# A brief review on HLA B27 and possible role of traditional medicinal plants in HLA B27 induce ankylosing spondylitis

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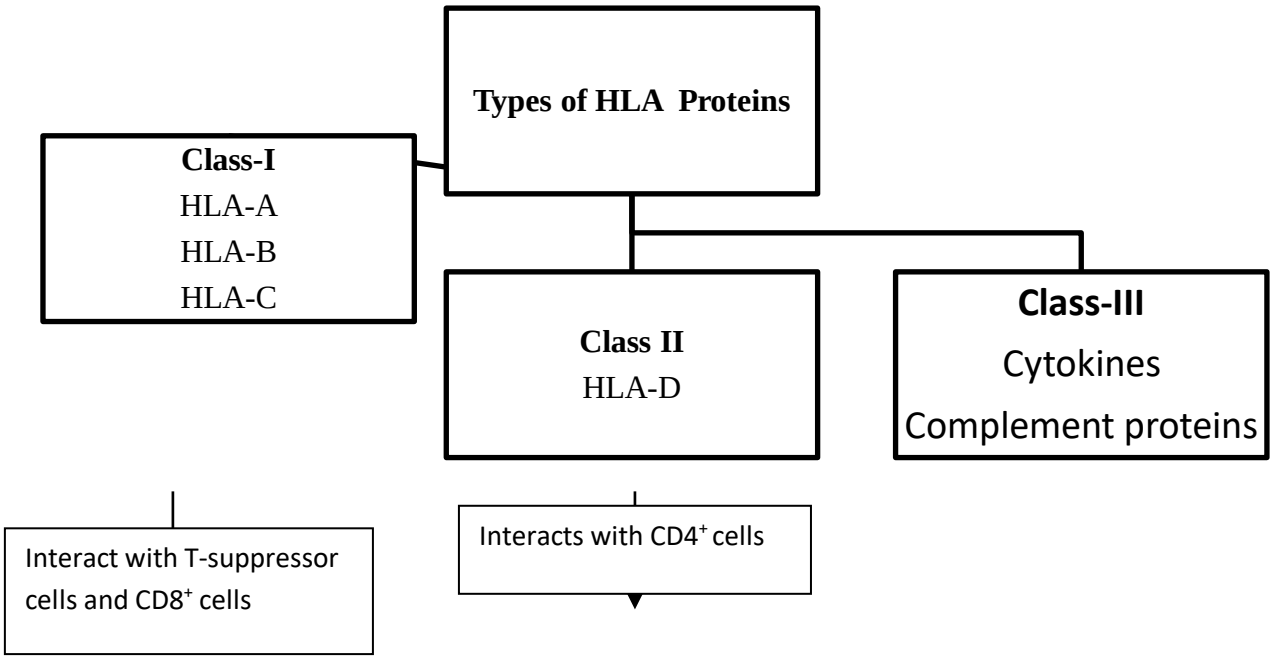
**Abstract:**
**In recent years advancement in the understanding of autoimmune disease at a molecular level has made a lot of options for treatment. Identification of novel receptors opens new doors for therapeutic strategies. HLA B-27 plays a triggering role in augmenting various autoimmune diseases. Consequently, autoimmunity could've been induced by distinctive features of its peptide-binding capacity or cell biology. Ankylosing Spondylitis impacting entire humans is the main problem of HLA B27 triggered the autoimmune disease. As there is no cure a medicine must have to be safe, effective, and well-tolerated without side effects throughout the life of patients. Currently used treatment options like NSAIDs, Steroids, and TNF alpha inhibitors are having major and serious side effects on long-term use. Therefore an alternative system of medicine can play a significant role in the management of such immune-modulated disease to prevent further worsening of symptoms and sustain the health condition. Therefore this review article discusses some vital herbs like Terminalia chebula, Zingiber officinale, Asparagus racemosus,Punica granatum, Myristica fragrans, Piper longum, Tinospora cordifolia, Leptadiniareticlata might be useful options in the management of HLAB27 induced autoimmune disease conditions.**
**Keywords: HLAB27, Ankylosing Spondylitis, TNF-alpha inhibitors, autoimmune disease**

**Introduction:** HLA stands for Human Leukocyte Antigen. HLA molecules are highly determined in terms of the peptide sequences they can present, and peptides not presented by HLAs remain invisible to the immune system.[1] Human leukocyte antigens are one of the most polymorphic genes in humans, with several thousand alleles encoding for functional polypeptides.[2, 3] Thus, these molecules play an important role in the regulation of the host's immune response as presenters of self-and/or foreign peptides/antigens to T cell receptors (TCRs) for initiating tolerance and cytotoxic T cell (CTL) or helper T cell response. [4]

**Types of HLA proteins:**




**HLA-B27 protein:** MHC Class I molecules are prime for the inception and propagation of immune responses [5, 6]. The classical hetero-trimetric MHC class I molecule is composed of three non-covalently bound individual polypeptides:
1. A highly polymorphic heavy chain (HC),

2. β2-microglobulin (β2m) light chain and
3. An oligopeptide, typically 8 to 10 residues in length. [5,6]

Nascent MHC class I molecules generally bind antigen peptides and shift them to the cell surface for presentation to the T-cell receptors (TCR) on T lymphocytes. [7] In the absence of β2m, HCs will misfold and ER-associated degradation may occur in the ER. Although, HLA-B27 appears to exhibit a tendency to misfold and a predilection for forming dimers or multimers. [8] HLA-B27 has three unpaired cysteine (C) residues at positions 67, 308, and 325, and four conserved cysteine residues at positions 101, 164, 203, and 259.[9] HLA B-27 protein is present on WBC cells than it is responsible for the affliction of WBC, which leads to an auto-immune disorder.

**Etiology:** The human leukocyte antigens (HLA) are gene loci on chromosome 6 that are found on all nucleated cells and are part of the major histocompatibility complex class-I of genes.[10] Its role is to provide endogenous antigens to cytotoxic T lymphocytes, such as peptides from viruses or intracellular pathogens. According to high-density genome mapping in autoimmune diseases; the MHC region is connected with disease risk in the majority of them. In animal research, the HLA-B27 allele is unique in that its presence alone can cause spondyloarthritis-like illness.[10] Despite multiple investigations into the HLA region and illness connections, the mechanism by which HLA-B27 predisposes people to spondyloarthritis is still unknown.

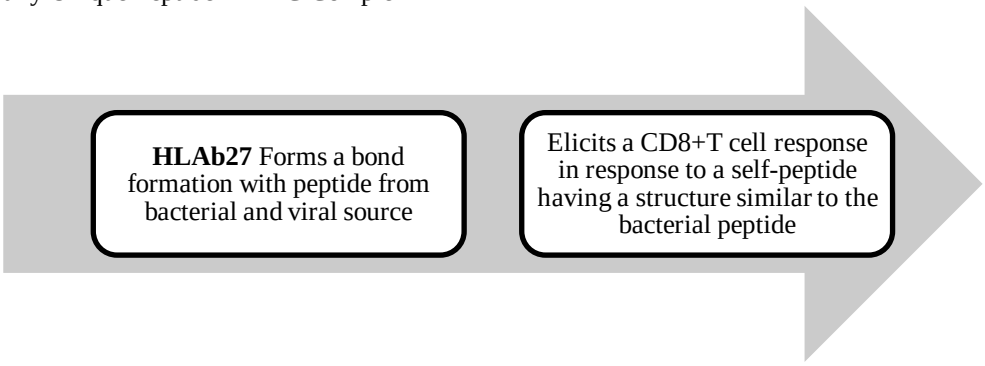
The main natural function of HLA class 1 molecules is to bind and present short antigenic peptides to cytotoxic T lymphocytes (CTL), [11] Previous studies have suggested that HLA B27 might predispose to spondyloarthritis by binding one or more specific 'arthritogenic' peptides and stimulating arthritogenic T cells.[12] Different molecular subtypes of HLA B27 have been identified, each with a different amino acid makeup in their peptide-binding groove [13,14] has led to studies of the disease association and peptide-binding specificity of different subtypes. There is some indication that HLA B*2706 and *2709, which earlier epidemiological studies suggest are not related to ankylosing spondylitis, are connected with ankylosing spondylitis (AS), [15] and may bind a subtly different set of peptides. If confirmed, these data would support the role of peptide binding in disease pathogenesis. Alternately, the unpaired cysteine at position 67 of the 1 helix may have an impact on the cell biology or immunogenicity of HLA B27. HLA B27 has the ability to produce peptides on its own, which HLA class 2 molecules can then present to T cells. [16, 17]

**Theories explaining the association of HLA B27 with the spondyloarthropathies**

- HLA B27 binds and offers 'arthritogenic' peptides to T cells
- HLA B27 is implicated in thymic selection of a T cell repertoire vulnerable to spondylo-arthritis
- HLA B27 has an atypical cell biology compared to other HLA class 1 molecules The free cysteine at position 67 of HLA B27 can be chemically changed, resulting in a 'altered self.'
- HLA B27 is a receptor for a bacterial ligand
- There is cross reactivity between antibodies directed against bacterial protein(s) and HLA B27.
- HLA B27-derived peptides are given to CD4+ T cells by HLA class 2 molecules when HLA B27 interacts with a bacterial super-antigen, causing nonspecific T cell activation.

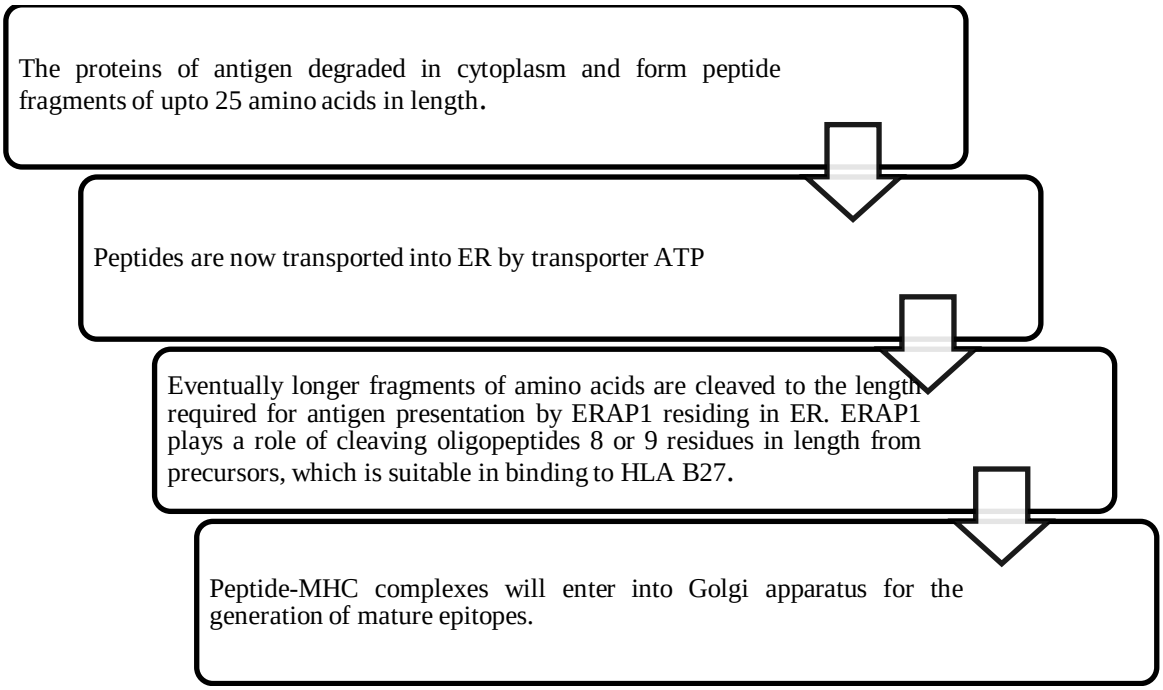
**Pathophysiology:**

Structurally Unique Peptide – MHC Complex [18]




This mechanism signifies 'molecular mimicry' theory. There is no conclusive evidence determining any of these peptides are indeed cross-reactive or self-peptides.[19] In the lack of functioning cluster of differentiation (CD)8+ T cells, illness signs appeared in HLA-B27/Hu2m-transgenic rats.[20]

**Role of HLA b27 in the pathogenesis of ankylosing spondylitis(AS):**




**HLA-B27 dimers on the cell surface and their receptors:** The "cell surface HLA-B27 homodimers" hypothesis proposes that the formation of disulfide bonds between the cysteine residue at C67 in the peptide-binding groove of two separate HC molecules generates homodimers without the participation of β2m, despite the low binding affinity of β2m and peptides with HLA-B27 HCs by hydrogen bonding, as well as HCs may form covalent homodimers via the 1 domain of C67. [21] HLA B27 is one of the important parameters in the pathogenesis of autoimmune disorders as it binds with immunoreceptors expressed on natural killer (NK) cells, myelomonocytic cells or lymphocytes [killer cell immunoglobulin-like receptors (KIR) and leucocyte immunoglobulin-like receptors (LILR)]. [20]

**HLA B-27 Status and Clinical Manifestation**

In patients with Alkylosis Spondylitis, a probable link between distinct clinical presentations and HLA-B27 status was discovered. HLA-B27 has been linked to a higher prevalence of uveitis and cardiac involvement in patients with Alkylosis Spondylitis, according to certain research. [22, 23]

Using regression analysis [24], showed that HLA-B27 positivity was associated with worse sacroiliitis on computed tomography imaging. The large-scale study revealed that HLA-B27(+) patients with AS have significantly more symptoms of spinal column involvement (lumbar spine and thoracic spine), hip joint involvement, and peripheral involvement than HLA-B27(−) patients with AS. [25]

Previous investigations showed that HLA-B27 (+) AS had a higher prevalence of hip joint involvement than HLA-B27 (-) AS[26,27]. Previous research studies found that HLA-B27(+) AS patients with AS had more uveitis/iritis and a worse visual prognosis than HLA-B27(-) AS patients. [28-32]

**Diagnostic importance of HLA B-27 test:**

1. Juvenile Rheumatoid Arthritis
2. Anterior Uveitis
3. Reactive Arthritis
4. Alkylosing Spondylitis

**Treatment/ Management:** Ankylosing spondylitis is treated with nonsteroidal anti-inflammatory drugs (NSAIDs), which are used as first-line therapy.[33] Continuous treatment has been shown in studies to slow structural progression, however, medication is largely used to reduce disease activity. TNF inhibitor medication is appropriate if a patient has active ankylosing spondylitis despite taking continuous NSAIDs. In comparison to the other TNF inhibitors, infliximab is less recommended among tuberculosis patients. In the context of IBD or uveitis, TNF inhibitors, which include monoclonal antibodies, are favored over Etanercept. The IL-17 inhibitors secukinumab and ixekizumab have shown efficacy in the treatment of axial spondyloarthritis that is comparable to TNF inhibitors. Tofacitinib should be explored above IL-17 inhibitors for IBD treatment due to the latter's lack of efficacy. Sulfasalazine may be used in patients with peripheral arthritis who have a high risk of infection. In individuals with active psoriatic arthritis and enthesitis, a TNF inhibitor is the first-line treatment. Clinical trials have indicated that Jak inhibitors are effective in the treatment of axial illness. Tofacitinib should be explored above IL-17 inhibitors for IBD treatment due to the latter's lack of efficacy. Sulfasalazine may be used in patients with peripheral arthritis who have a high risk of infection.

**Possible role of medicinal plants:** Traditionally and currently many Polyherbal or herbomineral formulations are on the market for the management of rheumatoid arthritis and other inflammatory disorders. The major determinant in this usage is to check whether prolong usage of such formulation in autoimmune diseases are immunomodulator in nature but the exact nature should be assessed. Ankylosing spondylitis is a type of reactive arthritis condition that develops usually after a Klebsiella infection and is most common in people who have the HLA-B27 gene. [34]

Ballota africana, Carpobrotus edulis leaves, Kigellia africana, Lippia javanica, Pelargonium fasiculatum, Syzygium cordatum (including bark), *Terminalia pruinoides*, and *Terminalia sericea* were found to be efficient K. pneumoniae inhibitors.

**1. *Terminelia Chebula:*** Selected bacteria that cause autoimmune disorders were prevented from growing by the fruit extract. Chebulic and ellagic acids, which are present in T. chebula fruit, have been found to prevent the growth of a number of bacteria.[35] Furthermore, numerous other investigations have shown that African and Indian Terminalia spp. are similarly effective inhibitors of K. pneumoniae and are thus intriguing possibilities for new AS prevention and treatment methods.

**2. *Zingiber officinale:*** Zingiber officinale demonstrated anti-inflammatory effects by blocking NF and protein kinase C (PKC) signalling pathways. 6-Gingerol in *Zingiber officinale* significantly suppressed Ikβα phosphorylation, NF-κβ nuclear activation, and PKC-α translocation which in turn inhibited Ca2+ mobilization and disrupted mitochondrial membrane potential in LPS-stimulated macrophages. As a result, expression of inducible nitric oxide synthase and TNF- was markedly repressed, which decreased inflammation. Numerous proteolytic enzymes included in ginger aid in preventing the prostaglandin and leukotriene-mediated pathways for inflammation. [37]

3. ***Asparagus Racemous:*** Asparagus root extract showed mixed Th1/Th2 immunomodulator and cytoprotective effects.[38] It has also been utilised for liver illnesses, liver inflammation, and a few infectious infections, according to earlier studies. Its potential as a mixed immunomodulator in the treatment of ankylosing spondylitis can be further assessed both individually and in formulations.[39]

4. ***Punica Grantum:*** By lowering inflammation and oxidative stress, Punica Grantum's phenolic component can manage the difficulties of osteoarthritis and rheumatoid arthritis. There were no significant negative effects associated with pomegranate consumption.[40] Pomegranate supplements that stimulate the PI3K/Akt/mTOR signalling pathway have been shown to lessen neuroinflammation. It was investigated for the aforementioned route in Alzheimer's disease.[41] ROS and malonaldehyde levels were elevated in the ankylosing spondylitis mouse model; punicalagin therapy considerably decreased ROS and malonaldehyde levels and greatly enhanced antioxidant status in ankylosing spondylitis BALB/c mice. This effect might be achieved by controlling the main inflammatory response pathway, JAK/STAT3 signaling. [42]

5. ***Myristica Fragrans:*** One of the components of *Myristica Fragrans* is myristicin, which inhibits NO, cytokines, chemokines, and growth factors in dsRNA-stimulated macrophages via the calcium pathway, exhibited anti-inflammatory characteristics. Myristicin has hepatoprotective properties via preventing macrophage TNF-alpha. When a formulation must be consumed over an extended period of time, this could be helpful. Additionally, it has strong anti-oxidant and osteoblast proliferation-stimulating properties. [43]

6. ***Tinosporia cordifolia:*** Key pro-inflammatory cytokines and chemokines, as well as mediators of bone remodelling and matrix degradation, were all inhibited by Tinospora cordifolia. Due to the fact that Th17 cells release IL-17, which is crucial in the aetiology of arthritis, tinosporia extract suppressed these cells.[44]

7. ***Leptadinia reticulata:*** It has anti-inflammatory, analgesic, and antioxidant properties. Additionally, it has shown immunomodulatory effects.[45] This plant has multiple used and the pharmaceutical industry's enormous demand. There are wide scope to utilize this plant in autoimmune disease especially like arthritis and ankylosing spondylitis.

**Discussion:** HLA B27 associated medical conditions and syndromes require an integrated or synergistic herbal drug treatment approach. Misfolding of HLA B27 and thereby increased IL-23 production suggested cellular integrity might play a critical role in regulating pathological complications.[46] There are many medicinal plants discussed in this review that possess and exhibited potential in the treatment of ankylosing spondylitis. HLA B-27 has been suggested major factor in ankylosing spondylitis and requires management with safe and effective treatment available at an affordable cost. The potential formulations might require the ability of cellular integrity, antioxidant activity, anti-inflammatory activity, and ability to inhibit the intracellular signaling pathways to prevent worsening of progression of HLA B27 induced AS. More synergistic herbal drug combinations are requiring establishing to combat such autoimmune complications. There is a dire need to work on targeting HLA B27-associated complications.

**Acknowledgement:** The authors expressed their sincere thanks to ATBU Harita Pharmaceuticals Pvt Ltd for providing support in preparing this work.

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