



A review on therapeutic potential of *Tinospora Cordifolia* and *Thunbergia Erecta* in polyherbal emulgel formulation for rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis is a chronic auto immune disorder that causes inflammation, pain, and joint deformities, affecting the quality of life of patients. Conventional treatments are effective but may produce adverse effects during long term use. Therefore, herbal-based topical formulations have gained attention as safer alternatives. This review focuses on the formulation and evaluation of a polyherbal emulgel containing *Tinospora cordifolia* stem extract and *thunbergia erecta* leaf extract for the management of rheumatoid arthritis. *Tinospora cardifolia* is also known as guduchi is a large crawling shrub which belongs to the family of menispermaceae and *Thunbergia erecta* (Benth) a perennial shrub belonging to the family of Acanthaceae. Both the plants possess significant anti-inflammatory, antioxidant, analgesic, and immunomodulatory activities that may help reduce joint inflammation and pain. The emulgel delivery system improves drug penetration, spreadability, stability, and patient compliance. The study also highlights formulation methods, evaluation parameters, and the therapeutic potential of the polyherbal emulgel as an effective topical approach for rheumatoid arthritis management.

Keywords: Anti-inflammatory Activity; Antioxidant Activity; Herbal Formulation; Polyherbal Emulgel; Rheumatoid Arthritis; Topical Drug Delivery.

ISSN: 2581-9143

Review Article

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Article Info

Received on: 29-06-2026

Revised on: 09-07-2026

Accepted on: 13-07-2026

DOI: <https://doi.org/10.33974/srtq4x30>



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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that significantly reduces quality of life. Unlike osteoarthritis, it results from immune dysfunction in which the body attacks its own synovial membrane, leading to persistent inflammation, pain, swelling, stiffness, and progressive joint deformity. It commonly affects small joints of the hands, wrists, and feet in a

symmetrical pattern, often resulting in disability if left untreated. ^[1]

Commonly used drugs for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and immunosuppressants. However, these are associated with adverse effects such as gastrointestinal disturbances, immunosuppression, and humoral imbalance. ^[2] Although no definitive cure exists, treatment options such as pharmacotherapy, physical therapy, and injection help manage symptoms, DMARDs act slowly, whereas NSAIDs and corticosteroids provide rapid relief, but long-term drug therapy is often costly and linked with side effects, leading to interest in alternative treatments such as herbal medicine. ^[3]

Topical drug delivery systems offer localized action by allowing drug penetration through the skin, bypassing first-metabolism. This result is improved bioavailability and sustained drug release. Drug release depends on the formulation base and physiochemical properties of the drug. ^[4]

Emulgels are semisolid formulations combining emulsions and gels by incorporating a gelling agent into oil-in-water or water-in-oil systems. ^[5] Lipophilic drugs are incorporated in oil-in-water systems, while

hydrophilic drugs are incorporated in water-in-oil systems. [6] Emulgel offer advantages such as ease of application, non-greasiness, good spreadability, thixotropy, emollient properties, and improved patient compliance. [7]

Tinospora cordifolia extract (TCE) possesses immunomodulatory, anti-proliferative, anti-angiogenic, and antibacterial activities and has shown efficacy in reducing arthritis severity in experimental models. [8-11] Similarly, *thunbergia* species have traditional use in treating inflammation and pyrexia and exhibit antibacterial, analgesic, antipyretic, antioxidant, and anti-arthritic activities. [12]

Disease profile (Rheumatoid arthritis):

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune inflammatory disease that mainly affects the joints and may also involve extra-articular tissues. [13] It occurs when the immune system mistakenly attacks the synovial membrane lining the joints, leading to inflammation, cartilage destruction, and bone damage. Common symptoms include joint pain, swelling, stiffness, fatigue, and weight loss. The exact cause of RA remains unknown, but recent evidence suggests that the disease develops through an interaction between genetic susceptibility, epigenetic changes, and environmental influences such as cigarette smoke, dust exposure, and alternations in the human microbiome. [14]

Etiology: The etiology of rheumatoid arthritis is multifactorial. Researchers believe that genetically predisposed individuals may develop RA after exposure to certain infectious or environmental triggers. Possible infectious agents associated with the disease include mycoplasma, cytomegalovirus, Epstein-Barr virus, rubella virus, and parvovirus. However, the exact infectious mechanism responsible for chronic inflammatory arthritis is still unclear. Several important risk factors contribute to the development of RA, including genetic and environmental factors, smoking, and changes in the human microbiome

Among genetic factors, the most important is the "shared epitope" present in the HLA-DRB1 allele. Individuals carrying this genetic marker have approximately a threefold higher risk of developing rheumatoid arthritis. Environmental influences also play a major risk of disease onset. Smoking is considered one of the strongest risk factors for RA and is especially associated with ACPA-positive rheumatoid arthritis. Lifestyle and dietary factors such as high intake of sugar, sodium, red meat, proteins, and iron, along with low consumption of vitamin D and antioxidants, may further increase disease risk. In addition, disturbances in the human microbiome contribute significantly to RA pathogenesis. A shift from a healthy symbiotic microbiome to a dysbiotic state results in abnormal microbial growth and reduced beneficial bacteria,

leading to alterations in on innate and adaptive immune responses. [15]

Pathophysiology: RA involves chronic immune-mediated inflammation of the joints. Genetic susceptibility, particularly involving HLA-DRB1 genes, combined with environmental triggers such as smoking or infections, causes protein modification through citrullination. These altered proteins stimulate the production of autoantibodies (ACPAs). The antibodies form immune complexes that activate immune cells within the joints. Activated T cells, B cells, and macrophages release inflammatory cytokines such as TNF- α , IL-1, and IL-6, which sustain inflammation. Persistent inflammation leads to synovial thickening and formation of pannus, an abnormal granulation tissue that invades cartilage and bone. Progressive joint destruction eventually causes pain, swelling, stiffness, deformity, reduced mobility, and systemic complications. [16-18]

Clinical complications: Rheumatoid arthritis may also produce several serious clinical complications. Depression is common among RA patients, especially those receiving corticosteroid therapy, affecting nearly 40% of individuals. Factors contributing to depression include socioeconomic status, age, sex, ethnicity, social support, disease severity, pain, and physical disability. [19] Infections are also another major complication and may result either from the disease itself or from immunosuppressive therapies such as biologics, steroids, and DMARDs. [20] RA patients are also at increased risk of malignancies, particularly lymphoma, whose incidence is approximately doubled. Lung cancer and skin cancer may also occur, especially in smokers and patients using long-term immunosuppressive drugs. Cardiovascular complications are significant causes of morbidity and include heart failure, ischemic heart disease, myocardial infarction, and coronary revascularization procedures. [21]

Diagnosis: RA is based on clinical findings, laboratory investigations, and imaging studies. physical examination typically reveals swollen, warm, tender joints along with muscle wasting around affected areas. Initial laboratory investigations include rheumatoid factors testing, erythrocyte sedimentation rate (ESR), and C-reactive protein (CPR) levels to assess inflammation cases, to exclude infections or crystal-induced arthritis. Baselines renal and hepatic function tests are important before initiating medications. Detection and positive predictive value for RA, although these antibodies are present in less than 60% of patients. [22]

Treatment: Rheumatoid arthritis aims to symptoms, prevent joint damage, and improve quality of life. Patient education regarding disease progression and treatment adherence is essential. Management, mainly includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying

antirheumatic drugs (DMARDs), and biologic agents. NSAIDs help reduce pain and swelling but do not alter disease progression and therefore should not be used alone. Corticosteroids relieve symptoms and slow joint destruction: however, they should be prescribed at low doses for short durations as bridge therapy, often alongside calcium and vitamin D supplements to reduce bone demineralization. DMARDs are the mainstay of treatment because they slow disease progression and improve long-term outcomes. Biologic agents specifically target inflammatory cytokines, signalling molecules, and immune cells responsible for joint destruction. [23]

Plant profile

***Tinospora cordifolia*:** *Tinospora cordifolia* is also known as gulvel or guduchi is a large crawling shrub which belongs to the family of menispermaceae. [24]



Figure 1: Stem of *Tinospora cordifolia*

Origin and distribution: *T. cordifolia* is a climbing shrub native to lower elevation in tropical areas of the Indian subcontinent and numerous types of trees.

It is indigenous to areas of India, Myanmar, Sri Lanka, China, Thailand, Philippines, Indonesia, Malaysia, Borneo, Vietnam, Bangladesh, North Africa, West Africa, And South Africa. It typically grows in deciduous and dry forests at elevations up to 100ft. [25]

Synonyms:

- *Menispermum cricum* Linnaeus
- *Tinospora gibbericaulis* handel-mazzetti
- *Tinospora mastersii* deils
- *Tinospora rumphii* boerlage
- *Tinospora thorelii* gagnepain

Taxonomy:

Kingdom	plantae
Division	Magnoliopsida
Super division	Spermatophyta
Class	Magnoliopsida
Order	Ranunculaceae
Family	Menispermaceae
Genus	<i>Tinospora</i>
Species	<i>Tinospora cordifolia</i> (wild) Miers

Vernacular names:

Tamil	Shindilakodi
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English	<i>Tinospora cordifolia</i>
Telugu	Tippa-teega
Malayalam	Amruthu, Chittamruthu
Kannada	Amrutha balli
Sinhala	Rasakinda
Hindi	Gurcha

Chemical constituents: The chemical constituents of *T. cordifolia* belong to different classes such as alkaloids, glycosides, steroids, phenolics, aliphatic compounds, polysaccharides responsible for its anti-inflammatory, immunomodulatory and antioxidant activities. Leaves are rich in protein (11.2%), calcium and phosphorus. [26] The stem contains alkaloids, terpenoids such as lupeol and palmatine, β -sitosterol and significant amounts of flavonoids and phenolic compounds clerodane furono diterpene glucoside (amritoside A, B, C& D) that contribute to therapeutic effects. [27]

Therapeutic uses: The is commonly used as traditional ayurvedic medicine and has several therapeutics properties such as jaundice, rheumatism, urinary disorder, skin diseases, diabetes, anaemia, inflammation, allergic condition, anti-periodic, radioprotective properties, etc. [28-29]

The root of Giloya (*t. cordifolia*) is used as potent emetic and for bowel obstruction.

The starch of this plant serves a beneficial household remedy for chronic fever, relieves burning sensation, increases energy and appetite.

T. cordifolia is useful in the treatment of helminthiasis, heart diseases, leprosy, rheumatoid arthritis, support the immune system, the body's resistance to infections, supports standard white blood cell structure, function, and levels. [30]

It also helps in digestive ailments such as hyperacidity, colitis, worm infestations, loss of appetite, abdominal pain, excessive thirst, and vomiting, and even liver disorders like hepatitis. [31-32]

***Thunbergia erecta*:** It is obtained from the plant *Thunbergia erecta* (Benth) a perennial shrub belonging to the family of Acanthaceae.



Figure 2: Leaf of *Thunbergia erecta*

Origin and distribution: *T. erecta* is an evergreen shrub plant growing to 4-6 feet tall and spread 5-8 feet with the round spread plant habit.

Thunbergia erecta native to tropical Australia, West Africa, South Asia and Madagascar this plant nowadays available in many Asia region such as India, Bangladesh, Pakistan and other countries. [33]

Synonyms: Meyenia erecta Benth

Taxonomy:

Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Division	Tracheophyta
Class	Equisetopsida
Subclass	Magnoliidae
Order	Lamiales
Family	Acanthaceae
Genus	<i>Thunbergia</i>
Species	<i>Thunbergia erecta</i>

Vernacular names:

English	Bush Clock Vine, King's Mantle, potato bush
Hindi	Nilkantha plant
Marathi	Chota Mynea, Mynia
Bangladesh	Nilghonta

Chemical constituents: A recent study by researchers looking into its potential medical benefits found that it contained a variety of compounds including triterpenoids, alkaloids, flavonoids, phenolics, tannins, saponins and carbohydrates. The *thunbergia erecta* plants are capable of producing a wide range of chemical compounds that are used to perform vital biological processes and to fend off parasitic creatures like fungi and insects. The methanolic extracts shows the presence of carbohydrates, proteins, alkaloids, tannins, steroids, flavonoids, and terpenoids. The extract contains terpenoids and triterpenes that increase its anti-arthritis properties, while phytosterols such β -sitosterol aid in stabilising membranes and lowering inflammation in joints. Saponins provide antimicrobial and surface-active properties. In addition, carbohydrates and proteins are presents as supportive constituents. [34-36]

Therapeutic uses:

Roots are used against patients in traditional medicine. The leaf is used for treating bile disorders, it is also given to children having worms. It is also used for insomnia, depression, and anxiety management in traditional medicine. *Thunbergia erecta* flower is used as acid-base natural indicator.

Using the petal of the flower of *thunbergia erecta* plant to make a natural dye. [37]

Mechanism of action: The polyherbal emulgel containing extracts of *Tinospora cordifolia* stem and *Thunbergia erecta* leaf exhibits anti-arthritis activity in rheumatoid arthritis through multiple mechanisms.

Tinospora cordifolia contains alkaloids, diterpenoid lactones and glycosides that suppress pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, thereby reducing synovial inflammation and joint damage.

Thunbergia erecta is rich in flavonoids and phenolic compounds that provide antioxidant activity and neutralize reactive oxygen species generated during chronic inflammation.

Both extracts also inhibit inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which decreases prostaglandin production and pain.

When delivered through an emulgel system, the phytoconstituents penetrate the skin and act locally at the inflamed joint, producing anti-inflammatory and antioxidant effects that help reduce swelling, pain, and stiffness in rheumatoid arthritis. [38-40]

Plant extract

***Tinospora cordifolia*:** Stems of *Tinospora cordifolia* were dried under shade for 7-10 days and pulverized by using an electrical grinder. Firstly, dried sample was extracted with solvent of methanol and acetone in the ratio of 70:30 (4000ml $\times$ 4 cycles) at 40 $^{\circ}$ C for 16 hours in Soxhlet apparatus. The residue was dried under reduced pressure by using a rotary vacuum evaporator. [41]

***Thunbergia erecta*:** The leaves of *thunbergia erecta* plants were dried under shade for four days. Then dried leaves were crushed into a coarse powder using blender machine. The prepared powder of *thunbergia erecta* respectively were macerated in methanol for 7 days. After filtration by cotton filter the filtrates were concentrated at 39 $^{\circ}$ C with the aid of rotary evaporator. [42]

Emulgel: Topical formulations are prepared in different consistency such as semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug. In each formulation with the active ingredients many excipients are used. Sometimes more than one formulation can be combined to enhance the drug delivery emulgel is such type of combination. It is the combination of emulsion and gel. [43]

Emulgel is prepared both in oil-in-water and water-in-oil type is used for hydrophobic drugs' delivery. [44]

The emulgel have many advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf life. [45]

The emulsion and gel preparations have their own properties. But the gels show some limitations as hydrophobic drug delivery. This limitation is overcoming by emulgel. By the use of gelling agent classical emulsion can be converted into emulgel. [46]

Types:

1. Based on type of emulsion phase:

Oil-in-water (O/W) Emulgel: The oil phase (with the drug) is dispersed in the water phase. Common for delivery of lipophilic (oil-soluble) drugs with better spreadability.

Water-in-oil (W/O) emulgel: The water phase is dispersed in the oil phase. Used when formulation requires improved penetration of hydrophilic (water-soluble) drugs.

2. Based on droplet size of emulsion in the gel: Emulgel types can also be classified by the size of the dispersed droplets in the emulsion phase that determines appearance, stability and drug delivery performance;

Macroemulgel: Contains relatively large droplets (>400 nm). Typically, opaque and the most common type in conventional topical products.

Nanoemulgel: Formulated using nano-emulsions with very small droplets (<100 nm). Provides enhanced skin penetration, improved stability and often better delivery of active drugs.

Microemulgel: Contains droplets in the nanometre range (10-100 nm) that are thermodynamically stable and transparent. Offers good drug delivery properties and physical stability. ^[47-48]

Advantages:^[49]

- Incorporation of hydrophobic drugs
- Better loading capacity
- Better stability
- Controlled release
- No intensive sonication
- Avoiding first pass metabolism
- Avoiding gastrointestinal incompatibility
- More selective for a specific site
- Improved patient compliance
- Convenient and easy to apply.

Disadvantages:

- Skin irritation on contact dermatitis
- The possibility of allergenic reactions
- The poor permeability of some drugs through the skin
- Drugs of large particle size are not easy to absorb through the skin.
- The occurrence of the bubble during formulation of emulgel. ^[50]

Formulation method:

STEP 1: Formulation of gel base, The gel base is formed by dissolving a known quantity of polymer into DDW by mixing at moderate speed using a magnetic stirrer and PH is adjusted to 5-6.5 using Triethanolamine and NaOH. ^[51]

STEP 2: Formulation of O/W or W/O type of emulsion, Formulation of Smix in the appropriate

ratio using a magnetic stirrer. Add the Smix into the oil phase dropwise under continuous stirring, which gives a clear emulsion. ^[52]

STEP 3: Formulation of emulgel, Add the prepared emulsion into gel base dropwise with continuous stirring using a homogenizer to get emulgel. ^[53]

Evaluation:

Physical appearance: The colour, consistency and homogeneity of the prepared formulation are visually inspected for observations of physical properties. ⁵⁴

pH measurement: A digital pH meter is used to determine the pH of all prepared emulgel. Calibration of the pH meter is performed before using a standard buffer solution. 1gm of the formulation is dissolved in distilled water until a uniform suspension is formed and is kept aside for 2 hours. After 2 hours the glass electrode is dipped in the suspension and the pH is measured. ^[55-56]

Rheological study: The viscosity of the prepared formulation is determined at 37°C using a cone and plate Brookfield viscometer. ^[57]

Spreadability: It is checked by “slip and drag” character of emulgel. To determine spreadability, the apparatus consisting a wooden block is provided by a pulley at one end. In the block a ground glass is fixed. 2g of emulgel is placed on it, and is covered with another glass slide as a sandwich. One kg of weight is placed on it and the spreadability is checked.

Centrifugation study: This method is used to determine the stability of emulgel. It is done only after one week of preparation. This study was done by using minicentrifuge at 3000 rpm for 30 minutes. ^[58]

Stability study: Stability studies are carried out by inducing stress at different temperatures and humidity (room temperature of 30°C±2°C, RH of 65%±5% and room temperature of 40°C±2°C, RH of 75%±5%) using a stability chamber with proper excipient quantity (API-0.1gm, oil-2.5gm, surfactant-6.665gm, co-surfactant-13,33gm, double-distilled water-27.15ml). The study is done for 1 month and observation is done for physical changes such as change in clarity, observance of turbidity and detection of particle growth. ^[59-60]

Skin irritation test: Skin irritation test is usually done in skin of human volunteers with proper written consent. The prepared formulation is applied to the skin of the hand and observation is done to check for any undesirable effects. ^[61]

Zeta potential: The zeta potential of the emulgel preparation is determined by zetasizer (Malvern zetasizer). The formulation is placed in a clear, disposable zeta cell and the result is determined. Before experimenting cuvettes are washed with methanol and then the sample is placed. ^[62]

Particle size and polydispersity index (PDI): The globule size of emulgel is measured at 25°C by using a zetasizer (Malvern zetasizer instrument, ZS90). The sample is diluted before the experiment. [63]

Swelling Index: 1mg of gel is placed on porous aluminium foil separately in a 50ml beaker that contained 10ml of 0.1N NaOH. The sample is removed from the beaker at various time intervals and kept in a dry place for some time after it is reweighed. [64-65]

$$\text{Swelling Index (SW)\%} = \left[\frac{(W_t - W_o)}{W_o} \right] \times 100$$

Where (SW) % = Equilibrium percentage swelling.
W_o = Original weight of emulgel at zero-time t, W_t = Weight of swollen emulgel.

Drug content determination: A spectrophotometer is used to determine the drug concentration in the emulsion. The drug content of an emulsion is determined by sonicating a known amount of emulsion in a solvent (Methanol). In a UV/Vis spectrophotometer, absorbance is measured after appropriate dilution. [66]

CONCLUSION

Rheumatoid arthritis is a chronic inflammatory disorder that results in joint pain, swelling and progressive deformation of the joints. Conventional therapies have been shown to be effective, but they are often accompanied by side effects during prolonged use. Thus, herbal formulations are increasingly being recognised as potential safer alternatives in the management of inflammatory diseases and conditions.

The current review reflects the use of *Tinospora cordifolia* stem extract and *Thunbergia erecta* leaf extract as herbal agents that may have a much better approach in the treatment of rheumatoid arthritis. *Tinospora cordifolia* has potent immunomodulatory, anti-inflammatory and antioxidative activities while *Thunbergia erecta* exhibits anti-inflammatory and analgesics properties. The combination of these two plant extracts may produce a synergistic therapeutic effect, helping to reduce inflammation, oxidative stress and joint degeneration associated with arthritis.

Incorporating this extract into an emulgel delivery system offers additional advantages such as improved drug penetration, better stability, enhanced patient compliance and controlled topical delivery. Emulgel formulations are particularly suitable for topical treatment of joint inflammation because they combine the properties of both emulsions and gels.

Overall, the polyherbal emulgel containing *Tinospora cordifolia* and *Thunbergia erecta* extracts represents a promising and effective topical approach for the management of rheumatoid arthritis. However, further pharmacological studies, formulation

optimization and clinical investigations are required to confirm its safety, efficacy and therapeutic potential.

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