

Review

Balancing Nutrition and Inflammation: The Role of a Healthy Diet in NLRP3 Inflammasome Activation

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Abstract

Research has shown that diet significantly influences the chance of developing chronic inflammatory diseases including inflammatory bowel disease, cardiovascular disease, obesity, type 2 diabetes and several types of cancer. Dietary components modulate the immune system by either promoting or mitigating inflammatory pathways. One such pathway is the activation of the NLRP3 inflammasome—a multiprotein complex that is involved in the innate immune response. The NLRP3 inflammasome is triggered by various stimuli including ionic flux, mitochondrial dysfunction, lysosomal damage and ROS. Upon activation through a two-signal process, an immune response is initiated that protects the body against pathogens and cellular stress. In a healthy body, this pathway is closely regulated to maintain homeostasis and prevent excessive inflammation that can result in tissue damage or chronic inflammatory diseases. Several components present in a human diet can activate or inhibit the NLRP3 inflammasome. To support a balanced diet, organizations like the WHO have developed dietary recommendations. These promote the consumption of fruits, vegetables, whole grains, lean proteins and healthy fats. These foods contain a variety of nutrients and bioactive compounds, including saturated fatty acids, cholesterol, omega-6 fatty acids and natural sugars, which are pro-inflammatory. At the same time, they also supply anti-inflammatory compounds such as monounsaturated fatty acids, antioxidants and probiotics. While current literature highlights the NLRP3 inflammasome as a critical regulator of inflammation, it lacks detailed insights into how the specific dietary components of a healthy diet influence its modulation. Therefore, this literature review elucidates the various mechanisms through which these dietary compounds modulate the NLRP3 inflammasome. The significance of maintaining a balance between pro- and anti-inflammatory components in the diet is highlighted by its role as a regulator of inflammatory diseases, for example, through mechanisms such as epigenetic pathways.

Keywords: NLRP3 inflammasome; DAMP; PAMP; healthy diet; pro-inflammatory triggers; anti-inflammatory triggers

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1. Introduction

Human health is largely dependent on proper nutrition because one in five adult deaths worldwide is thought to be caused by suboptimal diets [1]. The global nutritional

shift towards diets high in ultra processed foods that are more refined, calorie-dense and low in nutrients is partly responsible for the rapid rise in obesity and metabolic diseases, including diabetes, cancer and heart disease [2]. Additionally, these noncommunicable diseases (NCDs) are the world's leading cause of mortality [3]. Healthy diets are widely known for their benefits of avoiding chronic illnesses and improving general well-being. Given the increasing global focus on nutrition, acknowledged healthy diets, like those established by the World Health Organization (WHO) and the EAT-Lancet Commission's planetary health diet, have gained importance. They contain similar advice on prioritizing nutrient-dense, minimally processed foods, while promoting substantial consumption of fruits, vegetables, whole grains, lean proteins and healthy fats [4]. The main objective of these diets is to enhance health outcomes by maintaining optimal nutrient intake while protecting against NCDs, including diabetes, heart disease, stroke and cancer. The dietary advice emphasizes that a balanced, healthy diet varies depending on personal characteristics such as age, gender, lifestyle and level of physical activity, cultural context and availability of foods [5]. The fundamental ideas about a healthy diet; however, remain largely the same.

Research has shown that diet contributes to the development of a wide range of chronic diseases including cardiovascular disease, obesity, type 2 diabetes, cancers and neurological diseases [6]. Additionally, diet significantly affects the development of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) by modulating inflammation and gut microbiota [7]. More specifically, dietary components directly influence the immune system by either promoting or mitigating inflammation [8]. For example, components like fibre, antioxidants and omega-3 fatty acids are known to have anti-inflammatory properties as they help control immune responses, reduce oxidative stress and maintain a healthy gut flora [9,10]. Although the established guidelines for a healthy diet generally include anti-inflammatory foods, certain components such as sugars, saturated fats, or an imbalanced consumption of omega-6 fatty acids, can trigger pro-inflammatory pathways [11–13]. As dietary components have significant effects on the development of disease, they are also increasingly recognized for their use as a therapeutic method in managing diseases and alleviating the symptoms of various conditions. This highlights that it is necessary to understand the effects of diet and dietary components on the human body.

The NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome is a multiprotein complex that is an important sensor of the innate immune system which causes the release of pro-inflammatory cytokines and triggers pyroptosis, a form of programmed cell death, upon activation [14]. Besides its role in infection and inflammation, recent studies suggest that the NLRP3 inflammasome contributes to the development of non-alcoholic fatty liver disease (NAFLD), atherosclerosis, inflammatory arthritis, type 2 diabetes, obesity induced insulin resistance and neurological diseases [15]. More specifically, due to its critical role in inflammation, the NLRP3 inflammasome is increasingly studied as a therapeutic target for chronic diseases [16]. Interestingly, a growing body of literature shows that dietary components including fats, sugars, cholesterol, antioxidants and probiotics have a modulatory effect on the activation of the NLRP3 inflammasome [17]. Each of them having different effects on the pathway of inflammatory response, emphasizing the importance of a balanced diet where anti-inflammatory nutritional components can potentially alleviate the effects of pro-inflammatory components. While the literature highlights the NLRP3 inflammasome as a critical regulator of inflammation, it lacks detailed insights into how the specific dietary components of a healthy diet influence its activation and regulation. Therefore, this review will answer the question: "How do the dietary components of a healthy diet modulate the NLRP3 inflammasome, and what is the importance of balancing pro- and anti-inflammatory triggers?" To answer this question, findings from multiple research approaches will be synthesized. Through a critical

analysis of current research, this review will highlight key findings, limitations, and gaps, offering a comprehensive view of the connection between several dietary components and the NLRP3 inflammasome. Additionally, a personal perspective on the subject matter will be presented.

To ensure a critical evaluation of current research, we conducted a comprehensive search across multiple scientific databases, including PubMed and Google Scholar. These databases were chosen because of their extensive coverage of biomedical literature. The search included keywords such as “NLRP3 inflammasome”, “dietary components” and “chronic inflammation”. Results were refined according to study type and relevance using filters and Boolean operators (AND, NOT, OR, “...”). Data collection from databases took place from September to December 2024. All references were managed using EndNote™ 21.4 ensuring efficient organization and citation of included studies. Selection criteria to select relevant and high-quality studies for inclusion in this review, several predefined criteria were developed. First, articles were accepted if they directly evaluated how dietary factors affected the NLRP3 inflammasome, contained experimental in vitro or in vivo human or animal research and were published within the last 10 years to guarantee current results. Articles were specifically included if they elaborated on the cellular cascades and modulatory mechanisms influencing the NLRP3 inflammasome. For chapter 7, Balancing anti- and pro-inflammatory dietary components and the conclusion articles which explained a broader relationship between diet, inflammation and disease were used. Reviews and meta-analyses were used as background articles, to provide a broader context and to identify findings across studies. Articles that were not written in English were excluded from this review. Information in studies valuable for inclusion, was systematically extracted and categorized in a table using Microsoft® Excel. For every included study, the following general data was extracted: article title, authors, year of publishing, journal, number of times cited and study type. Next, studies were categorized based on the specific dietary component(s) they researched, and which model/system was used in the research. Additionally, corresponding mechanisms of NLRP3 modulation, main study findings and strengths and limitations of the study were noted. To critically assess the included studies in this review, each article was assessed based on its relevance to the research question. The primary criterion for evaluation was the clarity of the research design and how extensively the studies investigated the cellular mechanisms affecting the NLRP3 inflammasome. Studies were examined to determine whether their findings directly contributed to understanding the influence of specific dietary components on the NLRP3 inflammasome, with particular attention paid to the methodologies used to investigate these mechanisms. The quality of the experimental design of the studies was further analyzed and their findings compared to similar studies for the evaluation of their credibility. This critical evaluation process ensured that only high-quality and relevant studies were included in the synthesis of results. This approach, therefore, afforded a thorough and precise overview of the mechanisms by which dietary components influence the NLRP3 inflammasome.

2. The Immune Response

The immune system plays a central role in protecting the body from pathogens and toxic or allergenic substances that threaten the maintenance of homeostasis [18]. It is responsible for identifying and responding to a wide range of threats, including infections and tissue damage, by using a complex network of cells and signalling molecules. Besides eliminating these threats, the immune system must also avoid responses that could cause excessive damage to the body or disrupt beneficial microbes. In general, the immune response can be divided into an innate, nonspecific response and an adaptive, specific immune response [19]. The innate immune response acts rapidly and non-specifically after

a pathogen invades barriers like the skin, by activating immune cells such as macrophages, neutrophils and cytokines. In contrast, the adaptive immune response is slower but highly specific, involving B and T cells that recognize and target specific antigens [20]. Immunological memory is a crucial component of adaptive immunity, which facilitates a stronger and quicker reaction upon re-encounter with the same pathogen. While the innate and adaptive immune responses operate in essentially separate ways, an intact, complete immune response depends on their cooperation [18].

2.1. Adaptive Immune Response

The adaptive immune response is capable of generating antibodies and immune cells that are highly specific to certain pathogens [20]. To initiate a targeted immune response against a specific antigen, four critical steps or signals are required. The first step involves the uptake and presentation of the antigen to T lymphocytes. This process is carried out by specialized immune cells known as dendritic cells. In a healthy state, dendritic cells remain inactive, and their activation constitutes the second step. This activation occurs through a nonspecific reaction, where dendritic cells detect danger in the tissue via pattern recognition receptors (PRRs). Upon activation, dendritic cells express co-stimulatory receptors on their surface, which are essential for enhancing the interaction with T cells. The third step is the secretion of cytokines—specialized proteins produced by antigen-presenting cells like dendritic cells. These cytokines signal through specific receptors and play a crucial role in determining the type of T cell that will develop, thereby guiding the immune response in the appropriate direction [20]. In addition to these three signals, nutrients can be considered as a fourth signal that is critical for T cell activation, differentiation, and function. Nutrients influence the metabolic pathways of T cells, thereby impacting the overall efficacy of the immune response [21].

2.2. Innate Immune Response

The innate immune response is the first line of defence against pathogenic invasion [20]. The skin and other epithelial surfaces, containing tight junctions and mucus layers, prevent pathogens from penetration. However, these barriers are occasionally breached by microorganisms, after which the innate immune system will be activated. This immune response is triggered by the recognition of pathogen-associated molecular patterns (PAMPs)—molecules that are common to pathogens but are absent in the host [20]. These PAMPs trigger the innate immune response through inflammatory processes and phagocytosis by cells such as neutrophils and macrophages [22]. Effector cells of the innate immune response recognize PAMPs by use of PRRs which are located on the endosomal membrane and in the cytoplasm. Upon binding to PAMPs, PRRs initiate the synthesis and release of proinflammatory cytokines and other effector molecules, which subsequently stimulate the phagocytic activity of immune cells [22]. Toll-like receptors (TLRs), a type of membrane-bound PRRs, detect microbial pathogens and endogenous danger signals released by damaged host cells [23].

2.3. NLRs: Key Regulators of Innate Immunity

Another significant PRR family is the nucleotide-binding oligomerization domain-like receptors or NOD-like receptors (NLRs), which have diverse structures but similar functional domains [24]. NLRs consist of leucine-rich repeats (LRR) at the C-terminus, a central nucleotide-binding domain, and an N-terminal effector domain. The latter is variable among NLRs and facilitates interactions with other cellular components, influencing downstream signalling. When activated, NLRs trigger inflammatory reactions that control a variety of biological functions, such as antigen presentation, autophagy and inflammasome assembly [15]. Inflammasome activation subsequently triggers pyroptosis, a

violent and proinflammatory kind of lytic cell death in order to prevent intracellular pathogen proliferation and promotes their elimination [25].

3. The NLRP3 Inflammasome

As part of the body's defence mechanisms, the immune system detects internal danger signals that point to cellular damage or distress in addition to identifying exterior dangers, such as pathogens. These internal danger signals, also known as danger-associated molecular patterns (DAMPs) serve as indicators of cellular damage or infection. Unlike PAMPs, which are derived from external threats, DAMPs are derived from the host and play a crucial role in initiating an inflammatory response [14]. The activation of the NLRP3 inflammasome, a multiprotein complex that detects cellular stress and induces inflammatory responses, is triggered by these PAMPs and DAMPs and expressed in various cell types, predominantly those involved in the innate immune response. The NLRP3 inflammasome consists of three components: the NLRP3 sensor protein (containing a C-terminal LRR domain, a central ATPase-containing NACHT domain that mediates oligomerization, and an N-terminal pyrin (PYD) domain which recruits proteins for inflammasome complex formation), the ASC adaptor protein (apoptosis-associated speck-like protein containing a caspase recruitment domain), and caspase-1—an enzyme which processes inflammatory signals [26].

3.1. Activation of the NLRP3 Inflammasome

The NLRP3 inflammasome is activated by both endogenous (DAMPs) and exogenous (PAMPs) signals [15]. Currently, a two-signal model has been proposed for NLRP3 inflammasome activation; first there is a priming signal (signal 1) upon which follows an activation signal (signal 2) [27]. This process minimizes unintentional activation that might result in pathological inflammation while guaranteeing appropriate inflammatory responses. First, priming prepares the NLRP3 inflammasome for activation and assembly and involves transcriptional and post-translational modifications. DAMPs or PAMPs trigger the PRRs, such as the IL-1 β receptor, TNF receptor or TLRs on the cell membrane. This induces downstream signalling through adaptor proteins, such as MyD88 and TRIF, leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [28]. NF- κ B translocates into the nucleus and promotes the transcription of genes encoding NLRP3, pro-interleukin 1 β (pro-IL-1 β) and pro-interleukin-18 (pro-IL-18), which are normally expressed at low levels in resting cells. Figure 1A illustrates the priming step, where TLR signalling activates NF- κ B and induces the expression of inflammasome components. In addition to transcriptional regulation, the priming signal also induces post-translational modifications of NLRP3 that 'license' it for activation. For example, NLRP3 is deubiquitinated and phosphorylated, enabling the protein to respond to activation stimuli in the activation phase [27].

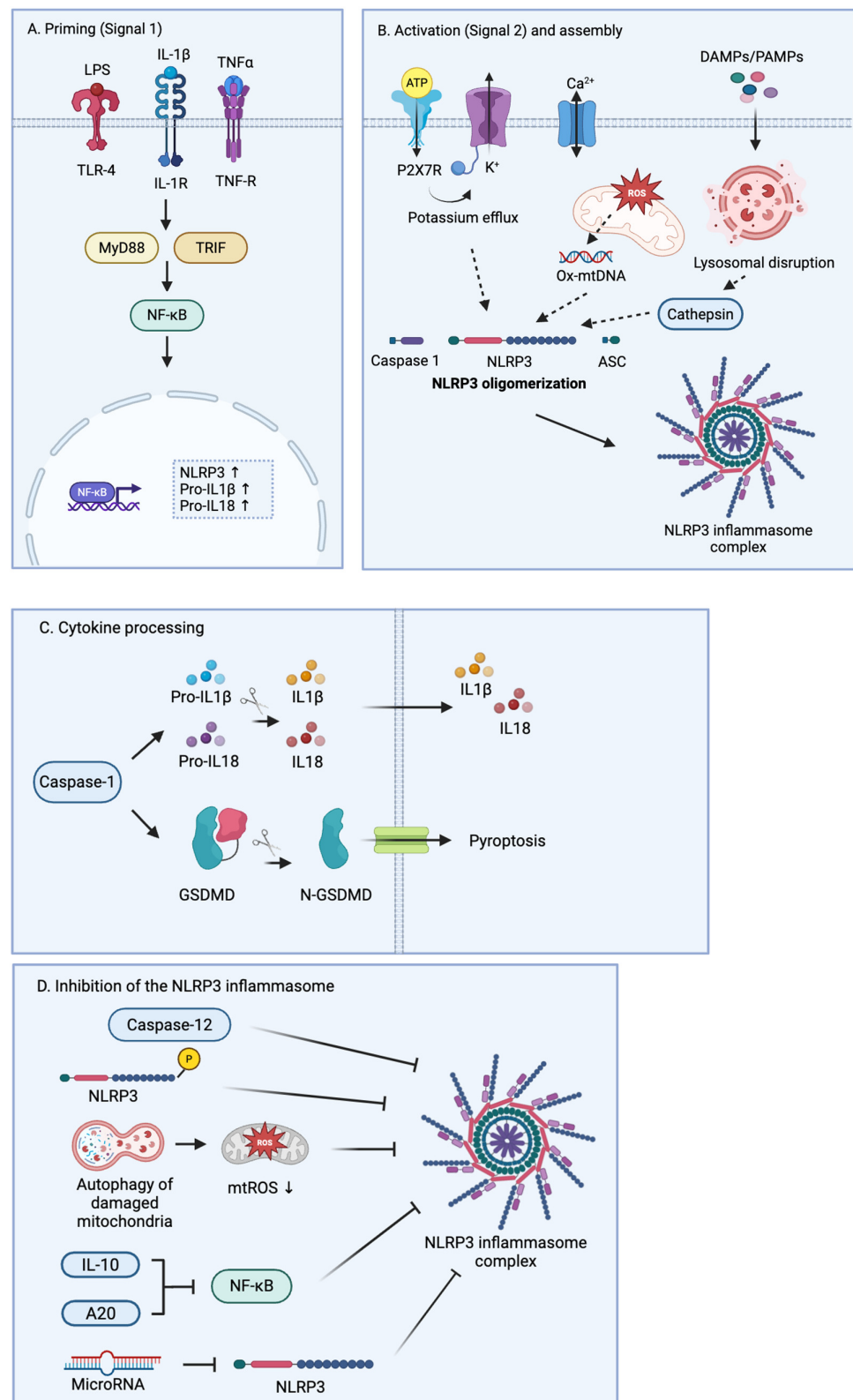


Figure 1. Canonical activation and regulation of the NLRP3 inflammasome: (A) priming, (B) assembly, (C) cytokine processing, and (D) inhibitory mechanisms. Created with BioRender.com.

After the priming signal, the activation signal (signal 2) follows. This phase occurs in response to several stimuli that initiate cellular cascades leading to the assembly of the

NLRP3 inflammasome complex. They include ionic flux, mitochondrial dysfunction, lysosomal damage, and the production of reactive oxygen species (ROS), caused by stimuli such as extracellular ATP, K⁺ ionophores, heme, pathogen-associated RNA, particulate matter and bacterial and fungal toxin components [27]. However, none of these have been shown to directly interact with NLRP3, and because of their biochemical differences, it is hypothesized that they rather trigger a similar cellular signal [27]. Potassium efflux is one of the most important processes in this phase. For instance, the P2X7 receptor is activated by extracellular ATP, which causes ion channels to open and intracellular potassium levels to rapidly decrease, which is a crucial trigger for NLRP3 activation. As NLRP3 stimuli result in either the release of calcium from the endoplasmic reticulum or its influx through plasma membrane ion channels; calcium mobilization also plays a part [27]. Increased calcium levels in the cytosol can cause calcium overload in the mitochondria, inducing mitochondrial dysfunction. NLRP3 activation has also been demonstrated to be facilitated by chloride efflux via CLIC channels, most likely through the promotion of conformational changes or protein–protein interactions [27]. Mitochondrial dysfunction also triggers NLRP3 inflammasome activation through the production of ROS [24]. Oxidized mitochondrial DNA (ox-mtDNA), which is released into the cytosol because of ROS generation, binds to NLRP3 to activate it. Additionally, excess mitochondrial ROS (mtROS) can interact with cellular components like thioredoxin (TRX) [27]. This leads to the dissociation of thioredoxin-interacting protein (TXNIP), which then binds to NLRP3 and promotes its activation. Additionally, mtROS amplify inflammatory responses through a feedback loop, sustaining NLRP3 activation.

Furthermore, it has been demonstrated that mitochondrial proteins including mitofusin-2 and mitochondrial antiviral-signalling protein (MAVS) bind to NLRP3, and promote inflammasome formation [27]. Lysosomal damage can also induce activation of the NLRP3 inflammasome. When particulate matter, including silica, cholesterol crystals, alum or asbestos is phagocytosed, lysosomes become unstable and cathepsins are released into the cytosol [27]. After lysosomal disruption, cathepsins (especially cathepsin B) function as mediators to encourage NLRP3 activation. Upon being triggered by these cellular processes—including potassium efflux, calcium mobilization, mitochondrial ROS production or lysosomal damage—the NLRP3 protein is activated. Once activated, NLRP3 oligomerizes and recruits ASC which acts as a scaffold connecting NLRP3 to caspase-1, leading to the assembly of a large molecular structure essential for the functioning of the inflammasome [14]. As shown in Figure 1B, these stimuli promote the assembly of the NLRP3-ASC-caspase-1 complex. This assembly activates caspase-1, which subsequently cleaves pro-inflammatory cytokines, pro-interleukin 1 β (pro-IL-1 β) and pro-interleukin-18 (pro-IL-18) into their active forms of interleukin 1 β (IL-1 β) and interleukin-18 (IL-18). Additionally, caspase-1 cleaves gasdermin D (GSDMD), which induces the release of these cytokines through pores in the cell membrane, resulting in pyroptosis [14]. Figure 1C summarizes the downstream consequences of NLRP3 activation, including cytokine maturation and gasdermin-D-mediated pyroptosis. Once the NLRP3 inflammasome has initiated the immune response, the body quickly activates various regulatory mechanisms to restore homeostasis and promote tissue healing. In a healthy body, the presence of ready-to-use NLRP3 protein is minimal, ensuring that the inflammasome is only activated when necessary to avoid chronic inflammation or excessive immune responses. The two-signal model ensures that NLRP3 activation remains a tightly regulated process which is critical to balance the need for host defence against pathogens and cellular stress while preventing excessive inflammation that potentially results in tissue damage or chronic inflammatory disorders [27].

3.2. Inhibition of the NLRP3 Inflammasome

There are several natural mechanisms by which NLRP3 inflammasome activation is regulated to prevent chronic inflammation. By preventing NLRP3-ASC connections or competing with caspase-1 for recruitment, endogenous inhibitors such as caspase-12 and pyrin domain-only proteins (POPs) disrupt the inflammasome's ability to assemble, which lowers cytokine processing [29]. Post-translational modifications, including ubiquitination by TRIM31, target NLRP3 for proteasomal degradation, while phosphorylation can directly prevent its activation [30]. By eliminating damaged mitochondria and lowering mtROS, autophagy also plays a crucial role in inhibiting the NLRP3 inflammasome [31]. Additionally, NF- κ B signalling is inhibited and priming of NLRP3 is limited by anti-inflammatory feedback mechanisms, such as IL-10 production and A20 activity [32]. Lastly, microRNAs have the proven ability to inhibit inflammasomes by binding to a conserved site of the NLRP3 transcript, thereby suppressing protein expression and inhibiting NLRP3 inflammasome priming [33]. Figure 1D visualizes these pathways through which inhibition of the NLRP3 inflammasome can take place.

Pharmacological Inhibitors

The NLRP3 inflammasome and its associated pathways are emerging as promising targets for the development of therapeutic strategies aimed at mitigating inflammation in IBD [34]. A comprehensive understanding of the regulatory mechanisms surrounding NLRP3 inflammasome activity is crucial, as it could lead to the invention of innovative therapies for this complex condition. Moreover, the NLRP3 inflammasome has been increasingly recognized as a potential therapeutic target in other immune-mediated inflammatory diseases [35–40]. Currently, diseases caused by overactivation of the NLRP3 inflammasome are often treated with IL-1 β antibodies or IL-1 β receptor antagonists [41]. However, they are relatively nonspecific and have low efficacy. Besides IL-1 β , pro-inflammatory cytokines like IL-18 are also products of NLRP3 inflammasome activation, contributing to disease pathogenesis. Additionally, IL-1 β is also produced in other pathways in the body causing inhibitors to have undesired immunosuppressive effects. Therefore, several pharmacological inhibitors which target specific components of the NLRP3 inflammasome have been developed. They are synthetic small molecule inhibitors targeting ASC oligomerization, NLRP3 ATPase, NLRP3 oligomerization or NLRP3 itself [41]. MCC950, also known as cytokine release inhibitory drug 3, is the most potent and selective NLRP3 inhibitor which binds to the NLRP3 NACHT subdomains, thereby limiting ATPase activity which brings NLRP3 into inactive state [42].

3.3. Dietary Components as Modulators of the NLRP3 Inflammasome

It is evident that the formation and activation of the NLRP3 inflammasome are typically triggered by DAMPs or PAMPs. However, recent research has demonstrated that a variety of other factors, including environmental pollutants and substances found in food—whether naturally occurring or intentionally added by the food industry—can also activate the NLRP3 inflammasome [34,43]. The presence of these external factors, combined with the readiness of NLRP3 for activation, can lead to chronic hyperactivation of the inflammasome, resulting in the release of DAMPs at high concentrations. This, in turn, triggers a cascade of immune responses, including macrophage activation, neutrophil infiltration, and excessive cytokine production, all of which contribute to a state of chronic inflammation [44]. To better conceptualize this process, think of NLRP3 as a pilot light. In individuals with a robust immune system—those who are “immune fit”—the pilot light remains largely inactive. However, in individuals with compromised immune fitness, due to factors such as ageing, sedentary lifestyles, Western diets high in ultra-processed foods, or obesity, the pilot light is perpetually active. Consequently, the second step of fully

igniting the inflammatory response is more easily achieved, leading to dysregulation of the NLRP3 inflammasome and the onset of chronic inflammation. On the contrary, there are also some natural products that have been identified as inhibitors of the NLRP3 inflammasome. For example, curcumin, extracted from the herbal supplement turmeric, which inhibits the NF- κ B signalling pathway, involved in NLRP3 inflammasome activation [45]. Additionally, β -Carotene, found in most fruit and vegetables, can bind to NLRP3's pyrin domain to selectively inhibit the inflammasome [46].

4. Definition of a Healthy Diet

A growing body of evidence proves that diet influences many processes in the human body including composition of gut microbiota and disease risk [47,48]. More specifically, dietary components significantly influence inflammatory pathways, which can lead to several NCDs [6]. The modulation of the NLRP3 inflammasome by dietary components highlights the significant influence of nutrition on inflammatory pathways. Therefore, it is important to understand what constitutes a healthy diet and how the dietary components of this diet modulate inflammatory mechanisms such as NLRP3 inflammasome activation.

4.1. Dietary Advice by the WHO

In 2020, the WHO published a fact sheet which included practical advice on how to maintain a healthy diet for adults and children [5]. Consumption of this varied pallet of dietary components is important to ensure intake of essential nutrients, support sufficient energy, boost the immune system, reduce risk of chronic disease and support digestive health [5]. For adults, a healthy diet includes:

- Fruit, vegetables, legumes (e.g., lentils and beans), nuts and whole grains;
- At least 400 g of fruit and vegetables per day;
- Less than 10% of total energy intake from free sugars (including added sugars and naturally present sugars in, e.g., honey);
- Less than 30% of total energy intake from fats where saturated fatty acid (SFA) intake should be reduced to less than 10% of total energy intake and trans fatty acids (TFAs) to less than 1%;
- Less than 5 g of salt per day.

Additionally, the WHO emphasizes that unsaturated fats (present in fish, nuts, olive oil, etc.) are preferred over saturated fats (present in butter, cheese, fatty meat, etc.) and trans-fats (both industrially produced and ruminant trans-fats and present in baked and fried foods, pre-packaged foods and meat from ruminant animals). In 2023, the WHO published three additional guidelines for saturated and trans-fatty acid intake, total fat intake and carbohydrate intake for adults and children based on the latest scientific study results [49]. They advise replacing SFAs and TFAs with polyunsaturated fatty acids (PUFAs) or monounsaturated acids (MUFAs) from plant sources. Additionally, carbohydrates must be sourced from foods naturally high in dietary fibres, such as whole grains, vegetables, fruits and legumes, highlighting the importance of carbohydrate quality. Currently, guidelines on PUFA and low-sodium salt substitutes are under development.

Besides the global advice by the WHO, countries generally establish a national nutrition guideline based on this advice. For example in the US, the Dietary Guidelines for Americans (DGA), are updated every five years to incorporate the latest science-based advice on a healthy diet [50]. The current 2020–2025 edition also emphasized intake of fruits, vegetables, whole grains and legumes while reducing sugars, saturated fats and salt. They advocate for healthy fat choices and reduction in intake of ultra-processed foods. Differences in comparison to WHO guidelines are found in recommendations for consumption of salt intake where the WHO advises less than 2000 mg/day and the DGA

advises 2300 mg/day. Also, the WHO recommends an ideal target of 5% of daily caloric intake from sugars where the DGA suggests less than 10%. Lastly, the WHO strongly discourages alcohol consumption where the DGA allows for moderate consumption (2 drinks/day for men and 1 drink/day for women). The EAT-Lancet Commission, a collaborative initiative of 37 leading scientists from 16 countries, has presented advice for a global healthy diet which is both beneficial to humans and the planet [51]. Their report, published in 2019, presents a strategy to feed an expected 10 billion people by 2050, while also sustaining the environment. In line with the WHO, they emphasize intake of plant-based foods such as fruits, vegetables, whole grains, legumes, nuts and seeds and limit intake of free sugars, saturated and trans-fats and salt. Where the WHO provides specific numerical targets of caloric intake, EAT-Lancet outlines a broader dietary framework. In conclusion, although minor differences, many global advises for a healthy diet include similar products.

4.2. Perceptions of a Healthy Diet

In addition to evidence-based guidelines and recommendations for a healthy diet, perceptions of what constitutes a healthy diet vary globally due to cultural, geographical, and economic factors. The Mediterranean diet is the most well-known and researched diet worldwide and is based on the Seven Countries Study by Ancel Keys [52]. This was the first major study to investigate effects of diet and lifestyle on cardiovascular disease in differing countries and cultures over a certain period. The diet is based on dietary patterns of countries bordering the Mediterranean Sea, such as Greece, Italy and Spain. It promotes a high intake of fruit, vegetables, whole grains, legumes and nuts like the previously mentioned diets. Additionally, the use of unsaturated fats (olive oil) and reduction in consumption of red meat is promoted. While EAT-Lancet suggests low-to-moderate dairy intake, the Mediterranean diet includes moderate amounts cheese and yoghurt. Also, while the WHO advises avoiding alcohol, the Mediterranean diet includes wine in moderation.

In recent years, perceptions of a healthy diet have evolved significantly, emphasizing reduced caloric intake, lower sugar consumption and decreased fat intake. This shift has led the food industry to replace natural dietary components like sugars with artificial low- and no-caloric sweeteners in products such as diet sodas, light dairy products, sugar-free sweets and various types of processed foods. Although exact numbers on consumption of these sweeteners remain unknown, there are several health risks associated with artificial sweeteners. For example, findings from large scale prospective cohort studies suggest a potential direct association between higher intake of artificial sweeteners and increased risk of cardiovascular disease and type 2 diabetes mellitus [53]. Additionally, while some human trials observed disruption of gut microbiota composition, other randomized controlled trials found no discernible effects on its composition, indicating the need for additional research [54]. However, the WHO already advises not to use artificial sweeteners to control body weight or reduce the risk of NCDs, due to a lack of long-term benefits and potential health risks associated with their use [55].

4.3. The Value of a Balanced Diet

Studies show that diets with low dietary inflammatory index (DII) scores are associated with reduced risks of chronic conditions like cardiovascular diseases, arthritis, and obesity-related inflammation [56]. Additionally, a systemic review has found that each unit increase in DII correlates with a 10% higher likelihood of elevated CRP levels, which contributes to systemic inflammation, highlighting the importance of a balanced diet to manage inflammation [57]. For example, fruit and vegetables are high in polyphenols, vitamin C and fibre acting as antioxidants and promoting gut health. Whole grains and

legumes are sources of fibre and SCFA precursors which improve gut microbiota diversity, thereby preventing a leaky gut and systemic inflammation [58]. Healthy fats, present in olive oil, fatty fish and nuts, is rich in MUFAs and omega-3 fatty acids which reduce pro-inflammatory cytokines and oxidative stress [9,59]. Additionally, the recommendation to limit sugar intake helps prevent inflammatory processes; however, it may lead to an increased consumption of artificial sweeteners, which can negatively impact health when consumed in excessive amounts [53].

5. Pro-Inflammatory Triggers in a Healthy Diet

The value of a balanced diet is universally recognized for maintaining health and preventing various types of diseases. More specifically, a growing body of literature supports the connection between dietary components, inflammation and activation of the NLRP3 inflammasome. While there is consensus about the inflammatory effects of the Western diet—characterized by high intake of sugar, red and processed meat, salt, pre-packaged and ultra-processed food—certain dietary components may contribute to chronic inflammation and disease. This is particularly true when these components are consumed in excess or imbalanced proportions, especially in sensitive individuals [60]. This chapter examines pro-inflammatory triggers in a healthy diet, focusing on specific nutrients and bioactive compounds such as saturated fatty acids (SFAs), cholesterol, natural sugars and artificial sweeteners. Additionally, the mechanisms through which these components influence NLRP3 inflammasome activation will be explained.

5.1. Saturated Fatty Acids

Saturated fatty acids (SFAs) are found in a healthy diet in animal products such as meat and dairy, but also in oils such as coconut and palm oil [61]. The most common types of SFAs in human diet are palmitic acid, stearic acid, lauric acid and myristic acid. Palmitic acid is one of the most abundant and has been associated with several health risks due to its potential to increase LDL cholesterol levels. Stearic acid, another extensively studied SFA, has a neutral effect on cholesterol levels and therefore has less potential to induce cardiovascular risk.

In the literature, palmitic acid and stearic acid are frequently studied in the context of inflammation and their role in activating inflammatory pathways such as the NLRP3 inflammasome. Research has shown that SFAs are able to activate the NLRP3 inflammasome in macrophages through several interconnected mechanisms. First, SFAs can be incorporated into polar lipids within the cell membrane where they cause increased phospholipid saturation [62]. This results in a more rigid and saturated cell membrane, destabilizing the Na⁺/K⁺ATPase pump, leading to an efflux of K⁺ ions from the cell. A low intracellular K⁺ concentration then triggers NLRP3 inflammasome activation [62]. Next, a study by Wen, Gris [63] explains NLRP3 inflammasome activation by the AMP-activated protein kinase (AMPK). In a mouse macrophage cell line, palmitate inhibits AMPK, which generally acts as a suppressor of inflammation and oxidative stress by suppressing ROS production by inhibiting NADPH oxidase. The inhibition of AMPK leads to mitochondrial dysfunction which increases production of mtROS; a trigger for activation of the NLRP3 inflammasome [12,63]. Additionally, this study shows that palmitate-induced AMPK inhibition impairs autophagy which causes an excess of damaged mitochondria and even additionally increased ROS production. Excess ROS, in combination with impaired autophagy, activates the NLRP3 inflammasome by oxidizing components of the inflammasome and triggering inflammasome assembly [12,63]. Another study found that palmitic acid can activate Toll-like receptor 4 (TLR4), a PRR present on the cell membrane. TLR4 activation enhances NF-κB pathway signalling which causes increased transcription of pro-inflammatory cytokines such as IL-1β and IL-18 which promote NLRP3

inflammasome formation. Lastly, SFAs like palmitic acid and stearic acid undergo intracellular crystallization in macrophages [64]. Upon uptake into the cell, the fatty acids form solid crystalline structures which disrupt lysosomal integrity. This causes lysosomal rupture and release of cathepsins into the cytoplasm which act as an activation signal for the NLRP3 inflammasome [64]. In conclusion, SFAs—more specifically palmitic acid and stearic acid—appear to consistently trigger NLRP3 inflammasome activation, contributing to inflammation and metabolic dysfunction.

5.2. Cholesterol

Cholesterol is a lipid molecule that is naturally present in a healthy diet as part of foods that also provide essential nutrients. For example, cholesterol is present in eggs, shellfish, dairy products and meat. Cholesterol mainly serves as a building block for cell membranes, steroid hormones and bile acid, necessary for fat digestion [65]. In the cell membrane, it regulates fluidity, rigidity and permeability of the lipid bilayer. However, excessive uptake of cholesterol leads to cholesterol accumulation in macrophages and other immune cells [66].

Cholesterol activates the NLRP3 inflammasome through several mechanisms that are extensively documented in the literature. First, cholesterol is prone to form crystals in macrophages and diet-induced atherosclerotic lesions [67]. Macrophages attempt to phagocytose these crystals, but the rigid structure and excessive volume of the crystals lead to lysosomal damage. This induces the release of cathepsins which serve as DAMPs that trigger activation of the NLRP3 inflammasome [67]. Cholesterol accumulation also triggers ER stress—another factor related to chronic inflammation. Excessive cholesterol destabilizes the ER membrane by altering the lipid composition, affecting its fluidity, which leads to calcium depletion [68]. This leads to the triggering of the unfolded protein response (UPR), a mechanism which restores ER homeostasis. However, when the UPR becomes overactive, it triggers inflammation by upregulating key inflammatory factors like IL-1 β and promotes oxidative stress, both of which are linked to the activation of the NLRP3 inflammasome [69]. However, studies directly researching the effect of cholesterol on the NLRP3 inflammasome via ER stress have yet to be performed.

In the presence of oxidative stress and due to exposure to ROS, cholesterol can take an oxidized form: oxLDL. Studies using in vitro human retinal pigment epithelial cell models and in vivo rat models have demonstrated that oxLDL is taken up by macrophages via TLR4, leading to upregulation of NF- κ B signalling and thereby activation of NLRP3 [69]. OxLDL also causes mitochondrial stress, leading to increased ROS production. This induces macrophages to initiate inflammatory signalling but also directly activates NLRP3 by causing mitochondrial damage, which releases mtDNA into the cytosol—a signal promoting inflammasome assembly [69]. Additional research demonstrates that when mechanisms for the efflux of cholesterol are compromised (e.g., due to deficiencies in transporters such as ABCA1 and ABCG1), cholesterol builds up inside macrophages, leading to the uptake of oxLDL and creating an environment that is pro-inflammatory and favourable to the activation of inflammasomes [70]. As excessive cholesterol enhances NLRP3 activation in a feed-forward manner, Westerterp's results highlight the significance of maintaining cholesterol homeostasis in managing inflammation. While most studies highlight the pro-inflammatory role of cholesterol, Thankam, Khwaja [71] presented an alternative perspective, suggesting that initial oxLDL exposure, as opposed to sustained elevated oxLDL levels, suppresses several key NLRP3 pathway mediators such as TLR4, ASC, NLRP3 and IL-18 in macrophages. This indicates that initial exposure to oxLDL might involve pathways that aim to limit inflammation and mitigate cellular damage, possibly as a survival response [71].

To study the effect of cholesterol on inflammatory pathways like NLRP3 inflammasome activation, mainly in vitro macrophage models and in vivo rodent models were used. Although these models are suitable to provide insight in how hypercholesterolemia contributes to inflammatory processes, it is important to note that they have limitations. Currently, human clinical trials specifically researching the effect of cholesterol on NLRP3 inflammasome activation are limited. However, some clinical studies have concluded that administration of cholesterol lowering therapeutics—statins—significantly reduces NLRP3 activation due to an increase in AMPK levels [72]. In conclusion, across the reviewed studies, there is a broad consensus about the pro-inflammatory effect of cholesterol and derivatives such as oxLDL on NLRP3 inflammasome activation. Frequently mentioned triggers are lysosomal rupture, ER stress, and mitochondrial dysfunction. However, results should be noted carefully as low levels of oxLDL are found to trigger a survival or protective reaction instead of inflammation.

5.3. PUFAs: Omega-6 Fatty Acid Imbalance

Polyunsaturated fatty acids (PUFAs) are essential fats characterized by multiple double bonds in their fatty acid chain, distinguishing them from monounsaturated fatty acids (MUFAs) and SFAs, which lack double bonds [73]. PUFAs need to be obtained through dietary sources and cannot be synthesized by the body. Omega-6 fatty acids, one of the main types of PUFAs, are found in vegetable oils, nuts, and seeds in the form of arachidonic acid (ARA) or its precursor linoleic acid (LA) or [74]. These fatty acids play critical roles in maintaining cell membrane structure, producing signalling molecules, supporting nerve health and are a significant energy source [74].

5.3.1. Omega-6 Activation of the NLRP3 Inflammasome

Despite their beneficial effects, omega-6 PUFAs, particularly ARA, have been linked to inflammation [74]. This is because ARA is a precursor of several pro-inflammatory lipid mediators such as eicosanoids, including prostaglandins and leukotrienes, which mediate inflammatory responses [74]. Supporting this, a study by Liu, Yeung [75] in myeloid-derived suppressor cells has shown that accumulation of ARA in the cell caused mitochondrial dysfunction and an increase in ROS; both triggers for NLRP3 inflammasome activation. Additionally, there is a broader evidence suggesting that excessive intake of omega-6 fatty acids relative to omega-3s promotes inflammation and increases the risk of chronic inflammatory diseases such as obesity, NAFLD and cardiovascular disease [76]. A Japanese cohort study, including 38,234 Japanese women, even found an association between omega-6 PUFA intake and breast cancer, further linking omega-6 imbalance to inflammatory and disease-promoting pathways [77].

5.3.2. Omega-6 Inhibition of the NLRP3 Inflammasome

On the contrary, omega-6 fatty acids have also demonstrated anti-inflammatory properties and the ability to inhibit the NLRP3 inflammasome under certain conditions. A study by Pereira, Liang [78] found that in LPS-primed bone marrow-derived macrophages (BMDMs), stimulated with nigericin to activate the NLRP3 inflammasome, ARA inhibited the NLRP3 inflammasome through the C-c-Jun N-terminal kinase (PLC-JNK) pathway. This is particularly significant because JNK plays a role in priming (signal 1), while PLC is involved in the activation (signal 2) of the NLRP3 inflammasome [27]. Furthermore, the same study investigated fasting volunteers and reported elevated plasma AA levels during fasting, which coincided with decreased IL-1 β production [78]. These findings emphasize a potential link between fasting, ARA and NLRP3 suppression, suggesting that ARA may serve as a key regulator in reducing inflammatory responses [78].

However, it is important to note that further studies are required to unambiguously link AA to reduced inflammation in in vivo models and validate the proposed mechanisms.

5.3.3. Contradictory Findings and the Importance of Balance

Adding to this complexity, findings regarding the role of omega-6 fatty acids in inflammation remain contradictory. Studies in healthy human adults have shown that increased intake of LA or ARA does not necessarily elevate the energy of inflammatory markers [74]. More specifically, epidemiological research suggests that LA and ARA might even be associated with reduced inflammation [74]. These conflicting results highlight the context-dependent effects of omega-6 fatty acids on the NLRP3 inflammasome and inflammation. It becomes increasingly clear that the balance between omega-6 and omega-3 fatty acids plays a critical role in determining their inflammatory potential. Excess omega-6 intake relative to omega-3s may promote inflammation, while a well-regulated ratio could support anti-inflammatory processes and NLRP3 suppression.

It is evident that lipids, particularly omega-6 fatty acids, are important regulators of the NLRP3 inflammasome, although the mechanisms remain incompletely understood and have not yet been extensively studied. Current research suggests that omega-6 PUFAs can both activate and inhibit the inflammasome depending on cellular conditions and external factors such as dietary balance. The available evidence underscores the necessity of maintaining an appropriate balance between omega-6 and omega-3 fatty acids to optimize health and reduce the risk of chronic inflammation.

5.4. Natural Sugars

Sugars are naturally present in healthy dietary components including fruits, fruit juices, honey, vegetables, brown rice, whole grain pasta and milk. These natural sugars are classified into several types, including monosaccharides, such as glucose and fructose, as well as disaccharides like sucrose (a combination of glucose and fructose) and lactose (a combination of glucose and galactose) [79]. Natural sugars are known to provide quick energy and offer nutritional benefits, such as having a lower glycemic index, which can enhance insulin sensitivity and help sustain energy levels [80]. However, over the past 30 years, sugar consumption has drastically risen worldwide, and excessive intake is widely recognized as a significant cause of NCDs [81]. In particular, overconsumption of glucose and fructose has been associated with oxidative stress, mitochondrial dysfunction and ER stress [13]. Consequently, emerging evidence shows that sugars, especially fructose and glucose, can activate the NLRP3 inflammasome via several key pathways. Because fructose and glucose are monosaccharides, they are more easily metabolized than disaccharides like sucrose and lactose which require first to be broken down into their monosaccharide components. Consequently, fructose and glucose are studied more for their direct effects on the NLRP3 inflammasome. Besides research in various cell lines, rodent models are widely used to simulate diseases like diabetes, obesity and NAFLD providing insights in the effect of high-glucose and high-fructose diets on NLRP3 inflammasome activation and related disease progression.

5.4.1. Mechanisms of NLRP3 Activation by Fructose

Fructose is absorbed passively from the intestines and metabolized in the liver where its metabolites contribute to lipogenesis, uric acid production, and generation of ROS; all which are factors known to promote activation of the NLRP3 inflammasome. Notably, fructose metabolism promotes lipogenesis, which leads to mitochondrial stress and overproduction of ROS [82]. Additionally, fructose has been shown to stimulate the enzyme NADPH oxidase, which further elevates intracellular ROS levels, in rat kidney cells [83]. Increased ROS acts as a DAMP, promoting assembly of the NLRP3 inflammasome.

Another study where rats were fed a high fructose diet showed an increase in hepatic ROS generation by sixfold when compared to chow fed rats [84]. Furthermore, ROS upregulate TXNIP, which binds directly to NLRP3, thereby triggering inflammasome activation [85]. Supporting this, a study on hepatic inflammation in rats consuming high-fructose diets demonstrated that fructose causes downregulation of mi-R200a, a microRNA that normally suppresses TXNIP expression [85]. This downregulation leads to the accumulation of TXNIP, which subsequently activates the NLRP3 inflammasome, highlighting the critical role of TXNIP regulation in fructose-driven inflammation. Moreover, fructose metabolism generally bypasses glycolytic regulation, leading to depletion of ATP, lipid accumulation and overproduction of uric acid [13,82]. The resulting accumulation of lipids induces ER stress, while uric acid itself functions as a DAMP, further contributing to the priming and activation of the NLRP3 inflammasome. Specifically, uric acid and ER stress upregulate the transcription of key inflammasome components such as NLRP3, ASC and pro-IL-1 β [84]. Additionally, lipid-induced ER stress triggers inflammatory signalling pathways, such as PERK and IRE1a, which contribute to NLRP3 priming by increasing the expression of related genes [86]. Together, these mechanisms illustrate how fructose metabolism promotes both the priming and activation of the NLRP3 inflammasome through a combination of ROS generation, TXNIP upregulation, uric acid accumulation and ER stress.

5.4.2. Mechanisms of NLRP3 Activation by Glucose

Elevated glucose levels are often used in research to activate the NLRP3 inflammasome, especially in the context of diseases like diabetes, where hyperglycaemia-induced NLRP3 activation contributes to inflammatory complications [87]. This highlights the fact that glucose is a consistent activator of the NLRP3 inflammasome under experimental conditions, allowing it to be used to study the efficacy of potential inhibitors of the inflammasome [85,88]. Elevated glucose levels have been shown to activate the NLRP3 inflammasome via various mechanisms. In rat-derived cardiomyocytes, high glucose conditions, in the presence of lipopolysaccharide (LPS), has been shown to increase ROS production [89]. This was supported by a study in mouse microglial cells, in which they were cultured in a high glucose environment where increased intracellular ROS accumulation was found to act as a DAMP to activate NLRP3 [90]. This study also found high glucose to enhance phosphorylation of NF- κ B p65 which primes the NLRP3 inflammasome for activation. Interestingly, this activation occurred independently of the TLR4/MyD88 pathway, which is a classical upstream regulator of NF- κ B signalling [27]. However, exact mechanisms through which high glucose enhances NF- κ B signalling remain unknown. Several other processes including increased expression of purinergic receptor P2X7R, phosphorylation of dsRNA-dependent protein kinase (PKR) and upregulation of TXNIP were found to be induced by high glucose and to stimulate signal 2 in NLRP3 activation [90,91].

5.4.3. AGEs

Advanced glycation end-products (AGEs) are formed by non-enzymatic glycation of proteins or lipids. They particularly form due to high-glucose diets where there are elevated glucose levels in the blood [92]. They can also be digested through food, particularly through foods cooked on high heat using cooking methods such as grilling, frying, roasting and baking. AGEs have been shown to promote NLRP3 inflammasome activation both in vivo and in vitro, in mouse models. The interaction between AGEs and their receptor (RAGE), triggers ROS production through upregulation of NADPH oxidase [92]. This leads to binding of TXNIP to the NLRP3 protein, directly activating the inflammasome complex. Besides production of ROS, other research in human dermal fibroblasts

highlights that the interaction between AGE and its receptor (RAGE) can also activate the NF- κ B signalling pathway, thereby priming the NLRP3 inflammasome [93].

In conclusion, there is an extensive body of evidence on the activating effects of fructose and glucose on the NLRP3 inflammasome. However, no studies were found on the synergistic effects of natural sugars on the NLRP3 inflammasome. However, this is of importance as a healthy diet includes several types of natural sugars, often in combination.

5.5. Artificial Sweeteners

Artificial sweeteners are commonly found in food and beverages to reduce sugar intake as they are non-nutritive chemical compounds that add sweetness without the calories of sugars [94]. Recommendations for a healthy diet often emphasize reducing sugar intake, leading many to replace sugar with artificial sweeteners as a perceived healthier option. Artificial sweeteners are therefore widely used in sugar-free sweets, diet drinks, baked goods and dairy products. There are several types of artificial sweeteners: saccharin, aspartame, acesulfame potassium (Ace-K), sucralose and steviol glycosides (Stevia) which differ in chemical structure and sweetness potency [94]. Numerous debates about the potential health risks associated with artificial sweeteners exist [95,96]. According to some studies, these substances may be involved in harmful health effects such as altered gut microbiome, cardiovascular risks, and metabolic disturbances.

Mechanisms of NLRP3 Interference

Research on the connection between artificial sweeteners and inflammation are emerging and ongoing. Several preclinical studies have linked artificial sweeteners to pro-inflammatory effects that could indirectly or directly influence NLRP3 activation pathways. Aspartame, for example, has been shown to worsen metabolic dysregulation and oxidative stress, especially in liver tissue [97]. Hepatic fibrosis, lipid peroxidation and the activation of inflammatory pathways, such as NF- κ B, have all been linked to long-term aspartame use in mice [97]. This indicates that oxidative stress from aspartame might predispose tissues to NLRP3 activation in specific metabolic contexts [98]. However, there is currently minimal direct evidence from human studies, which makes extrapolation of the applicability of these effects to human physiology questionable [99].

Additionally, Ace-K has also been linked to inflammatory effects through gut dysbiosis and changes in lipid metabolism. Research conducted on ApoE^{-/-} mice revealed that Ace-K increases hepatic lipogenesis and decreases β -oxidation, resulting in a lipid-rich environment that promotes inflammation and worsens atherosclerosis [100]. Pro-inflammatory signals may be triggered by this metabolic disruption, which may ultimately lead to NLRP3 activation. Furthermore, another study found that Ace-K caused substantial changes in the gut microbiota, which resulted in lymphocyte migration to the intestinal mucosa and breakdown of the intestinal barrier [101]. The NLRP3 inflammasome in the gut is known to be triggered by endotoxins and inflammatory mediators, which may rise because of the subsequent dysbiosis and barrier degradation [101]. This supports the more general hypothesis that metabolic endotoxemia and low-grade inflammation are two ways that gut dysbiosis caused by artificial sweeteners indirectly primes the NLRP3 inflammasome [102]. However, other studies propose that the effects can vary depending on a person's metabolic state and gut microbiome composition, leading to a variety of inflammatory responses [103].

In contrast, stevia, which is frequently presented as a 'natural' sweetener, has demonstrated anti-inflammatory properties. More specifically, stevia residue extract demonstrated its ability to downregulate inflammation by reducing oxidative stress and inhibiting the NF- κ B/NLRP3 pathway in a mouse model of renal inflammation [104]. This protective function may be explained by its polyphenolic compounds, which function as

antioxidants and reduce the generation of ROS, thereby preventing the activation of inflammasomes. However, it is crucial to note that research mostly concentrates on stevia extracts, rather than isolated steviol glycosides, which are used in food products. It is therefore questionable whether these anti-inflammatory effects observed in stevia extracts extend to the processed sweeteners used in food. Especially because most studies indicate that these compounds have less noticeable protective effects [105].

The inconsistent results among artificial sweeteners underscore persistent debates about their ability to cause inflammation and the role that NLRP3 activation plays. Data suggests that artificial sweeteners like aspartame, Ace-K and sucralose promote NLRP3 activation, while stevia might have protective properties. Additionally, although inflammasome activation pathways are demonstrated in animal research, especially in relation to oxidative stress, metabolic dysregulation and gut dysbiosis, there is still little and occasionally conflicting direct evidence in humans. Inconsistent results are possibly caused by variations in gut microbiota composition and metabolic reactions to artificial sweeteners [106]. Therefore, further clinical research is necessary to fully comprehend the effects of artificial sweeteners on NLRP3 activation and inflammation, especially in those with dysbiosis or those who are metabolically vulnerable.

6. Anti-Inflammatory Triggers in a Healthy Diet

A healthy diet contains several components that help mitigate inflammation by inhibiting the NLRP3 inflammasome. Key nutrients such as monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs) like omega-3, antioxidants (including polyphenols and vitamins C and E), dietary fibre and probiotics play a critical role in reducing oxidative stress and inhibiting inflammation. This chapter will explore the mechanisms and evidence behind these anti-inflammatory properties and their role in modulating the NLRP3 inflammasome.

6.1. Monounsaturated Fatty Acids (MUFAs)

MUFAs are a type of unsaturated fat found in foods like olive oil, avocados and nuts. Common forms of MUFAs are omega-7 fatty acids, such as palmitoleic acid, and omega-9 fatty acids, such as oleic acid [107]. Higher intakes of MUFAs, and lower consumption of SFAs, have consistently shown to decrease the risk of cardiovascular diseases [108]. While SFAs are known to increase inflammation, unsaturated fatty acids have an opposite effect by reducing cytokine release and ER stress [109,110].

Although there is limited evidence on the specific impact of MUFAs on inflammation, there is mounting evidence that they have anti-inflammatory properties [110,111]. A study in an hepatocyte cell line has shown that oleate, an ionized form of the MUFA oleic acid, protects against SFA-induced lipotoxicity by reducing ER stress, ROS production and activation of inflammation markers such as NLRP3 [112]. Additionally, oleate acts as a PPAR α agonist which activates SIRT1 thereby inhibiting the NF- κ B/NLRP3 pathway. [113]. Incubation mouse of bone-marrow derived macrophages and adipose tissue with oleate has shown to activate AMPK, showing another mechanism of NLRP3 inhibition [59]. Several animal studies support these findings, providing evidence for the anti-inflammatory effects of MUFAs. For example, mice fed a MUFA-rich diet for several weeks show decreased levels of pro-inflammatory markers such as IL-1 β and increased expression of anti-inflammatory markers like IL-4 and IL-10 [114]. However, it must be noted that this study does not particularly mention the NLRP3 inflammasome.

In conclusion, the evidence supporting the role of MUFAs inhibiting the NLRP3 inflammasome is growing but still limited. Studies including cellular models demonstrate that MUFAs, such as oleate and palmitoleate, inhibit NLRP3 activation through various pathways with animal studies further supporting these findings. However, most findings are

deduced from the wider anti-inflammatory advantages of a MUFA rich diet, including the Mediterranean diet, while direct evidence linking MUFA intake to NLRP3 inhibition in humans remains scarce. Therefore, more clinical research is required to validate these benefits.

6.2. PUFAs: Omega-3 Fatty Acids

Besides the earlier mentioned omega-6 fatty acids, another type of PUFAs are omega-3 fatty acids, which are well-known for their anti-inflammatory abilities. Omega-3s are commonly found in fish oils as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and in plant sources in the form of alpha-linolenic acid (ALA). Research has shown that omega-3 fatty acids, particular EPA and DHA, inhibit NLRP3 inflammasome activation in macrophages by reducing the release of ROS and modulating mitochondrial function [115]. A study by Yan, Jiang [116] shows that omega-3 PUFAs prevent NLRP3 inflammasome activation through binding to G protein-coupled receptors (GPR120 and GPR40), which signal through β -arrestin-2 (ARRB2) to inhibit caspase-1 activation and IL-1 β secretion, thereby limiting ER stress and oxidative stress in adipose and liver tissues. Another study confirms this mechanism by stating that omega-3 PUFAs bind to GPR40, which recruits ARRB2 to directly interact with NLRP3, preventing its mitochondrial localization and thereby reducing pro-inflammatory cytokine release [117]. Furthermore, omega-3 PUFAs upregulate AMPK expression and inhibit NF- κ B, a key transcription factor in gene expression and cytokine inflammation, through interacting with GPRs [73,118]. An in vivo study in obese human subjects who ingested fish oil supplementation showed a down-regulation of gene expression of IL-18, IL-1 β and caspase-1—all NLRP3 associated genes [115]. Additionally, it was shown that EPA and DHA acted on both visceral and subcutaneous adipose tissues [115]. PUFA metabolites, such as lipid peroxides and hydroxylated fatty acids, further modulate oxidative stress and redox balance, stabilizing cellular states and indirectly suppressing the NLRP3 inflammasome [118]. Overall, omega-3 PUFAs exert their anti-inflammatory effects by reducing mitochondrial and ER stress, regulating GPR signalling, and lowering ROS, making them crucial components of an anti-inflammatory diet.

6.3. Antioxidants: Polyphenols, Vitamin C and E

Antioxidants are substances that defend the body against ROS and oxidative damage, thereby preventing chronic inflammation [119]. They have the potential to neutralize free radicals which could otherwise cause cellular damage. Natural antioxidants are found in foods containing phenolic compounds or vitamin A, B, C and E including fruits, vegetables, nuts, and seeds. All of which are introduced by the WHO as rich sources of natural antioxidants. Research has shown that eating a diet rich in antioxidants can reduce the risk of developing diabetes, Alzheimer's disease, cardiovascular disease and several types of cancer [119].

6.3.1. Polyphenols

Polyphenols, a class of secondary metabolites, also have a suppressive effect on the activation of the NLRP3 inflammasome due to their immunomodulatory abilities [120]. They act in immunometabolic pathways in various ways, one of which is through interference with the assembly of NLRP3 in ER-mitochondria contact sites [121]. Thereby, inhibiting activation of the inflammasome through improvement of mitochondrial biogenesis and autophagosome-lysosome fusion [121]. Quercetin, a type of polyphenol prominent in the human diet, has been shown to suppress LPS-induced intracellular ROS production and NF- κ B activation in a microglia mouse cell line [122]. Additionally, quercetin treatment inhibited LPS-induced increase in the expression of NLRP3, caspase-1 and IL-1 β , in a concentration dependent manner, proving inhibition NLRP3 inflammation

activation [122]. Interestingly, this inhibition also prevents cleavage of GSDMD into its N-terminus and the formation of pyroptosis-related pores in the plasma membrane, thereby inhibiting pyroptosis [122]. Similarly to vitamin C, quercetin also decreases mitochondrial ROS generation through the promotion of mitophagy [122]. This restrains mtROS from functioning as a signal to assembly activators to promote and amplify NLRP3 inflammasome activation. In vivo, quercetin pretreatment even ameliorated LPS-induced depression-like behaviours and dopaminergic neuron loss in mouse models of depression and Parkinson's disease, by inhibiting microglial activation through the NLRP3/IL-1 β pathway. Thereby demonstrating quercetin's therapeutic effect on neuroinflammation-related neuronal injury [122]. Resveratrol, another natural polyphenol, has another interesting anti-inflammatory effect. Research by Misawa, Saitoh [123] has shown that resveratrol reduces the acetylation of α -tubulin, a key structural protein required for appropriate positioning of mitochondria and the ER to facilitate NLRP3 and ASC assembly. Disrupting the accumulation of acetylated α -tubulin therefore inhibits the formation of the NLRP3 inflammasome [123]. In conclusion, polyphenols act as potent antioxidants by scavenging ROS and promoting mitophagy which leads to a reduced release of ROS, disruption of acetylation of α -tubulin and inhibition of NLRP3 assembly.

6.3.2. Vitamin C

Several studies on the effects of vitamin C on the NLRP3 inflammasome have been performed. A study by Liu, Si [124] investigates the effects of vitamin C on age-related hearing loss, a condition wherein activation of the NLRP3 inflammasome has a key role. It was shown that vitamin C treatment reduced the production of inflammatory cytokines IL-1 β and IL-18, decreased cytosolic mtDNA levels and thus decreased NLRP3 inflammasome activation in auditory pathways of treated mice. Another study highlights how vitamin C treatment induces decreased ROS production, thereby suppressing activation of the AKT/mTOR pathway in cardiomyocyte cells. Deactivation of this pathway led to a reduced expression of NLRP3, caspase-1 and GSDMD, resulting in lower levels of IL-1 β and IL-18. In this study, vitamin C alleviated LPS-induced myocardial injury by inhibiting pyroptosis [125]. In vivo, vitamin C has shown its inhibitory effect on the NLRP3 inflammasome in bone marrow-derived macrophages, wherein the inflammasome was activated through treatment with LPS + ATP [126]. Increasing concentrations of vitamin C resulted in decreased IL-1 β and caspase-1 secretion. Additionally, ASC oligomerization was strongly inhibited indicating that vitamin C exerts a suppressive effect through altering the phosphorylation status of ASC. This inhibitory effect on the NLRP3 inflammasome was found to be due to the ability of vitamin C to scavenge mitochondrial ROS generation. In an LPS-induced mouse septic shock model, vitamin C treatment decreased inflammasome-dependent IL-1 β production upon LPS injection. Highlighting the inhibitory effect of vitamin C, both in vivo and in vitro [126].

6.3.3. Vitamin E

Vitamin E, specifically in its alpha-TOH form, accumulates in the mitochondria of inflamed rat cardiomyocytes, where it blocks ROS production [127]. Thereby reducing mtROS-dependent translocation of the NF- κ B p65 subunit into the nucleus and the expression of ASC [127]. Additionally, the unsaturated gamma-tocotrienol (γ T3) form of vitamin E, has also been shown to inhibit the NLRP3 inflammasome through various mechanisms [128]. In macrophages, treatment with γ T3 suppressed expression of *Cox2*, this was most likely through the inhibition of NF- κ B activation—the most critical factor for priming of the NLRP3 inflammasome [128]. Additionally, γ T3 was found to reduce the levels of lipid mediators, such as prostaglandins and leukotrienes, which are closely linked to inflammasome activation and inflammation. Another form of vitamin E,

recognized for its antioxidant effects, is gamma-tocopherol (GT). In alloxan-induced diabetic mice, GT supplementation significantly lowered the protein levels of NLRP3, procaspase-1, caspase-1, pro-IL-1 β and IL-18 in hepatocytes [129]. A decrease in NF- κ B levels was also identified in this in vivo model, confirming earlier mentioned in vitro results. A study by Dapuerto, Rodriguez-Duarte [130] proved the inhibitory effect of a vitamin E analogue on human macrophage-like cells (THP-1), by showing NF- κ B and ASC oligomerization inhibition upon stimulation with the analogue.

Taken together, it is evident that antioxidants like polyphenols, vitamin C and vitamin E exert an inhibitory effect on the NLRP3 inflammasome through various mechanisms. While reducing production of ROS is a well-known trait of antioxidants, other pathways including mitochondrial effects and lipid mediators remain understudied. Additionally, most research is performed on the effects of single antioxidants, while combinations of these substances or interactions with gut microbiota, might have differing effects.

6.4. Probiotics, Dietary Fibre and Short Chain Fatty Acids

Probiotics, like *Lactobacillus* and *Bifidobacterium*, interact with dietary fibre to produce metabolites like short-chain fatty acids (SCFAs), which regulate immune responses [131]. Probiotics are naturally present in a healthy diet in fermented dairy products, such as yoghurt and kefir, fermented non-dairy foods, such as sauerkraut and kimchi, and beverages like kombucha. Dietary fibre, found in foods like oats, nuts, seeds, fruits, whole grains and legumes, serves as the primary substrate for gut microbiota fermentation into SCFAs. The interplay between probiotics, dietary fibre, SCFAs, and the NLRP3 inflammasome is a complex area of research that highlights both the beneficial and detrimental effects of these components on inflammation.

6.4.1. Probiotics

Probiotics regulate activation of the NLRP3 inflammasome through direct and indirect mechanisms. Indirectly, they produce SCFAs that modulate inflammation, while directly, they interact with immune pathways, including Toll-like receptors, to influence immune responses [132]. For example, in vitro studies using a THP-1-derived macrophage cell line have shown heat-killed *Enterococcus faecalis*—a type of probiotic—inhibits NLRP3 activation [133]. In vivo studies further highlight these effects. Pig models infected with *Enterotoxigenic Escherichia coli* (ETEC) or fed high-fat diets demonstrated that *Clostridium butyricum* and multispecies probiotic formulations suppress NLRP3 inflammasome activation, reduce IL- β and IL-18 levels, and increase anti-inflammatory IL-10 expression [134]. In mouse models, bacteriocins produced by *Lactobacillus* species reduced proinflammatory cytokines and prevented excessive NLRP3 activation in high-fat diet-induced obesity [135]. Similarly, in hamster models, a multispecies probiotic formulation reduced NLRP3 and NF- κ B activation under stress and obesity-related conditions [136]. Furthermore, in a mouse model of IgA nephropathy, probiotics suppressed NLRP3 inflammasome formation by reducing ASC and caspase-1 expression [137]. These findings underscore the efficacy of probiotics in regulating NLRP3 activity and reducing inflammation in in vivo and in vitro models.

6.4.2. SCFAs

Probiotics ferment dietary fibre into SCFAs, such as butyrate, propionate and acetate, which can influence NLRP3 inflammasome activity. SCFAs have shown protective effects in multiple models of inflammation. For instance, in a mouse model of chronic kidney disease, sodium acetate and sodium propionate inhibited the NLRP3/ACS/caspase-1 pathway, reducing inflammation [137]. Similarly, BMDMs treated with acetate displayed reduced NLRP3 activation via GPR43 signalling, which decreased Ca²⁺ mobilization and

limited assembly of the NLRP3 inflammasome complex [138]. Additionally, butyrate has shown to promote autophagy in macrophages [139]. This occurs through the activation of AMPK and inhibition of mTOR, leading to the clearance of damaged mitochondria through mitophagy [139]. By facilitating the removal of dysfunctional mitochondria, SCFAs help reduce ROS production and thereby activation of the NLRP3 inflammasome.

6.4.3. Pro-Inflammatory Effects of SCFAs

However, SCFAs can also act as pro-inflammatory mediators in specific contexts, such as pre-existing inflammatory conditions. For example, in human monocyte-derived macrophages stimulated with Toll-like receptor (TLR) agonists to mimic IBD conditions, SCFAs (butyrate and propionate) enhanced NLRP3 activation [140]. This occurred through epigenetic modulation, inhibiting anti-inflammatory proteins like cFLIP and IL-10. Additionally, acetate has been found to increase IL-1 β production in macrophages by enhancing glycolysis, leading to hypoxia-inducible factor 1-alpha (HIF-1 α) activation and subsequent NLRP3 inflammasome activation [141]. These findings highlight the dual role of SCFAs, which can either suppress or promote NLRP3 activation depending on the inflammatory environment.

Interestingly, SCFAs exhibit contrasting effects on the NLRP3 inflammasome in different tissues and diseases. In colonic epithelial cells of DDS-induced colitis mice models, SCFAs, particularly acetate, activated the NLRP3 inflammasome via the metabolite-sensing receptor GPR43 [142]. This occurred through membrane hyperpolarization and calcium-dependent potassium efflux, which promoted inflammasome activation and IL-18 production. In contrast, a study by Zuo, Fang [143] demonstrated that acetate inhibits NLRP3 inflammasome activation in cardiac fibroblasts via GPR43 signalling. This suppression reduced NLRP3 activity, alleviating inflammation and protecting against atrial fibrillation [143]. These contrasting findings underscore the complexity of SCFA effects, as they can either activate or suppress the NLRP3 inflammasome depending on the cell type, signalling pathway and disease context. In conclusion, probiotics, dietary fibre, and SCFAs play a dual role in modulating the NLRP3 inflammasome, with effects that vary depending on the cellular and disease context. Figure 2 illustrates the opposing effects of pro-inflammatory and anti-inflammatory dietary constituents on NLRP3 inflammasome activation.

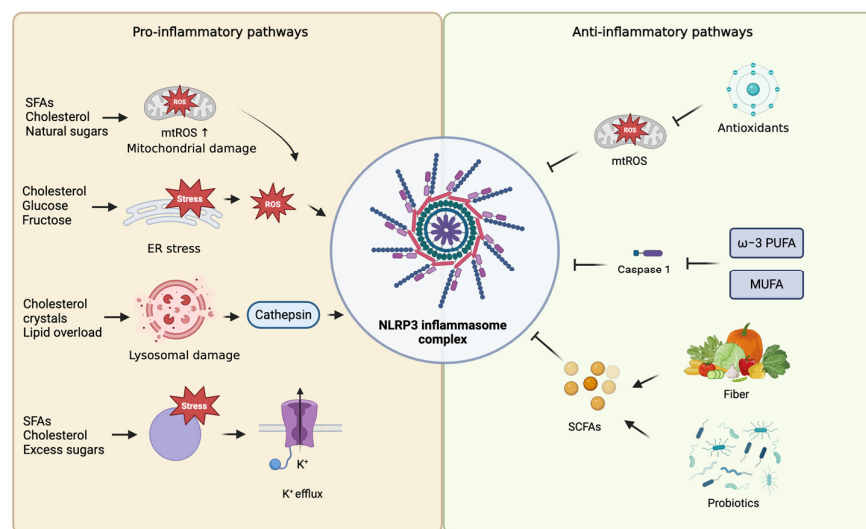


Figure 2. Dietary modulation of NLRP3 inflammasome activity: pro- and anti-inflammatory pathways. Created with BioRender.com.

7. Balancing Anti- and Pro-Inflammatory Dietary Components

It is evident that a healthy diet contains both pro-inflammatory and anti-inflammatory components which stimulate or reduce activation of the NLRP3 inflammasome. This effect depends on factors such as nutrient availability, levels of oxidative stress, gut microbiota composition and which types of cells are targeted (e.g., macrophages, epithelial cells, adipocytes, hepatocytes). On the one hand, SFAs, cholesterol, natural sugars and artificial sweeteners have been shown to stimulate the NLRP3 inflammasome in cellular and animal models (Figure 3). On the other hand, MUFAs, polyphenols, vitamin C, vitamin E and probiotics have been reported to suppress inflammasome activation. Interestingly, certain components, such as omega-3 and omega-6 PUFAs and SCFAs, can exhibit both pro- and anti-inflammatory effects depending on their context and balance. Highlighting the importance of maintaining a balanced diet as promoted by the WHO, and other official health organizations. However, it must be noted that this review only includes the discussion of a selection of dietary components, modulating the NLRP3 inflammasome.

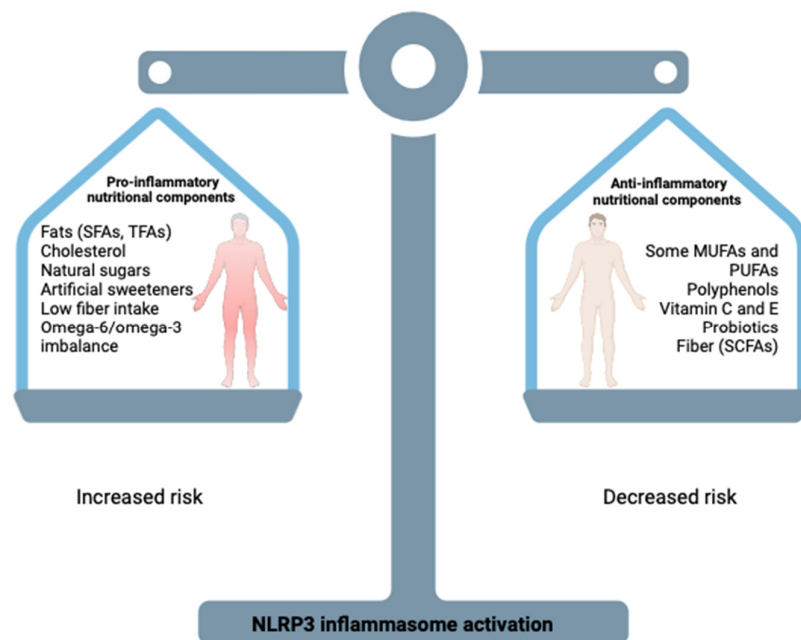


Figure 3. Visual summary of several dietary components which are associated with an increased or decreased risk of activating the NLRP3 inflammasome as is discussed in the current review.

7.1. The Food Matrix

As the human diet consists of a wide variety of foods, nutrients, and bioactive compounds, their effects should not be considered in isolation but rather as the result of their combined and cooperative interactions. This concept is also known as the ‘food matrix’ and describes the physical and chemical structure of a food product, including how its components interact and are organized [144]. Components of this food matrix can interact, thereby affecting nutrient absorption, digestion, modulation of gut microbiota and health outcomes [145]. For example, apples contain both fibre and flavonoids, a type of polyphenol, which have a synergistic relationship. However, clear apple juice, which lacks a cellular matrix, is high in fructose and low in fibre and may have negative nutritional effects by stimulating inflammation [146]. These interactions between and within dietary components must be considered when evaluating the (inflammatory) effects of diet.

7.2. Synergy in a Healthy Diet

The omega-6/omega-3 ratio is one of the most well-documented examples of dietary balance affecting inflammation. A large-scale study in the UK Biobank showed that a higher ratio of omega-6/omega-3 PUFAs was strongly associated with increased all-cause cancer and cardiovascular mortality [147]. A traditional hunter-gatherer diet had an estimated ratio of 1:1 omega-6/omega-3 ratio, whereas modern Western diets often exceed 15:1 due to large-scale use of vegetable oils and industrialized agriculture [148]. This imbalance favours inflammation, emphasizing the importance of a balanced diet including enough omega-3 PUFAs, as seen in the Mediterranean diet. Moreover, certain dietary components work synergistically to modulate inflammation. For example, the combination of antioxidants like vitamin E and omega-3 fatty acids amplifies their anti-inflammatory effects by reducing oxidative stress and suppressing pro-inflammatory cytokine production [149]. The Mediterranean diet is an example of a diet which integrates multiple anti-inflammatory elements such as olive oil (rich in MUFAs and polyphenols), fish (rich in omega-3s), fruits and vegetables (rich in polyphenols and fibre). The anti-inflammatory properties of these dietary components counteract the pro-inflammatory components of foods like red wine and certain meats, which are also part of the Mediterranean diet.

7.3. Diet as Regulator of Inflammatory Diseases

It has become well known that ‘unhealthy’ diets such as the Western diet are rich in SFAs, refined sugars and omega-6 PUFAs, while low in fibre and omega-3 PUFAs. These dietary imbalances are partly responsible for the development of inflammatory disorders including inflammatory bowel disease, obesity, type 2 diabetes, cardiovascular diseases and certain types of cancer [150]. Positively, diet can also improve health outcomes by reducing inflammation and therefore anti-inflammatory diets have gained attention as a method to modulate immune response. For example, the Groningen anti-inflammatory diet (GrAID) was developed based on the literature studying the effects of certain foods on the onset and course of IBD [151]. The GrAID provides patients with a list of foods that are beneficial or pro-inflammatory, and therefore detrimental, in the course of IBD. Thereby helping them to maintain an optimally balanced diet. Furthermore, type 2 diabetes, can be put in remission through a low calorie energy deficit diet [152]. However, it must be noted that this effect was mainly due to gap between energy required and taken in and not due to composition of the diet. Also, there was no particular benefit to avoiding foods frequently associated with inflammation, according to a randomized controlled feeding study of diabetic and pre-diabetic patients that examined the effects of an anti-inflammatory diet versus a control diet based on American Diabetes Association recommendations on body weight and inflammation markers [153].

7.4. Epigenetic Effects of Dietary Components

An interesting aspect is that diet can epigenetically regulate genes associated with inflammation, particularly in IBD [154]. Pro-inflammatory diets, rich in trans fats, SFAs, refined sugars, ultra-processed foods and additives, disrupt gut microbiota composition and increase DNA hypomethylation, histone modification, and dysregulates gene expression associated with inflammation [154]. These epigenetic changes alter the immune response and intestinal barrier function, worsening inflammatory processes in IBD [155]. On the other hand, anti-inflammatory diets influence DNA methylation and histone acetylation, leading to expression of anti-inflammatory genes by providing essential substrates for DNA methylation pathways [155]. For example, SCFAs derived from fibre inhibit histone deacetylases, thereby modulating the inflammatory response and inhibiting IBD progression [156]. Pro-inflammatory diets potentially also dysregulate the expression of non-coding RNAs, which play a crucial role in gene transcription and translation of

pro-inflammatory genes while anti-inflammatory diets have a role in restoring their function, thereby decreasing inflammation [157]. Additionally, environmental factors such as industrialization and use of antibiotics promote histone methylation or demethylation, leading to epigenetic modifications that reduce or induce the expression of certain genes. Altogether, this highlights the critical role of dietary modulation and balance in managing IBD through epigenetic pathways [154].

8. Conclusions

8.1. Need for Balance in NLRP3 Inflammasome Activation

Overactivation of the NLRP3 inflammasome is related to a variety of diseases including metabolic disorders, neurologic disorders, autoimmune and inflammatory disorders and tumorigenesis in several types of cancer. However, its role in pathogen defence, tissue repair and maintenance of gut homeostasis highlights that the NLRP3 inflammasome works as a molecular switch requiring tight regulation, rather than complete inhibition. As such, this dual role makes the development of therapeutic strategies difficult as over-suppressing the inflammasome could make individuals more susceptible to infections, disturb gut homeostasis and impair tissue recovery. This delicate balance underlines the need for precision medicine approaches, tailoring interventions to the individual patient's needs. Thus, future therapeutic strategies targeting the NLRP3 inflammasome should be directed toward its selective modulation rather than broad-spectrum suppression to achieve a balance between its beneficial and detrimental effects. This view is in line with an emerging emphasis on targeted treatments in immunology and inflammation research that may open perspectives for innovative solutions in the management of diseases related to NLRP3.

8.2. Methodological Challenges in NLRP3 Research

To fully exploit NLRP3 inflammasome's potential as a therapeutic target and to create novel, selective drugs, a thorough understanding of its biology is necessary. The biological characterization of the multimeric inflammasome complex, the discovery of the upstream signalling cascade that causes inflammasome activation and the downstream consequences brought on by NLRP3 activation have all been made possible by the development of tools, several of which are mentioned in this review. However, proving NLRP3 activation remains difficult due to its complex multiprotein structure with many signals modulating it. Additionally, an increase in mRNA of NLRP3 does not particularly indicate activation of the multiprotein inflammasome complex [158]. As transferability of used models is often insufficient, patient-derived induced pluripotent stem cell-derived disease models (iPS-DM) have been established to create patient-specific models of NLRP3-related disease. While this opens an exciting perspective on personalized insights, these models have not yet succeeded in fully mimicking the *in vivo* conditions. In conclusion, interdisciplinary collaboration and incorporation of novel technologies, including advanced imaging and multi-omics approaches, could tackle these challenges. Thereby promoting translation of NLRP3 research into actionable therapeutic strategies.

8.3. The Food Industry

Another broader challenge in applying a healthy dietary balance lies with the food industry which modifies products to align with health guidelines promoting a low-sugar, low-fat diet. Natural sugars are replaced by artificial sweeteners to reduce calories, and products labelled low in fat often contain added sugar, salt or emulsifiers to compensate for the lost flavour and texture. It is debatable whether these modifications are in fact healthier or just add another pro-inflammatory factor to the diet. The widespread

availability and affordability of processed, pro-inflammatory foods often make healthier options less accessible. Additionally, cultural and socioeconomic factors influence dietary patterns, creating barriers to adopting anti-inflammatory diets in some populations. Ultimately, the food industry's aim to reformulate dietary products to meet specific nutrient guidelines promotes an unhealthy diet rather than a healthy one. Instead of focusing on modified foods to meet guidelines, a more holistic approach emphasizing minimally processed, diverse, and nutrient-rich foods should be promoted. This shift is not limited to the food industry but should also be advocated for by regulatory bodies and via public awareness, to promote a truly healthy and balanced diet.

8.4. Implications for Further Research

Several large-scale human studies, exploring long-term effects of certain dietary components exist. Examples are the 'Women's Health Initiative' study which investigated the impact of a low-fat diet on the risk of death as a result of breast cancer and the 'EPIC-Oxford' Study which showed that vegetarians have a relatively lower risk of coronary heart disease and diabetes [159,160]. However, there is a lack of these types of studies, specifically examining the long-term effect of dietary components on NLRP3 inflammasome activation. This is possibly due to the complexity of pathways modulating the inflammasome and because there are limited biomarkers for determining the level of activation. Also, NLRP3 activation is influenced by (epi)genetic and environmental factors, differing per person, making it difficult to assign observed effects solely to dietary components in large-scale studies. Additionally, most large-scale studies on diet focus on broader health outcomes and complete clinical pictures. To address the current gaps in the literature, future research should focus on the development of biomarkers for measuring NLRP3 activity and integration of NLRP3 measurements in large-scale dietary studies. This way, the role of a balanced diet to maintain health via modulation of inflammatory complexes like the NLRP3 inflammasome will become more evident.

Although this is not a systematic review, it provides a comprehensive overview of how various components of a healthy diet modulate the NLRP3 inflammasome, highlighting the importance of maintaining a balance between pro- and anti-inflammatory triggers within the diet. This balance is important not only to prevent chronic inflammatory diseases but also for maintaining general immune homeostasis. This is evident from the interaction between certain nutritional factors and mechanisms like oxidative stress and mitochondrial dysfunction, which activate the NLRP3 inflammasome. The findings from this research highlight that while pro-inflammatory triggers such as saturated fats, cholesterol, and an imbalance in omega-6 to omega-3 fatty acids activate the NLRP3 inflammasome, anti-inflammatory components like monounsaturated fats, antioxidants, probiotics, and dietary fibre can counteract this activation. However, finding this balance may be difficult because many dietary components have dual roles and their effects are influenced by individual genetic predispositions, lifestyle choices, environmental circumstances and epigenetic effects. Moreover, targeting impaired mitochondria with novel mitophagy modulators derived from natural sources is also a promising approach [161]. Additionally, advances in the food industry, promoting intake of potentially pro-inflammatory dietary components, further complicate implementation of healthy, anti-inflammatory, diets. In conclusion, the role of dietary components in modulating the NLRP3 inflammasome, either promoting or mitigating inflammation, has attracted increasing interest. While dietary modulation of the NLRP3 inflammasome has a great potential to reduce inflammation and the associated diseases, several challenges remain in regard to fully understanding and applying these mechanisms. These challenges include handling the dual role of the NLRP3 inflammasome, limitations in current research methodologies, and the influence of the modern food industry on dietary patterns. Further research is required to

better understand the context-dependent effects of dietary components, which is essential to develop personalized dietary strategies that promote health through balanced nutritional choices.

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Abbreviations

The following abbreviations are used in this manuscript:

AMPK	AMP-activated protein kinase
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
BMDM	Bone marrow-derived macrophages
CD	Crohn's disease
DAMP	Danger-associated molecular patterns
DII	Dietary inflammatory index
GSDMD	Gasdermin D
IBD	Inflammatory bowel disease
IL-1 β	Interleukin-1 β
IL-18	Interleukin-18
LPS	Lipopolysaccharide
LRR	Leucine-rich repeat
MAVS	Mitochondrial antiviral-signalling protein
mtDNA	Mitochondrial DNA
mtROS	Mitochondrial reactive oxygen species
MUFA	Monounsaturated fatty acid
NCD	Noncommunicable diseases
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLR	NOD-like receptor
NLRP3	NOD-like receptor pyrin domain-containing 3
ox-mtDNA	Oxidized mitochondrial DNA
PAMP	Pathogen-associated molecular pattern
POP	Pyrin domain-only protein
PRR	Pattern recognition receptor
PUFA	Polyunsaturated fatty acid
PYD	Pyrin domain
ROS	Reactive oxygen species
SFA	Saturated fatty acids
SFA	Saturated fatty acid
TLR	Toll-like receptor
TRX	Thioredoxin
TXNIP	Thioredoxin-interacting protein
UC	Ulcerative colitis
WHO	World Health Organization

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