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"A COMPARATIVE STUDY OF ANTI- INFLAMMATORY AND ANALGESIC PROPERTIES OF PLANT RUTA GRAVEOLENS AND ALLOPATHIC MEDICINE"

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Abstract:
Inflammation is a complex biological response to pathogens and tissue damage, involving various immune cells and inflammatory mediators. Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used to mitigate inflammation and pain by inhibiting prostaglandin production through COX-1 and COX-2 enzyme inhibition. However, NSAIDs are associated with potential side effects, including gastrointestinal and renal issues. In contrast, Ruta graveolens, a plant from the Rutaceae family, has a long history of use in Ayurveda, Homeopathy, and Unani medicine. It contains a diverse array of compounds, including acridone alkaloids, coumarins, essential oils, flavonoids, and fluoroquinolones, which contribute to its anti-inflammatory and analgesic properties. This review article delves into the anti-inflammatory and analgesic properties of Ruta graveolens and compares them with those of allopathic medicines, particularly NSAIDs. We explore the mechanisms of action, clinical evidence, and safety profiles of both approaches. NSAIDs are effective at reducing inflammation and pain but come with notable side effects, including gastrointestinal and cardiovascular risks. In contrast, Ruta graveolens demonstrates potential as a safer alternative with fewer side effects, though more research is needed to establish its safety profile fully. We present the results of our comparative analysis, highlighting the strengths and limitations of each treatment option. Additionally, we discuss the chemical composition of Ruta graveolens and its traditional uses, shedding light on its diverse array of constituents, such as acridone alkaloids, coumarins, limonoids, and flavonoids. Furthermore, we provide insights into the methodology used for extracting Ruta graveolens, including aqueous, methanolic, and ethanolic extracts, and describe animal models used to assess anti-inflammatory and analgesic effects. Our analysis incorporates data from studies exploring the inhibition of sPLA2 enzyme, carrageenan-induced inflammation in rats, and the analgesic potential of Ruta graveolens.

Keywords: Analgesic agents, Anti- inflammatory agents, *Ruta graveolens*, NSAIDs, Comparative study

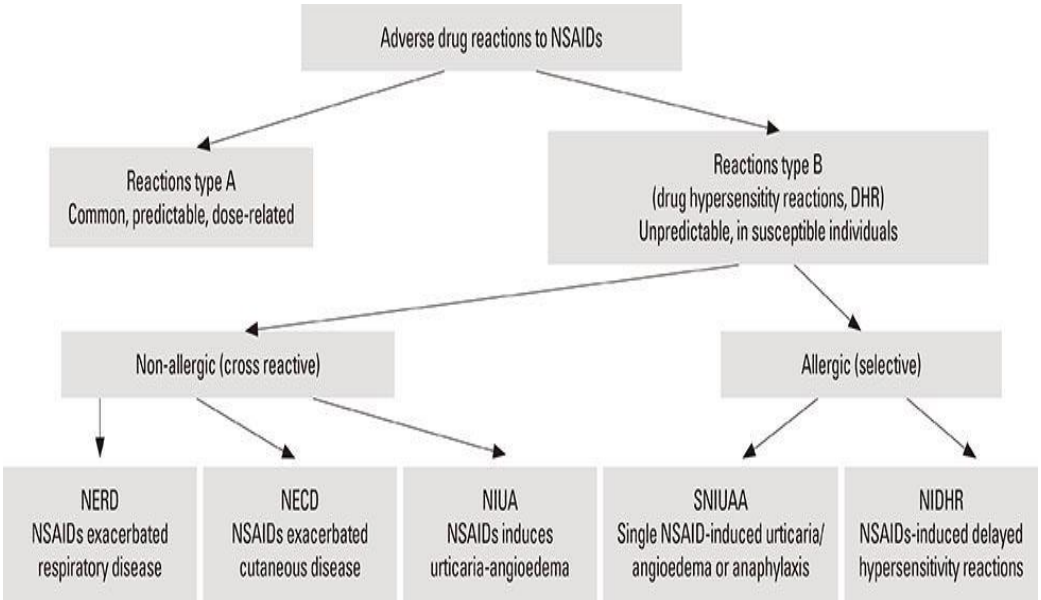
[1] INTRODUCTION:

Inflammation: Pathogens and tissue damage cause inflammation, which is a response. Immune cells, such as mast cells, macrophages, leukocytes, and neutrophils, are driven to the site of injury as a result of cellular damage or pathogen-associated molecular patterns (PAMPs) generated by pathogens. Following this, these cells discharge a range of inflammatory mediators, such as cytokines, histamine,

nitric oxide, leukotrienes, and prostaglandins. By binding to G protein-coupled receptors (GPCRs), cytokines including tumor necrosis factor (TNF) and interleukins (ILs) are released by macrophages to heal local damage and trigger the production of selectins and integrins. Mast cells release histamine, which causes vasodilation and raises vascular permeability. Nitric oxide is a gas that is generated by endothelial cells and diffuses into smooth muscle cells to relax them and aid in vasodilation. Leukotrienes and prostaglandins are created synthetically [1]. Generally, NSAIDs (Non- steroidal antiinflammatory agents) have been used as an anti -inflammatory agents. NSAIDs have analgesic, anti-inflammatory, and antipyretic actions by preventing the production of prostaglandins by inhibiting the COX-1 and COX-2 enzymes [2]. Analgesic medications, as they are commonly known, are used to treat pain in patients [3]. *Ruta graveolens L*. is an odoriferous herb of the Rutaceae family. It is the source of Rue or Rue oil, known in Hindi as Sadab or Satab. It's employed in Ayurveda, Homoeopathy, and Unani medicine [4]. The roots and aerial portions contain over 120 natural chemicals, primarily acridone alkaloids, coumarins, essential oils, flavonoids, and fluoroquinolones [4].

[1.1] Allopathic medicine for inflammation and pain:

Nonsteroidal anti-inflammatory medications (NSAIDs) have historically been used to treat pain by inhibiting the production of prostaglandin-producing enzymes. However, it is evident that NSAIDs also act through a number of different peripheral and central pathways in addition to peripheral suppression of prostaglandin synthesis to provide their analgesic effects [5].The two identified isoenzymes of prostaglandin G/H synthase, commonly known as cyclooxygenase (COX), known as COX 1 and COX 2, are inhibited by non-steroidal antiinflammatory medicines (NSAIDs), a broad class of therapeutic agents having analgesic and anti-inflammatory characteristics [6]. According to their effects on signal transduction and as anti-cytokine agents, new anti-inflammatory drugs are being discovered and developed. These drugs are now being hailed as the new treatments for diseases where cytokines and other nonprostaglandin components of chronic inflammatory and neurodegenerative diseases are manifest [7]. Regular use of NSAIDs is linked to nephrotoxicity and ultimately renal failure in addition to gastrointestinal and cardiovascular issues [8]. NSAIDs can be roughly categorized into salicylates, aryl and hetero aryl acetic acid derivatives, indole/indene acetic acid derivatives, anthranilates, and oxicams (enol acids) based on their chemical structure. Using classification helps pinpoint the underlying cause of NSAID hypersensitivity in a patient, which is crucial for effective management. NSAID hypersensitivity can lead to diverse symptoms like respiratory or skin issues, anaphylaxis, or organ-specific problems, appearing at varying times after drug use [8].



(**Fig.1** NSAIDs induced drug reactions [8])

[1.2] Botanical profile and traditional uses of *Ruta graveolens:*

A member of the Rutaceae family, *Ruta Graveolens* is an odoriferous, evergreen herb. The herb, often referred to as bitter herb or common rue, is cultivated in gardens all over the world and used in homeopathy. It is also grown as a spice, a medicine, and occasionally as an insect repellent. The soil must be hot and dry for the plant to grow. *R. Graveolens* has traditionally been used for a long time to treat pain, eye and skin issues, and rheumatism [9]. *Ruta graveolens*, commonly known as rue, is a fragrant and glandular herb often exhibiting a shrubby growth habit near its base. Found in gardens across India and various Western Asian countries, rue displays distinct morphological features. Its leaves are compound, composed of wedge-shaped segments that are elongated or linear in form. The flowers are arranged in umbels and take on a yellow hue. The stems surpass the capsules, accompanied by bracts. Notably, the sepals are triangular and pointed, while the petals are round and characterized by an oblong-obovate shape, with pectinate margins that end abruptly in a clawed structure. Capsules are shortpedicellate and obtuse, containing angled seeds [9].

(*Ruta graveolens* plants [10])

From a chemical perspective, Ruta graveolens harbours diverse constituents. Among them are Furano acridones and acridone alkaloids, including arborinine and evoxanthine [11]. Abundant coumarins and limonoids are also present [12]. Rutin and quercetin stand as the primary active flavonoids within Ruta graveolens. Rutin, first extracted from the plant's leaves, holds a significant presence. Additionally, the volatile oil of Ruta graveolens contains a notable concentration of aliphatic acids, alcohols, and ketones. The volatile oil showcases a composition dominated by various components, including 2-undecanone (33.9%), 2-Heptanol acetate (17.5%), 1-dodecanol (11.0%), geyrene (10.4%), 2-nonanone (8.8%), 2-Decanone (1.9%), Geijerene (1.6%), trans-piperitenone oxide (1.4%), cis-piperitenone oxide (1.2%), 2methyl-undecanal (1.1%), 2-dodecanone (1.1%), 2-nonanol (1.1%), and elemol (1.1%). These components constitute the essential oil extracted from the flowering aerial parts

of the plant. Ruta graveolens is characterized by a notable production of linear furanocoumarins, primarily psoralen and methoxypsoralen [13]. In the root of the plant, acridone alkaloids known as rutacridone, rutacridone epoxide, and gravacridondiol have been isolated [14]. Furthermore, an alkaloid named graveoline has been successfully extracted from the leaves of the plant [15].

[2] MATERIAL AND METHODOLOGY:

[2.1] Preparation of extract:

Plant materials gathering: *R. graveolens* aerial parts were obtained in Kerala's Kannur district. The plant was recognized and verified by Dr. Valsala devi G, University of Kerala's Department of Botany [16].

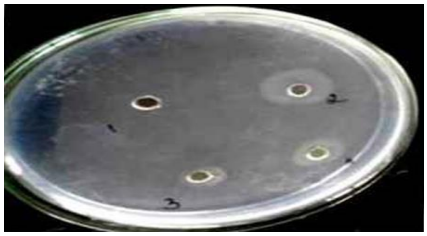
Aqueous extract: A quantity of 500 grams of aerial parts from *Ruta graveolens* was gathered, meticulously cleansed, and dried under the shade. Subsequently, the dried parts were crushed and introduced into a flask with a round bottom. To envelop the material, 500 ml of distilled water was incorporated. This mixture was then subjected to reflux within a water bath for a duration of 1 hour, maintaining a temperature range of 90 to 95 degrees Celsius. Following this, the liquid portion situated above the settled solids was eliminated, and the extraction procedure was replicated once more. The accumulated supernatants from both extraction rounds were amalgamated and strained using a Whatman No. 1 filter paper. The resultant filtrate underwent concentration through lyophilization at a lowered temperature. The residue resulting from this process was labelled as the aqueous extract [16].

Methanolic extract: For the manufacture of the extract, the plant's stem, leaves, and roots were collected and washed twice or three times in distilled water. Teepol (4% v/v) was used to sterilize the tissue, and it was thoroughly rinsed in sterile distilled water afterward. To make extracts, 10g of the sample was crushed in 100 cc of methanol. They spent the night in the shaker at room temperature. The extracts were filtered via filter paper after being squeezed through two layers of muslin cloth. The residues were then dried, weighed, and dissolved in the proper solvents to create extracts with various concentrations. The solvents were then evaporated to dryness to produce the residues [17].

Ethanolic extract: For the manufacture of the extract, the plant's stem, leaves, and roots were collected and washed twice or three times in distilled water. Teepol (4% v/v) was used to sterilize the tissue, and it was thoroughly rinsed in sterile distilled water afterward. To make extracts, 10g of the sample was crushed in 100 ml of ethanol. They spent the night in the shaker at room temperature. The extracts were filtered via filter paper after being squeezed through two layers of muslin cloth. The residues were then dried, weighed, and dissolved in the proper solvents to create extracts with various concentrations. The solvents were then evaporated to dryness to produce the residues [17].

[2.2] Anti- inflammatory of NSAIDs and *Ruta graveolens* on animal model:

The secretory PLA2 enzyme from Human Pleural Fluid (HPF) was exposed for inhibition to confirm the anti-inflammatory effect of R. graveolens ethanol and aqueous extract. In the egg yolk plate method, the ethanol extract inhibited the sPLA2 enzyme at a concentration of 50 g, followed by the water extract. For ethanol and water extract, the percentage of HPF-PLA2 inhibition was 66.6% and 46.6%, respectively [18].



(Fig.2: Inhibition of sPLA2 by egg yolk plate method. The well contains 1) control 2) 25µg of HPF-PLA2 3) 25µg of HPF-PLA2 and 50 µl ethanol extract 4) 25µg of HPF-PLA2 and 50 µl aqueous extract [18])

The study adapted a method (Winter et al., 17) with minor changes. They used 80 rats divided into groups of 10, fasting them for 12 hours and limiting water. This ensured consistent hydration and swelling. Paw inflammation was induced by injecting lambda carrageenan. Two control groups received saline and alcohol, while two reference groups got indomethacin and etodolac. Other groups were given varied doses of an extract. Paw size was measured before and after using a device. They calculated swelling reduction using a formula. In simple terms, they tweaked a method for paw swelling in rats, tested different treatments, and measured swelling before and after to see the effects [19].

[2.3] Analgesic activity of NSAIDs and *Ruta graveolens*:

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as a first-line pain management approach [20]. They work by inhibiting COX-1 and COX-2 enzymes, reducing prostaglandin synthesis and alleviating inflammation-induced pain. NSAIDs target peripheral nociceptors sensitized by inflammatory mediators, offering relief from sustained pain and hypersensitivity caused by tissue damage. Coxibs, which are COX-2 selective inhibitors, were designed to minimize gastrointestinal side effects associated with traditional NSAIDs [21]. Plant material of R. graveolens was collected from São Paulo, deposited in Mackenzie Presbyterian University herbarium (IDs 1259, 1260). Methanol extracted 800g material for 24 hours at room temperature. Residue underwent two more extractions; ethanol extract partitioned with hexane and chloroform. Hydroalcoholic extract discarded due to yeast growth. Obtained dried extracts: chloroform (CR; 730 mg) and hexane (HR; 255 mg). Mice received extracts after brief food withdrawal [22].

[3] FORMULATION DETAILS:

[3.1] Dosage form:

Aspects	Allopathic medicines	Herbal medicines
Examples	Ibuprofen (Advil), Na proxen (Aleve) [23]	*Curcuma longa*, *Boswellia serrata* [24], *Ruta graveolens* [9]
Mechanism of Action	Non-steroidal antiinflammatory drugs (NSAIDs) reduce inflammation by inhibiting enzymes (COX-1 and COX2) involved in the inflammatory process [25].	Herbal anti-inflammatories often work through various mechanisms, including inhibiting inflammatory mediators and antioxidant effects [26].
Analgesic (Pain relief)	Effective in reducing pain [27]	May provide pain relief, but generally milder compared to NSAIDs [26]
Anti- inflammatory	Effective in reducing inflammation [27]	May have moderate anti-inflammatory effects [26]
Side Effects	Potential for gastrointestinal issues, increased blood pressure, and others. Can be harsh on the stomach [28].	Generally considered safer with fewer side effects, but individual reactions may vary [29].
Long-term Used	Prolonged use of NSAIDs can lead to gastrointestinal ulcers, kidney problems, and other issues [30].	Herbal products may be gentler for long-term use, but more research is needed on their safety profile [29].

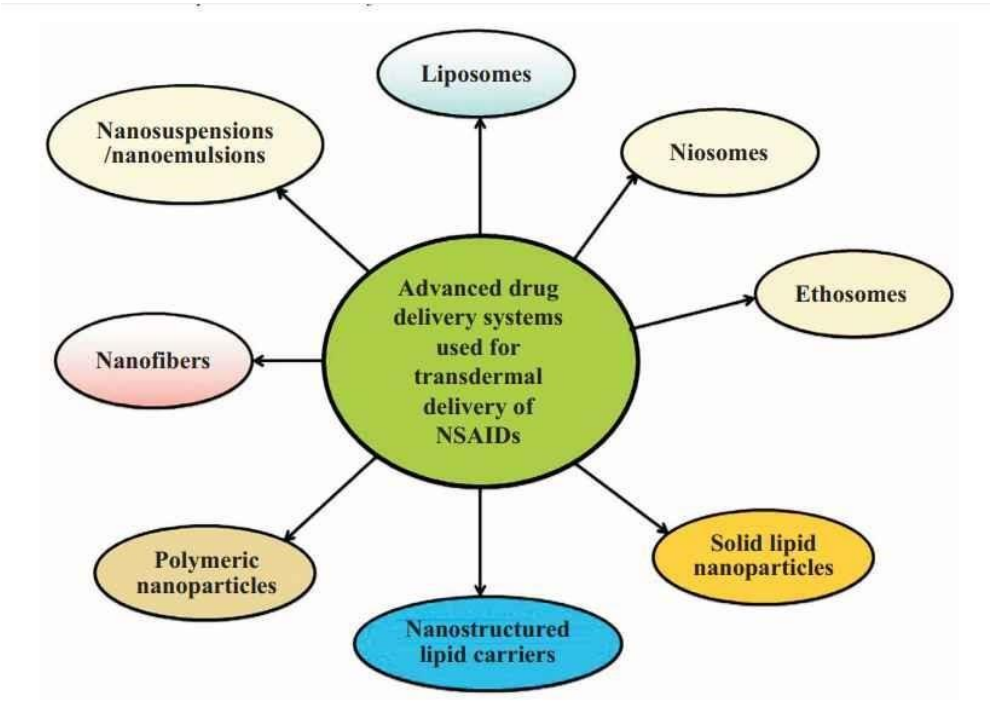
Prescription Required	Some NSAIDs require a prescription, while others are available over-the-counter [31].	Typically, available over-the-counter or as dietary supplements [32].
Interaction with medications	NSAIDs can interact with other medications, potentially causing adverse effects [33].	Herbal products may also interact with medications; caution is advised [34].

(**Table:1** Comparisons between Allopathic medicine and Herbal medicines)

[3.2] Route of administration of NSAIDs:

Oral administration- Ibuprofen is most commonly taken orally. It can be administered in different forms, such as conventional and chewable tablets, oral suspensions, and liquid capsules. Although ibuprofen is almost completely absorbed when taken orally, the speed of absorption depends on how quickly the formulation dissolves [35].

Dermal and transdermal drug delivery- Dermal drug delivery is a way to focus the healing effects of a medicine exactly where they're needed, without letting too much of it get into the rest of the body. On the other hand, transdermal drug delivery is a method to send medicine throughout the body while avoiding some initial processing in the liver. To make sure a medicine works well in certain skin layers or all over the body, it needs to be able to get through the outermost barrier of the skin, called the stratum corneum. How well this happens and how much medicine gets through the skin affects how well the treatment works [36].



[Fig.3 advance drug delivery systems used for trans dermal delivery of NSAIDs [37]]

Intravenous (IV)- Intravenous ibuprofen is effective for acute post-operative pain management and reducing opioid use. It also lowers fever in critical care settings. Recommended doses are 400-800 mg, with 800 mg for critically ill patients. A 30-minute infusion is standard, but a 57-minute rapid infusion is promising. Be aware of injection site pain, especially with rapid infusion. Extended use in hospitalized patients requires caution, particularly in those with significant health issues. Post-marketing surveillance is crucial due to limited long-term data. Intravenous ibuprofen is a useful short-

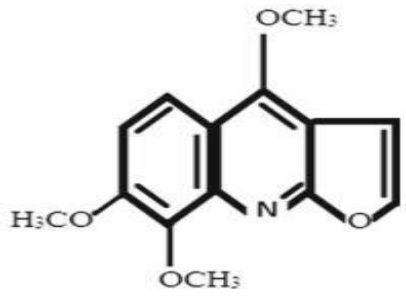
term option for post-operative pain and fever in adults without severe underlying conditions and for antipyresis in critically ill patients [38].

Rectal route- Ibuprofen is safe and effective for both children and adults, often comparable or even more efficient than acetaminophen in reducing fever. It has the added benefit of antiinflammatory properties. However, in cases where oral administration is challenging, such as with infants and small children who vomit or refuse to take the drug, rectal formulations like ibuprofen suppositories are used as an alternative. These suppositories for children are available in several European countries. Despite the frequent use of ibuprofen suppositories for pain and fever management, there is a lack of pharmacokinetic data regarding rectal ibuprofen administration [39]

[3.3] Effect of *Ruta graveolens* (clinical studies):

- The study involving women with hormone-receptor positive breast cancer treated with aromatase inhibitors (AIs), the addition of homeopathic medicines Ruta graveolens 5CH and Rhus Toxicodendron 9CH appeared to improve joint pain and stiffness over three months compared to those not using these remedies. Joint pain was a common side effect of AI treatment, but the homeopathic group had fewer and milder symptoms. These findings suggest potential benefits, but larger placebo-controlled studies are needed to confirm them. In France, complementary therapies like homeopathy are commonly used alongside conventional cancer treatment to manage side effects and improve the quality of life for cancer patients. Oncologists see these therapies as valuable in addressing issues such as musculoskeletal pain, neuropathies, hot flashes, sleep problems, anxiety, fatigue, and dry eyes [40].
- This study investigated the anti-inflammatory effects of the quinoline alkaloid skimmianine (SKM) from Ruta graveolens in a rat model of acute inflammation induced by carrageenan. SKM, at a dose of 5.0 mg/kg, significantly reduced paw oedema and lowered mRNA levels of pro-inflammatory markers TNF-a and IL-6. It also reduced levels of inflammatory mediators like PGE2 and NO, as well as the activity of enzymes COX-2 and 5-LOX. SKM treatment also decreased neutrophil infiltration, lipid peroxidation, and oxidative stress in the paw tissue. These findings suggest that SKM has potential as an anti-inflammatory agent with a multitargeted mechanism of action, making it a candidate for treating various inflammatory diseases

[41].



[Fig. 4 Chemical structure of Quinoline alkaloid skimmianine ($C_{14}H_{13}NO_4$) [41]]

[4] SAFETY AND SIDE EFFECTS:

The current review covers the state of the science regarding the efficacy and safety of NSAIDs used in newborns for which data are currently accessible, including ibuprofen. NSAIDs have been shown to be effective for treating a number of ailments, including fever and discomfort. NSAIDs are primarily used as principles of anti-inflammatory, for example children with inflammatory rheumatic disorders. little information is available about the majority of NSAIDs' safety in newborns. Renal, gastrointestinal, haematological, or immunologic adverse medication responses are possible [42].

Ibuprofen absorbs quickly and has a high plasma protein binding rate; the R isomer has a higher protein binding affinity than the S isomer. It is oxidatively metabolized in the liver by cytochrome

P450 (CYP) 2C9 and CYP2C8, and is primarily eliminated by the kidneys [43]. Ibuprofen can be given intravenously and as a suppository in addition to being taken orally in tablet and solution forms [44]. Acute renal failure, tubular interstitial nephritis, and papillary necrosis are among the possible renal side effects of NSAIDs, with the last being particularly linked to long-term use [45]. The majority of NSAID side effects affect the digestive system, with symptoms like nausea, dyspepsia, abdominal discomfort, diarrhoea or constipation, flatulence, and vomiting. Peptic ulcers, gastric bleeding, and stomach perforation are potentially fatal but extremely uncommon adverse effects in children [46].
Due to its anti-nociceptive and anti-inflammatory qualities, *Ruta graveolens* had been utilized as a treatment for a number of conditions, including cramps, hysteria, helminths, skin problems, and womb disease [47]. *Ruta graveolens* possesses acute and chronic antiinflammatory qualities that are at least three times stronger than those of sodium salicylate since at a dose one-third that of Sodium salicylate, they showed anti-inflammatory effects that were comparable. First off, the dosage for *R. graveolens* is based on concentrated extract, which includes some water and contaminants but has not been dried or processed (unlike SS granules) [48]. *Ruta graveolens' s* hydro extract, 5-metoxipsoralen, and 8-metoxipsoralen extracts all demonstrated strong antifungal effects in vitro [49]. Additionally, this plant's 7metoxi, 7-hydroxi, and 4-hydroxi coumarin extracts have a modest antifungal action [50].

[5] CONCULSION:

The comparative study between Ruta graveolens and allopathic medicines, particularly NSAIDs, highlights the potential of Ruta graveolens as an alternative approach to managing inflammation and pain. While NSAIDs have long been the conventional choice for these purposes, they are associated with notable side effects, including gastrointestinal and renal complications. Ruta graveolens, a plant with a rich history in traditional medicine systems, presents an intriguing alternative due to its diverse array of bioactive compounds, including acridone alkaloids, coumarins, essential oils, flavonoids, and fluoroquinolones. The analysis suggests that Ruta graveolens may offer a safer option with milder side effects, making it a potentially attractive choice for individuals who cannot tolerate the adverse effects of NSAIDs. However, it's essential to emphasize that more rigorous research and clinical studies are necessary to establish the full safety profile and efficacy of Ruta graveolens. Furthermore, the specific dosage forms and administration routes for Ruta graveolens should be explored to provide clear guidelines for its use. In conclusion, while Ruta graveolens shows promise as a natural remedy for inflammation and pain, further research, including well-designed clinical trials, is essential to validate its therapeutic potential fully. This comparative study opens the door to exploring alternative treatments for managing these common health issues, with the aim of providing safer and more effective options for patients.

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