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Rheumatoid Arthritis: Severity Classification, Factors Responsible, Pathophysiology, Current and Herbal Treatment

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Abstract

Rheumatoid Arthritis is the autoimmune disorder occurs due to the change in life style, improper diet plans, smoking, excessive alcohol consumption etc. It generally affects the joints and creates swelling and severe pain in joints which leads to further destruction of bone and cartilages. Due to autoimmune responses the factors like Tumor Necrosis Factor- α , Interleukins-1 are introduced to synovial and synovial membrane which creates the swelling and pain. These factors further produce reactive oxygen species and inducing osteoclasts which destruct the bone and cartilages. Along with the drugs the several natural herbal treatments are also available for the treatment of rheumatoid arthritis. This includes varies medicinal plants form which *acacia* species is more potent and efficient. *Acacia Senegal* is the plant which blocks the receptors and decreases the level of tumor necrosis factor- α . Present work on rheumatoid arthritis mainly covers classification, factors responsible, pathophysiology, severity, current treatment and its drawbacks, herbal treatment and its benefits in treatment of Rheumatoid Arthritis.

Keywords: rheumatoid arthritis, swelling, interleukins, cartilages, interleukins, bone erosion, *Acacia Senegal*, herbal treatment

1. Introduction

Bones are the prime constituents of Human Body as they have been affected by chronic diseases [1]. Nowadays, in the developed countries about 1% of population is suffering from the bone related chronic disease; Rheumatoid Arthritis (RA) [2]. Rheumatoid arthritis is a chronic autoimmune inflammatory disease predominantly characterized by inflammation of connective tissue that lines the inside of the joint capsule. Commonly RA It is accompanied by multi-organ disorders, along with pain, swelling, and stiffness of multiple joints. Joint destruction progresses rapidly resulting in irreversible dysfunction and deformation of the affected joints. Large

Sr. No.	Criterion	Definition
1.	Morning stiffness	It is defined as the uncomfortable state occurred at morning time in and around the joints, lasting for at least 1 hour before maximal improvement.
2.	Arthritis of 3 or more joints areas	Physician have to observe the occurrence of swelling or fluid in soft tissue simultaneously in more than 3 joints. Examples are PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
3.	Symmetric arthritis	When the same joint on the both side of body is involved.
4.	Arthritis of hand joints	In this at least a small part of a single hand is involved.
5.	Rheumatoid nodules	As physician observed, Subcutaneous nnodules, over bony prominences, or in juxtaarticular regions.
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.
7.	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on poster anterior hand and wrist radiographs, which must include erosion or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Table 1.
Criteria for classification of RA revised by American rheumatism association in 1987 [12].

Target population (Who should be tested?) Patients who		
1. Have at least one joint with definite clinical synovitis (swelling)*		
2. With the synovitis not better explained by another disease		
Classification criteria for rheumatoid arthritis-based on the score		
A	Joint involvement	Score
	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	>10 joints	5
B	Serology (depends on the results of tests)	
	Negative RF and ACPA	0
	Low positive RF and low positive ACPA	2
	High positive RF and high positive ACPA	3
C	Acute-phase reactants (depends on the results of tests)	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	>6 weeks	1

Table 2.
Rheumatoid arthritis classification criterion in 2010 [13].

numbers of peoples facing swelling and severe pain due to RA. There are several factors which leads to RA, but genuine causes are still unknown [3]. Generally occurrence of RA is due to genetic alterations and environments causes [4]. These genetic alterations are due to factors like change in lifestyle, smoking, autoimmune response excess alcohol consumption, etc. [5]. According to World health organism the Rheumatoid Arthritis is defined as autoimmune, inflammatory disease that is responsible for pain, stiffness, swelling, which further leads to the impairment in its function [6]. These are generally occurs in the joints like carpals, metacarpals and knee joints [7]. The respective joints which are suffered are becoming inflamed, leading to tissue damage, chronic pain, unsteadiness, and deformity [8]. Also the RA affects the eyes, lungs, heart, and mouth [9]. The untreated RA further leads to the bone and cartilage destruction and uncertain and sudden fractures [10]. The symptoms and further destruction can be reduced and prevented by proper treatment but total curation of RA is not yet invented [11]. Rheumatoid Arthritis classified as follow (Tables 1 and 2).

2. General classification

Figure 1 [14].

3. Pathophysiology

The worldwide scientists and researchers are only known that autoimmune response is responsible for the RA and genuine pathophysiology is still unknown [15]. So the different researcher gives different pathophysiologies. Form them the important two are explained below [16]. Generally the joints are mostly affected like wrist, knees, hand, ankles and feet. It is the autoimmune disorder means the body attacked by itself [17]. The immune system attacks to the joints and organ tissue [18]. The WBCs moves into the joint. They release chemicals called cytokines which attacks the cell of the synovial membrane. These chemicals cause synovial cells to release the other chemicals. They also cause synovial membrane to grow

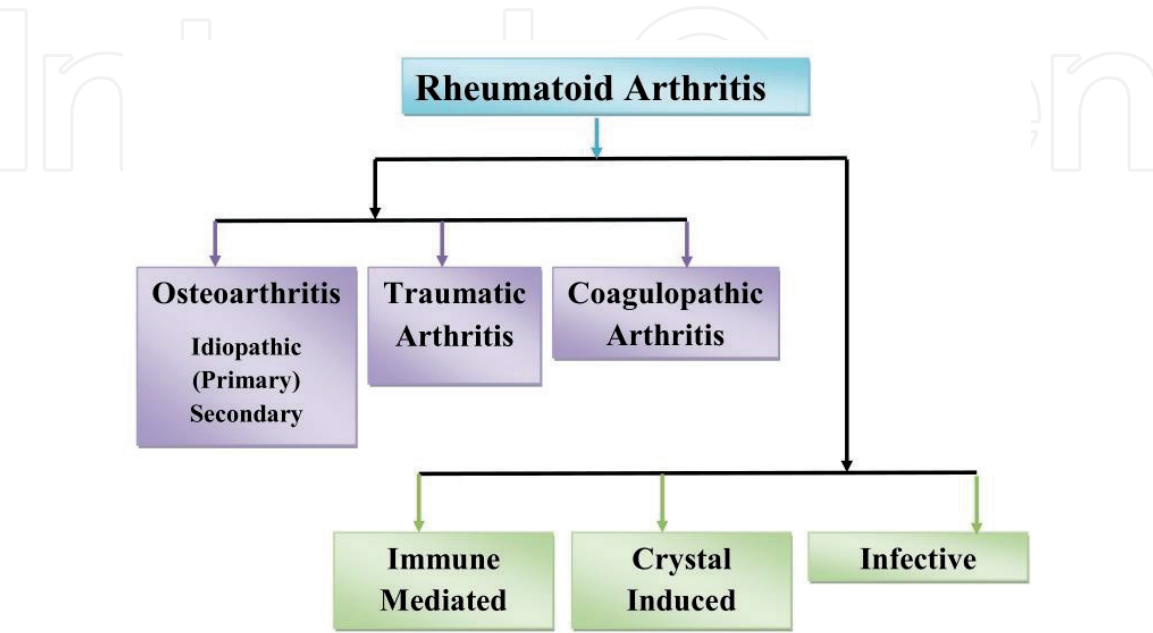


Figure 1.
General classification of rheumatoid arthritis.

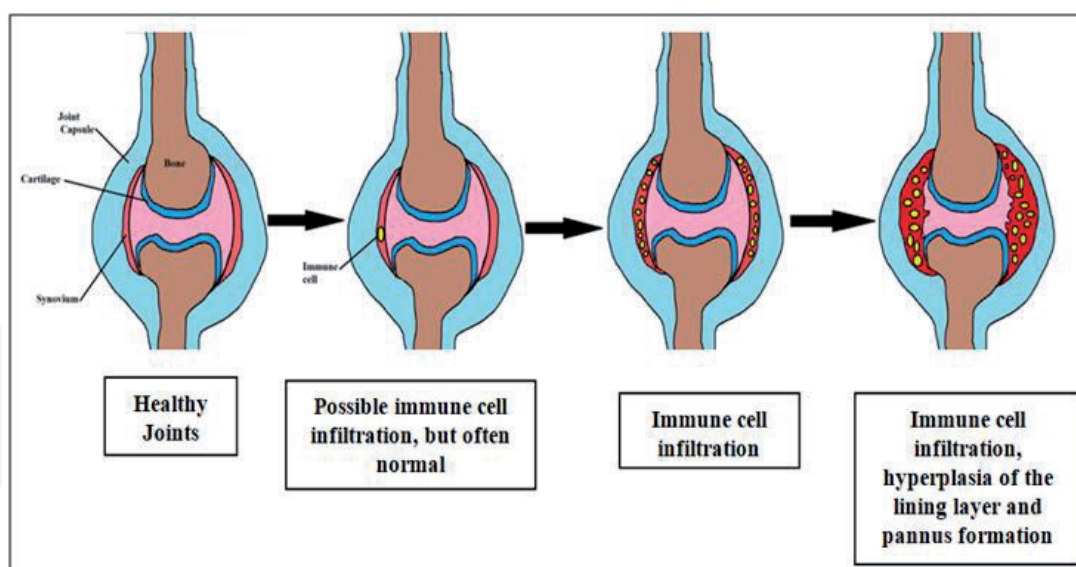


Figure 2.
Pathophysiology of rheumatoid arthritis.

new blood vessels and form a thicken area called pannus [19]. As the pannus grows day by day it invades and destructs the cartilages. Inflammation induces the fluid accumulation in the joint which lead to the further swelling and pain [20]. Due to this the free space between joints get decreases and form ankylosis and in some cases bones get fused to each other causing permanent disability of mobility of it (**Figure 2**) [21].

Another pathophysiology describes that around 7–65% of undifferentiated arthritis get converted into rheumatoid arthritis. In this the characteristic inflammatory mediators like monocytes and lymphocytes leaves the circulation and migrate to the synovium due to any autoimmune response occurs due to the reasons still unknown [22]. As the monocytes matured, the number of macrophages in the synovium gets increases. Some macrophages remain in the synovium further recruiting inflammatory cells. Other migrates towards or onto the hyperplastic synovial lining and get joined to the macrophage like and fibroblast like synovial sites. Simultaneously the APCs interact with the activated T-cells present, signaling the macrophages and they get bind to the synovial sites to release the inflammatory mediators like TNF- α and IL-1. TNF- α and IL-1 signals the additional recruitment of additional inflammatory cells from the blood, these cells also recruits the PMNs which migrate towards and crosses the hyperplastic synovial lining and enters in the joint space [23]. PMN releases the protease and ROs which get destroys nearby cartilages. Fibroblasts like synovial sites releases the additional proteases like MMP-1 and MMP-3 which also destructs the cartilages [24]. The fibroblast like synovial sites may release RANKL leading to nearby osteoclast which destruct the bones. This is the how RA get induced and develops [25].

4. Biosynthesis of TNF- α protein

On the cell membrane there are several receptors are present. There is a type known Toll-like receptors (TLR4) present on the cell membrane. When the lipopolysaccharides (LPS) are going to be attached to lipopolysaccharide binding proteins (LBP) and is transferred to CD14 (receptors of TNF superfamily). It activates two pathways from which one is for internucleus transcription of TNF mRNA and another is for intranucleus translation of TNF- α protein. In first activated pathway

through IRAK (Interleukin1 receptor associated kinase) and IKK (inducible I kappa β kinase) activates the p50 and p65 the NF κ Bs (nuclear factor kappa light chain enhancer). These NF κ Bs then get entered into the nucleus. Then due to them first transcription is done and pre-TNF mRNA forms which further converts into TNFmRNA by splicing maturation process. And then the TNFmRNA is exported to intranucleus portion. On other hand in the second pathway the MKK3,6 (mitogen activated protein kinase kinase) is activated and further activates p38. p38 then activates two constituents Mk2 (mitogen activated protein kinase activated protein kinase-2) and MNK1 (a kinase of the MAPKKADK family that can regulate

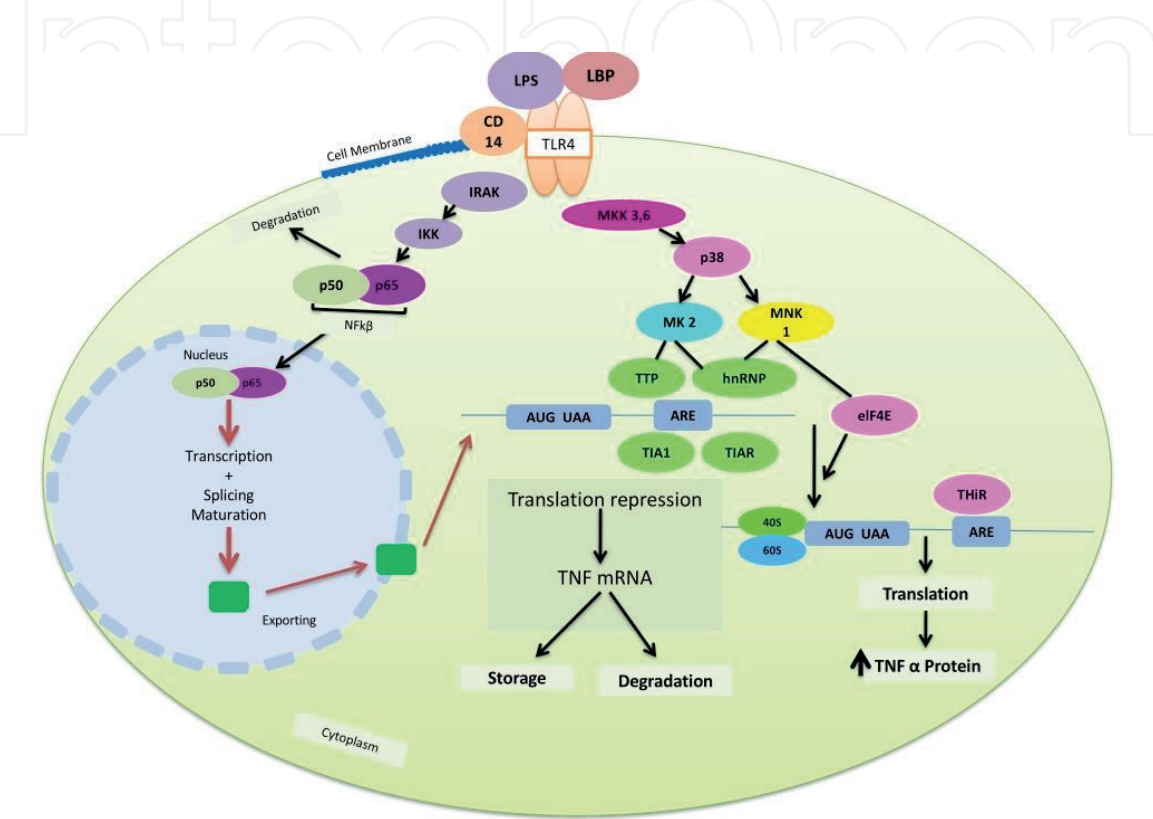


Figure 3.
Biosynthesis of TNF- α protein.

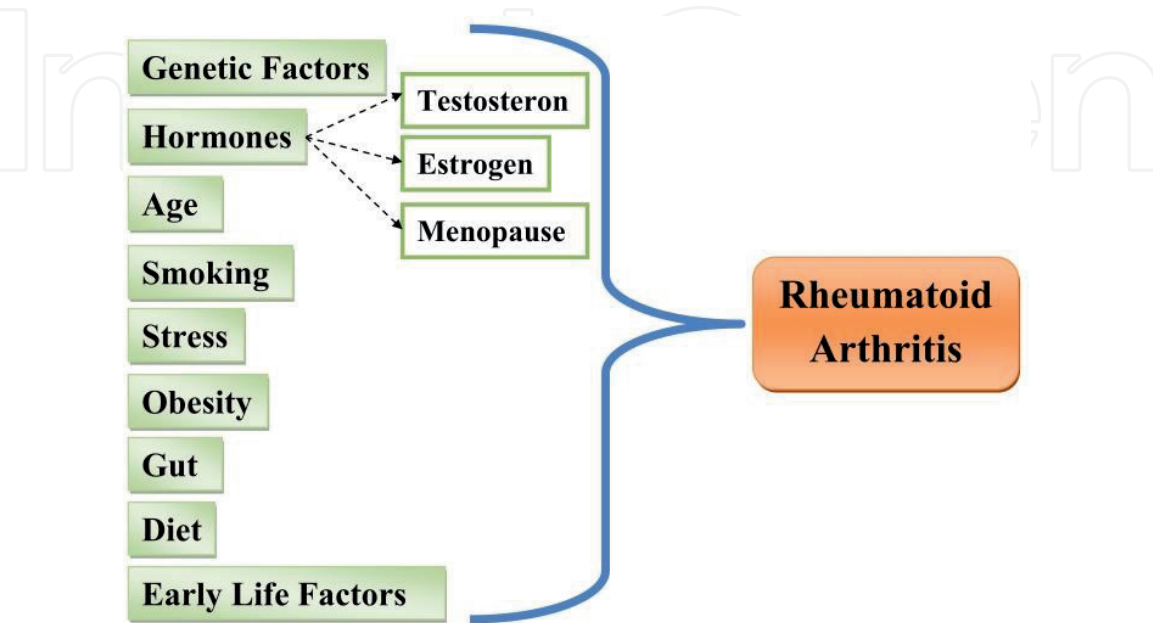


Figure 4.
Risk factors responsible for rheumatoid arthritis.

translation). They further promoted the formation of TTP (tristetraproline-zinc finger protein 36 homolog), hnRNP-A1 (heterogeneous nuclear ribonucleoprotein A1), TIA-1 (T-cell restricted Intracellular antigen 1), eIF4E (eukaryotic translation initiation factor 4E), HuR. These all are further going in the process of translation along with the TNFmRNA and forms the TNF- α protein (**Figures 3 and 4**) [26].

5. Risk factors responsible for rheumatoid arthritis

5.1 Genetic factors

If a person having occurrence of Rheumatoid Arthritis is his/her previous generations then he/she will be at high risk of availability of same disorder [27].

5.2 Hormones

There are some hormones present in human body which are responsible for RA. According to CDC (Centre of Disease control and prevention) the women are at high risk of RA as compare to the men [28]. The hormones responsible are as follows:

- a. Estrogen: Estrogen is a type of sex hormone which is also present in the male also, according to previously done research works it is proved that after menopause the estrogen received at replacement therapy is responsible for occurrence of RA [29].
- b. Testosterone: The disturbed level of testosterone in human body is leads to the RA. Many clinical studies are done on this case in 2018 [30].
- c. Menopause: The females after menopause having high physical stress and leads to disability in physical functions which results in symptoms of RA [31].

5.3 Age

According to CDC, persons in and after 60's are at more risk to suffering from RA [32].

5.4 Smoking

Smoking is a very dangerous addictive habit generally occurs in male, it leads to lots of life threatening diseases like lung cancer. It induces the autoimmune responses due to which RA happens [33].

5.5 Stress

As like above mentioned smoking the stress is also affects the immune system of human body and induces autoimmune responses which leads to traumatic experiences and further RA [34].

5.6 Obesity

Nowadays the world's most common disorder is obesity which create the various metabolic syndromes which leads to inflammation and further the RA [35].

5.7 Early life factors

According to the CDC the persons having low economic conditions are having higher exposure to RA. It is directly or indirect links to the factor Diet [36].

5.8 Previous history

The person having any history of occurrence of arthritis in his old generations then he/she might be on the high risk of arthritis.

5.9 Diet

Improper diet which leads to change in lifestyle is also responsible for occurrence of the rheumatoid arthritis [37–39].

6. Treatment

There are lot of research works done but yet no any proper treatment were found that will cure Rheumatoid Arthritis totally from its roots. Only some drugs were

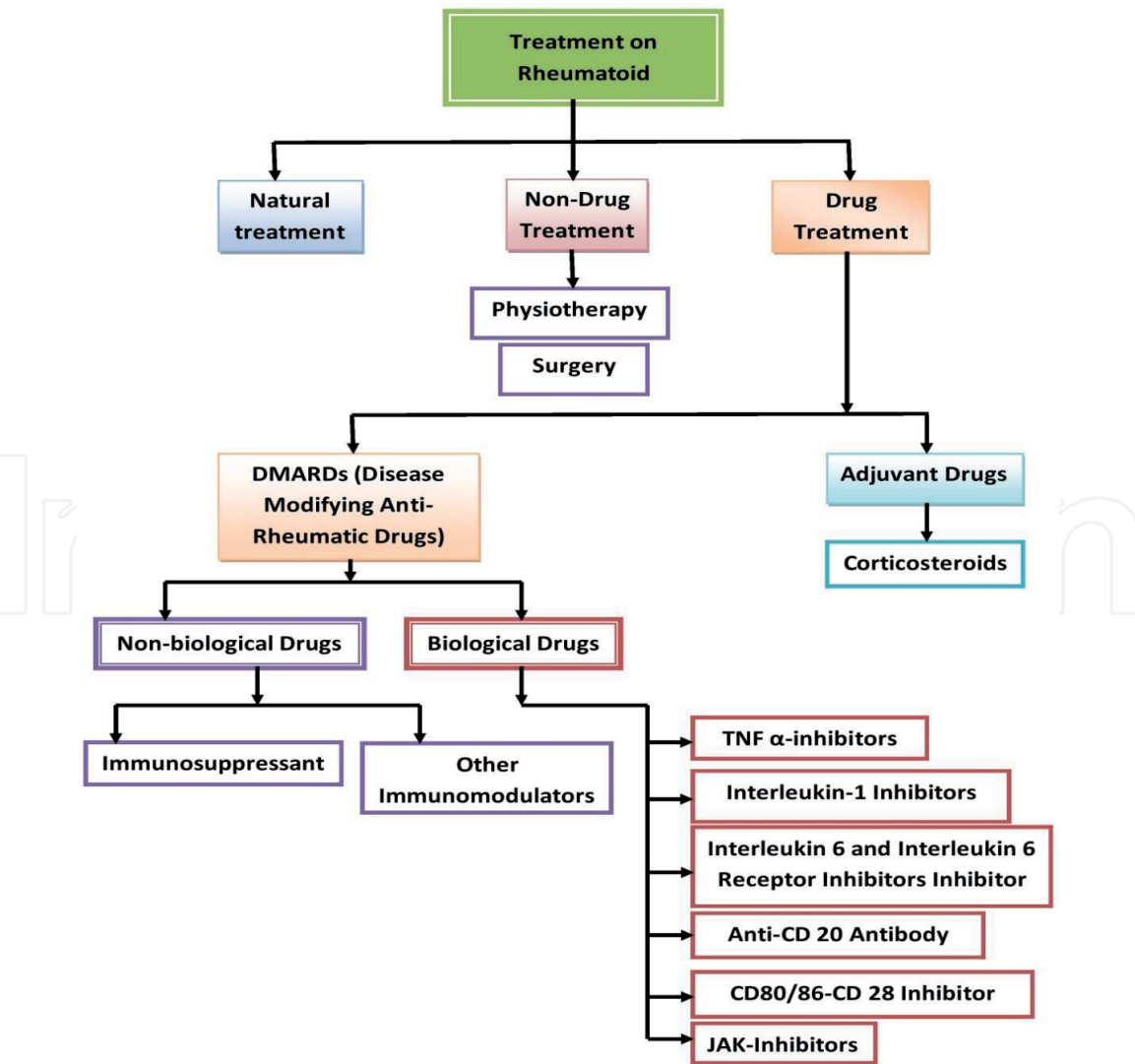


Figure 5.
Current treatment for rheumatoid arthritis.

evolved which reliefs from some of the symptoms and prevent further destructions of bones and cartilages [40, 41]. These drugs are having the side effects too. Some methods and aspects of treatment are as follows (**Figure 5**).

6.1 Natural treatment

There are varies species of plants available worldwide that are used for treatment of Rheumatoid Arthritis. Some majorly used plants are mentioned below with their Scientific name, Family, Local name (**Table 3**).

As like above mentioned plants there are many more plants are available with anti-rheumatic activity. The most efficient plant species is seems to be the Acacia species. Generally the Acacia species are act as a COX-1 and COX-2 inhibitors. The in vitro assay of Acacia species proved that they shows the COX-1 and COX-2 inhibitory action. Some species having activity with the extracts described below. The most potent species of Acacia is *Acacia Senegal* which is also called as Gum Arabica or Hashab gum. It is having properties or activity that decreases the level of TNF- α , ESR, SJC, TJC, VAS, DAS28 (**Table 4**) [42–44].

6.2 Non-drug treatment

6.2.1 Physiotherapy

Physiotherapy is one of the most prominent and painless technique to get rid off from rheumatoid arthritis which comes under non-drug treatment. It is a vital part

Sr. No.	Scientific Name	Family	Local Name
1	<i>Alpinia galangal</i> Linn.	Zingiberaceae	Arattai, Perarattai
2	<i>Anacyclus pyrethrum</i>	Asteraceae	Akkirakkaram
3	<i>Aphanamixis polystachya</i> wall	Meliaceae	Malampuluvan
4	<i>Aquilaria agallocha</i>	Thymeleaceae	Agalicundanam
5	<i>Argemone Mexicana</i>	Papaveraceae	Kutiyotti
6	<i>Callicarpa macrophylla</i> Vahl	Verbenaceae	Nallai
7	<i>Capparis deciduas</i>	Capparaceae	Senkam, Sirakkali
8	<i>Cardiospermum halicacabum</i> Linn.	Mudukkottam	Modikkottan
9	<i>Carthamus tinctorium</i> Linn.	Asteraceae	Senturakam, kusumba
10	<i>Cassia fistula</i>	Caesalpiniaceae	Konnai
11	<i>Catunaregum spinosa</i>	Rubiaceae	Madkarai
12	<i>Citrullus colocynthis</i> Linn.	—	Paitummatti
13	<i>Commiphora myrrha</i> Nees	Burseraceae	Vellaippapolam
14	<i>Commiphara wightii</i>	Burseraceae	Kiluvai
15	<i>Cordial dichotoma</i> Forst	—	Naruvili
16	<i>Coriandrum sativum</i>	Apiaceae	Kottamalli
17	<i>Euphorbia neriifolia</i> Linn.	Euphorbiaceae	Saturakkalli
18	<i>Euphorbia ligularia</i>	Euphorbiaceae	Llaikkalli
19	<i>Ficus benghalensis</i>	Moraceae	Alamaram
20	<i>Flacourtia jangomas</i>	Flacourtiaceae	Vaiyyankarai

Table 3.
Natural herbs used in effective treatment of rheumatoid arthritis.

Plant species	Plant Part	COX-1 (DCM extract)	COX-2 (DCM extract)
A. nilitica (L.) Wild. ex Del. subsp. Tomentosa	Bark	46.3 ± 6.7	83.9 ± 4.2
	Leaf	78.1 ± 0.3	89.5 ± 1.8
A. nubica Benth	Bark	39.6 ± 5	90.4 ± 4.6
	Leaf	77.4 ± 4.6	92.7 ± 0.2
A. senegal (L.) Wild. Subsp. senegal	Bark	17.5 ± 7.1	91.6 ± 5.9
	Leaf	71.9 ± 7.43	93.7 ± 3.4

Table 4.
Plant species having COX-1 and COX-2 inhibitor activity.

in the whole lines of treatment of rheumatoid arthritis in cases of both acute and chronic condition. These are several program as follows which are included in the physiotherapy as follows:

1. Exercise – the regular exercise like walking, running, cycling, yoga, swimming etc. are very useful aspects of physiotherapy.
2. Physical therapy – the physical therapy included the use of heat and ice along with the electrical stimulation in transcutaneous region, exercise having range of motion, gentle strengthening moves, etc. which helps to decreases the swelling and pain.
3. Occupational therapy – the person who helps the patients of rheumatoid arthritis in occupational therapy is called as occupational therapist whose work is to identify and detect the problem faced by the modify it as the patient feels compatible while dealing with these stuffs.
4. Mind – body therapies – these therapies are used to stabilize the mind and thinking of patient and to give rest to his/her body. It includes deep abdominal breathing, meditation, muscle relaxation in progressive manner, visualization, tai chi, counseling, acupuncture, hot and cold comfort bath, massage and rest.

6.2.2 Surgery

This is the last line of treatment in rheumatoid arthritis. Drugs are only able to reduce the symptoms and give relief from pain. But when the situation of patient get critical then the surgery becomes mandatory. And this helps in restoration of joint and its movements. There are several surgeries like spinal surgery, hip replacement surgery, knee replacement surgery, total joint replacement, carpal tunnel release, synovectomy, bone and joint fusion surgery [45–47].

6.3 Drug treatment (modern treatment strategies)

In the drug treatment there are two categories in drugs one is DMARDs which is major one and another is Adjuvant drugs which is minor one. The main aim of this type of drug treatment is to minimize the inflammation, swelling and pain in joints of patient. Also it prevent the further bone erosion and damage of articular cartilage after the diagnosis. The drug treatment helps the patient to get relief from the deadly pains and stabilize the joint functions and its motility.

6.4 DMARDs

DMARDs are referred as Disease Modifying Anti-Rheumatoid Drugs or (SAARDs) Slow Acting Anti-Rheumatoid Drugs. From the very old days the first line of treatment for rheumatoid arthritis was use of NSAIDS, but recently after lots of research on various aspects of rheumatoid arthritis the DMARDs are considered to be the first line of treatment as a Modern Treatment for Rheumatoid Arthritis. It is better to take more than two drugs of same class i.e. DMARDs alternatively because the DMARDs loses its potency with prolonged use. DMARDs are of two types one is non-biological type and another is biological type as follows: (Following are the types or classes of drugs are explained in the form of their examples).

6.5 Non biological drugs

6.5.1 Immunosuppressant

6.5.1.1 Azathioprine

Azathioprine get converted into the 6-Mercaptopurine by the enzyme thiopurine methyl transferase (TPMT) and suppress the cell mediated immunity very potently. It comes under purine synthetase inhibitor class. The Azathioprine selectively affect differentiation and function of T-cells and natural killer cells. It also minimizes the inflammation. In the modern treatment the Azathioprine is given with the corticosteroids due its steroid sparing effect (**Figure 6**).

6.5.1.2 Methotrexate

It is the dihydrofolate reductase inhibitor which has very prominent immunosuppressant and tremendous anti-inflammatory property. Methotrexate helps the patient to get relief very rapidly within 3 to 6 weeks. Therefore, it is more preferable than any other medicaments in initial treatment. Among all the DMARDs methotrexate is the first choice due to its most predictable response and long term sustainability. Mostly combined regimens of DMARDs includes methotrexate. If the above DMARDs are failed to treat the patient then the immunosuppressant like cyclosporine, chlorambucil, cyclophosphamide were used [48].

6.5.2 Other immunomodulators

6.5.2.1 Sulfasalazine

It is the drug of choice in second line of treatment or in combined regimen with methotrexate. Sulfasalazine is synthesized from sulfapyridine and 5-amino salicylic acid, it have the potent anti-inflammatory activity which is used in bowel and in ulcerative colitis. The exact mechanism of action is still not known. The SSZ variant of sulfasalazine was designed in 1938 specially for the treatment of rheumatoid arthritis. The main pharmacological effects of sulfasalazine are affecting the bacterial flora, inflammatory cell function and immunological process. The approximate mechanism of action of Nf-kB, osteoprotegerin (OPG) and RANK-ligand.

6.5.2.2 Hydroxychloroquin/chloroquin

Hydroxychloroquin is the drug used mostly to treat the malaria patient. Along with malaria it is also used in treatment of rheumatoid arthritis due to its low

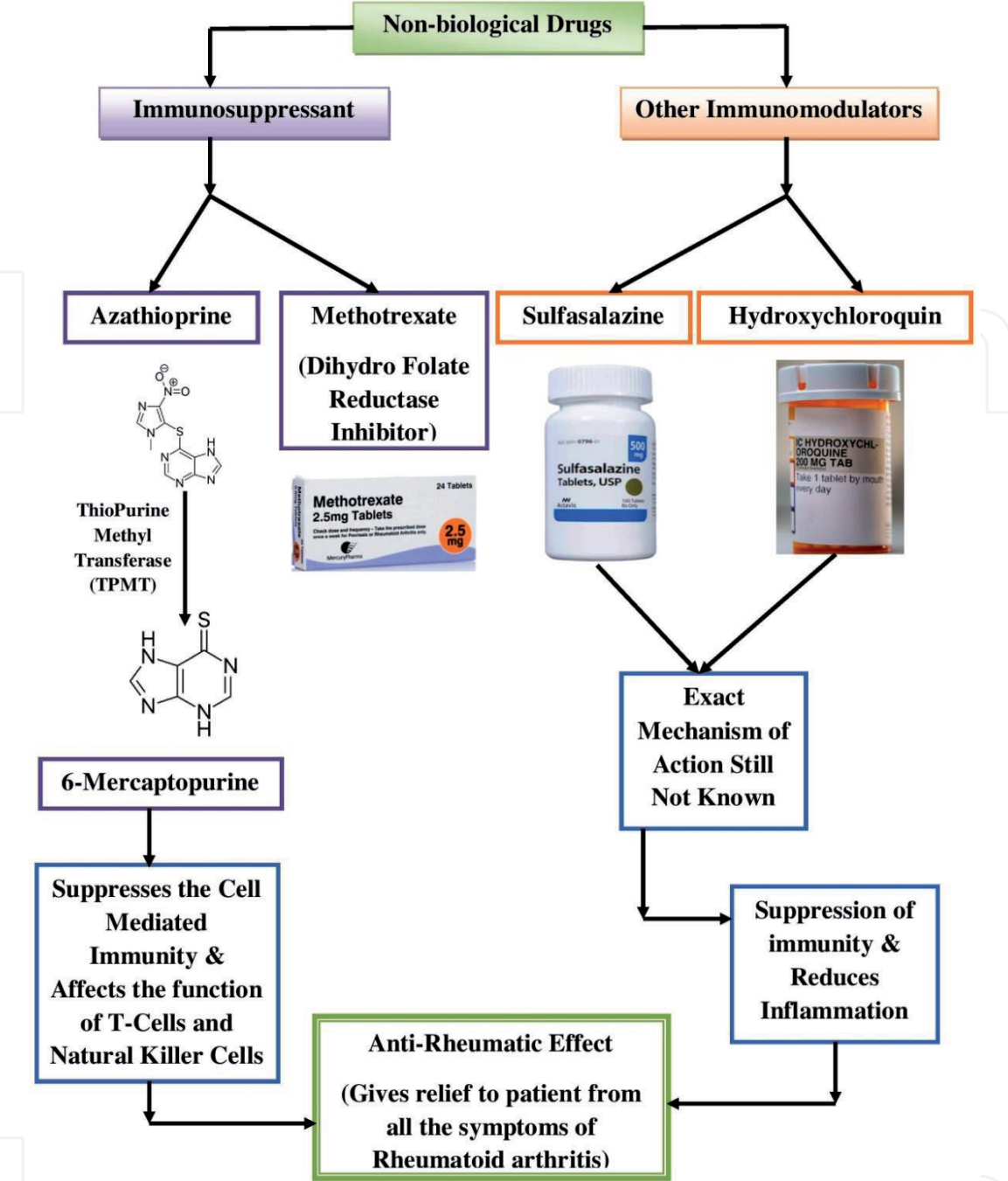


Figure 6.
Non-biological drugs for treatment of rheumatoid arthritis.

toxicity. Its exact mechanism of action is not elaborated yet but approximately it reduces the monocyte interleukin-1 along with inhibition of B-lymphocytes. Also it have some proposed mechanism of actions like stabilization of lysosomes and processing of antigens. This drug is advised only when small quantity of damage to join can recorded and it is must be taken with methotrexate or sulfasalazine [49].

6.6 Biological drugs

6.6.1 TNF-α inhibitors

TNF-α (Tumor Necrosis Factor alpha) is the most important responsible factors for the cause of rheumatoid arthritis. So, in modern treatment the mostly used drug is TNF-α inhibitors (Figure 7).

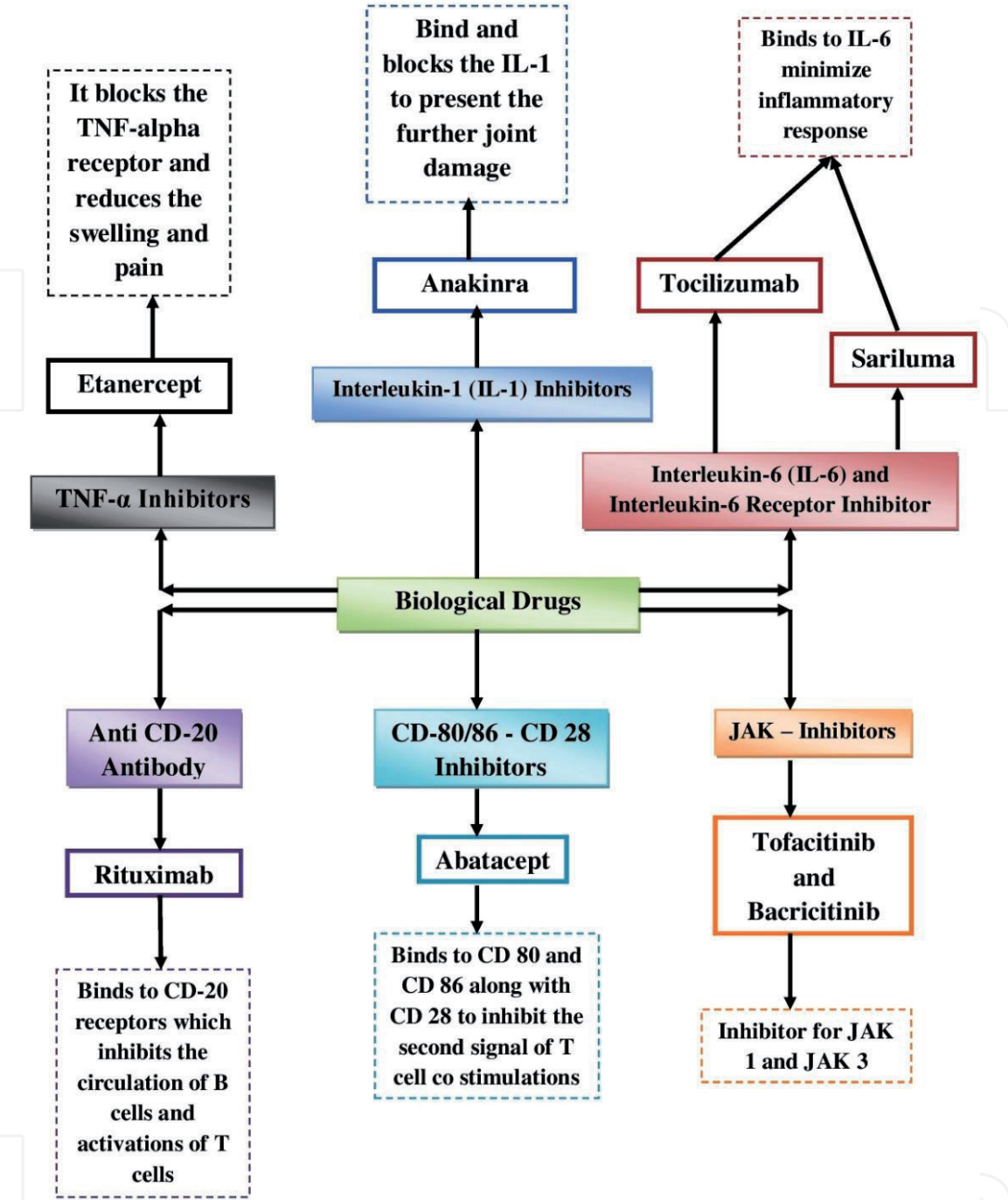


Figure 7.
Biological drugs for treatment of rheumatoid arthritis.

6.6.2 Etanercept

It is the subcutaneous injection which is composed of fusion protein of TNF – Receptor with FC portion of human IgG₁. It binds and blocks the TNF-α from activating the TNF-α receptors. There are also some drugs available in the class of TNF-α inhibitors like infliximab, adalimumab, certolizumab, golimumab.

6.6.3 Interleukin-1 (IL-1) inhibitors

Along with TNF-α, IL-1 is also the important responsible protein in etiology of rheumatoid arthritis. The IL-1 inhibitors are like Anakinra, Rilonacept, Canakinumab.

6.6.4 Anakinra

In 2001, USA and in 2002, Europe first launched this drug which was specially derived for rheumatoid arthritis treatment. This bind and blocks the IL-1 to prevent the further joint damage. Initially Anakinra was the main drug of modern treatment but nowadays it is used more in the treatment of the gout and polyserosities as compare to rheumatoid arthritis.

6.6.5 Interleukin-6 (IL-6) and interleukin-6 receptor inhibitor

In 1986 scientists was found the key cytokine moiety in the pathogenesis of rheumatoid arthritis named IL-6 which having prominent pro-inflammatory activity. To prevent this IL-6 inhibitors are derived.

6.6.6 Tocilizumab

It is the very first humanized recombinant IgG₁ monoclonal antibody which get binds to both the types of IL-6 that is soluble and membrane bound to block its action and to minimize the initiated inflammatory response.

6.6.7 Sarilumab

It is the second human immunoglobulin G1 IL-6 receptor antagonist monoclonal antibody working as same as above mentioned tocilizumab [50].

6.7 Anti CD-20 antibody

6.7.1 Rituximab

From 2006 onwards the rituximab was used in treatment of rheumatoid arthritis along with methotrexate and TNF- α as a combined dose regimen. It is the chimeric murine-human monoclonal antibody which get binds to CD-20 receptors which inhibits the circulation of B cells and activations of T cells.

6.8 CD-80/86: CD 28 inhibitors

6.8.1 Abatacept

It is the recombinant fusion protein given by in infusion and subcutaneous which is combination of part of FC domain of human IgG with extracellular domain of T cell inhibiting receptor CTLA4. It get binds to CD 80 and CD 86 along with CD 28 to inhibit the second signal of T cell co stimulations. It was given under combined dose regimen with methotrexate.

6.8.2 JAK: inhibitors

JAK (Janus-Kinase) is the cytoplasmic protein tyrosine kinase which is responsible for the signal transduction of the nucleus from the gamma chain (common) of plasma membrane receptor for the IL-2, IL-4, IL-7, IL-9, IL-15, IL-21. These all interleukins are the very important medications of many pro-inflammatory and inflammatory components like cytokines, interferons, interleukin-6. So to prevent and inhibit this the JAK inhibition are approved by FDA in 2012 in USA and by

EMA in European Union in 2017. The two main JAK inhibitors are tofacitinib and baccicatinib. Tofacitinib is the inhibitor for JAK 1 and JAK 3 with large affinity and for JAK 2 and tyrosine kinase 2 in with little affinity. It is used for severe arthritis either in monotherapy or with methotrexate. Also the baccicatinib is also works as same as tofacitinib [51].

6.9 Adjuvant drugs

6.9.1 Corticosteroids

Glucocorticoid is the most potent corticosteroid that can used at any stage in treatment of rheumatoid arthritis in modern treatment. It is used to minimize the swelling, pain and slowing down the joint destruction along with preventions of bone erosion as it have promising anti-inflammatory and immunosuppressant activity. Though it is administered in combination with first and second line drugs in the form of intraarticular injection it does not give total relief from rheumatoid process.

7. Drawbacks of modern treatment strategies

Among the DMARDs the dihydrofolate reductase immunosuppressant are causes the bone marrow depression, oral ulceration and G.I. upset. Methotrexate causes the liver cirrhosis when its is used in prolonged therapy. It is contraindicated in pregnancy, breast feeding, liver disease, active infection, leucopenia and peptic ulcer, hematological abnormalities, congenital deformities in pregnancy. Sulfasalazine produces neutropenia, thrombocytopenia, hepatitis, idiosyncrasy, skin reaction, pneumonitis, agranulocytosis, hemolytic anemia, reduction in male fertility. The regular blood count monitoring is necessary in case of this treatment. In case of treatment with Immunomodulators; due to prolonged use of hydroxychloroquin get accumulated in tissue and produces toxicity and other adverse effects like retinal damage, corneal opacity, rashes, graying of hairs, irritable bowel syndrome, myopathy, neuropathy. TNF- α blockers causes redness, itching and swelling at injection site along with occasional chest infection. Higher use of adjuvant drugs leads to patient becoming the steroid dependent along with over threatening disease and vasculities. On other hand IL-1 causes itching, pain and redness at the site of injection along with severe infections, decrease in WBC and platelets in some patients. The IL-6 inhibiting causes diverticulitis, purulent peritonitis, lowering the GI perforation, fistula, abscess, neutropenia, thrombocytopenia, hyperlipidemia, infections, liver enzyme elevation. Abatacept is not able to give with TNF- α inhibits due to do rise of severe infections. Also it causes hypersensitivity, anaphylaxis, anaphylactoid reactions, tuberculosis, sepsis. There is no any study available regarding that whether the drug is safe for pregnant woman or not. The anti-CD 20 antibodies are responsible for headache, fever, skin rashes, dyspnea, hypotension, nausea, rhinitis, pruritus and mild angioedema along with hypogammaglobinemia. There is very limited information related to the administration of this drug to pregnant woman. Along with this the JAK-inhibitors produces the hypotension, nausea, diarrhea, increase in LDL, HDL and total cholesterol, vein thrombosis, pulmonary embolism, upper respiratory tract infections. The JAK-Inhibitors are contraindicated in the patients with neutropenia, tuberculosis, severe infections, severe liver impairment and pregnancy. To overcome this all drawbacks the use of natural treatment on large scale is preferable [52].



Figure 8.
Survey on rheumatoid arthritis in Canada.

8. Severity

The Rheumatoid Arthritis is most likely available disease now in all over the world [53]. There is one survey run in Canada on “Self-reported prevalence and number of individuals with arthritis by age and sex, household population aged 15 years and older”, in 2007 and 2008 which is represented graphically below [54]. From the above graph it is clearly shown that the severity of RA is increased day by day and year by year in Canada in year 2007 and 2008 (**Figure 8**) [55].

9. Severity and survey in India

In India also the severity of RA is on large scale and the yearly surveys are done for its analysis and data were published. Following are some surveys made in various regions of India for RA by Indian Physicians and expert people of RA (**Table 5**) [56, 57].

Sr. No.	Year	Area of survey	Patient population size recorded
1	1988	Pune (Maharashtra)	110
2	1992	Nationwide	11931
3	1993	5 villages of Ballabhgarh township (Haryana)	39826
4	1994	West Bengal	4800
5	1995	Uttar Pradesh	74
6	2001	Bhigwan, Pune (Maharashtra)	5998
7	2003	Jammu (Jammu and Kashmir)	1014
8	2003	Lucknow (Uttar Pradesh)	148
9	2005	New Delhi	81
10	2005	Manipal (Karnataka)	141
11	2006	Lucknow (Uttar Pradesh)	102

Sr. No.	Year	Area of survey	Patient population size recorded
12	2006	New Delhi	211
13	2007	New Delhi	66
14	2007	Northern India	96
15	2007	Lucknow (Uttar Pradesh)	215
16	2007	Chennai (Tamil Nadu)	40
17	2009	Lucknow (Uttar Pradesh)	400
18	2009	Northern India	102
19	2009	Lucknow (Uttar Pradesh)	400
20	2009	Pune (Maharashtra)	8145
21	2011	Hyderabad (Andhra Pradesh; Telangana)	84
22	2011	Village of Ottoor (Kerala)	437
23	2012	Mumbai (Maharashtra)	93

Table 5.
Survey on rheumatoid arthritis by physicians and expert in India.

10. Conclusion

The Rheumatoid Arthritis is chronic autoimmune disorder occurs worldwide due to change in life style, unavailability of proper diet, hereditary characters, excessive alcohol consumption, etc. However the actual reason is still unknown. The Rheumatoid Arthritis is generally occurs in joints causing swelling and severe pain which further leads to destruction of bones and cartilages. First line treatment mainly includes synthetic drugs like Disease Modifying Anti-Rheumatic Drugs; monoclonal antibodies are now available for treatment for Rheumatoid Arthritis. Current treatment is not able to completely cure the Rheumatoid Arthritis form its roots as it has certain side effects such as bone marrow depression, oral ulceration, G.I. upset, skin reaction, pheumonitis, retinal damage, hypersensitivity, anaphylaxis, anaphylactoid reactions etc. So patients suffering from it require complete cure from it which leads to utilization of natural herbs for treatment of RA. Herbal treatment includes medicinal plants along with Acacia species which are mostly preferable because they are more potent, efficient; reduce pain and inflammation precisely along with lesser side effects. Medicinal herbs act is a blockers or inhibitors for the arthritis inducing factors. Due potential benefits of herbal medicines there is tremendous interest growing in medicinal herbs and there is need for more investigate in-vivo applicability. Currently severity of RA is rapidly growing day by day. Best current management pathway for RA contains identification, utilization of medicinally potent herbs along with physiotherapy which mainly include regular exercise like walking, running, cycling, yoga, swimming and acupuncture. As RA chronic disorder which creating permanent disability to joints which may leads to life threatening conditions; social awareness about RA and its remedies are needed.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

TNF- α	tumor necrosis factor
ESR	erythrocytes sedimentation rate
SJC	swollen joint count
TJC	tender joint count
VAS	visual analog score
DAS	disease activity score
RA	rheumatoid arthritis
DCM	dichloromethane
IL1	interleukins 1
PMNs	polymorphic nucleoneutrophills
ROS	reactive oxygen species
MMP1	MetrixMetalo-Protease 1
MMP3	MetrixMetalo-Protease 3
RANKL	receptor activating for nuclear factor kappa β ligands

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