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A Complete Review on *Rhododendron arboreum*: Phytochemistry, Pharmacological Activities and Future Prospectives



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ABSTRACT

Rhododendron arboreum, belonging to the dicotyledonous family- Ericaceae is a small shrub or tree having deep red to a pink-coloured cluster of flowers, which seeks everybody's attention towards this plant. It is the national flower of Nepal and the state flower of Nagaland (India). It is the most common species of *Rhododendron*, which is widely distributed in northeastern India. Due to various medicinal properties of this plant, it has been mentioned in the traditional medicine of India as well as other countries. Flowers of this plant were not only consumed by the local people of the mountainous region to make juice, jam, syrup, chutney, honey, squash, etc. but also for the treatment of severe diseases such as inflammation, diarrhoea, headache, bacterial and fungal infections. The present review focuses on the pharmacognostic features, phytochemistry, traditional uses, biological activities, and future perspectives of the plant and can help discover lead compounds from the indigenous plant species for the development of novel phytotherapeutic agents.



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INTRODUCTION

India is found to be a country with rich biodiversity and immense treasure of herbal plants and thus called a medicinal garden of the world. Plants are incredible, invaluable, and traditional sources for the treatment of several diseases in the form of medicines.(1) Rhododendron is one such plant that has been used as a traditional medicine in India as well as in other countries. The genus Rhododendron is very vast and includes various species that acquire a special place in the cultural as well as the economic life of the people. (2) There are about 80 species, 10 subspecies, and 14 varieties of Rhododendrons in India, of which maximum are widely distributed in different regions of the Himalayas at altitudes ranging from 1500 – 5500 m. (3) The generic name Rhododendron has been derived from the Greek word: ‘rhodon’ means ‘rose’ and ‘dendron’ means ‘tree’ and the specific epithet ‘arboreum’ means ‘tree-like’.(4) Among all the Indian Rhododendrons, *Rhododendron arboreum* (family-Ericaceae) is one of the most impressive species. It has been traditionally used for the treatment of inflammatory conditions, gastrointestinal disorders, pain, common cold, asthma, skin diseases, etc. Rhododendrons are also well-known for their toxic nature and some species have been traditionally used as a poison. (1) Despite its toxicity, it has been used in ancient medical systems such as Ayurvedic and traditional Chinese medicine and also in North American and European folk medicine. This plant also holds the Guinness Record for World’s Largest Rhododendron. (5, 6) It is also included in Ayurvedic formulation ‘Ashokaarishtha’ which possesses estrogenic and oxytocic activities.

The plant is originated in north-central India and is found in the Himalayas from Kashmir to Bhutan & in the hills of Assam & Manipur at altitudes of 1200-1400 m. *Rhododendron arboreum* is one of the most commonly found species and is widely distributed in northeast India, western ghats (subsp. *nilagiricum*), Bhutan, Nepal, China Thailand, Myanmar.(3) There are various sub-species of *Rhododendron arboreum* found in different regions as mentioned in Table No 1. Aesthetically beautiful red-colored flowers of this plant draw the attention of visitors towards it and also have some religious values. They are considered to be sacred and offered during worshipping in temples and monasteries. It is Nepal’s national flower and in India, it is entitled as the state flower of Nagaland and the state tree of Sikkim. (7)

DESCRIPTION

Kingdom	Plantae
Phylum	Magnoliophyta
Class	Angiospermae
Order	Ericales
Family	Ericaceae
Genus	Rhododendron
Sub-genus	Hymenantes
Species	<i>Rhododendron arboreum</i>

ORGANOLEPTIC CHARACTERS

Rhododendron arboreum is an evergreen or less often deciduous shrub or small tree about 5-10m in height.(3, 5) The trunk is branched and the bark is soft, rough, and reddish-brown. Leaves are generally monomorphic or rarely dimorphic, oblong and lanceolate, rounded to cuneate at base, acute, acuminate to obtuse at apex, crowded at the end of branches, dark green coloured (10-15 x 2-4 cm) with deeply impressed lateral veins(12-18 pairs). The indumentum is glandular or with branched hairs. The flowers are generally grouped in raceme or corymb (Figure No. 1). The corolla varies in shape from shallow lobed to polypetalous and the inflorescence is rarely axillary, 10-20 flowered, pink to deep crimson red-colored funnel-shaped corolla (3-5 cm), Calyx- fine cleft (1-2 cm), 10 Stamens-hypogynous declinings, Ovary-superior, white tomentose or glandular (5-15 locular), Filaments-filiform, Style-capitate, Anthers-ovate. The capsule is curved and finely lobed (3-4 x 1-2 cm). Seeds are compressed, spindle-shaped to ellipsoid or flattened minute with a thin obvolute membrane, and appendages on both ends in some cases.(2, 7, 8)



Figure No. 1: *Rhododendron arboreum* plant

VERNACULAR NAMES

Burans or Lalburansh Hindi/Garhwali

Laligurans Nepali

Adrawal Punjabi

Kamri and Cham Kashmiri

Dieng-tiw-saw Khasi

Baras Bengali

Eras Kumaoni

Billi or Allingi Tamil

Kattupoovarasu Malayalam

Pu Kannada



PHYTOCHEMISTRY

Various phytochemicals isolated from flowers, bark as well as leaves of *Rhododendron arboreum* include alkaloids, glycosides, terpenoids, steroids, anthraquinones, flavonoids, saponins, and tannins. About 208 compounds have been isolated from different species of *Rhododendron* as mentioned by Qiang *et al.* 2011.(9) Generally, phenols and flavonoids are considered to be the principle bioactive compounds of *Rhododendron arboreum*. Compounds like quercetin-3-rhamnoside, coumaric acid, rutin, quercetin, and some other phenolic compounds and amino acids are found in flowers.(10, 11) Glucoside, ursolic acid, α -amyrin, quercetin, dimethyl ester of terephthalic acid, epifriedilinol, companulin, ericolin, and some flavonoids have been isolated from leaves.(8, 12) Betulinic acid, ursolic acid acetate, leucopelargonidin, teraxerol, terpenoids, and steroids are found in the bark.(5, 13) Some alkaloids, anthraquinones, terpenoids, reducing sugars, saponins, tannins are also found in stem and roots (Table No. 2).

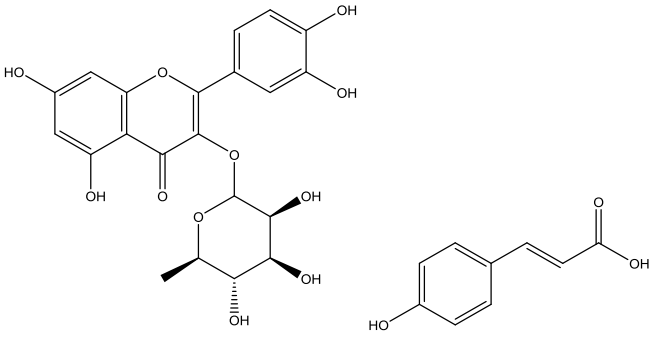
TRADITIONAL USES

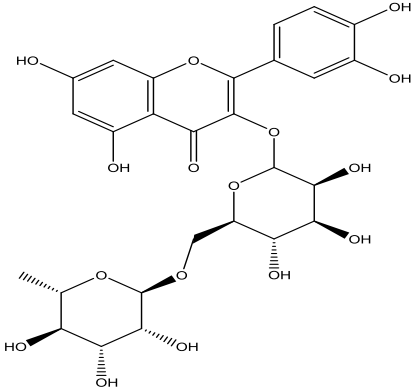
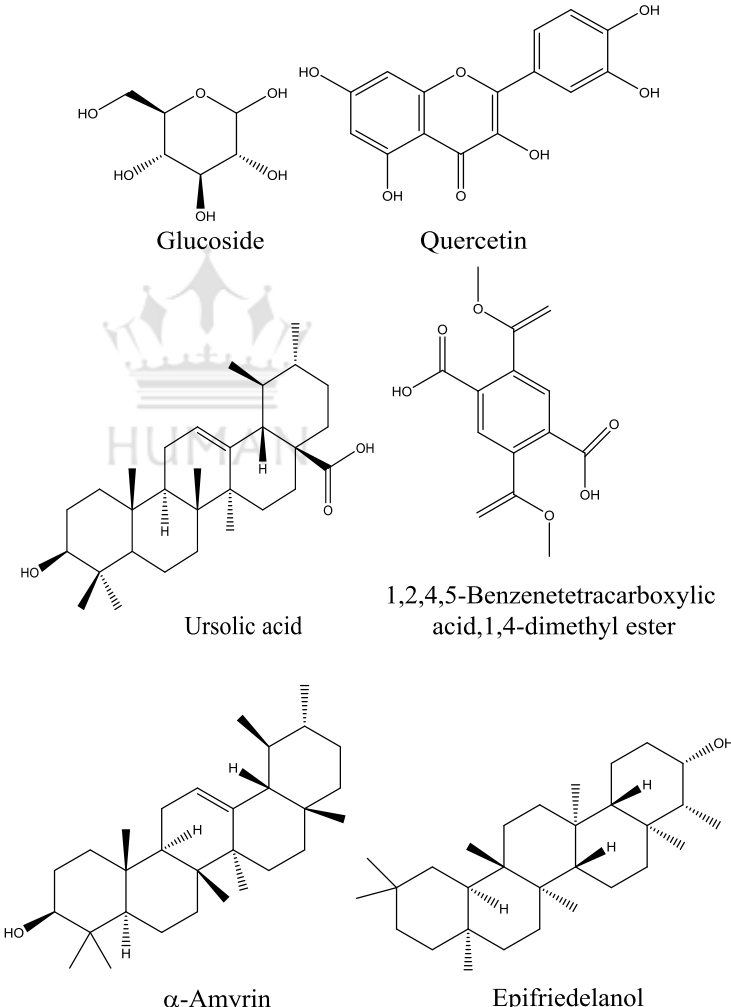
Flowers of *Rhododendron arboreum* have been used traditionally for making jams, jellies, and local drinks (sharbat). Local sharbat was considered to be very effective for the prevention of altitude sickness in hilly areas. The plant has been found as traditional medicine for diarrhoea, headache, stomach-ache, nasal bleeding, fever, and mental retardation. People of Himachal Pradesh use their flowers to make chutney (pickle). Fresh flowers are used for the treatment of diarrhoea, dysentery, and dyspepsia, and sometimes dried flower petals were fried in ghee and then used as a medicine for dysentery. The juice or squash of flowers is highly efficacious in case of diabetes, some heart diseases, and also for menstrual disorders. Fresh or dried flower petals are also used to remove stuck fish bones in the gullet.(4)

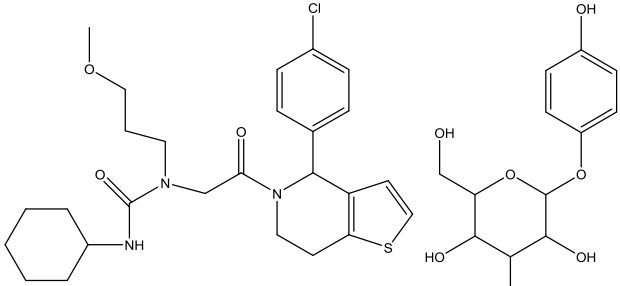
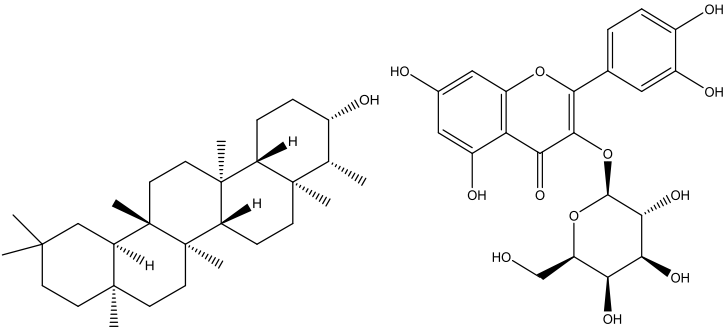
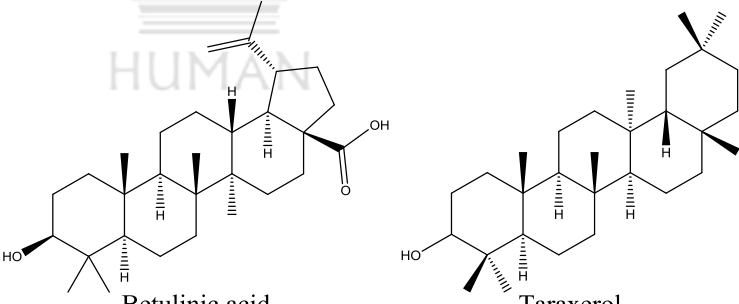
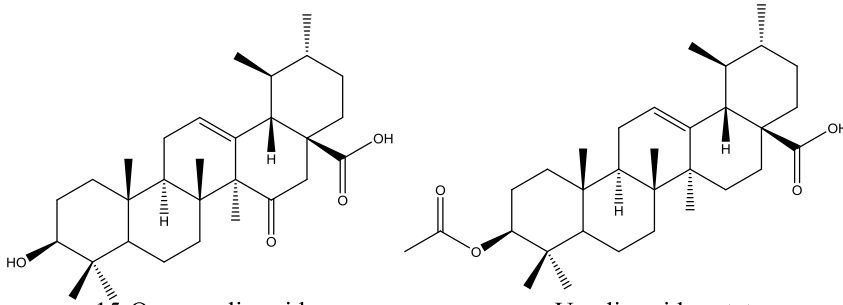
Table No. 1: *Rhododendron arboreum* sub-species (14)

S. No.	Sub-species	Characteristics	Distribution
1.	<i>Rhododendron arboreum</i> spp. Arboreum	Red flowers	Western Himalayas
2.	<i>Rhododendron arboreum</i> spp. Delavayii	Red flowers	Eastern Himalayas
3.	<i>Rhododendron arboreum</i> spp. Namomeum	White, pink, or red flowers	Central Himachal
4.	<i>Rhododendron arboreum</i> spp. Nilagiricum	Red flowers	Nilgiri hills
5.	<i>Rhododendron arboreum</i> spp. Zeylanicum	Orange-red flowers	Sri Lanka

Table No. 2: Bioactive constituents (along with their chemical structure) present in different parts of the *Rhododendron arboretum* plant (15, 16)

S. No.	Part of Plant	Bioactive compounds
1.	Flowers	 <p>Quercetin -3-rhamnoside</p> <p>Coumaric acid</p>

		 <p>Rutin</p> <p>Phenolic compounds, Saponins, Tannins, Xanthoproteins, Amino acids, Sugars, Vitamins, Organic acids, etc.</p>
<p>2.</p>	<p>Leaves</p>	 <p>Glucoside</p> <p>Quercetin</p> <p>Ursolic acid</p> <p>1,2,4,5-Benzenetetracarboxylic acid, 1,4-dimethyl ester</p> <p>α-Amyrin</p> <p>Epifriedelanol</p>

		 <p>Campanulin</p> <p>Ericolin</p>
		 <p>Epifriedelanol</p> <p>Hyperoside</p> <p>Flavone glycosides, Catechins, Flavonoids, and Anthocyanidins</p>
3.	Stem	Alkaloids, Tannins, Terpenoids, Glycoside saponins, Anthraquinones, Reducing sugars
4.	Bark	 <p>Betulinic acid</p> <p>Taraxerol</p>  <p>15-Oxo ursolic acid</p> <p>Ursolic acid acetate</p>

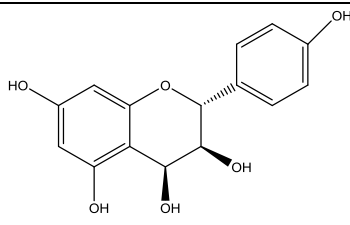
		 <p style="text-align: center;">Leucopelagonidin</p> <p style="text-align: center;">Terpenoids, Alkaloids, Tannins, Saponins, Reducing sugars, Anthraquinones, Steroids</p>
5.	Roots	Alkaloids, Anthraquinones, Terpenoids, Reducing sugars Saponins, Tannins

Table No. 3: Pharmacological activity of different parts of the *Rhododendron arboretum* plant

S. No.	Part of Plant	Pharmacological / Biological Activity	References
1.	Flowers	Anti-diabetic, Anti-inflammatory, Anti-microbial, Anti-diarrheal, Hepatoprotective, Anti-nociceptive, Anti-allergic, Anti-fungal, Free radical scavenging activity, Prevents blood dysentery, stomachache, Beneficial in case of high altitude sickness, mental retardation	(5, 15, 17, 18)
2.	Leaves	Anti-inflammatory, Cardioprotective, Anti-oxidative, Anti-fungal, Anti-allergic, Analgesic, Diuretic, Hepatoprotective, Alleviate headache and fever for the treatment of gout and rheumatic disorders, Relieve cold, cough, asthma, bronchitis, nasal bleeding, and lung infections, Beneficial in case of indigestion and post-delivery complications	(3, 5)
3.	Stem	For the treatment of bronchial asthma, hay fever, haemorrhage, Prevent cardiovascular diseases, Anti-cancer activity	(19)
4.	Bark	Excellent cold reliever, Anti-mutagenic, Anti-cancer, Anti-hyperlipidemic, Anti-inflammatory, Anti-oxidative, Anti-atherosclerotic, Anti-microbial	(5, 12, 19, 20)
5.	Roots	Anti-carcinogenic, Anti-inflammatory, Anti-nociceptive, Prevent cardiovascular diseases	(5, 21)

PHARMACOLOGICAL USES

As the plant consists of various bioactive phytoconstituents, it is found to have different pharmacological activities as mentioned in Table No. 3.

Anti-inflammatory activity

Agarwal and Kalpana, 1988, first reported the anti-inflammatory activity of *Rhododendron arboreum* aqueous, 50% ethanolic and methanolic extracts against PGE₂ (Prostaglandin E₂), carrageenan, histamine, and serotonin-induced rat hind paw edema. Various experimental animal models were used to determine the anti-inflammatory activity of ethanolic and ethyl acetate fractions of *Rhododendron arboreum* with comparison to the reference drug. (22) Verma *et al.* 2010, studied dose-dependent anti-inflammatory and anti-nociceptive activity of *Rhododendron arboreum* ethyl acetate extracts on arachidonic induced hind paw edema, Freund's adjuvant-induced paw arthritis, cotton pellet granuloma inflammation model ($p < 0.01$ in all cases).(23) According to Selloum *et al.* 2003, Swaroop *et al.* 2005, two main flavonoids i.e. quercetin and rutin isolated from *Rhododendron arboreum* extracts are responsible for the anti-inflammatory activity.(24, 25) Rutin is found to inhibit LOX (lipoxygenase), PLA₂ (phospholipase A₂) isoforms, and release of lysosymase and β -glucuronidase from neutrophils. It also inhibits the release of TNF- α , IL-6 and IL-1 β , ERK, and p38 activation and iNOS expression in LPS (lipopolysaccharide) stimulated cells.(26) Methanolic extracts of *Rhododendron arboreum* are also found to have anti-inflammatory and anti-nociceptive properties. (21)

Anti-diabetic activity

Bhandary and Kawabata, 2008, isolated hyperoside from the flowers of *Rhododendron arboreum* which was found to have anti-diabetic activity. It inhibited α -glucosidase in rat intestine with IC₅₀ = 0.76mM for maltase and IC₅₀ = 1.66mM for sucrose. This study revealed that flowers possess an anti-diabetic property that can be helpful to develop nutraceutical, functional food, or medicinal preparations for the treatment of diabetes or its complications.(6) Later, Verma *et al.* 2012, discovered its anti-hyperglycemic potential in streptozocin-induced diabetic rats. It was found to increase insulin secretion and glycolysis and reduced gluconeogenesis in streptozocin-induced diabetic rats. (27)

Cardioprotective activity:

Rhododendron arboreum has been also found to have cardioprotective activity. The ethanolic extract of its leaves shows *in vivo* preventive effect in the case of myocardial ischemia induced by isoproterenol. It was found that the activity of LDH (lactate dehydrogenase), ALT (alanine aminotransferase), and AST (aspartate aminotransferase) was decreased in the rat's serum on pre-treating with extract for about 42 days in a dose-dependent manner as compared to the rats treated with isoproterenol. Along with the cardioprotective effect, the antioxidant activity of the extract was also determined, which might be due to the presence of flavonoids.(2, 28)

Anti-microbial activity

Sonar *et al.* 2012, reported the antibacterial activity of aqueous and ethanolic extracts of *Rhododendron arboretum* flowers. They tested the anti-microbial activity of the isolated compound, quercetin against seven micro-organisms but it is found to be effective against *Escherichia coli* and *Staphylococcus aureus*. It exhibited activity up to a concentration of 12.5mg/ml. Lal *et al.* 2017, investigated the anti-microbial activity of *Rhododendron arboreum* plant extract on six bacterial pathogens: *S. Typhi*, *Shigella*, *E. coli*, *S. aureus*, *Pseudomonas*, *B. cereus*. It was found through the results of minimal inhibitory concentration results that even lower concentration of the extract was sufficient to inhibit the growth of all pathogenic microbes. Ethanolic extract was found to be effective against only *S. aureus* while methanolic extract was effective against all bacterias except *Shigella*.(29)

Hepatoprotective activity

Prakash *et al.* 2008, reported *in-vivo* hepatoprotective effects of *Rhododendron arboreum*. It was found that pretreatment with ethanolic extract of its leaves shows protective action in CCl₄-induced liver damage in rats. It shows a significant effect at the dose of 60 and 100 mg/kg. The ethanolic extract also leads to a decrease in the level of triglycerides and tissue cholesterol. (30) A similar type of study was performed by Verma *et al.* 2011, using ethyl acetate fraction of *Rhododendron arboreum* flowers to indicate hepatoprotective activity against CCl₄-intoxicated rats. The most effective concentration range was 100-400 mg/kg. Ethyl acetate extract also attenuated the increased activities of SGPT (glutamate pyruvate transaminase), SGOT (glutamic oxaloacetic transaminase), γ -GT (γ -glutamyl transferase), GST (glutathione S-transferase), *etc.* From the whole study, it was concluded that the effect

of its ethyl acetate fraction on liver protection was related to glutathione mediated detoxification as well as free radical scavenging activity.(12)

Anti-diarrhoeal activity

Verma *et al.* 2011, using the HPTLC method for the determination of hyperin (hyperoside), also reported the antidiarrhoeal activity of ethyl acetate fraction of *Rhododendron arboreum* flowers. The ethyl acetate fraction was found to be effective against castor oil & magnesium sulfate-induced diarrhoea.(12, 31) It was also investigated for the measurement of gastrointestinal transit using charcoal and castor oil-induced enter pooling. Oral administration of ethyl acetate fraction at 100, 200 and 400 mg/kg showed significant and dose-dependent ($P < 0.05-0.001$) anti-diarrhoeal potential in castor oil and magnesium sulfate-induced diarrhoea and reduction in propulsive movement in castor oil-induced gastrointestinal transit using charcoal meal in rats. It was concluded that ethyl acetate fraction could reduce castor oil-induced diarrhoea as well as the number of diarrhoeal faeces and the total weight of faeces as well, in a dose-dependent manner. Phytochemical screening including saponins, tannins, flavonoids, phytosterols, reducing sugars, and phenolic compounds revealed various secondary metabolites. It was indicated that tannins, reducing sugars, and sterols might be responsible for the mechanism of its anti-diarrhoeal activity.

Adaptogenic and Anti-oxidant activity

According to Prakash *et al.* 2007, leaves of *Rhododendron arboreum* possess anti-oxidant activity due to the presence of flavonoids. (Swamidasan *et al.* 2008) found the adaptogenic effects of ethanolic extract of *Rhododendron arboreum* on mice and rats by mitigating the effect of acute and chronic stress-induced biochemical and physiological perturbation. Various methods were used for the evaluation of adaptogenic activity such as swimming endurance, anoxia stress tolerance, and immobilization stress models. And there was an increase in anoxia stress tolerance and swimming endurance time on treatment with ethanolic extract at 250 and 500 mg/kg.(32, 33)

Anti-cancer and cytotoxic activity

In-vitro anticancer activity of alcoholic extract of *Rhododendron arboreum* leaves and flowers has been studied against crown gall tumor and MCF-7 breast cancer cell lines. Ethanolic extract of leaves was significantly effective against both MCF-7 breast cancer cell lines as well as crown gall tumors whereas flower ethanolic extract was effective in the

inhibition of crown gall tumors in potato discs.(4, 7) Nisar *et al.* 2013, also studied cytotoxic effects of methanolic extract of the plant.(19) 15-Oxoursolic acid isolated from the stem bark of *Rhododendron arboreum* was screened against five human cancer cell lines to determine its cytotoxic activity. IC₅₀ values being 2.3 ± 0.1 µM, 4.9 ± 0.2 µM, 9.2 ± 0.2 µM and 10.3 ± 0.1 µM were found for MDR 2780AD, Hep G2, H157, and NCI-H226 cell line respectively, and a very good effect was found against A498 cancer cell line with an IC₅₀ value being 32.8 ± 1.2 µM. This ensured a good cytotoxic potential of 15-Oxoursolic acid.(34)

TOXICOLOGICAL ASPECTS

Dried leaves of *Rhododendron arboreum* were known to be poisonous in the Himalayan regions of India. Also in traditional Indian medicine, local people were aware of its harmful effects when consumed in excess.(3) Generally, the other species of rhododendron are found to cause intoxication in humans and animals. Rhododendron honey obtained from the nectar of *Rhododendron luteum* and *Rhododendron ponticum* flowers lead to intoxication in the Black sea region of Turkey. It is commonly referred to as mad honey poisoning caused due to the presence of grayanotoxins which are toxic polyhydroxylated terpenes. Likewise, some other species were reported to cause poisoning in pets, and cattle and extracts of Rhododendrons showed *in-vivo* toxicity. (2)

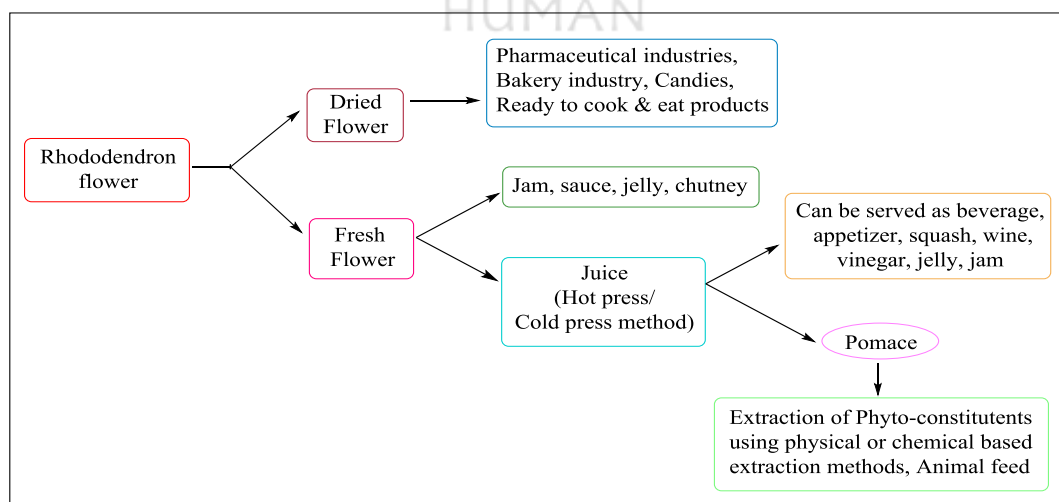


Figure No. 2: Future perspectives of *Rhododendron arboreum* flower (14)

CONCLUSION AND FUTURE PERSPECTIVES

It has been found that extracts of different parts of *Rhododendron arboreum* show various *in-vitro* as well as *in-vivo* pharmacological activities. The plant is effective against

inflammation, diabetes, diarrhoea, hepato-toxicity, cytotoxicity, and some cardiac disorders. But the current pharmacological data in most of the cases are limited to the studies on plant extracts, so more efforts are needed for the isolation of biologically active constituents. The present review also states the traditional uses of the plant. Fresh flowers had not only used as medicine but also for the preparation of juices jams and jellies. Developing sustainable use of *Rhododendron arboreum* can hold a good perspective for the livelihood of local people. More research is required to enhance its potential in pharmaceutical as well as other food and beverage industries. Also, there are some cases of rhododendron toxicity, so more efforts are needed to diminish the toxic effects and potentiate its medicinal values.





CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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