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THERAPEUTIC POTENTIAL OF *BERBERIS ARISTATA*: PHYTOCHEMICAL COMPOSITION AND HYPOGLYCEMIC EFFECTS

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ABSTRACT

Human reliance on plant-based resources for medicinal purposes dates back to ancient civilizations. Traditional medicine systems, such as those in Mesopotamia, Egypt, China, India, Greece, and Rome, have documented the extensive use of medicinal plants. One notable example is *Berberis aristata*, a spiny shrub indigenous to the northern Himalayan region, with historical significance in Ayurvedic medicine. This comprehensive review examines the botany, taxonomy, chemical constituents, and pharmacological activities of *Berberis aristata.* The plant, known for its rich content of berberine, demonstrates a diverse range of pharmacotherapeutic properties, such as anti-cancer, anti-microbial, anti-diabetic, analgesic, and antioxidative properties. These pharmacological properties validate its traditional uses and highlight it as a potential source of bioactive compounds to be developed into modern medicine. This review underscores the importance of further research to fully elucidate the therapeutic potential and mechanisms of action of *Berberis aristata*.

INTRODUCTION

Human dependence on natural resources for essential needs, particularly medicinal purposes, is a historical constant. Plants have been integral to advanced traditional system of medicine. Records from approximately 4600 years old from Mesopotamia documented the use of roughly 1000 plant-derived medicinal substances, including oils from Cedrus species and *Glycyrrhiza glabra* and *Papaver somniferum* (poppy juice), that sill remain is being utilized for treating ailments such as infections, cold and inflammation. Egyptian medical practices, dating to around 2900 BCE, are epitomized by the "Ebers Papyrus" from 3500 years ago, which lists more than 700 primarily plant-based drugs. Chinese Materia Medica contains extensive documentation, beginning with the Wu Shi Er Bing Fang, documents contain 52 prescriptions, and continuing with the Shennong Herbal and the Tang Herbal containing 850 drugs documentation. Similarly, Indian Ayurvedic texts, predating 1000 BCE, include the Charaka and Sushruta Samhitas, detailing 341 and 516 drugs, respectively. Greek and Roman contributions significantly advanced the systematic use of herbal medicines. Dioscorides, a Greek physician (~100 CE), meticulously documented the collection, storage, and application of medicinal herbs. Galen (130–200 CE), a prominent figure in Roman medicine, is noted for his complex prescriptions and drug formulations. During the Middle Ages (5th to 12th centuries), Arab scholars preserved and contributed to Greco-Roman medical knowledge, incorporating Chinese and Indian herbal resources.[1]

A plant that is known for is incredible therapeutic properties is *Berberis aristate*. This spiny shrub, *Berberis aristata*, sometimes called "*Daru haldhi* and *Chitra*," considered to be indigenous to the Himalayan mountainous region. It is widely spread over the Mountainous region of Himalaya, country of Bhutan and Sri Lanka and the hilly regions of Nepal.[2] The plant is common in the state of Himachal Pradesh and Uttarakhand. It thrives at altitudes ranging from 2000 to 3000 meters, particularly in the Kumaon and Chamba regions of Uttarakhand. Additionally, it can be found in the Nilgiri Hills in southern India.[3-5] *Berberis aristata* has been utilized in Ayurvedic medicine for an extensive period. Traditionally, the plant is employed for treating inflammation, promoting healing of wounds, addressing skin disorders, menorrhagia, jaundice, diarrhea and eye disorders. A particularly valuable Ayurvedic formulation, known as 'Rashut,' is made from this plant.[6-8] It is also been reported to reduced reproductive system toxicity,[9] restores lipid profile,[10] wound healing.[11] It is known by various vernacular names throughout the Indian subcontinent, in English: Indian Berberry, Sanskrit: *Katamkateri*, *Dirvi*, Gujrati: *Daruharidra*, *Daruhuladur*, Hindi: *Daruhaldi*, *Darhald*, Tamil: *Gangeti*, *Varatiu manjal*, Telugu: *Manupasupu*, Kannada: *Maradarishana*, *Daruhaladi*, Bengali: *Daruharidra*, Malayalam: *Maramanjal*, Marathi: *Daruhalad*, Oriya: *Daruharidra*, *Daruhalidi*, Punjabi: *Sumalu*, Urdu: *Darhald*.[2,12]

Taxonomy

Berberis aristata is spiny shrub which has historically been used for various medicinal applications by humans. The taxonomic classification of the *Berberis aristata* is depicted in the table1.

Table 1: Taxonomic classification of *Berberis aristata.*

Kingdom	***Plantae***
Phylum	*Tracheophyte*
Class	*Magnoliopsida*
Order	*Ranunculales*
Family	*Berberidaceae*
Genus	*Berberis L.*
Species	*Berberis aristata*

Macroscopical characters

This plant is an upright, spiny shrub that typically grows between 200 to 300 centimeters tall, stem is rigid and yellowish, while bark could be pale yellow to brownish on the outer and deep yellow on the inner surface, and can easily be manually removed in long strips. The spines are modified, hardened leaves, and measure about 15 mm in length.

Leaves

The arrangement of leaves can be found in tufts of 4-9 and have a verticillate phyllotaxy. They are simple, lanceolate, spiny, sessile toothed, leathery and acuminate with reticulate pinnate venation. Each leaf is approximately 50 mm long and 18 mm wide, exhibiting a dark green color over the top portion whereas a lighter green color on the lower surface.

Figure 1: Leaves of *Berberis aristate*.[13]

Flowers

The flowers of the plant are stalked, yellow, and complete, featuring both the male and female reproductive organs (hermaphroditic). They are cyclic, actinomorphic, and perigynous, with a fully opened flower having an average diameter of 1.25cm. The inflorescence of the flower is a simple to corymbose raceme, consisting of upto 16 flowers in each cluster. The calyx of the flower is yellow in color, it is polysepalous having six sepals (Three smaller and three larger in size), the are yellow, as well as actinomorphic and caducous with a 4 to 5 mm length. The corolla is polypetalous with six yellow, actinomorphic petals, each 4 to 5 mm in length. The androecium consists of six stamens, adnate, and 0.5 to 0.6 cm long. The gynoecium of the flower is singular, measuring 4-5 millimeter in length, having a broad stigma and a short style.

Figure 2: Flowers of *Berberis aristate*.[14]

Seeds

Each fruit contain 2 to 5 seeds, having different color from yellowish to pink. Every seed weighs approximately 25 milligram and has a volume of 29 microliters.

Fruits

The fruits are ovoid in shape and are typically covered with a bloom similar to that found on plums. Each fruit typically measures 7 mm in length and approximately 4 mm of diameter, weighs approximately 227 mg, and has a volume of 237 microliters. The fruit color is aconite violet.[7,8]

Figure 3: Fruits of *Berberis aristate*.[15]

Microscopic characters

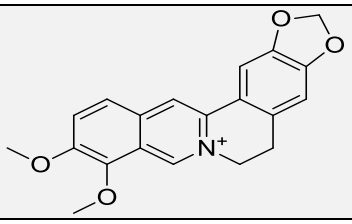
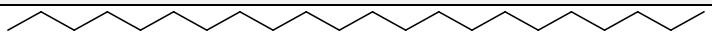
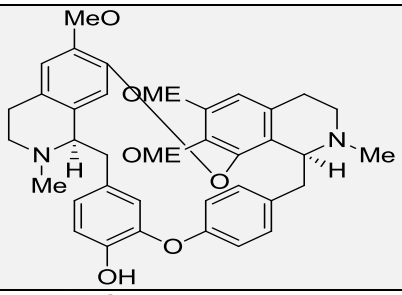
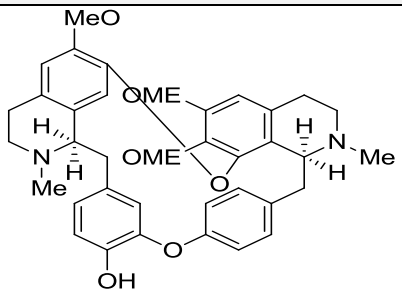
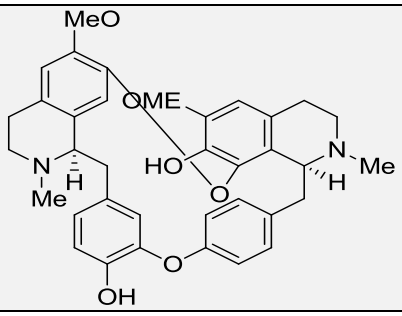
The stem has rhytidoma, and the cork is made up of three to forty-five squarish and rectangular cells with thin walls and a yellow tint that are organized radially. The irregularly shaped sieve elements have thin walls, and the contents of some of the cells are yellowish-brown. The phloem fibers are made up of one to four cells per row, arranged tangentially. These fibers are spindle-shaped, short, lignified, thick-walled, and have a large lumen. Secondary phloem rays cross the inside of the rhytidoma. These phloem rays run obliquely and consist of radially elongated parenchymatous cells, most of which contain single prismatic crystals of calcium oxalate. Additionally, prismatic crystals of calcium oxalate are present in certain rhytidoma cells. Within the

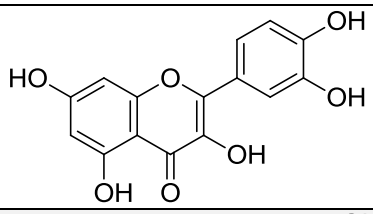
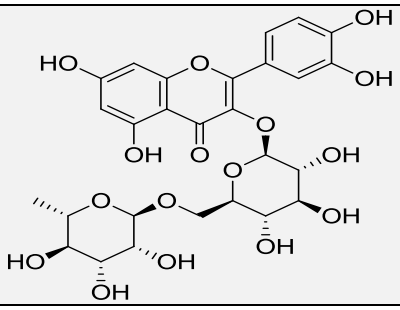
phloem ray cells, stone cells are sporadic and are typically found in groups rather than alone. The majority of these radially oriented, elongated stone cells (a few are rounded) contain solitary prisms of calcium oxalate crystals. Multiseriate phloem rays intersect the sieve elements and phloem fibers that make up the secondary phloem. Single to five rows of phloem fibers alternate with tangentially compressed cells, arranging the sieve elements in tangential bands. The phloem fibers have pointy ends, thick walls, are short, and are lignified. The broad secondary xylem is crossed by multiseriate xylem rays and contains xylem vessels, tracheids, and xylem fibers. Numerous, tiny to medium-sized xylem vessels can be found separately or in groups throughout the xylem region. While isolated vessels are cylindrical with rounded or protruding ends and spiral thickening, groups of vessels are usually oriented radially. The lignified, massive, thick-walled, lumen-wide, pointy tips of xylem fibers are all present. Xylem rays are made up of radially organized rectangular cells and are highly distinct, straight, and multiseriate. A few ray cells have brown contents. Each ray is 8 to 12 cells wide and 30 to 53 cells high.[2,8]

Chemical constituents

Berberis aristate has a rich diversity of phytochemicals which are responsible for the incredible therapeutic properties that it possesses. Studies have revealed that it contains alkaloids, coumarin, flavonoids, glycosides, polyphenols,[16] berberine an alkaloid which has been explored extensively for its pharmacological properties,[17] n-docosane.[18] There are many chemical compoinds found in different parts of *B. aristate*, some of them are depicted in the table2.[19]

Table 3: Structures of Chemical compounds found in *Berberis aristata*.

Name	Structure
Berberine	
n-Docosane	
Oxyacanthine	
Berbamine	
Aromoline	

Quercetine	
Rutin	

Pharmacological activities

Berberis aristata, has been extensively explored for its medicinal potential and has demonstrated phenomenal therapeutic properties. This plant is known for its rich content of berberine, an alkaloid that exhibits a wide range of pharmacological activities. Research has shown that *Berberis aristata* possesses anti-inflammatory, antimicrobial, antioxidant, and antidiabetic properties, among others. It's been traditionally employed in Ayurvedic and Chinese medicine as an effective medicine for treating various ailments such as infections, skin diseases, and digestive disorders.

Anti-Cancer

When comparing the methanolic extract of Berberis aristate to the mouse embryo fibroblast cell line (NIH/3T3), the MTT assay revealed a considerable cytotoxicity of the plant extract against the cell line for brain tumor (U-87 MG) and the mammary cancer cell line (MDA-MB-231). MDA-MB-231 and U-87 MG cells were only 25% viable at 40 µg of extract, however 50% of NIH/3T3 cells were viable. Being more poisonous to cancer cells than to normal cells suggests that the plant extract has anticancer activity. At different extract concentrations, variations in cell viability were also noted.[16] Using the MTT assay, Sharmila et al. assessed it for its anticancer potential as well and found that the extract of Berberis aristate had strong anti-proliferative properties.[20] In another study aimed at exploring the anti-cancer potential of *B. aristate, in vitro* anticancer activity of nanocarriers containing gelatin-lipid containing extract of *Berberis aristata* was evaluated using the SRB assay. The results demonstrated significant cytotoxicity, with an IC50 value of 4.73 ± 2.95 µg/mL against MCF-7 cells. This effectiveness then later was confirmed through flow cytometry and genotoxicity assays as well as the DAPI staining, which indicated the presence of proapoptotic bodies, providing evidence of apoptosis-mediated cell cytotoxicity. Additionally, the *in vivo* evaluation was conducted on female experimental mice to validate the anticancer property and the results were similar to those of standard drug, cisplatin. On the 10th day of the experiment, the GLN-BA at a dose of 10 mg per kg significantly lowered tumor volume by 35±11%, which was comparable with the 41±5% reduction observed with cisplatin at a dose of 3 mg/kg. Moreover, the molecular modeling study confirmed stability of the nano formulation that encapsulate the biologically active chemical constituent of *Berberis aristata*. Overall, these findings support the therapeutic effectiveness of *berberis aristata* encapsulated nanoparticles of gelatin-lipid in the treatment of mammary cancer, supporting the potential use of this medicinal plant as a prototype for cancer therapy.[21] In a different investigation, the anti-proliferative properties of diterpenes extracted from B. aristate were assessed against three cell lines: L20B, RD, and Hep2. They had cytotoxic effects that were considerable, with IC50 values ranging from 245 to 473 µg/mL. With an IC50 of 245 µg/mL, the most notable effect was seen against the RD cell line. A 21.58% inhibition was seen even at the lowest tested dosage (0.039 mg/mL). The diterpenes demonstrated an IC50 of 296 µg/mL for the Hep2 cell line and 473 µg/mL for the L20B cell line.[22]

Anti-microbial

The anti-microbial activity of B. aristata was assessed by Lamichhane *et al*. against a variety of bacterial stains, including C. albicans, P. aeruginosa, K. pneumoniae, S. typhi, S. aureus, and E. coli. It was discovered that the B. aristata extract lacked efficacy against K pneumonia and S aureus but exhibited strong activity against C. albicans, S. typhii, P. aeruginosa, and E. coli.[16] In a different investigation into the antimicrobial activity of B. aristate, Seema et al. examined the effects of several plant extracts on a range of bacterial strains, including Escherichia coli, Bacillus cereus, Staphylococcus aureus, Klebsiella pneumoniae and Streptococcus mutans. The assay's outcome showed that the extracts of ethanol and methanol had the highest activity, resulting in inhibitory zones of 12 mm against Klebsiella pneumoniae and 22 mm and 15 mm against Staphylococcus aureus, respectively. Strong inhibition was demonstrated by ethyl acetate extracts, which had zones of 24 mm against K. pneumoniae and 18 mm against S. aureus. The

pathogens' development was moderately reduced by hexane and aqueous extracts, but the chloroform extract showed only weak action.[23] Research was conducted to assess the efficacy of *B. aristata* extract against pathogens that cause eye infections. Additionally, the study sought to explore the antimicrobial potential of B. aristata methanolic stem extracts against six bacteria that cause eye infections: Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus viridans, Pseudomonas aeruginosa and Escherichia coli. The tests indicated that the extracts exhibited efficacy against three pathogens using the agar well diffusion method. With a 24.00 ± 0 mm inhibition zone and a MIC of 23.20 mg/ml, the antibacterial activity against E. coli was the highest, whereas Nocardia sp. had the lowest activity, with a 6.2 ± 0 mm inhibition zone and a MIC of 6.00 mg/ml. Standard antibiotic discs had similar inhibitory effects on Nocardia sp., S. pneumoniae, and E. coli.[24]

Anti-diabetic activity

The antidiabetic activity of the methanolic extract of *Berberis aristata* DC stem (MEBA) was investigated in a study using experimentally induced hyperglycemia with the help of streptozotocin in adult male Wistar rats. Blood glucose levels, lipid levels were compared against normal rats. In diabetic rats, repeated oral treatment of MEBA at dosages of 250 and 500 mg/kg dramatically increased HDL cholesterol levels while considerably lowering the levels of total cholesterol and triglycerides.[25] In a study, rats with streptozotocin-induced diabetes and normal rats challenged with sucrose were given two dose levels of the ethanolic extract of *Berberis aristata* root (100 and 200 mg/kg body weight) to test for antidiabetic effects. Both normal and diabetic rats' plasma glucose levels were considerably ($p<0.05$) decreased when the extracts were given orally at both dosages. After three hours and six hours of treatment, respectively, the antihyperglycemic effect peaked at 200 mg/kg dose, resulting in maximum reductions in blood glucose levels in diabetic rats. It showed that, in comparison to metformin, the ethanolic extract of *Berberis aristate*, displayed that it had the potential to lower the blood sugar levels dramatically in the experimental rats.[26]

Anti-inflammatory activity

In a study to assess *B. aristata* anti-inflammatory properties, A decrease in dose-dependent manner was seen in the paw edema (carrageenan-induced) and granuloma (cotton pellet-induced) paradigm after pretreatment with B. aristate hydroalcoholic extract. Comparing BAHE treatment to control, there was a substantial ($P < 0.01$) drop in serum levels of inflammatory cytokines. Pro-inflammatory indicators such as IL-1β, IL-6, TNF-R1, and COX-2 were shown to have decreased protein expression in activated macrophages, while peritoneal macrophages showed an upregulation of IL-10, an anti-inflammatory cytokine.[27] When compared against the groups who received extract treatment, the control group's levels of inflammation in the experimental animals were noticeably greater. In the group treated with *B. aristate*, the inflammatory cell count was 11.56 ± 2.44 × 10^5 ($P = 0.001$ vs. control) cells/mL, compared to 30.75 ± 7.33 × 10^5 cells/mL observed to be in control group. The control compared to the group treated with *B. aristata*, the aqueous humor protein concentration was 18.14 ± 4.98 and 3.16 ± 0.55, respectively. Furthermore, the aqueous TNF-α level in the *B. aristata*-treated groups was 654.09 ± 47.66 ($P < 0.001$ vs. control) pg/mL, compared to 976.29 ± 66.38 pg/mL in the control group.[28]

Anti-oxidant activity

An extract from Berberis aristate showed dose-dependent radical scavenging efficacy. Different sections of *B. aristata* showed radical scavenging efficacy in their methanolic extracts. The samples' total flavonoid concentration varied between 2.4 and 16.46 mg of quercetin per gram of dry weight, whereas their total phenolic content ranged from 11.04 to 65.30 mg of gallic acid equivalents (GAE) per gram of dry weight.[29] Using the DPPH assay, the antioxidant activity of B. aristate was evaluated; the results showed an IC50 value of 26 µg/ml and a 52% inhibition rate.[30]

CONCLUSION

Berberis aristata, a historically significant medicinal plant, continues to be a valuable resource in traditional and modern medicine. Its diverse pharmacological activities, particularly its anti-cancer, anti-microbial, anti-diabetic, anti-inflammatory, and antioxidant properties, are largely attributed to its rich content of bioactive compounds, such as berberine. The plant's wide range of therapeutic applications underscores its potential in developing new treatments for various ailments. This review highlights the need for continued research to further understand the mechanisms behind its pharmacological effects and to explore its full potential in drug development. Berberis aristata stands as a testament to the enduring relevance of plant-based medicines and their contributions to healthcare throughout history.

REFERENCES

1. Cragg, G.M. and D.J. Newman, *Natural products: a continuing source of novel drug leads.* Biochimica et Biophysica Acta (BBA)-General Subjects, 2013; 1830(6): 3670-3695.
2. *The Ayurvedic pharmacopoeia of India*. Government of India, Ministry of health and family Welfare department of AYUSH, New Delhi, 2007; 2(I).
3. Sabnarn, S., *Medicinal plant of Chammba.* India, 1964; 90: 50-63.
4. Joshi, M., *An ethnobotanical study of the Kumaon region of India.* Economic botany, 1971; 25(4): 414-422.
5. Chauhan, N.S., *Medicinal and aromatic plants of Himachal Pradesh*. 1999: Indus publishing.

6. Patel Pineshkumar, S., et al., *PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES OF BERBERIS ARISTATA: AN OVERVIEW*, 2019.
7. Parmar, C. and M. Kaushal, *Berberis Aristata: Indian: Wild Fruits*. Kalyani Publishers: New Delhi, 1982.
8. Rashmi, R., A. Rajasekaran, and J.P. Jagdish Pant, *The genus Berberis Linn.: a review*, 2008.
9. Mushtaq, F., et al., *Berberis aristata DC Extract Counteracts the High Fat Diet-Induced Reproductive Toxicity in Female Wistar Rats via Modulating Oxidative Stress and Resistance to Leptin and Insulin.* Endocr Metab Immune Disord Drug Targets, 2022; 22(14): 1390-1402.
10. Derosa, G., et al., *Berberis aristata/Silybum marianum fixed combination on lipid profile and insulin secretion in dyslipidemic patients.* Expert Opin Biol Ther, 2013; 13(11): 1495-506.
11. Shrivastav, A., A.K. Mishra, and A.K. Gupta, *Evaluation of Wound Healing Potential of Root Bark Extract of Berberis aristata and Molecular Docking Analysis of Berberis Phytoconstituents.* Curr Drug Discov Technol, 2023; 20(3): e210223213867.
12. Komal, S., et al., *Berberis aristata: A review.* Int J Res Ayurveda Pharm, 2011; 2(2): 383-388.
13. 2024 may15 2024]; Available from: https://stories.rbge.org.uk/wp-content/uploads/2017/06/Berberis-cropped.jpg.
14. *File:Berberis aristata - Indian Barberry on way from Govindghat to Gangria at Valley of Flowers National Park - during LGFC – VOF, 2019; (10). jpg*. may 15 2024]; Available from: https://commons.wikimedia.org/wiki/File:Berberis_aristata_-_Indian_Barberry_on_way_from_Govindghat_to_Gangria_at_Valley_of_Flowers_National_Park_-_during_LGFC_-_VOF_2019_%2810%29.jpg.
15. *File:Berberis aristata fruit.jpg*. [cited may 15 2024; Available from: https://commons.wikimedia.org/wiki/File:Berberis_aristata_fruit.jpg.
16. Lamichhane, B., et al., *Study of phytochemical, antioxidant, antimicrobial and anticancer activity of Berberis Aristata.* Journal of Tropical Life Science, 2014; 4(1): 01-07.
17. Gaba, S., et al., *An insight into the medicinal attributes of berberine derivatives: A review.* Bioorganic & medicinal chemistry, 2021; 38: 116143.
18. Katiyar, D., et al., *Isolation and characterization of n-docosane from heartwood of Berberis aristata.* International Journal of Pharmaceutical Sciences and Research, 2011; 2(2): 331.
19. Potdar, D., R.R. Hirwani, and S. Dhulap, *Phyto-chemical and pharmacological applications of Berberis aristata*. Fitoterapia, 2012; 83(5): 817-30.
20. Sharmila, K., et al., *Antibacterial, antioxidant, anticancer effects and GCMS analysis of Berberis aristata*, 2020.
21. Zaib, S., et al., *Green Synthesis of Gelatin-Lipid Nanocarriers Incorporating Berberis aristata Extract for Cancer Therapy; Physical Characterization, Pharmacological and Molecular Modeling Analysis.* ChemistrySelect, 2022; 7(45): e202203430.
22. Sood, H., et al., *Scientific validation of the antimicrobial and antiproliferative potential of Berberis aristata DC root bark, its phytoconstituents and their biosafety.* AMB Express, 2019; 9: 1-16.
23. Saxena, S., R. Negi, and S. Guleri, *Antimicrobial potential of Berberis aristata DC against some human bacterial pathogens.* Journal of Mycopathological Research, 2014; 52(2): 227-235.
24. Saravanakumar, T., et al., *Antimicrobial potential of Daruharidra (Berberis aristata DC) against the pathogens causing eye infection.* International Journal of Green Pharmacy (IJGP), 2014; 8(3).
25. Upwar, N., et al., *Hypoglycemic effect of methanolic extract of Berberis aristata DC stem on normal and streptozotocin induced diabetic rats.* Int J Pharm Pharm Sci, 2011; 3(1): 222-224.
26. Pareek, A. and M. Suthar, *Antidiabetic activity of extract of Berberis aristata root in streptozotocin induced diabetic rats.* Pharmacologyonline, 2010; 2: 179-185.
27. Kumar, R., Y.K. Gupta, and S. Singh, *Anti-inflammatory and anti-granuloma activity of Berberis aristata DC. in experimental models of inflammation.* Indian journal of pharmacology, 2016; 48(2): 155-161.
28. Gupta, S.K., et al., *The anti-inflammatory effects of Curcuma longa and Berberis aristata in endotoxin-induced uveitis in rabbits.* Investigative ophthalmology & visual science, 2008; 49(9): 4036-4040.
29. Bhatt, L.R., et al., *Antioxidant activity, total phenolic and flavonoid content of Berberis aristata DC. and Berberis thomsoniana CK Schneid. from Sagarmatha National Park, Nepal.* Pharmacognosy Journal, 2018; 10(6s).
30. Singh, J. and P. Kakkar, *Antihyperglycemic and antioxidant effect of Berberis aristata root extract and its role in regulating carbohydrate metabolism in diabetic rats.* Journal of ethnopharmacology, 2009; 123(1): 22-26.