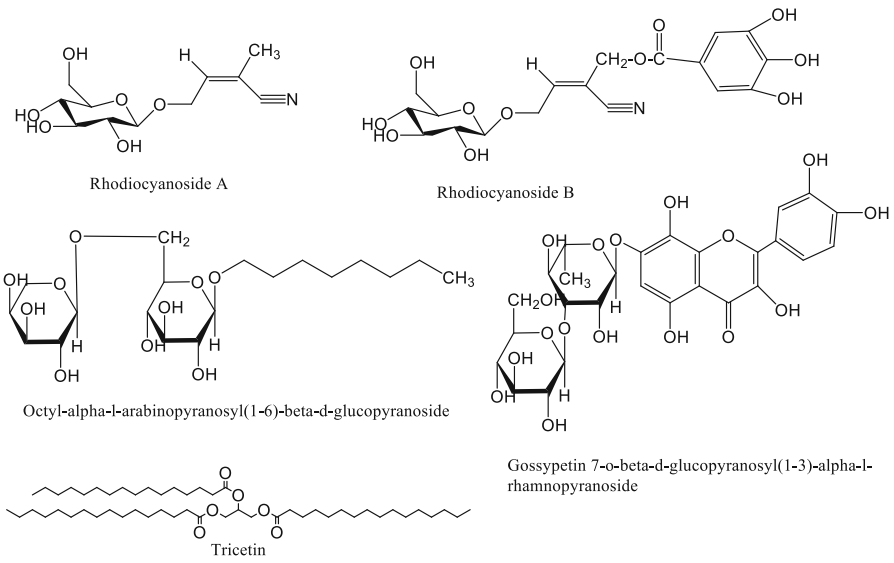


Fig. 23 Phytocomponents reported by Yoshikawa et al. (1995)

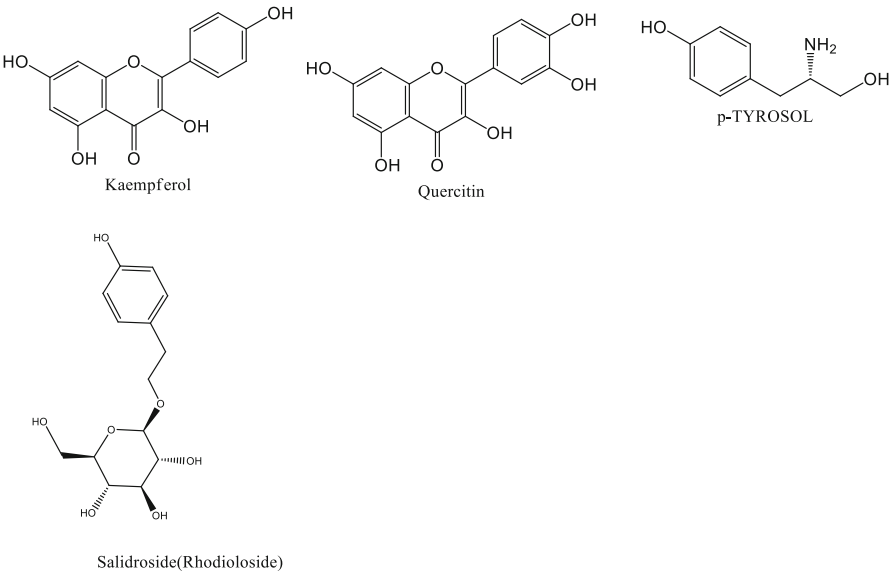


Fig. 24 Phytocomponents reported by Troshchenko and Kutikova (1967)

Schriner et al. 2009) because it does not elevate the major antioxidant defenses but due to activation of the antioxidant response element or degrading H_2O_2 (Schriner et al. 2009).

Rhodiola imbricata

Rhodiola imbricata is known to have many biological effects. There was a significant decrease in the cytotoxicity in comparison to control created by the tert-BHT (250 μM) by using the aqueous and alcoholic extract. Extracts have also reduced the ROS production which was developed by tert-BHT in the mitochondria which is comparable to the vitamin C. Addition of aqueous and alcoholic extract has no effect in GSH level in the tert-BHT-exposed macrophages. Treatment with the extract has six times increased the early apoptotic cells and three times increased the late apoptotic cells which were significantly low when treated with tert-BHT (500 μM). Comet assay revealed that 500 μM tert-BHT has applicably increased the single-strand break which has been reduced by the use of alcoholic and aqueous extract (Kanupriya et al. 2005). The DPPH assay study has reported to show significant inhibition of DPPH activity at 4.391 μg/ml in comparison to quercetin (3.824 μg/ml) and BHT (4.743 μg/ml) for 50% inhibition. The lipid peroxidation activity shows that *Rhodiola* aqueous extract has maximum scavenging activity at 500 μg/ml and minimum at 0.5 μg/ml where α-Tocopherol was used as a standard. The IC_{50} of extract was 5.12 and of standard was 4.89. For the superoxide ion radical, the IC_{50} of the extract, ascorbic acid, α-Tocopherol, and quercetin was 4.78, 3.36, 4.53, and 4.33 μg/ml. The aqueous extract has also reported to show ferric ion chelating activity; IC_{50} of the extract, α-Tocopherol, and quercetin was 5.33, 6.13, and 3.123 μg/ml. The hydrogen peroxide inhibition study revealed that the extract has a very high inhibition activity for hydrogen peroxide which is comparable to α-Tocopherol. The total flavonoid content in extract was reported to be 66.7 μg quercetin equivalent/mg, and total phenolic content was 240 ± 10 mg of gallic acid equivalent (Gupta et al. 2009). The acetone extract of *R. imbricata* was found nontoxic up to 2000 mg/ml and had shown no mortality in mice. This extract is reported to increase hematological count like RBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, leukocytes, and platelets at conc. of 400 mg/ml. It also has shown a comparable recovery to standard silymarin for paracetamol-induced hepatic damage; it has decreased the SGPT (88.43 ± 0.3 U/l), ALP(193.53 ± 0.3 U/l), and SGOT(79.56 ± 0.3 U/l) liver marker and had increased the concentration of total protein and enzymatic antioxidants. It has also prevented the oxidation of the liver cells after the administration of paracetamol (Senthilkumar et al. 2014). It is reported that *Rhodiola* extract stimulates interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) increase in human PBMCs and RAW 264.7 cell line. Reports also show an increase in the production of nitric oxide simultaneously which also activates the nuclear translocation of NF-κB in human PBMCs, which is comparable to the LPS which is a positive stimulant (Mishra et al. 2006). MTT assay of U87 cell line showed an increased survival of cells at doses between 25 and 125 μg/ml in case

of drug +radiation group. In vivo evaluation of revealed that intraperitoneal administration of hydro-ethanol extract rendered 83.3% survival (maximally effective dose, 400 mg/kg b.w.) 30 min prior to lethal (10 Gy) total-body γ-irradiation. The ability of hydro-ethanol extract to reduce the effect of lipid peroxidation induced by iron/ascorbate, radiation (250 Gy), and their combination was also analyzed, and it was found that it decreases in a dose-dependent manner. In a study aqueous extract of *Rhodiola* showed antiproliferative against K-562 cell line in 72 h incubation at a dose of 100 and 200 mg/mlin comparison to normal human peripheral blood lymphocytes or mouse macrophage cell line RAW-264.7 where there is no suppression. Aqueous extract was also found to induce intracellular reactive oxygen species which leads to apoptosis and arrested the cell progression at G2/M phase in K-562 cells. It also shows the anticancer activity which leads to an elevated NK cell cytotoxicity (Mishra et al. 2008). In vitro antioxidant activity was investigated by DPPH radical *R. imbricata* hydroalcoholic root extract which shows a greater correlation of inhibiting the free radicals with the increase in conc. of extract (Kumar et al. 2010b).

Rhodiola heterodonta

Study of the 80% EtOH extract of *R. heterodonta* (40 mg/kg) increased the survival rate of the treated mice under hypoxic conditions by 1.9 times compared with the untreated control have been reported. The survival time of mice under hypoxia increased by 192%, by injecting 80% ethanol extract of *R. heterodonta* which acts as an indication of adaptogenic activity (Grace et al. 2009). The research revealed that *Rhodiola heterodonta* extract has moderate adaptogenic effect and may be used as adaptogen. Also, low toxicity of *Rhodiola heterodonta* preparations has been demonstrated by histomorphological analysis of internal organs (Yunuskhodjaev et al. 2014). The total phenol and flavonoids of *Rhodiola heterodonta* root extract was found to be 79.21 ± 0.26 mg GAE/g and 269.3 ± 0.82 mg Qc/g, respectively (Kumar et al. 2010b).

Rhodiola crenulata

Rhodiola crenulata was reported to show increase in the glycogen synthesis and inhibits the lipogenesis by regulating the genes (glycogen synthase, glycogen synthase kinase 3β, CCAAT/enhancer-binding protein, fatty acid synthase, sterol-regulating element-binding protein 1c) related to the metabolism and process (Lin et al. 2016). It has been reported that the water and ethanol extract of *R. crenulata* has shown α-amylase inhibitory activity with an IC_{50} value of 98.1 μg total phenolic/ml and 120.9 μg total phenolic/ml. Besides this it also has reported to show an α-glycosidase inhibitory activity at an IC_{50} value of 60.3 μg total phenolic/ml and 60.2 μg total phenolic/ml (Kwon et al. 2006). A finding tells that its extract improved the functioning of the brain of rat model of Alzheimer's disease through protecting

neural stem cells by its key component salidroside which scavenged intracellular free radicals (Qu et al. 2012). *Rhodiola crenulata* was used in the treatment of chronic intermittent hypoxia-decreased cardiac fractional shortening and has shown a significant effective improvement, based on decreases in Fas, activated caspase 8, and FADD, activated caspase 3, compared to the hypoxia group. With treatment of *Rhodiola crenulata*, the cardiac mitochondrial-based apoptotic pathway in mice with chronic intermittent hypoxia was significantly decreased, which leads to decreases in pro-apoptotic protein levels like t-Bid, Bad, Bax, activated caspase-9, and activated caspase 3 as well as increases in anti-apoptotic protein levels p-Bad, Bcl-xL, and Bcl-2. Another pathway which is cardiac VEGF-related leads to a significant increase in protein p-PI3k, VEGF, and p-AKT level compared to the hypoxia group with treatment of *Rhodiola crenulata*, which is based on increased in pro-survival (Lai et al. 2015). *Rhodiola crenulata* extract and its bioactive components have reported to show a significant decrease in hypoxia-mediated endocytosis of the Na and K-ATPase because of the inhibition of the ROS-AMPK-PKC pathway in A549 cell line (Chen et al. 2015). It is reported that the extract also has estrogenic activity (Bassa et al. 2016). There is a reduction in proliferation, which stimulates differentiation and eliminates tumorsphere formation of in vitro glioblastoma multiforme cells with the effect of *Rhodiola crenulata*. The effects were associated with inhibition of Wnt/β-catenin signaling pathway (Guo et al. 2014). It also has effect on gluconeogenic gene expression by increasing the phosphorylation of AMPK level. It also reduced the plasma glucose level (Lee et al. 2015). Its treatment reduces the level of IFN-γ, high-sensitivity C-reactive protein, and CD8 (+) but increases in expression of CD4(+) CD25(+) FOXP3(+) and CD4(+) CD25(+) CD45(+) FOXP3(+) in the blood (Chen et al. 2015). A study for the survival rate of *Drosophila melanogaster* against the gut immunity raised by pathogen demonstrate that *R. crenulata* has increased the survival rates of adult flies and expression of antimicrobial peptide genes after pathogen or toxic compound ingestion. Moreover, it improved intestinal morphology and decreased levels of reactive oxygen species (Zhu et al. 2014). The compounds from *Rhodiola crenulata* extract were tested for xanthine oxidase (XO) inhibition activity in comparison to a known XO inhibitor allopurinol which has an IC_{50} value of 12.21 ± 0.27 μM. The compound B2-3′-O-gallate and 4-HAP reported an XO inhibitory effect, the half maximal inhibitory concentration values of compound were 15.62 ± 1.19 and 24.24 ± 1.80 μM, respectively, and there inhibition constants were 8.41 ± 1.03 and 6.16 ± 1.56 μM, respectively. These results suggest that β-2-3′-O-gallate and 4-HAP are potent XO inhibitors (Chu et al. 2014). Its use in Chinese prescription significantly decreases the level of serum glucose, lipid profile, blood urea nitrogen, urine albumin excretion, and urease activity which improves renal function. Chinese prescription could also affect oxidative stress. It could reduce the renal damage induced by hyperglycemia in type 1 diabetic rats. Its effects work by regulating the metabolism of glucose and lipid, the oxidative stress, and the microcirculation disturbance (Fu et al. 2013). *R. crenulata* phenolic-enriched extract was capable of

inhibiting the proliferation, motility, and invasion of human-derived MDA-MB-231 and mouse-derived V14 breast cancer cell lines. The extract also leads to death of the tumor cell lines by inducing autophagic-like vesicles but not the immortal human mammary epithelial cells (Tu et al. 2008). By activation of AMPK signaling, *Rhodiola crenulata* root extract (RCE) can regulate hepatic gluconeogenesis (Lin et al. 2016). The root extract of *R. crenulata* was found to improve insulin sensitivity and attenuate abnormal lipid metabolism in a rodent model of diabetes (Wang et al. 2012). Increase in glycogen synthesis and inhibition of lipogenesis, while regulating genes included in glycogen metabolism like glycogen synthase (GS), glycogen synthase kinase 3β (GSK3β), CCAAT/enhancer-binding protein (C/EBP), fatty acid synthase (FAS), and sterol regulatory element-binding protein 1c (SREBP-1c), have been reported by Lin et al. (Lin et al. 2016). The various phenolic compounds were found to be potent as antioxidants and could moderately stimulate IFN-γ expression (Zhou et al. 2015).

Rhodiola kirilowii

Rhodiola kirilowii extract was reported to protect against problems related to the heart and lungs while moving to high altitude, anticoagulative property and decrease the level of blood sugar (Zhang et al. 1989). *Rhodiola kirilowii* was found to have in vitro inhibitory activity against serine protease (NS3-SP). Serine protease is a potent target of antiviral screening against HCV (Zuo et al. 2007). It also have a great potential as cellular immunity enhancers. The in vitro studies revealed that the extracts stimulate activity of granulocyte and increased lymphocyte response toward mitogens, and in vivo experiment leads to enhance the ability of lymphocytes derived from parental strain mice which were fed with *R. kirilowii* aqueous and hydroalcoholic extracts, to induce local cutaneous graft-versus-host reaction in F1 hybrids (Wojcik et al. 2009). The in vitro activities against *Mycobacterium tuberculosis* of its extracts and pure components were evaluated by testing their minimal inhibitory concentration and minimal bactericidal concentration, and the compounds gallic acid and epigallocatechin gallate exhibited an in vitro inhibitory and bactericidal activities against *Mycobacterium tuberculosis* in different extent (Wong et al. 2008).

Rhodiola bupleuroides

The data available related to the species is very less. Still the report which is available in relation to this species shows that it has compounds which were evaluated for its inhibitory activity against α-glucosidase, and the results show that it has an IC_{50} of 278.28 ± 0.55 μM in comparison to the positive control (acarbose) at 210.40 ± 0.32 μM (Wang et al. 2016).

Rhodiola algida

Rhodiola algida found to increase immunity which was receiving chemotherapy post-mastectomy and also decreases oral ulcers. Thus *Rhodiola algida* has the potential to be used concurrently with chemotherapy to alleviate the occurrence of oral ulcers. The optimal concentration of *Rhodiola algida* favored the proliferation of lymphocytes (Loo et al. 2010). The clinical reports suggest that it regulates IL-2 in Th1 cells and IL-4, IL-6, and IL-10 in Th2 cells which effectively stimulate human peripheral blood lymphocytes, enhancing immune responses and its underlying immunomodulatory effects (Li et al. 2009). Its anticarcinogenic effect on MCF-7 breast cancer cells can lead to downregulation of protein levels of HIF-1α and HIF-2α, which are overexpressed under hypoxic conditions and increasing cell apoptosis. *R. algida* has a high potential to be antitumor agent (Iaremii and Grigoreva 2002). Beside its antitumor role, *R. algida* also have immunomodulatory agent (Li et al. 2009).

Rhodiola sachalinensis

The studies reported the hypnotic activity and sedative of salidroside from *Rhodiola sachalinensis* (Li et al. 2007). *Rhodiola sachalinensis* has found to have stimulating role for the nervous system, enhancing working efficacy, decreasing depression and microwave radiation, resisting anoxia, eliminating fatigue, improving sleep, preventing high altitude sickness, etc. (Khanum et al. 2005; Ming et al. 1988). Salidroside, which is a phenylpropanoid glycoside, has been reported to have anti-inflammatory activity (Lu et al. 2003). Crude extracts of *Rhodiola sachalinensis* was found to have high DDPH radical scavenging activity (Zhang et al. 2007). In the study with mice, salidroside showed that it enhances the sleep, by shortening the effect on the sleep latency and also prolonging the effect on the sleeping time in mice treated with hypnotic dosage of pentobarbital sodium (Li et al. 2007). The extract of *Rhodiola sachalinensis* was found to promote endurance and to increase the body's resistance against mental and physical stresses (Xu et al. 1998). The aqueous extract found to activate NF-ķB which enhances the induction of iNOS gene in RAW264.7 macrophages (Li et al. 2012). The root has been used to treat cold and flu-like symptoms, but the underlying mechanism is not known (Li et al. 2012). It has been also found to be hepatoprotective against cytotoxicity induced by tacrine in human liver-derived Hep G2 cells (Mishra et al. 2010). Kaempferol is a representative flavonol, and its derivative, kaempferol-6′-*O*-acetate, was reported to have hepatoprotective effect against cell death induced by TNF-α (Lu et al. 2003).

Rhodiola qundrifida

The plant extract was applied for the treatment of fatigue, blood pressure, dysentery, and genital diseases of women and as a stimulator of the nervous system (Saratikov

et al. 1967, 1978; Rohloff 2008; Mora et al. 2015; Yoshikawa et al. 1996). *Rhodiola qundrifida* reported to be antiallergic; rhodiacyanosides have inhibition effect on the histamine which were released from the rat peritoneal exudate cells which were sensitized with anti-DNP-IgE (Mora et al. 2015). The extract of *Rhodiola qundrifida* was found to be stimulatory in cell-mediated immunity (Rozewska et al. 2008a). *Rhodiola quadrifida* hydroalcoholic and aqueous extracts induce an immune modulatory effect on the mouse granulocytes activity which is evaluated by chemiluminescence test (Rozewska et al. 2008b). Its extract response toward the cell-mediated immunity is also evaluated by other tests like respiratory burst activity (RBA) and potential killing activity (PKA) tests (Siwicki et al. 2007; Rozewska et al. 2008a). *Rhodiola quadrifida* also have inhibitory in the highest (50 μg/ml) dose and granulocytes activity in lower doses (Wojcik et al. 2008).

In Vitro Propagation/Culture

In vitro study was done to develop the plant in lab condition to use for various medicinal purposes besides collecting the raw material from the wild environment and to develop the germplasm. The explant selection is a very crucial factor for the success of morphogenic potential of the isolated cells. There is an extensive use of biotechnological approach to increase the various metabolites of the plant (Grech-Baran et al. 2015). The explants will determine the organogenic as well as the genetic stability of the progeny after cloning. Leaves or leaf disks were the most potent and preferable explants for callus, shoot, and bud formation (Tasheva and Kosturkowa 2010). In a procedure for in vitro propagation of roseroots (*Rhodiola rosea*), a medicinal plant, was developed by using a RITA bioreactor system which includes liquid medium in combination with a gelled medium. Three clones were established on a basal medium (BM) for germinated seedlings on half strength Murashige and Skoog (MS) salts. Shoots of all three clones rooted in vitro in the growth regulator-free basal medium within 5–6 week of culturing with a frequency of 90–95% in all three clones. Plantlets obtained in vitro were adapted and transferred to soil with a survival rate of 85–90% (Debnath 2009). In a report a callus culture was established to produce the cinnamyl glycosides (Gyorgy et al. 2004). An in vitro micropropagation study was conducted for the plant in 24 modified Murashige and Skoog media (Tasheva and Kosturkowa 2010). A change in the media composition can effect in the metabolite production of the plant. The addition of methyl jamsonite in the callus culture of *Rhodiola sachalinensis* had increased the salidroside and polysaccharide content (Yu et al. 2011). A change in composition of media is also used for the establishment of the in vitro culture of *Rhodiola henryi* (Kang et al. 2010). The preservation study of callus has shown that the melatonin has improved the survival of callus *Rhodiola crenulata* (Zhao et al. 2011).

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