ISSN: 2644-2957

DOI: 10.33552/OJCAM.2026.09.000713

Online Journal of Complementary & Alternative Medicine

Iris Publishers

Mini Review

Green Tea Polyphenols as Multi-Target Complementary Therapeutics for Rheumatoid Arthritis

Praveen Deepak[1]* and Aftab Ahmad Khan[2]

[1]*PG Department of Zoology, S. S. College, Jehanabad, Bihar, India*

[2]*PG Centre of Zoology, Mirza Ghalib College, Gayaji, Bihar, India*

***Corresponding author:** Praveen Deepak, PG Department of Zoology, S. S. College, Jehanabad, Bihar, India

Received Date: August 10, 2026

Published Date: September 07, 2026

Abstract

Rheumatoid Arthritis (RA) is an autoimmune disorder marked by chronic systemic inflammation associated with persistent synovitis resulting in progressive destruction of cartilage and bone erosion particularly at the diarthrodial joints, which if untreated, may lead to permanent disability. Although considerable progress has been made in its treatment by the introduction of Disease-Modifying Antirheumatic Drugs (DMARDs), biologic therapies, and Janus kinase inhibitors, many patients still do not show significant improvement in the disease condition. Moreover, prolonged treatment is frequently associated with adverse effects and high treatment cost. Therefore, a need to identify complementary therapeutic approaches that are effective, safe and economical for the long-term treatment has been increasingly felt. These challenges have led to increasing interest in exploring natural products as potential therapeutic approaches for the management of RA.

Green tea (Camellia sinensis) contains several bioactive polyphenols, particularly catechins, which possess anti-inflammatory, antioxidant, and immunomodulatory activities and therefore known to regulate inflammation, oxidative stress, immune responses, cartilage destruction, and bone remodelling. These finding indicate that green tea polyphenol may serve as potential therapeutic candidates for the treatment of RA. However, further clinical studies are required to establish their efficacy and safety in the management of RA. The present review summarizes the therapeutic potential of green tea polyphenols as a complementary approach for the management of rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Green tea, Polyphenols, Catechins, Complementary medicine

Abbreviation: RA; Rheumatoid arthritis; DMARDs, Disease-modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; EGCG, Epigallocatechin gallate; ECG, Epicatechin gallate; EGC, Epigallocatechin; EC, Epicatechin; TNF-α, Tumour necrosis factor-alpha; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-17, Interleukin-17; NF-κB, Nuclear factor-kappa B; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; MAPK, Mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; Akt, Protein kinase B (PKB); **Nrf2, Nuclear factor erythroid 2–related factor 2; HO-1, Heme oxygenase-1; MMP, Matrix metalloproteinase;** ADAMTS-5, A Disintegrin and Metalloproteinase with Thrombospondin Motifs 5; Th17, T helper 17; RANKL, Receptor activator of nuclear factor-**κB ligand; RANK, Receptor activator of nuclear factor-κB;** ADMET, Absorption, distribution, metabolism, excretion, and toxicity; AI, Artificial intelligence; ML, Machine learning.

Introduction

Over the last two decades, considerable progress has been made in the treatment of rheumatoid arthritis (RA), yet many patients still do not achieve satisfactory disease control. The advent of Disease-Modifying Antirheumatic Drugs (DMARDs), biologic agents and targeted synthetic therapies (tsDMARDs) has improved the management of RA. Their clinical efficacy and patient well-being are still a goal due to a poor response to treatment, adverse effects, disease relapse and the high cost of long-term therapy. Therefore, the focus has now shifted to complementary therapeutic approaches, particularly those derived from natural products, which may simultaneously act on different inflammatory pathways involved in RA pathogenesis and help relieve disease symptoms [1]. RA is a chronic autoimmune disorder characterised by a sustained inflammatory process that affects the synovial joints, thereby leading to progressive damage of articular cartilage and bones.

The RA pathogenesis results from complex interactions among persistently activated immune cells, pro-inflammatory cytokines, oxidative stress, genetic background, and altered intracellular signalling pathways. These findings indicate that targeting one single molecular pathway cannot address the inflammatory process underlying joint inflammation, and, hence that a multi-pathway-based approach could be an interesting alternative for the adjunctive treatment of RA [2]. This limitation has prompted growing interest in multi-targeted therapeutic strategies - particularly plant-derived natural products - which can simultaneously modulate several of the dysregulated pathways implicated in RA pathogenesis. Among these natural products, green tea polyphenols have recently emerged as promising therapeutic agents because of their ability to modulate multiple interconnected inflammatory pathways that play important roles in RA pathogenesis [3]. The major molecular targets and integrated therapeutic actions of green tea polyphenols in RA are summarised in Figure 1.

Multi-Target Therapeutic Actions of Green Tea Polyphenols

Network pharmacology helps explain how natural products act in complex diseases such as RA. In contrast to many drugs prescribed today that are designed to interact primarily with one target, plant-derived compounds often mediate effects on multiple pathways simultaneously. The combined effects of these biological interactions may be particularly important in autoimmune disorders, which often result from dysregulation of several inflammatory pathways [4]. This broader view also provides a useful basis for exploring phytochemicals as complementary therapeutic agents.

Green tea, prepared from dried leaves of Camellia sinensis, has been consumed for thousands of years as a health-promoting beverage. Its advantages are mainly due to the naturally occurring polyphenols, especially from the catechins, which include the catechins Epigallocatechin Gallate (EGCG), Epicatechin Gallate (ECG), Epigallocatechin (EGC), and Epicatechin (EC). These compounds exhibit significant antioxidant, anti-inflammatory and immunomodulatory activities and have demonstrated significant effect in a variety of chronic inflammatory disorders [5]. Rather than functioning as independent bioactive constituents, these catechins collectively influence multiple biological processes associated with RA [6]. This multi-target behaviour distinguishes green tea polyphenols from many conventional therapeutic agents that are designed to inhibit a single molecular pathway [7]. Consequently, green tea polyphenols have emerged as attractive candidates for complementary management of RA.

Figure 1. Multi-target molecular mechanisms underlying the complementary therapeutic potential of green tea polyphenols in rheumatoid arthritis. Green tea polyphenols act on multiple interconnected inflammatory, oxidative stress, immune-regulatory, cartilage-degrading, and bone-remodelling pathways involved in rheumatoid arthritis. Their combined actions may reduce synovial inflammation and oxidative stress, modulate immune responses, protect cartilage, and limit bone erosion. These multi-target effects provide a biological rationale for their potential use as complementary therapeutics alongside conventional treatment. Several studies have reported that catechins can effectively reduce the production of pro-inflammatory cytokines, including Tumour Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Interleukin-17 (IL-17). These cytokines are important contributors to RA-associated inflammation and play a major role in promoting joint damage in RA [8,9].

The anti-inflammatory effects of catechins are not limited to cytokine suppression. They may also regulate key intracellular signalling pathways, including Nuclear Factor-Kappa B (NF-κB), Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), Mitogen-Activated Protein Kinase (MAPK), and Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/Akt) pathways [10]. These signalling pathways regulate genes involved in immune-cell activation and the production of inflammatory mediators, which can contribute to tissue damage over time. Their coordinated modulation may therefore produce broader immunomodulatory effects than selective inhibition of a single signalling pathway [11]. Modulation of inflammatory signalling may reduce cytokine production and, in turn, help limit oxidative stress, matrix degradation, osteoclast activation, and persistent synovial inflammation. Thus, the potential therapeutic effects of green tea polyphenols may arise from their combined action on several disease-associated molecular pathways rather than from inhibition of a single target. The principal molecular targets, biological effects, and therapeutic significance of green tea polyphenols in RA are summarised in Table 1.

Table 1: Major molecular targets and complementary therapeutic actions of green tea polyphenols in rheumatoid arthritis.

Molecular target/pathway	Effect of green tea polyphenols	Therapeutic significance
TNF-α, IL-1β, IL-6, IL-17	Decreased production of pro-inflammatory cytokines [3,9]	Reduced synovial inflammation
NF-κB	Inhibition of inflammatory signalling [9,11]	Suppressed inflammatory gene expression
JAK/STAT	Modulation of signalling activity [3,9]	Reduced inflammatory and immune activation
MAPK	Modulation/inhibition of MAPK signalling [3,9]	Decreased inflammatory signalling
PI3K/Akt	Modulation of pathway activity [3,9]	Regulation of cell survival and inflammatory signalling
Nrf2/HO-1	Activation of antioxidant defence [14]	Enhanced protection against oxidative stress
MMP-1, MMP-3, MMP-9	Inhibition of matrix-degrading enzymes [8,17,22]	Reduced cartilage and extracellular matrix degradation
ADAMTS-5	Inhibition of aggrecan-degrading activity [17,22]	Reduced aggrecan degradation
Th17/Treg	Modulation of Th17/Treg balance [3]	Improved immune regulation
RANKL–RANK	Inhibition of osteoclastogenic signalling [16,19,22]	Reduced osteoclastogenesis and bone loss

Translational Evidence and Current Challenges

Substantial experimental evidence suggests the possible therapeutic role of green tea polyphenols in RA. Recent studies indicate that these phytochemicals regulate several processes involved in the disease, including inflammatory signalling, oxidative stress, immune-cell function, cartilage degradation, and bone remodelling [12]. The observation of synergistic effects across various biological systems suggests that green tea polyphenols would ideally act as multitarget complementary therapies, instead of targeting single molecular pathways.

Green tea catechins can suppress the production of several pro-inflammatory cytokines, including Tumour Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Interleukin-17 (IL-17), which are important mediators of synovial inflammation and joint damage. Reduced cytokine production can limit the inflammatory response and thereby subsequent recruitment and activation of immune cells within the synovial tissue [8]. Apart from regulating cytokine production, green tea polyphenols affect several intracellular signalling pathways involved in inflammation. Experimental evidence suggests that these compounds are capable of suppressing the activation of NF-κB, JAK/STAT, MAPK, and PI3K/Akt pathways. As these pathways are closely related to each other, their combined action may provide wider anti-inflammatory effects than acting on a single molecular target alone [11,13]. Oxidative stress represents another major driver of RA progression. Excessive generation of reactive oxygen species amplifies inflammatory signalling, damages synovial membrane, and accelerates cartilage degeneration. Green tea polyphenols not only scavenge reactive oxygen species directly but also activate the nuclear factor erythroid 2–related factor 2 (Nrf2)/Heme Oxygenase-1 (HO-1) antioxidant pathway, thereby enhancing the expression of endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase [14]. This dual antioxidant action contributes to the preservation of synovial homeostasis and protection against oxidative tissue injury [15].

Green tea polyphenols contribute to the preservation of joint architecture as well [16]. They inhibit the expression of Matrix Metalloproteinases, Particularly MMP-1, MMP-3, and MMP-9, as well as A Disintegrin and Metalloproteinase with Thrombospondin Motifs 5 (ADAMTS-5), which is a key aggrecanase that are responsible for degradation of matrix proteins [17]. Consequently, use of green tea reduces the degradation of collagen and proteoglycans of the matrix, resulting in preservation of cartilage integrity that delays joint damage. The immunomodulatory effects of green tea polyphenols thus further strengthen their therapeutic potential. Several studies have reported that the green tea polyphenols reduce macrophage activation and regulate dendritic-cell maturation, while restoring the balance of pro-inflammatory Th17 cells and Treg cells for normal immune response [18]. Such coordinated regulation of innate and adaptive immune responses is able to reduce synovial inflammation while promoting immune tolerance in the patients.

Moreover, green tea polyphenols have been shown to inhibit osteoclast differentiation by inhibiting the Receptor Activator of Nuclear Factor-κB Ligand (RANKL)—receptor activator of nuclear factor-κB (RANK) signalling pathway, thereby maintaining bone integrity while reducing bone resorption [19]. This ability of green tea polyphenols is suggestive of their potential to slow disease progression rather than merely alleviate clinical symptoms [20]. Importantly, these biological effects are not achieved separately but result from the collective effects of green tea polyphenols on multiple inflammatory networks. This effect is evident by its suppression of inflammatory signalling that decreases cytokine production, which subsequently reduces oxidative stress, limits matrix degradation, attenuates osteoclast activation, and restores immune homeostasis. Thus, green tea polyphenols appear to regulate several pathways involved in RA rather than a single target. This supports their possible use as complementary agents in RA management (Figure 1).

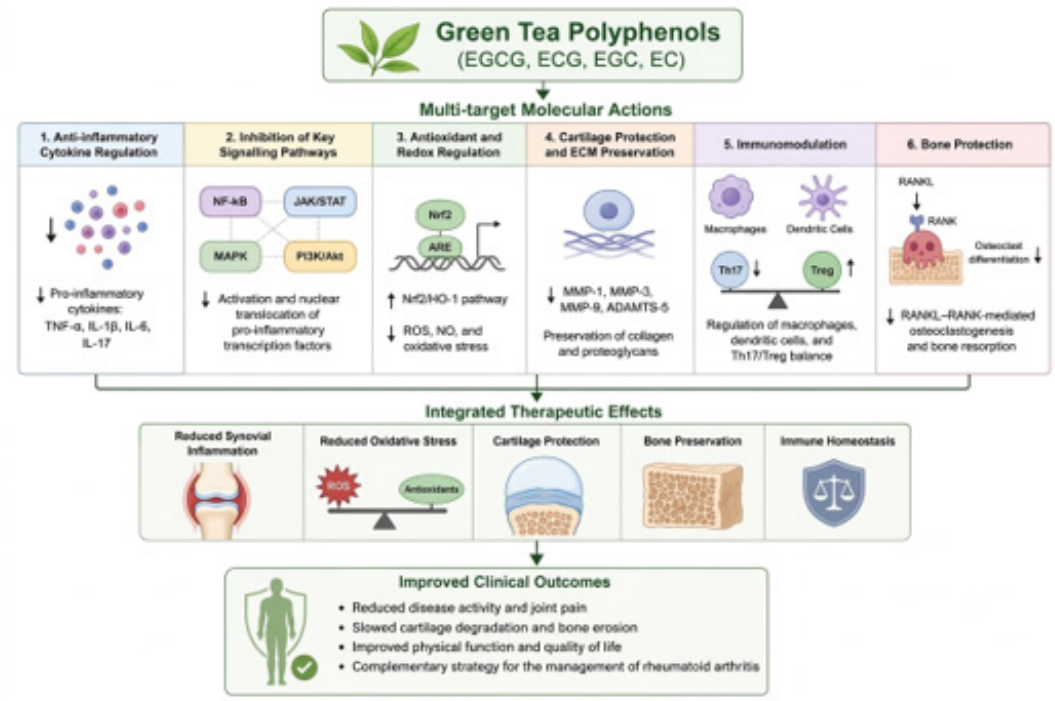

Figure 1: Multi-target molecular mechanisms underlying the complementary therapeutic potential of green tea polyphenols in rheumatoid arthritis.

Translational Evidence, Future Perspectives, and Conclusion

The therapeutic potential of green tea polyphenols is supported by a growing body of evidence. In this respect, in vitro studies have demonstrated their ability to suppress inflammatory cytokine production, inhibit synovial fibroblast proliferation, reduce oxidative stress, and downregulate matrix-degrading enzymes [21], while preclinical animal models of RA have consistently demonstrated reductions in paw swelling, inflammatory cell infiltration, cartilage destruction, and bone erosion following treatment with green tea polyphenols [22]. These findings collectively support the biological plausibility of green tea polyphenols as complementary therapeutic agents in RA.

Despite encouraging preclinical findings, clinical evidence remains limited. Available human studies are generally characterised by small sample sizes, differences in study populations, heterogeneous study designs, variable treatment durations, and differences in green tea formulations and dosages. Such variation among the groups makes it difficult to establish standard therapeutic recommendations. At present, there is insufficient clinical evidence to support their use as alternatives to conventional disease-modifying therapies. However, green tea polyphenols can be considered promising complementary agents. More clinical studies are required to determine the appropriate dose, pharmacokinetic behaviour and suitable formulation. Well-designed multicentre randomised controlled trials are also needed to establish their safety and efficacy in patients with RA.

In addition to limited clinical evidence, the low oral bioavailability of green tea polyphenols is an important challenge for their use in clinical practice [23]. There are a number of factors that compromise their therapeutic efficacy including poor bioavailability, poor intestinal absorption, rapid metabolism, and limited systemic stability [24]. Recent advances in drug delivery systems, including nanoformulations, liposomes, phytosomes, and polymeric nanoparticles, provide an opportunity to increase the catechin stability, improve bioavailability, and facilitate targeted delivery to inflamed synovial tissues. Computer-aided drug discovery approaches, including in silico Absorption, Distribution, Metabolism, Excretion, And Toxicity (ADMET) prediction and pharmacokinetic modelling, provide useful tools for identifying and optimising catechins and their derivatives with better drug-like properties. Such approaches support their further development and experimental evaluation [25].

Future Perspective

In our opinion, future research on complementary treatment of RA should focus not only on finding new herbal antioxidants, but also on understanding how natural products affect the different molecular pathways involved in disease progression. Green tea polyphenols provide a good example of this approach, as they affect inflammatory signalling, oxidative stress, immune responses, cartilage damage, and bone remodelling [26]. Their action on several disease-related processes makes them suitable candidates for further study as complementary agents in RA.

To understand these effects in greater detail, complementary medicine research needs to move beyond studies that mainly describe the pharmacological activity of natural products. Greater attention should be given to their molecular targets and the pathways through which they act [27]. Modern methods such as systems pharmacology, network pharmacology, molecular docking, molecular dynamics simulations, in silico ADMET prediction, pharmacokinetic modelling, Artificial Intelligence (AI), Machine Learning (ML), and multi-omics analysis provide useful tools to study compound-target interactions and the molecular networks affected by natural products [28]. Combining these computational methods with laboratory evidence may help in identifying promising phytochemicals, understanding their mechanisms of action, and evaluating their therapeutic potential in RA. The findings from computational analysis need to be confirmed through laboratory studies before clinical evaluation. Computational predictions should be used to guide further laboratory work rather than being treated as a replacement for experimental evidence [29,30].

Conclusion

The available evidence indicates that green tea polyphenols interact with multiple molecular targets involved in the pathogenesis of RA and have potential as complementary therapeutic agents. The demonstrated effect of tea polyphenols on inflammatory cytokines, intracellular signalling pathways, oxidative stress, immune-cell action, to bone remodelling and cartilage degradation suggests that they orchestrate and regulate many biological functions that contribute to pathogenesis and progression of RA. Although preclinical data appear promising, green tea polyphenols require substantial clinical translation before a regimen becomes a standard practice for the management of RA. Future research should involve directions are required that involve systems pharmacology approaches, targeted delivery of polyphenols, computer-aided drug design tools, and robust clinical trial investigation to enhance understanding of green tea polyphenols effectiveness, safety and clinical utility in RA.

References

1. Baig S, DiRenzo DD (2020) Complementary and alternative medicine use in rheumatoid arthritis. Curr Rheumatol Rep 22(10): 61.
2. McInnes IB, Schett G (2017) Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 389(10086): 2328-2337.
3. Wang S, Li Z, Ma Y, Liu Y, Lin C, et al. (2021) Immunomodulatory effects of green tea polyphenols. Molecules 26(12): 3755.
4. Alshehri ZS (2025) Therapeutic targeting of apoptosis-driven inflammation in rheumatoid arthritis: A biochemical and molecular modeling approach using plant-derived compounds. Int J Rheum Dis 28(9): e70423.
5. Cabrera C, Artacho R, Giménez R (2006) Beneficial effects of green tea-A review. J Am Coll Nutr 25(2): 79-99.
6. Yu H, Ning M, Long B, Ren M, Wang C, et al. (2026) (−)-Epicatechin and inflammation: Unraveling the role of microbial metabolites and interindividual metabolic variability. Front Microbiol 17: 1803543.
7. Ajaz F, Haddad J, Huda B, Yousuf M, Patnaik R, et al. (2025) Epigallocatechin gallate as a molecular therapeutic in heart failure and cardio-oncology: Mechanistic pathways and translational perspectives. Int J Mol Sci 26(21): 10798.
8. Singh BN, Shankar S, Srivastava RK (2011) Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. Biochem Pharmacol 82(12): 1807–1821.
9. Mokra D, Joskova M, Mokry J (2022) Therapeutic effects of green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. Int J Mol Sci 24(1): 340.
10. Santangelo C, Masella R (2021) Molecular aspects of dietary polyphenols in pregnancy. In: Molecular Nutrition: Mother and Infant. Elsevier, Amsterdam, The Netherlands, pp 233–264.
11. Liu T, Zhang L, Joo D, Sun S (2017) NF-κB signaling in inflammation. Signal Transduct Target Ther 2(1): 17023.
12. Rahaman SN, Lishadevi M, Anandasadagopan SK (2025) Unraveling the molecular mechanisms of osteoarthritis: The potential of polyphenols as therapeutic agents. Phytother Res 39(5): 2038-2071.
13. Abbasgholizadeh Rahimi S, Cwintal M, Huang Y, Ghadiri P, Grad R, et al. (2022) Application of artificial intelligence in shared decision making: Scoping review. JMIR Med Inform 10(8): e36199.
14. Luo J, Shen X, Lio CK, Dai Y, Cheng C, et al. (2018) Activation of Nrf2/HO-1 pathway by Nardochinoid C inhibits inflammation and oxidative stress in lipopolysaccharide-stimulated macrophages. Front Pharmacol 9: 911.
15. Phull A, Nasir B, Haq IU, Kim SJ (2018) Oxidative stress, consequences and ROS-mediated cellular signaling in rheumatoid arthritis. Chem Biol Interact 281: 121–136.
16. Shen C, Smith BJ, Li J, Cao JJ, Song X, et al. (2018) Effect of long-term green tea polyphenol supplementation on bone architecture, turnover, and mechanical properties in middle-aged ovariectomized rats. Calcif Tissue Int 104(3): 285–300.
17. Lee JH, Chung JH, Cho KH (2005) The effects of epigallocatechin-3-gallate on extracellular matrix metabolism. J Dermatol Sci 40(3): 195–204.
18. Del Cornò M, Scazzocchio B, Masella R, Gessani S (2014) Regulation of dendritic cell function by dietary polyphenols. Crit Rev Food Sci Nutr 56(5): 737–747.
19. Lin R, Chen C, Wang Y, Ho M, Hung S, et al. (2009) (−)-Epigallocatechin gallate inhibition of osteoclastic differentiation via NF-κB. Biochem Biophys Res Commun 379(4): 1033-1037.
20. Sirše M (2022) Effect of dietary polyphenols on osteoarthritis—Molecular mechanisms. Life 12(3): 436.
21. Oz H (2017) Chronic inflammatory diseases and green tea polyphenols. Nutrients 9(6): 660.
22. Ahmed S (2010) Green tea polyphenol epigallocatechin 3-gallate in arthritis: Progress and promise. Arthritis Res Ther 12(2): 208..
23. Yang J, Chen W, Chen J, Xie D, Wang Y, et al. (2025) Tea polyphenol epigallocatechin gallate and the gut–health axis: Unraveling structural characteristics, metabolic pathways, and systemic benefits. Adv Nutr 16(12): 100545.
24. Choi K, Park S, Kwon Y, Lee J, Kwon O, et al. (2022) Green tea extract and Piper retrofractum attenuate deoxycholic acid-induced damage and enhance the tight junction barrier: An analysis in a Caco-2 cell culture model and a DSS co-induced mouse model. SSRN Electron J (Preprint).
25. Brogi S, Ramalho TC, Kuca K, Medina-Franco JL, Valko M (2020) Editorial: In silico methods for drug design and discovery. Front Chem 8: 612.
26. Ohishi T, Goto S, Monira P, Isemura M, Nakamura Y (2016) Anti-inflammatory action of green tea. Anti-Inflamm Anti-Allergy Agents Med Chem 15(2): 74–90.
27. Cui G, Li M, Guo W, Gao M, Zhu Q, et al. (2025) AI-driven network pharmacology: Multi-scale mechanisms of traditional Chinese medicine from molecular to patient analysis. Comput Struct Biotechnol J 27: 5087-5104.
28. Liu Y, Zhu K, Peng W, Liu Z, Mao X (2026) Multi-omics and artificial intelligence for precision drug discovery and potential clinical applications. Signal Transduct Target Ther 11(1): 210.

29. Hussein MA, Munirathinam G (2026) Artificial intelligence-driven natural product discovery for cancer metastasis and chemoresistance: From computational prediction to preclinical validation. Cancers 18(5): 719.

30. Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, et al. (2022) Network pharmacology: Curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci 43(2): 136–150.