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The impact of *Amaranthus* diet on eicosanoid Profiles: Exploring the role in cancer treatment through cyclooxygenase (COX) and Lipoxygenase (LOX) pathways: A mini-review

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Abstract
Scientists worldwide have made significant progress in identifying various beneficial substances found in plants, known as nutraceuticals and phytochemicals, which can enhance the effectiveness of chemotherapy by inhibiting cell signaling mechanisms associated with chemo-resistance. However, there is a lack of research regarding the potential anticancer and chemo-preventative properties of numerous naturally occurring agents derived from *Amaranthus* plants, including nutraceuticals and phytochemicals. This mini-review aims to provide an up-to-date overview of the effects of an *Amaranthus*-based diet on the eicosanoid profiles of cyclooxygenase and lipoxygenase pathways for cancer treatment. Our research uncovered several promising agents isolated from amaranth plants, such as quercetin, rutin, apigenin, squalene, and certain phytosterols like spinasterol, which have demonstrated notable anticancer and anti-inflammatory properties. Furthermore, existing literature indicates that these nutraceuticals can effectively inhibit the biosynthesis of COX and LOX enzymes, consequently suppressing the production of eicosanoids such as prostaglandins, prostacyclin, and leukotrienes. Hence, the nutraceuticals and phytochemicals derived from amaranth plants have the potential to serve as valuable adjunctive therapies, enhancing the efficacy of existing chemotherapy as clinically beneficial anticancer chemosensitizers.

Keywords: Antiproliferation, *Amaranthus*, cancer, anticancer, eicosanoids, cyclooxygenase and Lipoxygenase

1. Introduction
Cancer remains a leading cause of death worldwide, accounting for approximately 10 million annual fatalities, or nearly one in six deaths (World Health Organization, 2022) [1]. The development of cancer involves the resistance of specific blood cells to growth-inhibitory signals, evasion of cell death, unlimited proliferation, angiogenesis, and tissue infiltration. Common therapeutic approaches for cancer management include surgery, radiotherapy, and systemic treatments such as chemotherapy, hormonal therapies, and targeted biological therapies (de Martel *et al*., 2018) [2]. However, these treatments often exhibit significant toxicity and side effects. To address these challenges, there is a critical need for the research and development of innovative cancer drugs that can selectively and effectively eliminate tumor cells while minimizing harm. In this context, the pharmaceutical industry is actively exploring the potential of specific peptides that possess precise and complex mechanisms to target and destroy cancerous cells. Small peptides offer attractive characteristics, including strong affinity, excellent selectivity, non-toxicity, defined spatial configuration within tissues, and rapid clearance from non-target cells and blood circulation. The discovery and modification of anticancer peptides are crucial in the ongoing fight against cancer. In recent years, nutraceuticals and phytochemicals have gained recognition in the biomedical industry due to their safety, cost-effectiveness, and ability to target multiple pathways associated with chemoresistance. Medicinal plants harbor various chemical constituents that exhibit natural antioxidant properties, either individually or in combination. Identifying and characterizing active compounds within plants hold promise for developing practical cancer prevention therapies.

Additionally, research has shown that consuming a diet rich in vegetables, fruits, and other plant-based products can reduce the risk of cancer and inflammatory conditions. Significant research has been conducted on the effects of dietary phytochemicals on gene expression and signaling pathways in relation to cancer. Additionally, the exploration of their impact on the epigenome of mammals is an actively developing field of study. *Amaranthus* spp, a plant with multiple bioactive compounds, represents a potential novel therapeutic option amidst the limited available treatment choices. *Amaranthus* is known for its abundance in lycopene, soluble peptides, polyphenols, proteins, unsaturated fatty acids, flavonoids, betalains, squalene, glucosinolates, betacarotene, and phenolic acids (Jimoh *et al.*, 2019) [3]. Notably, betalains found in amaranth plants have demonstrated a significant role in cancer treatment.

This short communication aims to provide recent insights into the role of an *Amaranthus*-based diet in anticancer strategies and the impact of its phyto compounds on eicosanoid profiles, specifically the Cyclooxygenase (COX) and Lipoxygenase (LOX) pathways, in the treatment of cancer.

2. An overview on the nutritional attributes, phytochemical composition, and health benefits of *Amaranthus*

2.1 Nutritional Attributes

The *Amaranthus* genus has garnered considerable attention due to its rich nutritional value, whether as leafy vegetables, grains, or ornamental plants (Lakshmi and Vimala, 2000; Manyelo *et al.*, 2020; Ruth *et al.*, 2021) [4-6]. It is a fast-growing crop with low production costs, making it one of the most affordable green vegetables or grains in tropical regions (Shukla *et al.*, 2016) [7]. Amaranth grains have been recognized for their significance as food and feed since 6700 BC, with numerous countries, including Africa, India, China, Southeast Asia, Mexico, and North and South America, acknowledging their importance (Shukla *et al.*, 2016) [7]. Amaranth can thrive under various soil and agro-climatic conditions, and certain species even grow in the wild (Katiyar *et al.*, 2000) [8]. It exhibits resistance to heat, drought, and major diseases (Nsimba *et al.*, 2008) [9]. The leaves of amaranth contain approximately 17.5% to 30.3% dry matter, primarily composed of protein, including 5% lysine, which makes it a highly desirable protein source (Oliveira and De Carvalho, 1975; Pedersen *et al.*, 1990) [10, 11]. Furthermore, it is rich in vitamins A and C, further enhancing its appeal as a food crop (Písaříková *et al.*, 2005) [12]. Amaranth's secondary metabolites include phenolic compounds known for their antioxidant properties, which are present in the leaves and other aerial parts of the plant. Additionally, amaranth is known to contain bioactive peptides and lunasin-like peptides, which are believed to possess properties such as anti-allergic, antioxidant, antihypertensive, and anticancer effects (Wolosik and Markowska, 2019) [13] (Figure 1). Both the seeds and leaves of amaranth are renowned for their use as herbal remedies and offer valuable nutraceutical benefits.

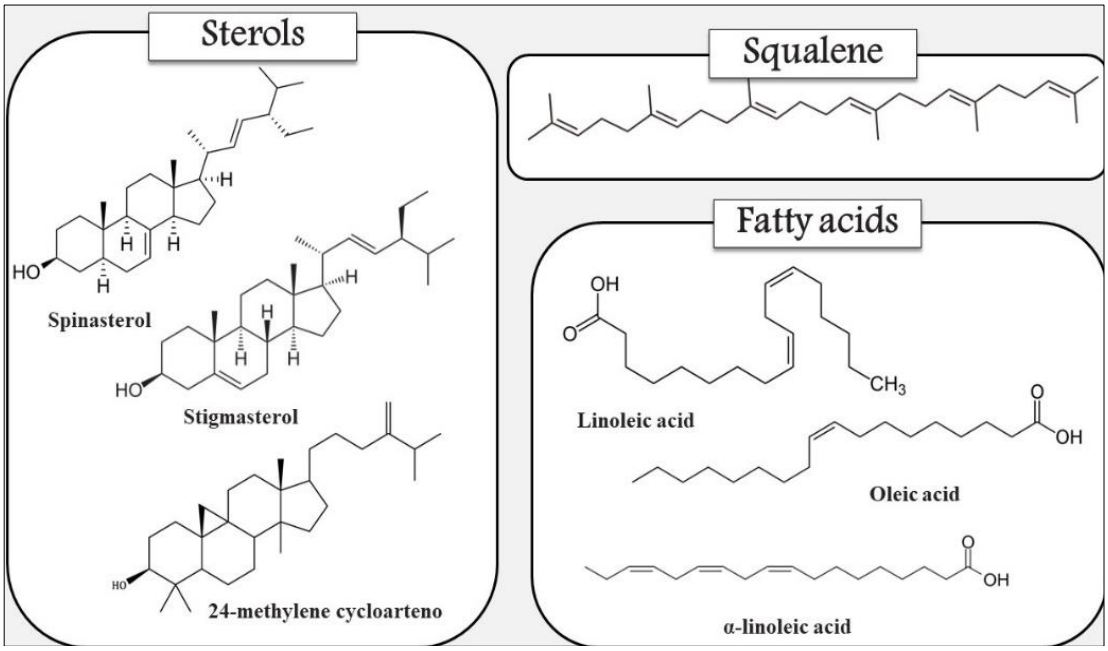

Fig 1: Principal non-phenolic nutraceuticals identified in Amaranth species.

2.2 Phytochemical composition

Preliminary phytochemical investigations have revealed the presence of flavonoids, saponins, and tannins in *Amaranthus* leaf extract, many of which are known for their antitumor properties (Kintzios, 2006) [14]. Among the nine identified flavonoids, naringenin, apigenin, catechin, and myricetin were newly reported in drought-tolerant vegetable amaranth (Figure 2). Amaranth grain has been found to be a rich source of various phenolic acids, including caffeic acid, hydroxybenzoic acid, protocatechuic acid, and ferulic acid (Alvarez-Jubete *et al.*, 2010, 2009) [15, 16]. Additionally, polyphenolic compounds such as rutin, nicotiflorin, and isoquercetin have been identified in amaranth grain (Pashikanti *et al.*, 2010) [17]. Recent reports have highlighted that amaranth contains substantial amounts of bioactive components, including polyphenols, L-ascorbic acid, beta-carotene, anthocyanins, and lutein (Das, 2016) [18].

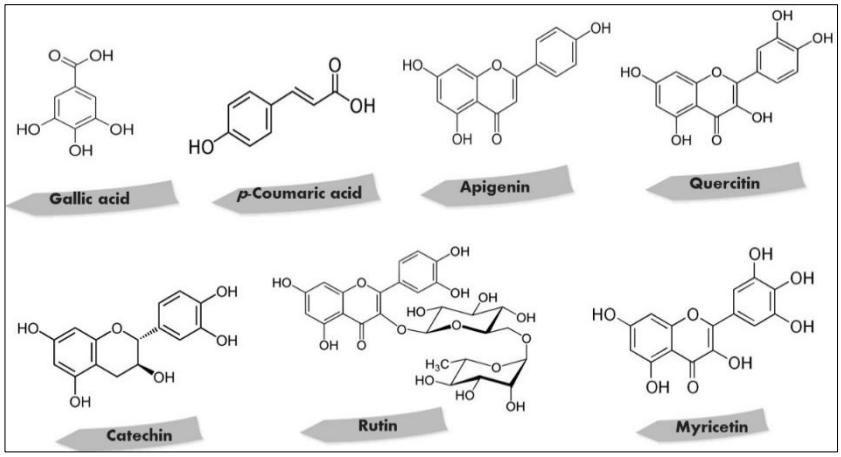

Fig 2: Phytochemical compounds detected and identified in amaranth

2.3 Health Benefits

Numerous investigations have explored the effects of an amaranth-based diet on biological and pharmacological activities in humans and animals, revealing its potential health benefits in various disorders including cardiovascular problems, endocrine disorders, immune system anomalies, tumors, cancers, and inflammatory conditions (Figure 3). These diverse health benefits can be attributed to the abundant presence of nutraceuticals (amino acids, proteins, fatty acids, vitamins, minerals, phytosterols, etc.) and phytochemicals (phenolic acids, flavonoids, tannins, coumaric acid, anthocyanins, etc.) in amaranth (Figure 3). For instance, a study examined the effects of a diet containing amaranth oil or squalene on antioxidant activity and immune response in patients with hyperlipoproteinemia and cardiac ischemia, showing positive immune effects with a diet containing 600 mg of squalene (Gonor *et al*., 2006) [19]. Another study reported the potential effectiveness of amaranth grain or oil against insulin deficiency, while demonstrating the inhibition of α-amylase by amaranth seeds, which reduces glucose absorption (Caselato-Sousa and Amaya-Farfán, 2012; Conforti *et al.*, 2005) [20, 21]. Several amaranth species have been found to possess high antioxidant capacity, with phenolic compounds showing significant antioxidant activity (Klimczak *et al.*, 2002; Paśko *et al*., 2009) [22, 23]. Additionally, amaranth grain has shown promise in the development of nonallergenic food products and has exhibited anti-allergy, liver health-promoting, anti-diarrheal, and anti-inflammatory properties (Hibi *et al.*, 2003; Kim *et al.*, 2006; Awouters *et al.*, 1978; Olajide *et al.*, 2004) [24-27]. These research findings indicate the potential of amaranth grains in the development of bioactive peptides targeting hypertension, anemia, and cancer.

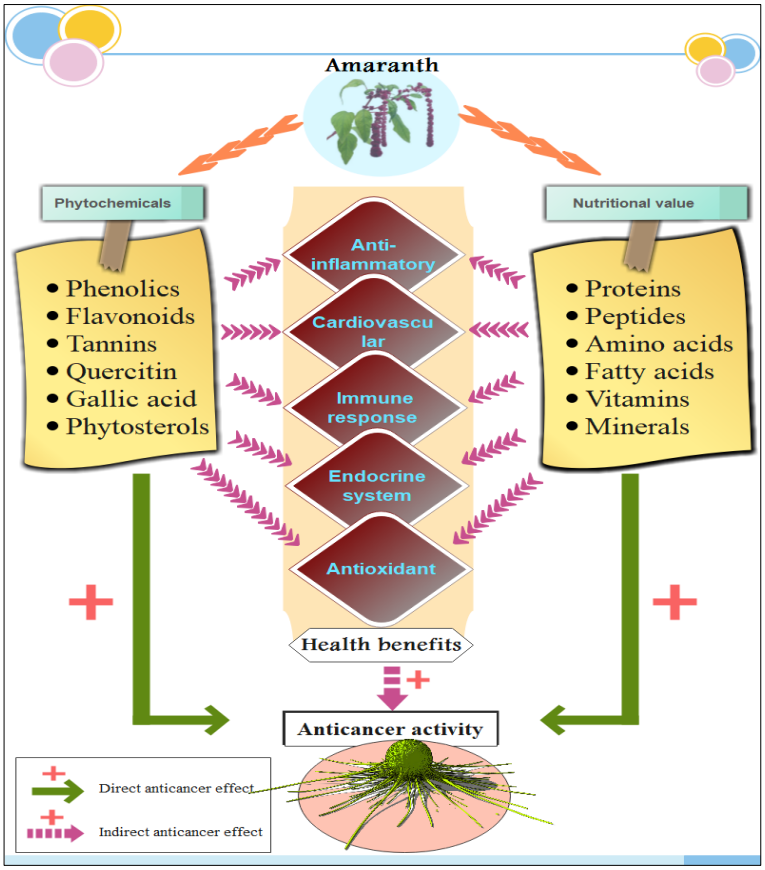

Fig 3: Direct and indirect effects of nutraceuticals and phytochemical compounds of Amaranth on cancer and tumors.

In the last decades, the attention of investigating natural bioactive phytochemicals and nutraceuticals from food has amplified as an alternative to pharmacological therapeutic strategies. In this respect, the use of nutraceuticals being most prominent since they are safe and economical and possess the ability of targeting different pathways of chemoresistance, and several of these natural and nutritional compounds display independent anticancer properties (Bharti *et al*., 2018) [28]. Taking this into consideration, numerous nutraceuticals and phytochemicals are involved in different phases of clinical assays and integrated in experimental studies that have revealed encouraging findings in both preclinical and clinical investigations. More interestingly, certain nutraceuticals have been shown to target cancer cells via the control of various cell signaling mechanisms and mediators that contribute to the manifestation of chemoresistance (Bharti and Aggarwal, 2002; Bhardwaj *et al*., 2007) [29, 30] or those responsible for inflammatory states and cancer developments including apoptosis, cell-cycle control, autophagy and metastasis (Bharti *et al*., 2018). [28]

Considering the foregoing, nutraceuticals from amaranth diet have received a lot of attention by pharmacologists to assess them against cancer and tumors. The integration of amaranth seeds into the diet was associated not only with health promotion but also with prevention of illnesses. Several studies demonstrated that amaranth is rich in phytochemical compounds and holds nutritional potential along with numerous pharmacological properties. Due to their interesting content of proteins, good fats and bioactive compounds with numerous pharmacological and biological properties and therapeutic virtues, the principal research activities on amaranths have focused mainly on their nutritive value (Paz *et al.*, 2021) [31]. The amaranths were assessed to be a reservoir of bioactive phytocompounds able to inhibit proliferation of cancer in the human body. In a recent study which was designed to evaluate the antioxidant, anti-proliferative and antimicrobial activity of stem and seed extracts of *Amaranthus hybridus* and *Amaranthus lividus*, respectively, the findings from this research suggested that both *Amaranthus* species have strong antioxidant and anti-proliferative effect on Swiss albino mice containing Ehrlich's ascites carcinoma cells (EAC cells). The anticancer activity revealed was mainly associated with the mitochondria mediated apoptosis of EAC cells (Al-Mamun *et al*., 2016) [32]. Mondal *et al* (2016) provided the first experimental evidence that isolated fatty acids from *Amaranthus spinosus* (14E, 18E, 22E, 26E)-methyl nonacosa-14, 18, 22, 26 tetraenoate) and demonstrated potential antiproliferative effect against hepatocellular carcinoma. This activity was mainly mediated via the induction of apoptosis in HepG2 human liver cancer cells (Mondal *et al*., 2016) [33]. In another similar study, Quiroga and co-authors demonstrated that amaranth lectin showed significant antitumor activity by inhibiting cell adhesion and exerting a cytotoxic action accompanied by cell apoptosis (Quiroga *et al*., 2015) [34]. Antitumor activity has also been demonstrated using proteins isolated from *Amaranthus mantegazzianus* seeds (Taniya *et al*., 2020) [35]. It has been proposed that the antiproliferative effect of this bioactive protein was improved by protease treatment. The pathway of the antiproliferative property seems to introduce an inhibition of cell proliferation and cell adhesion accompanied by the production of cell damage producing a permanent loss of cell viability (Barrio and Añón, 2010) [36]. In the same way, Sabbione and collaborators evaluated the antiproliferative activity of *Amaranthus mantegazzianus* proteins and peptides released after simulated gastrointestinal digestion on human colon cancer cell line HT-29; amaranth peptides obtained after simulated gastrointestinal digestion exerted significant antiproliferative activity over cell line studied. According to the findings of this study, the action was associated to induction of cell necrosis and apoptosis (Sabbione *et al*., 2019) [37]. Another study that aimed to compare the *in vitro* anti-cancer and antioxidant effect of *Amaranthus cruentus* protein, and hydrolyzates using three proteases (alcalase, pepsin and trypsin); trypsin hydrolyzate displayed the best antitumor potential amongst all test samples (Ramkisson *et al*., 2020) [38]. Obviously, the cytogenetic assay of *Amaranthus spinosus L*. aqueous extract in Allium cepa roots meristematic cells and human erythrocytes exhibited apoptosis induction and cytotoxic properties (Prajitha and Thoppil, 2017) [39]. In addition, the ethyl ether fractionation of *Amaranthus viridis* L. was evaluated *in vitro* for antitumor action against human colon cancer HT-29 cells; these results proposed that *A. viridis* L. is endowed with anticancer activities, where it is able to inhibit human colon cancer HT-29 cell growth in a dose-dependent manner through the induction of apoptosis and G0/G1 phase arrest (Jin *et al*., 2013) [40]. On the same note, results from a recent investigation revealed that methanol extraction of *Amaranthus spinosus* leaves showed significant antitumor activities in cancers of the breast, liver, colorectal and normal cell lines (Rajasekaran *et al*., 2014) [41]. Another comparative study which aimed to evaluate the phenolic contents, antioxidant, anti-inflammatory and anticancer activities of the methanolic extract of aerial parts from three species of amaranth: *Amaranthus dubius*, *A. tricolor*, *A. spinosus* and *A. viridis* revealed significant high antioxidant, anti-inflammatory and anticancer effects (House *et al.*, 2020) [42]. More recently, an unexploited method for the green synthesis of gold nanoparticles using the fresh leaf extract of *Amaranthus tricolor* demonstrated cytotoxic activity of the synthesized nanoparticles against human lung cancer cell line A549 (Punnoose *et al*., 2022) [43].

3. Effect of *Amaranthus* diet on Eicosanoid profiles of Cyclooxygenase and Lipoxygenase pathways in treating Cancer: Eicosanoids are defined as lipid mediators involved in numerous critical steps of the inflammatory response including those generated in cancer conditions. Amongst the compounds that have generated interest in the field of eicosanoid inhibitors are naturally occurring polyphenols of amaranth species, including the flavonoids, a class of bioactive plant compounds that exhibit several beneficial properties including anti-inflammatory and antioxidant capacities, decreased cardiovascular risks, and fight tumors and cancer. Recent findings indicate a linkage between eicosanoids, inflammation and cancer, that could serve as a potential therapeutic target for attenuating tumor growth (Greene *et al.*, 2011) [44]. Eicosanoids have been shown to generate enzymes, particularly 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) during biosynthesis; in fact, these enzymes are overexpressed in several cancers including breast, lung, and pancreas. Eicosanoids, including prostaglandins, lipoxins, resolvins, eoxins and leukotrienes, are products of local cell type specific arachidonic acid metabolism which are difficult to offer effective mediators

of inflammation including this occurring following the onset of oncological conditions (Zeldin, 2001; Serhan *et al*., 2015) [45, 46]. Interestingly, previous research that aimed to assess the anti-inflammatory activities of the methanol extract of *Amaranthus spinosus* L. leaves in different animal models, revealed the potent anti-inflammatory effect of this extract, suggesting that the mechanism of action deals with the inhibition of prostaglandin (eicosanoid) biosynthesis (Olajide *et al.*, 2004) [27]. Recently, the anti-inflammatory (using RAW 264.7 cells) and whitening activities of Amaranth (*Amaranthus* spp L.) seed extract was examined. In this study, *Amaranthus* spp L. seeds were extracted using 70% ethanol and fractionated using n-hexane, ethyl acetate, butanol, and dichloromethane. It was observed that EtOAc fractionation of *Amaranthus* spp L. seeds extract led to inhibition of the expression of PGE2, TNF-α and the protein level of COX-2 following a dose-dependent manner (Yi *et al.*, 2017) [47]. PGE2 (prostaglandins E2) are a group of physiologically bioactive lipid molecules so-called eicosanoids, they are also known as dinoprostones; recognized by their diverse hormone-like properties in animals. Prostaglandins play a deep impact over the migratory, adhesive, and invasive component of cells during the development of cancer. Microsomal prostaglandin E2 synthase-1 (mPGES-1) and Cyclooxygenase-2 (COX-2) are upregulated in inflammation and cancer (Menter and DuBois, 2012) [48]. The *A. viridis* leaf extract was shown to be an effective inhibitor of lipoxygenase (LOX) enzyme (Salvamani *et al.*, 2016) [49]. LOX are a class of lipid-peroxidizing enzymes which are involved in the catalyzation of the peroxidation of arachidonic acid and contribute to the generation of the pathogen state of many inflammatory disorders including cancers (Tamanoi and Bathaie, 2014) [50]. It was reported that *Amaranthus* species are interestingly rich in terms of polyphenolic compounds, particularly flavonoids and coumarins. In this respect, these two classes of phenolics have been shown to scavenge ROS and to enhance their generation, following experimental conditions. The interactions of these phytochemicals (characterizing *Amaranthus*) with ROS and with inflammation has also incited several investigations on their promising activities on the formation of proinflammatory eicosanoids derived from the COX and LOX pathways of arachidonic acid metabolism (Laughton *et al.*, 1991; Payá *et al.*, 1992; Alcaraz and Ferrandiz, 1987) [51-53].

Amaranthus contains other bioactive agents such as squalene, quercetin, rutin and phytosterols that have been shown to display chemo-preventative actions. Squalene is a natural lipid that belongs to the terpenoid family and is one of the precursors of cholesterol biosynthesis. This natural terpenoid is known as a fragile inhibitor of tumor cell proliferation, however, due to its potentiation effect, it is involved directly or indirectly in the treatment of cancer. Squalene has previously demonstrated tumorigenesis suppression activity in lung, colon, and skin cancers (Smith, 2004) [54]. In addition, it is also involved in the enhancement of immune responses to multiple allied antigens (Reddy and Couvreur, 2009) [55]. Recently, the adjuvant impact of squalene on tumor-transplanted mice along with anticancer drug doxorubicin (DOX) demonstrated the ability of SQ to significantly suppress the DOX-induced rise in prostaglandin E2 (PGE2) content in plasma of tumor-bearing mice. SQ inhibited the numbers of squirming response, formalin-induced pain and decreased COX-2, LOX and substance P expression in the tumor tissue in comparison with control animals. In addition, it contributed to enhancing the antitumor efficiency of the drug in allograft mice (Narayan *et al.*, 2019) [56]. Recent research results demonstrated that dietary squalene treatment may be effective in offering anti-inflammatory potential in DSS-induced acute colitis. Interestingly, western blot technique indicated that squalene inhibits COX-2 (Sánchez-Fidalgo *et al*., 2015) [57]. Another phyto-compound characterizing the chemical composition of amaranth is a phytosterol called spinastero. According to previous studies, this molecule displays antitumorigenic, anti-inflammatory, and anti-cervical, anti-breast, and anti-ovarian cancer properties (Villaseñor and Domingo, 2000) [58]. According to Brusco *et al*., the oral administration of α-spinasterol in mice led to the reduction of post-operative pain, as well as decreased cell infiltration in the injured tissue. In addition, α-Spinasterol decreased the mechanical allodynia induced by partial sciatic nerve ligation. It was further reported that α-Spinasterol contributed to the inhibition of COX-1 and COX-2 enzyme properties without fluctuating the body temperature of tested mice (Brusco *et al*., 2017) [59]. This particular triglyceride was described as fighting lung cancer (Huang *et al.*, 2009) [60], and it has proven anti-inflammatory, platelet-aggregation, and hemostatic effect.

Quercetin is a flavonoid that has been identified and isolated from many *Amaranthus* species, it was reported that this molecule suppresses COX-2 mRNA expression and downregulates *in vitro*, and ex vivo assays (Huang *et al.*, 2014) [61]. Furthermore, Kim *et al*. through their interesting study concluded that quercetin attenuated COX2, iNOS and the generation of oxidative stress irrespective of LOX pathway (Kim *et al.*, 2016) [62]. In a study that aimed to test the effect of quercetin on the inflammation conditions resulting from atherosclerosis disorders, and after administration of this nutraceutical in hypercholesterolemic diet in rabbits for 90 days, researchers observed that quercetin administration potentially altered the raised properties of inflammatory mediators such as cyclooxygenase and 5-LOX, 12-LOX, in HCD fed rabbits compared with regression control animals (Bhaskar *et al.*, 2013) [63].

Apigenin is another fascinating flavonoid identified in amaranth and whose pharmacological activities against cancer has been reported. Apigenin has been shown to inhibit cell growth, sensitize cancer cells to elimination by apoptosis, and hinder the development of blood vessels to serve the growing tumor. Interestingly, apigenin has been shown to reduce serum content of lipids, enhance hyperlipidemia, and improve atherosclerosis disorder in hyperlipidemia animal models. The molecular mechanism suggested may be associated with the inhibition activity of LOX-1 gene expression (Xu *et al.*, 2021) [64]. Kiraly and collegues reported that apigenin inhibits mouse skin tumorigenesis induced by the chemical carcinogens DMBA and TPA. Results from this study reported that apigenin is able to prevent skin tumor progression by inhibiting COX-2 (Kiraly *et al.*, 2016) [65]. Previous investigations demonstrated that apigenin suppressed LPS-induced COX-2 expression in RAW 264.7 cells. It was suggested that this downregulation could have been provoked by attenuation of Akt activation, or by inhibition of arachidonic acid production leading to the suppression of prostaglandins (eicosanoid) synthesis (Lee *et al.*, 2007) [66] (Figure 4).

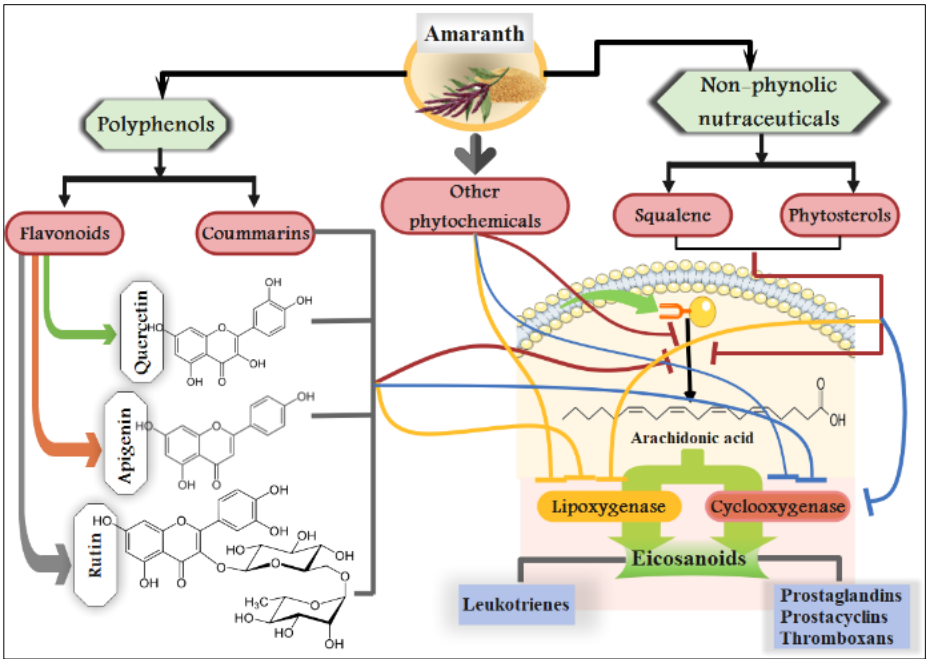

Fig 4: A schematic illustration showing the effect of amaranth diet on eicosanoid profiles of Cyclooxygenase and Lipoxygenase enzymes. On the left is LOX pathway (orange), leads to the production of the eicosanoids called "leukotrienes". On the right is the COX pathway, leading to thromboxane, prostacyclin and prostaglandins, via COX enzymes. Nutraceuticals and phytochemicals of *Amaranthus* interfere with COX, LOX enzyme production and/or by the inhibition of synthetizing arachidonic acid.

4. Conclusion

In conclusion, our review has highlighted the potential of the *Amaranthus* diet in exerting anticancer, cytotoxic, and antiproliferative effects. Specifically, we focused on the eicosanoid profiles of cyclooxygenase and lipoxygenase, which play crucial roles in the synthesis of eicosanoids from arachidonic acid. Our findings demonstrate that COX and LOX enzymes directly contribute to tumorigenesis by promoting tumor cell proliferation, survival, and growth. Moreover, these enzymes are involved in the inflammatory processes associated with cancer.

Extensive literature and research support the pharmacological and biological therapeutic properties of *Amaranthus* species, with several nutraceuticals isolated from amaranth, such as quercetin, rutin, apigenin, squalene, and phytosterols like spinasterol, exhibiting promising anticancer and anti-inflammatory effects. Notably, these nutraceuticals have demonstrated the ability to inhibit COX and LOX enzymes, resulting in the down regulation of eicosanoid biosynthesis, including prostaglandins, prostacyclin, and leukotrienes. Eicosanoids are bioactive lipids that play crucial roles in various pathological processes, particularly inflammation and cancer. Therefore, targeting these pathways holds potential for cancer therapy.

Although the current literature supports the potential of *Amaranthus* as a source of anticancer and antiproliferative compounds, the scarcity of clinical trial data in humans remain a limitation. Further research should focus on conducting clinical assays to validate the promising results observed in preclinical studies. Given that *Amaranthus* species are widely consumed as nutritious food, it would be interesting to explore their potential in clinical settings. Therefore, nutraceuticals and phytochemicals derived from amaranth hold promise as clinically useful anticancer chemosensitizers, which can be combined with existing chemotherapy to enhance treatment efficacy. Additionally, their ability to suppress tumor growth by interfering with eicosanoid pathways provides a rationale for the development of future generations of tailored cancer-preventive drugs.

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