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Review Article

Review on Management of Rheumatoid Arthritis by using Natural Herb

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ABSTRACT

Rheumatoid arthritis is an enduring inflammatory disease that is categorized by bumping off the joint and rigidity, bone and cartilage devastation all above the joints. It is an autoimmune disease or disease caused by factors like smoking, obesity, etc. Cytokines are the main inducers for rheumatoid arthritis which produce interleukin 1β and interleukin 6 factors that cause the devastation of synovium and cartilage present at the joints. The deformation of skeletal muscles is observed in an arthritic patient. The present review is a discussion on rheumatoid arthritis that includes etiology, pathology and pathogenesis, signs and symptoms, clinical complications, diagnosis, treatment, therapy, certain patents and applications. The patents include the development of numerous novel techniques for the management of rheumatoid arthritis and diseases associated with rheumatoid arthritis. The targets to treat rheumatoid arthritis are interleukins, tumor necrosis factor-alpha, sialoprotein I and several other factors. Different biomarkers are used for different types of rheumatoid arthritis and the mechanism also varies. Certain marketed formulations were enlisted. Recent trends in the management of rheumatoid arthritis are the main concept of this article.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often the bone and cartilage of joints are destroyed and tendons and ligaments weaken. All this damage to the joints causes deformities and bone erosion, usually very painful for a patient. Common symptoms of RA include

morning stiffness of the affected joints for > 30 min, fatigue, fever, weight loss, joints that are tender, swollen and warm and rheumatoid nodules under the skin. The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation. It can also affect young children even before the age of 16 years, referred to as juvenile RA (JRA), which is similar to RA except that rheumatoid factor is not found. In the West, the prevalence of RA is believed to be 1–2% and 1% worldwide.

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Clinically, the diagnosis of RA can be differentiated from osteoarthritis (OA) as the affected areas in RA are the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints. OA typically affects the distal interphalangeal (DIP) joint (Fig.1). OA is the most common type of arthritis and is caused by wear and tear rather than an autoimmune condition. It has no effects on the lungs, heart, or immune system. In addition, OA typically affects only one side of the body, as opposed to the symmetrical nature of RA. Another differentiating factor is that RA patients suffer from persistent morning stiffness for at least ≥ 1 h. Patients with OA may have morning stiffness but this typically resolves or decreases within 20–30 min.

The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease and rest. Treatments are generally customized to a patient's needs and depend on their overall health. This includes factors such as disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease. This review briefly highlights the classic and current treatment options available to address the discomfort/complications of RA. An exhaustive review was recently published by Smolenetal [1].

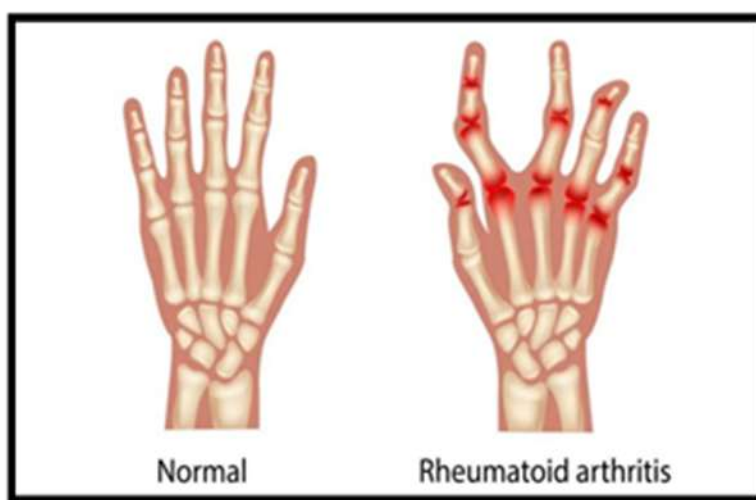


Fig. No. 1] Rheumatoid Arthritis Disease

SYMPTOMS:

Common Joint Symptoms:

- **Pain and tenderness:** Pain in the affected joints, both at rest and during movement.
- **Swelling and warmth:** The joints may appear swollen, feel warm to the touch, and be tender.
- **Stiffness:** A notable stiffness, particularly in the mornings or after periods of inactivity, often lasting for an hour or more.
- **Reduced motion:** Difficulty moving the affected joints and performing daily activities like making a fist or combing hair.
- **Symmetrical pattern:** Symptoms often affect the same joints on both sides of the body, such as both hands or both feet.

Systemic (Whole-Body) Symptoms

- **Fatigue:** A persistent feeling of tiredness and lack of energy.
- **Fever:** An occasional low-grade fever.
- **Loss of appetite:** A reduced desire to eat.
- **Bumps:** Some people may develop bumps (rheumatoid nodules) over the affected joints.

Other Potential Symptoms

- **Organ involvement:** In addition to joints, RA can also affect other body parts, including the eyes, skin, lungs, heart, and nervous system.
- **Symptoms of flares:** Symptoms can worsen significantly during "flares," which may be triggered by stress, viral infections or sudden changes in medication.

CAUSES

- **Immune system malfunction:** The immune system incorrectly identifies the synovium as a foreign threat, triggering an inflammatory response that damages cartilage and bone.
- **Genetic factors:** A family history of RA increases your risk and specific genes like those in the HLA-DRB1 region are linked to

a higher likelihood of developing the disease.

Environmental triggers

- **Smoking:** A well-known risk factor that not only increases the risk of developing RA but also leads to more severe disease symptoms.
- **Infections:** Certain viral or bacterial infections may trigger RA in genetically predisposed individuals.
- **Other environmental factors:** Exposure to certain kinds of dust and occupational fibres are also potential triggers.
- **Hormonal changes:** RA is more common in women, particularly during their childbearing years, suggesting a role for female hormones in the disease's development.
- **Microbiome and diet:** Changes in the gut microbiome and certain dietary patterns like a low intake of vitamin C and high intake of red meat have been linked to an increased risk of RA.
- **Obesity:** A higher body mass index (BMI) is associated with an increased risk of developing RA.
- **Periodontitis:** Infections in the mouth, such as gum diseases are associated with an increased risk of RA.

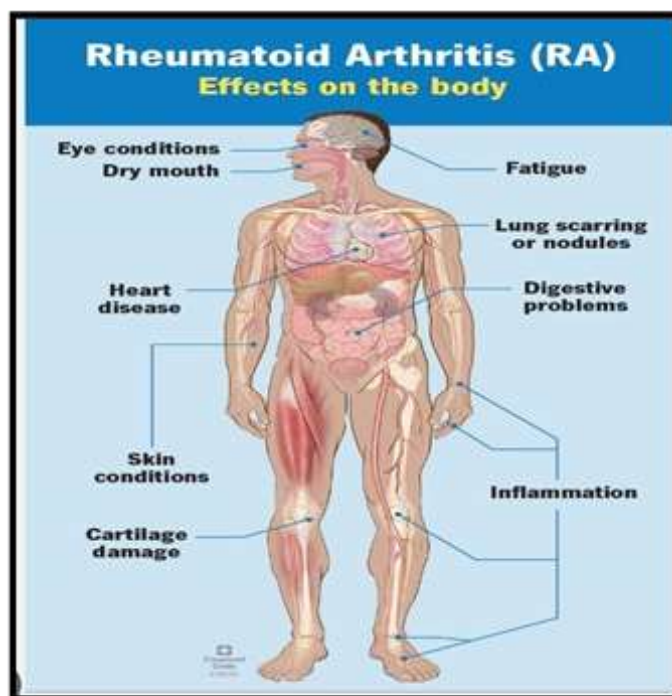


Fig. No. 2] Rheumatoid Arthritis Effect On The Body

PATHOPHYSIOLOGY

Although the pathophysiological mechanisms for RA are not fully elucidated, several hypotheses have been postulated. It has been reported that immunological processes can occur many years before symptoms of joint inflammation are noticed, the so-called pre-RA phase. The interactions between epigenetic modifications on the genomic structure and environmental factors can lead to modified self-antigens as in the case of immunoglobulin G (IgG), type 2 collagen and vimentin. These proteins with arginine residues can be converted to citrulline by peptidyl arginine deiminases in a post-translational modification called citrullination. Moreover, joint disorders like synovial hyperplasia or synovial infections can trigger cytokine release that may cause joint inflammation and also modified self-antigens.

Due to the susceptibility genes HLA-DR1 and HLA-DR4, the immune system is no longer able to recognize citrullinated proteins (vimentin, type

II collagen, histones, fibrin, fibronectin, Epstein-Barr nuclear antigen 1, α -enolase) as self-structures. Antigens are taken up by antigen presenting cells (APC), which are dendritic cells that are activated to initiate an immune response. The whole complex migrates to the lymph node, where the activation of CD4+ helper T cells takes place. Furthermore, the germinal centre of the lymph node contains B cells that get activated by reciprocal and sequential signals with T cells, an immunological process called costimulation.

An example of costimulation is the interaction between CD28 and CD80/86. At this level, B cells undergo somatic hypermutation or class-switch recombination and start to proliferate and differentiate into plasma cells that produce autoantibodies depending on the receptors of the precursor cells. Autoantibodies are proteins produced by an immune system that no longer discriminates self from non-self-structures, so self-tissues and organs are accidentally targeted. RF and ACPA are the most studied autoantibodies

involved in RA. RF is an IgM antibody with a testing specificity of 85% in RA patients, which targets the Fc portion of IgG, also called the constant region. It also forms an immune complex with IgG and complements protein, a complex able

to migrate in the synovial fluid. However, ACPA is more specific for RA and targets citrullinated proteins and after their binding interactions, immune complexes are formed with an accumulation in the synovial fluid [2].

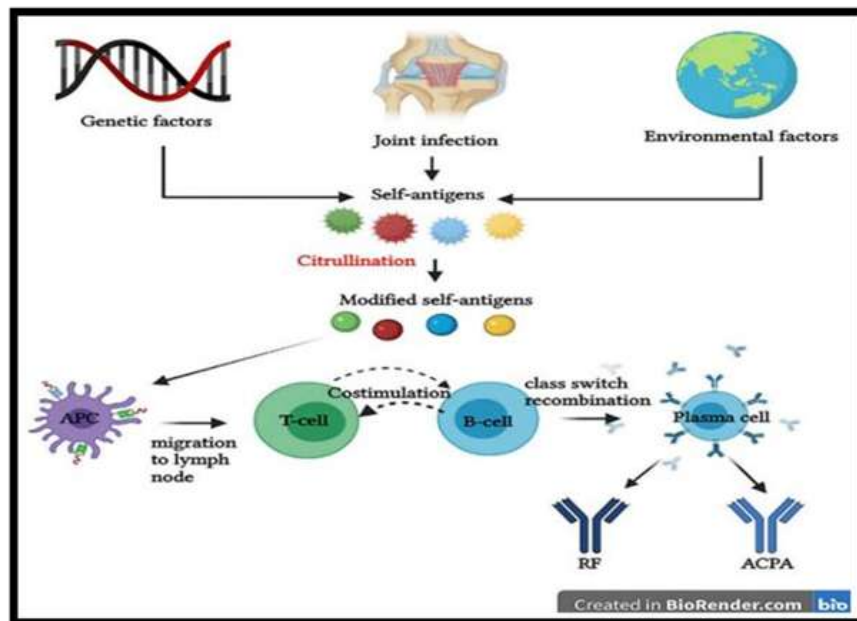


Fig. No. 3] Pathophysiology of Rheumatoid Arthritis.

DIAGNOSIS

Rheumatoid arthritis can be hard to diagnose in its early stages. That's because the early symptoms can be like those of other common conditions. During the physical exam, your healthcare professional checks your joints for swelling, redness and warmth. Your healthcare professional also may check your reflexes and muscle strength.

- **Blood tests:**

People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR) also called sed rate or C-reactive protein (CRP) level. This may show a higher level of inflammation in the body. Other blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

- **Imaging tests:**

You may have X-rays to track rheumatoid arthritis in your joints over time. MRI scans and ultrasound tests may help with diagnosis. They can show how bad the condition is(3).

MODERN TECHNIQUES USE IN THE TREATMENT OF ARTHRITIS

- **X-ray:**

X-ray imaging is the most widely accessible and used tool for the diagnosis of the knee OA, as it is a non-invasive method. It is comparatively inexpensive, rapid and easy to assess imaging technique in order to monitor disease progression. In addition to this, 4.1X-ray imaging can reflect the variations in the structure of bones at early stage.

- **Computed tomography (CT):**

CT is a 3D volume image of an organ. It is the most commonly used method to image the human body. In addition, CT also involves the injection of contrast agents and contact with significant ionising radiations that are the negatives of CT.

- **Magnetic resonance imaging (MRI):**

The non-invasive magnetic resonance imaging is also appropriate and widely used for rheumatoid arthritis diagnosis. It offers a precise diagnosis of the core pathophysiologic phenomena that occur in the myocardium of individuals suffering from RA e.g., myocarditis, vasculitis, and macro-/microcoronary artery disease. The disadvantage of this imaging modality is that it is expensive and inefficient for patients with retained metallic medical prostheses.

- **Positron emission tomography (PET):**

PET is a nuclear imaging modality that utilises radioactive material. It is generally taken up at places of active inflammation and offers improved visualisation of the target lesion. This technique perceives acceptance of positron-emitting radiotracers and allows exact measurement of volumes along with quantification of blood flow. Its disadvantages include high cost and ionising radiation.

- **Carotid ultrasound (CUS):**

CUS is currently the most effective non-invasive technique that provides the most robust and confirmed assessments of development of RA. It is also cost-effective imaging modality that gives disease information at an early stage of RA patients[4].

- **Surgery:**

Joint surgery in patients with RA reached a peak in the 1990s. However, a 2010 study showed decreased rates of joint surgery in RA patients 40–59 years of age. In contrast, patients older than 60 years had increased rates of surgery. Surgery is a last resort for the treatment of RA. Indications include intractable joint pain or functional decline due to joint destruction after all nonsurgical approaches have failed. At this point, the disease is considered “end-stage.” The goal of surgical management is to relieve pain for the patient and restore the function of the joints. A patient needing surgical treatment should be evaluated based on their customized needs because there are many different types of surgery.

A tenosynovectomy involves the excision of inflamed tendon sheaths or repairing a recent tendon rupture, most commonly in the hand. Radiosynovectomy is an alternative to surgical synovectomy; it involves intra-articular injection of small radioactive particles, is cost-effective and can treat multiple joints simultaneously. Repair of ruptured tendons can also be done through arthroscopy most commonly in the rotator cuff of the shoulder. Excision of an inflamed synovium via arthroscopy or open synovectomy is no longer commonly used due to the availability of more effective options. Another surgical option is osteotomy. In this procedure, weight-bearing bones are realigned to correct valgus or varus deformities most commonly in the knee. Joint fusion can be done to stabilize joints that are not easily replaceable such as the ankle, wrist, thumb, and cervical spine. A procedure for soft-tissue release can be done to correct severe contractures around joints causing decreased range of motion; this is an older procedure that is not commonly utilized. Small-joint implant arthroplasty can be done to reduce pain and improve hand function, most commonly in the metacarpophalangeal joints. Metatarsal-head excision arthroplasty is

done to alleviate severe forefoot pain. Lastly, a total joint replacement involves removing the damaged joint and replacing it with a metallic, plastic, or ceramic prosthesis. This is most commonly done in the shoulder, elbow, wrist, hip, knee, and ankle. The major contraindication for surgical joint replacements is the presence of active systemic articular infection.

NEWER MEDICATIONS

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine. It relieves symptoms and retards the progression of RA. It is recommended to be used in combination with MTX but can constitute a monotherapy if patients do not respond to MTX. Side effects include hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow damage .

Biologics, also known as biological DMARDs, are rapidly effective in retarding the progression of the joint damage caused by RA. They are considered to be a more “direct, defined and targeted” method of treatment . Nonetheless, biologics pose the problem of serious side effects, such as increased risk of infections. Other common side effects include neurologic diseases like multiple sclerosis and lymphoma .

Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are recommended if other second-line medications are not effective. Unfortunately, these medications

tend to be very expensive and their role in treating patients at various stages of RA and with various mechanisms of action is a matter of continuous investigation. They are often used in combination with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic medication has a different mode of administration[5].

HERB USED IN THE TREATMENT OF RHEUMATOID ARTHRITIS.

PLANT PROFILE:

EHRETIA LAEVIS ROXB.

- **Introduction:**

Ehretia laevis is a rare Indian medicinal plant used from the ancient period, it belonging to a member of the Boraginaceous or Borage family, and is native to India, Pakistan, Laos, Myanmar, Vietnam, China, and Bhutan. The *Ehretia laevis* Roxb. Is high valued medicinal plant and becoming rare in the state of Maharashtra. It has religious importance among Hindus. It is growing luxuriantly growing at Alandi near the Dnyaneshwar temple. The use of medicinal plants is increasing worldwide. The general information of *Ehretia laevis* given below [6].

Ayurveda, the science of life, though has its own principles, is incorporating new theories and drugs in it and presenting them according to its principles. Folklore Medicines, as the major remedy in traditional medical systems, have been used in medical practice form thou-sands of years and have made a great contribution in maintaining human health¹. A majority of the world’s population in developing countries like India still depend on herbal medicines to meet its health needs. India perhaps is the most unique country



endowed with the richest traditions of tribal or folklore medicine. These medicines are used by the traditional practitioners for various ailments like Fracture, Arthritis, Hyperlipidaemia, Hypertension, Kidney disorder Diabetics, Liver disorders etc. with therapeutic benefits. Scientific validation of these claims is re-quired for wider application of the herb in therapeutic practice.



Fig . No. 4] Ehretia laevis Roxb Plant

- **Kingdom:** Plantae.
- **Division:** Tracheophyta.
- **Class:** Magnoliopsida.
- **Order:** Boraginales
- **Family:** Boraginaceae.
- **Genus:** Ehretia.
- **Species:** *Ehretia laevis* (Roxb).

- **Botanical name:** *Ehretia laevis* Roxb.
- **Synonyms:** *Ehretia laevis* Var. *platyphylla* Merrill.
- **Common/Local Name:** Khanduchakka.
- **Regional and Other Names:** English: Ehretia, Gujarati: Vadhavaradi, Hindi: Bhairi, Chamror, Datranga, Tamoriya, Nepali: Datingal, Konkani: KaloGamdo, Marathi: Ajaanvruksha, Datrang, Tamil: Kuruviccai, Kalvirasu, Telugu: Tellajuvvi, Paldattam, Malayalam: Harandi, Sanskrit: Charmavriksha.
- **Habit and Habitat:** Small deciduous tree, with short stem and grey bark, occasionally common.
- **Native:** India, China, Bhutan, Pakistan, Laos, Myanmar.
- **Flowering and Fruiting Time:** January to April.
- **Flowers:** White, up to 8 mm.
- **Fruits:** A small drupe, at first red, at length black.
- **Microscopic Characteristics Of Ehretia Laevis Roxb:**



Fig. No. 5] Microscopic Characteristics of Ehretia Lavies Roxb.

▪ Properties and Uses

The inner bark of *Ehretia laevis* Roxb is used as food. Leaves are applied to ulcers and in headaches. Fruits are astringent, anthelmintic, demulcent, expectorant, diuretic, and used in the affection of urinary passages, diseases of lungs, and spleen. Powdered kernel mixed with oil is a remedy for ringworm. Seeds are anthelmintic [7].

Ayurveda, the science of life, though has its own principles, is incorporating new theories and drugs in it and presenting them according to its principles. Folklore Medicines, as the major remedy in traditional medical systems have been used in medical practice form thousands of years and have made a great contribution in maintaining human health.

A majority of the world's population in developing countries like India still depend on herbal medicines to meet its health needs. India perhaps is the most unique country endowed with the richest traditions of tribal or folklore medicine. These medicines are used by the traditional practitioners for various ailments like Fracture,

Arthritis, Hyperlipidemia, Hypertension, Kidney disorder Diabetics, Liver disorders etc. with therapeutic benefits. Scientific validation of these claims is re-quired for wider application of the herb in therapeutic practice.

The present study "Efficacy of Folklore plant Khanduchakka (*Ehretia laevis*Roxb.) Patra Siddha Tail in Sandhivata" assumes significance due to absence of any planned study on the folklore drug, which is widely practiced in certain parts of Maharashtra state specially In Vidharbha region for the treatment of Osteoarthritis. This plant is commonly used in Wardha district for fractures, sandhivata and wound healing by rural population. Local name of this plant is Khanduchakka. People from Wardha District are using Kalka or Kal-ka mixed with oil of this plant since many years. It was routinely employed by rural people for Sandhivata management, with surprising output. This folk tribal herbal drug not mentioned in standard Ayurvedic text, was found to be very effective in Osteoarthritis.

According to modern literature, Osteoarthritis is most common type of arthritis affecting the elderly

people. It is a slowly progressive joint disease and a major cause of disability, limiting activity and impaired quality of life especially in elderly people⁴. It is reported that these degenerative changes in joints arise from the age of 30 years & by the age of 65 years 80% of people may have radiographic evidence of osteoarthritis although only 25% may have symptoms.

Prolonged and apparently uneventful use of an herbal medicine may offer testimony of its safety and efficacy. The research approaches should differentiate between herbal medicines which have documented experience from along period of use with those herbs whose traditional use has not been established. Folk medicine lacks a modern scientific basis. It is important that modern

scientific studies be done on these medicinal plants so that the plants may be used as remedies in a more rational and scientific manner.

Today in the management of osteoarthritis people are commonly using long term NSAIDs COX-2 inhibitors, opioid analgesics, topical NSAIDs, intra-articular glucocorticoids. These drugs are expensive as well as having symptomatic relief but typically short lived. The present study was undertaken to evaluate the science behind such wonderful herb, to prove its properties on scientific ground, to provide cheap and safe option for Sandhivata, to effectively adopt the therapeutic uses of this plant and to help needy patients. Also, it would be one of the best options of crop cultivation to farmer for financial support^[8,9].



Fig. No. 6] Parts of *Ehretia laevis* Roxb

❖ BOTANICAL DESCRIPTION

A medium-sized tree, *Ehretia laevis* can grow as high as 12 metres. Its falling branches have dark green leaves that range in size from 1.2 to 3.8 cm in width and 2 to 7.8 cm in length. Obtuse lateral veins on each side of the midrib and a petiole that is only slender and 2-3 cm long characterise the shape of the leaves. The plant's bark is light grey and uneven. When full or mature, the white blooms turn into spherical orange fruits.

Phytochemistry Barks, leaves, and fruits of *E. laevis* have been identified as potential sources of phytoconstituents by ethnobotanical studies. Secondary and primary metabolites were extracted and isolated from, petroleum ether, chloroform, and methanolic extracts of the plant's bark and leaves as a result of phytochemical research. Pentacyclic triterpenoids, flavonoids, alkaloids, tannins, phenolic acids, hydrocarbons, aliphatic alcohols, fatty acids, ascorbic acid, amino acids, carbohydrates, benzoquinones, vitamins, and minerals are included in this list.

1. Betulinic Acid:

The reduced form of Betulinic acid is betulin (3-lup-20(29)-ene-3, 28-diol). It was the first organic compound to be isolated naturally from white birch bark (*Betula alba*), and its chemical composition was established in 1952. Betulin has a variety of pharmacological effects, including antibacterial, anti-inflammatory and anticancer effects.

2. Ursolic acid :

A well-known pentacyclic terpenoid of plant origin, Ursolic acid (3-hydroxy-urs-12-ene-28oic acid) has a wide spectrum of pharmacological effects including antiviral, antiulcer Osos, anti-inflammatory and anticancer activity.

3. α -Amyrin:

Ursolic acid's precursor -amyrin (3-hydroxy-urs-12-en) is mostly found in plants and has a variety of pharmacological properties including anxiolytic, depressive, anti-inflammatory, antihyperglycemic, and hypolipidemic properties. It was demonstrated that -amyrin could be a promising molecule for the alleviation of pain and inflammation when it was given to rats in a dose of 30 mg/kg. This substance considerably reduced inflammation brought on by partial sciatic nerve ligation as well as heat and mechanical hyperalgesia. Through the activation of cannabinoid receptors, the substance produces its prolonged antinociceptive effect.

4. Carbohydrates:

The phytochemical analysis of *E. laevis*' stem, bark and leaves revealed the presence of important amounts of primary metabolites such carbohydrates. The leaves included three types of carbohydrates, including lactose, D-mannitol, and maltose. vitamin: According to research on the

quantitative analysis of trace elements in *E. laevis* leaves, the presence of minerals and vitamins such vitamins C, E, A, riboflavin and thiamine gives the leaves nutritional value. By acting as an antioxidant by scavenging free radicals and an enzyme cofactor in cells, vitamin C significantly contributes to the prevention and slowing of the onset of many diseases.

5. Mineral:

One of the most important and critical ingredients in food and feed are minerals. The development of the brain, the health of the gastrointestinal tract (GIT), the formation and strength of bones and teeth and other structural and metabolic processes within the body are all significantly influenced by minerals. *E. laevis* is said to have edible fruits and inner bark. Experimental examination of the bark, fruits, and leaves of revealed considerable number of minerals to be present.

6. Miscellaneous:

From several *E. laevis* extracts, other minor chemical classes such 1,4-naphthoquinone, dioctyl phthalate, aliphatic hydrocarbons, fatty acids, esters, and benzofurans have also been discovered. One of the significant benzoquinones involved in the production of vitamin K is Lewison (1,4-naphthoquinone, 52). A brand-new naphthoquinone called Compound 52 was isolated from the aerial portions of *E. laevis* and had substantial antibacterial, antifungal, antiviral, and anti-inflammatory properties.

7. Apigenin:

The majority of apigenin (4',5,7-trihydroxyflavone) is consumed in food every day. The most common class of flavonoids in the plant kingdom is apigenin. Tea, oranges, onions, celery, parsley, beer, and wines are abundant. Because of

its many advantages and minimal toxicity, apigenin is popular among researchers and has been suggested for usage in nutraceuticals. Apigenin demonstrates a wide range of functions and is used to treat majority of apigenin (4',5,7-trihydroxyflavone) is consumed in food every day. The most common class of flavonoids in the plant kingdom is apigenin. Tea, oranges, onions, celery, parsley, beer, and wines are abundant. Because of its many advantages and minimal toxicity, apigenin is popular among researchers and has been suggested for usage in ncer, diabetes, forgetfulness, depression, and stroke. The therapeutic potential of apigenin as an antioxidant, anti-inflammatory, and anticancer compound is supported by numerous in vitro and in vivo investigation.

8. Tannins and Phenolic Acids:

Plant phenolic acids are an essential part of the human diet and are known for their pharmacological effects including their antioxidant, anticancer, antiallergic, antibacterial and anti-inflammatory activities. A specific phenolic acid's ability to act as an antioxidant is influenced by the quantity and location of its hydroxyl groups. Tannins are a subgroup of polyphenols. Numerous plants include tannins which are water-soluble chemicals with the capacity to precipitate proteins. As important antioxidants, polyphenols are also medicinal candidates in the prevention of numerous diseases. The two main phenolic acids found in this plant's leaves and stem bark are gallic acid and tannic acid.

9. Naringenin:

The flavanone group of flavonoids includes naringenin [5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one], which is mostly found in citrus fruits like oranges, lemons, grapes, and tomatoes.

It is a typical dietary source of polyphenols that is produced by hydrolysing narirutin or naringenin-7-rutinoside. Because of this flavonoid's therapeutic potential, including its antioxidant, antidiabetic, and anti-inflammatory qualities as well as its potential against malignancies and neurological illnesses, the scientific community pays close attention to it. Naringenin works as an antioxidant by scavenging the production of free radicals and raising the amounts of various antioxidant enzymes including glutathione peroxidase, catalase and superoxide dismutase.

10. Luteolin:

A flavone called luteolin (3',4',5,7-tetrahydroxyflavone) is found in many different fruits, vegetables and medicinal plants. Lutein is abundant in a number of vegetables including celery, parsley, onion leaves, broccoli, peppers, and carrots. Numerous biological characteristics of luteolin have been reported, including antioxidant, antibacterial, anticancer, and estrogenic regulator capabilities. In human oesophageal, colon, lung, and liver malignancies as well as human oral squamous malignant cells, luteolin has the power to induce apoptosis and create anticancer effects by triggering cell cycle arrest. In xenograft models, luteolin also causes apoptosis and suppresses proliferation of human prostate cancer cells. It functions in cancer through a number of methods, including invasion, cell cycle arrest or metastasis by lowering transcription factors, inhibiting kinases and inducing cell death.

11. Kaempferol:

Kaempferol (3,4',5,7-tetrahydroxyflavone) is a flavonoid that is a member of the flavanol class. Tea, beans, apple, strawberries, spinach and apples are all rich sources of it. Its many pharmacological actions including cardioprotective, hepatoprotective, anti-inflammatory, antioxidant,



anticancer, neuroprotective and antidiabetic characteristics have recently been proven by numerous studies. Skin, colon and liver tumours.

were among the cancers for which kaempferol was no to be helpful. Additionally, it has a propensity to scavenge free radicals such as hydroxyl,

superoxide anions, peroxides, and nitric oxide. The induction of adenosine triphosphate (ATP) and lipopolysaccharide (LPS) as well as the activation of AKT and PI3K in cardiac cells are all recognised mechanisms by which kaempferol inhibits inflammation [10].

Table No. 1] Chemical Constituents Of Ehretia Lavies Roxb.

Sr. No.	Part	Chemical Constituents
1	Leaves	Rutin, Tannic Acid, Ascorbic Acid, Naphthoquinone Derivative Minerals Such As Sodium (Na), Calcium (Ca), Magnesium (Mg), Zinc (Zn), Copper (Cu), Lupeol, Gallic Acid
2	Fruit	Botulin, Decanoic Acid, Phytol, Piperazine, Amyrin, Phthalic Acid, Phenylephrine
3	Bark	Tannins, Baurinol, Phytol, Phenylephrine

Table No. 2] Role Of Chemical Constituents

Sr. No.	Chemical Constituents	Role Of Chemical Constituents
1	Flavonoid (quercetin, kaempferol)	Antimicrobial, antioxidant, anti-inflammatory, anticancer and antimalarial
2	Decanoic acid	antiseizure
3	Gallic acid	Treating Alzheimer's and Parkinson's disease by inhibiting the development of amyloid fibrils
4	phenylephrine	Decongestant, Haemorrhoids, vasopressor
5	B-sitosterol	Boost immunity and prevent influenza, rheumatoid arthritis, psoriasis
6	Decanoic acid	antiseizure
7	Phytol	Antimalarial, Anti-inflammatory
8	α and β amyrin	Prevent persistent periodontitis-related bone loss.
9	Piperzine	Anti-helminthic
10	Phenylephrine	Decongestant, haemorrhoids, vasopressor
11	Betulin	Anti-inflammatory, Antipruritic, promotes skin cell differentiation, wound healing & cosmetic purposes. Inhibits the development of sterol regulatory element-binding protein (SREBPS) and reduces the production of cholesterol and fatty acids.
12	Lupeol	Chemoprotective, Anti-inflammatory and Antiprotozoal
13	Phthalic acid	Anti-viral against dengue, chikungunya
14	Ehretinine	Antimicrobial, anti-inflammatory, anticancer and antimalarial
15	Oleanolic acid	Antimicrobial, Neuroprotective, anti-inflammatory, anticancer and antimalarial

TOXICOLOGY

When a plant or isolated molecule shows no signs of toxicity or negative effects, its therapeutic potential is regarded as excellent. Toxicity studies are widely acknowledged to be extremely important for natural products as well as for their isolated compounds. Despite the fact that *E. laevis*

has a wide range of pharmacological activities that support its widespread traditional and customary uses as an antioxidant, analgesic, anti-inflammatory, antimicrobial, antiarthritic as well as treatment for a number of livers, skin, inflammatory, dysentery, infectious and dental issues. None of the research teams acknowledged any plant toxicity. The plant is also widely



recognized as food because tribal people eat its ripe fruits [11].

TRADITIONAL MEDICINAL USES

E. laevis contains bioactive compounds that address malignancy, obesity, blood sugar, cardiovascular diseases, blood pressure, lipids and muscle wasting reduces the risk of secondary complications in viral infections particularly COVID-19. It is effective against fungal and bacterial infections often associated with viral diseases. It helps to promote neural crest cell survival and also useful for conditions such as brain ischemia, strokes, seizures, Alzheimer's, and neural diseases. It promotes thyroid uptake aiding thyroid patients. Anticoagulant and antiplatelet properties are beneficial for older adults, bedridden individuals, and heart patients. It is used in Ayurveda and Unani medicine to treat respiratory issues like asthma, cough and cold. The Garasians tribe of Rajasthan uses a bark decoction for asthma, delivery pain and colds. Tribes in Jalpaiguri, West Bengal, use a bark paste for pain relief, particularly in the lower limbs. Gujjar tribes of Uttarakhand use *E. laevis* for treating liver diseases, including jaundice. Nomadic communities prepare a paste of soaked *E. laevis* seeds with *Amomum subulatum* powder mixed in milk to treat liver ailments. Tharu community in Udham Singh Nagar, Uttarakhand, uses seed paste for healing skin disorders. It supports recovery from schizophrenia, calcium absorption, muscle protein synthesis, post-surgery recovery and sports injuries. It provides benefits in osteoporosis, anxiety, mood disturbances, migraines, Alzheimer's dementia, hair loss, shingles, malignancy, heart diseases and aging. Leaves, stems, bark and fruits are utilized in dye production, cosmetics and wine manufacturing. The root has extract is applied for inflammation in Amravati, Maharashtra. Tribes in Dhule

(Maharashtra) use the stem as a toothbrush to treat mouth ulcers and gum problems. In Rajasthan, leaves are chewed to heal mouth blisters [12].

▪ **Biological Activity Of *Ehretia laevis***

Anti-inflammatory, Antiarthritic and Analgesic Activities

An ethnobotanical survey revealed that the tribes of rural and forest remote areas are still depending to a great extent on indigenous system of medicine. The community of Jalpaiguri district, West Bengal local people apply the paste from the bark of *E. laevis* to treat painful limbs. The bark juice of the plant can also be used traditionally in obstetric practice for the relief of delivery pain. The plant has been recommended as an ethnic remedy for pain and inflammation. In the community of Amravati District, Maharashtra, the people also apply the root extract for the cure of inflammation. Recently, in vivo studies established the anti-inflammatory potential of methanol, chloroform and aqueous extracts of *E. laevis*. including its potential for the treatment of arthritis, a condition characterized by chronic inflammation. Besides, the methanolic extract of *E. laevis* leaves has been investigated for its antiarthritic activity in induced arthritis models in rats. Phytoconstituents like hexadecenoic acid (palmitic acid), oleanolic acid and other fixed oils were suggested to be responsible for its antiarthritic actions. Although systematic scientific studies are still lacking, forthcoming work will probably produce interesting consequences and may provide a prospective remedial candidate from *E. laevis* for the treatment of inflammatory disorders.

▪ **Anti-Inflammatory Activity:**

Ehretia laevis Roxb extracts anti-inflammatory and antibacterial qualities were tested using agar



well diffusion and carrageenan-induced rat paw edema. The results of the investigation showed that the aqueous, methanolic and chloroform extracts had significant anti-inflammatory efficacy (paw volume decreases). Outstanding antibacterial action against both Gram-positive like *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative like *Pseudomonas aeruginosa*, *Escherichia coli* bacteria, with the best efficacy being demonstrated by the methanolic extract activity against *Aspergillus Niger* that is antifungal. According to these results, extracts from *Ehretia laevis* Roxb. Can be used as natural treatment for bacterial infections & inflammation \

▪ Antimicrobial Activity:

Ehretia laevis Roxb, leaf extracts loaded silver nanoparticles shows: antimicrobial activity against various microorganisms, larvicidal activity (70% kill rate against *Culex quinque fuscatus* larvae), cytotoxic activity against HeLa (Henrietta Lacks) and MCF-7 (Michigan Cancer Foundation-7) cancer cells (LC50 (Lethal concentration): 12.7 and 14.5 µg/mL), dye degradation efficiency (~85% Congo red degradation within 8 hours). These nanoparticles have potential applications in water purification, cancer treatment, insect control and textile industry.

▪ Miscellaneous Activities:

E. laevis had also been studied for its coagulant and edible properties. Moreover, several other parts of the plant were recommended for the treatment of jaundice, skin diseases and in bone fractures. In another ethnobotanical survey the folklore practitioner of Uttarakhand recommended the paste prepared from the seeds of *E. laevis* mixed with cardamom powder and to be administered with milk three times a day for the management of jaundice and in other liver problems. Recently, the coagulant potential of

extracts of *E. laevis* leaves has been evaluated, revealing that the coagulant potential of isopropanol extract is more significant than the acetone extract.

E. laevis has also been used by tribal people and recommended by folklore hakeem for the management and healing of fractures. Tickle et al. reported the use of paste prepared from the leaves of *E. laevis* for the management of fracture. The Kalka (paste) was applied in the form of lepan (applied locally) at the affected sites. The dressing is applied daily then covered by rubber pads and support has been provided using slabs of plaster of Paris. A bandage was applied over the whole part of the foot and leg. After the application of lepan for 10 days, it was found that the swelling and pain had been abridged gradually and patients became able to move without any kind of support. The assessment of swelling was done using the American Orthopaedic Foot and Ankle Scale (AOFAS). The X-ray reports of patients revealed that the application of lepan of the plant over the fractured portion for two weeks lead to callus formation and unite malunion of metatarsal. Sharma, et al. established that the Tharu community of Uttarakhand used the ground paste of leaves of *E. laevis* has been applied topically for the treatment of diverse skin disorders. In another study, the antidiabetic perspective of *E. laevis* has been established through electrochemical measurement using multi-walled nano carbon tubes.

▪ Wound Healing Activity :

A tribe of Wardha district of Maharashtra, India used *E. laevis* for the management of wound healing and found interesting results. Similarly, folklore practitioners of Garasia community of district Sirohi, Rajasthan also recommended the paste prepared from leaves of plant for early



healing of cuts. Thakre et al. reported the wound healing activity of paste made from leaves of

E. laevis. Investigators used paste in thirty-four patients and scrutinized the patients based on several parameters such as different age groups, gender, fresh, chronic, infected and noninfected. According to Bates-Jansen wound assessment, a specified quantity of paste has been applied after an interval of seven days. The results revealed that wounds were healed completely from minimum of seven days to maximum sixty-six days in all the patients except one.

Recently, a case report had been published on the local application of *E. laevis* (Khanduchakka Ghrit) in the treatment of anal fissure (Parikartika). It has been observed that after all the mandatory measures, the efficacy of the plant has been evaluated on the basis of clinical parameters such as bleeding, itching, pain and healing. Patients were found to be healed with no signs of bleeding, pain and itching after twenty days of local application on rectum fissure. The procedure of application was followed twice a day for the duration of one month. The assessments were carried out at 0, 7, 14 and 21 days. The follow up was also conducted after 30 and 45 days. Even during follow up assessment no signs of recurrence were reported. A broad antimicrobial spectrum of barks and leaves can be a probable rationale for its wound healing property. Till now, no investigational work is presented on the wound healing activity as well as in the management of anal fissures. So, there could be a wide scope for future research to figure out the possible mechanism and possible Phyto active metabolites for wound healing effects[13].

NEWER MEDICATIONS

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the

synthesis of ribonucleotide uridine monophosphate pyrimidine. It relieves symptoms and retards the progression of RA. It is recommended to be used in combination with MTX but can constitute a monotherapy if patients do not respond to MTX. Side effects include hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow damage.

Biologics, also known as biological DMARDs, are rapidly effective in retarding the progression of the joint damage caused by RA. They are considered to be a more “direct, defined and targeted” method of treatment. Nonetheless, biologics pose the problem of serious side effects, such as increased risk of infections. Other common side effects include neurologic diseases like multiple sclerosis and lymphoma.

Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi) and certolizumab pegol (Cimzia) are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are recommended if other second-line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of RA and with various mechanisms of action is a matter of continuous investigation. They are often used in combination with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic medication has a different mode of administration.

▪ Uses:

Table No. 3] Parts Of Plant And Their Uses

Sr. No.	Part Of Plant	Preparation Used	Ailment/Use
1	All Parts Of Plants	Decoction And Juice	Abdominal Pain
2	Root	Root Extract	Acute And Chronic Inflammations
3	Fruits	Juice Of Fruits, Decoction	Astringent, Diuretic, Demulcent
4	Fruits And Seeds	Decoction	Anthelmintic
5	Seeds	Three Times A Day, A Paste Made From Soaked Seeds And Amomum Subulatum Powder Was Administered With Milk	Liver Diseases/Jaundice
6	Bark	Bark Paste Has Been Used To Treat Pain, Particularly In The Lower Limbs	Analgesic
7	Bark & Stems	Decoction Of Stem And Bark	Diphtheria
8	Powder Of Flowers	Flower Powder Mixed With The Milk Has Been Used As An Aphrodisiac	Aphrodisiac
9	Powdered Kernel	To Treat Ringworm Infections, Oil Was Combined With Powdered Kernel And Administered Topically To The Afflicted Region	Ringworm Infection
10	Bark & Leaves	Bark Juice, Leaf Juice And Decoction	Asthma, Malaria And Fever
11	Leaves	Fresh Leaves Were Used To Make Ghrith, Which Was Then Administered Topically To The Anal Fissure Twice Daily For 21 Days.	Fissure
12	Leaves	After Making Kalka (Paste), It Was Smear All Over The Fracture. Cotton Roll & Pad Were Firmly Applied. Kalka Has A Thickness Of 0.5-1cm. For Two Weeks, This Kalka Lepana Was Maintained In Dressing For 24 Hours Per Day.	Fracture
13	Leaves	Ten Equal Portions Of Leaf Powder And Sugar Were Combined & Saken Orally Every Day With Goat Milk Or Curd	Dysuria
14	Leaves	The Leaves Were Mashed And Wounds Are Treated Topically with The Resulting Paste	Cuts And Wounds
15	Leaves	The Leaves Were Ground Into Powder And Mixed with Equal Parts Of Sugar	Mouth Blisters

MARKETED PRODUCT

Khandu chakka oil is an ayurvedic medicine containing natural ingredients for effective pain

relief, powerful blend of herbs and oils that works synergistically.





Fig. No. 7] Marketed Product Of Khandu Chakka

▪ **Collection of Plant sample**

Fresh matured plant sample of Khandu chakka (*Ehretia laevis* Roxb) having flowering and fruiting was collected from its natural habitat of Daga forest in Wardha District. Identification and Authentication of Plant The drug was identified and authenticated as *Ehretia laevis* Roxb. from FRLHT (Foundation of Revitalization of local Health traditions, Bangalore) as Specimen No-FRLH119707Khanduchakka plant Preparation of Medicine.

▪ **Material**

1. Fresh leaves of khandu chakka plant.
2. Khandu chakka patra kalka and kwath.
3. Til tail.
4. Siddha tail.
5. Khandu chakka oil was made by Snehapaka-kalpana.
6. Khandu chakka Oil.

▪ **Methodology:**

• **Study Design :**

It was an interventional study. A single blind randomized clinical study has been carried out on patients selected from OPD & IPD of Kaychikitsa department, MGACH & RC by considering inclusion and exclusion criteria.

• **Inclusion Criteria :**

- 1) Only knee joint osteoarthritis patient.
- 2) Patient in 30 to 65 year age group of either sex.

• **Exclusion Criteria :**

- 1) Patient with rheumatic arthritis, tubercular arthritis, infective arthritis, syphilitic arthritis, gout, traumatic arthritis and gonorrheal arthritis.
- 2) Patient with any systemic illness (Hepatic failure, renal failure, ischemic heart disease and malignancy) and structural deformities.
- 3) Patient with uncontrolled diabetes[14].

ECOLOGICAL IMPORTANCE

E. laevis possesses significant ecological importance. The robust root system helps to prevent soil erosion, particularly in riparian and degraded areas, making it an essential species for ecological restoration projects. The tree provides habitat and food for various birds, insects, and small mammals. Its small, fleshy fruits are a vital source of nourishment for frugivorous wildlife, contributing to seed dispersal and forest regeneration. It can thrive in dry conditions, making it suitable for afforestation in semi-arid regions and degraded lands. As a deciduous tree, it

contributes to carbon sequestration, playing a role in mitigating climate change. The tree's canopy provides shade and reduces local temperatures, improving the microclimate and aiding the survival of understory vegetation. Its flowers attract pollinators such as bees and butterflies, supporting local pollination networks essential for ecosystem health. In some regions, *E. laevis* is planted in community spaces and along roadsides, adding to the greenery and enhancing the ecological value of urban and rural landscapes [15].

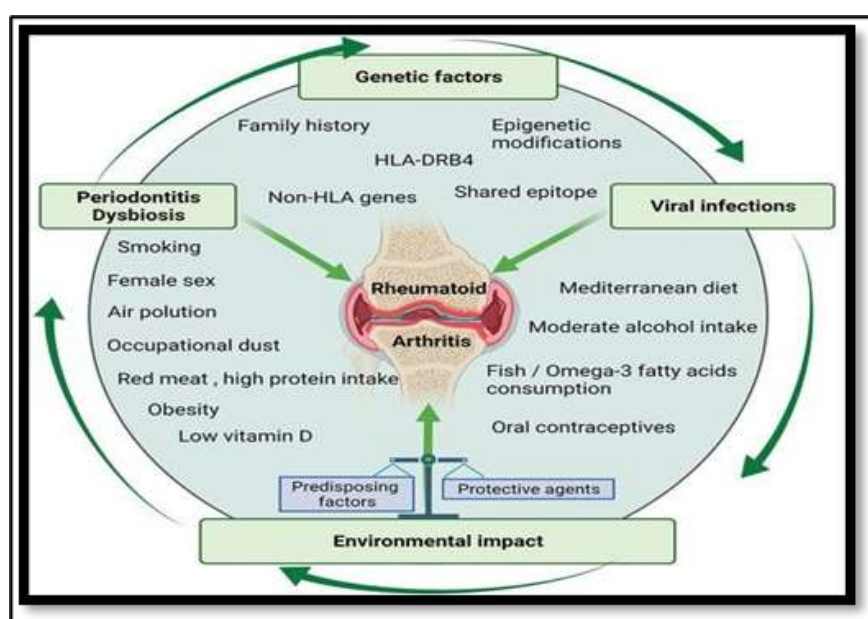


Fig. No. 8] Environmental Factors Affecting On Rheumatoid Arthritis.

CONCLUSION

Rheumatoid arthritis is a chronic autoimmune disease with the characteristic features of the destruction of synovium, cartilage and joints. Environmental and genetic factors play an important role in the development of rheumatoid arthritis with occurring pathological events. Many developments have been made to treat the disease and also the diagnosis of the disease. Surgeries are performed to remove the inflammation-causing agent (cytokines). Certain marketed formulations along with their classes have been enlisted in the table. Recent trends for treating the disease was

explained in brief. To avoid arthritis or in the management of arthritis, a healthy diet should be followed.

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