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ROLE OF ALOE VERA IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

Aloe Vera is one of the oldest medicinal plant and also considered as wonder plant because of its wide range of properties and uses. It is a main ingredient in many herbal medicines and many cosmetic products that are prepared now days. It has been used externally as well as internally in various disease conditions such as wound, burn, skin problems, spleen enlargement, liver diseases, asthma, jaundice, ulcers, constipation, helps in IBD, gastric and duodenal ulcer, and rheumatoid arthritis. Aloe is the dried juice of the leaves of Aloe barbadensis miller. It belongs to Liliaceae family. It contains many chemical constituents Vitamin A, C and E, enzymes such as carboxypeptidase, cellulase, lipase, alkaline phosphatase, brady kinase, anthraquinone, sugars like Acemannan and glucomannan, organic acid like salicylic acid, fatty acids like Cholesterol, campesterol, β-sisosterol and lupeol, Arachidonic acid, γ-linolenic acid. Hormones like auxin and gibberellin and minerals such as Calcium, Chromium, Magnesium and Zinc. These chemical constituents have anti-arthritic, anti-inflammatory, anti-oxidant, immunomodulatory and analgesic activity which confers its use in the management of rheumatoid arthritis. In this review paper role of Aloe Vera is elaborated in the management of rheumatoid arthritis focused on its chemical constituents and mechanism of action.

KEYWORDS-Aloe Vera, Anti-inflammatory, Immunomodulatory, Rheumatoid Arthritis, Herbal medicine.

SIBR (ALOE VERA)

INTRODUCTION [1,2,3,4]

Aloe is the dried juice of the leaves of Aloe barbadensis miller. It belongs to Liliaceae family. Aloe Vera is a perennial herb, with a short stem having 30-50 cm long leaves. Flowers are pendulous imbricated ,25-35 cm in length and bright yellow in colour. It is commonly found in dry places. It is Native of Arabia and Africa.

VERNACULAR NAMES [5,6,7,8]

Arabic-Sibr

Assamese -Musabhar, Machamber

Bengali - Ghritakalmi, Ghrit-Kumari, Musabhar, Kanya

English - India aloe, Small aloe

Gujrat: Eliyo, Eariy, Kunvar, Kumarpathy,

Hindi- Musabhar, Elva, Ghee-kanvar, Kumari, Chhota kanvar

Kannada- Karilola, Lobasara, Satra,

Kashmiri -Musabbar, Sibr, Kathaligida, Komarika

Malayalam -Chenninayakam, Kattavaza Kumari, Kattavala

Marathi- Korphad, Korkand

Oriya- Mushaboro, Kumari

Punjabi-Kalasohaga, Mussubar, Alua, Elva

Sanskrit-Kumarirasasambhava, Sahasara,

Tamil-Kattalai, Sotthukkatal Bhottu-Katrazhae,

Telugu - Musambaramu, Kalabanda

Urdu- Musabbar, Ailva

Unani-Sibr, Gheekwar.

FAMILY[2]

Liliaceae, Agavaceae

BOTANICAL NAME

Aloe barbadensis miller.

TEMPERAMENT[3]

Hot^{2}Dry^2

DOSE[4]

1-4 g

ACTION [7,10,11]

Mushil (Purgative)
Mudirr-i Hayḍ (Emmenagogue)
Moḥallil-i Waram (Anti-inflammatory)
Moharrik-i Kabid (Hepato-stimulant),
Muqawwī-i Medā (Stomachic-tonic),
Qātil-i Dīdān (Anthelmintic),
Mujaffif (Desiccant),
Qābiḍ (Astringent),
Munawwim (Hypnotic),
Mus'hil-i Sawda (Purgative of melancholic humour),
Musqiṭ-i Janīn (Abortifacient)

PARTS USED[5]

Mucilaginous tissue located in leaf parenchyma

Dried leaf juice.

THERAPEUTIC USES[6]

Bawaseer (Haemorrhoids), Inteshare Sha'ar (Hair fall), Kharishe Ain (Catarrhal/purulent ophthalmia), Deedane Ama (Antihelminthic), Dared-e-Ser (Headache), Ehtebase Tams (Amenorrhoea), Izame Tihal (Splenomegaly), Indemale Qurooh (Wound Healing), Iltehabe Meda (Gastritis),Yarqan (Jaundice), Malankholia (Malankholia), Nawaseer (Nasal polyps), Nafsuddam (Haemoptysis), Qabz (constipation), Shiqaqe Miqad (Fissure in Ano), Waja-ul-Mafasil (Arthritis), Warme Kabid (Hepatitis), Zoaf-e-Meda (Gastric weakness).

CHEMICAL CONSTITUENTS [5,6]

There are so many chemical constituents derived from Sibr such as; Acidic galactan, Arabinans, Gluco-galactomannan, Glucomannan, Polyuronide, Cellulose, 7-Hydroxyaloin, Aloe-emodin, Aloesaponarin I&II, Aloin A and B (barbaloin), Anthranol, Beta barbaloin, Chrysophanol glucoside, Isobarbaloin, Capric acid, Hexadecadienoic acid, Palmitoleic acid, Stearic acid, β-Carotene, Choline, Folic acid, Vitamin K, Vitamin D, Vitamin E, Arginine, Glutamic acid which play different role in different diseases. Some of the chemical constituents like Anthraquinone, Anthracene, Cinnamic acid, Anthranilic acid, Vitamins like A, C, E, B1, B2, B6 & B12, Minerals, Sugars like Acemannan, Organic acids like salicylic acids, Hormones like auxins and gibberellins, Fatty acids like Arachidonic acid, γ-linolenic acid possesses anti-inflammatory action, analgesic and anti-oxidant action. Along with these constituents several enzymes like alkaline phosphatase, carboxypeptidases and brady kinases have anti-inflammatory effect.

ANTI-OXIDANT AND ANTI-INFLAMMATORY CHEMICAL CONSTITUENTS [12,13]

ANTHRAQUINONES

The bitter aloes consist of free anthraquinones and their derivatives, Barbaloin, aloe-emodin-9-anthrone, lsobarbaloin, Anthrone-C-glycosides and chromones. It possesses powerful analgesic effects when given in small quantity**.**

VITAMINS

The plant contains many vitamins thiamine, niacin, riboflavin, vitamin B12, choline and folic acid in which Vitamins A, C and E are antioxidants.

ENZYMES

Enzymes found are Amylases, lipases, alkaline phosphatases, cellulases, catalases and peroxidases are biochemical catalyst whereas carboxypeptidases and brady kinases produces anti-inflammatory effect.

MINERAL

Minerals found are Calcium, Chromium, Magnesium and Zinc and few of them act as anti-oxidant.

SUGAR

Mannose-6-phosphate and Acemannan are the sugar found in it, Recently, a glycoprotein with anti-allergic properties, called alprogen and novel anti-inflammatory compound, C-glucosyl chromone, has also been isolated from Aloe Vera gel.

ORGANIC ACID

Organic acids found are Sorbate, Salicylic acid and Uric acid in which Salicylic acid is an aspirin-like compound possessing anti-inflammatory and antibacterial properties

HORMONES

Auxins and gibberellins that help in wound healing and have anti-inflammatory action.

FATTY - ACIDS

Cholesterol, campesterol, β-sisosterol and lupeol. Fatty acids like Arachidonic acid, γ-linolenic acid. All these have anti-inflammatory action and lupeol also possesses antiseptic and analgesic properties.

PHARMACOLOGICAL ACTIVITY [12,14,15]

Burn and wound healing activity.

Moisturising and Anti-aging activity.

Anti-oxidant activity.

Anti-inflammatory activity

Immunomodulatory activity

Anti-Diabetic activity

Anti-mutagenic activity

Anti-bacterial/fungal/ viral activity

Anti-arthritic activity

Laxative effect

Anti-septic activity

Anti-tumor activity

Anti-ulcer activity

Chronotropic activity

SUBSTITUTE

Turbud

PATHOGENESIS OF RA AND MECHANISM OF ACTION OF ALOE [15,16,17,18,19]

- The cytokines IL-1 and TNF play an important role by stimulating the cells of pannus to produce collagenase and other neutral proteases that contributes to local demineralization of bone by activating osteoclasts that accumulate at the site of local bone resorption and Aloe barbadensis mediates its action by decreasing the level of these cytokine -TNF and IL-1 in plasma.
- Prostaglandin E2 produced by fibroblasts and macrophages also contribute to bone demineralization and Aloe Vera reduces the production of prostaglandin E2.
- Macrophages are activated to produce pro-inflammatory cytokine and Aloe barbadensis significantly inhibits the expression of pro-IL-1, Nlrp3, caspase-1 as well as that of the P2X7 receptor via suppressing specific signal transduction pathways.
- The production of large amounts of cyclo-oxygenase and lipo-oxygenase pathway products of arachidonic acid metabolism by cells in the synovial fluid and tissue further aggravates the inflammation and Aloe Vera and also act by inhibiting COX- pathway and reduces the production of prostaglandin E2.
- Polymorphonuclear leukocytes can ingest the immune complexes, with the resultant production of reactive oxygen metabolites and Aloe barbadensis act through the alteration of primary and secondary metabolites via salicylic acid elicitation.
- Vasoactive mediators such as histamine produced by the mast cells that infiltrate the rheumatoid synovium may also facilitate Alprogen, an anti-allergic compound of Aloe Vera inhibits calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of various mediators like histamine, serotonin, SRSA, leukotrienes etc from mast cells
- Osteoclasts are prominent at sites of bone erosion and Emodin inhibit the osteoclast differentiation induced by monocyte- colony stimulating factor (M-CSF) and receptor activation of NF-B ligand in bone marrow macrophages.
- Pro-inflammatory cytokines tumour necrosis factor and the reactive free radical nitric oxide (NO) synthesised by Inducible NO Synthase (iNOS), aloe-emodin inhibited inducible nitric oxide synthase (iNOS), mRNA expression and nitric oxide (NO) production.
- Acemannan stimulates the release of fibrogenic cytokines by activating macrophages. Secondly, growth factors can bind to Acemannan which further promotes their stability and prolong their stimulation of granulation tissue. It also stimulates BMSCs proliferation, differentiated osteoblasts and enhanced synthesis of extracellular matrix.
- Aloe Vera stimulates the activity and proliferation of fibroblasts which in turn significantly increases collagen synthesis. This action is due to the presence of Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone that interacts with growth factor receptors on the fibroblast thereby stimulates its activity and proliferation.
- Aloe Vera breaks down the bradykinin as it contains brady kinase enzyme and reduces inflammation.
- Aloe Vera also act by scavenging superoxide anions, and this activity have seen attributed to the caffeoyl group of isorabaichromone, a derivative of aloe sin.

STUDIES OF PHARMACOLOGICAL ACTIVITY [17,18,20]

Healing properties

- Rajput et al.45 reported pharmacology and phytochemistry of saponin isolated from Aloe Vera for wound healing activity.
- Robbers et al.1996, reported presence of amino acid which are essential in wound healing process are present in Aloe Vera.
- Bozzi et al.2007 reported that it also contains many inorganic electrolytes like iron, potassium, magnesium, chromium, copper, sodium, calcium and zinc which are vital part of wound healing process. It stimulates the body to produce antibodies and starts wound healing by releasing growth factors.
- Eshun and He.2004, reported that Aloe Vera prevents scar formation during skin injury by stimulating the cell production and promoting the regeneration process at the deepest layers of the skin.
- Yadav et al further investigated the wound healing activity of aloe barbadensis by topical application

Anti-inflammatory action [16,17,20,21,22]

- Vazquez Beatriz et al 1994, studied the effects of aqueous, chloroform, and ethanol extracts of Aloe Vera gel on carrageenan-induced oedema in the rat paw, and neutrophil migration into the peritoneal cavity stimulated by carrageenan and demonstrated that the extracts of Aloe Vera gel have anti-inflammatory activity and suggested its inhibitory action on the arachidonic acid pathway via cyclooxygenase.
- Sarkar D et al ,2005 conducted a study to demonstrate the mechanism of action mediating the acute and chronic anti -inflammatory of leafy exudate of Aloe Vera in animal models of inflammation, conclude that it is partly mediated by reduced production of NO, which in turn prevents the release of inflammatory mediators.
- Zhu et al, evaluated the anti-arthritic roles of raw Aloe Vera gel and its effects in rat model where arthritis was induced by using Freund's Complete Adjuvant (FCA) and concluded that Aloe Vera plays a significant role in amelioration of rheumatoid arthritis induced paw oedema.
- In 1989, Davis et al. demonstrated the anti-inflammatory activity of Aloe Vera in diabetic mice, and in another study 1% carrageenan were used to induce inflammation similar to arthritis and reduction of vascularity of carrageenan inflamed synovial pouches by 50% after treatment with 10% Aloe barbadensis indicated the anti-inflammatory activity which was further strongly supported when number of mast cell was decreased by 48% compared to only 1% in carrageenan-treated mice. Finally, the increased number of fibroblasts strongly demonstrated that Aloe barbadensis stimulates fibroblasts to grow and repair.
- Langmead et al.18 reported Anti-inflammatory effects of Aloe Vera gel in human colorectal mucosa in vitro.
- Reuter et al.19 reported the anti-inflammatory potential of Aloe Vera gel (97.5%) in the ultraviolet erythema test.
- Lee et al.20 reported anti- inflammatory activity of Aloe Vera adventitious root extracts through the alteration of primary and secondary metabolites via salicylic acid elicitation.
- In 2011, Devaraj et al. showed both analgesic and anti-inflammatory properties in Aloe barbadensis leaf extract. Tail flick, hot plate and acetic acid tests were performed to demonstrate analgesic properties, while formaldehyde and carrageenan-induced rat paw oedema was conducted to investigate the anti-inflammatory effect.
- A study done by Radha and Laxmipriya 2015 exhibits strong anti-inflammatory effects due to the presence of anthraquinones and chromone.
- Peng et al,1991 revealed that Aloe Vera possesses anti-bradykinin activity because it contains a brady kinase enzyme, which breaks down the bradykinin and reduces the inflammation.
- Reynolds and Dweck ,1999 revealed that Aloe Vera gel is more effective against inflammation caused by prostaglandin synthesis as well as infiltration of leukocytes and is less effective against inflammation caused by allergenic agents.
- Egesie and his group conducted anti-inflammatory and analgesic activity on formalin induced hind paw oedema and acetic acid-induced abdominal writhing tests individually. Their studies revealed that Aloe barbadensis possessed strong analgesic and anti-inflammatory activities, which could be mediated through pain or inflammatory mediators or via central nervous system.
- Ghosh et al, investigated analgesic activity of Aloe barbadensis and observed potential analgesia from radiant heat method and hot plate method without any cytotoxicity.
- Hutter et al. identified a new chromone compound namely C glucosyl Chromone isolated from Aloe barbadensis and showed that this compound exhibited almost similar anti-inflammatory effect at same dose of hydrocortisone.

Immunomodulatory activity(7)

- Madan et al.25 reported Immunomodulatory properties of Aloe Vera gel in mice.
- Im et al.26 reported optimal molecular size of modified Aloe polysaccharides with maximum immunomodulatory activity.
- Zhang et al.27 reported antioxidative and immunomodulatory properties of two novel dihydrocoumarins from Aloe Vera.

Antioxidant activity(8)

- Aburjai and Natsheh, 2003; Eshun and He, 2004; Radha and Laxmipriya, 2015 reported that a number of antioxidants such as α-tocopherol, carotenoids, ascorbic acid, flavonoids, tannins, vitamin C and E are present in Aloe Vera.
- Lopez et al 2013 reveal antioxidant potential of the extracts of Aloe Vera (leaf and flower).
- Hammam 2008 reported that Aloe Vera has a dose dependent antioxidant effect, which is helpful in treatment of various diseases.
- Kang et al ,2014 investigated the antioxidant potential of a polysaccharide isolated from Aloe Vera gel, showed that it had a protective effect against dihydrochloride induced oxidative stress and cell death in kidney epithelial cells.

CONCLUSION

Aloe Vera is widely used in various disease conditions specially in skin diseases but it also plays a remarkable role in the management of rheumatoid arthritis. It is also mentioned in classical literatures that it possesses Moḥallil-*i Waram* (Anti-inflammatory) properties and modern scientific research on animals has also confirmed its anti-inflammatory, anti-oxidant, analgesic and immuno-modulatory activity. Therefore, it can be concluded that Aloe Vera is effective in the management of Rheumatoid arthritis.

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AUTHOR'S CONTRIBUTIONS

Each author contributed in data collection, analysis of the data, writing and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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