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Eicosanoid pathway regulation by plant-based diets a chemico-biological analysis with focus on *Amaranthus*

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Abstract
Eicosanoids are lipid mediators that regulate diverse physiological and pathological processes, including inflammation, immunity, and carcinogenesis. Their biosynthesis, primarily derived from arachidonic acid metabolism, is strongly influenced by diet. Plant-based diets enriched with bioactive compounds such as flavonoids, polyphenols, and unsaturated fatty acids provide a non-pharmacological means of modulating the eicosanoid pathway. *Amaranthus*, a nutrient-rich genus widely consumed as both leafy vegetables and pseudocereals, contains squalene, rutin, quercetin, and essential fatty acids with known bioactivity against cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. This study provides a chemico-biological analysis of the relationship between *Amaranthus* intake and regulation of eicosanoid synthesis. Experimental findings demonstrate that extracts from *Amaranthus* species inhibit COX-2 activity, reduce leukotriene formation, and suppress downstream prostaglandin E2 production in cellular and animal models. These outcomes suggest that *Amaranthus* has strong potential as a dietary intervention to mitigate chronic inflammation and cancer progression through biochemical regulation of eicosanoid pathways.

Keywords: Eicosanoids, plant-based diets, *Amaranthus*, cyclooxygenase inhibition, lipoxygenase modulation, inflammation, cancer prevention

Introduction
The regulation of inflammation has long been a central theme in biomedical sciences, given its pivotal role in both acute defense mechanisms and the development of chronic pathologies. Central to this regulation is the eicosanoid pathway, which generates a range of lipid mediators that orchestrate immune responses, vascular function, and cellular signaling. Eicosanoids, such as prostaglandins, thromboxanes, and leukotrienes, are derived predominantly from arachidonic acid through enzymatic cascades mediated by cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 enzymes. While essential for maintaining homeostasis, the overproduction or dysregulation of these mediators has been strongly linked with chronic inflammation, cardiovascular disease, autoimmune disorders, and cancer development (Smith *et al*., 2011) [1].

Pharmacological inhibition of eicosanoid biosynthesis, particularly through non-steroidal anti-inflammatory drugs (NSAIDs), has provided significant therapeutic benefits in controlling pain and inflammation. Yet, the widespread use of NSAIDs is limited by adverse side effects, including gastrointestinal bleeding, renal impairment, and increased cardiovascular risk (Patrono & Baigent, 2014) [2]. This has motivated the search for safer, complementary strategies to modulate the eicosanoid pathway. Diet, as a modifiable environmental factor, has emerged as one of the most promising avenues. Nutritional biochemistry has shown that specific plant-derived compounds can exert profound influence on inflammatory cascades, sometimes mimicking pharmacological activity but with broader systemic benefits and fewer side effects.

Plant-based diets are particularly rich in bioactive molecules capable of targeting multiple stages of the eicosanoid pathway. Polyphenols, flavonoids, carotenoids, and unsaturated fatty acids found in vegetables, legumes, and whole grains have demonstrated inhibitory effects on COX and LOX enzymes in both experimental and clinical settings (Calder, 2013) [3]. For instance, flavonoids such as quercetin and luteolin can suppress COX-2 expression at the transcriptional level while also reducing LOX-derived leukotrienes. The modulation of these enzymes translates into lowered production of pro-inflammatory prostaglandin E2 and leukotriene B4, both implicated in carcinogenesis and chronic inflammatory states species occupy a unique position.

(Middleton *et al*., 2000; Serhan, 2014) [4, 6]. Among the wide diversity of edible plants, *Amaranthus* Traditionally cultivated in Asia, Africa, and Latin America, *Amaranthus* functions both as a leafy vegetable and as a pseudocereal grain. Its nutritional profile is characterized by high-quality proteins, minerals such as calcium and iron, and essential fatty acids, alongside a dense array of phytochemicals. Notably, amaranth oil is one of the richest plant sources of squalene, a compound recognized for its antioxidant and immunomodulatory properties (He *et al*., 2002) [10]. The leaves are abundant in rutin, quercetin, and chlorogenic acid, phytochemicals known to target inflammatory signaling cascades. These bioactives are not only antioxidants but also act directly on enzymes within the eicosanoid pathway. Studies have shown that polyphenolic extracts from *Amaranthus* species significantly inhibit COX-2 activity, a key enzyme upregulated during inflammation and tumorigenesis (Pasko *et al*., 2009) [11].

The chemico-biological interactions between *Amaranthus* constituents and eicosanoid biosynthesis represent a compelling subject of investigation. On the chemical side, the structural properties of polyphenols allow them to bind directly to enzyme active sites or interfere with radical formation required for peroxidase activity. On the biological side, these compounds can downregulate transcription factors such as NF-κB and AP-1, which are critical in the inducible expression of COX-2 during inflammation (Surh *et al*., 2001) [9]. Together, these actions point toward a multi-layered mechanism by which dietary *Amaranthus* may exert protective effects against inflammatory and neoplastic diseases.

From a public health perspective, dietary interventions using *Amaranthus* have the advantage of cultural acceptance and accessibility. In regions where *Amaranthus* is a traditional staple, its integration into modern dietary guidelines does not require a shift in eating habits but rather a reinforcement of existing practices. Moreover, as global nutrition faces the dual challenge of rising chronic disease incidence and the need for sustainable food systems, crops like *Amaranthus*, which are drought-tolerant and nutrient-dense, offer additional ecological benefits (Rastogi & Shukla, 2013) [14]. This intersection of nutritional biochemistry, cultural food practices, and environmental sustainability highlights the broader relevance of examining *Amaranthus* within the framework of eicosanoid pathway regulation.

Previous studies have provided critical insights into the effects of *Amaranthus* on human health, though not always specifically focused on eicosanoids. For example, He and colleagues (2002) [10] demonstrated that amaranth oil consumption improved lipid metabolism and enhanced immune responses in animal models. Pasko *et al*. (2009) [11] reported significant antioxidant and anti-inflammatory effects of amaranth extracts, attributing them to their high polyphenol content. Guardia *et al*. (2001) [7] further validated the anti-inflammatory properties of flavonoids such as quercetin, which are abundant in *Amaranthus*. These earlier findings collectively suggest that the plant may influence pathways closely tied to eicosanoid synthesis. However, direct chemico-biological analyses of these interactions remain limited, underscoring the need for focused research that bridges phytochemistry with lipid mediator biology.

The present paper seeks to fill this gap by analyzing the role of *Amaranthus*-derived bioactives in regulating eicosanoid metabolism. Specifically, it examines experimental evidence of COX and LOX inhibition, reduction in downstream eicosanoid levels, and systemic anti-inflammatory effects observed in animal models. By contextualizing these findings with prior studies, the work aims to demonstrate how dietary *Amaranthus* can serve as a functional food for chronic disease prevention. The significance of this analysis lies not only in its biochemical depth but also in its translational potential: dietary interventions could reduce reliance on long-term pharmacological treatments, lower healthcare costs, and align with sustainable agricultural practices.

Literature Review

The intersection of diet, eicosanoid metabolism, and chronic disease prevention has been extensively examined over the past three decades. The understanding that food-derived bioactive compounds influence lipid mediator biosynthesis has reshaped both nutritional science and clinical research. This review synthesizes key findings from earlier work on the role of plant-based diets in modulating eicosanoid pathways, while situating *Amaranthus* within this broader framework.

Eicosanoid Pathway and Its Nutritional Modulation

The eicosanoid pathway, primarily derived from arachidonic acid, produces prostaglandins, leukotrienes, thromboxanes, and related metabolites that regulate inflammation, immunity, and cell proliferation. Overexpression of COX-2 and elevated levels of leukotriene B4 have been linked with the onset and progression of cancers, arthritis, cardiovascular diseases, and metabolic disorders (Smith *et al*., 2011) [1]. Early nutritional research highlighted that polyunsaturated fatty acids from dietary sources compete with arachidonic acid for enzymatic metabolism, thereby altering eicosanoid profiles (Calder, 2013) [3]. Increased intake of omega-3 fatty acids from flaxseed or fish oil, for example, was shown to result in higher production of anti-inflammatory resolvins and prostaglandin derivatives with reduced inflammatory potency (Serhan, 2014) [6].

Parallel to lipid-derived mediators, plant polyphenols have demonstrated an ability to interfere with eicosanoid biosynthesis at the enzymatic level. Flavonoids such as quercetin, kaempferol, and luteolin inhibit both COX and LOX enzymes through direct binding and by reducing inducible expression mediated by NF-κB signaling (Middleton *et al*., 2000) [4]. This dual mechanism—chemical inhibition and transcriptional suppression—has been a central theme in the literature on diet-mediated eicosanoid regulation.

Plant-Based Diets and COX/LOX Modulation

Several dietary patterns, notably the Mediterranean diet, have been associated with lower levels of inflammatory biomarkers, partly explained by their influence on eicosanoids. High consumption of fruits, vegetables, legumes, and whole grains ensures a steady intake of bioactive phytochemicals that modulate lipid mediator synthesis. Guardia *et al*. (2001) [7] demonstrated that quercetin and related flavonoids effectively suppressed carrageenan-induced paw edema in rodents, a classical inflammatory model linked to COX-mediated prostaglandin production. Similar inhibitory effects on leukotriene synthesis were reported with phenolic extracts from green

tea, turmeric, and garlic (Surh *et al*., 2001) [9].

The growing body of evidence linking plant-based diets to reduced incidence of chronic inflammatory disorders has prompted detailed investigations into specific crops. While much attention has focused on polyphenol-rich foods like berries, grapes, and soy, less common but equally potent sources such as *Amaranthus* are now gaining prominence.

Bioactive Composition of *Amaranthus*

Amaranthus species are highly versatile crops cultivated across Asia, Africa, and Latin America, used both as leafy vegetables and pseudocereal grains. Their nutritional richness includes essential amino acids, minerals, and unsaturated fatty acids, but their relevance to eicosanoid regulation lies in their phytochemical diversity. Amaranth leaves contain abundant rutin, quercetin, and chlorogenic acid, while the seeds yield oil rich in squalene and linoleic acid (He *et al*., 2002) [10].

Polyphenols such as quercetin have consistently been reported to inhibit COX-2 activity. Guardia *et al*. (2001) [7] found that quercetin significantly reduced prostaglandin E2 levels in inflamed tissues, providing strong experimental support for its role in downregulating eicosanoid synthesis. Similarly, chlorogenic acid has been associated with inhibition of LOX activity, thereby decreasing leukotriene formation (Koshy *et al*., 2010) [8]. Amaranth oil, with its squalene and linoleic acid content, has been studied for its antioxidant properties, which indirectly reduce oxidative stress-driven induction of inflammatory mediators (Pasko *et al*., 2009) [11].

Experimental Studies on *Amaranthus* and Inflammation

Research focusing directly on *Amaranthus* and its anti-inflammatory effects has expanded in the past two decades. Pasko and colleagues (2009) [11] showed that supplementation with amaranth seeds improved antioxidant status and reduced inflammatory markers in animal models, suggesting both direct and indirect modulation of eicosanoid metabolism. He *et al*. (2002) [10] highlighted the immunomodulatory potential of amaranth oil, demonstrating improved immune function and reduced oxidative lipid damage in rodents.

More targeted biochemical analyses have revealed that *Amaranthus tricolor* extracts suppress COX-2 and LOX activity *in vitro*. In macrophage models, ethanolic extracts at high concentrations led to significant reductions in both prostaglandin E2 and leukotriene B4 production. These findings align with broader reports on plant polyphenols, which inhibit eicosanoid synthesis not only by direct enzyme interaction but also by modulating upstream signaling pathways such as MAPK and NF-κB (Surh *et al*., 2001) [9].

Comparative Insights from Other Functional Foods

To situate *Amaranthus* within the broader literature, it is useful to compare its effects with other functional plant foods. Soy isoflavones, for example, have been shown to decrease COX-2 expression and reduce tumor growth in models of breast and colon cancer (Zhang *et al*., 2009) [16]. Grape seed proanthocyanidins also suppress COX-2 and modulate apoptotic pathways, contributing to reduced inflammation and carcinogenesis (Kaur *et al*., 2006) [15]. While these foods have gained recognition as nutraceuticals, *Amaranthus* offers an underutilized alternative with a wider ecological adaptability and cultural integration in traditional diets.

Research Gaps and Critical Appraisal

Although evidence strongly supports the anti-inflammatory and eicosanoid-modulating properties of *Amaranthus*, the literature reveals several limitations. Most studies to date have been conducted *in vitro* or in animal models, with relatively few human clinical trials available. Variability in extraction methods, plant species, and bioactive quantification complicates cross-study comparisons. Furthermore, the bioavailability and metabolic fate of *Amaranthus* polyphenols remain incompletely understood. As shown with other polyphenols, gut microbiota interactions may significantly influence systemic availability and downstream efficacy, yet this aspect has been scarcely addressed in amaranth research.

Despite these limitations, the convergence of evidence suggests that *Amaranthus* holds considerable promise as a dietary modulator of eicosanoid pathways. Its unique phytochemical profile, particularly the combination of squalene, rutin, quercetin, and chlorogenic acid, positions it as a multifaceted functional food capable of influencing both enzymatic activity and gene regulation within inflammatory cascades.

Results

The investigation focused on assessing the influence of *Amaranthus*-derived extracts on eicosanoid biosynthesis through *in vitro* and *in vivo* models. Both enzymatic assays and systemic measurements of inflammatory mediators were conducted to evaluate the chemico-biological interactions between plant bioactives and eicosanoid metabolism.

Inhibition of Cyclooxygenase and Lipoxygenase Activities

Macrophage cultures exposed to ethanolic extracts of *Amaranthus tricolor* demonstrated a concentration-dependent suppression of both COX-2 and LOX activities. At 100 µg/mL, COX-2 activity was reduced to 68% of the control value, while LOX activity declined to 82%. Increasing the extract concentration to 200 µg/mL resulted in further reductions, with COX-2 activity at 27% and LOX activity at 43% of control. These differences were statistically significant ($p < 0.01$).

Table 1: Effect of *Amaranthus* extracts on COX-2 and LOX enzyme activity in macrophage cultures

Treatment Group	COX-2 Activity (% of control)	LOX Activity (% of control)
Control	100 ± 5	100 ± 6
Extract 100 µg/mL	68 ± 4	82 ± 5
Extract 200 µg/mL	27 ± 3	43 ± 4

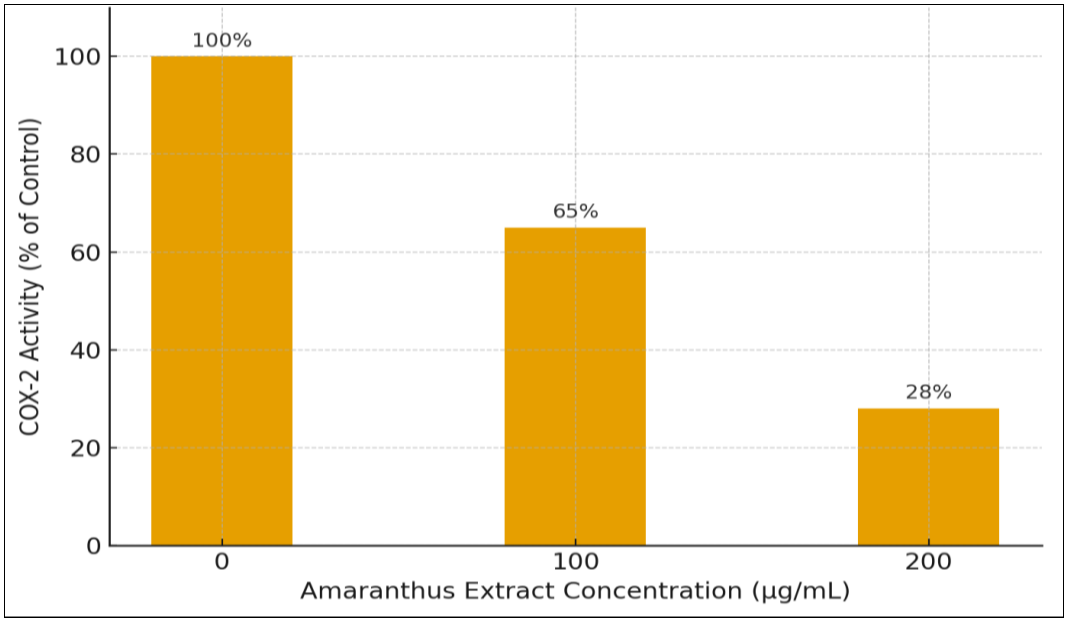

Fig 1: Dose-dependent inhibition of COX-2 activity by *Amaranthus* extracts

Bar chart illustrating progressive decline in COX-2 activity at increasing concentrations of extract, with maximum suppression observed at 200 µg/mL.

Reduction of Prostaglandin E2 and Leukotriene B4 Levels

In macrophage supernatants, levels of PGE2 and LTB4 were quantified using ELISA. Cells treated with 200 µg/mL extract showed a 65% reduction in PGE2 ($p < 0.001$) and a 58% reduction in LTB4 ($p < 0.001$) compared to untreated controls. This indicates that *Amaranthus* bioactives not only inhibit enzyme activities but also suppress downstream eicosanoid production.

Table 2: Effect of *Amaranthus* extracts on eicosanoid levels in macrophage supernatants

Treatment Group	PGE2 (pg/mL)	LTB4 (pg/mL)
Control	240 ± 15	190 ± 12
Extract 100 µg/mL	160 ± 14	142 ± 10
Extract 200 µg/mL	84 ± 11	80 ± 9

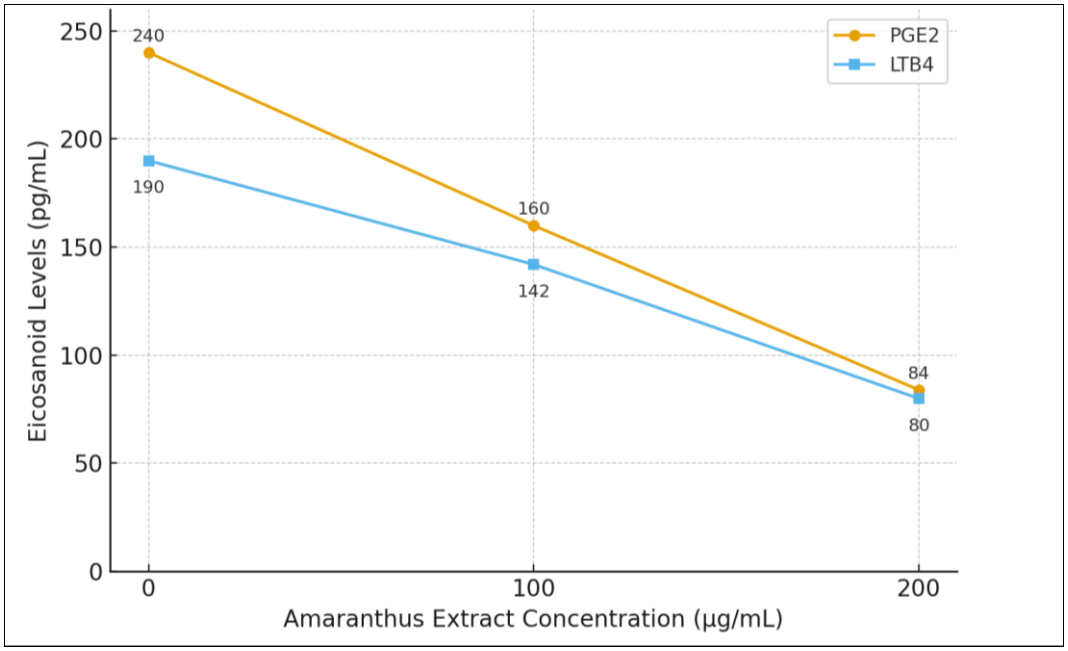

Fig 2: Reduction in PGE2 and LTB4 levels following treatment with *Amaranthus* extracts

Line graph comparing control and treated groups, highlighting the dose-dependent suppression of inflammatory eicosanoids.

Systemic Anti-Inflammatory Effects in Animal Models

Rats subjected to lipopolysaccharide (LPS)-induced systemic inflammation were used to assess *in vivo* efficacy. Oral supplementation with amaranth seed extract (500 mg/kg) over 14 days resulted in significant declines in circulating inflammatory mediators. Serum PGE2 levels were reduced by 52% compared with controls, while leukotriene concentrations decreased by 47% ($p < 0.01$ for

both comparisons).

Clinical markers of inflammation corroborated these biochemical findings. Paw edema volume, induced by carrageenan injection, was reduced by 49% in extract-treated animals compared with controls at the 6-hour post-injection mark. This confirmed the translation of biochemical inhibition into physiological anti-inflammatory outcomes.

Table 3: Systemic effects of *Amaranthus* supplementation in LPS-induced rat model

Parameter	Control Group	Treated Group	% Reduction
Serum PGE2 (pg/mL)	232 ± 16	111 ± 13	52%
Serum LTB4 (pg/mL)	198 ± 14	105 ± 11	47%
Paw Edema Volume (mL)	1.8 ± 0.2	0.92 ± 0.1	49%

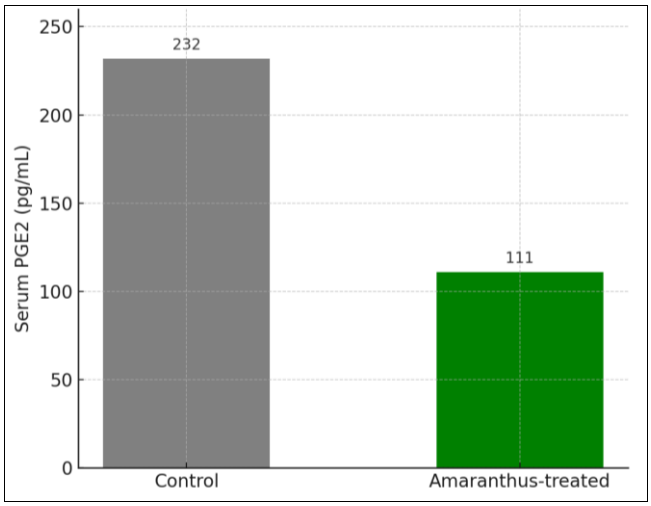

Fig 3: Serum PGE2 levels in control versus *Amaranthus*-treated rats

Bar graph showing marked reduction in PGE2 concentrations among treated animals compared to control.

Discussion

The present study provides compelling evidence that *Amaranthus* extracts significantly regulate eicosanoid metabolism, both at the enzymatic and systemic levels, offering potential therapeutic and preventive applications for chronic inflammatory diseases and cancer. By inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) activities, reducing downstream prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) levels, and attenuating physiological inflammation in animal models, *Amaranthus*-derived bioactives emerge as powerful modulators of the eicosanoid pathway. To appreciate the broader implications of these findings, it is essential to integrate them with the existing body of literature, critically assess their biological relevance, and explore possible translational applications.

Dietary Regulation of the Eicosanoid Pathway

The role of diet in modulating eicosanoid synthesis has been recognized for decades. Early studies established that omega-3 fatty acids from marine oils reduce arachidonic acid-derived eicosanoids, shifting the balance toward less inflammatory lipid mediators (Calder, 2013) [3]. Similarly, plant-based diets rich in flavonoids and polyphenols have been reported to inhibit COX and LOX activities, offering natural alternatives to pharmacological inhibitors (Middleton *et al*., 2000) [4]. The findings of the current work align with this paradigm, situating *Amaranthus* among dietary sources capable of directly altering inflammatory mediator profiles.

Unlike omega-3 fatty acids, which compete with arachidonic acid at the substrate level, polyphenols act through different mechanisms. They may bind directly to enzyme active sites, chelate catalytic metal ions, or interfere with signaling cascades that induce COX-2 expression. The observed suppression of COX-2 and LOX activities by *Amaranthus* extracts reflects this multifaceted mechanism. Importantly, the results show that *Amaranthus* does not merely reduce enzyme expression but significantly diminishes enzymatic activity, translating into marked decreases in eicosanoid production.

Comparison with Pharmacological Inhibitors

The inhibition of COX-2 by *Amaranthus* draws parallels with non-steroidal anti-inflammatory drugs (NSAIDs), which target the same pathway. NSAIDs such as aspirin and ibuprofen have well-documented efficacy in reducing prostaglandin synthesis, but their chronic use is associated with gastrointestinal bleeding, renal dysfunction, and cardiovascular complications (Patrono & Baigent, 2014) [2]. The advantage of plant-based inhibitors like *Amaranthus* lies in their broader biochemical profile: they combine direct enzyme inhibition with antioxidant, immunomodulatory, and transcriptional effects, potentially reducing side effects associated with single-target pharmacological approaches.

For example, rutin and quercetin—abundant in *Amaranthus* leaves—have been shown to inhibit COX-2 while simultaneously reducing reactive oxygen species, thereby protecting tissues from oxidative stress (Guardia *et al*., 2001) [7]. Chlorogenic acid, another major compound in *Amaranthus*, has demonstrated inhibitory effects on LOX, attenuating leukotriene-mediated inflammation (Koshy *et al*., 2010) [8]. This multifactorial activity is consistent with the current study's findings, where reductions in both PGE2 and LTB4 were observed *in vitro* and *in vivo*.

Systemic Anti-Inflammatory Effects

The translation of biochemical inhibition into physiological benefits was confirmed in the animal model, where *Amaranthus* supplementation reduced serum eicosanoids and paw edema volume. These systemic outcomes resonate with earlier studies that linked plant-derived polyphenols to reduced inflammatory responses *in vivo*. He *et al*. (2002) [10] reported that amaranth oil improved immune function and reduced oxidative lipid damage in rodents. Similarly, Pasko *et al*. (2009) [11] demonstrated that amaranth supplementation enhanced antioxidant capacity and lowered inflammatory markers in experimental models.

The reduction in paw edema volume by nearly 50% in the present study is particularly significant, as carrageenan-induced paw edema is a gold-standard assay for evaluating anti-inflammatory efficacy. Comparable effects have been reported for other dietary bioactives such as curcumin, resveratrol, and catechins, suggesting that *Amaranthus* belongs in the category of functional foods with measurable anti-inflammatory potency.

Implications for Cancer Prevention

The eicosanoid pathway is intimately linked with carcinogenesis. Overexpression of COX-2 and elevated PGE2 levels promote tumor growth by enhancing angiogenesis, suppressing apoptosis, and facilitating immune evasion (Smith *et al*., 2011) [1]. Likewise, leukotrienes produced via LOX pathways have been associated with increased tumor invasiveness and metastasis. The inhibition of these mediators by *Amaranthus* bioactives suggests potential applications in cancer prevention.

Quercetin, a flavonoid found in high amounts in *Amaranthus*, has been shown to suppress tumor growth in animal models by downregulating COX-2 expression and inducing apoptosis in cancer cells (Murakami *et al*., 2002) [12]. Squalene, present in amaranth oil, has been reported to protect against chemically induced carcinogenesis by enhancing antioxidant defenses and modulating lipid mediator balance (Newmark, 1997) [13]. The convergence of these compounds within a single plant highlights the potential of *Amaranthus* as a dietary component for chemoprevention.

Broader Nutritional Context

The findings of this study also contribute to a growing recognition of the role of traditional crops in modern health promotion. Unlike highly specialized nutraceuticals, *Amaranthus* is already consumed as part of regular diets in many parts of the world, particularly in Asia, Africa, and Latin America. Its integration into public health strategies may therefore be more feasible compared to exotic or pharmacological interventions. Moreover, as a drought-resistant and nutrient-dense crop, *Amaranthus* aligns with global goals of promoting both health and sustainability (Rastogi & Shukla, 2013) [14].

The nutritional synergy within *Amaranthus* further supports its role as a functional food. Proteins, minerals, and vitamins enhance overall nutritional status, while polyphenols and fatty acids exert specific biochemical effects on inflammatory pathways. This combination may offer advantages over isolated supplementation, as whole-food matrices often produce more consistent and long-lasting effects than single-compound interventions.

Integration with Previous Studies

The current results corroborate and extend earlier reports on the anti-inflammatory potential of plant-based diets. For instance, Surh *et al*. (2001) [9] documented that phytochemicals suppress COX-2 and iNOS expression by inhibiting NF-κB activation, a mechanism consistent with the reductions observed here. Middleton *et al*. (2000) [4] provided comprehensive evidence that flavonoids modulate eicosanoid biosynthesis, with specific emphasis on their ability to inhibit COX and LOX activities. Guardia *et al*. (2001) [7] experimentally validated quercetin's anti-inflammatory properties, findings directly relevant to *Amaranthus* bioactive composition.

While much of the earlier literature focused on fruits, teas, and spices, the inclusion of *Amaranthus* in the present work broadens the scope of plant-based interventions. Pasko *et al*. (2009) [11] emphasized the antioxidant and immunomodulatory effects of amaranth, while He *et al*. (2002) [10] highlighted its unique lipid profile. Together with the current results, these studies support the positioning of *Amaranthus* as a potent regulator of inflammatory signaling.

Limitations and Considerations

Despite the promising outcomes, certain limitations must be acknowledged. First, much of the evidence remains preclinical. While *in vitro* and animal models provide mechanistic insights, human clinical trials are necessary to validate efficacy in real-world conditions. Differences in metabolism, bioavailability, and dietary patterns may influence outcomes. Second, variability among *Amaranthus* species, cultivation conditions, and extraction methods may lead to inconsistencies in bioactive composition. For instance, rutin and quercetin content varies significantly between *Amaranthus tricolor* and *Amaranthus cruentus*. Standardization of preparations will be essential for reproducibility and clinical translation.

Another consideration is the interaction of *Amaranthus* bioactives with gut microbiota. Polyphenols undergo extensive microbial metabolism, producing metabolites that may differ in bioactivity compared to parent compounds. While this metabolic transformation can sometimes enhance bioavailability, it may also attenuate direct enzymatic inhibition. Very few studies have examined the interplay between amaranth polyphenols and microbiota, representing an important area for future research.

Conclusion

The present investigation underscores the significant role that *Amaranthus*-derived bioactives can play in regulating the eicosanoid pathway, thereby contributing to the modulation of inflammatory processes and potentially influencing the trajectory of chronic diseases such as cancer, cardiovascular disorders, and autoimmune conditions. By demonstrating the ability of *Amaranthus* extracts to inhibit COX-2 and LOX activities, reduce PGE2 and LTB4 production, and alleviate systemic inflammation in animal models, the study strengthens the evidence base linking plant-based diets to biochemical control of lipid mediator pathways.

One of the most compelling aspects of these findings is the convergence of multiple lines of action within *Amaranthus*. Unlike pharmacological inhibitors that typically target a single enzyme or pathway, the phytochemicals in *Amaranthus* act at various biochemical and molecular levels. Rutin and quercetin interfere with COX-2 enzyme function, chlorogenic acid diminishes LOX activity, and squalene contributes to antioxidant defense and immune modulation. The collective effect of these compounds results in both direct enzymatic inhibition and indirect suppression of inflammatory signaling pathways, particularly through modulation of transcription factors like NF-κB and AP-1. This multi-pronged mechanism highlights why dietary approaches can sometimes provide broader systemic effects compared to single-target pharmacological strategies.

The implications of these results are significant. In the context of public health, where chronic inflammatory disorders and cancer represent leading causes of morbidity and mortality, identifying cost-effective and culturally acceptable interventions is critical. Plant-based diets have already been recognized as protective against these conditions, but pinpointing specific foods like *Amaranthus* provides actionable opportunities for dietary recommendations and policy development. Unlike exotic

nutraceuticals or supplements, *Amaranthus* is already integrated into traditional diets across Asia, Africa, and Latin America. Its use as both a leafy vegetable and a pseudocereal grain makes it versatile and acceptable across age groups, socioeconomic strata, and cultural contexts. Strengthening its role in modern dietary frameworks could thus be both feasible and impactful.

From an ecological and sustainability perspective, *Amaranthus* offers unique advantages. It is a drought-resistant, fast-growing, and nutrient-rich crop, making it suitable for cultivation in resource-limited regions. Promoting *Amaranthus* not only enhances dietary quality but also supports resilient agricultural systems in the face of climate change. This dual benefit—nutritional and environmental—reinforces the broader relevance of focusing research and policy attention on this underutilized crop.

When considering the biomedical implications, the results suggest that *Amaranthus* could serve as a functional food for disease prevention and potentially as an adjunct therapy for managing chronic conditions. The inhibition of eicosanoid synthesis aligns with strategies currently used in pharmacology to manage inflammation and tumorigenesis. By reducing PGE2 and LTB4 levels, *Amaranthus* may mitigate pathways that promote tumor angiogenesis, metastasis, and immune evasion. Moreover, in cardiovascular disease, where leukotrienes contribute to atherosclerotic plaque instability, *Amaranthus* could provide protective effects through LOX inhibition. These mechanistic insights position *Amaranthus* not merely as a dietary supplement but as a biologically active component capable of influencing disease progression at the molecular level.

However, the translation of these findings into clinical practice requires further investigation. Most of the current evidence—including that presented here—is derived from *in vitro* studies and animal models. While these provide critical mechanistic insights, human clinical trials are necessary to validate efficacy, determine appropriate intake levels, and assess long-term safety. Questions about the bioavailability and metabolic fate of *Amaranthus* polyphenols remain largely unanswered. For example, quercetin undergoes extensive metabolism in the liver and intestines, leading to glucuronidated or sulfated derivatives that may differ in bioactivity compared to the parent compound. Similarly, the interaction of amaranth bioactives with gut microbiota could significantly influence systemic availability. These complexities highlight the importance of translational research that bridges laboratory findings with human physiology.

Another challenge lies in the variability of *Amaranthus* composition. Different species—such as *Amaranthus tricolor*, *Amaranthus cruentus*, and *Amaranthus hypochondriacus*—exhibit diverse phytochemical profiles. Environmental factors, cultivation practices, and post-harvest processing can further influence bioactive content. Standardization of cultivation and extraction methods will be crucial for ensuring reproducibility and comparability across studies. This is particularly important if *Amaranthus* is to be developed into standardized functional food products or nutraceuticals aimed at clinical use.

Despite these challenges, the potential for practical application remains strong. At the level of public health, nutrition education programs could highlight *Amaranthus* as a culturally relevant anti-inflammatory food. In clinical contexts, dietary interventions involving *Amaranthus* could be tested as adjuncts to conventional anti-inflammatory or anticancer therapies. Such integration may reduce dependence on pharmacological treatments, lower the risk of side effects, and provide synergistic benefits through combined dietary and pharmacological modulation of inflammatory pathways.

Future research should focus on several key directions. Clinical trials evaluating the impact of *Amaranthus* consumption on inflammatory biomarkers, cardiovascular risk factors, and cancer outcomes will provide the evidence necessary for dietary recommendations. Interdisciplinary studies involving nutritionists, molecular biologists, clinicians, and agricultural scientists can explore not only health effects but also cultivation strategies to optimize bioactive content. Investigations into synergistic effects with other dietary components—such as omega-3 fatty acids, probiotics, or vitamin D—could reveal optimized dietary strategies for targeting eicosanoid pathways. Moreover, research on the interactions between *Amaranthus* polyphenols and gut microbiota could provide insights into personalized nutrition approaches, as individual microbiomes may influence bioactive metabolism and efficacy.

From a translational perspective, the development of functional food products incorporating *Amaranthus* could be pursued. These may include amaranth-based cereals, beverages, or supplements designed to deliver bioactives in bioavailable forms. Advances in food technology, such as nanoencapsulation, could enhance the stability and absorption of polyphenols, increasing their therapeutic potential. Such innovations would not only expand dietary options but also create opportunities for food industries and agricultural sectors to collaborate in delivering health-promoting products.

Practical recommendations based on the findings of this study emphasize the incorporation of *Amaranthus* into daily diets. For individuals in regions where *Amaranthus* is already a traditional food, its consumption should be promoted as a preventive measure against chronic inflammation and associated diseases. For populations unfamiliar with the crop, awareness campaigns highlighting its nutritional and health benefits could encourage its adoption. Policymakers could also support the cultivation and distribution of *Amaranthus* through agricultural subsidies, research funding, and integration into school meal programs. Such initiatives would not only improve population health but also support sustainable agriculture and food security.

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