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An Integrated Approach to Harness the Anti-inflammatory Potential of *Achyranthes aspera* Linn

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Abstract

Plants have been used to overcome pathologic conditions and body ailments since the pre-historic period. A few plants e.g. *Borago officinalis*, *Curcuma longa*, *Rosmarinus officinalis*, *Zingiber officinale*, etc. are frequently used for treating inflammatory disorders, globally. Inflammation is a complex biological response of vascular tissue to different harmful stimuli and results in discomfort to the body. There is not a single medicine to treat all the inflammation at the time. In recent years plant-based medicines are evaluated for efficacy through phytopharmacology, molecular mechanisms, and clinical trials. The therapeutic ingredients of polyherbal formulations generally contain different chemical classes, and their efficacy is based on synergism. *Achyranthes aspera* is an abundantly available herb, globally, has been in use in Ayurveda, Siddha, and Unani system of medicine to cure many ailments like arthritis, asthma, cardiac disease, dermatological diseases, gynecological disorder, kidney stone, leprosy, wound, snakebite, malaria, pneumonia, dysentery, rabies, toothache, etc. The applications of *A. aspera* in pathological investigations have scientifically justified the traditional utilization. Further, phytopharmacological studies have highlighted its synergistic mechanism of action and revealed its vital role in modulating inflammatory reactions for fast recovery with the least side effects, though there are a few investigations.

Keywords

Anti-inflammatory herbs, Traditional uses, Phytopharmacology, *Achyranthes aspera*, Synergistic combination

1. Introduction

Inflammatory diseases are the major cause of morbidity and mortality [1]. Inflammation is a complex response of the vascularized connective tissues to the exogenous and endogenous stimuli as a protective response to injury caused by microorganisms, noxious chemicals, or physical trauma to destroy or inactivate the foreign matter, and its elimination [2]. The process usually subsides on completion of healing but sometimes it turns severe, even if it may be worse than the disease and even maybe fatal [3, 4]. It starts with initiation, chemoattraction of inflammatory cells, and activation to release inflammatory mediators. Increased temperature, pain, redness, swelling, loss of activeness, etc. are the classical sign of inflammation [5]. Different inflammatory mediators such as cytokines, digestive enzymes, eicosanoids (prostaglandins and leukotriene B4, C4, D4, E4), histamine, kinins (bradykinin), narcosis factor, neuropeptides, nitric oxide,

platelet-activating factors, serotonin, tumors, biological metabolites, complement proteins, and adhesion factors play important role in the pathogenesis of inflammation [6]. Different cells like basophils, connective tissue fibroblasts, eosinophils, lymphocytes, mast cells, monocytes, neutrophils, resident macrophages, etc., are involved in the pathogenesis of inflammation [7]. Inflammations based on the severity of cases have been categorized as acute, and chronic [8-10].

Traditional herbal medicines have derived from the rich scientific heritage of different traditional healing practices. The utilization and pattern of application are different for different diseases [11]. Further, these medicinal herbs are in use with a successful history of thousands of years [12, 13].

Currently, the market of herbal drugs to treat inflammatory diseases constitutes 83%, globally. It is expected to be more than 95% in the forthcoming years as the increased acceptability of these preparations [14-17]. Generally, herbs are used to promote health and restore the body's ability to regulate the various functions such as self-healing, and protection, but safety is always a matter of concern. Drew and Myers (1997) have reported that about 40% of the anticancer drugs of plant origin have successfully treated cancer, but they still have serious side effects [18].

The social priority to use herbal medicine is because of the cultural acceptability, lesser side effects, and better compatibility with the human body [11]. Different chemical classes of herbal origin such as alkaloids, and rographolide, coumarin, flavonoids, xanthone, sterols, terpenoids, withaferin-A, etc., have been proved effective to treat the inflammations [1, 19]. Anti-inflammatory drugs of synthetic origin are classified as steroidal and nonsteroidal types, which have severe adverse effects on patients with other body ailments [20]. Currently, both doctors and patients are looking for herbal remedies to treat inflammation and low immunity problems. A study on different folklores and traditional practices for better and safe treatment, even in combination, using *A. aspera* is to be availed.

2. Material and Methods

The computerized database search engines, such as PubMed, ScienceDirect, Google Scholar, and MeSH were used to search the research publications on 'anti-inflammatory herbals'. The keywords for searching the scientific publications in these databases were 'anti-inflammatory herbs', 'herbals', 'folklore', 'traditional healing practices', and 'polyherbal formulation'. Search hits that appeared were further segregated using key terms like 'traditional applications', 'market demand', and 'OTC product'. All the retrieved references were further manually scanned to ensure a full research article. The relevant articles were short-listed, and key findings were retrieved, analysed, and systematically compiled in the form of a current review article.

3. Results and Discussion

The literature search on anti-inflammatory traditional medicinal plants has revealed the scientific heritage of different healing systems, and the usage of different plant species to overcome different inflammations. Further, it has been revealed that the current market of herbal drugs to treat inflammatory diseases is expected to increase by 12% in forthcoming years [14-17]. The use of different plants to treat inflammation, promote health, and restore the body's ability has been recorded (Table 1). More recently, a trend to investigate anti-inflammatory herb for analgesic properties, isolation of active ingredient, dose determination, toxic properties, etc. have been in practice for safe uses [11]. Molecular investigations have deciphered that different class of phytochemicals have a role in treating different types of inflammation [1].

3.1 *Achyranthes aspera* Linn

Achyranthes aspera Linn. (Apamarg), fam. Amaranthaceae has been used for its medicinal properties in Allopathic, Ayurvedic, Homeopathic, Siddha, Unani-Tibbi, Naturopathy, and many more folklore remedies [79]. Traditional healers claim that the addition of *A. aspera* would enhance the efficacy of any drug of plant origin [80]. In Ayurvedic toxicology, *A. aspera* plant is used for the treatment of poisoning which destroys it or is eliminated from the body [81]. Traditionally, it is used for the treatment of asthma, diabetes, dysentery, fever, hypertension, and malarial fever. Its root extract has a potent insect hormonal molting activity. The whole plant decoction has diuretic properties, and the aqueous extract is used to treat pneumonia. *A. aspera* dried herb is used to treat colic in children, and dry leaves are used to treat asthma. Different extracts of leaves have been reported for antiperoxidative, hypoglycemic, and thyroid-stimulating properties. In ancient Indian literature, it is claimed as a significant abortifacient. *A. aspera* is a primary constituent of an herbal formulation namely, Naayuruvi Kuzhi Thailum, a formulation of Siddha system of medicine. It is quite effective in the management of asthma. In different folklore, the inflorescence, fruits, seeds, and roots of *A. aspera* are used to treat hydrophobia [82]. In the present article, we want to generate innovative ideas based on the pool of evidence to develop an anti-inflammatory modern herbal medicine using the *A. aspera*.

3.2 Phyto-constituents

A. aspera has alkaloids (betaine, achyranthine), amino acids, flavonoids, phenolics saponins, steroids, and triterpeno-

ids, the different chemical classes known for anti-inflammatory properties [83, 84]. Achyranthine is a water-soluble alkaloid isolated from *A. aspera*. It decreases the blood pressure and heart rate, dilated blood vessels, and increased the rate and amplitude of respiration in dogs and frogs [85]. The traditional claims of anti-inflammatory potential of *A. aspera*, current knowledge of its chemical composition, and standardization of therapeutic parameters have an array for new modern green medicine.

Table 1. Traditional anti-inflammatory herbs and properties

S. No.	Description of plant	Traditional uses	Phyto-pharmacology	
			Active ingredients	Pharmacological properties
1.	*Borago officinalis* L. (Borage) Family.: Boraginaceae	Seeds oil is a dietary supplement [21-23], used to treat arthritis, autoimmune disorders eczema, diabetes, multiple sclerosis, heart diseases, and cancer [24, 25]	Seeds have 28% γ-linolenic acid (GLA), and it is the highest of all the borage species [26]	GLA is a potent food supplement [24, 26], do not have any side effects. It is prescribed as an anti-inflammatory drug, but its seeds have a miscarriage risk during pregnancy [27]
2.	*Curcuma longa* L. (Turmeric) Family: Zingiberaceae	Its rhizome is used to treat rheumatoid arthritis (RA) [28]	Curcuminoids [29]	The rhizome is used to treat irritable bowel syndrome (IBS) (Bundy et al., 2004), maintain the amelioration of ulcerative colitis [30], and psoriasis [31].
3.	*Elaeagnus angustifolia* L (Oleaster) Family: Elaeagnaceae	It has analgesic effects. Fruits are used to cure asthma, fever, jaundice, tetanus, and rheumatoid arthritis [32]	Fruits are rich in proteins, sugar, vitamins, and minerals [32]	Aqueous extract of fruits is used to treat oral lichen planus (OLP) lesions [32], and it has anti-inflammatory properties [33, 34].
4	*Harpagophytum procumbens* (Burch.) DC. Ex Meisn (Devil's Claw) Family: Pedaliaceae	Roots are used to reduce swelling, pain, and inflammation [35].	Iridoid glycosides, harpagoside, and harpagide are the main ingredients [35].	To treat degenerative rheumatoid arthritis, osteoarthritis, tendonitis, kidney inflammation, and heart diseases [35-37]. Patients with ulcers, gallstone, and diabetes have been reported gastrointestinal upset, the side effect of *H. procumbens* [38].
5.	*Persea americana* Mill (Avocado) Family: Lauraceae	Fruits have excellent nutritional and medical value, and seed oil is edible [39].	Fats, fibres, proteins, vitamins, and minerals, but low sugar content. [39].	The use of avocado and soybean extracts together has been reported effective to treat mild to moderate vulvar lichen sclerosis (VLS) [20,40].
6.	*Oenothera biennis*L. (Evening Primrose) Family: Onagraceae	Seeds oil is used to cure rheumatic and arthritic problems, atopic dermatitis, psoriasis, premenstrual, and menopausal syndromes, and diabetic neuropathy [41].	The seed oil has ferulic, γ-linolenic acids, and linear aliphatic alcohols [41].	The seed oil has protective roles against pro-inflammatory agents [41], because of these reasons, it has more varied applications as an anti-inflammatory agent than the Borage oil [41.
7.	*Olea europaea* L. (Olive) Family: Oleaceae	Its oil is known as extra virgin olive oil (EVOO) [42. It is a main source of fat in the Mediterranean diet.	Mono-unsaturated fatty acids, moderate amount of saturated and poly-unsaturated fatty acids, traces of phenols, sitosterol, triterpenes, and pigments [43]	The oil is used to modulate postprandial plasma lipopolysaccharide, proinflammatory cytokines, TXB2 and LTB4, and reduce the risk of coronary heart disease and metabolic syndrome in patients [42, 43]. Its oral use accelerates the wound healing process even in second-degree and more burn wound patients [44].
8.	*Ribes nigrum* L. (Black Currant) Family: Grossulariaceae	Fruits and leaves are used in the Eurasian traditional medicine to treat a variety of body ailments and are popularly used to prepare 'cassis liqueur', a traditional alcoholic beverage in France [45]	The seed oil has omega-6-PUFA, γ-linoleic, and α-linoleic acids [45].	Oil is used to treat morning stiffness and reduce pro-inflammatory mediators [46]. Exocarp extract reduces heat shock proteins [47].
9.	*Rosa canina* L. (Dog Rose) Family: Rosaceae	Used to treat dog bites [48] asthma, bronchitis, cough, flu, gallbladder diseases, burns, vitamin C deficiency, colic, and lower urinary tract disorders [49-51]	Fruits have flavonoids [52, 53], GOPO,PUFAs, linoleic, and α-linolenic acids [54-56]	It has diuretic, anti-arthritis, and anti-rheumatic properties. Its other uses are to treat diarrhea, diabetes, and inadequate peripheral circulation [49-51, 57, 58].

10.	*Rosmarinus officinalis* L. (Rosemary) Family:Lamiaceae	Rosemary, a sacred plant symbolizes love and death. It is used in weddings and funerals as a symbol of enduring love and eternal bond by Greeks and Romans. Arabians believe that it maintains brain health and memory [59].	Volatile, and phenolic fractions are responsible for therapeutic properties [60].	Essential oil of rosemary is usedto treat inflammation [59], and gastric ulcers, and is considered better than Omeprazole [60].
11.	*Salvia officinalis*L. (Sage) Family: Lamiaceae	Its tea is used to treat digestive and circulation disturbances, asthma, angina, bronchitis, cough, excessive sweating, mouth and throat inflammations, depression, skin diseases, etc. [61, 62]	Carnosol, carnosic acid [63], and essential oil [64].	The plant is reported for anti-cancer, and anti-inflammatory properties [63, 65], but its essential oil does not have any immunomodulatory effects [64].
12.	*Spirulina platensis* (Nordstedt) Geitler (Blue-green algae) Family: Oscillateriaceae	It is used for centuries by humans as a food supplement [66]	Crude protein (5-70 %), vitamins, and minerals [66]	*S.platensis* has analgesic and antiarthritic properties [67]. It helps to control body weight, and no toxic effects have been reported [66].
13.	*Urtica dioica* L. (Stinging Nettle) Family: Urticaceae	Traditionally used as an aphrodisiac, diuretic, and anti-inflammatory herb [68]	Minerals and trace elements [68].	The lipophilic fraction has more anti-inflammatory potential than its traditional application [68].
14.	*Uncaria tomentosa* (Willd. ex Schult.) DC (Cat's Claw) Family: Rubiaceae	Traditionally, it is used to treat asthma, abscesses, fever, urinary tract infections, viral infections, and wounds [69]	Alkaloids, sterols, glycosides, organic acids, and triterpenes [69]	Osteoarthritis of the knee remiss after 4 weeks by inhibiting TNF-α and diminishing PGE2 production [70]
15.	*Vaccinium myrtillus*L. (Bilberry) Family:Ericaceae	*V. myrtillus*leaves were in use to treat diabetes mellitus before the discovery of insulin [71]	Phenolics [71, 72]	Phytopharmacological studies and clinical trials have not been supported the traditional application [71, 72]
16.	*Zingiber officinale*Roscoe (Ginger) Family:Zingiberaceae	The rhizome is used to treat pain, muscular aches, fever, sore throats, indigestion, and vomiting [73, 74]	Phenolics, vitamin C, β-carotene, flavonoids, tannins, and minerals [75].	The therapeutic effects depend on the rhizome quantity consumption [73]. It increases the serum corticosterone level and reduces proinflammatory markers [73,74]. Its extract in osteoarthritis (OA) patients enhances the function of ibuprofen and indomethacin [75-78]

3.3 Anti-inflammatory properties

Bhosale et al. (2012) have studied the anti-inflammatory properties of aqueous extract of *A. aspera*. Two types of extract namely aqueous extracts of *A. aspera* leaves (AEAAL) and aqueous extracts of *A. aspera* whole plant (AEAAW) were studied in albino mice using carrageenan-induced hind paw edema along with the phytochemical analysis and acute toxicity of extracts. Toxicological studies have revealed the toxic dose of AEAA to be more than 2,000 mg/kg. AEAA reduced the carrageenan-induced edema by 35.71-54.76% compared to the untreated control group, whereas Diclofenac sodium (10 mg/kg) has inhibited the edema volume by 42.85%. The results indicated that the AEAA (800 mg/kg body weight) has more significant anti-inflammatory activity when compared with the standard, and untreated control, respectively. Both extracts of *A. aspera* exhibit promising anti-inflammatory activity, which is rich in alkaloids, flavonoids, saponins, and triterpenoids [84].

Further, the alcoholic extract of the roots of *A. aspera* exhibits anti-inflammatory activity in Wistar rats in carrageenan-induced paw edema and cotton pellet granuloma test [80].

3.4 Anti-HSV activity

Mukherjee et al. (2013) have studied the herpessimplexvirus (HSV) with 95% methanolic extract of *A. aspera* roots, and oleanolic acid extracted from *A. aspera*, and reported that both methanolic extract and oleanolic acidinhibit HSV and their plaque formation in a dose-dependent manner [86].

3.5 Anti-HIV activity

HIV can spread in the body via either a cell-free (virus floating free in plasma) mode or a cell in the associated mode (virus particles that remain attached to or within the host cell after replication) involving direct cell-cell contact. *A. aspera* plant extract has been reported as an anti-HIV agent [87] and reported that the methanolic extracts of *A. aspera* and *Rosa centifolia* have anti-HIV activity [88].

3.6 Molecular docking

Dutta et al. (2021) have conducted a molecular docking investigation on the inhibitory efficiency of eight anti-HIV compounds from *A. aspera* extract against severe acute respiratory syndrome coronavirus (SARS-Cov-2). The binding energies and inhibition constant values of these eight compounds (with ACE2 protein of the human body, Mpro, and RdRp proteins of SARS-CoV-2) were compared with the three FDA-approved drugs (Chloroquine, Hydroxychloroquine, and Remdesivir). Most of the compounds were found with good binding energies and inhibition constant values compared to drugs. Further, the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile of these compounds reveals the safety of the human body. The highest inhibitory activity was achieved by oleanolic acid (OA) with binding energy values of -8.9, -7.6, and -7.4 Kcal/mol against ACE2, Mpro, and RdRp, respectively, reveals that OA has the highest binding affinity with the ACE2 receptor. Hence, OA is a potential therapeutic option for drug development to combat SARS-CoV-2, it has been concluded in the study [89].

3.7 Nephroprotective, anti-arthritic, and antioxidant activity

A. aspera whole plant has been reported for nephroprotective activity against lead acetate induced nephrotoxicity [90], and hypolipidemic activity [91]. Roots of the *A. aspera* are antioxidant, spermicidal activity [92]. Leaves of the plant have been reported for antioxidant, anti-fertility, anti-depressant, anti-cancer, and anti-microbial properties [92-95]. The whole aerial parts are reported as hepatoprotective and the seeds of the plant have anti-microbial activity [96].

3.8 Cardiovascular activity

Achyranthine, a water-soluble alkaloid isolated from *A. aspera* decreased blood pressure and heart rate, dilated blood vessels, and increased the rate and amplitude of respiration in dogs and frogs. The contractile effect of achyranthine at 0.5 mg/ml on frog rectus muscles has been reported less than that of the acetylcholine (0.1 mg/ml), and its spasmogenic effect was not blocked by tubocurarine [80].

3.9 Synergistic behavior

Natural products and related structures are sources of new pharmaceuticals, because of the immense variety of functionally relevant secondary metabolites of herbals [97]. Polyherbal therapy has often produced a promising effect in the treatment of diseases over a single herb. Polyherbal ingredients organized into certain formulas have been deciphered to have potential interaction effects such as mutual enhancement, mutual assistance, mutual restraint, and mutual antagonism [98, 99]. In the Ayurvedic and Unani systems of medicine polyherbal formulation is a common practice [100]. Polyherbal formulations are more effective in numerous diseases with safe high doses. Synergism has followed either pharmacodynamics or pharmacokinetics [101]. The capacity of herbs to ease the absorption, distribution, metabolism, and elimination of the other herbs is focused on pharmacokinetic synergism. Pharmacodynamics synergism includes the effect of active constituents with a similar therapeutic activity that is targeted by the diverse mechanism of action.

The combination of herbals may act on multiple targets at the same time with better relief which lacks in a single herbal formulation. These benefits have resulted in the popularity of polyherbal formulations compared to single herbal formulations [102]. In polyherbal formulation different molecules cure a disease by different mechanisms against a disease condition [103] in E-721B, a polyherbal formulation, which has *A. aspera* as an ingredient, is used to treat acute hypersensitivity in asthma patients. The process is supposed due to the synergistic effect of *A. aspera* with other ingredients [104]. *A. aspera* has a weak anti-viral activity [86], but has good antioxidant and anti-inflammatory properties [105]. The richness in ascorbic acid of *A. aspera* confers the antioxidant activity that boosts the immunity against infections like SARS-coronavirus [105, 106], the most desirable properties for alleviating inflammation due to SARS-coronavirus [83, 107], and utilization of *A. aspera* in the management of COVID-19.

4. Conclusions

The plant-based anti-inflammatory modern green medicines are the standardized plant extracts, and the abundant availability of *A. aspera* is an opportunity as an additional therapeutic armamentarium for chronic inflammatory diseases such as arthritis. It is proved to be a multipurpose medicinal agent that paves the way for further attention and research to identify the synergistic combinations that require more studies to refine the use and improvement of the efficacy of this valuable medicinal plant.

As nature always stands for symbiosis, the study of various phytoconstituents and the discovery of useful herbal combinations to produce a synergistically desirable effect is another thirst area of the present article. Although polyherbal formulation has various phytoconstituents and synergistically produces desirable effects may be supported by the *in-vivo* studies and safety evaluations.

Many more investigations have been conducted on *A. aspera* over many years, and current studies with molecular know-how are only a few but do not reveal any adverse reaction as medicine. Future studies to explore possible synergistic and adverse effects of *A. aspera* should be combined with current recommended pharmaceutical therapies and other adjunct treatments.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

GLA = gamma-linolenic acid
IBS = irritable bowel syndrome
OLP= oral lichen planus
EVOO = extra virgin olive oil
GOPO = galactolipid compound
PUFAs = polyunsaturated fats
RA = rheumatoid arthritis
TNF = Tumor necrosis factor
AEAAL = aqueous extracts of *A. aspera* leaves
AEAAW= aqueous extracts of *A. aspera* whole plant
HSV = herpessimplexvirus
HIV = human immunodeficiency virus
COVID-19 = *Coronavirus* disease

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