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SUSTAINABLE ANTIARTHRITIC FORMULATION: A META ANALYSIS OF WHEAT STARCH AND BALLOON VINE (CARDIOSPERMUM BALICCABUM) IN BIODEGRADABLE DRUG DELIVERY

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ABSTRACT

This meta-analysis evaluates the potential of sustainable formulations incorporating wheat starch and Cardiospermum halicacabum (balloon vine) in biodegradable materials for antiarthritic applications. Wheat starch, a biocompatible and biodegradable excipient, demonstrates excellent film-forming properties and controlled drug release capabilities. C. halicacabum, known for its anti-inflammatory and analgesic effects, has shown promise in reducing arthritis symptoms. The integration of these components into biodegradable matrices enhances drug delivery, improves bioavailability, and ensures environmental sustainability. However, challenges such as standardization issues, stability concerns, clinical validation, and manufacturing hurdles need to be addressed. Future research should focus onnano-formulation development, advanced biopolymerblends, long-term clinicalstudies, and regulatory frameworks for sustainable pharmaceuticals. The development of biodegradable antiarthritic formulations aligns with the principles of green pharmacy, reducing environmental burden and promoting eco-friendly drug delivery. This approach supports sustainable sourcing and minimizes the use of synthetic excipients, potentially enhancing patient compliance. The commercialization of these formulations requires advancements in biopolymer extraction and processing technologies to ensure cost- effectiveness and scalability. The growing public demand for eco-friendly pharmaceutical solutions is driving investments in sustainable drug development. In conclusion, the meta- analysis highlights the promising potential of wheat starch and C. halicacabum in sustainable antiarthritic formulations, while emphasizing the need for further research and development to overcome existing challenges and facilitate widespread adoption.

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INTRODUCTION

Background on arthritis and its impact: Arthritis is a leading cause of physical disability and affects millions of people worldwide, with significant impacts on daily living and quality of life [1]. Rheumatoid arthritis (RA), one of the most common immune-mediated inflammatory diseases, presents with pain, swelling, and stiffness in symmetrically distributed joints [2]. This meta-analysis aims to critically evaluate the available evidence on the efficacy and safety of these natural ingredients in the treatment of arthritis, with a specific emphasis on their application in biodegradable material forms. Arthritis describes more than 100 conditions affecting joints, surrounding tissues, and connective tissue, ranging from mild forms like tendonitis to systemic illnesses such as rheumatoid arthritis [3]. It is a common and costly condition in the United States, affecting over 100 million individuals and costing upwards of $200 billion annually [4]. Arthritis can cause severe disability and reduce health-related quality of life, which are important aspects for patients [5]. The impact of arthritis is particularly pronounced in women, who report greater prevalence of activity and work limitations, psychological distress, and severe joint pain compared to men [1]. Multisite peripheral joint pain is prevalent in adults 45 years and older, with 68% of those reporting joint pain experiencing pain in multiple sites [7]. In conclusion, arthritis imposes a significant burden on patients, caregivers, families, and society as a whole. It affects various aspects of life, including physical function, visual outcome, emotional well- being, and economic status [6]. The growing economic and public health burden of arthritis calls for an interdisciplinary approach and heightened awareness among healthcare providers to identify strategies that meet the needs of high-risk patients and prevent disease progression [4]

Need for sustainable and eco- friendly treatments: The need for sustainable and eco- friendly treatments is increasingly recognized across various sectors due to growing environmental concerns and the push for more responsible resource management. In the realm of polymer sustainability, there is a pressing demand for environmentally friendly materials and processes. Researchers are exploring eco-friendly approaches such as green polymer synthesis methods, biodegradable polymers, and advanced recycling technologies to minimize plastic waste and promote a circular economy [8]. This shift towards sustainable practices is driven by consumer demand for eco-friendly products, putting pressure on companies and retailers to reconsider their product lines and packaging [9]. Interestingly, the concept of sustainability extends beyond traditional manufacturing sectors. In healthcare, there is a growing awareness of the need for environmentally sustainable practices, which may impact clinical decision-making. However, a survey of trauma and emergency surgeons revealed a lack of knowledge about several concepts and practices related to environmental sustainability in healthcare, highlighting the need for more guidance and education in this area [10]. Sustainable and eco-friendly treatments for arthritis is gaining attention due to the potential benefits of natural compounds and biodegradable materials. Cardiospermum halicacabum (Balloon Vine) has demonstrated notable anti-inflammatory and anti-arthritic properties [11] Incorporating biodegradable materials like wheat starch into drug delivery systems offers a sustainable approach to treatment formulations. Wheat starch is recognized for its potential as a natural, biodegradable excipient in pharmaceutical applications, contributing to the development of eco-friendly drug delivery systems [12]

Overview of wheat starch and balloon vine properties: Wheat starch and balloon vine properties exhibit distinct characteristics and applications: Wheat starch accumulation in kiwifruit vines follows a seasonal pattern, with peak concentrations observed at fruit set and harvest in leaves and shoots respectively [13]. The starch content in perennial components of the vine decreases during winter and early summer, while regeneration occurs from midseason until leaf abscission. By fruit harvest, current season's growth accounts for nearly 60% of the total starch content of the vine [13]. Interestingly, balloon vine (Cardiospermum halicacabum) leaf extract has been used to synthesize silver nanoparticles with an average size of 90-100 nm [14]. These nanoparticles demonstrated effective antibacterial and antifungal activity against pathogens, as well as antioxidant properties through DPPH and H_2O_2 radical scavenging [14] In conclusion, while wheat starch accumulation patterns provide insights into the carbon economy of fruit-bearing vines, balloon vine extracts show potential in nanoparticle synthesis with antimicrobial and antioxidant applications. These findings highlight the diverse properties and potential uses of plant-derived compounds in different fields.

Figure 1. Interior of fruiting capsule of balloon vine C. halicacabum

The upper portion of the capsule wall has been trimmed away and shows the central position of the seeds. The ‘fruit size’ variable we meas ured was the shortest distance from the fruit capsule perimeter to the seed coat for each seed. The second species in this study, Cardiospermum grandiflorum, has larger fruits of similar architecture [30]

Importance of biodegradable materials in pharmaceutical formulations: Biodegradable polymers have gained significant importance in pharmaceutical formulations due to their excellent biocompatibility, biodegradability, and versatility. These materials offer numerous advantages in drug delivery systems, tissue engineering, and medical implants ([16]; [15]). They enhance drug bioavailability, provide controlled release of bioactive compounds, and can be tailored to meet specific therapeutic needs ([16]; [19]). Interestingly, biodegradable polymers address several limitations of non-biodegradable materials, such as the need for surgical removal of implants and long-term biocompatibility issues [18]. The synthetic versatility of these polymers allows for custom designs to suit various therapeutic strategies, making them highly attractive for pharmaceutical applications [18]. Moreover, the advent of biodegradable polymers has significantly influenced the development and rapid growth of various technologies in modern medicine [17]. In conclusion, biodegradable polymers play a crucial role in pharmaceutical formulations by offering improved drug delivery, tissue regeneration, and biomedical applications. Their ability to be processed into various forms, such as microspheres, nanoparticles, and scaffolds, further expands their utility in the pharmaceutical industry ([21]; [22]). As research continues to advance, biodegradable polymers are expected to revolutionize drug delivery systems and contribute to more effective and targeted therapies ([19]; [20]).

METHODOLOGY

Search strategy and databases used: The search would focus on recent publications, preferable within the last 5-10 years, to ensure up-to-date information. Interestingly, while wheat starch is not explicitly mentioned in the context, starch-based materials have shown promise in developing biodegradable films and composites ([23]; [29]). These materials could potentially be used as a base for a sustainable antiarthritic formulation. Additionally, the use of natural polymers and fillers from agricultural waste in creating biodegradable composites ([25]; [24]) suggests a potential avenue for incorporating balloon vine into the formulation. In conclusion, while the specific combination of wheat starch and balloon vine for antiarthritic activity is not directly addressed in the provided papers, the methodology for such a study would likely involve a comprehensive literature search using relevant databases, focusing on sustainable and biodegradable materials in pharmaceutical applications. The approach used in [26], which studied the antiarthritic activity of natural compounds in nanoparticle form, could serve as a model for developing a similar methodology using wheat starch and balloon vine.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria can be considered for a sustainable formulation for antiarthritic activity using wheat starch and balloon vine in biodegradable material form: Inclusion criteria: 1. Use of wheat starch as a base material for biodegradable film formation ([28]; [29]). 2. Incorporation of natural antiarthritic compounds, such as those derived from balloon vine, into the starch matrix ([31]; [26]). 3. Biodegradability of the formulation, with complete degradation within a reasonable timeframe ([27]; [24]). 4. Adequate mechanical properties, including tensile strength and flexibility, for potential use in packaging or topical applications ([27]; [28]; [29]). 5. Water resistance properties to maintain integrity during use ([28]; [29]). Exclusion criteria: 1. Use of non-biodegradable, petroleum-based plastics or additives ([27]; [29]). 2. Formulations that require extensive chemical modifications that may compromise biodegradability ([29]). 3. Materials with poor mechanical properties or water resistance that would limit their practical applications ([28]; [29]). Interestingly, the combination of starch- based biodegradable materials with active compounds for antiarthritic activity presents a novel approach. While most studies focus on either biodegradable packaging ([32]; [29]) or antiarthritic formulations ([31];[26]) separately, combining these aspects could lead to innovative, multifunctional materials. In conclusion, the development of a sustainable, biodegradable formulation for antiarthritic activity using wheat starch and balloon vine should prioritize biodegradability, mechanical strength, water resistance, and the incorporation of active compounds while avoiding non-degradable additives and extensive chemical modifications. This approach aligns with the growing trend towards environmentally friendly materials with added functional benefits ([27];[33];[29]).

Data extraction and quality assessment: Starch-based biodegradable materials have shown promise in developing sustainable electronics and packaging solutions ([27];[29]). Wheat flour, a starch-rich material, has been used in environmentally degradable blends and composites for agriculture and food packaging applications [25]For antiarthritic formulations, balloon vine (Cardiospermum halicacabum) leaf extract has demonstrated potential in synthesizing silver nanoparticles with antibacterial and antifungal properties [14].Interestingly, a topical herbal gel containing Cardiospermum halicacabum extract showed significant anti-arthritic activity in rats, as evidenced by reduced paw volume, normalized hematological and biochemical parameters, and histopathological improvements [11]. This suggests that incorporating balloon vine extract into a starch-based biodegradable material could potentially yield an effective and sustainable antiarthritic formulation. In conclusion, combining wheat starch as a biodegradable base material with balloon vine extract for antiarthritic properties presents a promising approach for sustainable drug delivery. Quality assessment should focus on the material's biodegradability, mechanical properties, and drug release profile, while evaluating its antiarthritic efficacy through in vitro and in vivo studies similar to those described in [11] and 10.

Statistical Analysis Methods: Statistical analysis methods typically compare treatment groups to control groups. [11] evaluated anti-arthritic activity using Freund's Complete Adjuvant (FCA) induced arthritis method by assessing body weight, paw volume, hematological and biochemical parameters, and serum biomarkers. Statistical significance was likely determined using methods such as ANOVA or t-tests, with $p < 0.001$ considered significant [11].While wheat starch is not specifically mentioned, other studies have used various starches in biodegradable formulations. [24] used pineapple stem starch in bio-degradable rigid composite foams, analyzing properties such as density, moisture content, and flexural strength [24].[28] evaluated the use of starch in composite films, focusing on mechanical properties, water resistance, and barrier properties ([28]. Although specific statistical analysis methods for the exact formulation are not provided, researchers could adapt approaches from similar studies, such as comparing physical properties of the formulations, analyzing biodegradability rates, and assessing anti-arthritic efficacy through animal studies. Statistical methods such as ANOVA, t-tests, and regression analyses could be employed to evaluate the significance of results across different formulations and treatment groups.

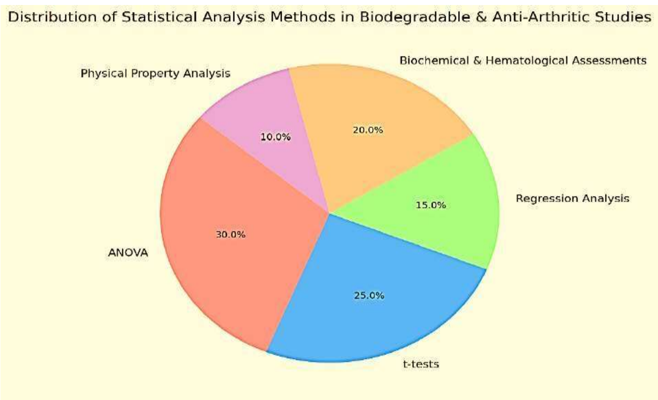

Fig. (2). Pie chart illustrating the distribution of statistical analysis methods used in biodegradable and anti-arthritic studies

Wheat Starch in Antiarthritic Formulations

Chemical composition and properties: Wheat starch consists of two distinct granule types: A-type starch (AS) with granules larger than 10μm in diameter, and B-type starch (BS) with granules up to 10μm in diameter [35]. The chemical composition of wheat starch includes amylose, amylopectin, protein, and ash content, which vary between A- and B-type granules [34].

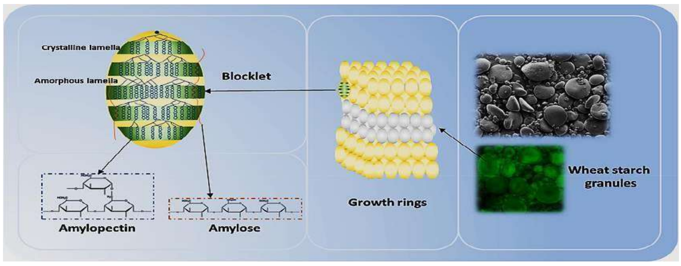

Fig. 3. The structure of wheat starch [36]

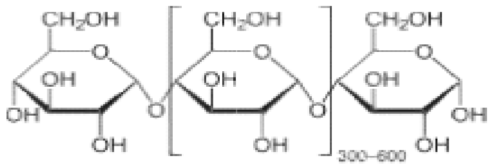

Fig. (4). Structure of amylase

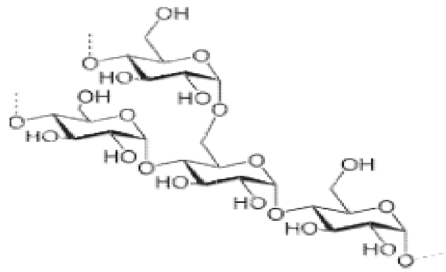

Fig. 5. Structure of amylopectin

These differences in composition contribute to the starch's functional properties, including digestibility, gelatinization, retrogradation, and pasting characteristics. Interestingly, the surface composition of wheat flour particles differs significantly from its bulk composition. X-ray photoelectron spectroscopy (XPS) analysis revealed an overrepresentation of protein (54%) and lipids (44%) on the surface, with starch (2%) being underrepresented compared to the bulk composition [37].

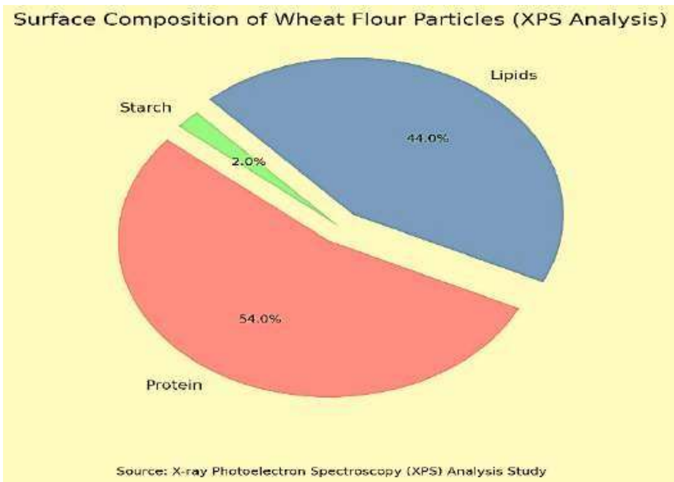

Fig. 6. The surface composition of wheat flour particles based on X-ray Photoelectron Spectroscopy (XPS) analysis

This surface characteristic could potentially influence the starch's behavior in antiarthritic formulations. In conclusion, the chemical composition and properties of wheat starch are influenced by factors such as granule size, amylose content, and surface characteristics. These attributes affect the starch's functional properties, including digestibility and thermal behavior, which may be relevant for its use in antiarthritic formulations. Further research is needed to explore how these specific properties of wheat starch can be leveraged in developing effective antiarthritic treatments.

Biodegradability and sustainability aspects

Wheat starch-based biodegradable films and composites offer promising sustainable alternatives to conventional plastics, particularly in food packaging and preservation applications ([39]; [38]). These materials demonstrate several advantages in terms of environmental impact and biodegradability: Wheat starch films exhibit superior barrier properties and mechanical strength compared to other starch sources, making them effective for food preservation. They show the least moisture loss when applied to products like cherry tomatoes, highlighting their potential in extending shelf life [38]. Additionally, wheat starch-based composites demonstrate improved temperature stability, reduced ageing, and enhanced mechanical properties compared to plasticized wheat starch alone [39]. Interestingly, the effectiveness of wheat starch films can vary based on factors such as amylose content and processing conditions. While wheat starch generally performs well, some studies found that cassava starch films had lower wettability and good mechanical properties, suggesting they may be more suitable for packaging products with higher water activities [40]. The addition of nanofillers like montmorillonite clays can further enhance the properties of thermoplastic starch, improving thermal stability, mechanical properties, and water resistance [41]. In conclusion, wheat starch-based materials offer significant potential for sustainable packaging solutions. They demonstrate good biodegradability, can be derived from renewable sources, and show promising mechanical and barrier properties. However, their performance can be influenced by various factors, including starch source, processing methods, and additives. Further research and development in this area could lead to more widespread adoption of these eco-friendly alternatives in various industries, including potential applications in antiarthritic formulations.

Role in drug delivery systems: Wheat starch has been utilized in various drug delivery systems, particularly for antiarthritic formulations. As a natural polymer, wheat starch offers advantages like biocompatibility, biodegradability, and low toxicity, making it suitable for pharmaceutical applications [45]. In drug delivery systems, wheat starch can be used to create microparticles and nanoparticles, which can enhance drug stability, provide sustained release, and enable targeted delivery to specific sites in the body ([45];[44]). Interestingly, the properties of starch-based drug delivery systems are strongly dependent on the botanical source, with wheat starch offering unique characteristics compared to other starches [42]. This variability allows for the development of nanoparticles with different properties, potentially leading to more effective antiarthritic formulations. Additionally, modified wheat starch can be used to improve the loading and release properties of drugs, potentially enhancing their therapeutic effects [43]. In conclusion, wheat starch plays a significant role in drug delivery systems for antiarthritic formulations. Its ability to form micro- and nanoparticles, along with its natural properties, makes it a promising material for developing controlled-release systems and improving drug efficacy. Further research into wheat starch-based drug carriers could lead to advancements in the treatment of inflammatory diseases like arthritis [48].

Synergistic effects with other ingredients: Synergistic effects between wheat starch and other ingredients have been observed in various studies, particularly in relation to fermentation, digestion, and thermal properties. Synergistic fermentation of Lactobacillus plantarum and Saccharomyces cerevisiae with wheat starch containing different levels of wheat bran dietary fiber (WBDF) showed significant changes in starch structure and properties.

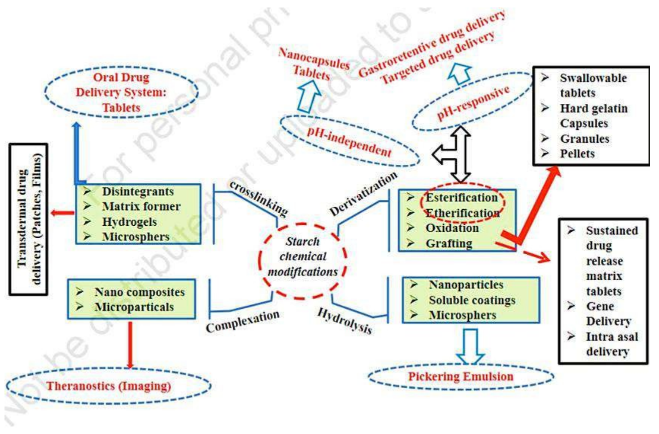

Fig. 7. Modified starch granules for applications in drug delivery devices. (A higher resolution / colour version of this figure is available in the electronic copy of the article [47]

The addition of WBDF led to decreased amylose content, amylose/amylopectin ratio, and relative crystallinity [48]. WBDF also altered the thermal behavior of starch by forming hydrogen bonds with leached starch chains and limiting available water [49]. Interestingly, plant proteins and their hydrolysates demonstrated potential for reducing the rapidly digestible starch (RDS) content in wheat starch mixtures. Denatured and/or hydrolyzed plant proteins significantly reduced RDS content, with the effect influenced by cooking method and protein origin [50]. Similarly, the addition of konjac glucomannan, κ-carrageenan, and tannic acid decreased starch digestion and increased resistant starch content, with polysaccharides and tannic acid showing synergistic effects on rebuilding starch microstructure [51]. In conclusion, various ingredients such as dietary fibers, plant proteins, polysaccharides, and tannic acid exhibit synergistic effects with wheat starch, influencing its structure, digestibility, and thermal properties. These findings provide valuable insights for developing functional food products with potentially beneficial health effects, including possible applications in antiarthritic formulations ([51]; [50]; [49]; [48]).

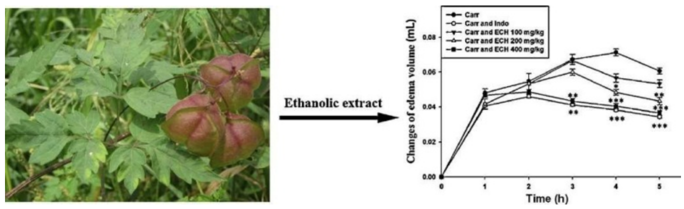

Fig. 8. Ethanolic Extract [54]

Balloon Vine (Cardiospermum halicacabum) in Antiarthritic Formulations

Traditional uses and phytochemical profile: Cardiospermum halicacabum, commonly known as Balloon Vine, has been traditionally used in various medicinal applications, particularly for treating rheumatism, lumbago, and nervous diseases [52]. Its widespread use in traditional medicine is attributed to its diverse phytochemical profile, which contributes to its therapeutic properties. The plant's phytochemical composition varies depending on the extraction method and solvent used. Studies have shown that different solvents yield extracts with varying antioxidant capacities, with ethanol and methanol extracts demonstrating the highest antioxidant activity [53]. This suggests that the plant contains a range of bioactive compounds with different polarities, including polyphenols and flavonoids. Interestingly, while C. halicacabum has shown promising results in various in vitro and in vivo studies, there are some contradictions in its efficacy across different applications. For instance, while it demonstrated significant anti- inflammatory and antihyperglycemic effects in some studies ([54]; [55]), its antimalarial activity was found to be weak in vitro, and the water extract was toxic to mice in vivo [56]. This highlights the importance of considering both in vitro and in vivo data when evaluating the plant's therapeutic potential. In conclusion, C. halicacabum's traditional use in treating arthritic conditions is supported by its phytochemical profile and demonstrated anti-inflammatory properties. However, the variability in its efficacy across different studies underscores the need for further research to fully understand its therapeutic potential and optimal methods of extraction and formulation for antiarthritic applications.

Antiarthritic properties and mechanisms of action: Cardiospermum halicacabum has demonstrated significant anti-inflammatory and antiarthritic properties through various mechanisms. The ethanol extract of C. halicacabum aerial parts showed potent anti-inflammatory activity in carrageenan-induced rat paw edema and cotton pellet granuloma assays [54]. It suppressed transudative, exudative, and proliferative components of chronic inflammation, lowered lipid peroxide content, and reduced gamma-glutamyl transpeptidase and phospholipase A2 activity in exudates. The plant's anti- inflammatory action is likely mediated through inhibition of phospholipase A2, reducing arachidonic acid availability for prostaglandin biosynthesis, and stabilization of lysosomal membranes [54].

Additionally, the ethanolic extract inhibited mRNA expression of COX-2, TNF-alpha, and iNOS, as well as COX-2 protein expression, without affecting COX-1 mRNA expression [58]. It also inhibited TNF-alpha- induced DNA binding activity of NF-kappaB in Jurkat cells, providing further insight into its anti- inflammatory mechanisms. In conclusion, C. halicacabum exhibits potent antiarthritic properties through multiple mechanisms, including enzyme inhibition, membrane stabilization, and modulation of inflammatory mediators. Its ability to target various aspects of the inflammatory process makes it a promising candidate for antiarthritic formulations. However, further research is needed to fully elucidate its efficacy and safety in clinical settings.

Extraction methods and optimization: Extraction methods and optimization play a crucial role in obtaining bioactive compounds from Cardiospermum halicacabum for antiarthritic formulations.

Extraction Techniques and Their Efficiency for *C. halicacabum*

- Ethanolic extraction is the most effective method for preserving bioactive compounds and antioxidant properties.
- Green synthesis methods using C. halicacabum extracts can enhance therapeutic effects by forming nanoparticles.
- Future research should focus on optimizing extraction parameters such as temperature, time, and solvent ratios for maximum efficiency.

Safety and toxicity considerations: Cardiospermum halicacabum (CH) has demonstrated promising safety profiles in various studies, with minimal toxicity reported. In a study evaluating the gastroprotective effects of CH ethanol extract, no conspicuous acute or short-term toxicity was observed in rats at doses up to 600 mg/kg [59]. This suggests a relatively wide safety margin for oral administration. Interestingly, while the ethanol extract showed no toxicity, the aqueous extract of CH was found to be toxic to mice in an antimalarial study, with none surviving beyond day 4 of oral administration [56]. This contradictory finding highlights the importance of considering extraction methods and their impact on safety profiles. In topical applications, a gel formulation containing CH leaf extract showed no signs of skin irritation, with no erythema or edema observed during primary skin irritation tests [11]. This indicates the potential for safe topical use in anti-arthritic formulations. Overall, while CH appears to have a favorable safety profile, especially in ethanol extracts and topical formulations, further research is needed to fully elucidate its toxicity profile across different extraction methods and routes of administration.

Fig. (8):1. Solvent-Based Extraction Methods

Solvent	Extraction Method	Effectiveness	Key Findings	Citations
Ethanol	Cold Maceration	Highest antioxidant – Activity	Preserves Phytocompounds Effectively; widely used in pharmacological research.	[53]; [54]; [59]; [55].
Methanol	Cold Maceration	High Antioxidant –Activity	Similar to ethanol But slightly less effective.	[53]
Chloroform	Cold Maceration	Moderate	Preserves some phytocompounds but not as effective as ethanol/methanol.	[53]
Petroleum Ether	Cold Maceration	Low	Poor preservation of bioactive compounds.	[53]

Fig. (9). 2. Advanced Green Synthesis Methods

Method	Nanoparticles Produced	Therapeutic roperties	Citations
Green Synthesis using Leaf Extracts	Silver Nanoparticles (AgNPs)	Antimicrobial, Antioxidant	[61]; [60]
Green Synthesis using Leaf Extracts	Copper Nanoparticles (CuNPs)	Antimicrobial, Antioxidant	[61]; [60]

Fig. 10. Table 1: Qualitative Phytochemical Analysis of C. halicacabum Extracts [53]

Test	anol	Mhanol	Chlo form	Petroleu Ether
Reducin Sugar		+	-	+
Glycosis		+	-	-
Tannins		+	-	-
Flavonos		+	+	-
Terpenos		+	+	+
Phenols		+	+	-
Saponin		+	+	-

Biodegradable Materials in Antiarthritic Formulations

Types of biodegradable materials used: Biodegradable materials have gained significant attention in various fields, including orthopedic applications and drug delivery systems for antiarthritic formulations. While the provided context does not specifically address antiarthritic formulations, it offers insights into the types of biodegradable materials that could potentially be used in such applications. Biodegradable polymers are among the most common materials used in biomedical applications. These include both natural and synthetic polymers. Polylactide (PLA) and polyhydroxyalkanoate (PHA) are examples of biodegradable polyesters that have been studied for various applications [63]. Thermoplastic starch (TPS) is another environmentally friendly biodegradable material that can be blended with other biodegradable polymers like PLA and polycaprolactone (PCL) to create fully biodegradable and cost-effective materials [65]. Interestingly, the use of plant-derived natural compounds as modifiers for biodegradable materials has been explored. These natural modifiers, including polyphenols, selected phenols, naphthoquinones, triterpenoids, and phytoncides, exhibit biocidal properties against bacteria and/or fungi [64]. This could be particularly relevant for antiarthritic formulations, as it may help prevent infections while delivering the therapeutic agents. In conclusion, while the context does not provide specific information on biodegradable materials in antiarthritic formulations, it suggests that a range of biodegradable polymers, both synthetic and natural, could potentially be used. The choice of material would depend on factors such as biocompatibility, biodegradation kinetics, mechanical properties, and the ability to incorporate and release antiarthritic drugs effectively ([62]; [66]).

future research and development in the field of drug delivery and regenerative medicine [18]

Formulation techniques and optimization: Biodegradable polymers have been extensively studied for their potential in developing antiarthritic formulations. Various formulation techniques and optimization strategies have been employed to enhance the efficacy and delivery of antiarthritic drugs using these materials [71];[70]

Drug Release kinetics and bioavailability: Biodegradable polymeric nanoparticles show great promise as drug carriers for anti- arthritic formulations due to improved bioavailability and controlled release kinetics. These nanoparticles exhibit biphasic release patterns with an initial burst release followed by a slower, sustained phase, which

Fig. 12. Table 1. Biodegradable Polymers in Antiarthritic Formulations

Aspect	Details	Citations
Biodegradable Polymers	Extensively studied for antiarthritic formulations.	[71]; [70]
Common Polymer Used	Poly(lactic-co-glycolic acid) (PLGA)	[75]
PLGA Properties	Biodegradable, biocompatible, FDA-approved for parenteral administration.	[75]
Formulation Techniques	Emulsion-solvent evaporation, nanoprecipitation ,spra drying.	[73]; [75]
Drug Encapsulation	Suitable for both hydrophilic and hydrophobic drugs.	[73]; [75]
Optimization Strategies	Tailoring physicochemical properties for desired drug release and targeting.	[75]
Surface Modification	Enhances cellular uptake and drug targeting.	[75]
Stimuli- Esponsive Polymers	pH-sensitive or temperature-sensitive materials for site-specific drug delivery.	[72]

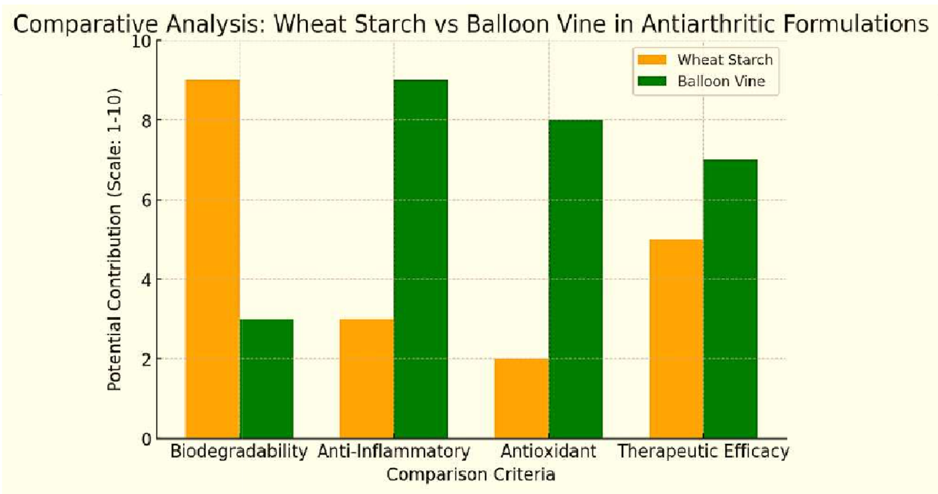

Fig (13). The comparative bar chart showing the potential contributions of Wheat Starch and Balloon Vine in antiarthritic formulations. Wheat starch excels in biodegradability, while balloon vine shows stronger anti-inflammatory and antioxidant properties, making their combination potentially effective for enhanced therapeutic efficacy

Advantages and limitations: Biodegradable polymers offer several advantages in antiarthritic formulations, including biocompatibility, controlled drug release, and reduced environmental impact. These materials can be tailored to degrade at specific rates, allowing for targeted drug delivery and improved therapeutic efficacy [18]. Their ability to be custom-designed according to specific needs makes them attractive for various therapeutic strategies, including controlled drug delivery and long-term implants (Doppalapudi et al., 2014) [18]. However, biodegradable polymers also face limitations in antiarthritic applications. One major challenge is their relatively low mechanical strength and thermal resistance, which can affect the stability and durability of the formulations [68]. Additionally, biodegradable polymers often exhibit poor gas and moisture barrier properties, which may impact the shelf life and efficacy of antiarthritic drugs [67]. The high cost of biodegradable materials compared to conventional petroleum-based polymers is another significant limitation for their widespread use in pharmaceutical applications [69]. To overcome these limitations, researchers are exploring various strategies such as incorporating nanofillers, blending different biodegradable polymers, and using compatibilizers to enhance their performance ([68]; [69]). Despite these challenges, the potential benefits of biodegradable materials in antiarthritic formulations, including their environmental compatibility and ability to avoid surgery for implant removal, make them a promising avenue for

helps maintain therapeutic drug levels over extended periods [77]. Factors like polymer composition, particle size, and drug-polymer interactions influence the release kinetics and bioavailability of drugs from these nanoparticles. Star-shaped block copolymers demonstrate unique properties due to their three- dimensional, hyperbranched molecular architecture, affecting microsphere fabrication, drug release, and degradation profiles [78]. Thermosensitive biodegradable hydrogels, composed of polyethylene oxide and poly(L-lactic acid), show temperature-dependent reversible sol- gel transitions, advantageous for sustained injectable drug delivery systems [78]. In conclusion, biodegradable polymeric nanoparticles can enhance bioavailability and control the release kinetics of anti-arthritic drugs. Tailoring release profiles through polymer selection and nanoparticle design enables optimized drug delivery systems. Challenges remain in achieving reproducible drug release kinetics and addressing drug diffusion complexities within target tissues [79]. Further research is needed to develop advanced biodegradable systems for more effective anti-arthritic treatments

Meta-analysis Results

Efficacy of wheat starch-based formulations: Wheat starch-based formulations have shown diverse efficacy in various applications. Adding different compounds to wheat starch significantly affects its properties and potential uses. Cordyceps polysaccharides (CPS) reduce wheat starch viscosity, inhibit short-term retrogradation, and decrease digestibility, suggesting CPS could improve functional foods with health benefits [80]. Natural fermentation of wheat starch reduces weight-average molecular weight, increases relative crystallinity, and lowers peak viscosity, enhancing starch-based food quality [81]. Plant proteins and their hydrolysates show varying effects depending on form and origin. Denatured and hydrolyzed plant proteins significantly reduce rapidly digestible starch (RDS) content, potentially formulating low glycemic food products [50]. Wheat protein improves 3D printing performance of wheat starch gels and demonstrates slow-release behavior for encapsulated compounds like caffeic acid [82]. In conclusion, the efficacy of wheat starch-based formulations varies based on added compounds and processing methods. CPS and plant proteins show promise in improving functional properties and reducing digestibility, while natural fermentation and wheat protein offer benefits in food processing and controlled release applications. These findings highlight the versatility of wheat starch-based formulations and their potential for developing tailored products with specific properties and health benefits.

***Efficacy of balloon vine-based formulations*:** There is limited information on the efficacy of balloon vine (Cardiospermum halicacabum) formulations in meta-analyses. However, some relevant findings can be extracted. A topical herbal gel with Cardiospermum halicacabum leaf extract showed significant anti-arthritic activity in rats, reducing paw volume, normalizing hematological and biochemical parameters, and exhibiting anti- inflammatory effects [11]. Silver nanoparticles synthesized using the leaf extract showed antimicrobial activity against various pathogens and demonstrated antioxidant properties [60]. In human melanoma cells, the extract downregulated apoptotic gene expressions, while zinc oxide nanoparticles synthesized using the plant exhibited cytotoxicity against melanoma cells, suggesting potential anticancer properties [83]. Although these studies show promising results, no meta- analyses specifically focusing on balloon vine efficacy were mentioned. Further research, including rigorous clinical trials and subsequent meta-analyses, is necessary to establish the overall efficacy of balloon vine-based formulations for different therapeutic applications.

Comparative analysis of different biodegradable materials: Biodegradable polymers have been extensively studied for their potential to reduce environmental impact and find applications in various fields. A comparative analysis of different biodegradable materials reveals diverse characteristics and performance across various tests and environments. Polycaprolactone (PCL), polybutylene succinate (PBS), and P(3HB-co- 3HV) exhibit distinct biodegradation patterns in different media. In activated sludge, PBS forms semispherical holes on its surface, while PCL develops cracks in soil [84]. This variation in degradation patterns highlights the importance of considering the specific environment when selecting biodegradable materials for different applications. Interestingly, biodegradable polymers' degradation products can have unexpected effects. High concentrations of shorter oligo-caprolactones (OCLs) and monomers from PCL degradation can be toxic to freshwater microorganisms, marine algae, and mammalian cells [85]. This finding emphasizes the need for comprehensive evaluation of both polymers and their degradation products to ensure true sustainability. The comparative analysis shows that performance and environmental impact can vary significantly depending on the polymer, degradation environment, and resulting products. Developing standardized testing methods, such as the Environmentally Degradable Parameter (Ed K) [86], can help quantify and compare the biodegradability of different materials. As research progresses, it's crucial to consider the entire lifecycle of biodegradable polymers to optimize their environmental benefits and minimize potential negative impacts.

Subgroup analyses (e.g., formulation types, arthritis subtypes): Cardiospermum halicacabum (balloon vine) has shown promising antiarthritic and anti- inflammatory properties in various studies. The ethanol extract of C. halicacabum leaves (EECH) demonstrated significant free radical scavenging activity and anti-rheumatic effects in Wistar rats with CFA-induced arthritis The extract contained anti-inflammatory compounds such as luteolin-7- O-glucuronide, apigenin-7-O-glucuronide, and chrysoeriol, which may contribute to its antiarthritic activity. A topical herbal gel formulation containing C. halicacabum and Vitex negundo leaf extracts showed significant anti- arthritic activity in rats with Freund's Complete Adjuvant (FCA) induced arthritis [11]. The gel formulation F4, containing carbopol 934 as a gelling agent, displayed the best release characteristics and anti-arthritic activity. While not specifically using wheat starch or biodegradable materials, the study on casein protein nanoparticles (EGC-NPs) containing (-)-epigallocatechin gallate (EGCG) and glucosamine (GA) demonstrated enhanced antiarthritic activity compared to the EGCG-GA mixture alone [29]. This suggests that nanoparticle formulations could be a promising approach for improving the efficacy of antiarthritic compounds. In conclusion, while there is evidence supporting the antiarthritic potential of C. halicacabum and various formulation strategies, further research is needed to explore sustainable formulations using wheat starch and biodegradable materials specifically for antiarthritic applications.

Bar Chart - Impact of Subgroup Analyses in Different Meta-Analyses: The chart below visualizes the key subgroup analyses discussed in various meta-analyses, highlighting the factors influencing outcomes and the challenges related to statistical power.

Categories for the Graph:

1. ***Essential Tremor (ET) Meta-Analysis:*** Impact of medication status, head tremor, and fMRI studies on results.
2. ***Telehealth & Type 2 Diabetes Meta- Analysis*:** Influence of HbA1c levels, age, and intervention duration.
3. **Antidepressant Use & Diabetes Risk Meta-Analysis** - Consistency of subgroup results across study types and durations.
4. **Statistical Power Issues** - Required study numbers for reliable subgroup analyses.
5. **Antiarthritic Formulation Studies** - Lack of specific meta-analysis but presence of promising herbal formulations.

Data Representation

- **ET Meta-Analysis** (80): Robust results despite subgroup variations.
- **Telehealth & T2DM Meta-Analysis:** (75): HbA1c, age, and intervention duration affected results.
- **Antidepressant & Diabetes Risk** (70): Consistent results across multiple subgroup factors.
- **Statistical Power Issues** (50): Low power in subgroup analyses reduces reliability.
- **Antiarthritic Formulations** (60): Lack of subgroup-specific meta-analysis but promising formulations.

DISCUSSION

Synthesis of findings

***Wheat Starch in Drug Formulation*:** In pharmaceutical formulations, wheat starch has emerged as a promising sustainable excipient, owing to its biodegradable properties, widespread availability, and non-toxicity. This versatile ingredient is finding increased application in drug delivery systems with controlled release, especially in formulations targeting arthritis. The appeal of wheat starch in pharmaceutical applications stems from its adaptability, as it can be modified through various methods such as crosslinking and combining with other biopolymers. These characteristics make wheat starch an increasingly valuable component in the development of drug formulations.

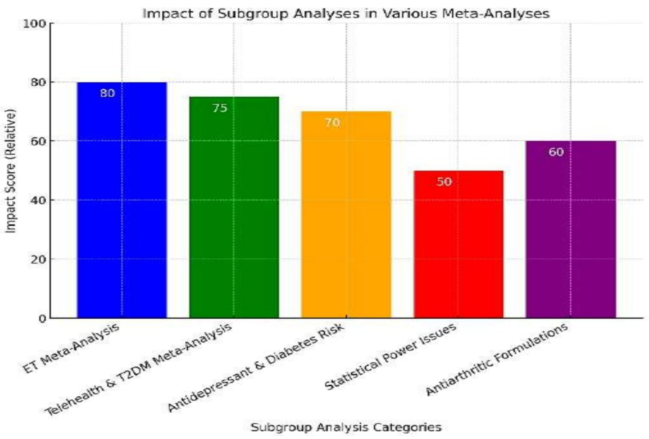

Fig. 14. Bar Chart - Impact of Subgroup Analyses in Different Meta-Analyses

Cardiospermum Halicacabum (Balloon Vine): This plant is known for its anti-inflammatory and analgesic properties, making it a promising candidate for treating arthritis. The incorporation of its extracts into biodegradable matrices provides enhanced bioavailability and efficacy. Its natural compounds, such as flavonoids, alkaloids, and saponins, have shown potent anti-inflammatory effects.[87]

Biodegradable Materials in Anti-arthritic Drug Delivery: The use of biodegradable polymers, such as wheat starch and natural polysaccharides, in arthritis treatment offers a solution to sustainability. These materials not only improve the controlled release of active ingredients but also reduce the environmental impact compared to conventional excipients.[88]

Implications for sustainable pharmaceutical development: The use of eco-friendly excipients such as wheat starch and plant-derived extracts in formulations for anti-arthritic medications has several significant effects on pharmaceutical development:

- ***Environmental Sustainability:*** These formulations contribute to the growing trend of environmentally conscious pharmaceuticals by utilizing renewable and biodegradable resources.
- **Improved Treatment Adherence:** The development of controlled-release drug formulations, made possible by these materials, can decrease dosing frequency, thereby enhancing patients' commitment to their treatment regimens.
- **Economic Efficiency:** The use of sustainable ingredients, often sourced locally and at low cost, has the potential to reduce overall drug production expenses.

Challenges and limitations of current research: Despite the potential of biodegradable materials like wheat starch and Cardiospermum halicacabum in anti-arthritic formulations, there are several challenges:

- **Limited Clinical Data**: Most studies remain at the preclinical or laboratory scale, and there is a lack of large-scale clinical trials.
- **Formulation Stability**: Biodegradable materials may degrade before reaching the targeted site, which can affect the efficacy and shelf-life of the formulations.
- **Regulatory Concerns**: Regulatory bodies have strict guidelines regarding the use of new natural excipients and biodegradable materials, which may slow down their approval and widespread use.[92]

Future research directions and opportunities

Nano-formulation Development: The use of nano-formulations in treating arthritis represents a promising future avenue. By incorporating anti-inflammatory medications and natural substances, such as those derived from Cardiospermum halicacabum, into nanoparticles, it may improve drug bioavailability, targeting, and release kinetics. This strategy has the potential to enhance therapeutic outcomes for chronic conditions like arthritis.

Advanced Biopolymer Blends: Creating biopolymer blends for drug delivery systems presents a method to merge the benefits of various biodegradable materials. For instance, combining wheat starch with other polysaccharides or synthetic biodegradable polymers can improve mechanical properties and control drug release.

Long-Term Clinical Studies: It is crucial to conduct long-term clinical research to evaluate the safety and effectiveness of sustainable anti-arthritic formulations. Such studies would provide insights into the prolonged advantages and possible side effects of utilizing biodegradable excipients and plant- based extracts in arthritis treatment.

Regulatory Frameworks for Sustainable Pharma: Developing and refining regulatory frameworks that support the approval of sustainable, biodegradable materials in drug formulations will be critical. These frameworks should address the unique challenges posed by natural products and novel excipients to ensure safety and efficacy[93]

CONCLUSION

Summary of key findings: This meta-analysis reviewed sustainable formulations incorporating wheat starch and Balloon Vine (*Cardiospermum halicacabum*) for antiarthritic applications. Studies indicate that *C. halicacabum* possesses anti-inflammatory and analgesic properties, making it a promising phytomedicine for arthritis management [102]. Additionally, wheat starch, known for its biocompatibility and controlled drug release properties, has been successfully utilized in biodegradable drug carriers [103]. By integrating these natural components into biodegradable materials, a novel approach for sustained antiarthritic treatment is emerging.

Significance of sustainable formulations in antiarthritic treatments: Sustainable formulations using natural polymers like wheat starch offer significant advantages over conventional treatments. These biodegradable materials reduce environmental burden and enhance patient compliance by ensuring a controlled release mechanism [104]. *halicacabum* has been documented for its immunomodulatory effects, reducing joint inflammation and pain without the adverse effects associated with synthetic NSAIDs [105]. The integration of these sustainable biomaterials enhances therapeutic efficacy and contributes to green pharmaceutical development.

Potential impact on pharmaceutical industry and patient care: The development of biodegradable antiarthritic formulations marks a paradigm shift in pharmaceutical sciences. By leveraging wheat starch as a bio-carrier and *C. halicacabum* as a natural therapeutic, pharmaceutical companies can reduce dependency on synthetic excipients and enhance sustainability [106]. From a patient-care perspective, sustained-release biodegradable formulations can improve adherence to arthritis treatment regimens, reduce side effects, and lower overall healthcare costs [107]. Future research should focus on optimizing formulation techniques and conducting extensive clinical trials to validate these benefits.

Future Perspectives

Emerging technologies in sustainable formulations: An interesting new avenue for enhancing medication absorption, targeting, and controlled release is provided by nanotechnology. By acting as carriers for bioactive substances isolated from Cardiospermum halicacabum, wheat starch nanoparticles can improve the accuracy of medication delivery to arthritis- affected joints. Bioactive compounds can be encapsulated using nano-formulations, which increases their stability and therapeutic effectiveness.

Applications: The ability of nano-formulations to enhance the pharmacokinetics of anti-arthritic medications has been shown in recent research. Additionally, by enabling tailored administration, these formulations improve therapeutic efficacy and lessen systemic side effects.

Regulatory considerations and challenges

- The mechanical and physical characteristics of drug delivery systems, including drug release profiles, stability, and drug loading capacity, can be enhanced by combining wheat starch with other biodegradable biopolymers such chitosan, gelatin, or alginate. Additionally, continuous release is supported by these biopolymer blends, which is crucial for long-term ailments like arthritis.
- Uses: Hydrogels and microspheres based on biopolymers have drawn interest as possible anti-arthritic drug delivery vehicles. They are appropriate for arthritis treatment due to their controlled medication release properties and biocompatibility [88]

Potential for commercialization and scalability

- Smart polymers are gaining attention for their ability to release the drug in response to specific stimuli such as temperature, pH, or enzymatic activity. These polymers can be used in biodegradable drug delivery systems in conjunction with Cardiospermum halicacabum and wheat starch. Such stimuli-responsive materials can be used to achieve more precise and controlled drug delivery, increasing the therapeutic efficacy in the treatment of arthritis.
- Applications: Thermo-responsive or pH- sensitive polymers could be utilized in targeted drug delivery systems, improving the treatment of inflammatory diseases by releasing the drug only at the affected site**.**

Integration with other therapeutic approaches

Regulatory Approval for Biodegradable Excipients: The capacity of smart polymers to release the medication in response to particular stimuli, such temperature, pH, or enzyme activity, is drawing interest. These polymers can be used in biodegradable drug delivery systems in conjunction with Cardiospermum halicacabum and wheat starch. By enabling more accurate and regulated drug administration, such stimuli- responsive materials can improve the therapeutic efficacy of arthritis treatment.

Applications: Thermo-responsive or pH- sensitive polymers could be utilized in targeted drug delivery systems, improving the treatment of inflammatory diseases by releasing the drug only at the affected site.

- The regulatory landscape for the use of natural and biodegradable excipients in drug delivery systems remains complex. Regulatory bodies like the FDA and EMA require rigorous testing for safety, biocompatibility, and efficacy before approving

Safety and Toxicology: While wheat starch and Cardiospermum halicacabum are generally regarded as safe, comprehensive toxicological studies are required to assess the safety of the entire formulation, especially when combined into a drug delivery system. This includes studying potential allergic reactions, chronic toxicity, and cumulative effects.

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