Review Article
Volume 11:2, 2025

Journal of Pharmacognosy & Natural Products

ISSN: 2472-0992 Open Access

A Comprehensive and Updated Mini-Review on Anti-Influenza Properties of Honey

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Abstract

Respiratory tract infections encompass a range of infections impacting different parts of the respiratory system. These are broadly categorized into Upper Respiratory Tract Infections (URTI), which involve the nose, sinuses, and throat, or lower respiratory tract infections, affecting the airways and lungs. Influenza, often referred to as the "flu," is a highly contagious viral infection predominantly caused by influenza viruses is one of an URTI. This review focuses on anti-influenza effects of honey highlighting key findings from various studies. *In-vitro* research demonstrates that honey, particularly *Castanea crenata* and *Tilia amurensis*, significantly reduces influenza virus replication in cell models and enhances immune response mechanisms. The studies highlighted the activation of the IFN signaling pathway as a crucial mechanism. This involves the stimulation of JAK-STAT signaling pathway, leading to the formation of the ISGF3 transcription factor complex. Honey was found to boost the immune response by increasing the production of inflammatory cytokines (IL-6, TNF-α, and IFN-β) and enhancing the expression of Interferon-Inducible Transmembrane Protein (IFITM3), a key player in obstructing viral entry. Clinical studies showed that honey, in various forms, could alleviate symptoms of URTIs like cough and sleeping difficulties, likely due to its anti-viral properties. All these findings suggest the potential of honey as a natural, effective treatment for influenza. However, human studies are limited, with existing Randomized Controlled Trials (RCTs) focusing on Upper Respiratory Tract Infection (URTI) symptoms like cough, not specifically influenza. Future research should not only include double-blind RCTs involving adults and children but also further *in-vitro* studies to explore different honey types and mechanisms related to treatment of influenza.

Keywords: Upper Respiratory Tract Infections (URTI) • Influenza • Apoptosis • Honey • JAK-STAT signaling pathway • Cytokines

Introduction

Respiratory Tract Infections (RTI) are infections that can affect any part of the respiratory tract. Based on that, it is classified either as Upper Respiratory Tract Infection (URTI) that affect nose, sinuses, and throat or lower respiratory tract infection affecting airways and lungs. Influenza, commonly known as the "flu," is a viral infection that spreads easily and mainly is caused by influenza viruses. Influenza viruses are part of the virus family known as “Orthomyxoviridae,” characterized as RNA viruses with varied antigenic properties. These viruses are categorized into three primary types: A, B, and C. Types A and B are commonly associated with flu epidemics and outbreaks, while type C typically causes occasional, mild upper respiratory symptoms. Influenza A viruses are categorized into various subtypes according to their surface proteins, Neuraminidase (NA) and Hemagglutinin (HA). Among these, two specific subtypes of influenza A: A (H_3N_2) and A (H_1N_1) along with two lineages of influenza B virus, B-Yamagata and B-Victoria, are prevalent across the globe. Among these, two specific subtypes of influenza A: A (H_3N_2) and A (H_1N_1) along with two lineages of influenza B virus, B-Yamagata and B-Victoria, are prevalent across the globe. As per World Health Organization (WHO), approximately, every year, one billion cases of seasonal influenza occur, with 3 to 5 million of these being severe. This infection primarily targets the upper respiratory system, including nose, throat, bronchi, and sometimes lungs. However, it can also affect other parts of the body, such as muscles, brain, and heart. People often recuperate within a few days from influenza, but it can affect, particularly, vulnerable populations such as pregnant women and individuals with weakened immune systems. The potential complications arising from influenza, such as pneumonia and exacerbations of pre-existing pulmonary and cardiac conditions,

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Received: 04 December, 2023, Manuscript No. JPNP-23-121986**; Editor assigned:** 06 December, 2023, PreQC No. JPNP-23-121986 (PQ); **Reviewed:** 20 December, 2023, QC No. JPNP-23-121986; **Revised:** 23 April, 2025, Manuscript No. JPNP-23-121986 (R); **Published:** 30 April, 2025, DOI: 10.37421/2472-0992.2025.11.351

should not be underestimated. Additionally, influenza, in different studies, has been found to be associated with a variety of neurological complications, including Reye s syndrome, transverse myelitis, aseptic meningitis, Guillain-Barr syndrome, encephalomyelitis, and various focal neurological disorders.

Immunization is the best method to prevent seasonal influenza, but its efficacy may be reduced if there is a discrepancy between antigens in the vaccine and actual virus strains found in the community. The use of anti-influenza drugs like Oseltamivir, often leads to various ADRs like delirium, suicidal thoughts, and hallucinations, as well as multi-drug resistance, therefore encouraging the consideration of alternative solutions like natural products. Additionally, it has been demonstrated that many of them combat infectious diseases using mechanisms similar to those of chemical drugs. Honey, one such natural product, has gained attention from researchers as an effective means to counteract viral diseases by virtue of its anti-oxidant, anti-inflammatory, and immune strengthening properties due to various chemical constituents, especially, phenolic compounds like Chrysin, Quercetin, and Kaempferol. Recent scientific investigations have illuminated the potential effectiveness of honey and it s components in combating influenza, with research indicating its ability to strengthen the immune system and mitigate symptoms. Honey exhibits its therapeutic potential through interactions with numerous molecular targets within the human body. This multifaceted interaction is exemplified by its influence on critical cellular signaling pathways like Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. The JAK/STAT pathway plays a pivotal role in the immune response, mediating the actions of cytokines and growth factors, which are crucial in defense of body against viral infections like influenza. Moreover, components of honey have also been identified to interact with mitochondrial apoptotic proteins. These proteins are integral to the process of programmed cell death. By modulating these apoptotic pathways, honey contribute to the containment of viral infections at a cellular level.

A significant body of review studies has focused on honey for the treatment of COVID-19, as evidenced by multiple sources in the literature, a comprehensive survey of existing publications reveals a notable gap when it comes to influenza as we did not find any review study related to the treatment efficacy of honey for influenza. Therefore, the objective of this article is to discuss the efficacy of honey for the treatment of influenza and to suggest future research directions.

Literature Review

Methods

We performed a literature search on Goggle Scholar and PubMed by using combinations of Medical Subject Headings (MeSH) terms: “Influenza”, “Honey”, and “Upper respiratory tract infection”. All studies written in English, with full texts available, that focused on honey as a treatment for influenza, *in-vitro*, *in-vivo*, Randomized Controlled Trials (RCTs) for Upper Respiratory Tract Infections (URTIs) where influenza could be a contributing factor, were included in the review. Any studies not meeting these specific requirements were excluded. There was no restriction based on the year of publication and the search was extended till 2023. Additionally, references from these studies were further explored.

Results

After applying the specified inclusion criteria to 61 articles, we found 21 relevant studies, which are discussed in the respective section. These studies include 6 *in-vitro* experiments, which shed light on the molecular and cellular interactions between honey and the influenza virus, and 8 RCTs. It is noteworthy that the RCTs identified in the literature primarily focused on URTIs, not exclusively on influenza. However, influenza was considered a potential contributing factor to URTI symptoms in these studies. Finally, there were 7 studies that were concerned with the chemical constituents of honey that showed anti-influenza activity.

Epidemiology of influenza

While influenza can impact individuals of all ages, certain groups are more susceptible to severe illness and complications. These include elders, people with chronic health conditions like chronic cardiac, metabolic, pulmonary, neurodevelopmental, liver, and hematologic diseases and conditions in which people have weakened immune systems like HIV and cancer or those undergoing treatments that suppress immunity, such as those undergoing chemotherapy or steroid treatment. Healthcare workers are particularly at risk of contracting influenza due to their frequent exposure to patients, and they have a higher chance of transmitting the virus, especially to those who are more vulnerable. As per WHO, approximately, every year, one billion cases of seasonal influenza occur, with 3 to 5 million of these being severe. The illness results in 290,000 to 650,000 respiratory-related deaths each year. Notably, 99% of influenza-related lower respiratory tract infection deaths in children under the age of five occur in developing countries. Symptoms typically appear 1 to 4 days following infection and generally persist for about a week.

The only influenza pandemic of the 21st century so far occurred between 2009 and 2010, triggered by the A (H_1N_1) pdm09 virus that is more commonly known as swine flu. Originating in Mexico, this virus was called swine flu due to its genetic composition, which included quadruple assortment of genes from humans, birds, and pigs. The pandemic mostly resulted in mild infections, partly because older populations had some level of immunity, leaving younger individuals more vulnerable. The virus impacted over 214 countries, resulting in approximately 284,000 deaths, with 18,449 of these being confirmed in the laboratory. From 2010 to 2020, numerous instances of human infections caused by avian influenza strains were documented, involving strains such as H_7N_3, $H_{10}N_8$, H_5N_6, $H_{10}N_8$, H_9N_2.

As per the recent data of Integrated Health Information Platform-Integrated Disease Surveillance Programme (IHIP-IDHP) of India, states have reported a total of 3038 laboratory-confirmed cases of various influenza subtypes with H_3N_2 being predominant, from 1st January to 9th March, 2023. The latest data after March is not given.

Chemical constituents of honey

Honey is composed of a blend of water, enzymes, sugars, amino acids, organic acids, phenolic acids, flavonoids, vitamins, volatile substances, and minerals. Its various attributes, such as taste, color, and aroma, depend on factors like types of flower and their origin, climatic and weather conditions, and species of honeybee. Additionally, the way honey is processed, packaged, and stored also influences these characteristics. Honey primarily consists of sugars (90-95%), with monosaccharides like fructose and glucose making up 75% of its composition, and 10 to 15% comprising disaccharides such as sucrose, maltulose, turanose, kojibiose, maltose, nigerose, isomaltose, trehalose, as well as trisaccharides like maltotriose and melezitose. It also contains trace amounts of various other sugars. Additionally, honey contains proteins with proline being the most prevalent amino acid.

Scientific studies indicate that all honey varieties contain organic acids, constituting approximately 0.57% of their composition. These acids contribute to mild acidity and electrical conductivity of honey, as well as impact its color and flavor. These organic acids are either produced during the conversion of nectar to honey or are derived directly from the nectar. A wide array of organic acids is found in honey, such as aspartic acid, citric acid, formic acid, fumaric acid, galacturonic acid, acetic acid, 2-hydroxybutyric acid, glutamic acid, Kynurenic Acid (KYNA), α-hydroxyglutaric acid, malonic acid, glyoxylic acid, lactic acid, gluconic acid, pyruvic acid, isocitric acid, α-ketoglutaric acid, malic acid, shikimic acid, 2-oxopentanoic acid, methylmalonic acid, propionic acid oxalic acid, tartaric acid.

Honey contains trace amounts of several vitamins, including those in the vitamin B group such as riboflavin (B_2), thiamine (B_1), biotin (B_8 or H), pantothenic acid (B_5), nicotinic acid (B_3), and folic acid (B_9), vitamin C, and pyridoxine (B_6). Among these, vitamin C is found in different honey varieties and contributes to its antioxidant properties.

Honey contains various enzymes, including oxidase, invertase, amylase, and catalase. The primary enzymes are glucose oxidase, invertase, and diastase which play a crucial role in the formation of honey. Glucose oxidase transforms glucose into hydrogen peroxide, offering antimicrobial benefits, and gluconic acid, aiding in calcium absorption. Invertase breaks down sucrose into glucose and fructose. Amylase enzyme breaks long starch chains into maltose and dextrin. Catalase aids in converting hydrogen peroxide into oxygen and water.

Phenolic compounds, a significant group of chemicals found in honey, constitute about 50-500 mg/Kg of honey. These compounds are recognized for their anticarcinogenic, antithrombotic, immune-modulating, antiatherogenic, anti-inflammatory, analgesic including anti-microbial activity. The phenolic compounds of honey are categorized into two types: Non-flavonoids (phenolic acids) and flavonoids. In honey, phenolic acids are mainly found as hydroxycinnamic acid and hydroxybenzoic acid. Hydroxybenzoic acids in honey are comprised of vanillic acid, ellagic acid, salicylic acid (2-hydroxybenzoate), gallic acid, syringic acid. Some flavonoids in honey include vanillic acid, syringic acid, caffeic acid, p-coumaric acid, ferulic acid, kaempferol, quercetin, chrysin, ellagic acid, luteolin, chlorogenic acid, 3 and 4-hydroxybenzoic acid, and benzoic acid. Some of these flavonoids that have been attributed to anti-influenza activity in different studies are also given in the next section.

Discussion

Anti-influenza effects of honey

We have reviewed various studies concerning the impact of honey on the influenza virus, accompanied by an exploration of underlying mechanisms.

A study reported anti-influenza properties of *Castanea crenata* honey in Raw264.7 macrophage cells. These cells are frequently utilized as a mouse macrophage model to examine cellular response to microorganisms. When these cells were pre-treated with the honey in the concentration of 1.25, 2.5, and 5 mg/mL and infected by Green Fluorescent Protein (GFP) encoding influenza virus a strain-A/PR/8/34, there was a decrease in the expression of GFP by 16.9%, 38.3%, and 53%, respectively as compared to the control group (P<0.001). The honey significantly decreased hem-agglutination and the expression of viral proteins that is Polymerase Acidic (PA), Polymerase Basic (PB1), and M2 (P<0.001). Moreover, they reported that CH enhanced the expression of Mitochondrial Antiviral Signaling (MAVS) protein, and Retinoic Acid-Inducible gene (*RI* -); these proteins are known to interfere with the virus replication.

The same authors published another article but in this, they used *Tilia amurensis* honey with the same objective. Pre-exposure of Raw264.7 to the honey enhanced the generation and release of inflammatory cytokines that is IL-6 and TNF-α, and IFN-β. Additionally, the honey raised Interferon (IFN)-Inducible Transmembrane Protein (IFITM3). IFITM3 is a protein that disrupts the entry and replication of the virus. The innate immune response, guided by IFN, serves as a strong initial defense against external pathogens. The signaling of IFN is crucial in forming innate immune response. When IFN binds to receptors on the cell surface, it triggers a cascade of signals that lead to diverse alterations in cellular characteristics. A key characteristic of IFN signaling includes the stimulation of the Janus Kinase (JAK)-STAT signaling pathway.

Furthermore, as per Zou H, et al. when this pathway is activated, proteins, STAT1 and STAT2 combine to form a heterodimer, which, along with IFN Regulatory Factor 9 (IRF9), creates the transcription factor complex, ISGF3 [1]. This complex is then transported to the cell nucleus, where it binds to ISREs, kickstarting the transcription of numerous Interferon-Stimulated Genes (ISGs). The products of these genes are responsible for anti-viral activities. Sulaimaan S, et al. reported that the group of influenza-vaccinated people who took 20 g Tualang honey twice daily for 42 days had reduced acute respiratory symptoms like sore throat, cough, and rhinitis as compared to the control group who did not take the honey [2]. No mechanism found for the effect and the difference was non-significant.

Watanabe K, et al. reported anti-influenza activity of Manuka honey in their experiment with Madin-Darby Canine Kidney (MDCK) cells [3]. After plaque inhibition test, it was observed that pre-treating cells with manuka honey significantly decreased plaque formation (at a concentration of 6.25 mg/mL, plaques reduced to 13.7 0.8%, and at 25 mg/mL, plaques were completely absent). This result suggests that the honey possesses potent virucidal capabilities. However, it is noteworthy that no mechanism was held responsible for this activity. There is a chemical in Manuka honey which is a reduced derivative product of pyruvic acid, Methylglyoxal (MGO), this chemical was evaluated in a study for its anti-influenza B virus activity. MGO was effective in suppressing the replication of influenza B virus, demonstrating 50% inhibition at concentrations varying between 23-140 M in MDCK cells. No mechanism was found to be attributed for the activity. Vahed H, et al. reported that ginger, garlic, and honey mixture effectively diminished the replication of the influenza H_1N_2 virus in human lymphocyte [4]. However, since this *in-vitro* study used honey in combination with other herbs, it is unclear if the observed activity can be specifically attributed to honey.

Due to insufficient research, the studies which are reviewed above are the only studies we found in the literature that are directly related to anti-influenza activity of honey found, so, to make our review more comprehensive and to achieve the objective of our review, we have reviewed those studies in which either honey has been found to be beneficial for Upper Respiratory Tract Infections (URTI) due to the fact that influenza is an URTI or its chemical constituents has been found to be effective as anti-influenza.

In a clinical trial by Paul IM, et al. which was conducted to find the treatment comparison between buckwheat honey and dextromethorphan, it was found that honey was effective in alleviating nighttime cough and sleep disturbances of their child caused by URTI [5]. However, the difference was non-significant. A survey based on questionnaires was conducted by Sebo P, et al. among primary care patients to investigate which out of 72 non-prescription herbal remedies are used by them for the treatment of URTI symptoms: Common cold, sore throat, and cough [6]. The majority (94%) of patients who used these home remedies (lemon/thyme/honey/herbal tea) found them to be effective. However, the effect is mixed and it cannot be concluded that it was due to honey.

A study which was conducted on children with URTI under 5 years of age, found that 36% of mothers who were using honey, ginger, and black piper, found improvement in their children while 28% of mothers who used turmeric and milk found improvement in the symptoms of URTI. Cohen HA, et al. in their Randomized Controlled Clinical Trial (RCT), compared three types of honey that is 10 g of either citrus honey, labiatae honey or eucalyptus honey with silan date extract as placebo for treating nocturnal cough and difficulty in sleeping associated with URTI [7]. They found that all the individual honey groups had better improvement in the severity of cough as compared to the placebo group ($P<0.001$). A similar effect was found in alleviating sleep difficulty ($P<0.001$). The same authors in another single-blind RCT reported that the polysaccharide-resin-honey improved URTI associated cough as compared to carbocysteine syrup ($P<0.05$).

A randomized double-blind trial which was conducted by Raessi MA, et al. found that there was a significant difference between pre and post-treatment scores of persistent post-infectious cough when it was treated by the mixture of honey and coffee for one week ($p<0.05$) while the difference was not significant in the control group who were given Guaifenesin (p 0.05). The authors of this trial also concluded that honey mixed with coffee can serve as a substitute treatment for Persistent Post-Infectious Cough (PPC). Ayazi P, et al. conducted a clinical trial on children to compare the effects of two types of honey with diphenhydramine on sleep quality and cough [8]. A significant difference between both the types of honey and diphenhydramine was found with respect to severity, frequency of cough, and sleep quality ($P<0.001$). The two types of honey were from two different companies of Iran. The primary limitation of the study was its lack of a double-blind methodology. Furthermore, the reason of the cough was not mentioned but the authors of the study emphasized that in URTI, viruses are the predominant cause, with bacteria responsible for fewer than 10% of these cases. However, the study suggests that honey has properties that are effective against viruses.

Sopo SM, et al. compared Levodropropizine (LDP) and Dextromethorphan (DM) with honey and milk to treat non-specific cough in children in an RCT [9]. In the group treated with honey and milk, 80% experienced therapeutic efficacy, compared to 87% in the group receiving over-the-counter drugs with a p-value of 0.25. It is difficult to say that the above effect was due to honey alone due to the presence of milk. All the clinical studies are summarized in Table 1.

Authors (Year of publication)	Design of study	Participant demographics	Results	Conclusion
Sebo P, et al.	Cross-sectional	1,012 patients associated with cough associated with URTI	The majority (94%) of patients who used home remedies (Lemon/thyme/honey/herbal tea) found	These reatments can be safely suggested s alternative options for managing symptoms of ear,

			them to be effective as compared to onion syrup (77%)	nose, and throat conditions in primary healthcare settings
Sopo S, et al.	RCT	134 children with non-specific acute cough	80% therapeutic success in the honey and milk group and 87% in the OTC medication group (p=0.25)	Milk and honey mixture is at least as effective as DM or LDP in treating non-specific acute cough in children
Ayazi P, et al.	Clinical trial	87 pediatric patients with cough due to URTI	A significant difference between both the types of honey and diphenhydramine was found with respect to severity, frequency of cough, and sleep quality (P<0.001)	Honey appears to be more effective than DPH for treating pediatric cough
Raessi MA, et al.	Double-blind RCT	97 adults with Persistent Post-Infectious Cough (PPC)	A significant difference between pre and post treatment scores of persistent post-infectious cough when it was treated by the mixture of honey and coffee for one week (p<0.05)	Honey combined with coffee is effective for treating PPC and can be considered as an alternative treatment option
Cohen HA, et al.	Double-blind RCT	300 children with cough associated with URTI	Honey had better improvement in the severity of cough as compared to the placebo group with silan date extract (P<0.001)	Honey could be a more favorable option for managing cough associated with URTI
Cohen HA, et al.	Single-blind RCT	150 children with cough associated with URTI	Polysaccharide-resin-honey improved URTI associated cough as compared to carbocysteine syrup (P<0.05)	Polysaccharide-resin-honey syrup was linked to a quicker improvement in cough
Paul IM, et al.	Double-blind RCT	105 children with URTI nocturnal symptoms, illness ≤ 7 days	Honey was effective in alleviating nighttime cough and sleep disturbances of their child caused by URTI. However, the difference between honey and DM was non-significant	Honeynmay be a more favorable option for sleep disturbances and cough
Joshi P, et al.	Quantitative research	75 children	36% of mothers who were using honey, ginger, and black piper, found improvement in their children while 28% of mothers who used turmeric and milk found improvement in the symptoms of URTI	Herbal remedies may be used for cough

Note: RCT: Randomized Controlled Trial; URTI: Upper Respiratory Tract Infection; OTC: Over-The-Counter; DM: Dextromethorphan; LDP: Levodropropizine; DPH: Diphenhydramine; PPC: Persistent Post-Infectious Cough

Table 1. A summary of all the clinical studies related to honey for the treatment of upper respiratory tract infection.

Kaempferol, which is one of the major flavonoid found in honey, has been associated with anti-influenza activity. Sithiasarn P, et al. reported that kaempferol effectively reduced the production of influenza A nucleoprotein in A549 epithelial cells infected with the severe avian influenza H_5N_1 virus strain A/Thailand/Kan-1/04 [10]. Another important flavonoid is quercetin, which in a study conducted by Wu W, et al. found to be effective against influenza A [11]. They reported that quercetin had the ability to suppress influenza infection across various strains, such as A/Aichi/2/68 (H_3N_2), A/FM-1/47/1 (H_1N_1), and A/Puerto Rico/8/34 (H_1N_1) with half maximal Inhibitory Concentrations (IC_{50}) being 2.738 1.931, 7.756 1.097, 6.225 0.467, and 7.756 1.097 g/mL, respectively. The mechanism of action was attributed to the binding of quercetin with Hemagglutinin (HA2) subunit of influenza A. This interaction is crucial for mediating the fusion of the viral envelope with the membrane of a cell.

Influenza A has been found to induce cell apoptosis after cell infection. Liu Y, et al. found that Chrysin (a chemical constituent of honey) significantly hindered the mitochondrial apoptotic pathway induced by influenza A virus, modifying the Bax/Bcl-xl balance and diminishing the activation of caspase-3 and 9 [12]. Furthermore, Chrysin was capable of inhibiting the cell cycle arrest in the G0/G1 phase triggered by Influenza A virus, achieved by decreasing the expression levels of P21 and P53. Kim SR, et al. also reported that Chrysin inhibited cell death of A549 cells due to a strain of influenza A virus; influenza A/Puerto Rico/8/34 (A/PR/8) by multiple mechanisms; Chrysin increased the phosphorylation of Mammalian Target Of Rapamycin (mTOR), thereby, inhibiting autophagy activation [13]. It decreased LC3 and LC3 B-positive puncta levels in the infected cells. Moreover, Chrysin reduced the nucleoprotein expression of virus in A549 cells.

As per the United States Department of Agriculture (USDA), luteolin in the concentration of 0.28 mg is present in 100 gram of honey. Luteolin has been found with anti-influenza activity. Lee IK, et al. reported that luteolin efficiently blocked the neuraminidase (an enzyme which is found on the surface of influenza virus) activity of H_3N_2, H_1N_1, and H_5N_1 influenza viruses and the results from the

Cytopathic Effect (CPE) reduction assay indicated that luteolin diminished the damage to MDCK cells caused by these influenza viruses [14]. Yan H, et al. found that luteolin inhibited the expression of the coat protein I complex, which is associated with the entry of the influenza A virus and its endocytic pathway in MDCK cells [15]. In a study by Yu WY, et al. it was found that luteolin targeted NOX4 to suppress the NF-κB/MLCK pathway [16]. This action reduces the cytokine release triggered by the influenza virus and minimizes the damage to pulmonary microvascular endothelial cells, thereby protecting the pulmonary endothelial barrier. All the given mechanisms are illustrated in Figure 1.

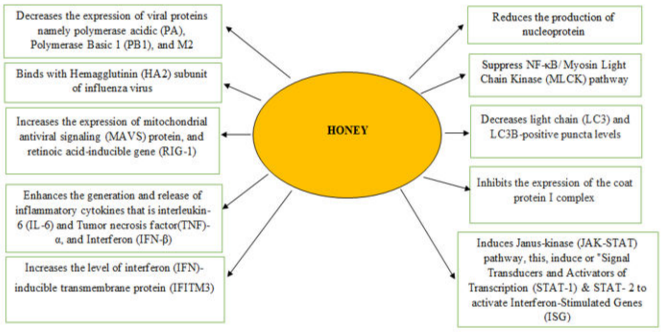

Figure 1. Illustration of different mechanisms by which honey confers anti-influenza effects.

This figure illustrates the diverse biochemical and immunological pathways through which honey exerts its anti-influenza effects. Key mechanisms include:

- Suppression of NF-κB/MLCK pathway, reducing inflammation and viral replication.
- Binding with HA2 subunit of influenza virus, potentially inhibiting viral entry.
- Decreasing LC3 and LC3 B-positive puncta levels, indicating an effect on autophagic processes.
- Enhancing the expression of MAVS protein and RIG-1, boosting innate immune responses.
- Inhibiting the expression of the coat protein I complex, possibly affecting viral assembly or release.
- Modulating inflammatory cytokines (IL-6, TNF-α, IFN-β), playing a role in immune response orchestration.
- Inducing the JAK-STAT pathway and activating ISGs (STAT-1 and STAT-2), enhancing antiviral defences.
- Increasing the level of IFITM3, which impede viral entry or replication.

These mechanisms collectively underscore potential of honey as a multifaceted antiviral agent.

Adverse effects

Although honey offers nutritional and medicinal benefits, it is susceptible to both microbial and non-microbial contamination. It can also contain residues of herbicides, heavy metals, and pesticides from the environment. Allergy to honey is rare, but there could be an allergic reaction to either pollen or bee proteins in honey. Furthermore, honey might include toxic substances, such as grayanotoxins in "mad h oney" derived from Andromeda flowers. Studies by Dur, et al., Yaylaci, et al., Erenler, et al. and Karabag, et al. have linked various cardiac issues, including acute myocardial infarction, bradycardia, asystole, and junctional rhythm with mad honey intoxication [17-20]. Consequently, to guarantee the safety of honey, adherence to specific standards and regulatory measures is essential.

Conclusion

Though there are unsubstantial number studies related to honey for the treatment of influenza and the studies are mostly *in-vitro*. Honey, in these studies, have clearly performed well and proved to be efficacious against influenza through different mechanistic pathways. Importantly, honey reduces the expression of different viral proteins and increases the level of pro-inflammatory cytokines which chemo-attract immune cells. However, there is still the need of further studies in humans. Several RCT have been performed by using honey but they have focused on the effectiveness of honey in treating symptoms like cough due to URTI rather than specifically for influenza. However, they indicate the possibility of honey efficacy to combat with URTI like influenza. Furthermore, it is also important to emphasize the need for double-blind RCT involving adults, in addition to children, in this area of research. Finally, conducting research using various types of honey is another potential area that needs to be explored.

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How to cite this article: Roy, Vikas C and Rajni Bala. "A Comprehensive and Updated Mini-Review on Anti-Influenza Properties of Honey." *J Pharmacogn Nat Prod* 11 (2025): 351.