Potential Therapeutic Benefits of *Aloe barbadensis* in Treatment of Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease characterized with a chronic, systemic inflammation which primarily affects synovial joints. A significant percentage of the world population including notably the aged groups suffers from such a disabling and painful condition that can result in substantial loss of normal functioning and mobility, if not adequately treated. Natural products have always been a potential source of alternative therapy and lead compounds for various diseases. A good number of anti-inflammatory or immunomodulatory plant extracts (and phytochemicals thereof) seem to exist whilst several of them have been specially studied in the context of RA. One potential example in this regard includes *Aloe barbadensis*. Over 75 active components have already been identified in *Aloe barbadensis* leaf gels and some of them have been implicated as immunomodulatory compounds and as such beneficial against RA, based on animal studies. This paper aims at critically reviewing the evidence of beneficial role as well as possible mechanism of such action of *Aloe barbadensis* preparations in RA and related complications.

Keywords: Rheumatoid arthritis, wound healing, anti-inflammatory, anthraquinones, polysaccharides.

1. INTRODUCTION

Rheumatoid Arthritis (RA) is considered as a chronic multisystem autoimmune disease in which various joints in body are affected. Multiple symptoms of RA include pain, swelling, stiffness and even loss of mobility [1-7]. Development of RA follows several steps where initially it starts from the synovium, which is a membrane that surrounds a joint and acts as a protective sac containing the lubricating liquid known as synovial fluid. In addition to cushioning joints, the fluid provides nutrients and oxygen to the cartilage made up of slippery collagen tissue positioned at the ends of the bone. In RA, the abnormal immune responses fabricate a destructive molecule which gradually annihilates the collagen of cartilage, narrows the joint space and finally damages bone [8-11]. In progressive RA, destruction of the cartilage is accelerated due to accumulation of fluid and immune system cells in the synovial fluid to produce a pannus composed of thickened synovial tissue [8, 12]. More enzymes are manufactured by pannus which further devastate the nearby cartilage, aggravating the area and attracting more inflammatory white cells, thereby perpetuating the process [12].

Though extensive research have been carried out to determine the exact mechanism of inflammation raised in arthritis and consequent tissue destruction, the precise mechanism(s) are yet to be elucidated [13]. On the basis of massive research on the pathpophysiology behind RA, it appears that development of RA follows a series of complex chain of events. Upon encounter with antigen regarding class II major histocompatibility complex (MHC) on an antigen presenting cell, T cells become prepared to be active which is only possible after receiving the second signal *via* CD28 molecule on the T cell surface [14, 15]. T- cells are further activated by cytokines (IL-1, IL-6, IL-12, IL-15, IL-23), T cell receptor (TCR), tumor necrosis factor (TNF) and transforming growth factor which further differentiate the T -cells to anti T helper 1(T_H1) and T helper 17 (T_H17) [16-19]. The cytokines secreted from the T_H17 cells then activate macrophage which further amplifies inflammation and progress cartilage damage and inflammation. In addition extension of macrophage infiltration into the synovium enhances the severity and progression of RA. Recent evidences suggest that the novel cytokines IL-17, IL-18 and RANK ligand (RANKL) are also behind the etiology of the progression of RA [20-22]. These cytokines stimulate synovial fibroblasts and chondrocytes in the adjacent articular cartilage to secrete the enzymes. Furthermore, these enzymes degrade peptidoglycan and the cartilage, which subsequently leads to tissue destruction [19]. Finally

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ankolysis is developed due to fibrosis signing the loss of ability to move.

Recent epidemiological study shows that about 1% people all over the world are now affected with rheumatoid arthritis and which exerts significant impact on the quality of life [22]. In all population, it is more prevalent among women rather than men. Generally, RA is developed (almost in 80% cases) from the mid of fourth decade in life to the last of fifth [23]. Medications and lifestyle changes are considered as treatment for RA. Conventional treatment provides non steroidal anti-inflammatory drugs (NSAIDs) and steroids (typically cortisone injection) [24]. Though these drugs ease the pain, they are incapable to repair damaged tissues. Although a broad range of drugs are prescribed for managing the pain and slowing the progression of RA, no drug is known to cure the disease completely. Moreover stomach ulcer is an adverse effect observed in RA patients regularly partaking NSAIDS [25, 26]. These undesirable side effects frequently force the patients to look for complementary and alternative medicine (CAM) [27]. A recent survey indicates that people suffering from chronic pain in RA and those dissatisfied with allopathic treatment are more prone to seek alternative medicine, where 60-90% arthritis patients use CAM [28]. Therefore, it is highly desirable to find out a potential alternative to eradicate the drawbacks of present allopathic treatment.

Natural products from plants have played a remarkable role to cure and avert different diseases from ancient times [29-31]. A study conducted by World Health Organization (WHO) has reported that about 80% of world's population relies on traditional medicine [32]. In USA, nearly 121 drugs are prescribed today, where 90 of them come from the natural sources particularly from plants in a direct or indirect manner [30].

As a corollary, herbal remedies can be accepted to satisfy patients having RA as well as to address the drawbacks associated with present treatment methods with allopathic drugs. Among all investigated plants (list of plants is presented in Table **1**), it is scientifically palpable that *Aloe barbadensis* have a pivotal role to lessen the unbearable pain and inflammation associated with RA [33].

The objective of this present review is to evaluate the therapeutic potential of *Aloe barbadensis* in rheumatoid arthritis. We have also aimed to present a summary of mechanism of action of specific phytochemicals of *Aloe barbadensis* to reduce the pain claimed by RA-affected patients.

2. *ALOE BARBADENSIS*

2.1. Morphological and Taxonomical Information

Kingdom	Plantae
Phylum	Anthophyta
Class	Monocotyledonae
Subclass	Liliidae
Order	Liliales
Family	Aloeaceae
Genus	*Aloe*
Species	*barbadensis*

Table 1: Some Reported Constituents of *Aloe barbadensis*

Groups	Examples
Anthraquinones	Aloin, barbaloin, isobarbaloin, anthranol, aloetic acid, ester of cinnamic acid, aloe-emodin, aloesin, emodin, chrysophanic acid, resistanol, anthrone-6-glycosides.
Polysaccharides	Cellulose, glucose, mannose-6-phosphate, glucose-6-phosphate, aldopento, L-rhamnose
Mnerals	Zinc, selenium, calcium, manganese, copper, chromium, iron, potassium, phosphorus, sodium.
Amino acid	Essential amino acids: Isoleucine, leucine, lysine, methionine, phenylalanine, threonine, valine and tryptophan. Non-essential amino acids: alanine, arginine, asparagine, cysteine, glutamic acid, glycine, histidine, proline, serine, tyrosine, glutamine, and aspartic acid.
Vitamins	A, B1, B2, B3, B5, B6, and B12, C, and E.
Enzymes	Amylase, bradykinase, catalase, carboxypeptidase, cellulase, lipase, oxidase, alkaline phosphatase, proteolytiase, creatine, phosphokinase
Sterols	Cholesterol, campesterol, luperol, and β- sitosterol
Miscellaneous	Prostaglandins, tannins, magnesium lactate, resins, mannins, and proteins such as lectins, monosulfonic acid, and gibberlin.

Aloe barbadensis Miller (Family: Aloeaceae) is a succulent plant having fleshy, thick, serrated, lanceolate shaped green to grayish leaves and is strongly considered a beneficial agent for wound healing, protecting mucous membrane, treating ulcer, preventing diabetes, and being effective in skin care [34-37]. Belonging to a member of Liliaceae group, it is widely found in subtropical and tropical areas of the world. Among all 400 species of aloe, *Aloe barbadensis* Miller [syn. *Aloe vera* (L.)] is considered to be the most biologically active plant. Besides acting as a therapeutic agent, it has long been used in dietary supplements and for cosmetic purposes [36]. The lower leaves of the plant are used as the source of *Aloe barbadensis* gel. The gel is considered to be the clear, odorless, and tasteless pulp following removing the surface layer of the leaf [38]. Though there is yet to be any standardization, the International Aloe Science council (IASC), which is an international trade association, requires adherence to certain specifications for certification of *Aloe barbadensis* products [39].

2.2. Chemical constituents of *Aloe barbadensis*

Aloe barbadensis contains over 200 reported constituents and 75 of these have reported biological activities [41-43]. Some of the various ingredients of *Aloe barbadensis* have been presented under different groups (Table **1**).

3. RELEVANT PHARMACOLOGICAL ACTIVITIES OF RA-ASSOCIATED SYMPTOMS

The exact mechanism to eliminate the pain, inflammation and wound associated with rheumatoid arthritis by *Aloe barbadensis* has not clearly been explored. Various *in vitro* and *in vivo* experiments have been carried out to explore the novel lead compounds of *Aloe barbadensis* which display either anti-inflammatory or wound healing properties or both together along with analgesic activity. The following sections will examine in depth the therapeutic potential of *Aloe barbadensis* gel as well as individual phytochemical constituents against RA.

3.1. Aloe barbadensis Gel as a Beneficial Agent Against RA-Associated Symptoms

Aloe displays mainly three types of function in rheumatoid arthritis - regeneration of cells in wound healing, anti-inflammatory, and analgesic agent. In 1989, Davis *et al*. demonstrated the anti-inflammatory activity of *Aloe barbadensis* in diabetic mice where these were selected due to poor wound healing properties of the diabetic animals [44]. Anti-inflammatory activity was observed in streptozotocin induced diabetic mice where pure gibberellin (present in *Aloe barbadensis*) was used for comparison. In both cases, similar inhibitory effect against inflammation was observed indicating the anti inflammatory effect of *Aloe barbadensis.* In their next study, Davis' group experimented with a pouch wall resembling the synovium by administrating air under skin [45]. To induce inflammation similar to arthritis, on day 7, pouch bearing mice were treated with 1% carrageenan. 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 [45].

Study by Budai *et al.* has explored the molecular mechanism behind the anti-inflammatory activity of *Aloe barbadensis* [46] by determining the effect of *Aloe barbadensis* on the molecular mechanisms of Nlrp3 inflammasome-mediated IL-1β production in LPS-activated human THP-1 cells and monocyte-derived macrophages. Their findings show that *Aloe barbadensis* significantly reduces IL-8, TNFα, IL-6 and IL-1β cytokine production, depending on dosage. The inhibitory effect was substantially more pronounced in the primary cells. Expression of pro-IL-1β, Nlrp3, caspase-1 as well as that of the P2X7 receptor in the LPS-induced primary macrophages were significantly inhibited by *Aloe vera*. Furthermore, *Aloe barbadensis* also significantly inhibited LPS-induced activation of signaling pathways like nuclear factor-κB (NF-κB), p38, JNK and ERK in these cells. Altogether, they found for the first time that *Aloe barbadensis* -mediated strong reduction of IL-1β appears to be the consequence of the reduced expression of both pro-IL-1β as well as Nlrp3 inflammasome components *via* suppressing specific signal transduction pathways. Furthermore, the expression of the ATP sensor P2X7 receptor was also downregulated by *Aloe vera*, which could also contribute to the attenuated IL-1β cytokine secretion [46]. Anti-inflammatory effect of *Aloe barbadensis* by decreasing the level of TNF and IL-16 in plasma was further observed by Duansak *et al*. [47]. A further study by Kallaya reported that by inhibiting the production of TNF, *Aloe barbadensis* aided to alleviate inflammation [48].

By using carrageenan induced-edema as *in vivo* model, Vázquez's group reported the significant anti-inflammatory effect by *Aloe barbadensis* gel [49]. The aqueous extract of the gel inhibited the production of prostaglandin E2 (PE2) and extract of ethanol reduced the number of neutrophils. Their study showed that aloe gel extracts exhibited anti-inflammatory effect on the arachidonic acid pathway *via* cyclooxygenase inhibition [49].

In vitro experiments were carried to evaluate the anti-inflammatory activity of aqueous extract of *Aloe barbadensis* gel in peripheral blood mononuclear cell through MMP inhibition studies by Vijayalakshmi and her group [50]. Gelatin zymography was conducted to detect the activities of MMP-9, and RT-PCR was performed to confirm the findings. Significant inhibition in MMP-9 activities was observed depending on the concentration of *Aloe barbadensis* extract.

Excessive production of TNF and NO can play a crucial role behind inflammation in RA. Study carried out by Sarkar and his group demonstrated that gel of *Aloe barbadensis* possesses both acute and chronic anti-inflammatory activity [51]. This was due to reduction of NO production which consequently inhibited the synthesis of prostaglandin.

In 2011, Devaraj *et al.* showed both analgesic and anti-inflammatory properties in *Aloe barbadensis* leaf extract [52]. Tail flick, hot plate and acetic acid tests were performed to demonstrate analgesic properties, while formaldehyde and carrageenan-induced rat paw edema was conducted to investigate the anti-inflammatory effect. Depending on dose, *Aloe barbadensis* significantly reduced inflammation. Additionally, potential analgesic activity was observed in acetic acid-induced writhing as well as hot plate experiments.

Wound healing activity of *Aloe barbadensis* was further investigated by Yadav *et al*. by topical application [53]. *Aloe barbadensis* strongly accelerated wound healing in experimental rats. Collagen synthesis was significantly increased, which was confirmed by biochemical studies. Another study by Nandanwar *et al*. demonstrated significant wound healing activities of *Aloe barbadensis* with cow ghee [54]. Fernanda's group showed that wound healing activities of *Aloe barbadensis* was accelerated when microcurrent was applied simultaneously [55]. Oryan and his group demonstrated that *Aloe barbadensis* accelerated wound healing effects on cutaneous wound in rat model [56].

Egesie and his group conducted anti-inflammatory and analgesic activity on formalin induced hind paw edema and acetic acid-induced abdominal writhing tests individually [57]. 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. Analgesic activity of *Aloe barbadensis* was investigated by Ghosh *et al*. [58]. They observed potential analgesia from radiant heat method and hot plate method without any cytotoxicity.

3.2. Specific Phytochemicals of *Aloe barbadensis* Providing Beneficial Effects in RA

3.2.1. Anthraquinones of Aloe barbadensis in RA

One of the major groups of compounds of *Aloe barbadensis* is anthraquinones, which have been strongly identified as potent inhibitors of inflammation [59, 60]. Chemical structures of some anthraquinones having beneficial effect in RA treatment are presented (Figure **2**). It has been claimed that emodin from *Aloe barbadensis* can play a major beneficial role in RA. The mechanism through which emodin can play a beneficial role in arthritis has been shown by Hwang *et al*. [61]. The authors reported that emodin can inhibit the nuclear translocation and DNA binding of NF-κB subunits, which are correlated with its inhibitory effect on cytoplasmic IκBα degradation. In addition, they showed that emodin inhibited the osteoclast differentiation induced by momocyte- colony stimulating factor (M-CSF) and receptor activation of NF-κB ligand in bone marrow macrophages [61].

Figure 1: Aloe barbadensis.

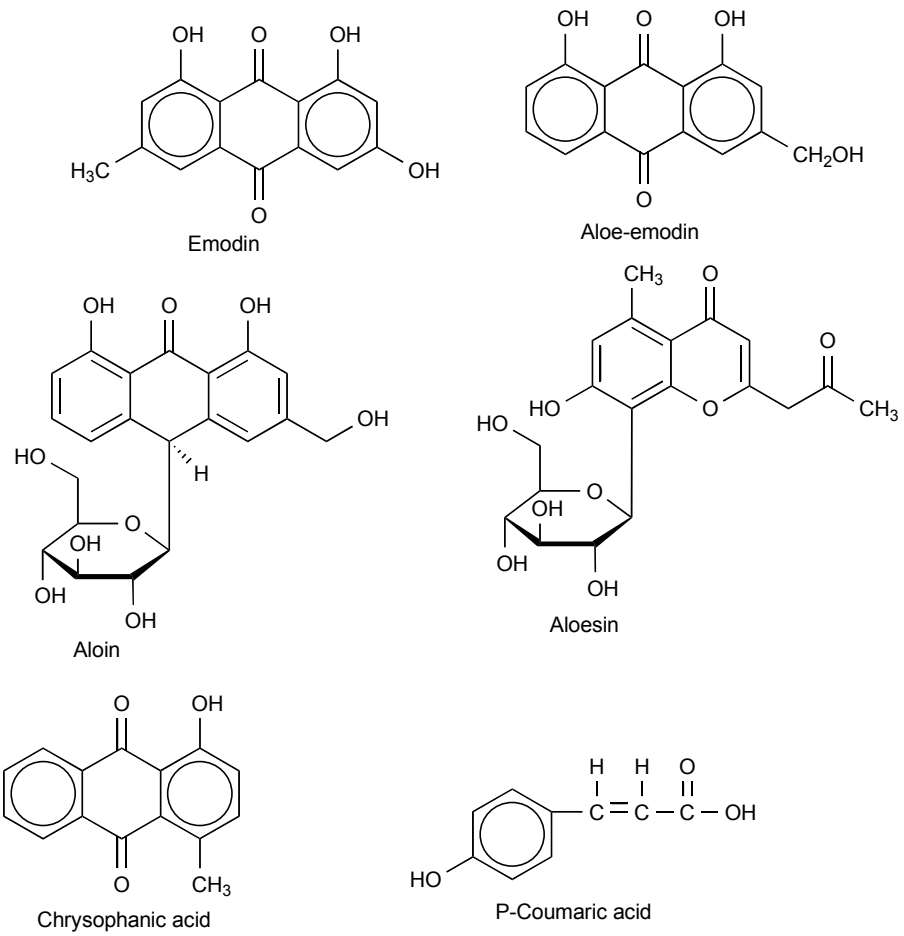


Figure 2: Chemical structure of emodin, aloe-emodin, aloin, aloesin, and chrysophanic acid as representatives of anthraquinones having anti-inflammatory effects.

It is plausible that the anti-inflammatory effect of constituents of *Aloe barbadensis* gel like aloin, and aloe-emodin is due to their polyphenolic structure. This has been experimentally shown by Park *et al.*, where in their study they used these phytochemicals against LPS-stimulated NO and prostaglandin E2 (PGE2) release in RAW 264.7 macrophages [62]. Their result indicated that aloe-emodin inhibited inducible nitric oxide synthase (iNOS) mRNA expression and nitric oxide (NO) production. In addition, the level of cyclooxygenase-2 (COX-2) mRNA and PGE2 production were suppressed by aloe-emodin. On the other hand aloin suppressed the production of NO, but not PGE2 production. They concluded that aloin and aloe-emodin possibly suppressed the inflammatory responses by blocking iNOS and COX-2 mRNA expression [62].

In *in vivo* experiments, Zhu *et al*. have discussed the mechanism of aloe-emodin (isolated from ginger) in arthritic mice [63]. Collagen induced arthritis was developed in mice by immunization with bovine type-II collagen. On day 21, the mice were treated with aloe-emodin till 42nd day from the immunization. The severity of the disease was significantly alleviated as based on the observation of hind paw swelling. Level of TNF and IL- 6 in the plasma was considerably decreased while production of prostaglandin and COX-2 protein expression was inhibited remarkably [63].

Results from the investigation by Ha *et al.* strongly supports this mechanism where in their study they used emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) isolated from the root of *Rheum palmatum* L. in interleukin 1 beta (IL-1β) and lipopolysaccharide (LPS)-stimulated RA synoviocytes under hypoxia [64]. Depending on doses, emodin remarkably inhibited IL-1 β and LPS-stimulated proliferation of synoviocytes. Beside this, inhibition of pro-inflammatory cytokines – (TNF-α, IL-6and IL-8), matrix metalloproteinases-1 and 13 (MPS-1 and MPS-13), as well as VEGF as an angiogenesis biomarker in IL-1 β and LPS-treated synoviocytes was observed. Furthermore, not only activity of histone deacetylase (HDAC) was inhibited

but also suppression of expression of HDAC1 in the observable cells under hypoxia was seen [64]. Though the source of emodin in the above study was different, but as a constituent of *Aloe barbadensis,* it may be said that emodin of *Aloe barbadensis* may have similar strong influence towards alleviation of inflammation in RA.

Recently, *in vivo* dual activities, as anti-inflammatory and wound healing agent, of Aloe gel (isolated from *Aloe littoralis*) were evaluated by Hajhashemi *et al*. in rats [65]. Anti-inflammatory activity was conducted in carrageenan induced paw edema in rat, while wound healing was observed by creating burn wound following a well established method [66]. They observed potential anti-inflammatory and wound healing activities, and reported that emodin played the major role in mediating these activities. Similar activities of *Aloe barbadensis* were also evaluated by Somboongwong *et al*. in Wistar rats but they did not mention the exact mechanism behind the beneficial effects [67].

3.2.2. Polysaccharides of Aloe barbadensis in RA

Among all polysaccharides of *Aloe barbadensis*, mannose-6-phosphate has been claimed to have both wound healing and anti-inflammatory activities (Figure **3**) [68]. In wounds, the polypeptide hormones known as growth factors communicate among the cells by binding with the cell surface receptors (usually a fibroblast receptor) and initiate the biological response to wound healing. It has been revealed by different groups that insulin like growth factor II and mannose – 6 – phosphate bind to different binding site of the same receptor and stimulate fibroblast surface receptor. In

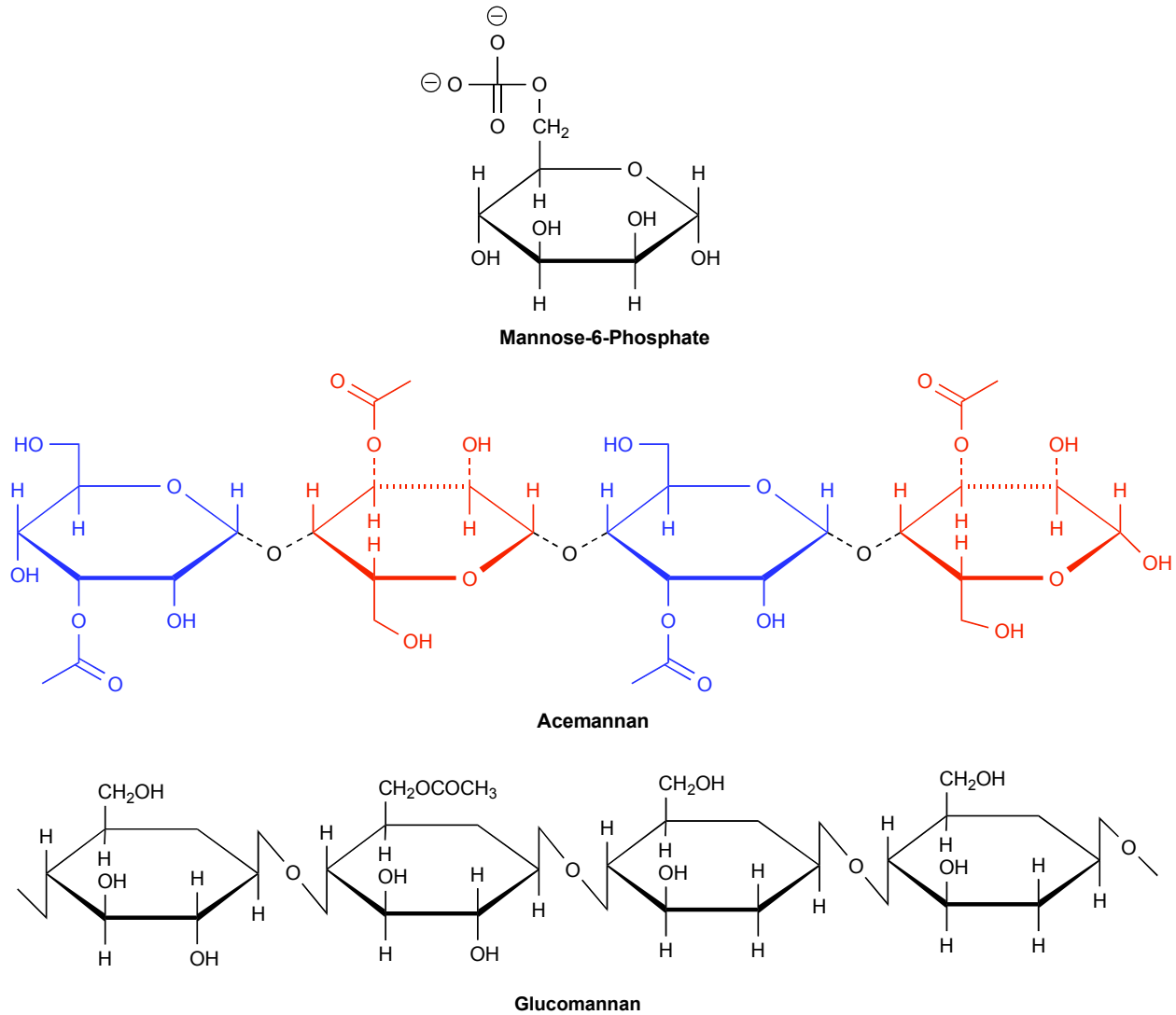


Figure 3: Chemical structure of mannose–6-phosphate, acemannan and glucomannan as major polysaccharides of *Aloe vera* having anti-inflammatory and wound healing activities.

this regard, Davis *et al.* has demonstrated by using mannose–6– phosphate isolated from *Aloe barbadensis* that it can also participate in wound healing and anti-inflammatory activities in adult male ICR mice [68]. However, the exact mechanism of action is remains to be elucidated.

Other polysaccharides of *Aloe barbadensis,* namely, acemannan and glucomannan have been shown to accelerate wound healing (Figure **3**) [69, 70]. The mechanism of action of acemannan appears to be a two-step process. Firstly, 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 [69]. In another study carried out by Boonyagul *et al.* indicated that acemannan of *Aloe barbadensis* stimulated BMSCs proliferation, differentiated osteoblasts and enhanced synthesis of extracellular matrix [71].

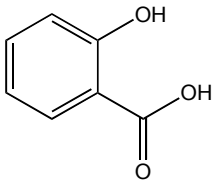
3.2.3. Enzymes of Aloe barbadensis in RA

Enzymes of *Aloe barbadensis* have also been claimed to have anti-bradykinin action. Akira *et al.* investigated bradykinin degrading behavior from an aloe species, *Aloe arborescens*, on isolated guinea pig ileum *in vitro* [72]. Their experiments demonstrated that glycoprotein of *Aloe arborescens* strongly activated against bradykinin and produced des-Phe^{8}-Arg9 and des-Arg9- bradykinin indicating the presence of carboxypepdiase N- and P- like enzymes. In their study, following similar methods, a glycoprotein was isolated from *Aloe saponaria* and this glycoprotein degraded Gly4-Phe5 and Pro7-Phe8 bonds of bradykinin [73]. Obata and Shelton groups independently showed that carboxypeptidase of aloe aided to ease this pain by breaking down bradykinin [74, 75]. The bradykinase is another enzyme of *Aloe barbadensis*, which is reported to have anti-inflammatory activity [70].

3.2.4. Sterols and other Phytochemicals of Aloe barbadensis in RA

Acceleration of wound healing activity by growth hormones of *Aloe barbadensis* was observed by Davis' group where they explained that the aloe hormones masked the wound healing inhibitors like sterols and few amino acids. From the same study they also demonstrated that sterols of *Aloe barbadensis* significantly reduced inflammation [76].

Rajeswari *et al*. reported that lupeol and salicylic acid of *Aloe barbadensis* juice act as analgesics (Figure **4**, structure of salicylic acid) [69, 76]. They also reported that the fatty acids, cholesterols, campesterol and β-sitosterol of *Aloe barbadensis* exhibited anti-inflammatory effects [70, 77]. In last decade 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-inlammatory effect at same dose of hydrocortisone [78]. A pharmacological study carried out by Saito and his group reported that the glycoprotein Aloctin A (isolated from Aloe arborescens) reported significant reduction of arthritis activity by this compound on adjuvant arthritis in rat [79].



Salicylic Acid

Figure 4: Chemical structure of salicylic acid, a constituent of *Aloe barbadensis* as anti-inflammatory agent.

4. CONCLUSION

Rheumatoid arthritis is a debilitating disease affecting millions of people throughout the world and is more present in elderly people. The disease affects mobility and as such the affected population has to suffer both physically with possible concomitant mental depression. Available allopathic drugs cannot cure the disease and relieves only the symptoms and also are not without adverse effects, and so there is a need for newer drugs to treat this disease. Since plants have always proved to be a rich source of drugs (e.g. quinine, artemisinin, reserpine, vincristine, vinblastine, to name only a few), they may prove a useful source of newer drugs against RA. Indeed, some of the discussed phytochemicals present in *Aloe barbadensis* can provide relief to RA patients through promoting wound healing, as well as reducing inflammation and relieving pain, which are common symptoms of RA-affected patients. From that view point, *Aloe barbadensis* and its phytochemical constituents has the potential for further studies leading to newer and more efficacious drugs against rheumatoid arthritis.

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