Review Article

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# A review on ethnomedicinal and phytopharmacological potential of traditionally wild and endemic plant *Berberis tinctoria* Lesch.

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## ABSTRACT

**Introduction:** *Berberis tinctoria* an evergreen shrub, endemic and predominantly found at a higher altitude of the Nilgiri Biosphere Reserve, India. This leaf and fruit are edible, which are also used in homeopathic remedies for countless illnesses. **Objectives:** *B. tinctoria* with diverse ethnomedicinal uses was focused in the prevailing study to detailed the phytochemical and pharmacological properties for further imminent research in this species. **Materials and methods:** Published data in this review were all gathered from the online bibliographical databases: PubMed, Elsevier, Scopus, Google Scholar, Web of Science, and local ethnic community peoples of Kurumba and Toda. **Results:** *B. tinctoria* was used as a Ayurvedic and homeopathy medicine by the tribal communities. The previous findings of *B. tinctoria* were used for skin diseases, wound healing, inflammatory, menorrhagia, diarrhea, jaundice, and a snakebites. The phytochemical studies revealed that secondary metabolites, antioxidants, and antimicrobial activity as a result of major alkaloid isoforms of berberine, berbamine, jatrorrhizine, etc. **Conclusion:** *B. tinctoria* is an important plant due to the presence of bioactive phytochemicals, especially berberine protoberberine group of benzylisoquinoline. As a result of its diverse ethnopharmacological importance, as well as numerous commercial products and novel bioactive compounds yet to be discovered for future drug discovery and development.

**Keywords:** Alkaloid, Anticancer, Berberine, *Berberis tinctoria*, Benzylisoquinoline, Western Ghats

## INTRODUCTION

Plants are the elemental source of numerous traditional medicines throughout the world since ancient days and it is believed that plants are the promising remedy for numerous diseases. The biodiversity of India is tremendous and unique with various climates, topology, and habitat, the Western Ghats is considered as one of the biodiversity hotspots among 25 in the world.[1] This mega biodiversity region is being the source of ethereal plant resources yielding treasured medicinal, aromatic, food, and other industrial products apart from harboring huge wilderness and eco-tourism.[2] Traditional plant-based medicinal systems (Ayurveda, Yoga, Naturopathy, Homeopathy, Siddha, and Unani) were invented, thrived, and practiced till date, especially in the developing countries. India's varied climatic conditions and different soil architecture forms distinct geographical regions which have caused a wide distribution of medicinal plant species, the richest sources of resource allocation of nature.[3] Ancient civilizations valued the plants more as they accord for food, shelter, and medicine,[4] many people assuming that medicinal plants were tenacious to find and urge a lot of effort. The medicinal uses of plants have been developed through many investigations in wild animals, ethnobotanical trail, and errors by the tribal community. Ayurveda, a traditional system of medicine using extensive modalities to devise health and welfare, the elemental desire is to restore the physical, mental, and emotional balance in patients, thereby improving health and preventing diseases.[5] The plant-based products have no precarious effect on the ecosystem,[6] and currently, about 70–80% of population of the developing countries depending on herbs and herbal products for their primary health care because of their cheap, easy availability, and with slight or no side effect.[7] However, among the estimated 250,000–400,000 plant species, only 6%

have been studied for biological activity and about 15% have been investigated phytochemically.[8] Slowly, the traditional knowledge on the uses of plants is diminishing by the cause of several reasons, including a shift in the attitude of the present generation more toward Western lifestyle, increased usage of allopathic medicines along declining interest of younger generations to carry forward the traditional system. It is therefore imperative to document the valuable information on plant species usage before it completely disappears.[9] On the contrary, most pharmaceutical companies showing interest recently in plant-based drugs because of the widespread belief that "green medicine" is safe and more reliable than expensive synthetic drugs.[10] Therefore, it is necessary to evaluate herbs properly. *Berberis tinctoria* Lesch. is one of the herbs mentioned in all ancient scriptures, used as an ancient Ayurvedic medicine and homeopathic remedy for uncounted illnesses.[11,12] Globally, the genus *Berberis* (Family – Berberidaceae) is represented by 450 species distributed largely in South East Asia, China, Japan, and Africa.[13] The first taxonomic account of the Berberidaceae in the Indian subcontinent[14] includes six genera and 17 species. Schneider revised the genus *Berberis* during 1905 and 1908 and recorded 13 new species and one variety in India. While[15] revising the Flora of India, this family included 54 species of *Berberis*, one species of Epimedium and 13 species of Mahonia from the present political boundaries of India. Therefore, "Berberides" was considered one of the most primitive families of angiosperms having a high number of disjunction or discontinuous genera. *Berberis* spp. richness, endemism, and distribution in IHR have been analyzed.[16] The present study in *B. tinctoria* helps to identify the knowledge gaps in traditional uses, pharmacological studies, toxicity profiling, clinical trials, and other relevant research in this medicinally important plant. Preceding reviews of other individual species of *Berberis* spp. are also available, but the scientific evidence of *B. tinctoria* is still lacking. Hence, this review will help to classify the latent and patent potentials of *B. tinctoria* to researchers to explore the further studies on biological and chemical properties of this particular species.

## Taxonomical Classification

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Ranunculales
- Family: Berberidaceae
- Genus: Berberis
- Species: *B. tinctoria* Leach.

## VERNACULAR NAMES

- English: Nilgiri barberry
- Tamil: Oosikala
- Kannada: Jakkalahannu
- Malayalam: Kozhikkal-mullu.

## BOTANICAL DESCRIPTION

*B. tinctoria* is an evergreen shrub; endemic to South Western Ghats, predominantly found in the higher altitude of The Nilgiris, Tamil Nadu, India.[17] Figure 1 shows the habit of the plant which is in variable size and form, often 1–2 m high,


**Figure 1:** (a) Habit of *Berberis tinctoria*, (b) leaves, (c) flower, and (d) fruit

4 m high in the forest; stems furrowed, pale brown; wood very tough, bright yellow; spines 3-fid, 1.5–3 cm long. Leaves are entire, obovate with 1 or 2 spinules, young leaves are obtuse, mucronate, 1.5–3.5 × 0.7–1.3 cm thick and purple, papillose, dull above, pruinose beneath with petioles 2–5 mm long. Flowers are racemose or panicle (10–20) which are 3.5–5 cm long, yellow; with pedicels, 5–10 mm are red prophylls 1 × 0.5 mm. Outer sepals are obovate, acute 7 × 5 mm; the inner whorls are ovate or obovate, obtuse, 4 × 2.5 mm. Petals are obovate, 6 × 4.5 mm, clawed; claws glandular at the base. Stamens 5 mm long, shortly apiculate, ovary stipitate. Berries spindle shaped, 9–10 × about 5 mm excluding 1–1.5 mm long dry style attached to round stigma, purplish-red turning dark blue with glaucous bloom.[18]

## ETHNOBOTANICAL AND TRADITIONAL USES

Ethnobotany is a study of plant habitat and its practical uses through the traditional knowledge of local culture and people. There has been an increasing interest toward the scientific study of human and plant interaction in the natural environment among the scientist, anthropologists, and practitioners of indigenous medicinal systems.[19] The genus Berberis with various species is not only known as food, which is mainly used in Ayurveda and homeopathic remedy, many tribal communities used *Berberis* plants for medicine preparation as specified ethnobotanically in traditional medicine.[20] Furthermore, the Toda, Kota, and Irula tribal peoples are used this as laxative and tonic for ulcer, asthma, toothache, swelling, and blood purifier, as well as the plant is locally available they prepare mosquito coils and used as a mosquito repellent to prevent malaria and other related diseases.[6,21-23] In addition to that, it is also used in skin diseases, wound healing, inflammatory, menorrhagia, diarrhea, jaundice, and eye infections, also leaf juice found to be a better remedy for snakebites.[22-25] The fruit was edible and has rich in nutritional values. Figure 2 shows the various uses of *B. tinctoria*. The various ethnobotanical and ethnopharmacological activities of different parts of *B. tinctoria* are shown in Table 1.[6,21-29]

## PHYTOCHEMICAL AND NUTRITIONAL PROPERTIES

*B. tinctoria,* one of the endemic plant species, especially root, leaf, fruit, and stem, is extensively used for the treatment of several human diseases by the tribal practitioner in the Nilgiris. The presence of a high amount of carbohydrates, proteins, and amino acids in *B. tinctoria* revealed that it can be used as good nutritional food. The secondary metabolites analyzed in the fresh fruits were 410 ± 0.082 mg gallic acid equivalents/100 g and total flavonoid content is 320 ± 0.012 mg quercetin equivalents/100 g.[30] Alkaloids are known to be the most potent anti-inflammatory agents of the naturally occurring secondary metabolites,[31] where the plant *B. tinctoria* has a higher amount of alkaloids. Almost all different *Berberis* plant species have been explored by distinct researchers but they all are counterfeit the chemo-taxonomical identification, variability studies among the same or different plants or species and isolation, and identification of various medicinally important chemical constituents from this genus. Although the stem and root of *B. tinctoria* were found to be the same, the leaves have variable chemical constituents.[32] Diverse phytocompounds have been isolated and identify over the last half century such as terpenoids, anthocyanins, alkaloids, lipids, flavonoids, vitamins, sterols, lignans, proteins, and carotenoids from *Berberis* plant species.[33,34] Alkaloids are the preeminent bioactive chemical constituents of *Berberis* spp.,[21] reported that alkaloids of *B. tinctoria* are calculated through HPTLC densitometric method and it's found that 3.36% berberine is present as berberine hydrochloride. The leaves and fruits have been eaten by local peoples without knowing the nutritional values. Hence, this documented review will serve as a glossary for further development of the plant into a product.

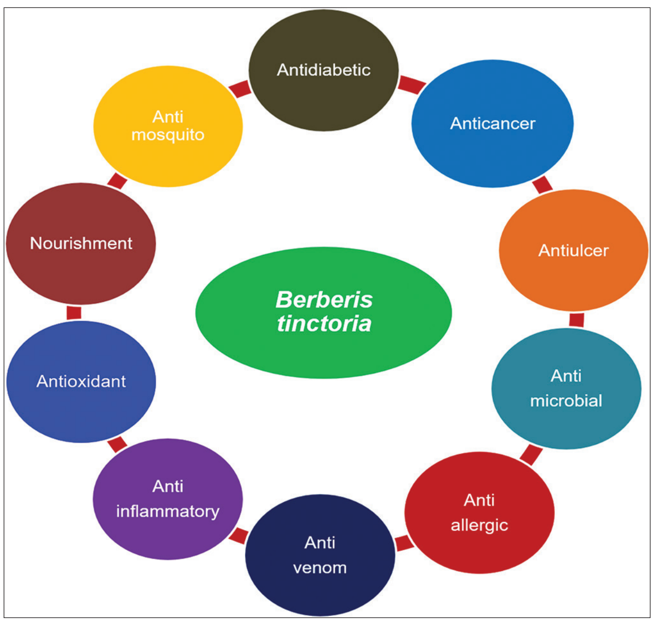


**Figure 2:** A broad spectrum of pharmacological activities of *Berberis tinctoria*

## BIOACTIVE COMPOUNDS

Plants are the leading source for many traditional practices all over the world since ancient times and also contribute contemporary remedies to mankind with affluent sources of phytocompounds. Preceding studies reported that *B. tinctoria* is one of the considerable plants used in Ayurveda for several remedies, used as an alternative tonic for demulcent, diuretic, and diaphoretic, and also used in the treatment of syphilis, diarrhea, jaundice, chronic rheumatism, skin diseases, and urinary disorders. Many scientific pieces of the evidence of *B. tinctoria* validate its resourceful biological functions that support the traditional use in the orient. The genus *Berberis* is well known for its medicinal uses, *Berberis* root is one of the best plant-based drugs in India.[35] The extensive use of different *Berberis* spp. in folkloric medicine has paved the way for their phytochemical analysis of its bioactive compounds.[36] The root, stem, leaf, and fruit of various *Berberis* spp. are recognized for their alkaloids and the alkaloid compounds of various *Berberis* spp. are given in Table 2.[5,32,37-67] Among the several bioactive compounds, berberine is the primary constitutes having various pharmacological actions. Therefore, some common phytocompounds of *Berberis* spp. mainly yellow-colored alkaloids such as berberine, palmatine, jatrorrhizine, columbamine, reticuline, allocryptopine, berbamine, oxycanthine, and aromoline have been reported already[68] and are presented in Figure 3. *B. lycium* root extracts

**Table 1:** Ethnopharmacological/economical application of the *Baptisia tinctoria*

| Serial number | Part of the plant | Ethnopharmacological/economical application | References |
|---|---|---|---|
| 1 | Root | Antibacterial | [26] |
| 2 | Root | Skin disease and jaundice | [21] |
| 3 | Root | Diarrhea and intestinal parasitic infections | [22] |
| 4 | Root | Antibacterial and antifungal activity | [27] |
| 5 | Leaves | Hepatoprotective and antioxidants | [28] |
| 6 | Leaves | Natural mosquito coil | [6] |
| 7 | Leaves | Snakebite and indigestion | [23] |
| 8 | Fruit | Jams and jellies | [29] |
| 9 | Fruit | Antidiabetic | [24] |
| 10 | Root, young shoot | Jaundice | [25] |

**Table 2:** List of alkaloids isolated from various *Berberis* species

| Serial numbr | Compounds | Plant part | Berberis Species | References |
|---|---|---|---|---|
| 1 | Amurenine | Young shoot | *B. amurensis* | [39] |
| 2 | Aromoline | Root bark | *B. aristata, B. vulgaris, B. heteropoda* | [5,40,41] |
| 3 | Baluchistanamine | Root | *B. baluchistanica* | [42] |
| 4 | Berbamine | Stem, stem bark, root, root bark, fruit, leaf | *B. aristata, B. asiatica, B. corallina, B. floribunda, B. francisci- ferdinandi, B. jaeschkeana, B. kawakamii, B. lamberti, B. mingetsensis, B. petiolaris, B. thunbergii, B. tinctoria, B. vulgaris* | [37,38,40,41,43,44] |
| 5 | Berberine | Stem, stem bark, root, root bark, fruit, leaf, young shoot, aerial part | *B. aristata, B. asiatica, B. amurensis, B. chitria, B. corallina, B. crataegina, B. floribunda, B. francisci-ferdinandi, B. guimpeli, B. himalaica, B. iliensis, B. jaeschkeana, B. kawakamii, B. lamberti, B. mingetsensis, B. petiolaris, B. thunbergii, B. tinctoria, B. vulgaris, B. lycium, B. aetnensis, B. libanotica* | [37,38,40,41,44-47] |
| 6 | Berberine phenoxide, | Stem bark | *B. aristata* | [48] |
| 7 | Berberine tannate | Root bark | *B. hispanica* | [49] |
| 8 | Berberubine | Aerial part, shoot | *B. sibirica* | [50] |
| 9 | Bersavine | Root bark | *B. vulgaris* | [51] |
| 10 | Chenabine | Root | *B.lycium* | [44] |
| 11 | Chillanamine | - | *B. buxifolia* | [52] |
| 12 | Chitraline | Root | *B. calliobotrys* | [53] |
| 13 | Columbamine | Stem bark, root, root bark | *B. asiatica, B. floribunda, B. lamberti, B. vulgaris* | [37,38,41,44] |
| 14 | Corydaline | Root | *B. floribunda* | [44] |
| 15 | Epiberberberine | Root | *B. floribunda* | [44] |
| 16 | Gilgitine | Root, bark | *B. lycium* | [44] |
| 17 | Himanthine | Bark | *B. himalaica* | [44] |
| 18 | Hydroxyberberine | Stem | *B. amurensis* | [41] |
| 19 | Ilicifoline | - | *B. ilicifolia* | [54] |
| 20 | Isocorydine | Leaf, stem, aerial part | *B. heterobotrys* | [55] |
| 21 | Isotettrandine | Root | *B. kawakamii, B. tinctoria* | [37,38] |
| 22 | Jatrorrhizine | Root, root bark | *B. asiatica, B. chitria, B. floribunda, B. iliensis, B. kawakamii, B. lamberti, B. tinctoria, B. tschonoskyana, B. dictyophylla* | [56,57] |
| 23 | Jhelumine | Root | *B. lycium* | [44] |
| 24 | Kalashine | Root | *B. calliobotrys* | [53] |
| 25 | Karachine | Root bark | *B. aristata* | [40] |
| 26 | Magnoflorine | Root | *B. mingetsensis, B. tschonoskyana, B. crataegina, B. lycium, B. kansuensis* | [47,57] |
| 27 | Muraricine | Root bark | *B. vulgaris* | [51] |
| 28 | Nummularine | Leaf | *B. nummularia* | [32] |
| 29 | Obaderine | Root, stem | *B. iliensis, B. tschonoskyana* | [38,43] |
| 30 | O-methylcorydine-N-oxide | Whole plant | *B. chitria* | [58] |
| 31 | O-methylpakistanine | Root | *B. calliobotrys* | [53] |
| 32 | Oxyacanthine | Young shoot, root, seed, leaf, aerial part, root bark, young shoot. | *B. aristata, B. asiatica, B. chitria, B. corallina, B. floribunda, B. thunbergii, B. tinctoria, B. tschonoskyana, B. chitria, B. vulgaris* | [37,38,40,43,58] |
| 33 | Oxyberberine | Stem bark, root | *B. asiatica, B. tinctoria, B. tschonoskyana* | [37,38,40] |
| 34 | Pakistanamine | Stem bark, root | *B. asiatica, B. baluchistanica, B. calliobotrys* | [41,53,59] |

*(Contd...)*

**Table 2:** (*Continued*)

| Serial numbr | Compounds | Plant part | Berberis Species | References |
|---|---|---|---|---|
| 35 | Palmatine | Root park, whole plant, root, stem bark. | *B. aristata, B. chitria, B. crataegina, B. floribunda, B. jaeschkeana, B. lycium, B. tinctoria, B. dictyophylla, B. kansuensis, B. amurensis, B. petiolaris* | [37,38,40,43,44,56,57,60-62] |
| 36 | Penduline | Root, bark | *B. corallina* | [37] |
| 37 | Pronuciferine | Aerial part | *B. coletioides* | [63] |
| 38 | Pseudoberberine | Stem bark | *B. aristata* | [40] |
| 39 | Punjabin | Bark | *B. Lycium* | [44] |
| 40 | Reticuline | Leaf, stem, fruit | *B. heterobotrys, B. heteropoda* | [39,64] |
| 41 | Shobakunine | Root | *B. kawakamii, B. tschonoskyana* | [37,38] |
| 42 | Sindamine | Bark | *B. lycium* | [44] |
| 43 | Sotetrandrine | Root bark | *B. vulgaris* | [65] |
| 44 | tetrahydropalmatine | Stem bark | *B. asiatica* | [41,43] |
| 45 | Thalicmidine, | Leaf, young shoot | *B. turcomanica* | [66] |
| 46 | Turcamine | Leaf | *B. turcomanica* | [67] |
| 47 | Turcomanidine | Leaf | *B. turcomanica* | [67] |
| 48 | Turcomanine | Young shoot | *B. turcomanica* | [67] |
| 49 | Umbellatine | Root, bark | *B. insignis* | [44] |
| 50 | Yatroricin | Stem bark | *B. vulgaris* | [37,38] |

*B. amurensis: Bombus amurensis, B. aristata: Berberis aristata, B. vulgaris: Berberis vulgaris, B. heteropoda: Berberis heteropoda, B. baluchistanica: Berberis baluchistanica, B. asiatica: Buddleja asiatica, B. francisci-ferdinandi: Berzercon francisci-ferdinandi, B. jaeschkeana: Berberis jaeschkeana, B. kawakamii: Berberis kawakamii, B. lamberti: Bacula lamberti, B. mingetsensis: Brucella melitensis, B. petiolaris: Banksia petiolaris, B. thunbergii: Berberis thunbergii, B. tinctoria: Baptisia tinctoria, B. chitria: Berberis chitria, B. crataegina: Berberis crataegina, B. guimpeli: Berberis guimpeli, B. himalaica: Berberis himalaica, B. iliensis: Berberis iliensis, B. aetnensis: Berberis aetnensis, B. libanotica: Berberis libanotica, B. hispanica: Berberis hispanica, B. sibirica: Berberis sibirica, B. lycium: Berberis lycium, B. buxifolia: Bossiaea buxifolia, B. calliobotrys: Berberis calliobotrys, B. ilicifolia: Banksia ilicifolia, B. heterobotrys: Berberis heterobotrys, B. tschonoskyana: Berberis tschonoskyana, B. dictyophylla: Berberis dictyophylla, B. kansuensis: Berberis kansuensis, B. nummularia: Biscogniauxia nummularia, B. coletioides: Berberis coletioides, B. turcomanica: Berberis turcomanica, B. insignis: Brighamia insignis*

yield 80% dry weight but only traced amount of alkaloids is reported.[69] Bhardwaj and Kaushik recorded nearly 55 *Berberis* plant species and their biological activities,[68] also distinct numbers of alkaloids have been isolated and identified over the past 60 years worldwide from different *Berberis* spp.[33] Berberine is an isoquinoline alkaloid widely used in East Asia for immense symptoms; also, the neuroprotective effects of berberine in Alzheimer's disease were reported recently.[70]

*B. tinctoria* root has been reported with the same alkaloid compounds, the berberine, and so[37,38] which is significant to *Berberis* spp. reported by Srivastava and Rawat[21] with many bioactivities of the medicinal and food-related evidence. *B. tinctoria* fruit is edible by the local tribes as well as Ramachandran *et al*. reported that the fruit is used to prepare Jam and Jellies.[29] The underutilized wild edible fruits are more nutrients than the other consumable fruits available in the market.[71] Adding the scientific pieces of evidence to the chemical constituents present in the fruits of *Berberis* having health benefits would be an effective phenomenon for nutraceutical industries. By recognizing the potential of wild fruits in India, many research groups are now exploring its phytochemical and pharmacological properties in that the genus *Berberis* confirmed the claims of the species traditional uses. The collection of discrete research reports on this species during the present review revealed that *B. tinctoria* is a potential plant with diversed benefits to the society and for developing novel pharmaceutical products in human health care.

## ANTIOXIDANT PROPERTIES

The antioxidant properties of plant extracts have been attributed to their polyphenolic compounds and its predominant action is to delay the oxidation of molecules by inhibiting the free radical's oxidizing chain reaction which results in oxidative damage reduction in the human body.[72] The DPPH$^{\cdot}$ radical has been widely used to estimate the plant and food compounds scavenging activity against free radicals by donating hydrogen atom.[73] Iron is an essential element for normal physiological activity when it undergoes Fenton reaction forms adverse hydroxyl radicals which contribute to oxidative stress,[74] also hydroxyl radicals are formed from superoxide and hydrogen peroxide, in the presence of metal ions, such as copper and iron. Among the oxygen radicals, hydroxyl radicals are the most active and unstable induce severe biological damage to the adjacent living cells.[75] Antioxidants are the reductants that inactivate the oxidants known as redox reactions where one reaction species reduced by an oxidant of antioxidants. The ferric reducing assay measured the reducing ability of any substances[76,77] reported that the reducing power of low and high molecular phenolics and alkaloids have high antioxidant activity for scavenging of free radicals. It has been also proved that the potential antioxidants through *in vitro* ferric-reducing antioxidant power assay increased the total antioxidant capacity of blood plasma.[78]

During the reaction of oxygen with superoxides such as $N_2O_4$, $NO_3^-$, $NO_2$, $NO_2^+$, and $N_3O_4$, nitric oxide or reactive

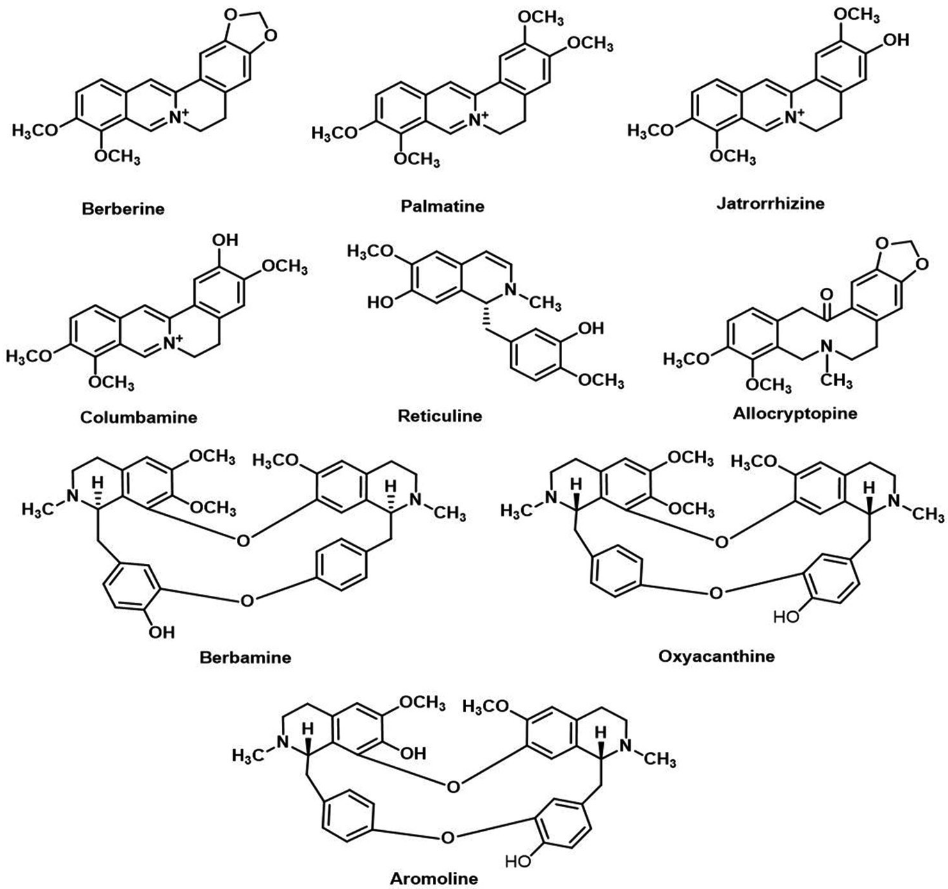


**Figure 3:** Major alkaloids present in the plants belonging to *Berberis* spp.

nitrogen species (RNS) were formed which are highly reactive compounds responsible for altering the structural and functional behavior of many cellular components. The plant-based products have the equity to neutralize the effect of NO formation and also preventing excessive NO generation and its ill effects in the human body by counteracting the chain reactions of NO implicated for inflammation, cancer, and other pathological conditions.[79] *B. tinctoria* methanol fruit extract expressed scavenging activity toward DPPH·, nitric oxide, hydroxyl ion, and superoxide anion radicals is ranged from 1.063 to 2.364 mM TE/g also wield strong reducing the metal chelating capacity of Fe3+ ($EC_{50}$ = 45.24 +1.42 µg $mL^{-1}$) and noticeable reduction of erythrocyte hemolysis ($EC_{50}$ = 71.1+0.22 µg $ml^{-1}$). The methanolic extract of leaves was good hepatoprotective and antioxidant potential in animal models with the dose of 150 mg/kg and 300 mg/kg which result in a significant decrease in the levels of serum enzymes, bilirubin, and lipid peroxidation while increasing the levels of glutathione, catalase, and superoxide dismutase.[28,30] In the conclusion of all reported findings, *B. tinctoria* is a potentially valuable dietary resource with many alkaloids, phenolics, and flavonoids that have got much attention in the day-to-day life due to their antimutagenic, antitumor, and antioxidant activities. Therefore, the alkaloids rich plant species *Berberis* point that it could be used as a potent antioxidant. The review obtained strongly toward prospective underexploited potential plant displayed remarkable antioxidant activities to scavenge the ROS and RNS. Furthermore, berberine has been characterized with remarkable antioxidant and anti-inflammatory activities with promising efficacy against diabetes mellitus. It has remarkable changes in oxidative stress markers, antioxidant enzymes, and pro-inflammatory cytokines in diabetic animals.[80] The secondary metabolites of the plant extract were found to possess higher antioxidant activity and significant positive correlation analyses were demonstrated between secondary metabolites and antioxidant activities.[81]

## ANTIMICROBIAL ACTIVITY

On the inconsistent of the synthetic drugs, the antibacterial activity of the phytocompounds has prodigious therapeutic values to alleviate many infectious diseases with lower side effects. Nowadays, clinically numbers of effective antibiotics are becoming inefficient due to the development of drug resistance so the potential to establish phytocompounds from higher plants against microbes is in progress. Therefore, the plant-based bioactive compounds are one of the outclass substitutes for antibiotic-resistant human pathogens.[82] *B. tinctoria* root bark methanolic extracts showed significant antibacterial and antifungal activity; also, the different solvent extracts petroleum ether, benzene, chloroform, ethyl acetate, methanol, and water of *B. tinctoria* root against nine bacterial pathogens *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Escherichia coli*, *Salmonella typhi*, *Salmonella* spp., *Staphylococcus* *aureus*, *Klebsiella pneumoniae*, *Aeromonas hydrophila,* and *Pseudomonas aeruginosa* were also reported.[27] The maximum zone of inhibition was observed in chloroform extract against *P. aeruginosa* 25 mm. The evolution of the antibacterial activity of ethnomedicinal plants curing wounds and skin diseases by the Irula tribes revealed that the plant possessed potential antibacterial activity against pathogenic bacteria.[30] *B. aristata* and *B. tinctoria* are the common allied species in the Nilgiri Biosphere Reserve, India. *B. aristata* root and *B. lyceum* stem extracts of 0.3 μg/mL expressed low minimum inhibitory concentration values; the major alkaloid berberine may be responsible for antimicrobial activity.[36] Vignesh *et al*. recently reported that *B. tinctoria* extracts have effective antimicrobial active compounds such as phenolic acids, flavonoids, saponins, and alkaloid compounds that cause microbial cell death.[81] The investigations concluded that continuing the purification of crude extracts and isolation of active principles are essential for improving the antibacterial potential which leads to new molecules for commercial use.

## ANTI-MOSQUITO PROPERTIES

Mosquitoes are the large-scale vector for the transportation of several communicable diseases such as dengue fever, malaria, and yellow fever which cause millions of deaths and allergic responses in humans including local skin and systemic reactions.[83,84] The plants are considered as an alternative and eco-friendly source for controlling mosquitoes, because of the presence of bioactive compounds which act against specific targets such as insects and pests; also, it does not construct any hazardous effects to the ecosystem. Some popular practices are followed to avoid the mosquito bites such as fumigation, burning green leaves, mosquito coils, and sprays by local peoples; smoke is a universal common method to repel the biting mosquitoes[85] also plants are frequently added to the fires to enhance the repellent properties of the smoke. The Nilgiris tribes were using *B. tinctoria* leaves to prepare natural mosquito coils, which are locally known and cheap natural repellents with mosquito larval control agents. Visalatchi and Jeyabalan were investigated that *B. tinctoria* methanolic leaves extract possesses remarkable ovicidal activity with development effects against *Culex quinquefasciatus* mosquitoes. Researches demonstrated that naturally, available mosquito repellents are better than inorganic insecticides which are expensive and environmentally hazardous.[6] Kumar *et al*. also reported the anti-mosquito property of *B. tinctoria* leaf-based synthesis of silver nanoparticle (AgNPs) and leaf extract of *B. tinctoria* was toxic against larval instars. Both the leaf extract and AgNPs showed reduced toxicity against the mosquito natural enemies *Mesocyclops thermocyclopoides* and *Toxorhynchites splendens*.[86] Hence, these natural products are generally preferred to control mosquitoes due to their biodegradable, inexpensive, and environmentally safe nature. These results could encourage the research findings for novel active natural compounds from medicinal plants offering an alternative to synthetic insecticides for the control of mosquito in mature and immature stages.

## ANTIULCER ACTIVITY

Ulcers, an open sore, characterized by sloughing of inflamed dead tissue of the skin or mucus membrane and loss of superficial tissues.[87] Ulcers are most common in skin extremities, gastrointestinal tract and may be encountered in any site; there are many types of ulcers such as peptic ulcer, mouth ulcer, genital ulcer, and esophagus ulcer of these ulcers peptic ulcer is seen among many peoples. Peptic ulcers are characterized by the erosion of the stomach or duodenum lining.[88] The medico provides vast information about ethnomedicinal herbs used as antiulcer agents and is proved by many researchers. The current impasse of modern medicine in the management of various ulcers approaches the traditional medicine for novel and effective treatment patterns also introduced well-being protocols for many gastrointestinal disorders.[89] *Berberis* spp. resulted in antiulcer activity also had adequate evidence from traditional and scientific sources for their efficacy in the management of ulcers. Phytocompounds derived from the plants have been used to treat various human diseases since the dawn of medicine and the phytocompounds mainly target the defensive system along with lowering the acid secretion. Approximately 50% of new chemical entities from natural products were introduced during the past two decades. Recent technological advances in drug innovation have renewed its interest in natural products.[90] *B. tinctoria*, *B. aristata,* and *B. asiatica* are grown on the Nilgiris hills and Western Himalayas; the chemical constituents of these plants were reported that the roots and wood have a rich yellow alkaloid "berberine" bitterly nature, which dissolves in acids and forms salts of the alkaloid; where root contains two more alkaloids. Berberis plants possessed antiulcer as well as cytoprotective ability which could be attributed to the presence of the alkaloid.[89,91] Therefore, efforts should be directed toward the isolation and characterization of the active phytocompounds and elucidate the relationship between their structure and activity. Hence, pharmacologists should step forward to evaluate potential herbal drugs against ulcer and standardized them for clinically effective and globally competitive.

## ANTIDIABETIC ACTIVITY

Diabetes is one of the most common endocrine disorders that originate from abnormalities of either insulin secretion or insulin action or both. The control of diabetes is critical because of the number of complications and prevalently increasing worldwide.[92] Medicinal plants and their derivatives in traditional medicine have been used for the treatment of diabetes mellitus and its complications, but there is no scientific validation for their effectiveness against diabetes.[93] The usage of herbal medicine against diabetes is increasing worldwide by cause of its lower side effect, easy access, efficacy, and low cost. More than 1200 distinct plant varieties have been used to treat diabetes, and half of the numbers are used in traditional medicine.[94] The antidiabetic and antioxidant effect of *B. tinctoria* leaf methanol extracts 150 mg/kg and 300 mg/kg for 14 days in streptozotocin-induced diabetic rats showed a significant reduction in blood glucose levels.[28] In the study, diabetic mellitus was characterized by the reduction of the pancreatic β-cells to release sufficient insulin which induces the activity of glucose metabolizing enzymes under the dosage of the berberine bioactive compound, as well as the antioxidants and antihyperlipidemic potential in streptozotocin-induced diabetic rats were also studied. Berberine activates the adenosine monophosphate-activated protein kinase (AMPK) and improves insulin sensitivity also promotes the regeneration and functional recovery of β-cells.[95] The alkaloids inhibited oxidative stress and inflammation in a variety of tissues including the liver, adipose tissue, kidney, and pancreas. Mechanisms of the antioxidant and anti-inflammatory activities of berberine were complex, which involved multiple cellular kinases and signaling pathways, such as AMP-activated protein kinase (AMPK), mitogen-activated protein kinases, nuclear factor erythroid-2-related factor-2 pathway, and nuclear factor-κB pathway.[80] Therefore, the metabolites of *B. tinctoria* were investigated for their biological activity against inflammation and diabetes. The interaction of polyphenols between the antioxidants, antidiabetic, and anti-inflammatory was also validated to promote the development of natural products against diabetic disorders.[81] These results evident the antidiabetic activity of *B. tinctoria*, hence, the future studies should focusing the phytomedicine-based drug delivery against diabetes.

## ANTICANCER ACTIVITY

Earlier reports stated that *Berberis* is affluent alkaloid genera from the stem, stem bark, root, and root bark; also, there are reports such as characterization of phytochemicals from other parts such as leaves, fruits, and flowers. Alkaloids are the prime bioactive constituents of *Berberis* spp.; also, major alkaloids reported from them are berberine, berbamine, palmatine, columbamine, jatrorrhizine, and oxyacanthine.[37,58] The most influential alkaloid compound is berberine, a quaternary isoquinoline alkaloid naturally found in all plant parts of *Berberis* spp., also *B. tinctoria* has a significant amount of berberine reported by Srivastava and Rawat.[21] Berberine has good therapeutic effects against cancer, tumor, and neurological disorders.[48,96] The leaf methanol extract of *B. tinctoria* has been investigated for its antioxidants and hepatoprotective effects on paracetamol 750 mg/kg induced acute liver damage in Wistar albino rats; also, the biochemical parameters such as serum glutamate oxalate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin, and total protein activities were reported.[28] The researchers claimed that high concentrations of berberine could cause breaking of DNA strands, inhibit proliferation, and induce apoptosis also causes genotoxic effects.[97] The increasing evidence showed that trace amounts of berberine lower cholesterol levels in humans and possess anticancer and antitumor properties, which exert direct antiproliferative and pro-apoptotic effects toward tumor cells. Cholesterol reducing drugs are most commonly prescribed to elderly patients having more incidence of cancer, therefore, potential antitumor drugs could cure both the incident.[98] Worldwide, there is a trend of revival interest in plant-based drug owing some limitations than synthetic drugs such as high cost, side and adverse effects, and development of multidrug resistance in target pathogens, competently peoples are turning back to nature and natural products, especially herbal- and plant-based drugs, because they came to know that Nature's Chemistry is far greener, safer, and environment friendly. Globally, the development of novel drugs from the ethnomedicinal uses of a plant species from particular culture prompts the research in its phytochemical constituents and biological activities.

## ANTI-INFLAMMATORY ACTIVITY

Nowadays, the marketing around the health-promoting effects of anti-inflammatory is being increased, where medicinal plants are the main remedy with various natural anti-inflammatory compounds. *Berberis* spp. most of these plants are rich in secondary metabolites and essential oils of therapeutic importance, especially, berberine, an effective alkaloid for anti-inflammatory activities.[99] The GC–MS analysis of *B. tinctoria* bark acetone and methanol extracts identified and documented some anti-inflammatory compounds such as stigmasterol, taraxasterol, and berberine.[100] The comparative studies of anti-inflammatory activity of *B. tinctoria* were effective, where the ethyl acetate fruit extract showed maximum inhibition of 95.2% at 500 μg/mL compared to the leaf and stem extract by inhibiting heat-induced bovine serum albumin denaturation. The berberine and berbamine compounds in *B. tinctoria* and its various synthetic derivatives are considered as the next-generation anti-inflammatory drugs.[81]

## ANTI-VENOM ACTIVITY

Snake anti-venom immunoglobulins (anti-venoms) are the only specific treatment for envenoming by snakebites, which play a crucial role in minimizing mortality and morbidity.[101] Snakebite has been a major cause of mortality across tropical countries including the Indian subcontinent. The present review deals with the enormous amount of ethnobotanical work performed in the past few years involving the use of different plants against snakebite in India.[102] In Ayurveda, *Berberis* spp. have been traditionally used for the treatment of scorpion sting and as an antidote for the treatment of snakebite.[103] The Nilgiri hill Toda tribe people are using *B. tinctoria* leaf juice to treat snake venom harming.[23] Many countries have started documentation, cultivation, scientific evaluation, and sustainable utilization of medicinal flora used by traditional people. It is the right time for us to exercise and propagate our ethnic knowledge against human mortality and morbidity.

## ANTI-ALLERGIC ACTIVITY

The prevalence of allergic diseases has increased in recent years and although, lots of anti-allergic allopathic medicines available on the market, these drugs are not always able to improve the quality of life of patients which cause chronic allergic conditions, such as asthma and allergic rhinitis, so there is a need to seek complementary alternative medicine.[104] In Ayurvedic medicine, raw juice of *B. aristata* alone or in combination with other ingredients shows efficacy against allergic conjunctivitis.[20] Daruhaldi (*B. aristata*) is used in Ayurvedic medicine for a long time, in the Institute of Applied Food Allergy center, it has been used as an anti-allergy agent and they reported the anti-allergy property of phytoconstituents such as berberine, berbamine, palmatine, oxycanthine, jatrorrhizine, and columbamine. *B. tinctoria* also had the same chemical constituents and same time local ethnic community is also used it as anti-allergy medicine for skin diseases.

## COVID-19 (SARS-COV-2 VIRUS)

Plant-based medicines are a useful tool in the discovery of drugs from traditional practice. The plant alkaloids represent a highly diverse group of chemical compounds classified into different classes such as pyrrolizidines, pyrrolidines, quinolizidines, indoles, tropanes, piperidine, purines, imidazole, and isoquinolines.[105] Nowadays, by the cause of SARS-CoV-2 (or COVID-19), people are facing global risk and scientists are attempting to investigate new antiviral vaccines. *B. tinctoria* are important due to the presence of bioactive compounds, especially the berberine from the protoberberine group of benzylisoquinoline and recent studies have shown it is potential in treating COVID-19.[106] *B. tinctoria* crude extracts and purified components provide a good source for the synthesis of novel anti-viral drugs. The characterization of anti-viral mechanisms from such natural sources has highlighted the interaction with the cycle of viral life, such as viral entry, replication, assembly, and release, in addition to virus-host addressing specific interactions. Antiviral secondary metabolites can target viral proteins (polyphenols), the lipid envelope (essential oils and other lipophilic PSMs), and viral nucleic acids (intercalating alkaloids).[107] DNA intercalating drugs inhibit DNA and RNA polymerases, protein biosynthesis, and, consequently, viral replication, may be more easily available than the isolated alkaloids. They might be useful as adjunctive therapeutics in the treatment of viral infections such as SARS-CoV-2 but need to be investigated in more detail.

## TOXICITY STUDIES

Previous findings showed that *B. tinctoria* formulations are safe and there are no adverse or toxic effects reported from this plant. *B. tinctoria* methanolic leaf extract causes paracetamol-induced hepatic damage in rats, the mortality is caused by some neural and muscular disturbance by the presence of a variety of active compounds such as cytotoxic diterpenoids, lactones, and flavonoids.[6] Vignesh *et al*. reported that 16 macro and micro mineral profiles using the ICP-MS method with a very low amount of toxic contents such as lead, arsenic, and nickel were reported.[81] *B. tinctoria* fresh leaf and fruit have been eaten by the Nilgiris tribal peoples which show no adverse or toxic effects.

## NATURAL PRODUCTS PREPARATION USING *B. TINCTORIA*

Many researchers reported pharmacological uses of *Berberis* species and lots of commercial products are already in markets such as *Berberis* root powder, barberry liquid extract, *Berberis* plant paste, *Berberis* shop, face wash, fairness creams, ointments, tonic, herbal tea, caramels, jam, and jellies. *B. tinctoria* potential mosquito repellent has been proved on this review so we are planned to produce eco-friendly mosquito repellent liquid and coils from *B. tinctoria* leaves and stem extracts. Mosquitoes rank among the utmost widespread and supreme significant transporters of infectious parasitic diseases that affect many millions of people every year.[108] In several ethnobotanical assessments, plant repellents are used worldwide. The botanical families encompassing the highest number of larvicidal plant extracts are represented by Asteraceae, Fabaceae, and Lamiaceae, which display a long history as either food or medicine all around the world.[109] It does not cause any toxic to domestic animals and humans and can be easily biodegraded. Mosquito coils are prepared from solid pastes or powders comprising pyrethroids and additional volatile chemicals, containing formaldehyde.[110] As compared to synthetic compounds, botanical metabolites are increasingly realized as potential replacements to chemical insecticides. Due to the less impact on the environment and low budget, plant-based repellents attracted great attention from people. The use of biological-derived products of plant origin is recommended because they are effective, environmentally friendly, and generally have low toxicity. Commercial available plant-derived essential oils and secondary metabolites are very effective for good repellents and their insecticidal agents that can be incorporated into integrated vector control approaches. *B. tinctoria* is highly toxic even at low doses proven to be useful for larvicidal, pupicidal, and adulticidal activity. The larvicidal effect against the different larval stages of the most abundant mosquito species *C. fasciatus* shows a toxic effect expressed high mortality to the controls.[6] The search for natural products, particularly plant extracts that can be used as mosquito repellents. Nowadays, plant and microbial sources are increasingly used for vector control programs because they have been shown to have the potential to be effective, more target specific than chemical insecticides, and ecofriendly. Although the advance and utilization of plant-derived metabolites are cost effective in the developing countries, there are still several issues that need to be addressed to allow for mass production. The separation of the active principles from *B. tinctoria* responsible for the mosquitocidal activity can promote to help the development of eco-friendly plant-based mosquito coil for controlling mosquito vectors for future evaluation.

## CONCLUSION AND FUTURE PROSPECTS

*B. tinctoria,* an endemic high-altitude plant available in the Nilgiris, has diverse bioactive compounds such as berberine and berbamine, with a spotlight of different mechanisms underlying its multispectrum activity led us to investigate and provides a critique regarding the pharmacokinetic and pharmacodynamic features of this economically important plant. The literature survey implies that plant-derived alkaloids exhibit antimalarial, antimicrobial, antioxidant, antifungal, antidiabetic, anti-viral, and anticancer activities. In this review, we have concluded many accomplishments of *B. tinctoria* in the context of ethnobotany, phytochemistry, pharmacology, and pharmaceutics. Therefore, we hope that in the future, studies may be carried out to prove the potential of this plant, also more work can be done on tissue culture and climatic conditions to grow this plant because of its verge of endangering. There exist some scientific issues in fundamental research and applied research, which is proposed here and needs prompt solutions. Therefore, we hope that in the future, this literature review will provide valuable background information and help researchers to understand and utilize this traditional phytomedicine to the greatest extent; also, the novel bioactive targets are yet to be discovered for future drug development.

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## AUTHORS' CONTRIBUTIONS

All authors contributed equally to this study.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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