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Review Article

The anti-inflammatory properties of honey: A natural remedy for modern health challenges

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Abstract

Inflammation is a fundamental biological response to harmful stimuli playing a crucial role in the body's defense mechanisms against pathogens, toxins and injuries. While acute inflammation is a protective response that aids in tissue repair chronic inflammation ac led to long-term health issues such as arthritis, cardiovascular disease and cancer. The management of inflammation is essential for maintaining overall health and anti-inflammatory agents are pivotal in modulating the inflammatory response. Although conventional anti-inflammatory drugs like NSAIDs and corticosteroids are effective heir side effects have spurred interest in natural alternatives. Among these honey stands out due to its rich composition of bioactive compounds, including phenolic acids, flavonoids, enzymes and antioxidants, which contribute to its anti-inflammatory properties.

The mechanisms include modulation of pro-inflammatory cytokines, inhibition of NF-κB and other inflammatory pathways, antioxidant activity and regulation of immune cell responses. Various types of honey such as Manuka, buckwheat and acacia honey along with regional varieties are examined for their distinct anti-inflammatory effects. Additionally, the therapeutic applications of honey in managing autoimmune disorders, chronic inflammatory conditions, respiratory infections and wound healing are discussed. The review addresses factors affecting honey's anti-inflammatory potency, quality control, potential limitations and future research directions highlighting its promise as a natural therapeutic agent.

Keywords: Inflammation, Honey, Manuka, Buckwheat, Acacia honey, Natural remedy, Anti-Inflammatory.

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1. Introduction

Inflammation is an essential biological response that occurs in the body when faced with harmful stimuli such as pathogens, toxins, injuries and irritants. This complex process entails the activation of the immune system which seeks to eliminate the source of injury, clear away damaged cells, and initiate the repair of tissues. There are two main types of inflammation: acute and chronic. Acute inflammation is a short-lived response characterized by redness, swelling, heat and pain, which helps the body to recover swiftly from injuries or infections.[1] In contrast, chronic inflammation is long-term and may result from persistent infections, autoimmune disorders or environmental factors often leading to tissue damage and contributing to various diseases, including arthritis, heart disease and cancer.[2]

Inflammation serves as a protective response; however, when it becomes uncontrolled or excessive, it can result in tissue damage and contribute to chronic diseases. Thus, managing inflammation is essential for overall health. Anti-inflammatory agents are vital in alleviating these adverse effects. They function by regulating the inflammatory response either by inhibiting the production of pro-inflammatory substances such as cytokines, prostaglandins and leukotrienes, or by promoting the body's natural healing mechanisms.[1] While traditional anti-inflammatory medications including non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are effective they often carry side effects like gastrointestinal problems, cardiovascular

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risks and immune suppression. This has sparked a growing interest in natural alternatives that provide anti-inflammatory properties with fewer adverse effects.[3]

Nature has consistently been a vital source of therapeutic agents with various natural products revealing promising anti-inflammatory characteristics. Traditionally, herbs, spices, essential oils, and natural sweeteners like honey have been employed for their medicinal properties.[4] These natural products are rich in diverse bioactive compounds such as polyphenols, flavonoids, essential fatty acids and alkaloids which can affect inflammatory pathways. Honey is particularly noteworthy due to its exceptional combination of antioxidants, enzymes, vitamins and minerals, making it an effective natural anti-inflammatory agent. Its ability to regulate immune responses, mitigate oxidative stress and enhance tissue repair has made it a valuable resource in addressing both acute and chronic inflammatory issues.[4,5]

2. Discussion

In this review, we will explore the anti-inflammatory properties of honey, its mechanisms of action and its potential applications in modern medicine.

2.1. Composition of honey

Honey is a natural sweet substance produced by bees from the nectar of flowers. Its composition can vary depending on the floral source, geographical region, and processing methods.

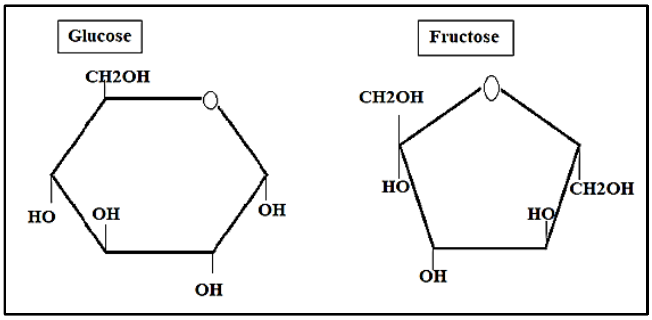

Figure 1: Structure of sugars

1. Carbohydrates (80-85%): Honey contains a variety of sugars, specifically three types. The predominant sugar is fructose making up approximately 41% followed by glucose at around 34% and sucrose which accounts for only 1 to 2% (**Figure 1**).[6] The proportions of these sugars can vary based on the source of the nectar such as the type of flowers visited by the bees and are influenced by the enzyme invertase. This enzyme, which helps convert sucrose into glucose and fructose, is found in the flowers and also within the bees themselves.[7]
2. Water (15-20%): The water content affects honey's shelf life and crystallization tendency.
3. Proteins and enzymes (0.1-0.5%): Includes enzymes like diastase, invertase and glucose oxidase, which play roles in honey's metabolism and health benefits.
4. Vitamins and minerals: Small amounts of B vitamins (B1, B2, B3, B5 and B6), vitamin C and minerals such as calcium, magnesium, potassium and iron.
5. Amino acids: Trace amounts of free amino acids contributing to the flavor and nutritional value.
6. Antioxidants: Phenolic acids, flavonoids and other polyphenolic compounds.
7. HMF (Hydroxy methyl furfuraldehyde): HMF is an organic compound with a six-carbon heterocyclic structure that features both aldehyde and alcohol (hydroxymethyl) functional groups. The core of its structure is based on furan rings, with the formyl and hydroxymethyl groups attached at the second and fifth positions, respectively (**Figure 2**). This compound appears as a solid yellow substance, characterized by a low melting point and high solubility in water.8,9

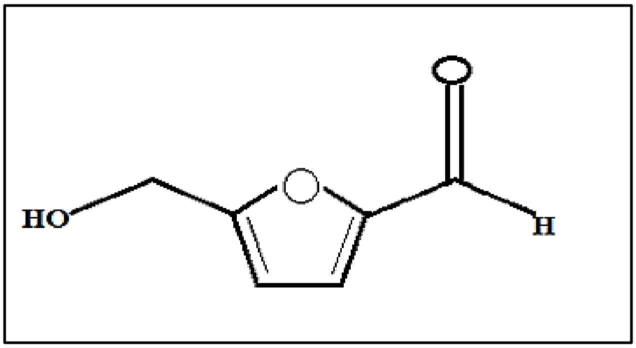

Figure 2: Chemical structure of Hydroxy Methyl Furfuraldehyde

3. Nutritional Profile of Honey

Honey comprises a range of mineral substances, with potassium being the most significant, making up roughly one-third of the total mineral content, along with various other elements as illustrated in **Table 1**. Studies have demonstrated that the levels of trace elements in honey are largely determined by its floral source. The mineral content is approximately 3.68% [11] and while this may not seem substantial, it contributes to the overall value of honey for human consumption. The minerals found in honey include potassium, chlorine, sulfur, calcium, sodium, phosphorus, magnesium, silicon, iron, manganese and copper.[12] Generally, darker honey varieties are richer in minerals than their lighter counterparts, although there are instances where some darker types may have lower mineral levels than certain lighter ones.[13]

Honey is calorie-dense due to its high sugar content, providing approximately 64 calories per tablespoon (21 g).

1. *Energy:* High (mainly from sugars)
2. *Carbohydrates:* 17-18 g per tablespoon
3. *Proteins:* 0.1 g per tablespoon
4. *Fats:* Negligible
5. *Vitamins & minerals:* Provides micronutrients like potassium (for heart health), magnesium and trace elements.[10,12]

Table 1: Minerals in honey in relation to human requirements[15]

Mineral	Average Amount (mg/100g)	% of RDI per 100g
Calcium (Ca)	4.4-9.2	0.4%-.09%
Iron (Fe)	0.06-1.5	0.4%-8.4%
Magnesium (Mg)	1.2-3.5	0.3%-0.9%
Phosphorus(P)	1.9-6.3	0.2%-0.6%
Potassium	13.2-16.8	0.4%-0.5%
Sodium (Na)	0.0-7.6	0%-0.3%
Zinc (Zn)	0.03-0.10	0.3%-4.0%
Copper (Cu)	0.003-0.10	0.3%-10.0%
Manganese (Mn)	0.02-0.4	1.0%-20.0%

4. Bioactive Compounds Contributing to Anti-Inflammatory Activity

Honey contains several bioactive compounds that exhibit anti-inflammatory properties[14] it contains phenolic acids, flavonoids, hydrogen peroxide, methylglyoxal, bee defensin-1 and organic acids. These compounds work synergistically to reduce oxidative stress, inhibit inflammatory pathways and prevent microbial growth, contributing to honey's anti-inflammatory and antimicrobial properties, especially in wound healing and infection control (**Table 2**).

Table 2: Showing the bioactive compounds with their anti-inflammatory effects

Bioactive Compounds	Description	Anti-Inflammatory Effects
Phenolic Acids	Caffeic acid, Ferulic acid, p-coumaric acid	Reduce oxidative stress linked to inflammation
Flavonoids	Chrysin, Quercetin, Kaempferol	Inhibit inflammatory pathways (e.g., NF-κB pathway), reducing pro-inflammatory cytokines
Hydrogen Peroxide	Produced enzymatically in honey	Exhibits antimicrobial and anti-inflammatory effects, though present in low concentrations
Methylglyoxal (MGO)	Especially in Manuka honey	Strong antimicrobial and anti-inflammatory properties
Bee Defensin-1	A protein found in honey	Exhibits antimicrobial and immune-modulating effects
Organic Acids	Gluconic acid	Maintains an acidic environment, inhibiting bacterial growth and reducing inflammation

4.1. Mechanism of anti-inflammatory action of Honey

Honey has long been celebrated for its anti-inflammatory qualities and recent scientific research confirms its effectiveness in regulating inflammation via multiple pathways.

Inflammation serves as the body's innate immune response to pathogens, leading to the activation of various cellular and humoral immune mechanisms. Concurrently, oxidative stress occurs when there is an imbalance favoring the excessive production of free radicals over antioxidant defenses. The relationship between inflammation and oxidative stress is mediated through several signaling pathways. Reactive oxygen species (ROS) generated by mitochondria activate various transcription factors, such as NF-κB, ERK, P38, JNK and MAPK, which are involved in the production of pro-inflammatory cytokines and mediators.[16]

The initiation of an uncontrolled inflammatory response, coupled with oxidative stress, significantly contributes to the pathophysiology of chronic conditions, including psychiatric, cardiovascular, traumatic, metabolic and autoimmune diseases. Recent studies have increasingly suggested that honey may help mitigate chronic inflammation and oxidative stress as well as influence related gene expression.[17] Additionally, several transcription factors, including Nrf2, ERK1/2, NF-κB, c-Jun and AP-1, have been identified as key players in these processes. These factors are crucial for various biological functions, particularly in the synthesis of antioxidant substances and inflammatory cytokines.

5. These Different Steps Involve in the Mechanism of Honey

5.1. Suppression of NF-κB signaling

Honey inhibits the NF-κB pathway, a central regulator of inflammation. Polyphenols in honey prevent the degradation of IκBα, the inhibitory protein that traps NF-κB in the cytoplasm. This blocks NF-κB's translocation to the nucleus, reducing the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). For example, Greek fir and chestnut honey significantly lowered TNF-α and iNOS levels in LPS-induced septic mice.[18]

5.2. Modulation of MAPK Pathways

Honey downregulates mitogen-activated protein kinase (MAPK) signalling, including p38 and Erk1/2, which are involved in amplifying inflammatory responses. This suppression further curbs the production of pro-inflammatory mediators.[19]

5.3. Antioxidant Activity

Honey's flavonoids and phenolic compounds neutralize reactive oxygen species (ROS), reducing oxidative stress that exacerbates inflammation. These compounds also activate Nrf2, a transcription factor that enhances antioxidant defences (e.g., superoxide dismutase). For instance, Greek honey restored cytochrome P450 enzyme activity in inflamed liver tissues, mitigating oxidative damage.[20]

5.4. Enzyme and cytokine regulation

1. *iNOS/COX-2 Inhibition:* Honey suppresses iNOS (reducing nitric oxide) and COX-2 (lowering prostaglandins), both critical in inflammatory cascade.
2. *Prostaglandin and nitric oxide modulation:* By altering these mediators, honey reduces edema and pain in wounds.[21]

5.5. Immune system modulation

Honey stimulates macrophages and lymphocytes to release growth factors (e.g., TNF-α) that promote tissue repair while dampening excessive inflammation. It also enhances phagocytosis and B-/T-cell proliferation, balancing immune responses.

5.6. Physical and chemical properties

Low pH of Honey's acidity inhibits protease activity in wounds, preventing degradation of healing factors[22] and Osmotic Effect which is High sugar content dehydrates bacteria, reducing infection-driven inflammation.

6. Mechanism of pro-Inflammatory Cytokines

6.1. Dual role in inflammation

1. *Role of inflammation in wound healing:* Honey-derived compounds promote wound healing by stimulating inflammation: The biological process of wound healing is intricate and involves the coordinated interactions of many cell types, signaling chemicals and extracellular matrix elements. Primarily through immune cell recruitment and activation, the early inflammatory phase is essential for starting tissue healing.[23]

2. *Stimulation of pro-inflammatory cytokines by honey:* Recent research has demonstrated how some therapeutic honeys, especially jelly bush and manuka honey can control the inflammatory response during wound healing. Research has demonstrated that these honeys increase the release of important pro-inflammatory cytokines, mostly from monocytes and macrophages, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6).[24]By attracting neutrophils and other immune cells to the wound site, this cytokine production promotes the efficient removal of infections, necrotic tissue and cellular debris.

3. *Immunological and cellular effects:* the pro-inflammatory environment that these honeys provide might be a key cue to start the proliferative stage of wound healing, which is marked by angiogenesis, fibroblast activation and re-epithelialization.[25] Acute wound healing appears to be accelerated by regulated pro-inflammatory stimulation, such as that produced by bioactive chemicals in manuka and jelly bush honeys, even if chronic inflammation might be harmful. This points to a possible therapeutic use of these natural compounds in wound care, especially when inadequate or delayed inflammation hinders healing.[26]

4. *Anti-inflammatory effects of honey in chronic and systemic inflammatory conditions:* Acute inflammation is necessary to start the healing process, but chronic inflammation is a defining feature of many diseases and frequently results in tissue damage that worsens over time. In a number of chronic and systemic inflammatory models, such as liver damage, neuro-inflammation and stress brought on by exercise, honey may have important anti-inflammatory effects, according to new research.[27]

5. *Suppression of pro-inflammatory cytokines:* honey has the ability to suppress important pro-inflammatory cytokines including interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). The resolution of inflammation is aided by the simultaneous promotion of the production of anti-inflammatory mediators such as interleukin-10 (IL-10) (**Table 3**) and interleukin-1 receptor antagonist (IL-1ra)[28] Heterotrigona itama honey, for example has been demonstrated to lower TNF-α level by 12% and IL-8 levels by 11% in macrophage cultures indicating that it has the ability to alter immune cell activity at the cellular level.[29]

6. *Promotion of anti-inflammatory mediators:* The anti-inflammatory properties of honey have also been discovered in human research with physically active people. Honey supplementation significantly reduced post-exercise levels of TNF-α and IL-6 by 20–30% in athletes engaging in intense exercise. Increased cytokine production during vigorous exercise can hinder recovery, increase tiredness and cause systemic inflammation, these decreases are clinically significant.[30]

Table 3: Cytokine modulation pathways

Cytokine	**Pro-Inflammatory Context**	**Anti- Inflammatory Context**
TNF-α	During the process of wound healing	Through the inhibition of TNF-α converting enzymes

IL-6	A higher level of macrophage activation	decreased by inhibiting the NF-κB pathway
IL-1β	When there is acute inflammation, it released	downregulated in models of gastric ulcers

7. Molecular Mechanism

7.1. Phenolic compound activity

The pathophysiology of inflammation and tissue damage, especially in chronic disorders is significantly influenced by oxidative stress. It results from an imbalance between the body's antioxidant defense systems and the generation of reactive oxygen species (ROS).[31] The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling system, which controls the production of several pro-inflammatory cytokines, chemokines and adhesion molecules is one of the major routes impacted by oxidative stress. Honey contains large amounts of two important families of polyphenolic chemicals, flavonoids and phenolic acids, which have been shown to have strong antioxidant qualities.[32] By neutralizing ROS such hydrogen peroxide, hydroxyl radicals, and superoxide anions, these substances function as free radical scavengers. NF-κB's redox-sensitive activation is downregulated by flavonoids and phenolic acids which assist reduce oxidative stress by lowering the formation of ROS.[33]

Flavonoids, specifically quercetin, kaempferol, and chrysin, as well as phenolic acids, including caffeic acid and ferulic acid, have been demonstrated to suppress the binding of NF-κB to DNA and prevent its translocation to the nucleus.[34] This in turn attenuates the expression of TNF-α, IL-1β, IL-6 and other downstream inflammatory mediators. Not only does this antioxidant-mediated inhibition of NF-κB lower inflammation, but it also helps to repair damaged tissue, protect cells and stop the evolution of chronic inflammation.[35]

Therefore, honey's antioxidant capacity, which is mostly ascribed to its flavonoid and phenolic acid content, is essential to its anti-inflammatory properties, especially by reducing oxidative stress and NF-κB activation. This demonstrates honey's therapeutic value in situations where oxidative stress is a major pathogenic characteristic.[36]

7.2. Dose- dependent effects

By generating extracellular matrix components, especially collagen, which is necessary for tissue strength and structural integrity, fibroblasts play a key role in the wound healing process.[28] Numerous in vitro investigations have shown that honey affects fibroblast activity in a concentration-dependent manner, affecting collagen deposition as well as cell proliferation.[37]

It has been demonstrated that honey increases collagen synthesis and promotes fibroblast proliferation at low doses, usually between 0.5 and 1 mg/liter. It is thought that honey's abundance of carbohydrates, vitamins, amino acids and trace elements all of which assist cellular metabolism as well as its bioactive components, such flavonoids and phenolic acids, which alter cell signalling pathways, are what achieve this pro-proliferative impact. These concentrations of increased collagen synthesis lead to quicker re-epithelialization, granulation tissue development, and increased wound strength.[38]

7.3. Cell- type specificity

By producing cytokines and chemokines, monocytes and macrophages two essential elements of the innate immune system coordinate the inflammatory response. Depending on their level of activation and the inflammatory setting, honey has been demonstrated to have varying effects on these immune cells, especially differentiating between acute and chronic stages of inflammation.[39]

Monocytes exposed to certain honeys, such manuka or jelly bush, show strong production of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in the early phases of immunological activation.[40] This activation facilitates debris removal and starts the wound healing process by encouraging the recruitment of more immune cells to the site of damage or infection. The body's natural acute inflammatory response, in which brief cytokine bursts serve as a protective and restorative mechanism is mirrored by such stimulation.[41]

Honey seems to change the behaviour of macrophages toward resolution in the setting of chronic inflammation, when they frequently take on a more persistent and dysregulated pro-inflammatory phenotype. Pro-inflammatory mediators, especially TNF-α and IL-8, are significantly suppressed in macrophages treated with honey in chronic inflammatory models.[42]

8. Variability Factors

8.1. Honey source

The botanical source of honey has a major impact on its immunomodulatory properties; different floral sources provide diverse profiles of bioactive substances such flavonoids, phenolic acids and enzymes. Significant variations in how different honeys affect cytokine production, both in vitro and in clinical situations result from this compositional heterogeneity.[43]

In vitro, jelly bush honey (Leptospermum polygalifolium), which is closely related to manuka honey, has shown strong immunostimulatory properties. Pro-inflammatory cytokine release was markedly increased and TNF-α level were up to 2.5 times higher than those of untreated control cells.[44] The high activation of innate immunity pathways shown by this substantial cytokine production is most likely the result of downstream NF-κB signalling and Toll-like receptor (TLR) engagement. This kind of action might be helpful in acute wound situations when improved bacteria clearance and immune cell recruitment are crucial.[45]

8.2. Inhibition of NF-κB and other inflammatory pathways

The roles of NF-κB and other inflammatory pathways play in chronic inflammation and diseases like diabetes, cancer and autoimmune disorders make them important targets for therapy. In order to balance safety and effectiveness, inhibition techniques concentrate on interfering with important signalling nodes.

9. Pathway Inhibition of NF-κB

9.1 Targeting canonical pathways

1. IKK complex inhibitors: By specifically inhibiting IKKα/β, ACHP and IKK 16 prevent NF-κB activation and IκBα phosphorylation.[46] BMS 345541 has anti-inflammatory properties and functions as an allosteric IKK inhibitor. IKK activity is indirectly suppressed by salinomycin and aspirin.[47]
2. Inhibitors of the proteasome: Bortezomib reduces NF-κB nuclear translocation and inhibits the proteasome to stop IκBα breakdown.
3. Blockers of nuclear translocation: IκBα super-repressor and tacrolimus (FK-506) stop NF-κB subunits from getting into the nucleus.[48]
4. Inhibitors of DNA binding: PPAR agonists and glucocorticoids prevent NF-κB from binding DNA.
5. Non-canonical pathway targeting: In pathways involving NIK (NF-κB-inducing kinase), disulfiram and (-)-DHMEQ prevent NF-κB activation.

9.2. Additional Inflammatory routes

9.2.1. MyD88/TLR Signaling

Dorzolamide (DZD) decreases pro-inflammatory cytokines including TNF-α and IL-6 by interfering with the MAL-PKCδ-p38 MAPK axis in TLR4 signalling.

Gefitinib suppresses AP-1-mediated inflammation by blocking MAL-c-Jun interactions.

9.2.2. AMPK and NLRP3 inflammasome

SGLT2 inhibitors, such as empagliflozin and dapagliflozin, activate AMPK which is in turn inhibits NF-κB signalling and NLRP3 inflammasome activity.[49]

9.2.3. Kinases and oxidative stress

1. Celastrol and Withaferin A modulate ROS-related pathways while inhibiting NF-κB.
2. BAY 11-7082 decreases oxidative stress in diabetes animals and permanently inhibits IκBα phosphorylation.

9.2.4. Considerations for therapy

1. *Drug repurposing:* Current medications such as emetine and sunitinib exhibit unexpected NF-κB inhibitory actions which present chances for repurposing in inflammation and cancer.
2. *Particulars challenges:* Immunosuppression and toxicity are hazards associated with global NF-κB inhibition. MAL-PKCδ disruption is one example of a targeted method that may increase safety.[50]

10. Antioxidant Activity and Its Role in Reducing Inflammation

1. Role of antioxidants: Antioxidants help reduce inflammation by neutralizing free radicals, thereby lowering oxidative stress and preventing cellular damage.
2. Antioxidants in honey: Honey naturally contains a variety of antioxidants, including:
3. Enzymes: Glucose oxidase, catalase.
4. Vitamins: Vitamin C (ascorbic acid).
5. Bioactive compounds: Flavonoids, phenolic acids, carotenoids, organic acids, Maillard reaction products, amino acids and proteins.

10.1. Benefits over synthetic antioxidants

Unlike synthetic antioxidants, honey is natural and free from harmful side effects.

11. Additional Health Benefits

Honey's antioxidant properties not only reduce inflammation but also offer neuroprotective and antidepressant effects, especially under physical, emotional or mental stress.[51,52]

11.1. Different Antioxidant Types

Two primary classes of antioxidants can be distinguished:

11.1 Endogenous antioxidants

The body spontaneously produces these endogenous antioxidants. Glutathione, superoxide dismutase and catalase are important examples.

11.2. Exogenous antioxidant

An exogenous antioxidant is one that is derived from food. They consist of vitamins (like C and E), minerals (like selenium) and phytochemicals (such carotenoids and flavonoids).

11.3 Mechanisms of action

There are multiple ways in which antioxidants reduce inflammation.

1. *Scavenging Free Radicals:* Antioxidants help stop oxidative damage to cells and tissues by scavenging free radicals .[53]
2. *Inhibiting inflammatory pathways*: A number of antioxidants have the ability to alter signaling

pathways that contribute to inflammation, including the nuclear factor-kappa B (NF-kB) pathway which is essential for controlling the immune response.

3. *Supporting immune function:* By improving immune cell function, antioxidants can encourage a healthy inflammatory response.[54]
4. Free radical scavenging is a key mechanism through which antioxidants reduce inflammation. This process involves neutralizing free radical unstable molecules that can cause oxidative stress and damage cellular components such as lipids, proteins and DNA. Oxidative stress is closely linked to inflammation, as it triggers the release of pro-inflammatory cytokines and activates inflammatory pathways.

11.4. Mechanism of free radical scavenging in reducing inflammation

11.4.1. Neutralization of reactive oxygen species (ROS):

1. Free radicals like superoxide and hydroxyl radicals are neutralized by antioxidants, which donate electrons to stabilize these reactive molecules.
2. For example, enzymes like superoxide dismutase (SOD) convert superoxide radicals into hydrogen peroxide which is then broken down into harmless water and oxygen by catalase.[49]

11.4.2. Reduction of oxidative stress

By decreasing the levels of ROS, antioxidants prevent oxidative damage to cellular structures including membranes and DNA. This reduces the activation of pro-inflammatory pathways such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) which is a major regulator of inflammation.[48]

1. *Inhibition of pro-inflammatory mediators*: 1. Antioxidants can directly inhibit the production of inflammatory cytokines like TNF-α, IL-6 and IL-1. For instance, flavonoids and polyphenols have been shown to attenuate cytokine levels while enhancing antioxidant enzyme activity.[53] 2. Compounds such as rutin and theobromine from Ilex paraguariensis (yerba mate) significantly inhibit nitric oxide secretion and TNF-α production, reducing inflammation.

2. *Enhancement of antioxidant enzyme activity:* Antioxidants boost endogenous enzymes such as glutathione peroxidase and catalase which detoxify peroxides and maintain cellular stability. Increased activity of these enzymes correlates with reduced lipid peroxidation and inflammation.

3. *Disruption of free radical chain reactions:* Non-enzymatic antioxidants like vitamins C and E interrupt free radical chain reactions by stabilizing unpaired electrons. This prevents further generation of ROS that could perpetuate inflammation.

11.5. Inflammation and the NF-κB pathway

The cytoplasm contains NF-κB attached to its inhibitory protein, IκBα. IκBα is phosphorylated and degraded as a result of proinflammatory signals (such as TNF-α, IL-1, and LPS) activating the IκB kinase (IKK) complex. This causes NF-κB (usually a p50/p65 heterodimer) to be released which enables it to move into the nucleus and activate genes for adhesion molecules, chemokines and cytokines (such as TNF-α and IL-6).[55] (**Figure 3**)

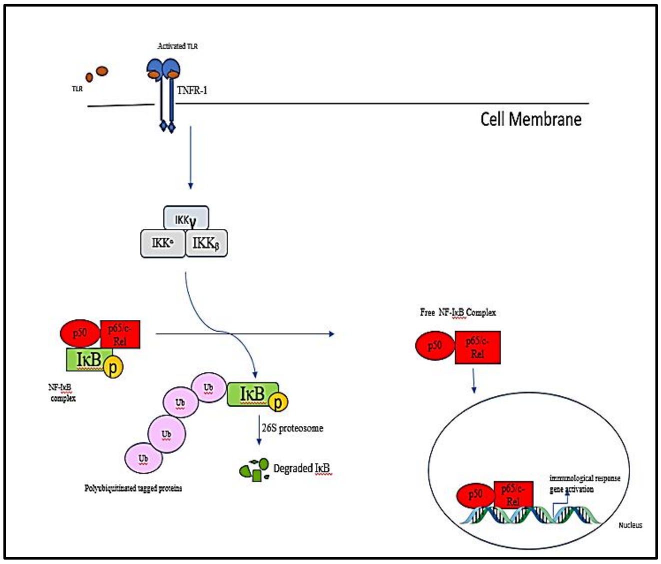

Figure 3: Mechanism of NF-κB Pathway

11.6. Antioxidants prevent the activation of NF-κB

1. *IκBα degradation inhibition:* By inhibiting IKK activity, antioxidants like as pyrrolidine dithiocarbamate (PDTC) and N-acetylcysteine (NAC) stop IκBα from degrading. By trapping NF-κB in the cytoplasm this stabilization of IκBα prevents its proinflammatory transcriptional activity.[56]

2. *Redox-sensitive mechanisms:* Redox-sensitive cysteine residues are present in the IKK complex. Reactive oxygen intermediates (ROI) produced during inflammation are neutralized by antioxidants and are essential for IKK activation. For instance, IKK is directly oxidized by hydrogen peroxide ($H2O_2$) but this is counteracted by antioxidants such glutathione or vitamin C, which stops NF-κB activation.[57]

12. Improvement of Immune Cell Activity

1. **Vitamin A** promotes natural killer (NK) cell activity aids in T and B cell differentiation and proliferation and triggers macrophage phagocytosis.
2. **Vitamin E** enhances the activity of lymphocytes and shields cell membranes from oxidative damage.[55]
3. **Zinc** enhances epithelial defenses against infections, regulates inflammatory cytokines and promotes the death of infected cells.[58]

12.1. Types of honey with strong anti- inflammatory effects

Manuka Honey (New Zealand)

Key Compounds: Methylglyoxal (MGO), phenolics, flavonoids

12.2. Mechanisms

1. Inhibits pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
2. Modulates NF-κB and MAPK pathways
3. Suppresses COX-2 and iNOS[59,60]

12.3. Benefits

1. Effective for gingivitis, ulcerative colitis and wound healing.
2. Antimicrobial and promotes tissue repair.[61]

12.4. Gelam honey (Malaysia)

Key Compounds: Phenolics, flavonoids, antioxidants

12.5. Mechanisms

1. Reduces TNF-α, IL-6, NO, PGE2
2. Inhibits NF-κB and COX-2
3. Attenuates oxidative stress[60]

12.6. Benefits

1. Reduces swelling and inflammation
2. Useful in cardiovascular, neurodegenerative and inflammatory diseases[62,63]

12.7. Tualang honey (Malaysia)

Key Compounds: Phenolics, flavonoids, HMF

12.8. Mechanisms

1. Inhibits TNF-α, IL-6, and NF-κB activation
2. Comparable to corticosteroids but safer

12.9. Benefits

1. Effective in burn wound healing
2. Natural alternative for managing inflammation[64,65]

12.10. Greek honeys (Arbutus, Chestnut, Fir)

Key Compounds: Phenolic acids, flavonoids

12.11. Mechanisms

1. Inhibits NF-κB, MAPK pathways
2. Suppresses COX and iNOS activity

12.12. Benefits

1. Strong antioxidant and anti-inflammatory effects
2. Supports immune and overall health

12.13. Kanuka honey (New Zealand)

Key Compounds: Phenolic compounds

12.14. Mechanisms

Modulates toll-like receptor (TLR) pathways

12.15. Benefits

1. Reduces inflammation in wound healing
2. Clinically useful, though less potent than Manuka

12.16. Kelulut honey (Tropical regions, Trigona bees)

Key Compounds: Polyphenols, antioxidants

12.17. Mechanisms

1. Reduces TNF-α and IL-6
2. Lowers oxidative stress and inflammation

12.18. Benefits

1. Effective under hyperglycemic conditions
2. Promising for managing inflammation in diabetes[60,63]

These honeys exhibit strong anti-inflammatory properties due to their rich content of bioactive compounds like phenolics and flavonoids. Their mechanisms include inhibition of key inflammatory signaling pathways (e.g., NF-κB), reduction of pro-inflammatory cytokines (e.g., TNF-α) and antioxidant activity.

13. Mechanisms of Action

Honey supports healing through multiple actions: its low pH and high sugar content create an antibacterial environment, while hydrogen peroxide and bioactive compounds add antimicrobial effects. It reduces inflammation by lowering prostaglandins and boosting nitric oxide for better blood flow and tissue repair. Rich in antioxidants, honey protects cells from damage and promotes faster healing. It also stimulates tissue growth by enhancing fibroblast activity and collagen production. Additionally, honey's acidic nature improves oxygen delivery and inhibits harmful enzymes, while its osmotic effect helps cleanse wounds and deliver nutrients to support recovery.[66-68] (Table 4)

Table 4: The therapeutic effects of honey in a clear and organized format

Therapeutic Effect	Mechanism/Action
Antibacterial Properties	- Low pH inhibits bacterial growth- High sugar creates osmotic effect - Contains hydrogen peroxide and antimicrobial compounds (flavonoids, phenolics)

Anti-inflammatory Effects	- Reduces prostaglandins (↓ pain, swelling, fever) - Increases nitric oxide (↑ blood flow, tissue repair)
Antioxidant Activity	- Rich in flavonoids and phenolic compounds - Neutralizes free radicals - Protects cells from oxidative damage
Promotion of Tissue Growth	- Stimulates fibroblasts, collagen production, angiogenesis and epithelialization - Enhances granulation and wound closure
Acidic Environment	- Improves oxygen release from hemoglobin - Inhibits protease activity, preserving tissue
Osmotic Effect	- Draws fluid into wound (flushes out debris & bacteria) - Delivers nutrients to aid healing and maintain sterility

14. Honey in the Management of Inflammatory Diseases

1. Honey in Autoimmune Disorders: Modulates immune responses by reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6). Helps manage inflammation in conditions like lupus and multiple sclerosis.
2. Role in Chronic Inflammatory Conditions: Alleviates symptoms in arthritis and inflammatory bowel disease (IBD). Reduces joint swelling, pain, and gut inflammation through antioxidant and anti-inflammatory effects.
3. Application in Respiratory Infections and Allergies: Soothes irritated airways and reduces coughing. Acts as a natural antihistamine, easing allergy symptoms and boosting respiratory immunity.

15. Honey Role in Wound Healing and Tissue Repair

Honey has been recognized as a safe, cost-effective, potent natural agent in wound healing and tissue repair due to its multifaceted regenerative properties (antibacterial, anti-inflammatory, antioxidant) and make it an invaluable tool in modern medicine.

1. *Acute wounds:* Honey has been effective in treating burns and lacerations by promoting rapid healing and minimizing scar formation.
2. *Chronic wounds:* Studies have shown that honey accelerates healing in diabetic ulcers, venous leg ulcers, pressure injuries, and other non-healing wounds.[66,67]
3. *Manuka honey:* Manuka honey is particularly noted for its antimicrobial properties and ability to stimulate angiogenesis and re-epithelialization.
4. *Combination therapies:* Honey combined with silver nanoparticles or incorporated into hydrogels has shown enhanced efficacy in wound contraction and tissue regeneration.[68-70]

16. Function in Tissue Healing

Honey is an advantageous component in tissue engineering materials like electrospun meshes, cryogels and hydrogels, due to its bioactive qualities.

1. Promotes the infiltration of fibroblasts necessary for collagen and extracellular matrix synthesis.
2. Reduces chronic inflammation by modulating immune responses.
3. Enhances the production of VEGF, supporting angiogenesis and better blood flow.[62]

17. Potential Limitations and Challenges

Honey's therapeutic use faces challenges such as variability in its composition, as the levels of bioactive compounds like flavonoids and phenolics depend on botanical and geographic origins, leading to inconsistent effects and difficulties in standardizing dosages.[71] Additionally, overconsumption poses risks, especially for diabetics due to its high sugar content, while some individuals may experience allergic reactions from pollen or bee protein residues. Honey is also unsuitable for infants under one year due to the risk of botulism.[72] (**Table 5**).

Table 5: Table summarizing the potential limitations and challenges of using honey therapeutically

Challenge	Description
Variability in Honey Composition	Bioactive compounds like flavonoids and phenolics vary based on botanical and geographic origins.
	Seasonal and regional differences affect consistency in therapeutic effects, making standardization and outcome prediction difficult.
Risks of Overconsumption and Allergic Reactions	High sugar content can raise blood sugar levels, posing risks for diabetic individuals.
	Possible allergic reactions (e.g., rashes, respiratory issues) due to pollen or bee protein residues.
	Risk of infant botulism prevents use in children under one year.

18. Future Perspectives and Research Directions

Recent studies highlight honey's anti-inflammatory effects through its influence on molecular pathways like NF-κB, MAPK and TLR, with a focus on bioactive compounds such as CAPE, flavonoids and phenolic acids. Future research aims to identify the specific components responsible for modulating immune responses.

At the same time, there's growing interest in using honey in therapeutic applications, including honey-based hydrogels, wound dressings and tissue scaffolds. Standardizing honey extracts for consistent efficacy offers a promising natural alternative for treating inflammation, wounds and metabolic disorders.

19. Conclusion

Honey is known for its potent anti-inflammatory properties, attributed to its abundant bioactive components such as flavonoids, phenolic acids, enzymes and antioxidants. These compounds collaborate to reduce pro-inflammatory cytokines (including TNF-α, IL-6 and IL-1β) inhibit pathways like NF-κB and COX-2 and enhance the production of anti-inflammatory cytokines like IL-10. Its inherent capacity to regulate oxidative stress and immune responses positions honey as a valuable tool in inflammation management. Honey is recognized as a potent natural remedy due to its wide-ranging antimicrobial, antioxidant and healing characteristics. Its effectiveness in addressing wounds, inflammatory conditions and aiding tissue regeneration is backed by both historical practices and new scientific findings. Ongoing studies and efforts to standardize honey could lead to the development of honey-derived therapeutic products, providing safer and more natural options compared to synthetic medications for managing inflammation.

20. Authors' Contributions

GV, BS, AK, GK, PK, MS conceived and designed the study, performed the literature search and wrote and edited the manuscript. The author has read and approved the final manuscript. Data authentication is not applicable.

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None.

22. Conflict of Interest

None.

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