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Research Article

COMPARATIVE EVALUATION OF *BARBERIS ARISTATA* EXTRACT AS SYSTEMIC ADMINISTRATION AND LOCAL APPLICATION IN MANAGEMENT OF CHRONIC PHARYNGITIS

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ABSTRACT

Pharynx is a cross road between respiratory tract and alimentary canal and is a frequent site of inflammatory pathologies. Chronic pharyngitis is not a life threatening disorder but surely an incapacitating malady by virtue of its recalcitrant behaviour, frequent antibiotic consumption and compromised social output and quality of life and hence can not be nominated as innocuous disease by any stretch of imagination per se. *Berberis aristata* DC. (Family - Berberidaceae) or *Daru Haridra* in *Ayurveda* is historically and time tested drug used primarily in inflammatory disorders. The usage of *Berberis aristata* is well documented in non healing wounds, infective disorders of the eye, hepatobiliary stimulation, chronic inflammatory mucosal disorders and skin diseases. Berberine which is chief phytochemical active constituent of *Barberis aristata* as has got proven action as an anti inflammatory, anti hyperplastic, immunomodulation, enhancement of delayed T cell mediated activity, anti oxidant, anti pyretic, analgesic and cytoprotective actions. Present randomized, single blind, prospective, unicenteral experimental clinical trial intends to compare to effectiveness of *Barberis aristata* extract as systemic administration and local application (oral rinse) by ramifying clinically diagnosed 120 chronic pharyngitis patients into two trial groups. Paired 't' test was used to evaluate the individual effectiveness of the trial drugs and also to compare the outcome of the two trial drugs administration as an inter group comparison. Statistical analysis conspicuously reflected the superior outcome in favour of systemic usage of *Barberis aristata* extract than that of oral rinse and the difference may be attributed to the fact that constant salivation had restricted the contact time of the drug on inflamed mucosa to a few minutes only and flushing is the end result of the locally applied drug invariably, but this incapacitation is bypassed by making the drug systemically available. No unwarranted, unpredictable and toxic action was observed in any stage of the clinical study and the usage of Barberis aristata extract may be a potentially adjuvant in the management of chronic pharyngitis with least side effects.

Key words: Pharyngitis, *Barberis aristata*, Berberine, Ayurveda, Immunomodulation.

INTRODUCTION

There are enumerable ailments but only few of them are most common in world population affecting the health scenario worldwide. The disease 'Pharyngitis' is certainly one of these ailments and may be regarded as a frequent disease of upper respiratory tract. In recent years, there has been a significant change in life style, dietary patterns with growing affluence, rapid industrialization, socioeconomic development and increase in life expectancy. These factors have probably subtly influenced the increased prevalence of the disease pharyngitis. Pharynx is a cross road between respiratory and alimentary routes, so this region is highly prone for the infection as the pathogens get their way from both nasal and oral routes. Chronic Pharyngitis remains the common cause of morbidity, social embarrassment and impaired performance for the patients. Chronic Pharyngitis has high tendency to reoccur, the reoccurrence of the disease also leads to sense of frustration and decline of spirits both to the patients and clinician. Still no significant treatment regime is available which can effectively combat this malady. The myriad nature of organisms involved in the disease often complicates the picture. The long duration treatment of antibiotic in the chronic pharyngitis often discourage the patients and his involved family members, apart from that limited surgical role is observed in treatment of this disease. Patient often feels himself ill which frequently is out of the proportion of the disease. The disease profile certainly attracts the physician but the outcome seems to be enigmatic. A meticulous approach is the need of the time for the prudent approach of this particular disease.

Herbal medicines are now in great demand in the developing world for primary healthcare not because they are inexpensive but also for better cultural acceptability, better compatibility with the human body and minimal side effects. Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries for primary healthcare. However among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity, and about 15% have been investigated phytochemically.

Present clinical study was formulated to evaluate the nature of the disease, course of the disease and management with the help of some a time tested and clinically established drug with antimicrobial, anti-inflammatory and immunomodulator properties which hence drives for the selection of *Barberis aristata* as a trial drug for the present study. The prime objective was to compare the effectiveness of Barberis aristata in two different forms of administration i.e. systemic and local. *Barberis aristata* extract has been explored in various clinical studies for inflammatory mucosal pathologies

but a comparison between its local and systemic effect on mucosal diseases is still scarcely available in the medical science literature. The extract of *Barberis aristata* extract was condensed in the form of tablet for the oral/systemic administration and the aqueous extract preparation was formulated in the form of oral rinse/gargle to be used as local application.

Ethnobotanical traits

The plant is native of the whole range of Himalaya mountains at an elevation 2000 to 3500 metres. It also abundantly cultivated in Nilagiri range in Southern India. The shrub grows upto 1.5 – 2.0 metres in height with a thick woody root covered with a thin brittle bark. The leaves are cylindrical, straight, tapering, very sharp, hard having smooth spines. The flowers are numerous, stalked, arranged in drooping racemes and yellow in colour. The fruit is a small berry shape, ovoid and smooth [1].

Berberis aristata DC. (Family - Berberidaceae) is one of the herbs mentioned in all ancient texts of Ayurveda. Charaka (father of medicine in Indian system of medicine) and Sushruta (father of surgery in Indian system of medicine) have documented its different properties along with various uses for the treatment of numerous ailments. As it resembles in its properties to those of *Haridra* or Haldi in Hindi (*curcuma longa*), both the herbs have been mentioned together as *haridra dvaya*, meaning two types of *haridras* viz. *haridra* and *daruharidra*. Charaka has categorized *daruharidra* as *stanyasodhana* (detoxification of mother milk), *lekhana* (a reducing agent), *arsoghna* (anti – haemorrhoidal property), *kandughna* (anti pruritis traits), *sveda janya* (sudation property) and *Rasayana* (rejuvenative and detoxification). *Sushruta* have mentioned it as a wonderful ropana medicine (wound healer medicine)**.**

Phytochemistry of *Barberis aristata*

The chemical analyses of the roots of *B. aristata* showed the presence of alkaloids, amino acids, flavonoids, phenol, proteins, sterols/terpenes, reducing sugars, non-reducing sugars, resins, saponins and tannins. The plant contains berberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxyacanthine and taxilamine. Berberis aristata contains protoberberine and bis isoquinoline type of alkaloid. Four alkaloids, pakistanine, 1-O methyl pakistanine, pseudopalmatine chloride and pseudoberberine chloride were also isolated from Berberis aristata. The major alkaloid found in Berberis aristata is Berberine having yield of 2.23% followed by palamatine. Variation of Berberine content in root and stem of Berberis aristata with altitude has been documented. It was found that plants growing at lower altitude have more Berberine content. Berberine content in plant is also influenced by potassium and moisture content of soil [2,3]. Solubility in water and alcohol were found to be 81.90% in water and 84.52% in 50% in alcohol. Loss on drying was found to be 5.32%. Total phenol and flavonoid content were found to be 0.11% and 2.8% respectively[4].

MATERIALS AND METHODS

The present work is randomised, interventional, prospective and single centre study comprising chronic pharyngitis patients of either sex in the age group of 12-70 years. The patients for the research were selected from Department of *Shalakya Tantra* OPD, M.S.M. Institute of *Ayurveda*, B.P.S. *Mahila Vishwavidyalaya, Khanpur Kalan*, Haryana. Established and diagnosed patients satisfying inclusion/exclusion and criteria of assessment were selected after having written and informed consent from the patient to participate in the study on a recorded and standardized proforma. The patient was also briefed about the research protocol, duration of trial and possible negative outcome prior to the consent. An official permission from institution's research ethical committee and hospital core committee was also taken before the commencement of the trial vide letter no. MSM/EC/SKT/ 2012-18.

Statistical analysis

The data was analysed for statistical significance by using statistical package for social sciences (SPSS Inc. Chicago, USA, 17.0). The student's' test (paired) were used to analyze the data for in pre/post protocol. For all analysis the 'p' value used for statistical significance was 0.05.

Aims and objectives

- To compare the effectiveness of herbal drug *Barberis aristata* extract as an oral drug (systemic administration) and local application (oral rinse/gargle).
- To evaluate the overall effectiveness of *Barberis aristata* extract in combating the signs and symptoms of Chronic Pharyngitis.
- To document the hazardous/unwanted effect of the trial drug if any.

Selection of the patients

Inclusion criterion:

- Clinically diagnosed patients of Chronic Pharyngitis.
- Patients of age group 12-70 years.
- Patients having various clinical features depicted in criteria of assessment later.

Exclusion criterion:

- Patients exhibiting clinical features of pharyngitis with clinical complications viz. quinsy (peritonsillar abscess), parapharyngeal/ retropharyngeal abscess etc.
- Patient having concomitant malignant growth of oral cavity and pharynx.
- Patients having established features of chronic rhinosinusitis as an etiological factor of chronic pharyngitis.

Criteria of assessment with Grading and scoring system

As consensus is lacking in otolaryngological ambit regarding a globally acceptable grading and scoring system of pharyngitis, Visual analogue scale (VAS) was used for the grading and scoring of clinical features in the present study [Table 1].

Study design and preamble of drug protocol

Diagnosed patients of Pratishyaya i.e. rhinosinusitis, satisfying the inclusion criteria were randomly by table method were divided into following two trial groups. A total of 146 patients were enrolled in the present trial of which 16 patients were dropout/lost in follow up and 10 patients were consciously randomly not included to meet the commitments of the synopsis, made earlier. A total of 120 patients were thus subjected in this trial after ramifying them into two trial groups elaborated as under (Table 2).

Preparation of Aqueous extracts and solidified extract in tablet form

Fresh roots of *B. aristata* duly certified and authenticated from the Pharmacology department were procured and thoroughly washed in sterile double distilled water (DDW), surface sterilized in 70% ethanol (v/v) and then again washed three times in sterile DDW. The sterilized material were meshed and ground with a sterile pestle and mortar in sterile distilled water. The homogenized tissue was centrifuged at

7,000 rpm for 15 minutes; supernatant was filter-sterilized and used as oral rinse as a trail drug [3]. The liquid extract was heated on a medium intensity temperature and solidified with binding agent which was acacia gum for the present trial. The solidified *B. aristata* extract was formulated to 500 mg tablets to be used as a systemic administration drug for the study. Both the forms of *Barberis aristata* extract was prepared by the well stocked institute pharmacy segment itself.

Table 1: Criteria of assessment with Grading and scoring system:

Clinical feature	0	1	2	3	4	5
Irritation of Throat	No	Mild	Moderate/bothersome	Moderately Severe	Severe	Very Severe
Odynophagia	No	Mild	Moderate/bothersome	Moderately Severe	Severe	Very Severe
Fever	No	Mild	Moderate	Moderately Severe	Severe	Very Severe
Halitosis	No	Mild	Moderate/bothersome	Moderately Severe	Severe	Very Severe
Otalgia	No	Mild	Moderate/bothersome	Moderately Severe	Severe	Very Severe
Congested Pharyngeal Wall	No	Mild	Moderate	Moderately Severe	Severe	Very Severe
Lymphoid Granules	No	Mild	Moderate	Moderately Severe	Severe	Very Severe
Mucosal Oedema	No	Mild	Moderate	Moderately Severe	Severe	Very Severe
Hypertrophy of pharyngeal wall	No	Mild	Moderate	Moderately Severe	Severe	Very Severe
Cervical Lymphadenopathy	No	Mild	Moderate	Moderately Severe	Severe	Very Severe

Table 2: Study design and preamble of drug protocol

Trial group	Drug	Mode of administration	Total no. of patients	Dosage	Duration Of trial	Follow up
I	*Barberis aristata* extract	Oral rinse/gargle	60	40 ml, thrice daily for 5 minutes each	14 days	3 weeks
II	*Barberis aristata* extract	Oral/systemic	60	2 tablet of 500 mg each, thrice daily	14 days	3 weeks

Table 3: *Barberis aristata* extract as an oral rinse

Sign and Symptoms	n	Mean		X(d)	%age of relief	SD±	SE±	t value	P value
		BT	AT	BT-AT					
Irritation of Throat	10	2.80	0.30	2.50	89.28	0.52	0.16	15.00	p<0.001
Odynophagia	10	1.80	0.20	1.60	88.88	0.69	0.22	7.23	P<0.001
Fever	5	1.80	0.20	1.20	85.70	1.20	0.45	6.00	P<0.05
Halitosis	9	1.80	0.50	1.30	72.22	0.50	0.17	8.00	P<0.001
Otalgia	4	2.00	0.50	1.50	75.00	0.58	0.29	5.19	P<0.05
Congested Pharyngeal Wall	10	2.90	0.80	2.10	72.41	0.58	0.18	11.69	P<0.001
Lymphoid Granules	10	1.80	1.20	0.60	33.33	0.52	0.16	3.60	P<0.05
Mucosal Oedema	8	1.80	0.50	1.30	72.22	0.52	0.18	7.51	P<0.001
Hypertrophy of pharyngeal wall	9	2.00	1.40	0.60	30.00	0.53	0.18	3.16	P<0.05
Cervical Lymphadenopathy	10	1.50	0.70	0.80	53.33	0.42	0.13	6.00	P<0.001

Table 4: *Barberis aristata* extract as systemic administration

Sign and Symptoms	n	Mean		X (d)	%age of relief	SD±	SE±	t value	p value
		BT	AT	BT-AT					
Irritation of Throat	10	2.90	0.00	2.90	100.00	0.32	0.10	29.00	p<0.001
Odynophagia	9	1.60	0.20	1.40	87.50	0.88	0.29	5.29	p<0.001
Fever	4	1.20	0.00	1.20	100	0.50	0.25	5.00	p<0.05
Halitosis	10	1.60	0.40	1.20	75.00	0.42	0.13	9.00	p<0.001
Otalgia	5	1.20	0.00	1.20	100.00	0.45	0.20	6.00	p<0.05
congested Pharyngeal Wall	10	2.90	0.60	2.30	79.31	0.82	0.26	8.83	p<0.001
Lymphoid Granules	9	2.10	1.30	0.80	38.09	0.44	0.14	5.29	p<0.001
Mucosal Oedema	10	2.20	0.40	1.80	81.81	0.78	0.24	7.21	p<0.001
Hypertrophy of pharyngeal wall	10	2.00	1.30	0.70	35	0.48	0.15	4.58	p<0.001
Cervical Lymphadenopathy	10	2.30	0.50	1.80	78.26	0.42	0.13	3.50	p<0.001

Table 5: Inter group comparison of effectiveness of *Barberis aristata* as systemic usage and oral rinse

Sign and Symptoms	Trail group I Mean score		Trail group II Mean score		% relief difference	S.E.	t value	p value
	B.T.	A.T.	B.T.	A.T.				
Irritation of Throat	2.80	0.30	2.70	0.20	10.72	0.19	2.05	> 0.05
Odynophagia	1.80	0.20	1.70	0.30	1.38	0.38	0.53	> 0.05
Fever	1.80	0.20	1.50	0.00	14.29	0.24	0.40	> 0.05
Halitosis	1.80	0.50	1.50	0.50	2.78	0.26	0.00	> 0.05
Otalgia	2.00	0.50	1.00	0.00	25	0.34	0.00	> 0.05
Congested Pharyngeal Wall	2.90	0.80	2.80	0.60	6.9	0.31	0.31	> 0.05
Lymphoid Granules	1.80	1.20	1.70	1.10	4.76	0.22	0.44	> 0.05
Mucosal Oedema	1.80	0.50	2.10	0.50	9.59	0.34	2.04	> 0.05
Hypertrophy of pharyngeal wall	2.00	1.40	1.90	1.40	5	0.22	0.88	> 0.05
Cervical Lymphadenopathy	1.50	0.70	1.40	0.50	24.93	0.18	5.30	<0.05

OBSERVATIONS AND RESULTS

Barberis aristata extract, both as oral rinse and systemic administration were evaluated as an individual treatment (Table 3 and Table 4) by Student 't' test (paired). Inter group comparison which was the prime objective of the study was also performed on different preconceived criterion of assessment (Table 5).

DISCUSSION

Anti inflammatory action of *Berberis aristata*

Inflammation of the posterior pharyngeal wall, posterior pharyngeal wall lymphatic tissue and the interstitial tissue of the pharyngeal wall is found to be a hallmark of chronic pharyngitis. The concept of superantigen, intercellular bacteria and emergence of resistant strains of the bacteria are procuring centre stage now a day and making the chronic pharyngitis as sinister and indolent pathology. Berberis aristata has got a significant anti inflammatory properties which is substantiated by various randomized controlled clinical trials. *Barberis aristata* has got also proven role in combating various mediators of inflammation such as tumor necrosis factor (TNF) and other cytokines. The roots of *B. aristata* contain significant amounts of the isoquinoline alkaloid berberine having well known for their anti inflammatory activity [3]. The aqueous extract of the roots of *B. aristata* (500–1000 mg/kg) was found to have a significant anti-inflammatory effect in rats with drug induced paw edema; the effect was comparable to that of 10 mg diclofenac sodium. The alkaloid berberine from *B. aristata* has anti-inflammatory effects and has been found to be useful in cases of trachoma. Berberine has also been found to be effective in experimental herpetic uveitis too. Berberine was also shown to abolish acetaldehyde-induced NF-B activity and cytokine production in HepG2 cells in a dose-dependent manner. The reduced severity of inflammatory changes observed in histopathological examination and clinical manifestations in the inflamed eye was the result of significant inhibition of vascular and cellular inflammatory responses. The release of chemical mediators of inflammation is also suppressed secondary to inhibition of the cellular response. The suppression of vascular and cellular inflammatory responses by berberine was evidenced by significantly low levels of inflammatory cells, proteins, and TNF levels [5].

Berberine, the protoberberine alkaloid widely distributed in the plant kingdom, was capable of suppressing inflammatory agents-induced cytokine production in lung cells. Inhibition of cytokine production by berberine was dose-dependent and cell type-independent. Moreover, the suppression of berberine on the cytokine production resulted from the inhibition of inhibitory κB-α phosphorylation and degradation [6]. Procollagen expression in human dermal fibroblasts regulated by berberine is observed in clinical trial which also justify the use of baberis aristata historically in aging skin, non healing wounds, local application in apthous ulcers, skin ulceration and acne vulgaris. UV induced skin inflammation is potently inhibited by Barberine significantly [7]. The methanolic extract of *Barberis aristata* is also found to be effective in inhibitors of leukotriene biosynthesis which in an inseparable event of a inflammatory process [8].

Antimicrobial properties

Apart from having a potent anti inflammatory property berberine which essential is the most important chemical constituent of *Barberis aristata* do possesses a significant antibacterial trait sprawling amongst verity of bacteria including gram positive, gram negative and anaerobes also [9,10,11]. Even anti fugal and activity against yeast has also been documented which conspicuously reflect the effectiveness of *Berberis aristata* in the management of chronic pharyngitis as pharyngitis specially of childhood/adolescent age which has got bacterial element (> 30%) much higher than that of adult subjects (about 15%). Bacterial pharyngitis is also different from the viral pharyngitis in a sense that virus involved in pharyngitis are found to be epitheliotropic (mucosal/superficial) rather than deep mucosal and interstitial one which prominently is a distinct feature of bacterial pharyngitis. This very observation can also justify the superior effectiveness of systemic usage of *Berberis aristata* than the oral rinse or local application. Apart from that the constant salivation restrict the contact time of the drug on inflamed mucosa to a few minutes only and flushing is the end result of the locally applied drug invariably but this incapacitation is bypassed by making the drug systemically available. Unintentional swallowing also comprehensively reduces the contact time of the trail drug with the diseased mucosal surface viz. chronic pharyngitis.

Anti hyperplastic action

Hypertrophy of the posterior pharyngeal bands, altered interstitial cell cytological features and excessive fibrous tissue lay down is also a pathological event that has been associated with chronic pharyngitis because of repeated and multiple pharyngeal inflammatory episodes**.** Berberine significantly attenuated the increases in lipid peroxidation, protein bound carbohydrates and enhanced the anti oxidative status. Berberine prevents the appearance of malignant morphology and ultrastructural changes of drug induced cancer by producing apoptosis like changes. Thus berberine inhibits hyperplastic transformation by the induction of antioxidant defence system and ability to induce apoptotic like changes and hence elucidating its anti hypertrophy role [12,13].

Vitro treatment of androgen-insensitive (DU145 and PC-3) and androgen-sensitive (LNCaP) prostate cancer cells with berberine inhibited cell proliferation and induced cell death in a dose-dependent (10–100 Mmol/L) and time dependent (24–72 hours) manner without affecting the growth of normal epithelial cells. Treatment of non neoplastic human prostate epithelial cells (PWR-1E) with berberine under identical conditions did not significantly affect their viability either [14].

Immunomodulatory activity

Posterior pharyngeal wall has got organized immunologically active MALT (mucosa associated lymphatic tissue) but unfortunately the tissue itself got infected in a pharyngitis episode and a drug which possess immunomodulation property invariably will have a favourable outcome in combating the pathophysiogical appearance of the disease. Berberine specifically augments cell-mediated immune response as observed in the leukocyte migration inhibition (LMI) tests. Berberine strongly inhibited in vitro the proliferative response of mouse spleen cells and exhibited a immunosuppressive property. Berbamine, an ingredient of Berberis, which itself is widely utilized in Chinese folk medicine has been used as a source of leukogenics, anti-arrhythmics and anti-hypertensives. In recent years the immunosuppressive effects of berbamine has been demonstrated. In order to further investigate the value of berbamine as an immunosuppressive agent, the delayed type hypersensitivity reaction (DTH) response with sheep red blood cells (SRBC), the mixed lymphocyte reaction (MLR)

and a skin model of allograft rejection on mice has been studied. Berbamine showed suppressive effects on DTH and MLR and significantly prolonged allograft survival compared with untreated transplanted mice [2]. *Berberis aristata* could reduce the damage to mitochondrial function, by scavenging free radicals and thereby preventing uncoupling of oxidative phosphorylation, deactivation of enzymes of electron transport chain, generation of lipid peroxides, oxidation of phospholipids ultimately inhibiting the signalling wave propagation to the mitochondria death receptor (membrane bound cytochrome *c*) which generally leads to apoptosis [15]. In a nutshell *Barberis aristata* by virtue of presence of its active phytochemical constituents can potentially introduce its anti inflammatory, antimicrobial, antihyperplastic and focal immuno enhancing properties which can successfully adjuvant the current frustrating management of chronic pharyngitis in a rather toxicity free manner.

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