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The medicinal plant *Berberis aristata* and its endophytes for pharmacological applications: Current research and future challenges

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ABSTRACT

Exploring medicinal plants for their natural products to benefit humanity has been a practice since ancient times. *Berberis aristata*, also known as tree turmeric or Indian barberry, has a dominant spot in conventional medicine for 2500 plus years. In the latter years, this particular species has gained prime attention in pharmaceutical zone due to its scarcity. The plant and its formulations are used to treat numerous human health threats including cancer, diabetes, diarrhea, wound relieving, infections of eyes and ears, gynecological disorders, and HIV-AIDS. The bioactive compounds present in *B. aristata* are found to contain anti-inflammatory, antioxidant, and anti-microbial properties. The plant is critically jeopardized species of Indian Himalaya due to the collection of its roots at a large scale for obtaining berberine alkaloid and its conservation is of great concern. At present, isolation of endophytic entities from remedial plants revolutionized the path of discovering drugs from medicinal plants. Endophytes can produce the same bioactive as their host plant as well as another bioactive to address a variety of human health issues. The review examines the bioprospecting of *B. aristata*, a medicinal shrub from the family Berberidaceae, and its associated endophytes for the production of bioactive compounds with application to human health. Finally, the review provides a comprehensive outlook on the current status and future prospects of bioprospecting *B. aristata* and its endophytes to combat future human health threats is an exciting area of research that should be further explored.

1. INTRODUCTION

India, being a part of the global biome, is home to several remedial plants [1]. The traditional systems of Indian medicine such as ayurveda, unani, siddha, and homeopathy have identified and used several medicinal plants for curing a lot of diseases [2]. Medicinal plants are plants that have been used for centuries to treat and prevent illnesses and diseases. Their use dates back to ancient civilizations and they are still being used today in various sections of the world, particularly in traditional and folk medicine [3]. Many scientific studies have been conducted on medicinal plants and their therapeutic importance, leading to the development of modern medicines. Medicinal plants are important for many reasons. They are valuable source of natural compounds and active ingredients that can be used to treat various ailments [4]. In particular, they are often used to treat conditions that do not respond to conventional treatments. They can also be used to supplement existing treatments, providing additional therapeutic benefits [5]. Furthermore, they have been used to promote overall health and well-being, as well as to prevent illnesses. Medicinal plants are also important because they provide a more sustainable and environmental friendly source of medicine. Unlike traditional medicines, they are not produced in a laboratory but are grown in the wild and harvested sustainably [6].

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Medicinal plants have proven to cure an enormous range of health issues and diseases including inflammation, pain, digestive issues, skin problems hypertension, and other disease. In a study revealed that the medical plant Sarpagandha (*Rauvolfia serpentina*) has been reported for treating diseases such as hypertension, diabetes, insomnia, and other nervous disorders [7]. Similarly, turmeric (*Curcuma longa*) is extensively used in treating skin diseases, digestive problems, and arthritis. Other medicinal plants such as Ashwagandha (*Withania somnifera*), Amla (*Emblica officinalis*), Aloe vera (*Aloe vera*), and Brahmi (*Bacopa monniera*) have a huge potential in treating various ailments [8].

Berberis aristata, commonly known as Indian barberry, is a species of flowering shrub native to the Himalayan region [9]. It is widely distributed in India, Nepal, Bhutan, Sri Lanka, and few regions of Southern Asia. It is an evergreen shrub of *Berberidaceae* family. It is a small, evergreen, bushy shrub that grows up to 4 m in height. Its leaves are small, oblong-ovate, and dark green in color, while its flowers are yellow-colored and appear in clusters where the branches end. The fruits are small, yellow-green drupes which are edible when ripe. The root of the plant is bitter and pungent in taste [10]. This herb is used in traditional medicine for its astringent, diuretic, and tonic properties. It is also used in Ayurveda to treat a number of skin conditions, such as eczema psoriasis, and acne. It is also found beneficial for curing fever, jaundice, eye diseases, inflammation, digestive ailments, intestinal parasites, and urinary problems. Its roots and leaves are used in formulating tonics which are beneficial in fever, abdominal pain, and digestive disorders. The fruits are used to make jams, preserves, and syrups, and are also used to flavor foods and beverages [11].

In addition, the leaves bark, and berries of the plant are used in traditional ayurvedic remedies for digestive disorders, respiratory issues, and fever. In recent years, the plant has also been used in modern medicine as an anti-inflammatory, anti-microbial, and anti-diabetic agent. Furthermore, the plant has been found to have antioxidant and hepatoprotective properties as well [12].

Endophytes are those microbial entities which reside inside plant tissue without causing any harm to the host plant [13]. These micro-organisms have a symbiotic relationship with the plant, as they benefit from the carbon and other nutrients produced by the plant, while the plant benefits from the nutrients and growth factors provided by the endophytes [14]. Endophytes are present in a large sector of plants, including trees, grasses, and medicinal herbs. In recent years, endophytes have gained considerable recognition from the pharmaceutical industry, due to their potential to synthesize novel active compounds [15]. Endophytes have already been shown to produce a variety of compounds that have antibacterial, antifungal, antiviral, and anti-inflammatory properties. The various pharmaceutical industries are continuous searching a new or better drug for treating many diseases. Endophytes are a promising source of novel active compounds that may provide new treatments for a wide range of diseases. In addition, endophytes can produce compounds that are useful for treating cancer, diabetes, and neurological disorders [16].

The pharmaceutical industry has developed various methods for isolating and culturing endophytes to obtain their active compounds [17]. These methods include direct isolation from plant tissue, culture-independent approaches, and culture-dependent approaches. Direct isolation from plant tissue involves extracting endophytes from the plant using various techniques such as filtration, centrifugation, or chemical extraction. Culture-independent approaches involve the use of molecular techniques to isolate endophytes from plant tissue without the need for culturing [18]. Culture-dependent approaches involve the use of specialized media to culture endophytes *in vitro*. Once the endophytes are isolated, they are screened for the presence of novel bioactive compounds. The active compounds can then be analyzed and characterized using various techniques such as high-performance liquid chromatography, mass spectrometry, and nuclear magnetic resonance imaging. After the compounds are identified, they can be synthesized and tested for bioactivity in animal models [19].

The pharmaceutical industry has made considerable progress in the isolation and characterization of endophytic-derived active compounds. Several novel active compounds have been identified and are currently being investigated for their potential therapeutic applications. In spite of the progress made in the pharmaceutical industry, there is still much to be learned about the potential of endophytes as a treasure house of novel active compounds [20]. They have the potential to revolutionize the pharmaceutical industry. Despite the challenges associated with the use of endophyte-based pharmaceuticals, research is ongoing to identify novel compounds and develop methods for their extraction and purification. The present review deals with medicinal plant *B. aristata* and its endophyte for pharmacological applications.

2. *B. ARISTATA* IN AYURVEDA MEDICINE

B. aristata, popularly prevalent as Indian barberry, is a widely used herb in traditional Ayurvedic and Unani systems of medicine [9]. It is used for various medicinal purposes, such as to treat fever, inflammation, jaundice, skin diseases, anemia, stones in kidney, and infections of urinary tract [21]. The roots, its bark, and fruit are utilized in Ayurvedic formulations. Almost all the plant parts possess anti-inflammatory, anti-bacterial, anti-fungal, and anti-oxidant properties [22]. It is also practiced as a tonic for improving digestion and appetite, and as an astringent to treat bleeding. In addition, it is known to treat liver disorders, eye-related diseases, and snake bites. In traditional medicine, a decoction of the root of *B. aristata* is commonly practiced as a diuretic for curing disorders of urinary tract. The juice of the root is used to treat jaundice, and its bark is used in relieving fever, inflammation, and skin diseases [23]. The leaves of the plant are used to treat anemia, while the fruit of the plant is used as a laxative and to treat digestive disorders. The root and stem extracts of *B. aristata* and its formulations are used in treating diarrhea, hemorrhoids, gynecological problems, HIV-AIDS, osteoporosis, diabetes, eye and ear infections, wound healing, jaundice, skin diseases, and malarial fever. A very special preparation “Rasaunt” is prepared from this plant using bark and the lower part of the stem. It works as a mild purgative and aids in curing various diseases [24].

B. aristata is enormously practiced in conventional Indian Ayurveda. It is proven to be beneficial in a large number of health conditions, such as, fever, inflammation, jaundice, skin diseases, anemia, kidney stones, and infections of urinary tract. Many plant parts possess anti-inflammatory, anti-bacterial, anti-fungal, and anti-oxidant properties, making it a proficient drug for so many health conditions. In ayurvedic formulations, it is used in combination with other herbs such as Amalaki (*Phyllanthus emblica*), Bhumiamalaki (*Phyllanthus niruri*), Guduchi (*Tinospora cordifolia*), and Haritaki (*Terminalia chebula*) [25].

3. *B. ARISTATA IN* UNANI MEDICINE

B. aristata is a species of barberry which is used as a medicinal plant in Unani pharmacy. It is called as Za’farānKuhī in Unani. It is extensively practiced in Unani medicines for treating numerous diseases such as

fever, piles, cough, bronchitis, and skin issues. It has potential as an anti-inflammatory, anti-microbial, and anti-oxidant agent. Hence, *B. aristata* is considered as a valuable drug. It is utilized in relieving jaundice, liver ailments, urinary tract infections, urinary calculi, kidney diseases, skin diseases, digestive disorders, and complications of diabetes. It also has potential as an antiseptic, antidiarrheal, and anti-inflammatory agent [26]. Its roots are used as tonic and in treating various skin conditions. It also helps in improving the functioning of the liver and gallbladder [27]. It is utilized in relieving fever, inflammation, pain, rheumatic problems, cough, asthma, and bronchitis. The root bark is extensively utilized in treating diabetes. *B. aristata* when combined with some other medicinal herbs becomes an effective drug to treat diarrhea and dysentery. It is also utilized in treating appetite loss, anorexia, and indigestion. Furthermore, *B. aristata* also has been used for treating eye diseases, piles, and dysuria [28].

4. PHARMACOLOGICAL IMPORTANCE OF *B. ARISTATA*

B. aristata, popularly called as Indian barberry, is a plant species that has significant biological importance for human beings [29]. The plant contains several alkaloids, such as berberine, which have been found to have various medicinal properties. Berberine is found to contain antimicrobial, anti-inflammatory, and antioxidant properties, which can help in treating several diseases, including diabetes, heart diseases, and gastrointestinal disorders [30] [Table 1]. The plant's roots and stem bark are commonly practiced in conventional Ayurveda and Unani pharmacy to cure various ailments. This species has also been found to possess it potent antitumor activity, making a promising candidate for developing new anticancer drugs. In addition, its fruit is found to be a great source of Vitamin C, which can help in strengthening the immune system thereby, preventing various infections [31]. From the foregoing observation on the pharmacognosy of root, stem, and leaf of *B. aristata* DC, the salient diagnostic characters of three parts have been presented, which can allow one to differentiate it from other substitutes and or adulterants [21]. The most important pharmaceutical properties of *B. aristata* including anti-pyretic, gynecological, anti-diarrheal, and cardiotonic activity, anti-inflammatory, anti-cancer, anti-diabetic, hepatoprotective, anti-PAF, anti-lipidemic, anti-HIV, anti-microbial, ophthalmic, and dermatological [22,32]. *B. aristata* is a valuable plant species with numerous biological properties that make it important for human health and well-being.

4.1. Antibacterial Potential

The problems with human health have gotten worse over the past few years as extremely contagious diseases and resistant microbe strains have emerged [33]. The need to find new antimicrobials from natural sources, including microbial sources such as bacteria and fungi as well as non-microbial sources such as animals and plants, is thus an alarming task for physicians and pharmacists. The genus *B. aristata* plays an important role in various traditional medicinal systems [34]. Approximately 500 species of *B. aristata* have been distributed within various geographical regions. Various species including *B. vulgaris*, *B. aristata*, *B. chitria*, *B. aetnensii*, *B. aquifolium*, *B. darwinii*, *B. heterophylla*, *B. integerrima*, *B. lyceum*, *B. orthobotrys*, *B. umbellate,* etc. have been reported worldwide [35]. Studies have demonstrated that *B. aristata*, a plant species native to India, has strong antibacterial activity. Various research groups have isolated active compounds from the plant and investigated their antibacterial properties. The active compounds, including berberine, palmatine, and magnoflorine, have been found to have significant antibacterial activity against various bacterial species, including *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *and Salmonella typhi* [36]. In addition, studies have shown that aqueous and alcoholic extracts of *B. aristata* are effective against some bacteria, including *S. aureus* and *E. coli*.

Abass *et al*. [37] found that extracts of *B. aristata* had antibacterial activity against *E. coli* and *S. aureus.* The authors achieved good results thereby concluding that the extracts of the plant could be utilized as a capable source of natural antibacterial compounds. In a study by Sood *et al*. [35] also found that extracts of *B. aristata* had antibacterial activity against gram-positive and gram-negative bacteria including *S. aureus, P. aeruginosa, and K. pneumoniae*. In a study concluded that plant extract are a potential source of organic antibacterial substances.

Saxena *et al*. [38] studied the antibacterial activity of *B. aristata* extracts against five Gram-positive and four Gram-negative bacterial strains. The results showed that the ethanolic extract of *B. aristata* exhibited potent antibacterial activity against all the tested bacterial strains. Sati *et al*. [39] evaluated the antibacterial activity of ethanolic, methanolic, and hexane extracts of *B. aristata* against five bacterial strains and found that the ethanolic extract of *B. aristata* had the significant antibacterial activity against all the tested bacterial strains. Singh *et al*. [40] evaluated the antibacterial activity of *B. aristata*

Table 1: Biological role of major phytochemicals and various plant parts of *Berberis aristata*.

S. No.	Phytochemicals	Plant part	Biological role
1	Berberine	Root, Stem, bark and Fruits	Anti-inflammatory, antioxidant, antidiabetic, anticancer, hepatoprotective, potential benefits in cardiovascular diseases, metabolic disorders, and neurological disorders.
2	Epiberberine	Root	Antioxidant, anti-inflammatory, antidiabetic, potential benefits in metabolic disorders.
3	Palmatine	Root and Stem bark	Antimicrobial, anti-inflammatory, antioxidant, potential benefits in cardiovascular diseases and metabolic disorders.
4	Jatrorrhizine	Root and Stem bark	Antidiabetic, anti-inflammatory, antioxidant, helpful in cardiovascular diseases and metabolism-related disorders.
5	Berbamine	Root and Stem bark	Antitumor, anti-inflammatory, antioxidant, Antilipidemic potential benefits in neurological disorders.
6	Aromoline	Root	Antiplasmodial, potential benefits in neurodegenerative diseases.
7	Karachine	Root bark	Antioxidant and anticancer.
8	Taxilamine	Root bark	Antioxidant and anticancer.
9	Pakistanine	Root bark	Antidiabetic and antioxidant.
10	Quercetin	Root bark	Anticancer, anti-inflammatory, and antihistamine.
11	Columbamine	Root bark	Anticancer, anti-proliferative and anti-vasculogenic, and antidiabetic.

against eleven bacterial species. The results of this study showed that the hydroalcoholic of *B. aristata* had the strongest antibacterial activity against all the tested bacterial strains. This study concluded that *B. aristata* has been showed potential antibacterial activity against Gram-positive and Gram-negative bacterial strains

The antibacterial activity of *B. aristata* is attributed to the containment of a large number of bioactive compounds such as alkaloids, tannins, flavonoids, and terpenoids. The alkaloids present in *B. aristata* are berberine, oxyacanthine, berbamine, and palmatine, which exhibit antibacterial activity [41]. The tannins present in the plant are reported to possess antibacterial activity against bacterial species. The terpenoids present in the plant are responsible for its antifungal, antiviral, and antibacterial activities [42]. The research also suggests that *B. aristata* has the potential to be used as an antibacterial agent against a range of bacterial infections.

4.2. Antifungal Potential

Recent studies have also demonstrated the antifungal activity of *B. aristata*. The antifungal activity of this plant is mainly attributed to the berberine, which is a dominant compound of this plant. Studies have reported that berberine possesses antifungal activity against an enormous fungal sector [29]. Specifically, berberine was found to deteriorate *Candida albicans* growth and cause cell death by inducing apoptosis [43]. Other studies have also demonstrated that berberine hampers the growth of *Fusarium oxysporum* by disrupting its cell membrane. Furthermore, it has been reported that berberine has the capability to chelate metal ions, thus preventing the growth of fungal cells. In addition, berberine inhibits the enzymes of ergosterol biosynthesis, which is an important structural component of cell membranes of fungi. Apart from berberine, other components of *B. aristata* also contribute to its antifungal activity. For example, gallic acid, a polyphenolic compound found in the plant, was found to possess antifungal activity against a variety of fungi. Similarly, tannins, which are polyphenolic compounds present in *B. aristata*, have been found to retard growth of *Aspergillus niger* and *Trichophyton mentagrophytes* [44].

In addition, ethanol extracts of this plant were also found to possess antifungal activity. Studies have proven that the ethanol extract of *B. aristata* is effective against a wide range of fungi, including *A.* niger, Cladosporium, Rhizoctonia, Alternaria, Trichoderma, Penicillium, Curvularia, Paecilomyces and Rhizopus [45]. Furthermore, it has been reported that the ethanol extract of *B. aristata* is effective against *C. albicans* at a concentration of 200 mg/mL. In another similar study by Shahid *et al*. [46], the antifungal activity of aqueous, and ethanolic extracts of *B. aristata* was carried out against *C. albicans* and *A. niger.* The results of this study showed that the ethanolic extract demonstrated the highest antifungal activity against both fungi, as compared to aqueous extract. This suggests that the berberine prevalent in the ethanolic extract is exhibiting the observed antifungal activity. In a similar work by Sharma *et al*. [47] the antifungal activity of aqueous, ethanolic, and methanolic extracts of *B. aristata* was evaluated. The results proved that the aqueous extract of the plant had the highest antifungal activity against both fungi, with the ethanolic extract showing the lowest activity. This indicates that the berberine prevalent in the aqueous extract is accountable for the observed antifungal activity.

In a recent work by Rizwan *et al*. [48], the antifungal activity of *B. aristata* was evaluated against clinical isolates of *Candida*. The results showed that the *B. aristata* is 98.5% more sensitive than fluconazole (42.3%) and voriconazole (29.2%) sensitivity against isolates of *Candida*. It is an established fact that antifungal activity of *B. aristata* is mainly due to berberine, alkaloid compound that retards the growth of the cell wall of fungi, biosynthesis of ergosterol, and functions of mitochondria [49]. Overall, the available evidence indicates that *B. aristata* possesses antifungal activity against a wide range of fungal species thus; *B. aristata* may be a potential source of natural antifungal agents.

4.3. Antiviral Potential

The stem bark of *B. aristata* is widely utilized in conventional Indian medicine for curing a number of health complications such as fever, dysuria, and enlarged spleen. In addition, it is known to possess antiviral activity [50]. Several studies have demonstrated the antiviral activity of *B. aristata* against a huge range of viruses, including herpes simplex virus, human cytomegalovirus, adenovirus, and rotavirus. The inhibitory impact of three naturally occurring antiviral substances, curcumin, picroliv, and berberine assessed, against FMuLv-induced erythroleukemia in BALB/c mice and found suppression of the progression of leukemia induced by friend murine leukemia virus [51]. In addition, the bark extracts of *B. aristata* to combat Paramoxyviridae infection. Hemagglutination assay provided anti-viral activity of the extract at 1/16 dilution in four HA viral concentrations. The viability on vero cell lines was precisely 92.8%, at this concentration [52]. Overall, these studies suggest that *B. aristata* has promising antiviral properties and could be a promising natural therapeutic drug for curing various viral infections. Extensive research is required to explore the potency of *B. aristata* as an antiviral drug [28].

4.4. Antidiabetic Activity

Recent clinical and preclinical studies suggest that berberine obtained from *B. aristata* has a great effect on the homeostasis of glucose [34]. Berberine increases insulin receptor mRNA expression through kinase C-dependent protein as promoter in cultured human liver cells and skeletal muscle [53]. In another study, methanolic extract of dried and powdered root was given to normal rabbit and diabetic albino rabbit which was induced with alloxan. The results so obtained proved that *B. aristata* roots contain potent and orally effective antidiabetic component which either triggers the formation of insulin or shows insulin-like effect [54]. Antihyperglycemic effect was seen in alloxan-induced diabetic rat when the rat was orally administered with methanolic and ethanolic crude extract of stem of *B. aristata*. This further, confirmed the antidiabetic potential of this herb [55]. In an animal study, rats were injected with 35 mg/kg of streptozotocin to induce diabetes and hyperglycemia in them. The overall experiment was conducted using seven groups of rats consisting of diabetic untreated and treated rats with 75/150/300 mg/kg berberine, rosiglitazone 4 mg/kg and fenofibrate 100 mg/kg, and a control group. It was observed after 16 weeks of treatment, that the diabetic rats showed alteration in pancreas to body weight ratio, insulin level, insulin sensitivity index, malonaldehyde content, and superoxide dismutase activity. Whereas rats treated with 150 and 300 mg/kg berberine showed near control levels in the evaluating parameters. These observations intensively proved that berberine has a protective effect for diabetes by increasing insulin expression, B-cell regeneration, antioxidant enzyme activity, and decreasing lipid peroxidation [56]. Another study demonstrated the molecular mechanism of berberine against insulin resistance, where the drug was found to increase insulin sensitivity through activation of insulin receptor [53].

4.5. Hepatoprotective Activity

Roots of *B. aristata* have reserved a dominant place in ayurveda for the treatment of jaundice since ancient times. Pre-treatment of animals with berberine 4 mg/kg; orally twice daily for 2 days prevented the acetaminophen or CCl4-induced rise in serum levels of alkaline phosphatase and aminotransaminases aspartate transaminase and alanine transaminase, suggestive of hepatoprotection. Post-treatment with three successive oral doses of berberine 4 mg/kg every 6 h reduced the hepatic damage induced by acetaminophen, while CCl4-induced hepatotoxicity was not modified, suggesting a selective curative effect against acetaminophen [57]. Hepatoprotective activity was investigated in dried aerial part of *B. aristata* against CCl4-induced liver injury in rats. The study demonstrated that the results thus obtained were comparable to standard drug sylimarine [58]. Shoot and fruit crude extract showed resistance against Paracetamol and rodents induced with CCl4-induced liver toxicity [59].

4.6. Anticancer Activity

Recent scientific studies have identified several active compounds in this plant that may have anticancer activity. Berberine, one of the major bioactive components of *B. aristata*, has been studied extensively for investigating its anticancer properties [34]. The alkaloid has been shown to stop the carcinogenesis which was induced in a dose-dependent way in small animals by 20-methylcholanthrene or N-nitrosodiethylamine [60]. In one study, berberine was proved to retard the growth of human colon cancer cells *in vitro*. It was also found to induce apoptosis in these cells. In addition, berberine has been found to inhibit the growth of various other types of cancer cells, such as breast, prostate, and lung. Berberine has also been studied for its potential to modulate the activity of certain signaling pathways that are involved in cancer progression [61]. For example, it has been found to inhibit the activity of EGFR and vascular endothelial growth factor (VEGF), two proteins that are involved in the growth and spread of tumors. It has also been observed to inhibit the activity of PI3K/Akt, a signaling pathway that is often dysregulated in cancer cells. Quercetin, another active compound, has been found to inhibit the growth of cells responsible for prostate and breast cancer [62]. Kaempferol, another compound present in *B. aristata*, has been found to retard the growth of lung and pancreatic cancer cells. Methanolic extract of *B. aristata* stem was found to be very effective against human colon cancer cell lines by inhibiting HT29 cells [63].

4.7. Anti-inflammatory Activity

Scientific studies have proven that the *B. aristata* has anti-inflammatory activity [34]. The root extract contains various active components including berberine, palmatine, and berbamine which are the prime triggers for its anti-inflammatory activity [28]. These compounds have been reported to suppress the synthesis of pro-inflammatory mediators, including cytokines, chemokines, and prostaglandins. In addition, these compounds are believed to inhibit the activation of NF-kB, a major transcription factor involved in the regulation of inflammation. Studies have shown that the root extract has significant anti-inflammatory effects against carrageenan-induced paw edema in rats [46]. The extract also showed inhibitory effects on the production of pro-inflammatory mediators such as nitric oxide, prostaglandin E2, and tumor necrosis factor-alpha. Furthermore, the extract was found to retard the release of histamine and leukotriene B4. These findings suggest that the root extract of *Berberis aristata* has potential anti-inflammatory activity. *B. aristata* extract supplementation resulted in down-regulation of IL-1 β, IL-6, TNF-R1, NF-κB, and VEGF expression in an adjuvant-induced arthritis model [64]. *In vivo* studies have also demonstrated that the root extract of *B. aristata* can reduce inflammation in animal models of arthritis, colitis, and airway inflammation. Therefore, the root extract of *B. aristata* may be useful in the treatment of inflammation.

4.8. Antioxidant Activity

Recent studies have found that *B. aristata* possesses antioxidant activity due to several phytochemicals present in it, such as alkaloids, tannins, phenolics, flavonoids, and other compounds [65]. Antioxidants are molecules that have the potential to neutralize free radicals, which are reactive oxygen species (ROS) generated by environmental stressors such as UV radiation, pollutants, and other environmental toxins. Free radicals are known to cause cell damage, which may cause chronic diseases such as cancer, cardiovascular disease, and neurological disorders [66]. Studies have shown that *B. aristata* has significant antioxidant activity due to its capability to scavenge free radicals, reduce oxidative stress, and protect cells from damage caused by toxins. The plant is a good source of phenolic compounds, which are known to possess strong antioxidant properties [37]. These compounds are able to scavenge free radicals and inhibit the production of ROS. In addition, the plant contains alkaloids, tannins, and flavonoids, which act as chelators and scavengers of free radicals and also possess antioxidative properties [67].

B. aristata also contains several minerals such as iron, zinc, calcium, phosphorus, and magnesium, which are essential for the body's normal functioning and also possess antioxidant properties [68]. These minerals help to reduce oxidative damage caused by free radicals and protect cells from damage. Furthermore, studies suggest that the plant extract also contains several essential oils such as thymol, caryophyllene, carvacrol, and linalool, which have strong antioxidant properties [69]. The antioxidant activity of *B. aristata* has been studied in various *in vitro* and *in vivo* models. Studies have shown that the methanolic extract of *B. aristata* has a potent antioxidant activity. The extract was found to scavenge free radicals and inhibit lipid peroxidation. It also exhibited significant effects against oxidative damage induced by H_2O_2 and $FeSO_4$. The extract was also found to inhibit the production of nitric oxide, a free radical that is involved in the inflammatory process [44].

4.9. Anti-lipidemic Activity

Recently, research has begun to focus on the anti-lipidemic properties of *B. aristata*, as it has been proved to have a significant effect on the levels of cholesterol and triglycerides in the blood [70]. The anti-lipidemic activity of *B. aristata* is thought to be due to the presence of four major bioactive compounds, namely, berbamine, berberrubine, berberine, and oxyacanthine [71]. These compounds are thought to act on various receptors and enzymes, leading to a decrease in the absorption of dietary lipids and an increase in the metabolism and excretion of cholesterol. Furthermore, these compounds are believed to have antioxidant and anti-inflammatory effects, which may contribute to their anti-lipidemic activity. The anti-lipidemic activity of *B. aristata* has been studied in a number of animal studies. For example, a study on rats found that supplementation with *B. aristata* resulted in a significant reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Furthermore, the study found that the anti-lipidemic effect was dose-dependent, with higher doses resulting in greater reductions in cholesterol and triglycerides [72].

A similar study on rabbits found that supplementation with *B. aristata* resulted in a significant reduction in total cholesterol and LDL

cholesterol. The anti-lipidemic effect was greater in rabbits that received higher doses of the supplement. In addition, the study found that plant was able to reduce the formation of atherosclerotic plaques in the aorta, suggesting that it may have beneficial effects on cardiovascular health [73]. In addition to animal studies, the anti-lipidemic activity of *B. aristata* has also been studied in humans. The administration of *B. aristata* (stem powder powder as add on therapy in patients of Type 2 diabetes highly significantly reduce FBS, lipids, and lipoproteins level and improve glycemic control as well as lipid profile with no major adverse effects [74]. Overall, the evidence from animal and human studies suggests that *B. aristata* may be an effective natural remedy for reducing cholesterol and triglycerides in the blood. Furthermore, the anti-oxidant and anti-inflammatory properties of plant may contribute to its anti-lipidemic activity. As such, it may be a useful supplement for those who are looking to reduce their risk of cardiovascular disease.

B. aristata is a valuable source of traditional medicine for various diseases [28]. Berberine has enormous beneficial effects like immune-stimulation through increasing blood flow supply to the spleen [75]. Both animal research and clinical trials have showed that berberine administration prevented chemical-induced ventricular tachyarrhythmia, stimulated cardiac contractility, and lowered peripheral vascular resistance and blood pressure [76]. This plant is also utilized as wound healing agent. Research was carried out on male adult goat where aqueous and alcoholic extracts were used in the form of ointment on open wounds. The results obtained were quite promising [77]. Decoction of stem bark of the plant showed significant protection against cisplatin-induced nephrotoxicity [78].

5. EXPLORING ENDOPHYTES FROM MEDICINAL PLANT

Endophytes are known to harbor almost all the plants on the earth. They live in the tissues of plants and show a wide relationship with plant ranging from mutualism to parasitism [79]. These are significant sources of new drugs, such as quinones, phenolic acids, alkaloids, saponins, steroids, terpenoids, and tannins that carry great potential for anti-insect, anticancer, immunosuppressants, antibiotics, antimicrobial, and other pharmacologically relevant properties [41]. At present, endophytes are well-known as important agents of natural bioactive products because there are enormous populations of such microbes inhabiting millions of unique biological niches [80]. However, until date, less plants have been reported as endophyte diversity and their susceptibility to synthesis bioactive secondary compounds. For exploring endophytes for bioactives, the choice of the plant to be used is important. Therefore, for centuries, these storehouses of drugs are used as an alternative source of medicine and now, are considered a significant source for exploring endophytes Kaul *et al*. [81] to meet the demand for useful and new compounds essential to fight various pathogens affecting human health.

Exploring endophytes for the production of new chemical entities for pharmaceutical and therapeutic purposes [Figure 1], from *B. aristata* reduces the exploitation of medicinal plants that become endangered and at the same time showing advantage in terms of cost, thus by such studies, we can explore novel bioactives from endophytes and at the same time conserving our biodiversity.

5.1. Fungal Endophytes from *B. aristata* and its Biological Activity

The endophytic fungi associated with *B. aristata* have been explored for their capability to synthesize antimicrobial and antioxidant compounds. There are only one or two reports of isolated endophytes from *B. aristata* and evaluating them for biological activities. Sharma *et al*. [82] isolated fungal endophytes from leaves stems and root tissues of the plant for the very first time. 131 fungal endophytes were isolated belonging to 18 species and 10 genera from 330 surface sterilized segments of different tissues of *B. aristata*. The antibacterial potential of isolated fungal endophytes was evaluated and found different degree of antibacterial activity in crude ethyl acetate and ethanolic extracts of the 20 endophytic fungal isolates at concentration of 1 mg/mL against both Gram-positive and Gram-negative bacteria. Isolated endophytes were tested for their antifungal activity against *Microsporum canis*, *C. albicans*, *Penicillium chrysogenum*, *Colletotrichum capsicii*, *Aspergillus fumigatus*, and *Alternaria alternata.* Twelve endophytes exhibited inhibition tendency against almost all the test pathogens.

Antioxidant potential of endophytes was also studied and promising results were obtained. The free radical scavenging activity of the crude extracts increased in a concentration-dependent manner, indicating that they possess the ability to donate protons and might be used as inhibitors or scavengers of free radicals, possibly acting as primary antioxidants. Similar kind of study was also done by our group [83]. In Antibacterial activity, the fungal isolate and filtrate, FBL-5 showed the highest activity against *S. aureus*, whereas, among bacterial isolates and filtrates, FBL-13 was shown to possess the highest antibacterial activity against *Pseudomonas alcaligenes*. The plant extract exhibited the highest antibacterial activity against *P. alcaligenes*. While FBL-5 and FBL-13 isolate and filtrate showed prominent antifungal activity against *C. albicans*, *P. chrysogenum,* and *Aspergillus niger.*

6. FUTURE PROSPECT AGAINST MULTI-DRUG RESISTANCE AND ESKAPE PATHOGENS

Endophytic entities from medicinal plants have become increasingly important as capable agents for combating drug-resistant and ESKAPE pathogens. These are a group of bacteria and fungi species that cause a number of diseases in humans and animals, including infections of the urinary tract, skin, and bloodstream. Drug-resistant and ESKAPE pathogens are of considerate attention, as they are resistant to many of the antibiotics used to treat infections. The potential of endophytes to combat drug-resistant and ESKAPE pathogens has been reported in various studies [84,85]. In addition, some endophytic microorganisms have been known to synthesize compounds that activate the immune system, helping to fight off invading pathogens. Endophyte-based strategies to combat drug-resistant and ESKAPE pathogens are being developed in both research and commercial settings. Endophytes are also being used to produce compounds that activate the immune system, helping to fight off invading pathogens. In addition, endophytes are being used to produce compounds with anti-inflammatory and anti-tumor activities. The long-term prospects for endophyte-based strategies to combat drug-resistant and ESKAPE pathogens are promising. Endophyte-based strategies offer a safe, sustainable, and cost-effective alternative to traditional antibiotics, which are becoming increasingly ineffective against drug-resistant and ESKAPE pathogens [86]. In addition, endophytes have been demonstrated to produce compounds with activity against a wide range of bacterial and fungal pathogens, making them a potential solution for a variety of infectious diseases. The future of endophyte-based strategies to combat drug-resistant and ESKAPE pathogens will depend on continued research into the mechanisms of action of endophyte-produced compounds and the development of more effective delivery systems. Extensive research is needed to understand the potential impacts of endophyte-based strategies on human and animal health, as well as the environment [87]. With continued research and development, endophyte-based strategies may be used to combat drug-resistant and ESKAPE pathogens in the future.

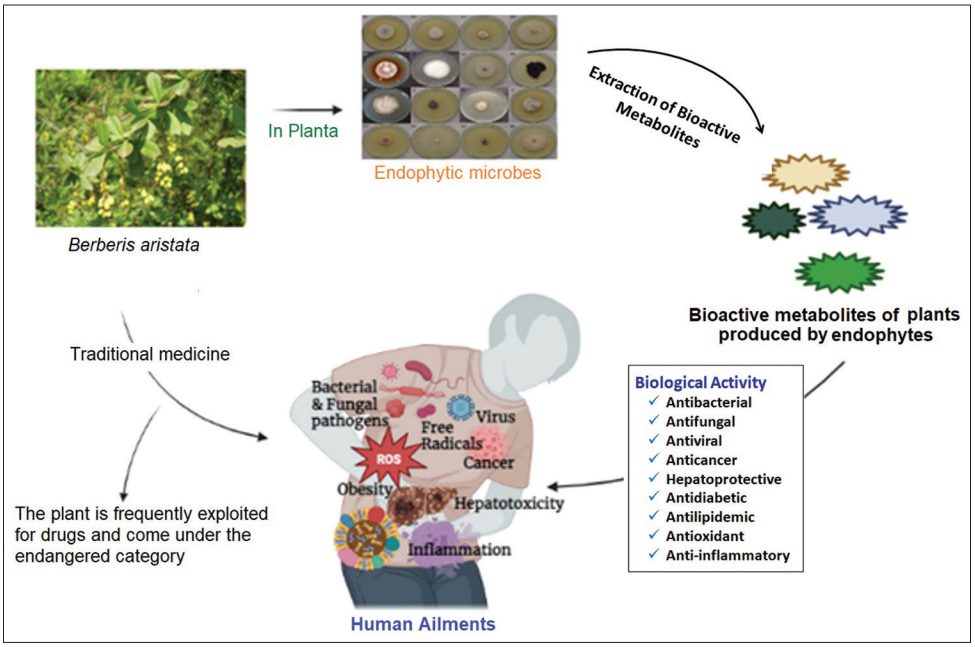

Figure 1: Exploration of endophytes of *Berberis aristata* for production of bioactive metabolites of plant.

In recent years, researchers have been investigating the potential of endophytes from *B. aristata* to fight MDR [88] and ESKAPE pathogens. In one study, a range of endophytes were isolated from the leaves, stems, and roots of the plant. These endophytes were then tested against a range of MDR and ESKAPE pathogens, including *E. coli*, *K. pneumonia*, *Acinetobacter baumannii*, *and P. aeruginosa* [89]. The results proved that the endophytes were effective against all of the tested pathogens, with some of the endophytes exhibiting up to 90% inhibition of bacterial growth.

7. CONCLUSIONS

A growing number of people throughout the world are turning to herbal or natural medicines as supplemental or alternative treatments. Many of these pharmaceuticals are made chemically, while others are made directly from plants. *B. aristata* had showing its potential as hepatoprotective immunomodulatory, anti-depressant, antimicrobial, anticancer, and advancement in drug delivery formulations. To show its anti-leprotic, anti-fertility, and anti-neoplastic properties, extensive research is needed. Therefore, additional research may be done to demonstrate the effectiveness of this medicinal plant in the untapped areas. To further enhance its bioactivity, contemporary biotechnology techniques might be used. However, there is now a need to conduct molecular and clinical investigations to better comprehend this plant's potential for future medication discovery and development. It is necessary for research into the plant's translational potential as well as insights to potential novel bioactivities and targets. This could increase the therapeutic plant's commercial value substantially.

8. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

11. ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

12. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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