



Review

Phyto-chemical and pharmacological applications of *Berberis aristata*

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ABSTRACT

In the recent years, the interest and research in medicinal plants have increased in a great deal. *Ayurvedic* medicines and formulations developed from ancient Indian herbal systems are renowned for their various important applications. *Berberis aristata* – an Indian medicinal plant, which belongs to the family Berberidaceae is an *ayurvedic* herb used since ancient times. It is also known as *Indian berberi*, *Daruharidra*, *Daruhaldi*, *Darvi* and *Chitra*. The plant is useful as anti-pyretic, anti-bacterial, anti-microbial, anti-hepatotoxic, anti-hyperglycaemic, anti-cancer, anti-oxidant and anti-lipidemic agent. *B. aristata* extracts and its formulations are also useful in the treatment of diarrhoea, haemorrhoids, gynaecological disorders, HIV-AIDS, osteoporosis, diabetes, eye and ear infections, wound healing, jaundice, skin diseases and malarial fever. This review aims to highlight the ethnobotany, pharmacognosy and pharmacological uses of *B. aristata* which will give insights in developing potentially new bioactives from the plant scaffolds. This review will also highlight the patenting trends, the new compositions developed using the actives from *B. aristata* and the different assignees involved in filing patents.

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Contents

1.	Introduction	818
2.	Ethnopharmacology	818
3.	Phytochemistry	819
4.	Pharmacological activities	820
4.1.	Hepatoprotective activity	820
4.2.	Anti-diarrheal activity	821
4.3.	Anti-PAF (platelet activating factor) activity	821
4.4.	Cardiotonic activity	821
4.5.	Anti-diabetic activity	823
4.6.	Anti-cancer activity	823
4.7.	Anti-inflammatory activity	823
4.8.	Anti-microbial activity	823
4.9.	Ophthalmic	823
4.10.	Activities related to CNS	823
4.11.	Miscellaneous	824
5.	Patents on <i>B. aristata</i>	824
5.1.	Year wise patent filing activity	826
5.2.	Assignee analysis	826
5.3.	Technology analysis	826
5.4.	Important patents related to <i>B. aristata</i>	826

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6. Other <i>Berberis</i> species of pharmacological importance	827
7. Conclusion	828
References	828

1. Introduction

“Ayurveda” is a traditional medicine system which was developed during the Vedic times, around 5000 years ago. The herbal remedies described in it take us “back to the nature” which makes use of plants, metals and its oxides termed as “*bhasmas*” for the treatment of various ailments. One of the traditional medicinal plants from *ayurvedic* system is known as *Berberis aristata* (*Daruharidra*) and its herbal formulations are used to treat malaria, bleeding, fever, skin and eye infections, jaundice, diarrhoea and hepatitis for a long time. Its traditional use as anti-microbial, anti-bacterial, anti-pyretic, immunostimulant, laxative, anti-haemorrhagic and anti-inflammatory agent is also well known.

B. aristata is an erect spinous shrub which is hard and yellow. It is majorly found growing in the sub-Himalayan regions and Nilgiri Hills of southern India. The plant contains a number of important phytochemicals which are alkaloids of the type proto-berberine, isoquinoline, bisbenzyl-isoquinoline and other bioactive constituents like flavonoids and phenolic acids. The traditional Indian and Chinese medicinal systems reveal that almost every part of this plant has some significant medicinal value. Its roots, stem, bark, leaves, rhizomes and fruits are used in many classical *ayurvedic* preparations like *Rasaut*, *Darvyadi kvatha*, *Darvyadi leha*, *Darvyadi taila*, *Rasanjana*, *Dasanga lepa* and many more. Extracts obtained from the plant find application in pharmaceuticals, nutraceuticals and cosmetic preparations.

2. Ethnopharmacology

Traditionally *B. aristata* is well-known for its properties such as *Lekhaniya* – reducing toxicity and unnecessary fats, *Arshoghna* – anti-haemorrhoidal, *Stanyasodhana* – lactodepurant, *Ropana* – a wound healer, *Svedala* – promotes sweating, *Rasayana* – rejuvenative, *Kandughna* – anti-pruritic and can also be used for treating skin disorders. *B. aristata* i.e. *Daruharidra* – resembles in its properties to those of Turmeric i.e. *Haridra*, hence both the herbs have been mentioned together as *Haridra dvaya*, meaning two *Haridras* viz. *Haridra* and *Daruharidra*.

It is an important commodity in the folklore medicine of India used for allergies, metabolic disorders, ophthalmia and other eye diseases and as a laxative. It is one of the 73 plants which are used to treat skin diseases traditionally in Nepal and other surrounding villages [1]. A multi-herbal formulation containing *B. aristata* is used for treating bleeding piles in some rural parts of India [2]. Traditional anti-osteoporosis activity of *B. aristata* was confirmed when ovariectomized (OVX) rats were tested for the aqueous methanol extract of the plant. These findings suggested that the ethnic use can be continued in treatment of osteoporosis, joint pain and menopause [3].

Ethnobotanical studies indicate that *Rasaut* – decoction of *B. aristata* leaves, is used as an alternative and deobstruent and commonly used to treat skin diseases, menorrhagia, diarrhoea, cholera, jaundice, eye and ear infections, as well as urinary tract

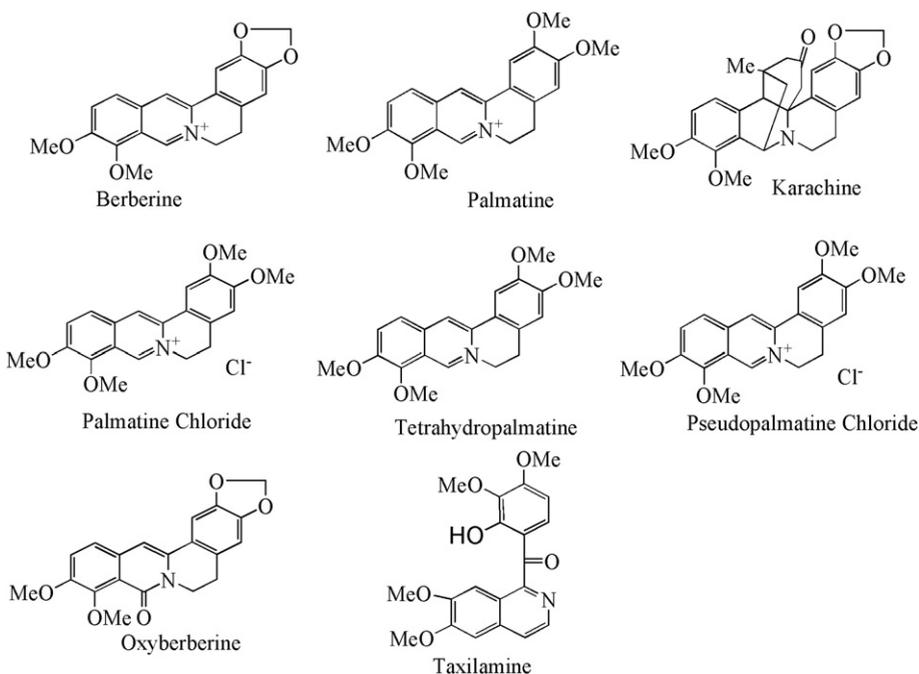


Fig. 1. Protoberberine alkaloids from *Berberis aristata*.

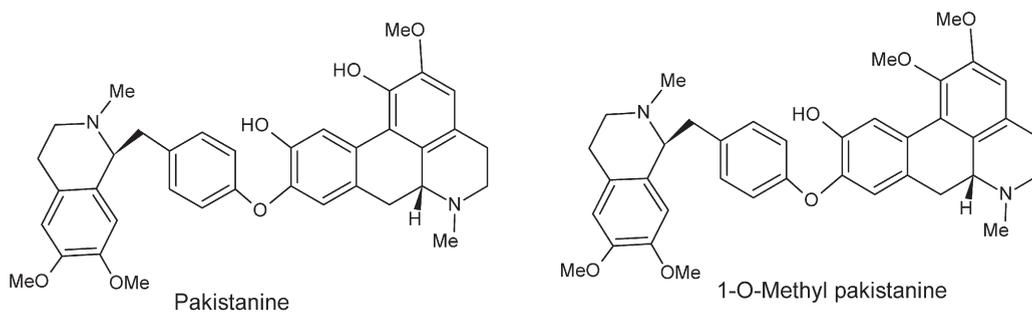


Fig. 2. Isoquinoline alkaloids from *Berberis aristata*.

infections. *Rasaut* also shows anti-bacterial, anti-fungal, anti-inflammatory, analgesic, and anti-pyretic activities [4–7].

Its root decoctions are used to treat eye diseases in *Bhotiya* communities in the Himalayan ranges in India [8]. Furthermore, *Malani* tribal communities from Himachal Pradesh, India use it to cure skin diseases, jaundice, piles and malaria. Its fruits are eaten as laxative and anti-scorbutic [9].

In Garhwal Himalaya, *B. aristata* is used as a psychomedicine for treating exorcism in children [10]. The plant root is useful in treating jaundice [11]. In Nepal, the plant's fruit and leaf juice are used for treating diarrhoea and dysentery while its bark and root decoction are used to treat jaundice and fever [12]. Some Himalayan tribes residing in Sikkim and Darjeeling in India use the plant extract as anti-diabetic and anti-hepatopathic [13].

3. Phytochemistry

Alkaloids are the major type of phytoconstituents present in *B. aristata* (Figs. 1–5). The root bark of the plant contains a protoberberine alkaloid – karachine [14] along with aromoline, oxyberberine, oxyacanthine, berbamine, and berberine chloride [15]. *B. aristata* flower contains various polyphenolic flavonoids like quercetin, rutin, meratin and acids like E-caffeic acid and chlorogenic acid [16]. Alkaloids like pakistanine, 1-O-methylpakistanine, pseudopalmitine chloride and

pseudoberberine chloride were isolated from the bark of the plant [17]. Another alkaloid taxilamine was also obtained from this plant [18]. Alcoholic extraction of the powdered bark of *B. aristata* after concentration and filtration gave berberine, tetrahydropalmatine, tetrahydroberberine, palmatine and palmatine chloride or its mixtures [19,20]. The ethanolic extract of heartwood of *B. aristata* reveals the presence of n-docosane which is an aliphatic hydrocarbon [21].

The early precursor for the formation of this plants alkaloids is an amino acid i.e. L-tyrosine. Tyrosine is metabolized directly to dopamine and this is accomplished through the enzyme known as tyrosine hydroxylase. It is shown by the experiments that, dopamine and p-hydroxyphenylacetaldehyde (both derived from tyrosine) undergo condensation to give norcoclaurine, which gets further converted to N-methylcoclaurine through the formation of intermediate coclaurine. Phenolic oxidation coupling of bezyloisoquinoline alkaloids like N-methylcoclaurine gives rise to the formation of bisbenzylisoquinoline alkaloids i.e. oxyacanthine, aromoline and berbamine [15]. The biosynthesis of these alkaloids is shown in Fig. 6.

3'-Hydroxylation of N-methylcoclaurine gives rise to formation of 3'-hydroxy-N-methylcoclaurine and further 4'-O-Methylation of 3'-hydroxy-N-methylcoclaurine by 4'-O-Methyltransferase forms the important intermediate called

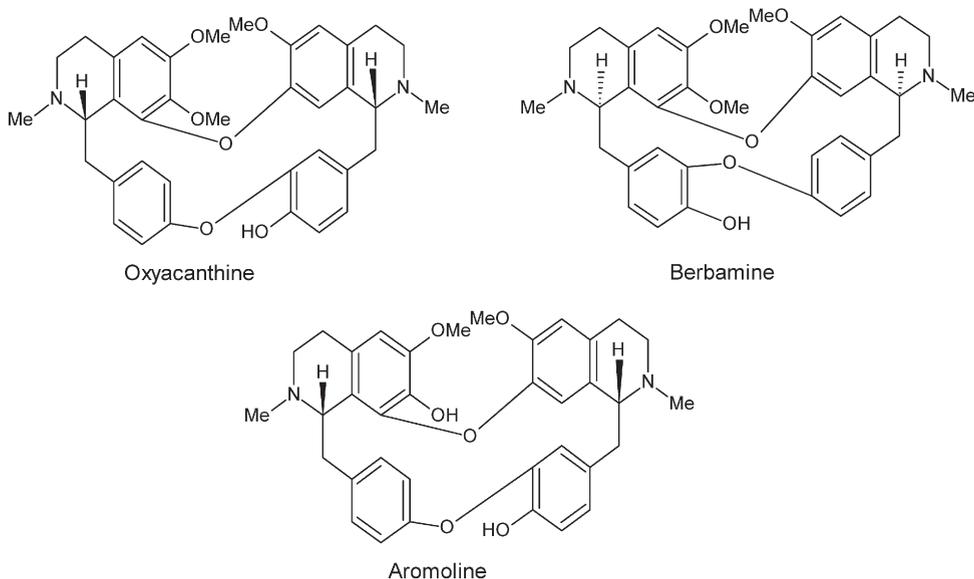


Fig. 3. Bisbenzylisoquinoline alkaloids from *Berberis aristata*.

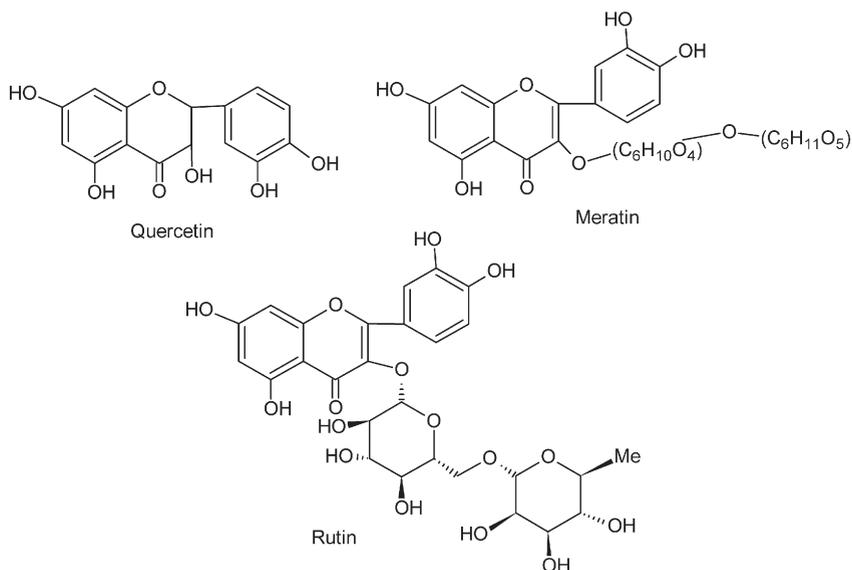


Fig. 4. Flavonoids from *Berberis aristata*.

S-reticuline. S-reticuline is a central intermediate which gives rise to the formation of berberine, palmatine, oxyberberine, palmatine chloride, karachine and taxilamine [14,18]. The formation of different protoberberine alkaloids starting from S-reticuline is described in Fig. 7.

Berberine is one of the major and important alkaloids found in *B. aristata* which possesses important pharmaceutical activities. Detection, monitoring and quantification of berberine in this plant are now made simple, precise and sensitive with HPTLC and spectrophotometric methods [22]. HPTLC fingerprinting of root and bark of this plant along with two other *Berberis* species i.e. *Berberis asiatica* and *Berberis lycium* was performed for its berberine content. The results showed that root of the plant shows more berberine content than the bark [23].

The studies for micronutrients and heavy metal concentration showed the presence of metals such as cadmium, lead, chromium, zinc, iron and manganese in the rhizome of the plant [24]. Further, a comparative study of *B. aristata* along with the other herbs showed higher amount of chromium compared to other nine herbs of study.

4. Pharmacological activities

B. aristata i.e. *Daruharidra* is officially noted in *Ayurvedic & Siddha Pharmacopoeia* of India. Due to its various

pharmacological activities it is an important part of polyherbal formulations in the treatment of different diseases and disorders. A brief review on the different type of activities as reported for the plant is summarised below.

4.1. Hepatoprotective activity

The effect of *B. aristata* (*Daruharidra*) was tested on the hydraulic permeability of water in the presence of bile salt through a transport cell model, which showed prevention of the toxic effect of bile salts in various hepatic disorders by cell membrane stabilizing property [25]. It was observed that a formulation containing *B. aristata* reduced the rate of infection of hepatic amoebiasis tested by evaluating experimental amoebic liver abscess in golden hamsters and in immunomodulation studies [26]. The plant has also been tested for hepatobiliary disorders where it reduced acetaminophen-induced rise in serum alkaline phosphatase, GOT (glutamic oxaloacetic transaminase) and GPT (glutamic pyruvic transaminase) levels [27]. A polyherbal formulation known as Hepjaun syrup and its modifications containing *B. aristata* possess significant hepatoprotective activity and it is therefore useful in treating liver diseases or damages [28]. Aqueous-methanol extract of the plant fruits exhibits hepatoprotective action partly through MDME (microsomal drug-metabolizing enzymes) inhibitory

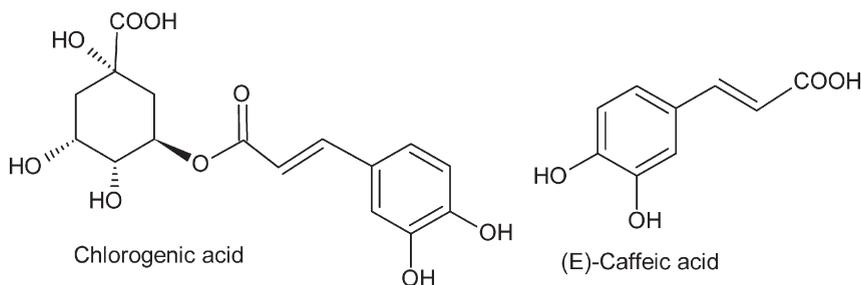


Fig. 5. Acids from *Berberis aristata*.

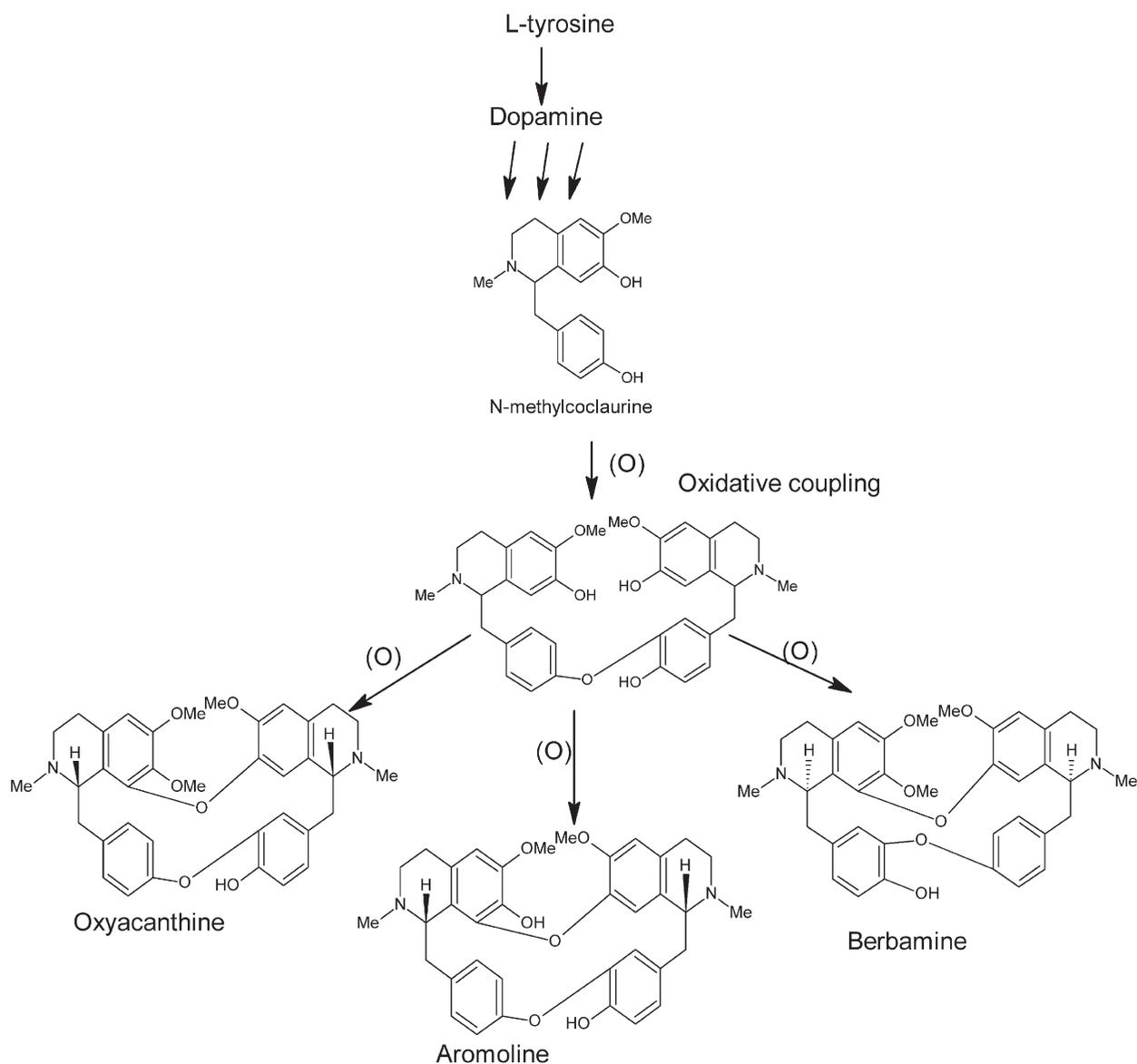


Fig. 6. Biogenetic relation – bisbenzylisoquinoline alkaloids.

action [29]. In isolated rat hepatocytes, berberine has an inhibitory action on potassium and calcium currents which may be involved in hepatoprotection [30]. Studies show that cytochrome P-gp (P-glycoprotein) and P-450 may play important roles in the regulation of hepatobiliary excretion and liver metabolism for berberine in rats [31]. In Chinese medicines berberine is also known to be effective against liver fibrosis [32].

4.2. Anti-diarrheal activity

Chemical fingerprint evaluation for the *B. aristata* extracts were carried out in vitro and in vivo which confirmed its anti-diarrheal activity [33]. Its active constituent berberine inhibits intestinal secretory response of *Vibrio cholerae* and *Escherichia coli* enterotoxins, hence finds application in the acute diarrheal diseases [34]. As seen from the studies, berberine (10 mg/kg) prolonged the latent period and decreased the incidence and

severity of diarrhoea induced by 2 and 4 g cholera toxin/kg in rats. Further, a crude dried preparation of *B. aristata* inhibited cholera toxin-induced diarrhoea [35].

4.3. Anti-PAF (platelet activating factor) activity

Alcoholic extract of the root of *B. aristata* has been studied on rabbit platelets and indicated that it inhibits the PAF (platelet activating factor) induced aggregation of platelets and the 3H-PAF binding [36]. It is also found that plant active berberine selectively inhibits platelet aggregation by interfering with the collagen-mediated adhesion process [37].

4.4. Cardiotoxic activity

B. aristata is also useful in treating cardiovascular diseases [38]. It was speculated that in the isolated cardiac tissues, *B.*

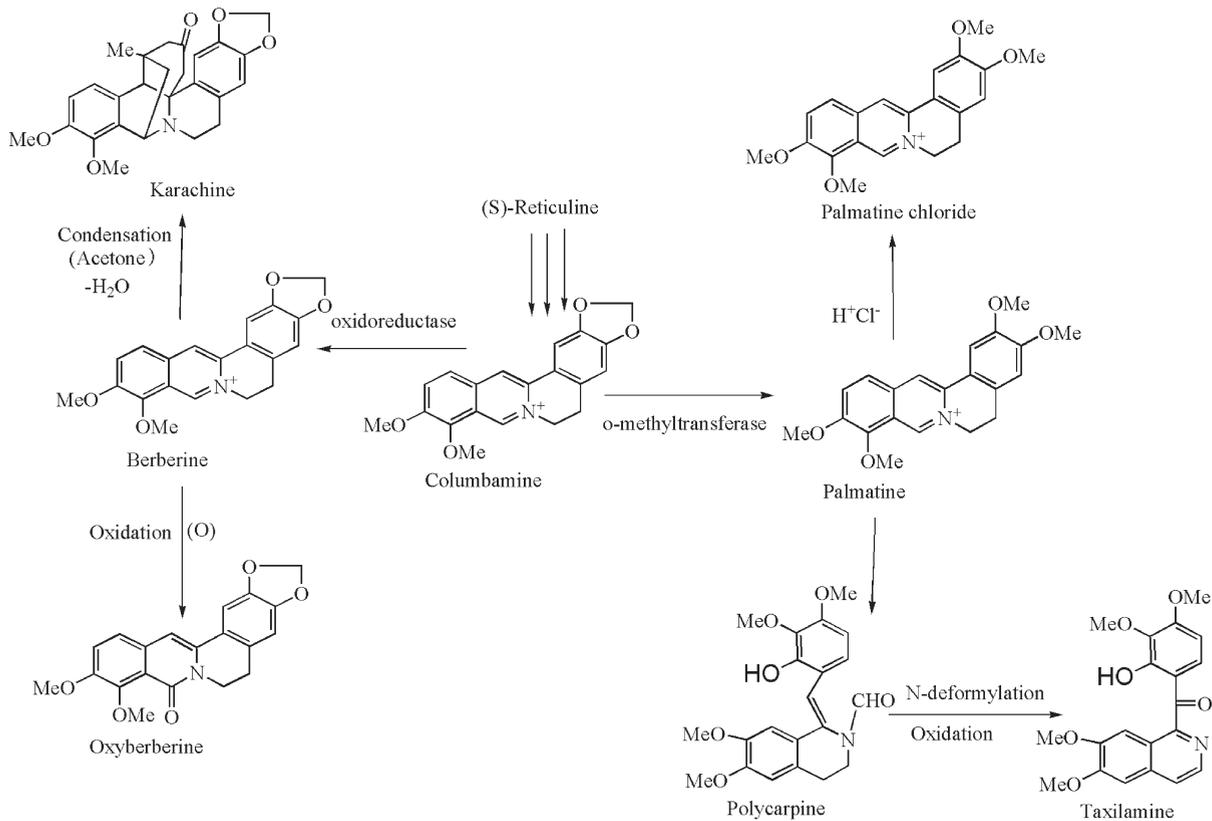


Fig. 7. Biogenetic relation – protoberberine alkaloids.

aristata fruit extract exhibits a positive inotropic action. It is observed that the active principles of the plant cause a selective inotropic effect, involving – in the form of the modulatory effect on actin myosin co-operativity, which is a novel mechanism of action [39]. The bio-chemical study on *B.*

aristata revealed that a significant reduction in serum cholesterol, triglycerides and low density lipoprotein levels was noted and an increase in thrombin and fibrinogen time was noted when the study was performed on healthy rabbits of either sex [40].

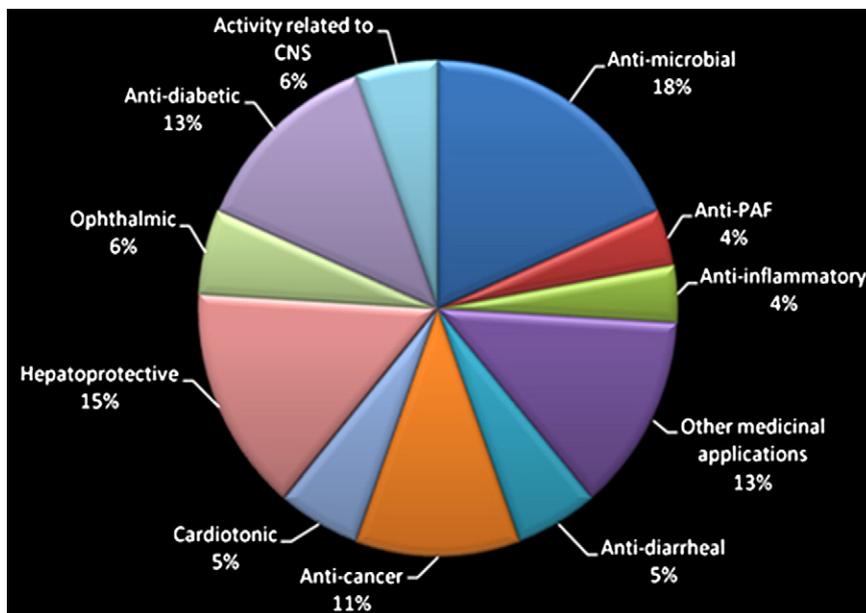


Fig. 8. Pharmacological applications of *Berberis aristata* (Scientific Literature Analysis).

4.5. Anti-diabetic activity

B. aristata plant stem is used in Indian traditional medicine for treating diabetes mellitus [41]. The ethanolic extract of *B. aristata* shows anti-diabetic activity in alloxan induced diabetic rats. Roots of this plant also possess anti-hyperglycaemic activity [42]. It is further revealed that root extract of *B. aristata* has a strong anti-hyperglycaemic and anti-oxidant potential to regulate glucose homeostasis through decreased gluconeogenesis and oxidative stress. The plant hence plays an important role in metabolic disorders [43]. *B. aristata* is also included in herbomineral formulations such as D-400 which is used to treat diabetes mellitus [44]. Hypoglycaemic and hypolipidemic activity of the methanolic extract of *B. aristata* (MEBA) stem was observed when a study was performed on diabetic rats. This MEBA enhances activity of enzymes involved in bile acid synthesis and its excretion, so this may decrease serum cholesterol and triglycerides. MEBA reduces the serum Tg (Thyroglobulin) of streptozotocin induced diabetic rats and may prevent the progression of CHD (coronary heart disease). So it can be considered as an important anti-diabetic agent [45]. Studies related to berberine show that it acts through several mechanisms, including mimicking insulin; improving insulin action by activating AMPK (5' adenosine monophosphate-activated protein kinase); reducing insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression; inducing glycolysis; and on incretins by promoting GLP-1 secretion and modulating its release, and by inhibiting DPP-IV [46]. DPP-IV inhibiting activity of *B. aristata* makes it a potential anti-diabetic agent [47].

4.6. Anti-cancer activity

Methanolic extract of the stem of *B. aristata* induces a concentration dependent inhibition of HT29 cells, with an IC₅₀ value of 1.9648 µg/ml after 72 h of inhibition. The cytotoxic activity against the H29 colon cancer cells was investigated in this extract. So it can be used as anti-cancer herb for colon cancer [48]. The plant alkaloid berberine is also used to treat chemical carcinogenesis as it significantly inhibits the carcinogenesis induced by 20-methylcholanthrene or N-nitrosodiethylamine [49]. It is found that the butanolic fraction containing berberine inhibits NFκB activity (both promoter and DNA binding) in PC-3 cells, which can lead to an effective method in the treatment of prostate cancers [50]. Berberine is found to inhibit implanting tumour and cachexia in vivo through the induction of NM23-H1 expression which suggests its future application as a potential drug for nasopharyngeal carcinoma i.e. NPC [51].

It was observed that berberine (5–50 µM) inhibited cell growth in neuroblastoma SK-N-SH and SK-NMC cells through induction of apoptosis. This can suggest its effectiveness as an anti-cancer and anti-tumour agent [52]. The use of this plant during cisplatin-therapy reduces cisplatin-induced nephrotoxicity by decreasing lipid peroxidation formation [53].

4.7. Anti-inflammatory activity

Topical instillation of aqueous extracts of *Curcuma longa* and *B. aristata* showed potent anti-inflammatory activity against endotoxin-induced uveitis in rabbits [54]. An ophthalmic formulation of *Unani* eye drop containing stem wood

of *B. aristata* is effective in inflammatory and allergic conditions of the eyes. Anti-inflammatory activity against turpentine liniment-induced ocular inflammation in rabbit's eye was observed. This test formulation was observed as H₁-receptors blocker and it antagonizes effect of histamine on the tissue, thus showing anti-histaminic activity in isolated guinea pig ileum [55].

4.8. Anti-microbial activity

B. aristata and its phytoconstituents are well known since ancient times in treating diseases caused due to different microorganisms. Berberine extracts and decoctions have demonstrated significant anti-microbial activity against a variety of microbes including bacteria, viruses, fungi, protozoans, helminths, and chlamydia [56–58]. The herbal gel formulation containing this plant extract was found to be active against resistant strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Corynebacterium* species. Hence this formulation is found to be an effective medicine for skin infections [59]. Similarly the plant also found to possess anti-*Helicobacter pylori* activity due to which it is used to treat ulcers or gastrointestinal disorders [60].

Effect of berberine sulphate salt on the growth of *Trichomonas vaginalis* in vitro was compared to the efficacy of metronidazole as a reference drug. The anti-pathogen activity was observed and the results suggest that berberine sulphate is more safe and a possible replacement in metronidazole resistant cases [61]. Berberine obtained from rhizomes of *B. aristata* blocked spore germination of most of the fungi. Hence, berberine alone or in combination with other bioactives such as santonin can be used for controlling diseases in plants [62]. Root extracts and hexane extracts [63] of *B. aristata* showed anti-fungal activity against different fungal pathogens [64].

Berberine inhibited in vitro multiplication of amastigotes in macrophage culture and their transformation to promastigotes in cell free culture. Hence it is a useful agent to treat visceral leishmaniasis [65].

4.9. Ophthalmic

The formulations called 'Netrabindu', 'M.D.H drops and capsules' and 'Madhudarvyadi eye drops' containing *B. aristata* are used for treatment of conjunctivitis [66] and similarly an ayurvedic formulation containing this plant is used to treat complications of cataract [67]. Ayurvedic preparation which is *Anjana* called *Elanir kujambu* contains *B. aristata*. It is a good medicine for treatment of eye diseases and infections because of its anti-microbial and anti-bacterial activity [68].

4.10. Activities related to CNS

It is observed that berberine exerts anti-depressant-like effect in various behavioural paradigms of despair, possibly by modulating brain biogenic amines (norepinephrine, serotonin and dopamine) [69]. Studies on berberine also indicate that, it can be effective in various CNS (central nervous system)-related disorders like Alzheimer's disease, schizophrenia, mental depression and anxiety [70]. A tablet called as Geriforte containing *B. aristata* extract is used to treat mental and physical incompetence in aged people [71].

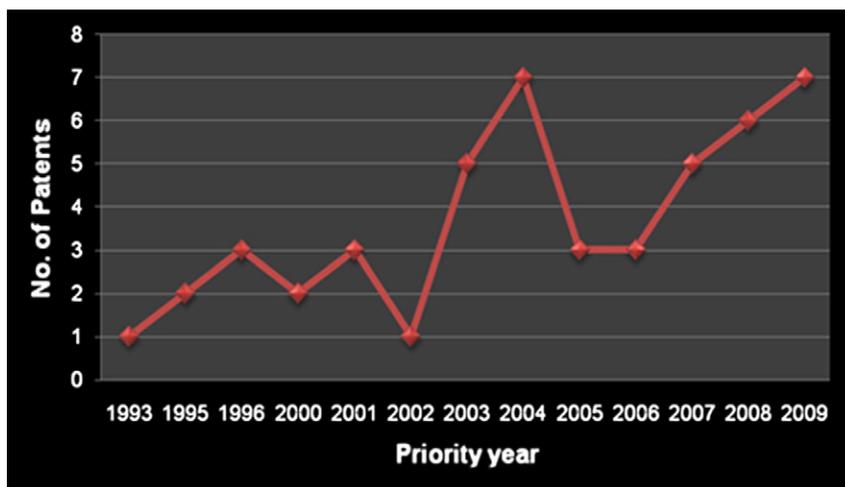


Fig. 9. Year wise patent filing activity for *Berberis aristata*. The patents filed in 2010 and 2011 are not considered for analysis as the data would be incomplete. (Patent applications are published after a period of 18 months from the date of filing.)

4.11. Miscellaneous

Ayurveda considers *B. aristata* as of *Ruksha guna* and it is able to influence *Dipana* and *Pachana* properties, which can lead to its use as a hypolipidemic agent [72]. It is a traditional natural resource for wound healing [73] having the property as “*Vranaropaka*” according to *ayurveda*. *Acne vulgaris* can be treated with the cream SK-235 (Clarina), which contains *B. aristata* and other herbs. This cream shows good dermatological activity without side reactions [74]. *B. aristata* extract is one of the important ingredients of anti-haemorrhoidal tablet Pilex used in the treatment of bleeding piles [75,76].

Mebarid – an effective *ayurvedic* formulation for gastrointestinal disorders contains *B. aristata* which is found to possess anti-diarrheal, anti-motility and anti-ulcer activities [77]. The studies on the plant also reveal the radical scavenging effect on the stable DPPH radical with IC₅₀ (95.9%) resulting in good antioxidant activity which suggests that it can be used to treat diseases caused due to free radicals [78].

Fig. 8 depicts the focus of the research papers on *B. aristata*. It is seen that the plant is well explored for its anti-microbial properties. *B. aristata* bioactives and its formulations are also shown to be an active hepatoprotective, anti-diabetic and anti-cancer agents.

5. Patents on *B. aristata*

Scientists in research institution and academics are very often piled with scientific literature published in peer reviewed journals, but this literature has poor objective information on the technological strategies being adopted by the commercial companies in their research laboratories. This is because of the fact that technologies during their development phase are often protected by proprietary secrecy and are least visible. Patents are the largest single source of technical information in the world. It is estimated that between 70 and 75% of the information in patents is not available elsewhere. Looking at the breadth and depth of the knowledge that they capture, it is clear that patents are an important source of technological intelligence that companies can use to gain strategic advantage.

Patents vary in scope, purpose and ultimate value. Very few of the patents may be economically very significant but many patents are technically important because they lead either directly or indirectly to follow – on developments, which may also be patented. Some patents have high business significance because competitors may often try to “invent around” such key developments to maintain or capture market positions.

The analysis of patent activity in a particular technical area provides good evidence regarding the degree of interest taken by firms and inventors. It can also show the technological advances and recent developments in the particular area.

The patents filed and granted on the use of *B. aristata* alone or in combination with other bioactives or plant extracts were also considered for the review. They are searched on different patent databases such as DII (Derwent Innovation Index), CAS (Chemical Abstract Services) and patent offices of various countries e.g. Europe, United States, India, China, Korea, Japan and WIPO. Search was also carried out on databases like Patestate managed by CSIR-URDIP, India and PAMEP (Patents on Aromatic Medicinal and Economic Plants) developed by the Department of Biotechnology and URDIP, India.

The patent search and analysis retrieved 48 patents of interest which claim *B. aristata* for its medicinal and other important properties. Analysis of these patents reveal that most of the patents mainly claim the use of for *B. aristata* for dermatological disorders, diabetes, cancer, HIV-AIDS, haemorrhoids, oral problems, heart and liver diseases, metabolic and gynaecological disorders, treating wounds, pyrexia, fever, diseases caused by microorganisms like bacteria, fungi, microbes, parasites, pathogens etc. It is also found to be useful in cosmetic preparations used for skin care, treating alopecia, chronic skin disorders, as a skin whitening agent, for preventing pigmentation, to slow the ageing process etc.

Table 1 lists the patent numbers, title and the pharmacological area for which *B. aristata* is one of the active as disclosed in the patent documents.

Table 1
Patents on *Berberis aristata*.

Patent no.	Publication date	Title	Activity
KR2011051820	18-05-2011	Composition containing lacquer tree used as feed additive for livestock.	Immunostimulant
IN2009DEL01056	26-11-2010	Herbal ophthalmic composition for common eye ailments.	Anti-microbial
US20100239603	23-09-2010	Combinations of botanical extracts for promoting cardiovascular health.	Cardiotonic
JP2010202634	16-09-2010	Crude drug containing composition used for improving metabolic syndrome, obesity and liver function, comprises <i>Garcinia</i> , <i>Terminalia belleria</i> , <i>Commiphora mukul</i> , <i>Gymnema sylvestre</i> , <i>Boswellia serrata</i> and <i>Salacia reticulata</i> .	Anti-lipidemic
WO2010104595	16-09-2010	Methods and compositions for the treatment of metabolic and cardiovascular disorders.	Anti-lipidemic, anti-diabetic, cardiotonic
JP2010195731	09-09-2010	Agent useful for whitening skin and preventing and suppressing pigmentation and liver spots by inhibiting Dopa oxidase activity, contains extract of plant e.g. <i>Berberis vulgaris</i> and <i>Berberis aristata</i> .	Dermatological (Dopa oxidase inhibitor activity)
US7771757	10-08-2010	Nasal irrigation solutions and methods of using the same.	Anti-microbial, anti-inflammatory
KR2010084909	28-07-2010	Feed additive containing medicinal herb composition.	Immunostimulant
US20100178367	15-07-2010	Herbal formulation for wound healing.	Anti-microbial, anti-fungal, wound healing
US20100143510	10-06-2010	Intramammary teat sealant.	Anti-infective, anti-bacterial, anti-fungal
WO2010032267	25-03-2010	Herbal formulation for prevention and treatment of diabetes and associated complications.	Anti-diabetic
WO2010029562	18-03-2010	Bioactive composition for the treatment of the HIV/AIDS and method for manufacturing and using the same.	Anti-HIV
US7658954	09-02-2010	Synergistic anti-pyretic formulation.	Anti-pyretic
EP2149377	03-02-2010	Compositions containing berberine and/or analogues thereof or extracts containing it, for the prevention and treatment of alterations of the lipid and carbohydrate balance.	Anti-lipidemic
IN2009DEL01212	01-01-2010	Broad spectrum polyherbal formulation for treatment of alopecia and chronic skin disorders.	Dermatological-anti-microbial
IN2009KOL01123	27-11-2009	Herb-based nutritional composition for correction of metabolic disorders.	Anti-cancer
IN2008CHE00849	09-10-2009	<i>Berberis aristata</i> plant extract comprises extract or concentrate of plants belonging to <i>Berberis</i> , which includes <i>Berberis aristata</i> or their mixtures, and extracts, which are isolated from different parts of <i>Berberis aristata</i> plant.	Cardiotonic
IN2005DEL02645	02-10-2009	Herbo-mineral compound formulation for management of maturity-onset diabetes mellitus.	Anti-diabetic
EP2090315	19-08-2009	Method and system for producing medicinal alcohol as a prophylactic or remedy for cancer, HIV, AIDS and autoimmune diseases.	Anti-inflammatory
IN2004DEL01330	19-06-2009	Herbal composition for treatment of HIV and process of preparing the same.	Anti-HIV
US20090136469	28-05-2009	Formulation for oral administration with beneficial effects on the cardiovascular system.	Cardiotonic
DE102007040798	02-04-2009	Herb mixture, useful e.g. to slow the ageing process, comprises e.g. <i>Crocus sativus</i> , <i>Elettaria cardamomum</i> , <i>Cinnamomum zeylanicum</i> , <i>Hedychium spicatum</i> , <i>Terminalia chebula</i> , <i>Trichosanthes dioica</i> , <i>Coleus forskolin</i> and <i>Berberis aristata</i> .	Anti-ageing
KR20090032617	01-04-2009	An anti-cancer medicine including berberine.	Anti-cancer
WO2008126088	23-10-2008	Anti-pyretic vasodilators.	Anti-pyretic
US20080081781	03-04-2008	Methods and compositions for the treatment of metabolic syndrome.	Anti-lipidemic, Cardiotonic
WO2008007215	17-01-2008	<i>Berberis aristata</i> plants extracts for treating osteoporosis and the extraction process thereof.	Osteopathic, cytostatic, anti-arthritis
EP1411951	26-09-2007	Enteral compositions for the prevention and/or treatment of Sepsis.	Anti-microbial, anti-bacterial
IT2007MI0988	16-08-2007	Potentialiation of antitumor chemotherapy and (or) radiotherapy by using a plant-derived food supplement.	Anti-cancer
US20070098649	03-05-2007	Method and composition for controlling oral pathogens.	Anti-inflammatory, anti-bacterial, anti-microbial
US20070065394	22-03-2007	Compositions effective in altering the perception of malodour.	-
US20070027176	01-02-2007	Compositions for veterinary and medical applications.	Anti-microbial
US20060223838	05-10-2006	Methods and compositions for the treatment of hyperlipidemia.	Anti-hyperlipidemic
IN2004CHE0679	02-06-2006	Side effect-less curing medicine for diabetes mellitus by immunopathy.	Anti-diabetic
IN218675	24-03-2006	Herbal composition for controlling blood sugar level comprises e.g., <i>Melia azadirachta</i> (Neem Bark) and <i>Syzygium cumini</i> (Jamun or Black Berry).	Anti-diabetic
WO2005030232	02-03-2006	Herbal compositions for effective treatment of AIDS, preparation thereof and method for treatment of AIDS patients.	Anti-HIV
JP2005325025	24-11-2005	Composition for treating and preventing diabetes comprises crude drug component of Guggul, Licorice, Balsam Pear, <i>Gymnema sylvestre</i> ,	Anti-diabetic

(continued on next page)

Table 1 (continued)

Patent no.	Publication date	Title	Activity
IN2001DEL00767	01-07-2005	<i>Boerhavia diffusa</i> , Guduchi, Amla, Turmeric and Neem, and mineral component. Herbal intrauterine bolus for livestock involves herbs selected from <i>Paedaria foetida</i> , <i>Azadirachta indica</i> , <i>Ficus religiosa</i> , <i>Ficus henghalensis</i> , <i>Ficus racemosa</i> , <i>Asparagus racemosus</i> , <i>Berberis aristata</i> , <i>Curcuma longa</i> , <i>Glycyrrhiza glabra</i> .	Gynaecological
IN2000DEL0346	11-03-2005	Herbal composition for treatment of bovine mastitis in cows.	Anti-inflammatory
IN9600325	04-03-2005	Anti-AIDS <i>ayurvedic</i> medicine/composition comprising herbal extract and minerals.	Anti-HIV
IMMUM00325			
IN2003MUM0462; IN207185	11-02-2005	Process for preparation of skin care composition by combining micro-nutrients with <i>ayurvedic</i> substances.	Dermatological-wound healing
WO2004092078	28-10-2004	Herbal water treatment method for prosperity of biological.	Anti-bacterial
JP2003095856	04-03-2003	Skin care preparation with high safety and anti-ageing effect.	Dermatological – skin care, anti-ageing
US6455077	24-09-2002	Herbal composition and method of manufacturing such composition for the management of gynaecological disorders.	Gynaecological
US5856487	05-01-1999	Application of protoberberine alkaloid, berberine, an immunosuppressive agent.	Immunosuppressive
JP10158184	16-06-1998	Cell adhesion inhibitor/novel use of extract isolated from <i>Berberidaceae</i> plant as cell adhesion inhibitor.	Cell adhesion inhibitor, anti-allergic, anti-inflammatory, cancer metastasis inhibiting and immunosuppressant.
US5693327	02-12-1997	Herbal compositions.	Anti-inflammatory
US5591436	07-01-1997	Composition for a dietary supplement for the treatment of haemorrhoids.	Anti-haemorrhoidal
DE4327792	06-04-1995	Natural antimicrobials, insecticides, acaricides and nematocides for plant protection – are prepd. From <i>Rosa</i> , <i>Allium</i> , <i>Brassica</i> , <i>Mahonia</i> , <i>Sambucus</i> , <i>Pelargonium</i> and/or <i>Hypericum</i> plants.	Anti-microbial, insecticidal

5.1. Year wise patent filing activity

Patent filed and issued worldwide on *B. aristata* alone or its formulations were considered, which reveal that the patents are spread over the last two decades. Priority year was considered for the analysis. Further the patents filed in 2010 and 2011 are not considered as the data would be incomplete due to the reason that the patent applications are only published after a period of 18 months from the date of filing. The year wise analysis as depicted in Fig. 9 reveals that the highest numbers of patent applications are filed for *B. aristata* and its important formulations during year 2004 and that there is an increase in the overall filings over the years.

5.2. Assignee analysis

The simplest indication of an assignee's patent activity in this area is the total number of patents produced. According to Fig. 10, Indian researchers and companies are found most active in exploring this traditional plant and its medicinal properties. Dabur has obtained 3 patents which comprise *B. aristata* in their herbal formulation for different uses. Similarly Indian pharma company Avestha Gen and companies like Kao korp and Green Kanpo from Japan have obtained 2 patents each.

5.3. Technology analysis

The pharmaceutical activity was considered herein as the technology for the analysis. This technology analysis highlights that *B. aristata* is used as an anti-microbial and anti-diabetic agent on large scale for a long time. Nowadays, anti-HIV activity of this plant is being explored, which has given

medicinal researchers a new way to discover medicines for HIV-AIDS. It is also explored for its dermatological activity and finds application in medicines as well as cosmetics. Further, the different important pharmacological activities like anti-cancer, cardiotoxic, anti-pyretic, anti-haemorrhoidal, anti-lipidemic, metabolic, gynaecological and anti-arthritis activity are also well studied (Fig. 11).

5.4. Important patents related to *B. aristata*

Patent analysis reveals that most of the filings relate to herbal compositions which contain *B. aristata* extract along with other botanical extracts to form the crude drug. These formulations are used to treat metabolic and cardiovascular disorders.

Further *B. aristata* extract also finds applications as a cosmetic ingredient when used in combination with other herbal extracts particularly to prevent skin pigmentation and also enhance skin whitening (JP2010195731), similarly it is also used in anti-ageing herb mixture (DE102007040798) and (JP2003095856).

The analysis also reveals that some of the assignees have evaluated the use of *B. aristata* plant extract alone to be effective in the treatment of osteoporosis and other bone disorders by inhibiting bone resorption and stimulating bone formation (WO2008007215).

The extract when administered orally in a daily dosage of 0.1–2000 (preferably 10–1000) mg or parenterally in a dosage of 10–500 mg acts as a cell adhesion inhibitor to inhibit cancer metastasis and to treat or prevent allergies, inflammation, rheumatoid arthritis and/or chronic arthritis (JP10158184). The use of berberine containing formulation as an anti-cancer agent is described in patent (KR20090032617).

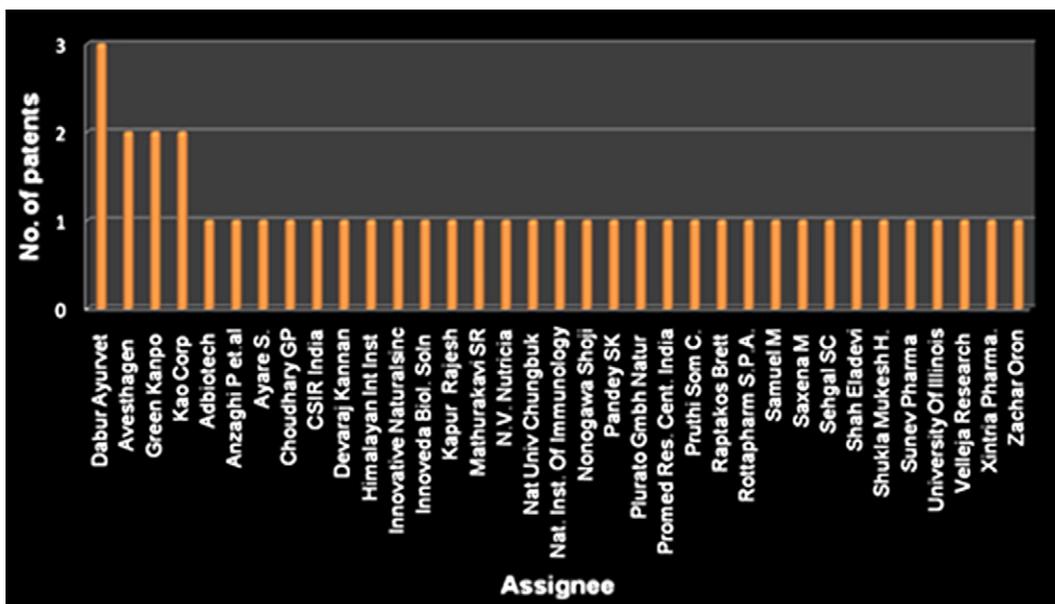


Fig. 10. Graphical representation for assignee analysis.

The bioactive berberine is useful as an immunosuppressive to control graft versus host reaction, to protect immunocompromised and non-immunocompromised individuals against septic shock, to inhibit the response of T-cell lymphocytes against allogenic or antigenic stimulus, to inhibit or block T cell activation and to suppress TNF-induced effects on the target cells (US5856487).

B. aristata and its formulation are described as anti-HIV agent in patents (WO2010029562), (IN240422), (WO2005030232) and (IN9600325). A method for the treatment of the signs and symptoms of HIV/AIDS by removal of HTV antigen glycoproteins is discussed in (WO2010029562).

B. aristata extract shows low toxicity and hence can be further evaluated for its efficacy in pharmaceutical and

cosmeceutical compositions either alone or used in combination with other herbal extracts.

6. Other *Berberis* species of pharmacological importance

Studies on different *Berberis* species from Berberidaceae family, show the importance of the plants in this family and their effective pharmacological applications. Many of them are used as herbal medicine for a long time.

Table 2 describes the plants from important *Berberis* species other than *B. aristata*. It is observed that, the plants like *Berberis lyceum*, *Berberis vulgaris*, *B. asiatica*, *Berberis koreana*, *Berberis croatica* are found to have more explored for their pharmacological importance. The plants show anti-

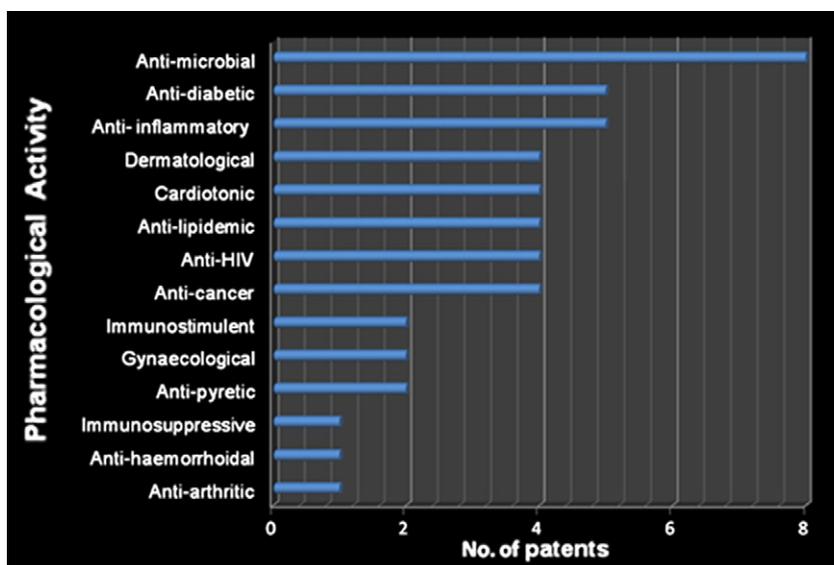


Fig. 11. Technology analysis for *Berberis aristata*.

Table 2
Important *Berberis* species and their pharmacological properties.

Plant name	Pharmacological properties/use
<i>Berberis lyceum</i>	Effective for treatment of piles [8], pesticidal [79], effective in reducing serum total cholesterol, triglyceride and LDL and increasing HDL [80], wound healing activity [81], anti-diabetic [8,82], anti-cancer [83], anti-microbial [84], immunomodulatory and hepatoprotective [85]
<i>Berberis vulgaris</i>	Anti-histaminic and anti-cholergenic [86], anti-inflammatory [87], anti-bacterial [88], vasodilatory and anti-hypertensive [89,91,94], useful in Neuronal disorders and cardiovascular activity [90,94,97], useful in hepatocarcinogenesis [92,93], anti-arrhythmic and anti-cancer [94], anti-babesial [95], anti-oxidant [96,98,99], anti-microbial and positive effects on blood rectification and also on gastrointestinal, endocrine, immune system and central nervous system [97], cytoprotective [98], anti-urolithic [100], anti-diabetic [101], anti-coagulant [102], anti-colic [103]
<i>Berberis asiatica</i>	anti-microbial [8], useful for affection of eyes, skin disease, jaundice, and rheumatism [104], anti-oxidant [105]
<i>Berberis aetnensis</i>	Anti-microbial [106,107], anti-fungal [108]
<i>Berberis koreana</i>	Anti-inflammatory [109,113], Anti-oxidant [110], anti-cancer [110–112,114]
<i>Berberis croatica</i> Horvat	Free-radical scavenging capacity and anti-oxidant [115], anti-microbial [116]
<i>Berberis thunbergii</i>	Anti-bacterial [117], anti-microbial [118]
<i>Berberis buxifolia</i>	Anti-microbial [119], anti-oxidant [120]
<i>Berberis mucrofolia</i>	Bark decoction is used in lymph disorder and swelling [12]
<i>Berberis chilensis</i>	Hypotensive [121]
<i>Berberis valdiviana</i>	Anti-plasmodial and cytotoxic [122]
<i>Berberis crataegina</i>	Anti-inflammatory, analgesic and febrifuge effects [123]
<i>Berberis heterophylla</i>	Anti-microbial [124]
<i>Berberis integerrima</i>	Hepatoprotective [125]
<i>Berberis cretica</i>	Anti-malarial [126]
<i>Berberis pachycantha</i> Koehne	Anti-hepatotoxic [127]
<i>Berberis hispanica</i>	Anti-cancer, effective when tested with cervical cancer cells [128]
<i>Berberis microphylla</i>	Anti-oxidant [129]
<i>Berberis holstii</i>	Effective infusion for coughs, malaria, stomach-ache, sexually transmitted infections and pneumonia [130]
<i>Berberis darwinii</i>	Alzheimer's disease therapy [131]

cancer, anti-diabetic, anti-microbial, anti-oxidant, hepatoprotective, cardiogenic and many more pharmacological important activities. Research and studies on *Berberis* species will provide a new hope for different treatments in today's medical field.

7. Conclusion

As per the review presented herein – *B. aristata* is a traditional medicinal plant used in *Ayurvedic*, *Chinese* and other medicinal systems in the world for a long time. Every part of this plant and its principal active constituents like berberine has gained importance for its different pharmaceutical activities. The most important pharmaceutical properties of this

plant include anti-diabetic, anti-microbial, anti-cancer, anti-lipidemic, anti-HIV, anti-pyretic, anti-inflammatory, anti-PAF, anti-diarrheal, gynaecological, hepatoprotective, ophthalmic, dermatological and cardiogenic activity. The plant extract also finds applications in skin care cosmetic compositions. Current research and studies on this plant and its active constituents are providing newer insight for leading medicines and cosmetics for future development.

The review as presented herein including both scientific and patent art will drive the research strategy and support innovation management. Such an analysis will also help in identifying the research gaps for generating intellectual property. Integrating activities for IP search and analysis in technology strategy formulation leads to higher probability of success in the newer technology ventures. Thus the data and studies presented in this review will help in new product planning, R&D investment evaluation and R&D productivity measurements.

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