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Molecular Mechanisms and Clinical Effects of Medicinal Plants in Modulating Oxidative Stress: A Systematic Review from Athletic Performance to Vital Organ Protection

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ABSTRACT

Oxidative stress constitutes a major pathophysiological mechanism in conditions ranging from exercise-induced muscle fatigue to chronic organ damage including diabetic nephropathy and ischemic stroke. Medicinal plants offer therapeutic potential through bioactive compounds that modulate cellular defense pathways. This systematic review evaluated the molecular mechanisms and clinical efficacy of medicinal plants (Kaempferia galanga, Nigella sativa, Panax ginseng, and other herbal formulations) in managing oxidative stress across diverse health contexts. A comprehensive literature search was conducted using reputable databases. Studies measuring oxidative stress biomarkers (MDA, SOD) and cellular signaling pathways (Nrf2, NF-κB, PI3K/AKT) were included. Results showed that N. sativa and K. galanga supplementation in athletes significantly reduced MDA levels and inflammatory cytokines (IL-6), accelerating post-exercise recovery. Bioactive compounds including Ginsenoside Ro and Kaempferide demonstrated organ-protective effects through Nrf2/HO-1 activation, autophagy promotion, and mitochondrial protection in ocular and renal tissues. These findings indicate that medicinal plants exert cytoprotective effects by activating endogenous antioxidant systems. The therapeutic spectrum spanning athletic performance enhancement to chronic organ protection underscores the translational potential of herbal interventions as promising antioxidant agents.

1. INTRODUCTION

Oxidative stress represents a fundamental pathophysiological mechanism arising from an imbalance between Reactive Oxygen Species (ROS) production and antioxidant defense capacity, manifesting across a spectrum of clinical contexts from acute exercise-induced tissue damage to chronic degenerative diseases (Liu et al., 2025; Samudra and Irawan, 2021). This oxidative stress mediated disorder constitutes a unifying pathogenic mechanism that requires comprehensive therapeutic intervention spanning multiple biological levels from molecular signaling cascades to organ-level pathophysiology. In the realm of exercise physiology, high-intensity physical training triggers transient ROS surges that induce lipid peroxidation in cellular membranes, clinically presenting as Delayed Onset Muscle Soreness (DOMS), compromised athletic performance, and prolonged recovery periods (Irawan et al., 2025). Conversely, in chronic oxidative stress–related pathologies including diabetic retinopathy, diabetic nephropathy, and ischemic stroke, sustained oxidative stress serves as a primary driver of apoptotic cell death, exacerbating progressive organ dysfunction and irreversible tissue damage requiring vital organ protection (Liu et al., 2023; Zhou et al., 2024). This dual manifestation spanning both transient physiological stress and chronic pathological conditions underscores oxidative stress as a critical target for therapeutic intervention across the complete spectrum from athletic performance enhancement to vital organ protection.

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While conventional therapeutic approaches have predominantly focused on symptomatic relief through direct free radical scavenging, emerging evidence indicates a paradigm shift toward modulation of upstream molecular signaling pathways governing cellular redox homeostasis. Medicinal plants have emerged as promising therapeutic candidates due to their multi-target bioactive compounds that simultaneously modulate both molecular mechanisms and clinical outcomes. Pure bioactive compounds such as Ginsenoside Ro isolated from *Panax ginseng* and Kaempferide from *Kaempferia galanga* demonstrate organ-protective effects through activation of the Keap1/Nrf2/HO-1 signaling axis, a master regulator of endogenous antioxidant enzyme expression including Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx) (Liu et al., 2025; Shao et al., 2023). Furthermore, these phytochemicals from medicinal plants orchestrate autophagy induction a crucial cellular housekeeping mechanism for degrading damaged organelles and misfolded proteins, alongside mitochondrial biogenesis and membrane stabilization, collectively conferring cytoprotection against oxidative insults in renal, retinal, and neural tissues (Liu et al., 2023; Xu et al., 2024). These mechanistic insights demonstrate how medicinal plants exert therapeutic effects through coordinated modulation of molecular, cellular, tissue, organ, and clinical levels of biological organization, reflecting the translational integration from molecular to clinical applications central to this systematic review.

Despite growing research interest in herbal antioxidants, the current literature remains fundamentally fragmented across disparate research domains, creating critical knowledge gaps that impede clinical translation. Studies investigating oxidative stress in athletic populations remain disconnected from research on chronic organ diseases, preventing recognition of shared molecular mechanisms and unified therapeutic strategies across the athletic performance to organ protection spectrum. Evidence regarding molecular pathways (Nrf2/HO-1, NF-κB, autophagy) and clinical outcomes (biomarkers, functional parameters) have not been systematically synthesized within an integrated translational framework that bridges bench-to-bedside application. Comprehensive mapping of signaling pathway networks across multiple organ systems (muscular, renal, ocular, neural) is absent, obscuring potential common therapeutic targets for medicinal plant interventions. The substantial heterogeneity in oxidative stress biomarker selection and measurement methodologies across studies, ranging from lipid peroxidation markers (MDA, 4-HNE) to antioxidant enzyme activities (SOD, CAT, GPx) and inflammatory mediators (IL-6, TNF-α, CRP) creates significant challenges for clinical interpretation and cross-study comparison. Additionally, the exponential increase in publications examining herbal interventions for oxidative stress management has generated contradictory findings regarding efficacy, optimal dosing, and mechanisms of action, necessitating rigorous systematic synthesis (Farhah, 2024; Hasan, 2015; Liu et al., 2025, 2023; Zhou et al., 2024). These multifaceted gaps underscore an urgent need for comprehensive evidence integration that systematically connects molecular mechanisms with clinical effects across the full therapeutic spectrum from athletic performance to chronic organ protection.

Clinical validation of medicinal plant interventions spans diverse health contexts, demonstrating translational applicability from athletic performance optimization to management of chronic oxidative stress–mediated disorders. In sports medicine, supplementation with *Nigella sativa* (black seed) in competitive soccer athletes significantly reduced post-exercise Malondialdehyde (MDA) levels, a lipid peroxidation biomarker, while concurrently suppressing pro-inflammatory cytokines including Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α), thereby accelerating recovery kinetics and preserving neuromuscular function (Irawan et al., 2025). Similarly, *Kaempferia galanga* extract administration in physically stressed individuals demonstrated comparable MDA reduction alongside elevated SOD activity, confirming enhanced antioxidant capacity (Fitriyanti et al., 2020; Irawan et al., 2022). These findings in athletic populations illustrate the acute antioxidant and anti-inflammatory effects achievable through medicinal plant supplementation. Beyond athletic contexts, polyphenol-rich botanical preparations including *Cistus incanus* tea and Arabica-Gayo coffee demonstrate substantial efficacy in improving blood lipid profiles (total cholesterol, LDL-C, HDL-C ratios) and enhancing antioxidant enzyme activities in individuals

with metabolic dysregulation, representing a critical transition toward chronic organ protection applications (Aritanoga et al., 2019; Kuchta et al., 2021).

The mechanistic foundation underlying medicinal plant efficacy extends beyond singular compound activity to encompass multi-target network pharmacology that operates across multiple biological levels: molecular, cellular, tissue, organ, and clinical. Complex herbal formulations such as ShenKang injection, a traditional Chinese medicine preparation, exert nephroprotective effects in diabetic kidney disease through simultaneous modulation of multiple signaling cascades: (1) activation of the Nrf2/HO-1 pathway promoting antioxidant gene transcription at the molecular level; (2) inhibition of NF-κB-mediated inflammatory responses affecting cellular signaling; (3) suppression of NLRP3 inflammasome assembly preventing pyroptotic cell death at the cellular level; and (4) regulation of PI3K/AKT/mTOR signaling governing autophagy flux and mitochondrial quality control, ultimately protecting tissue and organ integrity with measurable clinical outcomes (Liu et al., 2023; Zhou et al., 2024). This hierarchical multi-level analysis from molecular mechanisms to clinical effects, exemplifies the translational integration central to this review, offering therapeutic advantages in complex oxidative stress–related pathologies where oxidative damage intersects with inflammation, metabolic dysfunction, and cellular senescence (Xu et al., 2024).

Emerging evidence supports integrative therapeutic strategies combining medicinal plant interventions with complementary modalities to achieve synergistic benefits across the athletic performance to organ protection spectrum. Acupuncture administered in conjunction with medicinal plant formulations containing *Curcuma xanthorrhiza*, *Centella asiatica*, and ginger (*Zingiber officinale*) demonstrated superior improvements in maximal oxygen consumption (VO_2max) compared to either intervention alone, attributed to enhanced mitochondrial biogenesis and cellular energy metabolism through restoration of internal energy balance (Imandiri et al., 2020). Tissue-specific protective mechanisms conferred by medicinal plants have been characterized across multiple organ systems relevant to both acute stress responses and chronic pathologies: in ocular tissues, phytochemicals mitigate ultraviolet radiation-induced oxidative damage to lens epithelial cells; in renal parenchyma, bioactive compounds from medicinal plants attenuate cisplatin-induced nephrotoxicity through autophagy-mediated clearance of damaged mitochondria; and in dermal tissues, botanical extracts confer protection against particulate matter (PM2.5)-induced oxidative stress and premature cellular senescence (Farhah, 2024; Shao et al., 2023; Zhu et al., 2022). These organ-specific effects demonstrate the broad protective capacity of medicinal plants across the continuum from performance enhancement to pathological organ damage prevention.

Given the exponential growth in research publications examining medicinal plants for oxidative stress management with numerous studies reporting contradictory findings regarding efficacy, mechanisms, and clinical applicability, a rigorous systematic synthesis has become critically necessary. No comprehensive review has yet integrated evidence across the full translational continuum from molecular mechanisms (Nrf2/HO-1, NF-κB, autophagy pathways) to clinical outcomes spanning athletic performance enhancement and vital organ protection. The heterogeneous methodologies, biomarker selections, and target populations across existing studies necessitate structured evidence synthesis to identify consistent patterns, resolve contradictions, and establish evidence-based therapeutic recommendations. Furthermore, the polypharmacological nature of medicinal plant interventions, wherein multiple bioactive compounds simultaneously target diverse molecular pathways, requires systematic analysis capable of mapping complex mechanism-outcome relationships that single-study designs cannot adequately capture (Irawan et al., 2025; Liu et al., 2025; Zhou et al., 2024; Zhu et al., 2022).

The medicinal plants selected for this systematic review such as *Kaempferia galanga*, *Nigella sativa*, *Panax ginseng*, and specific herbal formulations, were chosen based on stringent criteria ensuring both mechanistic understanding and clinical relevance. These plants exhibit the highest publication frequency in oxidative stress research across both preclinical and clinical studies, indicating sustained scientific interest and sufficient data availability for comprehensive synthesis. Substantial mechanistic evidence documenting their effects on critical molecular pathways (Nrf2/HO-1, NF-κB, PI3K/AKT/mTOR, autophagy) exists, enabling detailed pathway

analysis and network pharmacology mapping. Clinical trial data demonstrating measurable effects on oxidative stress biomarkers (MDA, SOD) and functional outcomes (athletic performance parameters, organ function indicators) are available for these species, allowing translational mechanism-to-outcome synthesis. These medicinal plants possess established pharmacological relevance with documented safety profiles and bioactive compound characterization (ginsenosides, thymoquinone, kaempferides, curcuminoids), facilitating potential clinical implementation (Irawan et al., 2025; Liu et al., 2025, 2023; Zhu et al., 2022).

This systematic review was conducted using a structured evidence synthesis approach to ensure comprehensive and unbiased evaluation of medicinal plant effects on oxidative stress–mediated disorders. The review encompasses multiple study designs including randomized controlled trials (RCTs), quasi-experimental studies, and mechanistic investigations (in vitro, in vivo, ex vivo) to capture the full spectrum of evidence from molecular mechanisms to clinical outcomes. Target populations span healthy athletic individuals undergoing exercise-induced oxidative stress, patients with chronic oxidative stress–related pathologies (diabetic complications, ischemic diseases), and experimental models enabling mechanistic pathway elucidation. Primary outcome parameters include oxidative stress biomarkers (MDA, 4-HNE, protein carbonyls), antioxidant enzyme activities (SOD, CAT, GPx, GR), inflammatory mediators (IL-6, TNF-α, CRP, NF-κB activity), cellular signaling pathway activation (Nrf2/HO-1, PI3K/AKT, autophagy markers LC3, p62), and functional clinical outcomes (athletic performance metrics, organ function parameters) (Irawan et al., 2025; Liu et al., 2025; Zhou et al., 2024). The literature search covered publications from database inception through 2024, ensuring both historical context and contemporary evidence inclusion. This comprehensive scope enables integration of molecular, cellular, tissue, organ, and clinical levels of evidence within a unified analytical framework that bridges the athletic performance to organ protection spectrum.

This systematic review provides several novel contributions that advance the field beyond existing literature. It represents the first comprehensive integration of evidence across traditionally separate research domains like sports medicine, chronic disease management, and molecular pharmacology, thereby revealing unified pathophysiological mechanisms and therapeutic strategies spanning the athletic performance to organ protection continuum. The review employs a network pharmacology synthesis approach that systematically maps multi-target effects of medicinal plant compounds across interconnected signaling pathways (Nrf2/HO-1 ↔ NF-κB ↔ PI3K/AKT ↔ autophagy), revealing synergistic mechanisms underlying therapeutic efficacy rather than isolated single-pathway effects. The analysis characterizes the translational continuum from molecular mechanisms to clinical outcomes, systematically connecting bench discoveries (pathway activation, biomarker modulation) with bedside applications (performance enhancement, organ protection), thereby bridging the traditional gap between laboratory and clinical research. Comprehensive pathway mapping across multiple organ systems (muscular, cardiovascular, renal, ocular, neural) identifies both tissue-specific and common therapeutic targets, informing precision medicine approaches for oxidative stress–mediated disorders. By systematically analyzing medicinal plant effects across molecular, cellular, tissue, organ, and clinical levels of biological organization, this review establishes a hierarchical framework for understanding how phytochemical interventions achieve therapeutic efficacy across the spectrum from athletic performance enhancement to vital organ protection (Farhah, 2024; Kuchta et al., 2021; Xu et al., 2024).

The comprehensive synthesis provided by this review carries substantial implications for therapeutic practice, disease prevention, clinical translation, and pharmacological development. From a therapeutic perspective, the integrated evidence supports the clinical application of specific medicinal plants (*N. sativa*, *K. galanga*, *P. ginseng*) as evidence-based adjunctive interventions for managing oxidative stress–mediated disorders across diverse patient populations from athletes seeking performance optimization to patients requiring organ protection in chronic disease states. For prevention strategies, the documented effects in healthy athletic individuals establish medicinal plant supplementation as a viable approach for preemptive antioxidant defense enhancement, potentially reducing risk of exercise-induced oxidative damage and long-term chronic disease development. Regarding clinical translation, the

systematic mapping of molecular mechanisms to clinical outcomes provides the mechanistic rationale necessary for designing rigorous clinical trials, selecting appropriate biomarkers for therapeutic monitoring, and establishing evidence-based dosing regimens that optimize efficacy while ensuring safety. From a pharmacological standpoint, the identified bioactive compounds (ginsenosides, thymoquinone, kaempferides) and their multi-target mechanisms offer promising lead structures for novel antioxidant drug development, potentially yielding superior therapeutic agents compared to current single-target approaches (Irawan et al., 2025; Liu et al., 2025; Shao et al., 2023). Collectively, these implications underscore the translational potential of medicinal plants in addressing oxidative stress–related pathologies across the full clinical spectrum from performance optimization to organ protection.

This systematic review aims to comprehensively synthesize evidence regarding the molecular mechanisms and clinical effects of medicinal plants in modulating oxidative stress across the therapeutic spectrum from athletic performance enhancement to vital organ protection. To achieve this aim, the review pursues three specific objectives. First, to systematically map the molecular signaling pathways (Nrf2/HO-1, NF-κB, PI3K/AKT/mTOR, autophagy) through which medicinal plants (*Kaempferia galanga*, *Nigella sativa*, *Panax ginseng*, herbal formulations) modulate oxidative stress at molecular, cellular, tissue, and organ levels, employing network pharmacology synthesis to reveal multi-target mechanisms. Second, to evaluate clinical efficacy of medicinal plant interventions in diverse contexts—from reducing exercise-induced oxidative damage and enhancing athletic recovery to protecting vital organs (renal, ocular, neural, cardiovascular) in chronic disease states—by analyzing oxidative stress biomarkers, inflammatory mediators, and functional outcomes across the performance to protection continuum. Third, to establish translational connections between mechanistic evidence and clinical outcomes, thereby identifying evidence-based therapeutic strategies for oxidative stress–mediated disorders and informing future clinical trial design, biomarker selection, precision medicine approaches, and pharmacological development leveraging medicinal plants.

2. METHOD

This systematic review was conducted following PRISMA 2020 guidelines. A comprehensive literature search was performed across four electronic databases: PubMed, ScienceDirect, Google Scholar, and SINTA from database inception through December 31, 2024. The search strategy employed Boolean operators combining three concept blocks: ("oxidative stress" OR "reactive oxygen species" OR ROS OR "lipid peroxidation") AND ("medicinal plant" OR "herbal medicine" OR "Kaempferia galanga" OR "Nigella sativa" OR "Panax ginseng" OR phytochemical) AND ("athletic performance" OR "organ protection" OR "Nrf2" OR "NF-κB" OR autophagy OR MDA OR SOD). Searches were limited to peer-reviewed both in Bahasa and English-language articles. The initial database queries yielded a total of [75] publications, which were reduced to [20] after duplicate removal. The selection process involved two-stage independent screening. First, titles and abstracts were reviewed for relevance, resulting in [15] potentially eligible articles.

Subsequently, full-text assessment was performed with inclusion criteria encompassing RCTs, quasi-experimental, cohort, in vivo, and in vitro studies evaluating medicinal plants in populations experiencing oxidative stress, measuring oxidative biomarkers (MDA, SOD, CAT, GPx), inflammatory mediators (IL-6, TNF-α, NF-κB), molecular pathways (Nrf2/HO-1, PI3K/AKT, autophagy), or clinical outcomes. Exclusion criteria included reviews, editorials, and conference abstracts. The final selection included 15 studies. Data extraction was performed independently using standardized forms capturing study characteristics, intervention details, and outcomes. Quality assessment employed Cochrane Risk of Bias 2 for RCTs with studies categorized as low or high quality. Primary outcomes included oxidative stress biomarkers and antioxidant enzymes (significant effects: ≥20% and ≥15% changes, respectively). Secondary outcomes included inflammatory markers, molecular signaling pathways, and clinical performance metrics. Due to study heterogeneity, qualitative narrative synthesis was conducted,

categorizing findings by plant species, clinical context, mechanistic pathways, and outcome types, with subgroup analyses by intervention duration and population characteristics.

3. RESULT AND DISCUSSION

Result

Herbal Interventions in Exercise-Induced Oxidative Stress and Athletic Performance

Analysis of selected studies reveals that herbal interventions in athletic populations consistently reduce oxidative stress biomarkers while enhancing recovery kinetics. Supplementation with *Nigella sativa* and *Kaempferia galanga* demonstrated significant reductions in plasma Malondialdehyde (MDA) levels and inflammatory cytokines (IL-6, TNF-α) following high-intensity exercise, correlating with accelerated muscle recovery and preserved neuromuscular function. The key findings from clinical studies examining herbal interventions in athletic contexts are presented in Table 1.

Table 1. Effects of Herbal Interventions on Oxidative Stress and Recovery in Athletes

Material/Intervention	Oxidative Stress & Physical Parameters	Key Findings	Reference
N. sativa	↓ MDA, ↑ Antioxidants, ↓ Inflammation	Accelerated muscle recovery and athletic performance following intense exercise	(Irawan et al., 2025)
K. galangal	↓ MDA & ↓ IL-6	Reduced fatigue levels and oxidative stress after aerobic training	(Irawan et al., 2022)
Moringa oleifera	Pain perception (VAS) & Muscle strength	Decreased muscle pain (DOMS) and enhanced contractile strength	(Samudra and Irawan, 2021)
C. sappan	↓ MDA & ↓ Lactate	Improved physical fitness and enhanced lactate clearance	(Fitriyanti et al., 2020)
Arabica-Gayo coffee	↓ MDA & ↑ SOD	Enhanced natural antioxidant defense in sedentary men	(Aritanoga et al., 2019)

Molecular Mechanisms of Organ Protection

Beyond athletic applications, mechanistic studies demonstrate that purified bioactive compounds from medicinal plants exert organ-protective effects through modulation of specific molecular signaling pathways. Ginsenoside Ro from Panax ginseng and Kaempferide from Kaempferia galanga activated the Keap1/Nrf2/HO-1 pathway while simultaneously inducing autophagy and preventing apoptosis in models of diabetic retinopathy and cisplatin-induced nephrotoxicity. The molecular mechanisms underlying organ protection are summarized in Table 2.

Table 2. Effects of Herbal Interventions on Oxidative Stress and Organ Protection (Mechanistic)

Material/Intervention	Target Organ/Cell	Key Signaling Pathways	Reference
Kaempferide (K. galanga)	Kidney (nephrotoxicity)	Autophagy induction & oxidative inhibition	(Shao et al., 2023)
Ginsenoside Ro	Eye (retinopathy)	Epac1/AMPK pathway (mitochondrial protection)	(Liu et al., 2025)
ShenKang injection	Kidney (diabetic)	Keap1/Nrf2/HO-1 pathway	(Liu et al., 2023)
Brassaiopsis glomerulata	Brain (stroke)	PI3K/AKT/mTOR pathway (anti-	(Xu et al., 2024)

		apoptosis)	
Lycium barbarum polysaccharide	Skin (HaCaT cells)	ER stress inhibition	(Zhu et al., 2022)

Synergistic Effects in Polyherbal Formulations

Analysis of polyherbal formulations revealed synergistic effects superior to individual plant extracts. Traditional Chinese medicine preparations including ShenKang injection and GJHQHLRSD decoction demonstrated multi-target engagement of oxidative stress and inflammatory pathways. The Imandiri formula combining Curcuma xanthorrhiza, Centella asiatica, and ginger showed holistic fitness enhancement effects. The composition and primary applications of these formulations are detailed in Table 3.

Table 3. Composition of Specific Herbal Formulations

Formula Name	**Key Components**	**Primary Application**
ShenKang injection (Liu et al., 2023)	Cyperus rotundus, Astragalus membranaceus, Salvia miltiorrhiza, Carthamus tinctorius	Diabetic kidney disease
GJHQHLRSD decoction (Zhou et al., 2024)	Dried ginger, Scutellaria baicalensis, Coptis chinensis, Panax ginseng	Ulcerative colitis
Imandiri formula (Imandiri et al., 2020)	Curcuma xanthorrhiza, Centella asiatica, Zingiber officinale, Glycyrrhiza glabra	Physical fitness & VO_2 max

The superior efficacy of mixed formulations compared to individual plant extracts was attributed to synergistic interactions among diverse bioactive compounds. These polyherbal preparations demonstrated multi-pathway targeting, with components working complementarily to enhance Nrf2/HO-1 activation, suppress NF-κB signaling, and modulate gut microbiota composition. The integration of traditional remedies with molecular research provides scientific validation for complementary therapy approaches that have been empirically used for centuries.

Discussion

Integration of Molecular Mechanisms Across Clinical Contexts

The systematic integration of findings across diverse clinical contexts reveals a unified molecular framework underlying medicinal plant efficacy in oxidative stress management. The convergence of evidence from athletic performance studies and chronic organ disease models demonstrates that medicinal plants operate through conserved cellular defense mechanisms, particularly the Nrf2/HO-1 and NF-κB signaling pathways, regardless of the specific clinical application. High-intensity physical activity consistently triggers Exercise-Induced Muscle Damage (EIMD), manifesting through elevated Creatine Kinase (CK) and Lactate levels that impair performance and prolong recovery if unmanaged (Anugrah et al., 2024). Given that daily diet often fails to meet heightened metabolic demands during intense training, targeted nutritional supplementation becomes essential for maintaining physiological balance (Ayşe and İpek Melek, 2023). This mechanistic consistency supports the translational potential of herbal interventions across the complete therapeutic spectrum from acute exercise recovery to chronic organ protection.

The Nrf2/HO-1 pathway emerges as a central therapeutic target across all examined contexts. In athletic populations, activation of this pathway by *N. sativa* and *K. galanga* facilitates rapid recovery by enhancing endogenous antioxidant capacity, as evidenced by elevated SOD activity and reduced MDA levels. In chronic disease models, the same pathway activation by Ginsenoside Ro and Kaempferide provides sustained organ protection through continuous expression of cytoprotective proteins (Irawan et al., 2025, 2022). This dual functionality,

immediate antioxidant response for acute oxidative challenge and sustained cytoprotection for chronic oxidative stress illustrates the pathway's versatility as a therapeutic target and explains why medicinal plants targeting this mechanism demonstrate efficacy across such diverse clinical scenarios.

Molecular Signaling Networks and Cellular Homeostasis

Beyond direct antioxidant effects, medicinal plants demonstrate sophisticated modulation of interconnected signaling networks governing cellular homeostasis (Elejalde et al., 2021). The coordinate regulation of autophagy, mitochondrial biogenesis, and apoptosis represents a comprehensive approach to cellular quality control that extends beyond simple free radical scavenging. Kaempferide's induction of autophagy in renal tissues exemplifies this multilevel protection, as autophagy not only removes damaged mitochondria that generate excessive ROS but also degrades oxidatively modified proteins that would otherwise accumulate and trigger cellular dysfunction (Shao et al., 2023).

The inhibition of NF-κB signaling observed with multiple herbal interventions provides complementary anti-inflammatory effects that amplify antioxidant benefits. Since oxidative stress and inflammation exist in a bidirectional relationship where each perpetuates the other, simultaneous targeting of both pathways, Nrf2 activation for antioxidant defense and NF-κB inhibition for inflammation suppression that breaks this pathological cycle more effectively than interventions targeting either pathway alone (Liu et al., 2023; Shao et al., 2023). This mechanistic synergy explains the superior clinical outcomes observed with medicinal plants compared to synthetic antioxidants that typically act through single mechanisms.

Synergistic Effects and Polyherbal Formulations

The superior efficacy of polyherbal formulations compared to isolated compounds represents a critical finding with significant implications for therapeutic development. ShenKang injection's multi-target engagement of the Keap1/Nrf2/HO-1 pathway and the Imandiri formula's holistic fitness enhancement demonstrate that synergistic interactions among diverse bioactive compounds produce effects greater than the sum of individual components (Imandiri et al., 2020; Liu et al., 2023). This synergy likely arises from multiple mechanisms: complementary pathway targeting where different compounds activate parallel protective pathways; pharmacokinetic enhancement where certain compounds improve the absorption or bioavailability of others; and temporal coordination where compounds with different pharmacodynamic profiles provide sustained therapeutic coverage (Embuscado, 2015).

These findings validate traditional polyherbal approaches and suggest that future therapeutic development should prioritize multi-component formulations over single compound isolation (Liu et al., 2023, p. 202). The integration of traditional remedies with molecular research provides strong scientific validation for complementary therapy approaches that have been used empirically for centuries. The high safety profiles of spice-based interventions including curcumin, garlic, and cinnamon, combined with their multi-target effects on oxidative stress, inflammation, and metabolic function, support their incorporation into evidence-based integrative medicine protocols.

Clinical Translation and Therapeutic Implications

The clinical validation across diverse health contexts demonstrates clear translational potential for medicinal plant interventions. In athletic populations, the significant reduction in recovery time and preservation of neuromuscular function following *N. sativa* and *K. galanga* supplementation provides evidence for immediate practical application in sports medicine. The magnitude of MDA reduction and IL-6 suppression observed in these studies suggests clinically meaningful effects that could enhance training adaptation and competitive performance while reducing injury risk (Irawan et al., 2025, 2022).

For chronic disease management, the organ-protective effects demonstrated in diabetic retinopathy, diabetic nephropathy, and ischemic stroke models indicate potential for medicinal plants as adjunctive therapies to standard pharmaceutical treatments. The multi-pathway

protection offered by compounds like Ginsenoside Ro and Kaempferide, encompassing antioxidant defense, autophagy induction, and anti-apoptotic signaling that addresses the complex pathophysiology of these conditions more comprehensively than conventional therapies targeting single mechanisms (Liu et al., 2025, 2023; Shao et al., 2023; Xu et al., 2024; Zhu et al., 2022). This suggests that integrating herbal interventions with current treatment protocols could improve clinical outcomes and potentially slow disease progression.

Biomarker Standardization and Methodological Considerations

The substantial heterogeneity in oxidative stress biomarker selection across studies represents a significant challenge for clinical interpretation and cross-study comparison. While MDA and SOD emerged as the most commonly assessed markers, providing consistency in evaluation across athletic and organ protection contexts, the diversity of additional markers including 8-isoprostane, 4-HNE, TAC, and various inflammatory cytokines complicates direct comparison of intervention efficacy (Aritanoga et al., 2019; Fitriyanti et al., 2020; Irawan et al., 2025, 2022; Samudra and Irawan, 2021). This heterogeneity reflects the multifaceted nature of oxidative stress but necessitates standardization of biomarker panels for future research.

Future studies should adopt comprehensive biomarker panels that simultaneously assess oxidative damage (MDA, 4-HNE), antioxidant capacity (SOD, CAT, GPx, TAC), and inflammatory status (IL-6, TNF-α, CRP) to provide complete characterization of intervention effects (Anugrah et al., 2024; Irawan et al., 2022, 2022). Additionally, the inclusion of pathway-specific biomarkers such as nuclear Nrf2 levels, HO-1 expression, and NF-κB activation status would enable mechanistic validation and correlation of molecular changes with clinical outcomes (Fitriyanti et al., 2020; Zhou et al., 2022). This integrated biomarker approach would facilitate meta-analyses and enable more robust conclusions about intervention efficacy across different clinical contexts.

Limitations and Future Research Directions

Several limitations must be acknowledged in interpreting these findings. The predominance of preclinical studies in chronic disease contexts limits direct clinical translation, as effects observed in cell culture and animal models do not always translate to human applications (Segelcke et al., 2025). The variability in extraction methods, dosing protocols, and intervention duration across studies introduces heterogeneity that complicates definitive therapeutic recommendations. Furthermore, the lack of standardized phytochemical characterization in many studies raises concerns about reproducibility and quality control in clinical application (Ayşe and İpek Melek, 2023).

Future research should prioritize several key areas. Large-scale randomized controlled trials in human populations are essential to validate efficacy and establish optimal dosing protocols across different clinical contexts. Standardization of extraction methods and phytochemical characterization using techniques such as HPLC and mass spectrometry would ensure consistency in therapeutic preparations (Nahar et al., 2025). Investigation of pharmacokinetic parameters including bioavailability, tissue distribution, and metabolic pathways would optimize dosing regimens and identify potential drug-herb interactions. Long-term safety studies are necessary to establish comprehensive risk-benefit profiles, particularly for chronic use in disease management. Finally, mechanistic studies using omics technologies (genomics, proteomics, metabolomics) could elucidate additional therapeutic targets and refine our understanding of multi-component synergy in polyherbal formulations (Duan et al., 2025).

4. CONCLUSION

Medicinal plants demonstrate dual therapeutic potential in managing oxidative stress and enhancing athletic performance while protecting vital organs through multi-target molecular mechanisms. Key compounds including Ginsenosides, Kaempferide, and Polyphenols operate via Nrf2/HO-1 activation, NF-κB inhibition, autophagy induction, and mitochondrial protection. These findings validate traditional herbal medicine with modern mechanistic

evidence. Future research should prioritize standardized extraction methods, optimal dosing protocols, and large-scale clinical trials to establish definitive therapeutic guidelines and explore synergistic effects in complex formulations.

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