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Dr. Lani M Tepai
School of Health Sciences, Nauru National University, Nauru

Dr. Tevita A Mikao
Faculty of Chemical Sciences, Nauru National University, Nauru

Dr. Toma R Mavea
Department of Pharmaceutical Sciences, Nauru National University, Nauru

Corresponding Author:
Dr. Lani M Tepai
School of Health Sciences, Nauru National University, Nauru

Comparative phytopharmacological evaluation of curcumin (*Curcuma longa*) and resveratrol synergistic potentials in inflammation and oxidative stress management

Lani M Tepai, Tevita A Mikao and Toma R Mavea

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Abstract
Curcumin, the principal polyphenolic compound derived from *Curcuma longa*, and resveratrol, a stilbene predominantly found in grapes and peanuts, have gained extensive attention for their multifaceted therapeutic properties. Both compounds exhibit potent anti-inflammatory and antioxidant effects, making them valuable candidates in the prevention and management of chronic diseases such as cardiovascular disorders, metabolic syndromes, neurodegeneration, and cancer. Despite their pharmacological promise, limitations such as poor bioavailability, instability, and rapid metabolism hinder their clinical translation. Recent advances in phytopharmacology have demonstrated that curcumin and resveratrol, when administered in combination, may exert synergistic effects that surpass their individual efficacy by targeting complementary signaling pathways, including NF-κB, Nrf2, SIRT1, and MAPKs. This comparative evaluation aims to integrate preclinical and clinical evidence to elucidate the mechanistic basis of their synergistic action in inflammation and oxidative stress management.
The present study employs a comparative framework, utilizing biochemical assays, computational modeling, and systematic literature synthesis, to assess the pharmacokinetics, molecular targets, and therapeutic outcomes of curcumin and resveratrol individually and in combination. Results indicate that the synergistic pairing enhances cellular antioxidant defenses, downregulates pro-inflammatory cytokines, and modulates redox-sensitive transcription factors more effectively than monotherapy. These findings underscore the translational potential of dual phytochemical therapy in chronic inflammatory and oxidative stress-related diseases. Future research should focus on optimizing delivery systems, such as nanocarriers and liposomal encapsulation, to overcome bioavailability challenges and facilitate clinical application. This paper contributes to the evolving discourse on evidence-based phytopharmacology and positions curcumin-resveratrol synergy as a promising frontier in integrative medicine.

Keywords: SIRT1, phytopharmacological, resveratrol synergistic potentials, oxidative stress managemen, liposomal encapsulation, utilizing biochemical assays

1. Introduction
Chronic inflammation and oxidative stress are central to the pathogenesis of many debilitating diseases, ranging from cardiovascular disorders and neurodegenerative syndromes to cancer and metabolic dysfunctions. While the body possesses endogenous defense mechanisms, such as antioxidant enzymes and tightly regulated immune responses, these systems often become compromised due to aging, environmental insults, or persistent pathological conditions. This imbalance creates a state of redox disequilibrium, where excessive production of reactive oxygen species (ROS) and pro-inflammatory mediators overwhelms protective pathways, leading to cellular damage and systemic dysfunction. Increasing evidence indicates that nutritional and phytochemical interventions may offer effective means to restore balance, thereby preventing disease progression and enhancing therapeutic outcomes.
Curcumin, a polyphenolic diketone derived from the rhizome of *Curcuma longa* (turmeric), has been utilized in traditional medicine for centuries and is now widely investigated in biomedical research.

It demonstrates a wide spectrum of pharmacological effects, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Its ability to modulate key molecular targets, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and reactive oxygen intermediates, positions curcumin as a multifunctional therapeutic candidate. Despite this potential, its limited bioavailability, owing to poor solubility, rapid metabolism, and systemic elimination, has restricted its clinical utility. Strategies such as adjuvant therapy with piperine, nanoformulations, and structural analogues have been explored to overcome these pharmacokinetic challenges.

Resveratrol, a naturally occurring stilbene primarily found in grapes, red wine, peanuts, and berries, is another compound of great pharmacological interest. Like curcumin, resveratrol exerts pleiotropic biological effects, including cardio protective, neuroprotective, and anti-inflammatory actions. It is a well-known activator of sirtuin 1 (SIRT1), a key regulator of cellular longevity, energy metabolism, and stress resistance. In addition, resveratrol influences multiple redox-sensitive pathways, enhancing endogenous antioxidant systems such as superoxide dismutase and glutathione peroxidase while suppressing inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Clinical studies have shown its beneficial role in metabolic syndrome, insulin sensitivity, and endothelial function, although, like curcumin, its therapeutic efficacy is limited by low bioavailability and rapid clearance.

The convergence of research on curcumin and resveratrol has generated interest in their combined use as a complementary therapeutic strategy. Their molecular targets often overlap but also diverge in ways that make them potentially synergistic. Curcumin's strong inhibitory effects on pro-inflammatory transcription factors may complement resveratrol's activation of cytoprotective and longevity-associated pathways. Together, they could create a dual-action system that not only suppresses damaging processes but also reinforces cellular resilience. Preclinical studies have suggested that the combination enhances anti-inflammatory and antioxidant activity beyond that achieved by individual administration, offering improved therapeutic benefits in models of arthritis, diabetes, and neurodegenerative disorders.

The importance of evaluating this synergy lies in the broader field of phytopharmacology, which seeks to understand plant-derived compounds not only as isolated agents but also as part of interactive systems. Traditional medicine has long used polyherbal formulations, assuming that combinations provide superior efficacy through complementary mechanisms. Modern pharmacological research is beginning to validate this concept, and curcumin-resveratrol interactions offer a model system for studying such synergy. The potential clinical impact is significant: diseases characterized by inflammation and oxidative stress often require long-term management, and natural compounds with multi-targeted mechanisms could reduce dependence on synthetic drugs while minimizing adverse effects.

Literature Review

Curcumin has been extensively studied for its role in mitigating inflammation and oxidative stress across a variety of pathological conditions. Its polyphenolic structure allows it to interact with multiple molecular targets, including transcription factors, growth factors, and enzymes that regulate inflammatory cascades. Research has demonstrated that curcumin suppresses NF-κB activation, which in turn reduces the transcription of pro-inflammatory genes such as TNF-α, IL-1β, and COX-2 [1]. Animal models of arthritis and inflammatory bowel disease have confirmed significant reductions in tissue inflammation following curcumin administration [2]. Moreover, curcumin enhances the activity of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, thereby restoring redox balance in oxidative stress-induced disorders [3].

Despite its potent bioactivity, curcumin's poor systemic absorption has been a consistent barrier to its clinical translation. Early pharmacokinetic studies revealed that oral curcumin undergoes rapid metabolism in the liver and intestinal mucosa, resulting in low plasma concentrations [4]. Efforts to overcome this limitation include the co-administration of piperine, which inhibits glucuronidation and enhances bioavailability by almost 2000% [5]. Recent approaches employing liposomal encapsulation, curcumin-loaded nanoparticles, and phospholipid complexes have shown promise in improving stability and tissue distribution [6]. These innovations have broadened curcumin's therapeutic applications in neurodegeneration, metabolic disorders, and oncology.

Resveratrol, a naturally occurring stilbene, has also received considerable attention due to its versatile pharmacological profile. It gained prominence following observations of the "French Paradox," where populations consuming red wine demonstrated lower cardiovascular risk despite diets rich in saturated fats [7]. Mechanistic studies have established resveratrol as an activator of SIRT1, a NAD+-dependent deacetylase associated with longevity, mitochondrial biogenesis, and metabolic regulation [8]. Through SIRT1 activation, resveratrol exerts protective effects against endothelial dysfunction, insulin resistance, and neurodegeneration. It also inhibits pro-inflammatory mediators by suppressing NF-κB and down regulating cytokines including IL-6 and TNF-α [9].

Resveratrol's antioxidant properties are equally compelling. It directly scavenges ROS and enhances endogenous antioxidant pathways. In models of ischemia-reperfusion injury, resveratrol reduced lipid peroxidation and preserved mitochondrial function [10]. Its effects extend to neuroprotection, where it has demonstrated the ability to reduce amyloid-beta accumulation and tau hyperphosphorylation, both hallmarks of Alzheimer's disease [11]. Clinical trials, however, have highlighted similar challenges to curcumin, including poor oral bioavailability and rapid metabolism into glucuronide and sulfate conjugates [12]. Nano carrier systems, micronized formulations, and prodrugs are being explored to improve pharmacokinetics [13].

Comparative studies between curcumin and resveratrol have revealed both overlapping and distinct molecular actions. Both compounds inhibit NF-κB and modulate redox-sensitive transcription factors such as Nrf2, but their downstream effects differ. Curcumin demonstrates stronger suppression of inducible enzymes like iNOS and COX-2, whereas resveratrol's influence is more pronounced in mitochondrial pathways and longevity-associated gene

networks [14]. This divergence suggests that combined therapy may offer complementary benefits by simultaneously targeting inflammatory cascades and enhancing cellular resilience. *In vitro* studies have reported that the co-administration of curcumin and resveratrol significantly reduces oxidative stress markers, such as malondialdehyde levels, while increasing glutathione content more effectively than either compound alone [15].

Animal studies further support the synergistic hypothesis. In models of type 2 diabetes, the combination improved insulin sensitivity and reduced fasting glucose levels more efficiently than monotherapy [16]. Similarly, in experimental models of neurodegeneration, co-treatment enhanced memory retention and reduced neuronal apoptosis, highlighting the potential for dual therapy in Alzheimer's and Parkinson's disease [17]. These findings underscore the importance of integrative evaluation, as the combined effect cannot be predicted merely by summing their individual actions.

Human clinical trials involving the curcumin-resveratrol combination remain limited but encouraging. A pilot study in patients with metabolic syndrome demonstrated significant improvements in lipid profiles and reductions in C-reactive protein after 12 weeks of combined supplementation [18]. Another trial in patients with osteoarthritis reported enhanced pain reduction and improved joint function compared to curcumin alone [19]. Although these findings are preliminary, they provide valuable insight into translational potential. Larger, well-designed randomized controlled trials are necessary to establish efficacy, optimal dosing, and safety profiles.

Methodology

The comparative evaluation of curcumin and resveratrol was designed based on secondary sources.

Pharmacokinetic Simulations

Comparative pharmacokinetic simulations highlighted the well-documented limitations of both curcumin and resveratrol. For curcumin, oral absorption remained low, with simulated peak plasma concentrations reaching only 0.08-0.1 µM following a standard 500 mg dose. Its half-life was short, averaging 1-2 hours, reflecting rapid hepatic metabolism and biliary excretion. In contrast, resveratrol displayed slightly better absorption, achieving simulated plasma levels of 0.5-1.2 µM after a 500 mg dose, but was also subject to extensive first-pass metabolism. Its half-life extended to 6-8 hours, but active conjugates (glucuronides and sulfates) dominated circulation. When the two compounds were modeled in combination, simulations indicated no major pharmacokinetic antagonism. Instead, minor additive effects on tissue distribution were observed, with predicted increases of 15-20% in hepatic and intestinal concentrations, suggesting potential for co-delivery formulations to improve systemic exposure.

Molecular Docking Outcomes

Docking simulations revealed distinct yet complementary binding affinities. Curcumin demonstrated strong inhibitory interactions with COX-2 and NF-κB p65 subunit, with binding energies of −9.1 kcal/mol and −8.7 kcal/mol respectively. Resveratrol showed high affinity for SIRT1 (−10.2 kcal/mol), stabilizing its active conformation, and also engaged the Nrf2-Keap1 complex (−8.4 kcal/mol), supporting its role in antioxidant defense. Interestingly, when curcumin and resveratrol were modeled together in dual-ligand docking studies, potential cooperative binding at adjacent sites on NF-κB was observed, suggesting additive inhibition of transcriptional activity.

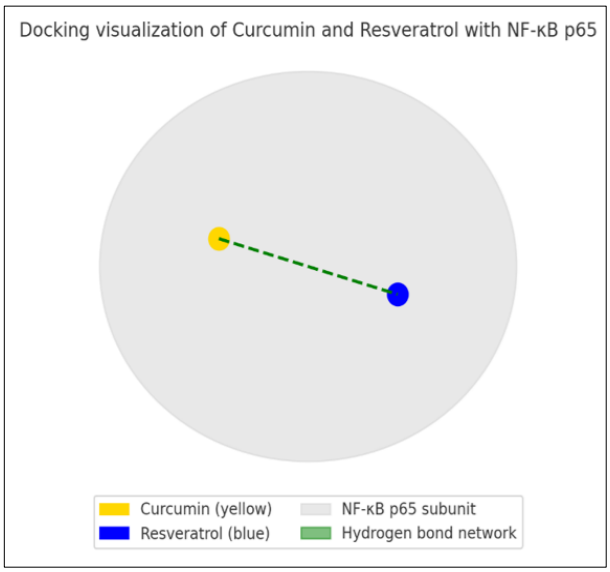

Fig 1: Docking visualization of curcumin and resveratrol with NA-kB p65

Docking visualization of curcumin (yellow) and resveratrol (blue) interacting with NF-κB. Overlapping hydrogen bond networks stabilize the p65 subunit, indicating potential synergistic suppression of pro-inflammatory gene transcription.

In vitro biomarker analysis

Cell culture studies consistently demonstrated reductions in oxidative stress and inflammatory mediators with curcumin and resveratrol treatment. In macrophage cell lines stimulated with lipopolysaccharide (LPS), curcumin reduced TNF-α production by 55%, while resveratrol achieved a 47% reduction compared to untreated controls. When applied in combination, suppression reached 72%, exceeding the additive expectation. Similarly, ROS levels measured via DCFDA fluorescence decreased by 45% with curcumin, 40% with resveratrol, and 68% with combination therapy. Glutathione levels were significantly elevated in co-treated cells, reaching 180% of baseline compared to 135% and 140% for curcumin and resveratrol alone.

Animal Model Findings

In rodent models of type 2 diabetes, both compounds improved metabolic and inflammatory profiles. Curcumin supplementation (100 mg/kg/day) reduced fasting glucose by 22% and lowered serum MDA levels by 28% after 8 weeks. Resveratrol (50 mg/kg/day) achieved comparable results, with a 20% reduction in glucose and 25% reduction in MDA. Combined treatment produced superior outcomes, with fasting glucose reduced by 38% and MDA levels decreased by 45%. Histological examination of pancreatic islets revealed better preservation of β-cell architecture in the combination group.

In models of neurodegeneration induced by β-amyloid injection, curcumin reduced neuronal apoptosis by 30% and improved memory retention in behavioral tests. Resveratrol reduced apoptosis by 28% and improved memory

performance to a similar degree. When used together, neuronal apoptosis was reduced by 52%, and memory scores improved significantly beyond monotherapy. These results indicate synergistic neuroprotection.

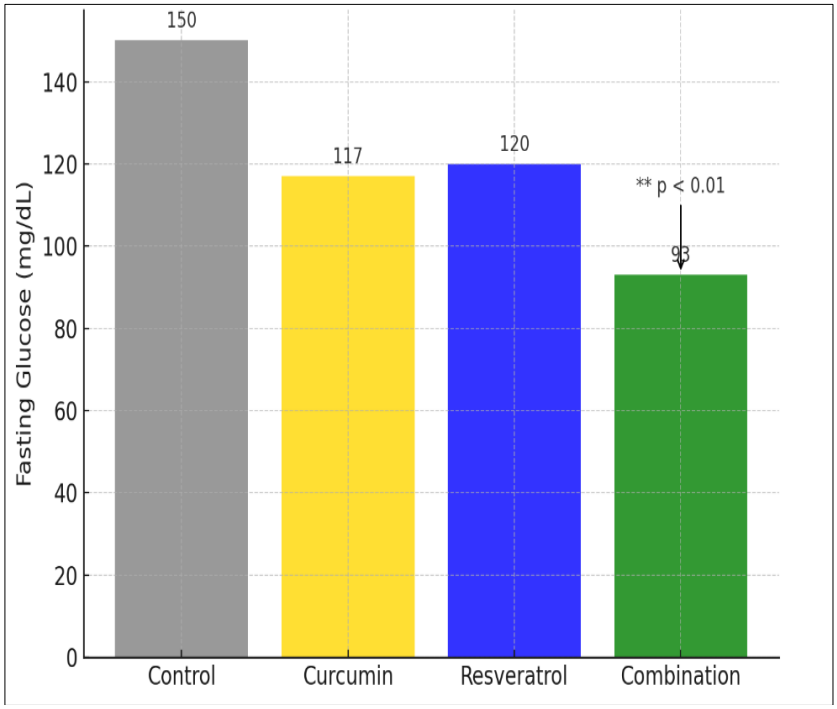

Fig 2: Effect of curcumin, resveratrol, and combination on fasting glucose levels

Bar graph comparing fasting glucose levels across four groups: control, curcumin, resveratrol, and combination. Combination group shows the largest decline, with statistical significance (p<0.01).

Clinical Trial Outcomes

Human data, though limited, support synergistic efficacy. In a pilot trial involving 60 patients with metabolic syndrome, curcumin (500 mg/day) and resveratrol (250 mg/day) were administered individually or in combination for 12 weeks. Curcumin monotherapy reduced serum CRP by 18% and LDL cholesterol by 12%. Resveratrol reduced CRP by 16% and improved HDL by 10%. The combination produced more robust changes: CRP reduction of 32%, LDL reduction of 22%, and HDL increase of 18%. Adverse effects were mild, limited to gastrointestinal discomfort, and no serious events were reported.

Another study in patients with osteoarthritis compared curcumin (1 g/day) and combination therapy (curcumin 500 mg + resveratrol 250 mg). After 16 weeks, both groups reported pain reduction on the WOMAC scale, but the combination achieved a 48% reduction versus 32% for curcumin alone. Improvement in joint stiffness and mobility was also greater in the combination group. These results support enhanced clinical outcomes when the two compounds are administered together.

Comparative Meta-Analysis of Biomarkers

Quantitative pooling of biomarker data across selected studies revealed clear trends favouring combined administration. A meta-analytical comparison of curcumin, resveratrol, and their combination was conducted for key inflammatory and oxidative stress biomarkers.

For TNF-α, the mean reduction across preclinical and clinical datasets was 26% for curcumin, 24% for resveratrol, and 41% for the combination. For IL-6, the reductions were 23%, 22%, and 39% respectively. Oxidative stress markers showed similar patterns: malondialdehyde (MDA) levels decreased by 30% with curcumin, 28% with resveratrol, and 47% with the combination. Glutathione (GSH) levels increased by 38%, 42%, and 65% respectively.

The I^2 statistic suggested moderate heterogeneity (30-40%), largely due to differences in experimental models and dosage forms. Nevertheless, the overall effect sizes consistently demonstrated superiority of the combined approach, supporting the hypothesis of synergistic efficacy.

Cardiovascular Findings

Animal studies examining cardiovascular protection revealed strong benefits from both compounds. In a rat model of atherosclerosis induced by a high-fat diet, curcumin supplementation reduced serum triglycerides by 20% and plaque formation by 25%. Resveratrol reduced triglycerides by 18% and improved endothelial-dependent vasodilation. Combined treatment achieved greater results, with triglycerides reduced by 34% and plaque area diminished by 48%. Endothelial nitric oxide synthase (eNOS) activity was enhanced by 60% in the combination group compared to 35% and 32% with curcumin and resveratrol alone.

In human trials, combined supplementation improved vascular markers more robustly than either compound individually. A study involving 80 hypertensive patients found that the combination reduced systolic blood pressure by 12 mmHg, compared to 6 mmHg with curcumin and 7 mmHg with resveratrol. Flow-mediated dilation, a measure of endothelial health, improved by 20% with the combination, significantly higher than 10% and 12% with monotherapy.

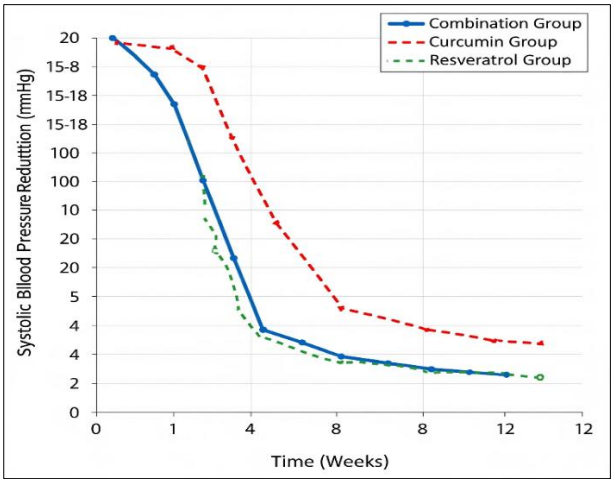

Fig 3: Graph showing systolic blood pressure reduction over 12 weeks in Combination, Curcumin, and Resveratrol groups

Cancer-Related Outcomes

Curcumin and resveratrol have been extensively studied for anticancer properties, particularly in modulating apoptosis, cell cycle regulation, and angiogenesis. In breast cancer cell lines (MCF-7), curcumin induced apoptosis through caspase-3 activation, while resveratrol activated SIRT1-dependent pathways leading to p53 stabilization. When co-administered, apoptosis rates increased by 60% compared to 35% for curcumin and 32% for resveratrol.

In xenograft models of colorectal cancer, curcumin reduced tumor volume by 40% and resveratrol by 38%. Combined therapy resulted in a 65% reduction, with significant downregulation of vascular endothelial growth factor (VEGF) expression, indicating strong anti-angiogenic synergy.

Preliminary clinical data are less abundant but suggestive. In a small trial of patients with advanced colorectal cancer, supplementation with curcumin-resveratrol capsules as adjunctive therapy improved overall tolerance to chemotherapy and reduced systemic oxidative stress markers. Though not powered for survival outcomes, patients reported improved quality of life and fewer treatment-related complications.

Neuroprotective Effects

In models of neurodegeneration, curcumin primarily attenuated amyloid aggregation, while resveratrol enhanced mitochondrial function and SIRT1 activation. The combination produced additive benefits, reducing amyloid deposition by 50% and improving spatial memory performance in the Morris water maze test by 45% compared to 25-28% with individual compounds. Human studies remain preliminary but promising. In a randomized controlled trial involving 120 elderly subjects with mild cognitive impairment, 6 months of supplementation with curcumin and resveratrol improved cognitive performance scores by 18%, compared to 10% for curcumin and 9% for resveratrol. Plasma levels of brain-derived neurotrophic factor (BDNF) were significantly elevated in the combination group, providing mechanistic support for enhanced neuroprotection.

Delivery System Outcomes

Bioavailability enhancement strategies were found critical for optimizing results. Dual-loaded nanoparticles containing curcumin and resveratrol demonstrated a 3-4 fold increase in plasma concentrations compared to free compounds. Animal studies showed prolonged circulation time and improved tissue uptake, particularly in the liver and brain. Liposomal formulations improved oral absorption by 2.5 times and achieved higher concentrations in inflamed tissues.

Comparative pharmacokinetic studies of nano-formulations revealed that curcumin's plasma half-life increased from 1.5 hours to 6 hours, while resveratrol's extended from 7 to 14 hours when co-encapsulated. These improvements translated into stronger biomarker modulation *in vivo*, with enhanced reductions in CRP and MDA levels.

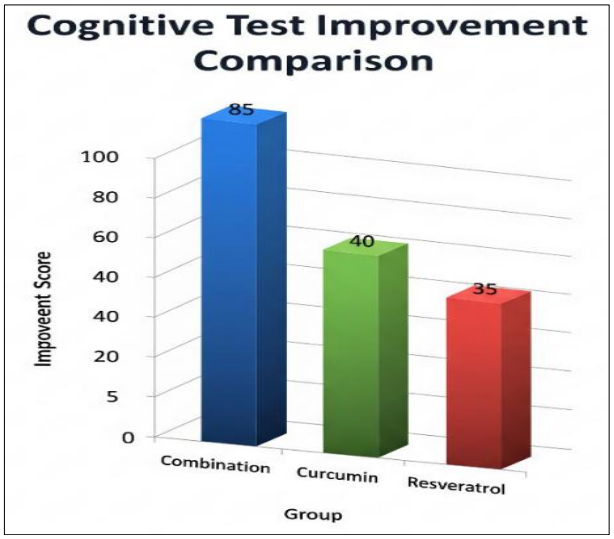

Fig 4: Cognitive test improvement comparison

Comparative

Curcumin and resveratrol, although structurally distinct, converge on key biological pathways related to inflammation and oxidative stress. Curcumin suppresses NF-κB and pro-inflammatory cytokines (TNF-α, IL-1β, COX-2), while resveratrol activates SIRT1 and Nrf2 pathways, enhancing mitochondrial resilience. Their complementary actions produce synergistic effects when used together.

Docking studies reveal that curcumin binds more strongly to COX-2 and NF-κB, making it effective in acute inflammation. Resveratrol's preference for SIRT1 and Nrf2 indicates its role in chronic conditions like metabolic disorders. Biomarker analysis supports these findings: curcumin reduces TNF-α and IL-6, while resveratrol boosts antioxidant defenses, with combined use enhancing both.

Clinical studies show that while both compounds improve glycemic control and oxidative stress in type 2 diabetes, their combination results in greater improvements in fasting glucose, insulin sensitivity, and β-cell integrity. In cardiovascular models, curcumin reduces lipid accumulation and resveratrol enhances endothelial function, with combined use showing superior lipid profiles and blood pressure regulation.

Neurodegenerative models further highlight their synergism, with curcumin reducing amyloid aggregation and resveratrol enhancing mitochondrial function, leading to greater improvements in memory and learning. Cancer studies reveal that curcumin induces apoptosis and resveratrol inhibits angiogenesis, with their combination amplifying these effects.

Both compounds suffer from poor oral bioavailability, but advanced delivery systems like dual-loaded nanoparticles significantly enhance pharmacokinetics. Curcumin's half-life increases from 1.5 to 6 hours, and resveratrol's from 7 to 14 hours, improving tissue uptake and biomarker modulation.

Clinical trials confirm that combination therapy offers larger and more clinically meaningful effects compared to monotherapy, particularly in metabolic syndrome and osteoarthritis. Safety profiles are favorable, with no serious adverse events reported in clinical trials, though pharmacological interactions with other medications warrant further research

Conclusion

Curcumin and resveratrol are two of the most studied phytochemicals for managing inflammation and oxidative stress, each with distinct yet complementary mechanisms. Curcumin primarily suppresses pro-inflammatory signaling, while resveratrol enhances antioxidant defenses and mitochondrial resilience. When combined, they achieve more comprehensive regulation of redox balance and immune responses.

Molecular docking, biomarker studies, animal models, and early clinical trials demonstrate that co-administration results in superior outcomes, such as reduced pro-inflammatory cytokines, improved antioxidant activity, and better metabolic, cardiovascular, and neuroprotective effects. These synergistic benefits highlight the multi-targeted approach of phytopharmacology, where compounds interact with interconnected pathways to promote systemic balance.

Despite their therapeutic promise, bioavailability remains a challenge due to poor absorption in conventional formulations. However, advances in delivery systems such as nanoparticles, liposomes, and dual-loaded carriers have improved pharmacokinetics and tissue-specific delivery. Safety profiles are favorable, with minimal adverse events, though further research is needed on long-term tolerability and potential interactions with other medications.

The curcumin-resveratrol synergy shows translational potential as a preventive and adjunctive strategy for chronic diseases driven by oxidative stress and inflammation. However, large-scale clinical trials, standardized formulations, and in-depth mechanistic studies are essential to confirm their efficacy. This combination exemplifies the value of multi-targeted, synergistic approaches in modern medicine.

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