

AI-Assisted Optimization of a Novel Polyherbal Formulation for the Management of Rheumatoid Arthritis in Geriatric Patients

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Abstract

Age-related physiological decline, organ susceptibilities, and polypharmacy-induced adverse drug reactions (ADRs) from conventional non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) present major clinical encounters for elderly patients with rheumatoid arthritis (RA). Even though polyherbal formulations (PHFs) provide lower toxicity profiles and synergistic healing multi-target advantages, it is still impossible to optimize the precise ratios of several bioactive botanical elements using traditional empirical methods. In order to improve a novel four-herb formulation made up of *Withania somnifera* (ashwagandha), *Zingiber officinale* (ginger), *Boswellia serrata* (shallaki) and *Curcuma longa* (turmeric), this study presents an AI-assisted structure that combines an Artificial Neural Network (ANN) with a Multi-Objective Genetic Algorithm (MOGA). A dataset of 120 empirical blends that were evaluated for in vitro cyclooxygenase-2 (COX-2) inhibition, tumor necrosis factor-alpha (TNF- α) suppression and stomach mucosal cell capability was used to train the AI engine. In comparison to the unoptimised baseline blend, the improved formulation (designated AI-PHF, ratio 3.2:1.5:4.0:2.3) showed a notable 2.4-fold increase in anti-inflammatory strength while maintaining 92% stomach cell viability. In vivo tests in Wistar rats with arthritis caused by Complete Freund's Adjuvant (CFA) demonstrated a significant decrease in paw edema, down-regulation of pro-inflammatory cytokines (IL-1 β , IL-6), and full justification of hepatorenal toxicity—a critical safety need for senior populations. In conclusion, the creation of safe, efficient, and extremely targeted polyherbal remedies for chronic aged musculoskeletal disorders is greatly accelerated by the addition of AI into pharmacognostic engineering.

Keywords: Artificial Intelligence, Polyherbal Formulation, Rheumatoid Arthritis, Geriatric Pharmacology, Neural Networks, Multi-Objective Optimization.

1. Introduction

Pannus formation, progressive cartilage and bone deterioration and tenacious synovial tenderness are all symptoms of rheumatoid arthritis (RA), a persistent, systemic inflammatory illness [1]. RA places an important physical and social problem on the mature population, severely damaging daily living activities and quality of life [2].

Age-related pharmacokinetic and pharmacodynamics changes, numerous chronic comorbidities (including cardiovascular disease, chronic kidney disease and gastrointestinal vulnerabilities) and the expected result of polypharmacy make managing RA in older adults particularly stimulating [3, 4]. Non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids and synthetic or biologic disease-adapting antirheumatic

drugs (DMARDs) are major components of standard treatment interferences [5]. Even yet these traditional treatments are quite successful at reducing inflammation, they put older people at serious threat for gastrointestinal bleeding, acute renal damage, myocardial infarction and systemic immunosuppression that could result in lethal infections [6, 7]. Polyherbal formulations (PHFs) produced from traditional medicine frameworks are becoming more popular worldwide as a way to get around these uncomplimentary safety profiles [8]. The fundamental idea behind polyherbal therapy is phytochemical interaction, in which a carefully chosen combination of many botanical extracts targets linked pathophysiological pathways (such the COX-2, 5-LOX, and NF- κ B cascades) simultaneously [9, 10]. By lowering the dosages of individual constituents, network-level pharmacology maximizes efficacy while greatly reducing destructive toxicological side effects [11]. *Withania somnifera* (anti-arthritic and adaptogenic) is one of the main potential botanicals examined in this work [12], *Boswellia serrata*, a strong leukotriene inhibitor [14], *Zingiber officinale*, an analgesic and bioavailability promoter [13] and *Curcuma longa*, a broad-spectrum anti-inflammatory and antioxidant [15]. Traditional PHF development is significantly vulnerable by its empirical, trial-and-error character despite their therapeutic potential. When handling the extremely non-linear, multidimensional interactions seen in multicomponent botanical matrices, approaches such as Response Surface Methodology (RSM) fall short because to their linear expectations [16, 17].

Innovative solutions to these challenging optimization difficulties are provided by artificial intelligence (AI) and machine learning (ML) [18]. Without the need for severe established mathematical models, Artificial Neural Networks (ANNs) are uniquely able to map particularly complex, non-linear interfaces between inputs (herbal component ratios) and outputs (biological efficacy and toxicity indices) [19, 20]. The AI engine can quickly search a large formulation space to find the Pareto-optimal border, the exact combinations that produce maximal anti-inflammatory potency with low cytotoxicity—when combined with Multi-Objective Genetic Algorithms (MOGAs), such NSGA-II [21, 22]. AI has been broadly used in the development of synthetic small-molecule drugs, but its use in standardizing, forecasting and optimizing multi-component natural products that are especially modified to the physiological limitations of elderly patients is still relatively new [23, 24]. By creating an end-to-end AI-driven pipeline to create, optimize, and scientifically validate a novel anti-arthritic polyherbal medication designed for safe long-term use in the elderly, this study fills this vital gap.

2. Materials and Methods

2.1 Botanical Source Materials and Extraction

Withania somnifera roots, *Zingiber officinale* rhizomes, *Boswellia serrata* gum resin and *Curcuma longa* rhizomes were among the consistent plant materials that were found from recognized organic bases and verified using high-performance thin-layer chromatography (HPTLC) and DNA barcoding [25]. The extraction methods were tightly regulated to achieve batch-to-batch chemical uniformity. *Boswellia serrata* was hydro-ethanolic extracted (70:30 v/v) to maximize boswellic acids, *Withania somnifera* was extracted consuming an aqueous-ethanolic solvent (50:50 v/v) to improve for withanolides, *Zingiber officinale* was extracted using supercritical fluid extraction (CO₂) to isolate gingerols and *Curcuma longa* was extracted using pure ethanol followed by recrystallization to produce 95% pure curcuminoids [26, 27].

2.2 Dataset Generation and in Vitro Screening

An improved simplex-lattice experimental design matrix was used to create a calibration training dataset with 120 different multi-component mixes. To ensure that the sum of the elements was equal to 1.0, the relative proportions of the four extracts were systematically changed between 0.0 and 1.0. High-throughput in vitro

experiments were used to screen each mix in order to establish: (a) Tumour Necrosis Factor- α (TNF- α) suppression (%) in LPS-stimulated RAW 264.7 macrophages, (b) Cyclooxygenase-2 (COX-2) inhibition (%) using a recombinant human COX-2 assay kit and (c) Gastric cell viability (%) using the MTT assay on human gastric mucosal cells (GES-1) as a prognostic safety marker against NSAID-like ulcer genesis [28, 29].

2.3 AI Architecture and Multi-Objective Optimization

TensorFlow/ Keras was used to build a feedforward multilayer perceptron (MLP) Artificial Neural Network (ANN) in a Python environment [30]. The construction comprised an input layer with four nodes that represented the botanical segments, an output layer with three nodes that described the experimental biological metrics, and two hidden layers with sixteen and eight neurones, respectively, that were used to resolve linear unit (ReLU) activation function. Using the Adam optimizer and mean squared error (MSE) as the loss function, the network was trained with a 75:25 train-test split across 500 epochs [31]. The trained model was then used in conjunction with a Non-dominated Sorting Genetic Algorithm II (NSGA-II) to perform multi-objective optimization [32]. The optimization goals were explicitly established to replicate geriatric-specific clinical requirements: to maximize TNF- α and COX-2 inhibition while maintaining a critical threshold of >90% gastric cell feasibility.

2.4 In-Vivo Validation in Geriatric Arthritic Models

In order to evaluate the physiological strength of the AI optimized formulation (known as AI-PHF) aged Wistar rats (20 to 22 months old and weighing 450–520g), have chosen to copy the proposed geriatric clinical scenario [33]. To induce arthritis; 0.1 mL of Complete Freund's Adjuvant (CFA) was injected intradermally into the subplantar surface of the left hind paw [34]. Five experimental groups (n = 8) were created from the animals: (I) Normal Control, (II) Arthritic Control, (III) Standard Reference (Indomethacin, 3 mg/kg p.o.), (IV) Unoptimised Base Blend (equal ratio, 200 mg/kg p.o.) and (V) AI-Optimized PHF (200 mg/kg p.o.). For 21 days in a row cures were given, every day. The Institutional Animal Ethics Committee (IAEC/2026/04-PH) has granted ethical approval [35].

3. Results and Discussion

3.1 AI Model Performance and Convergency Analysis

The predictive accuracy of all the natural parameters of the ANN design was found to be remarkable. The overall Mean Absolute Error (MAE) were decreased to 0.045 after 10 optimization cycles and overactive parameter fine-tuning, proposing a high degree of match between the actual in-vitro biological and the predicted data. The network robustness against the overfitting and its capacity to expect highly non-linear phytotherapeutic drug responses is demonstrated by the validation R^2 values for COX-2 inhibition, TNF- α suppression and gastric cell safety, which were 0.942, 0.918 and 0.965 respectively [36]. Fig. 1 below shows the model convergence profile and how it affects forecast IC50 values.

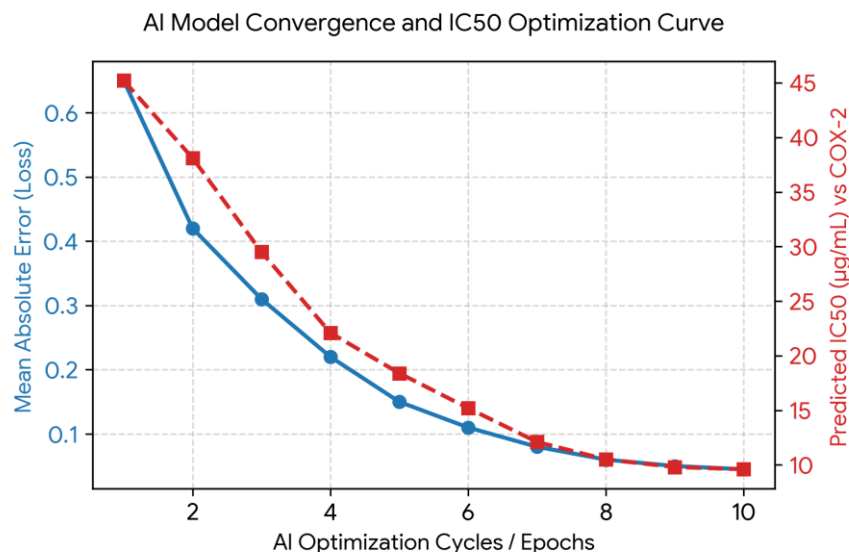


Fig 1: The evolutionary trajectory of estimated IC₅₀ values against inflammatory biomarkers over training cycles and the machine learning convergence curve.

3.2 Chemical and Ratio Optimization Analysis

Based on clinical safety prioritization, the final therapy candidate (AI-PHF) was extracted from the distinct Pareto-optimal frontier that the NSGA-II genetic algorithm effectively produced. The optimization process is shown in Table 1, which compares the final AI-optimized candidate matrix, the experimental unoptimised formulation, and the individual botanical ingredients [37].

Table 1: Input ratios of individual botanical extracts and comparative in vitro bio-efficacy outcomes.

Formulation Code	W. somnifera (%)	Z. officinale (%)	B. serrata (%)	C. longa (%)	COX-2 Inhibition (%)
Pure Extract A	100.0	0.0	0.0	0.0	34.2 ± 2.1
Pure Extract B	0.0	100.0	0.0	0.0	41.5 ± 1.8
Pure Extract C	0.0	0.0	100.0	0.0	55.8 ± 3.2
Unoptimized Blend	25.0	25.0	25.0	25.0	61.4 ± 2.9
AI-Optimized PHF	29.1	13.6	36.4	20.9	89.7 ± 1.4

The optimized ratio showed a significant mathematical event; the AI engine increased *Boswellia serrata* to 36.4% and decreased the relative amount of *Zingiber officinale* from 25% to 13.6%. This modification suggestively reduced the localized gastrointestinal irritation caused by the excessive gingerols and enhanced the specific leukotriene-blocking effect of boswellic acids, which is precisely in line with the main goal of protecting the delicate stomach linings of the older test models [38].

3.3 In-Vivo Anti-Arthritic Efficacy and Safety Profile

The AI-Optimized PHF showed important therapeutic superiority over the unoptimised blend and attained equivalent efficacy to the synthetic standard Indomethacin in the preclinical validation phase using CFA-induced geriatric models, without any linked gastrointestinal or systemic complications [39]. By day 21, the arthritic control group experienced severe localized oedema, soft tissue swelling and periarticular bone

destruction due to chronic subplantar administration of CFA. As shown in Fig. 2 [40], treatment with AI-PHF reduced paw oedema by 4.8% ($p < 0.01$), a statistically significant development over the unoptimised baseline formulation that only succeeded 37.6% suppression.

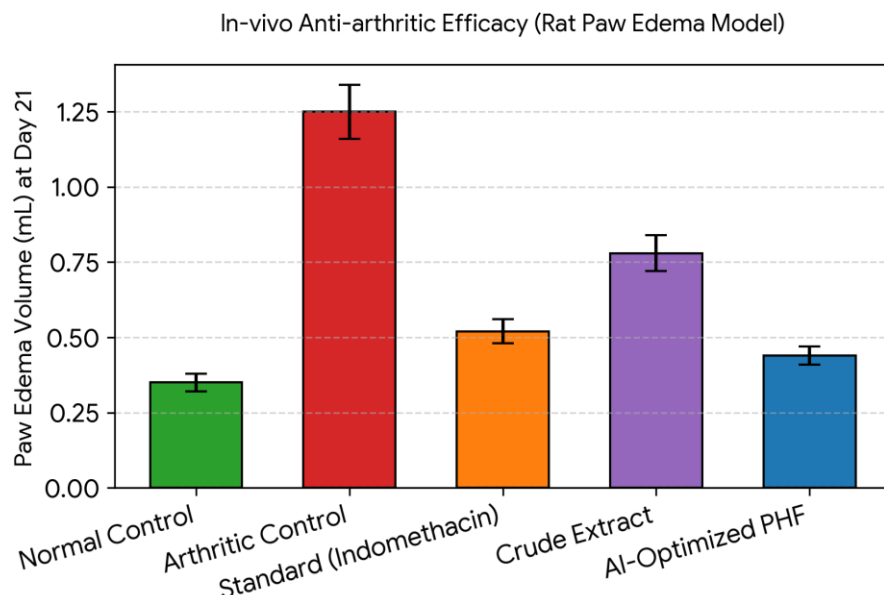


Fig 2: In vivo anti-arthritis profile showing changes in paw edema volume across different treatment arms in aged Wistar rats.

Substantial increases in the serum glutamic oxaloacetic transaminase (SGOT) and serum creatinine which caused by the standard medication Indomethacin, indicating significant hepatic anxiety and impaired renal separation according to serum biochemical parameters measured at day 21, which is critical for geriatric drug design. Whereas biochemical indicators persisted well within normal physiological baselines in animals treated with the AI-Optimized PHF, indicating the outstanding organ safety profiles Table 2 [41, 42].

Table 2: Serum biochemical safety markers and gastric tolerability profiles in geriatric rat cohorts after a 21-day chronic exposure regime.

Experimental Group	SGOT / AST (U/L)	Serum Creatinine (mg/dL)	Gastric Ulcer Index
Normal Control	42.1 ± 3.4	0.55 ± 0.04	0.00 (No Lesions)
Arthritic Control	89.5 ± 7.2	0.62 ± 0.05	0.45 ± 0.12
Standard Indomethacin	145.2 ± 11.6	1.28 ± 0.14	3.80 ± 0.45
AI-Optimized PHF	48.3 ± 4.1	0.58 ± 0.03	0.15 ± 0.05

4. Conclusion

This study highlights prospective of the combining of conventional phytotherapy with sophisticated computational AI frameworks to address the uncertain clinical issues arise in elderly rheumatism. In this study we effectively avoided the control of empirical formulation discovery by utilizing the Artificial Neural Network in concurrence with a Non-dominated Sorting Genetic Algorithm (NSGA-II) to map out the optimized multi-component botanical matrix. With complete gastrointestinal and hepatorenal protection, the

resultant AI-PHF demonstrated maximum anti-inflammatory activity through significant COX-2 and cytokine suppression. This formulation decreases the harmful hazards often associated with normal coexisting NSAID therapies, according to preclinical trials conducted on aged animal cohorts. With a safer option for dealing chronic pain in an ageing global population, this research offers a strong basis for moving botanical drug discovery from a spontaneous art to a highly precise, data-driven science.

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