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Journal of Nutrition and Food Processing

Hülya Çiçek *

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Research Article

Litchi Chinensis Polyphenols Targeting the Oxidative Stress–Inflammation Axis in Chronic Diseases

Hülya Çiçek

Professor, MD, Department of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye.

Corresponding author: Hülya Çiçek., Professor, MD, Department of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye.

Received date: April 16, 2025; **Accepted date:** May 04, 2025; **Published date:** May 14, 2026

Citation: Hülya Çiçek (2026), *Litchi Chinensis* Polyphenols Targeting the Oxidative Stress–Inflammation Axis in Chronic Diseases, *J. Nutrition and Food Processing,* 9(3); **DOI:10.31579/2637-8914/361**

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Abstract

The decisive role of oxidative stress and low-grade chronic inflammation in the pathogenesis of chronic non-infectious diseases (obesity, type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and certain types of cancer) has been clearly demonstrated by advances in molecular biology and immunometabolism. Under physiological conditions, the accumulation of reactive oxygen species (ROS), which are involved in cellular signaling, exceeds the antioxidant defense capacity, leading to mitochondrial dysfunction, impaired energy metabolism, and accelerated tissue damage through lipid peroxidation, protein oxidation, and DNA damage.a The bidirectional and self-perpetuating cycle between oxidative stress and inflammation facilitates the development of clinical outcomes such as endothelial dysfunction, atherosclerosis, pancreatic β-cell damage, and hepatic steatosis in the litchi chinensis; polyphenols; oxidative stress; inflammation; nrf2; nf-κb context of metabolic syndrome. In this context, the Nrf2/Keap1 pathway, which regulates cellular redox homeostasis, and the NF-κB axis, the main regulator of the proinflammatory response, emerge as two key targetable regulatory networks. Increasing evidence in recent years shows that dietary polyphenols not only exhibit direct antioxidant effects but also create multi-targeted biological effects by activating Nrf2-mediated endogenous defense systems while suppressing NF-κB signaling. This review comprehensively evaluates the potential of polyphenol-rich extracts (flavan-3-ols, proanthocyanidins, and phenolic acids) obtained from the pericarp and seed of Litchi chinensis to modulate the oxidative stress–inflammation axis via the Nrf2/Keap1 and NF-κB pathways. In light of in vitro and in vivo findings, bioavailability, formulation strategies, and the value-added use of food industry by-products are discussed, revealing the translational potential of these phytochemicals in the prevention and supportive treatment of chronic diseases.

Key words: litchi chinensis; polyphenols; oxidative stress; inflammation; nrf2; nf-κb

Introduction

The decisive role of oxidative stress and low-grade chronic inflammation in the pathophysiology of chronic non-infectious diseases (obesity, type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, and certain types of cancer) has been clearly demonstrated over the past twenty years through advances in molecular biology, metabolism, and immunology. [1]. While reactive oxygen species (ROS) are known to play a role in cellular signaling under physiological conditions, the accumulation of ROS beyond the capacity of antioxidant defense mechanisms leads to irreversible biomolecular damage such as lipid peroxidation, protein oxidation, and DNA damage. This process disrupts cellular energy metabolism, triggers mitochondrial dysfunction, and ultimately accelerates tissue dysfunction and chronic disease progression. Particularly in metabolic syndrome, characterized by obesity and insulin resistance, the oxidative stress burden accompanying adipocyte hypertrophy and ectopic fat accumulation paves the way for the formation of an inflammatory microenvironment and deepens the systemic complications of the disease.

The bidirectional and self-perpetuating relationship between oxidative stress and inflammation forms the sustainable pathophysiological basis of chronic diseases. Increased ROS levels activate inflammatory signaling pathways, while immune cells (macrophages, neutrophils) activated during the inflammatory process produce more ROS, increasing the oxidative load. This vicious cycle paves the way for clinical outcomes such as endothelial dysfunction, atherosclerosis development, pancreatic β-cell damage, and hepatic steatosis [2]. Therefore, the development of agents with multiple mechanisms of action that simultaneously target oxidative stress and inflammation is among the key priorities of current translational research for the prevention and treatment of chronic diseases.

In this context, the Nrf2 (nuclear factor erythroid 2–related factor 2)-mediated antioxidant defense system and the NF-κB (nuclear factor kappa B)-mediated inflammatory response stand out as two fundamental regulatory axes of cellular homeostasis [3,4]. Nrf2 is a transcription factor that plays a central role in maintaining intracellular redox balance and is suppressed by the Keap1 protein in the cytosol under basal conditions. Under oxidative stress conditions, Nrf2 dissociates from Keap1 and

translocates to the nucleus, inducing the expression of heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), glutathione synthesis enzymes (GCLC, GCLM), and phase II detoxification enzymes, thereby protecting the cell against oxidative damage. In contrast, the NF-κB signaling pathway regulates the transcription of proinflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, and inflammation-related enzymes such as COX-2 and iNOS; its chronic activation contributes to tissue damage and fibrosis development. The functional antagonism between these two pathways highlights the clinical importance of coordinated regulation of antioxidant and anti-inflammatory responses.

Dietary flavonoids and phenolic acids stand out as phytochemical agents capable of affecting multiple molecular targets in this context [5]. These compounds exert biological effects not only through their direct free radical scavenging properties but also through their capacity to activate endogenous antioxidant defense systems by regulating cellular signaling pathways. Flavan-3-ols such as epicatechin, catechin, and proanthocyanidins increase HO-1 expression by activating the Nrf2 pathway; phenolic acids such as chlorogenic acid and rutin can reduce inflammatory cytokine production by suppressing NF-κB activation (Figure 1).

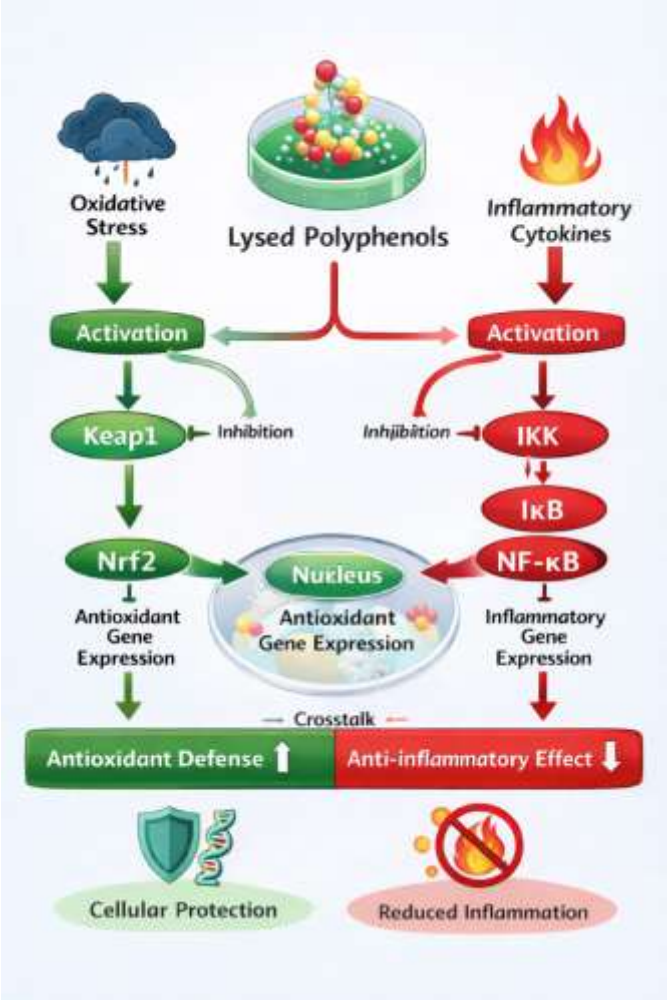


Figure 1: Nrf2/NF-κB pathways and the effects of leached polyphenols on these pathways.

In addition, these compounds have been reported to regulate energy metabolism by activating the AMP-activated protein kinase (AMPK) pathway, supporting mitochondrial biogenesis, and improving insulin signaling. Litchi chinensis Sonn. fruit is considered a strategic plant resource for functional food and nutraceutical development, not only as a rich source of carbohydrates, vitamins, and minerals, but also due to its rich phytochemical content concentrated in the pericarp and seed [6–8]. In particular, the high concentrations of epicatechin, proanthocyanidins, and anthocyanins in the pericarp fraction explain its potent antioxidant and anti-inflammatory potential. The triterpenes and saponins found in the seed fraction have been associated with biological effects such as cell membrane stabilization, suppression of inflammatory signaling pathways, and modulation of apoptotic processes.

The use of L. chinensis pericarp and seed in traditional Eastern medicine for pain, inflammation, and gastrointestinal disorders is consistent with modern pharmacological findings. Experimental studies have shown that polyphenol-rich extracts of this plant reduce oxidative stress markers, suppress inflammatory cytokine production, and improve metabolic parameters [9,10]. However, it should be noted that the current evidence is largely based on in vitro and animal models, and confirmatory studies at the clinical level are limited. Therefore, the biological effects of L. chinensis based on its ethnopharmacological use need to be comprehensively evaluated using modern molecular mechanism data and addressed from a clinical translation perspective.

Current research on *Litchi chinensis* presents a compelling case, though one that requires a measured approach. In vitro models have consistently highlighted its potential to bolster antioxidant defenses and modulate critical pathways like **Nrf2** and **NF-κB**, while animal studies reinforce these findings by demonstrating tangible improvements in metabolic health and inflammation. However, the leap to human application is currently hampered by a significant lack of rigorous, large-scale clinical trials using standardized extracts. Consequently, while the mechanistic evidence is strong, we must be cautious about overstating its clinical efficacy; until we have more robust human data, any claims regarding its

role in preventing or treating chronic diseases should be viewed as preliminary and interpreted with professional skepticism.

The aim of this review is to systematically evaluate the potential role of Litchi chinensis in the prevention and supportive treatment of chronic diseases by integrating its traditional usage knowledge with its pharmacological effects revealed through its phytochemical profile and multiple molecular targets. In this context, existing experimental evidence will be critically discussed, translational gaps will be identified, and guiding recommendations for future clinical research will be presented.

Methods

For this study, existing information in the literature was synthesized and compiled from a critical perspective. During the research process, all data up to January 2026 was thoroughly searched in prestigious databases such as PubMed, Scopus, and Web of Science. The searches focused particularly on the Litchi chinensis (lychee fruit) and its polyphenol content, effects on the body as Oxidative stress, Nrf2, and NF-κB mechanisms, absorption of components in the body, critical substances found in the fruit as hypolysine A and methylenecyclopropylglycine.

Taxonomıc Posıtıonıng, Tradıtıonal Pharmacologıcal Use

Litchi chinensis Sonn. (Sapindaceae) is a long-lived, evergreen tree that grows in subtropical and tropical climate zones. Botanically, this species can reach 10–15 meters in height and has opposite, leathery leaves and racemose flowers. Its fruit, valued for economic and nutritional purposes, consists of a lignified and pigmented pericarp on the outside, a juicy and sugar-rich aril (edible part) in the middle layer, and a single large seed (kernel) on the inside. The aril fraction is rich in carbohydrates, ascorbic acid, and potassium and stands out for its energy and micronutrient contribution. In contrast, the highest bioactive concentration from a pharmacological perspective has been reported in the pericarp and seed fractions [1,3,9]. In particular, the pericarp's richness in epicatechin, proanthocyanidins, and anthocyanins is among the key factors explaining this tissue's potent antioxidant and anti-inflammatory properties. The leaves are also rich in epicatechin and condensed tannins and have been widely used in traditional applications.

Ethnopharmacological records indicate that L. chinensis has been used for centuries in Chinese, Vietnamese, and Southeast Asian medicine. Decoctions prepared from the pericarp and seeds have been reported to be used for epigastric pain, dyspeptic complaints, and inflammatory symptoms; they have also been evaluated as expectorants and cough suppressants [11,12]. Leaf infusions have been recorded as being used for fever reduction, the alleviation of febrile-inflammatory conditions defined as “excess heat,” and as supportive treatment for infection-like conditions. These traditional patterns of use are biologically consistent with the anti-inflammatory and antimicrobial effects demonstrated in modern experimental studies [13,14]. Indeed, it has been reported that pericarp and leaf extracts suppress the NF-κB-mediated inflammatory response and exhibit in vitro activity against various Gram-positive/Gram-negative bacteria.

When we look at Nrf2 modulation, the effects are highly context-dependent. While activating Nrf2 is generally a good thing—it boosts our internal antioxidant defenses by inducing enzymes like HO-1, NQO1, and glutathione—it’s not a "more is always better" situation. In fact, chronic or constant Nrf2 activation has been linked to tumor progression and drug resistance in certain cancers. This means we can't just assume that systemic, long-term activation is universally beneficial. Moving forward, research needs to pin down the specifics: how these effects vary across different tissues, what the dose-response curves look like, and the consequences of long-term exposure. Similarly, the inhibition of NF-κB is a bit of a balancing act. On one hand, suppressing it is great for lowering pro-inflammatory cytokines and reducing inflammation. On the other hand, if you inhibit it too much, you might actually weaken the body’s natural immune defenses. Ultimately, the goal isn't total, global suppression; it’s about achieving immunomodulatory balance—finding that "Goldilocks zone" where we manage inflammation without compromising our ability to fight off threats.

The difference in the pharmacological potential of different parts of the plant is closely related to phytochemical distribution. While the aril fraction primarily provides nutritional benefits, the polyphenols and triterpenes concentrated in the pericarp and seed determine the therapeutic effect potential. This situation necessitates a scientific re-evaluation of the fact that the pericarp and seed are mostly separated as waste after the aril is made available for consumption in the food industry. Indeed, considering the pericarp as industrial waste presents a significant opportunity in terms of sustainable bioactive substance extraction and the circular economy perspective [15,16]. Evaluating the pericarp and seed as functional food components or nutraceutical raw materials stands out as a strategic approach in terms of both reducing environmental burden and creating economic added value. The botanical characteristics and traditional uses of L. chinensis provide a biologically coherent framework with modern pharmacological findings. The systematic evaluation of the phytotherapeutic potential of the plant's inedible fractions, particularly the pericarp and seed, paves the way for more effective use of this species in translational research as a functional food and supportive therapeutic agent.

General Profıle of Phytochemıcal Composıtıon

The phytochemical class that forms the basis of Litchi chinensis' pharmacological effects is polyphenols and flavonoids, which are concentrated in the pericarp and leaf tissues. High-performance liquid chromatography (HPLC) and mass spectrometry-based analyses have revealed high concentrations of phenolic compounds such as epicatechin, catechin, proanthocyanidin A1/A2, rutin, and chlorogenic acid in the pericarp and leaves [17,18]. The quantitative distribution of these compounds shows significant differences depending on cultivar, harvest time, degree of ripeness, and processing conditions. In particular, it has been reported that proanthocyanidins constitute a large portion of the total phenolic content in the pericarp fraction; this has been considered the main determinant of the pericarp's strong antioxidant capacity.

The biological effects of polyphenols are based not only on their direct free radical scavenging capacity but also on their metal chelation and cellular signaling pathway modulation properties. The main antioxidant mechanisms of these compounds are the inactivation of hydroxyl and superoxide radicals via hydroxyl groups, the suppression of the Fenton reaction by forming complexes with transition metals such as Fe^{2+} and Cu^{2+}, and the termination of lipid peroxidation chain reactions [19]. This multifaceted effect profile explains the high capacity of pericarp extracts in in vitro antioxidant tests such as DPPH, ABTS, and FRAP. Furthermore, epicatechin and proanthocyanidins have been reported to increase HO-1 and NQO1 expression by activating Nrf2-mediated endogenous antioxidant defense systems.

The degree of polymerization of proanthocyanidins is a critical parameter in terms of biological effect. It has been reported that oligomeric proanthocyanidins with low degrees of polymerization have higher bioavailability, while fractions with high degrees of polymerization show limited absorption in the gastrointestinal tract [20]. However, it has been suggested that high molecular weight proanthocyanidins may be broken down into phenolic acids by the microbiota in the colon, thereby exerting an indirect systemic effect. This suggests that the biological effects of L. chinensis polyphenols are shaped not only by direct absorption but also by gut microbiota-mediated biotransformation processes.

The characteristic red color of the pericarp is derived from anthocyanin derivatives, primarily cyanidin-3-glucoside [21]. The amount of anthocyanins varies depending on the degree of fruit ripeness, exposure to sunlight, and storage conditions. In addition to their potent antioxidant properties, these pigments have been reported to exert beneficial effects on vascular functions. By increasing nitric oxide (NO) bioavailability in

endothelial cells, supporting vasodilation, and reducing endothelial dysfunction, they may contribute to mechanisms that lower cardiometabolic risk.

The anti-inflammatory effects of anthocyanins are also noteworthy. Experimental models have shown that they suppress NF-κB-mediated pro-inflammatory gene expression and reduce the production of cytokines such as TNF-α and IL-6. However, the limited oral bioavailability of anthocyanins suggests that the biological effect occurs largely through metabolites. Their conversion by the gut microbiota into smaller phenolic acids such as protocatechuic acid and ferulic acid is considered the primary mediator of systemic biological activity [22]. This microbiota-dependent conversion may be an important determinant of interindividual differences in biological response.

Triterpenes (particularly oleanolic acid and its derivatives), phytosterols, and saponins identified in L. chinensis kernel and pericarp fractions offer a biological effect profile that is distinct from but complementary to that of polyphenols [23]. Oleanolic acid derivatives have been reported to increase cell membrane stabilization, preserve mitochondrial membrane potential, and exert cytoprotective effects by modulating apoptotic signaling pathways. These compounds have also been shown to reduce the inflammatory response by suppressing the NF-κB and MAPK pathways.

The amphiphilic structure of saponins allows them to interact with membrane lipids and modulate cellular permeability. This property has raised the possibility that some saponins may exhibit immunomodulatory effects and be considered as natural adjuvants [24]. However, it is known that saponins can cause gastrointestinal irritation at high doses, and dose optimization and safety profile should be carefully evaluated for the therapeutic use of these compounds. Phytosterols, on the other hand, are suggested to contribute to improved lipid profiles by reducing intestinal cholesterol absorption.

Fruit aroma and antimicrobial potential are shaped by volatile terpenoids and esters found in the fruit. These volatile compounds have been reported to contribute to antimicrobial activity by disrupting bacterial membrane integrity [25]. Furthermore, these compounds have the potential to be evaluated as natural preservatives in food products.

Trace elements such as ascorbic acid (vitamin C), potassium (K), and magnesium (Mg) not only increase the nutritional value of L. chinensis but also play a complementary role in the antioxidant effect of polyphenols. Vitamin C supports the continuity of the antioxidant network by helping to reduce the oxidized forms of flavonoids in the redox cycle. Minor metabolites (organic acids, sugar alcohols, and some amino acid derivatives) are considered complementary components that contribute to the physiological effects of the fruit.

The phytochemical profile of L. chinensis offers a multi-layered biological effect network consisting of polyphenols, anthocyanins, triterpenes, saponins, and volatile compounds. The interactive effects of these compounds indicate that the plant has a multi-targeted phytotherapeutic potential rather than being a single “antioxidant” source.

Pharmacologıcal Actıvıtıes And Mechanısms Of Actıon

Litchi chinensis pericarp, leaf, and seed extracts exhibit significant free radical scavenging activity in in vitro antioxidant capacity tests such as DPPH, ABTS, and FRAP [17]. This biological effect has been reported to correlate strongly with high phenolic load (epicatechin, proanthocyanidins, chlorogenic acid) [15]. The neutralization of ROS via the hydroxyl groups of phenolic compounds, the chelation of transition metals such as Fe^{2+} and Cu^{2+}, and the breaking of lipid peroxidation chain reactions constitute the fundamental antioxidant mechanisms.

In cellular models, L. chinensis polyphenols have been shown to increase Nrf2 nuclear translocation; concurrently, HO-1, NQO1, and GCLC expression has been demonstrated to increase [24]. This molecular response provides significant protection against oxidative stress-induced cytotoxicity in hepatocytes. The preservation of mitochondrial membrane potential, suppression of cytochrome c release, and decreased caspase activation suggest that the cytoprotective effect occurs through the maintenance of mitochondrial integrity [25].

The anti-inflammatory effects of L. chinensis extracts are related to the inhibition of the NF-κB pathway. In experimental models, decreased COX-2 and iNOS expression and significant reductions in TNF-α and IL-6 levels have been reported [30]. Proanthocyanidins have been shown to attenuate TLR4-dependent signaling and modulate macrophage activation by suppressing MAPK (ERK, JNK, p38) pathways. The analgesic effect is thought to be secondary to decreased prostaglandin synthesis.

Experimental studies have shown that flavonoids increase permeability by disrupting bacterial membrane integrity and inhibit intracellular enzymatic targets [13]. The more pronounced effect observed against Gram-positive bacteria is explained by differences in cell wall structure. Findings regarding antiviral effects are largely in vitro; evidence exists that flavonoids can weaken viral entry and replication stages [27]. However, pharmacokinetic and bioavailability barriers must be overcome for these effects to translate into clinical significance.
The inhibition of α-glucosidase and α-amylase enzymes by L. chinensis extracts may contribute to the reduction of postprandial hyperglycemia [28]. Furthermore, the regulation of lipid metabolism via AMPK activation has been associated with improvements in triglyceride and LDL-cholesterol levels. Increased GLUT4 translocation in adipocytes and support for insulin signaling pathways are proposed as mechanisms that increase insulin sensitivity.

Therapeutıc Potentıal, Formulatıon Approaches, And Translatıonal Perspectıves

The conversion of extracts obtained from Litchi chinensis pericarp and seeds into nutraceutical and functional food products is of strategic importance in terms of the value-added utilization of food industry by-products [14]. The high polyphenol content and strong antioxidant capacity of the pericarp enable its evaluation as a sustainable source of bioactive compounds on an industrial scale. However, the limited stability and low bioavailability of polyphenols in the gastrointestinal tract are fundamental translational barriers that limit their clinical efficacy potential.

In this context, advanced formulation approaches such as microencapsulation techniques (spray drying, complex coacervation), phospholipid complexes (phytosome technology), and nanoemulsion systems are proposed to enhance the solubility, stability, and intestinal absorption of L. chinensis polyphenols [29]. It has been suggested that nano-carrier systems may increase systemic exposure by facilitating epithelial barrier passage; at the same time, targeted release profiles to the target tissue may allow biological effects to be achieved at lower doses. However, the long-term safety, biological distribution, and potential accumulation risks of nanoformulations should be carefully evaluated.

A major hurdle in moving this research from the lab to the real world is bioavailability. Right now, there is a significant "concentration gap": while many *in vitro* studies use polyphenol levels between 10–100 µM, these numbers simply don't match human biology. In reality, peak plasma concentrations of flavan-3-ols after oral intake are often less than 1 µM. Furthermore, anthocyanins are metabolized so rapidly that they have very low systemic availability, and high-molecular-weight proanthocyanidins struggle with even minimal intestinal absorption. This means that the impressive biological effects we see in a petri dish might not actually happen inside the human body under normal physiological conditions. It is highly likely that microbiota-mediated metabolism—how our gut bacteria break these compounds down—plays a much bigger role in their systemic activity than previously thought. Until we have solid pharmacokinetic data on absorption rates, metabolite profiles, tissue

distribution, and elimination kinetics, any clinical claims remain purely speculative.

Another critical issue from a clinical translation perspective is the standardization of extracts. Variability between batches in herbal preparations is influenced by numerous factors, such as harvest time, cultivation conditions, extraction method, and solvent type. Therefore, standardization based on specific marker compounds (e.g., total proanthocyanidin content or specific flavonoid profile) is essential for reliably establishing dose-response relationships in clinical studies [30]. Furthermore, pharmacokinetic studies to define bioavailability, metabolism, and elimination profiles are fundamental requirements for the interpretability of clinical efficacy data.

Since the regulation of nutraceutical products varies from country to country, regulatory compliance also poses a significant translational barrier to the marketing of L. chinensis-based preparations. Clinical claims must be scientifically supported, and efficacy and safety must be demonstrated through randomized controlled trials. In this context, well-designed intervention studies are needed in individuals with chronic disease risk profiles such as obesity, dyslipidemia, or prediabetes.

Safety, Toxıcıty, And Clınıcal Lımıtatıons

The consumption of L. chinensis aril (fruit pulp) as food is generally considered safe in the general population; however, toxicological data on the seeds and concentrated fractions are more limited. In particular, some seed-derived compounds have been reported to have hypoglycemic potential; incorrect or excessive consumption in the pediatric population may lead to severe hypoglycemia [31]. These cases indicate that the assumption of safety in traditional use may not apply to concentrated preparations.

Long-term toxicity studies, data on drug-plant interactions, and safety during pregnancy/lactation are insufficient. The potential inhibitory or inducing effects of polyphenols on cytochrome P450 enzymes may affect the pharmacokinetics of concomitantly used drugs. Therefore, caution is warranted, especially in patients using drugs with a narrow therapeutic range [32]. In preclinical toxicity studies, the effects of high-dose extracts on liver and kidney function parameters have shown heterogeneous results; this highlights the need for dose standardization and clear definition of the safety window.

The lychee fruit (especially the seed and aril parts) contains cyclopropyl amino acids found in nature, namely methylenecyclopropylglycine (MCPG) and hypoglycin A (HGA); these compounds can cause serious toxic effects on human metabolism, particularly in conditions of starvation or low glycogen reserves. MCPG and HGA inhibit key enzymes involved in fatty acid β-oxidation and gluconeogenesis pathways, causing disruptions in energy metabolism and impaired glucose synthesis. This metabolic blockage reduces the liver's capacity to replenish glucose; as a result, blood glucose levels can drop rapidly and severe hypoglycemia can develop. This effect is more pronounced in children with limited glycogen stores and in individuals with malnutrition. The toxic effects of methylenecyclopropylglycine and hypoglycin A have been associated with Jamaican vomiting sickness and similar clinical presentations and can lead to serious consequences such as neurological symptoms, convulsions, coma, and death by disrupting hepatic energy metabolism [33].

Epidemiological studies have linked seasonal acute toxic encephalopathy (AES) cases observed in areas with high lychee production, such as the Muzaffarpur region of India, to MCPG and HGA. In these cases (including 390 children in 2014), blood glucose levels were found to be significantly low (≤70 mg/dL), and HGA and MCPG metabolites were detected in the urine samples of the majority of cases; levels were markedly higher compared to controls. Litchi consumption and skipping dinner were reported to be statistically associated with AES. These data indicate a strong link between MCPG/HGA toxicity and hypoglycemic encephalopathy [34].

Furthermore, quantitative analysis studies have revealed that MCPG and HGA levels vary in the aril of different Litchi chinensis varieties; the presence of these toxins at levels of mg/kg in some varieties provides critical data for potential exposure and risk assessments [35].

Due to these biochemical risks, quantitative analyses of MCPG and HGA content, bioavailability studies, determination of safe consumption thresholds, and completion of validation processes for the removal of these toxins are required for the use of L. chinensis seed or aril fractions as functional foods or nutraceuticals. Special safety warnings and concentration limits should be established in formulations, particularly for pediatric, malnutrition-prone, and metabolically stressed populations.

Advanced delivery systems as microencapsulation, phytosomes, nanoemulsions may improve stability and intestinal absorption. Long-term safety of nanoformulations is not fully established and tissue accumulation risk remains insufficiently characterized. Regulatory approval will require robust toxicological and pharmacokinetic datasets.

The majority of the current evidence is based on in vitro and animal models. The paucity of human studies limits the clinical generalizability of the results. Furthermore, the use of different extraction protocols reduces the comparability between studies and complicates meta-analytic synthesis. This methodological heterogeneity represents a significant obstacle to drawing strong clinical conclusions regarding the therapeutic potential of L. chinensis [33].

Future Perspectıves And Research Gaps

Polyphenol-rich extracts obtained from the pericarp and seed of Litchi chinensis possess pleiotropic biological effects that can simultaneously modulate key signaling pathways associated with oxidative stress and inflammation (particularly Nrf2/ARE and NF-κB) and, in this respect, stand out as a candidate with high translational value for the development of functional food components and phytopharmaceutical products. The combined assessment of antioxidant, anti-inflammatory, metabolic regulatory, and cytoprotective effects suggests that this plant could provide a rational biological basis for the prevention or supportive treatment of chronic metabolic disorders such as obesity, insulin resistance, dyslipidemia, and non-alcoholic fatty liver disease. However, a significant portion of the current literature is limited to in vitro systems and animal models, and evidence regarding clinical efficacy is still insufficient. Therefore, to strengthen the clinical translation process, it is necessary to design randomized controlled clinical trials using chemically standardized extracts; to elucidate in detail the bioavailability, metabolic fate, and pharmacokinetic profiles of bioactive compounds; and to systematically evaluate long-term safety, tolerability, and potential drug–plant interactions [34,35]. Furthermore, elucidating the contribution of the polyphenol–gut microbiota interaction to systemic biological effects will enable the development of personalized nutraceutical strategies, thereby strengthening its transferability to clinical practice.

Conclusıon

Litchi chinensis possesses pleiotropic biological effects that can modulate molecular pathways associated with oxidative stress and inflammation (particularly the Nrf2/ARE and NF-κB axes) at multiple target levels, thanks to its rich phytochemical content, primarily consisting of polyphenols, anthocyanins, and saponins. These properties position the species as a candidate with high translational potential for the development of functional food components and phytopharmaceutical products. However, as the current evidence is largely based on preclinical models, clinical validity needs to be strengthened. To advance the clinical translation process, it is critical to conduct randomized controlled clinical trials using chemically standardized extracts, detailed pharmacokinetic evaluations, and long-term safety analyses. Litchi chinensis pericarp and

seed extracts exhibit mechanistically plausible antioxidant and anti-inflammatory effects mediated through modulation of Nrf2 and NF-κB signaling pathways in experimental systems. Nevertheless, current evidence is predominantly preclinical.

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DOI:10.31579/2637-8914/361

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