REVIEW ARTICLE AGROBIOLOGICAL RECORDS
ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
Open Access Journal

HONEY: A MIRACULOUS DRUG

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ABSTRACT

Honey has been used as food and traditional medicine for centuries. It contains different bioactive molecules that make honey a wonder of nature. These molecules are responsible for the pharmacological activities of honey. We have reviewed the evidence of honey's medicinal properties. Antibiotics along with antioxidant and anti-inflammatory effects and the factors playing role in these roles are elaborated. The antiviral effect of honey is attributed to two different pathways that eventually lead to curing the viral infection. Honey is also associated to cure fungal and allergic diseases that was difficult to cure via use of allopathic medicine due to development of resistance and cytotoxic side effects of such drugs. This review also presents comprehensive data on the honey being an antidiabetic, anti-cancer and immunity boosting agent and its main suggested mechanisms. All these therapeutic characteristics of honey are being explored by scientists and are comprehensively reviewed.

***Keywords*:** Honey, Immunity Booster, Antibacterial, Antiviral, Antioxidant, Antifungal, Anticancer, Antidiabetic.

Article History (2022-12137) || Received: 25 Dec 2022 || Revised: 28 Dec 2022 || Accepted: 30 Dec 2022 || Published Online: 31 Dec 2022

1. INTRODUCTION

Honey is consumed by mankind for centuries ago. First it was used as a sweetener with advances in mankind it uses were discovered in medical science (Israili 2014). Praises for honey are even present in 5000 old writings i.e., therapeutic use were described by Papyrus Ebers in his writings (Bryan and Smith 1930). In 2000 BC it was used in China as medicine (Jones 2009). Qualities of honey are accepted by different religions i.e., Greek, Jewism, Christianism, Hinduism, and Islam. Constituents of honey are different in different types of honey (White and Doner 1980). They all depend on certain factors like environment where the hive is located, type of bee which is manufacturing the honey and source from which nectar is collected i.e., floral or non-floral (Rao et al. 2016). Biochemically honey is mixture of different types of sugars, flavonoids, proteins, minerals, enzymes, polyphenols, polypeptides, and different sorts of vitamins (Alvarez-Suarez et al. 2010). In each type of honey, the quantity of these constituents differs. This difference leads to variation among honey color, therapeutic activity, density, and taste. These compounds synergistically support each other and as a combination, honey proves itself a wonder. 80% of the properties of honey are common throughout the world. Various techniques are developed to differentiate honey types. Nuclear magnetic resonance is one of them (Schievano et al. 2010).

As a treatment, honey is used in a number of different human as well as animal diseases (Eteraf-Oskouei and Najafi 2013; Grego et al. 2016). Clinically honey has proven itself as an antibacterial, antifungal, anti-inflammatory, antioxidant, anticancer and antidiabetic drug (Anyanwu 2012; Al-Hatamleh et al. 2020; Yupanqui Mieles et al. 2022). This all is attributed due to different physical and chemical characteristics of honey. Low pH, high viscosity, osmotic pressure and presence of certain compounds make it a medically important agent (Mandal and Mandal 2011). Mechanism for each pathway is different and discussed in detail. Some bioactive molecules have shown antiviral effects that may be proved as antiviral in later studies (Al-Hatamleh et al. 2020). Levan and ascorbic acid are still ambiguous in nature and its exact mechanism whether it is antiviral or not, has not been discovered yet (Rairakhwada et al. 2007).

The purpose of writing this whole review is to show the research gap that exists in discovering the hidden pathway that will help the veterinary as well as medical field to overcome the diseases. Although it is proven that honey is an antimicrobial still there is no research that supports this evidence in systemic use. Similarly antiviral pathways need to be worked on. Therapeutic bioactive molecules extraction and their use as a means of drug can be a possibility. It can be used in those patients who are intolerant or allergic to any compound present in honey.

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2. Honey as an Anti-bacterial Agent

Honey acts as anti-bacterial agent because of certain qualities. Honey is highly viscous, and its water content is too low, its acidic nature and presence of hydrogen peroxide makes it a wonder drug. Methylglyoxal is a major non peroxide component helping in reducing bacterial propagation (Weston 2000). Non-peroxidase glycoproteins and glycopeptides also have a role in making honey an antibacterial agent. These all factors collectively contribute and have a significant role in the antibacterial effect of honey (Mavric et al. 2008). The proportional association between bacterial contamination and unbound water with water molecules is termed as water activity. It is observed that 0.562 to 0.62 is the normal range of water activity (Olaitan et al. 2007). Bacteria requires water activity range to be in the range of 0.94-0.99 for growth (Blickstad 1984). In this way honey doesn't allow bacteria to grow by limiting the water content (White and Doner 1980). Sugar concentration in honey is reported to be 70 to 80% (Singh and Singh 2018). This high concentration upon feeding induces osmosis in the living cells (Kumar et al. 2010). Osmosis plays an important role in killing the pathogenic bacteria. No doubt, type of bacteria matters while bacterial inhibition along with the aqueous concentration (Mavric et al. 2008). When the water content of honey is less, and sugar concentration is more. It will make honey strongly hypertonic. This will result in bacterial inhibition because the bacterial cell will shrink and ultimately die (Molan 1992). This all happens because high sugar concentration will facilitate moving water out of the bacterial cell. It is observed that if honey is applied over a weeping or exudating wound it will result in dilution of honey. Sugar concentration of honey will reduce and so its anti-bacterial activity. It will become effective only against some of the species (Albaridi 2019). During research it is observed that artificial honey is not effective against bacteria even if it is prepared in accordance with the natural honey sugar concentration (Molan 1992). This gives rise to question that what are the other factors that are responsible for its antibacterial activity.

Most bacteria require a pH range of 6.5-7.5 for proper growth (Visser et al. 1996) but the pH of honey is quite acidic having range of 3.2 to 4.5 (Adadi and Obeng 2017). It is one of those factors that makes the honey antibacterial in nature. This acidic nature of honey is due to presence of gluconic acid that is 0.5% w/v present in honey (Hossain et al. 2022). Some bacteria that are acidophilic in nature are not killed by this mechanism (Johnson 1995). For those bacteria honey has an efficient killing machinery of hydrogen peroxide (Bizerra et al. 2012). It is a very effective oxidizing agent. Low water content and acidity renders the enzyme inactive in honey i.e., glucose oxidase. Upon dilution water content increases and makes glucose oxidase active and it catalysis glucose and hydrogen peroxide is formed. 5 to 100µg Hydrogen peroxide per gram of honey is the maximum range of production of hydrogen peroxide and this is achieved by 30 to 50% diluting the honey (White et al. 1963). Level of hydrogen peroxide increase in the honey with increased lifetime and dilution is the vital point in its production (Majtan et al. 2014). In half an hour this level may tend to be 2.5mmol and increase on double rate on increase in incubation period (Bang et al. 2003). Scientists did research and found the range of hydrogen peroxide that was 1mM average value (Bogdanov 1997). Range of hydrogen peroxide between 1 to 2.5 is effective enough to kill *Escherichia coli* in only 15min (Imlay and Linn 1986; Brandi et al. 1987).

Catalase is naturally present in honey and an inverse relation exists between glucose oxidase and catalase (Huidobro et al. 2005). So, hydrogen peroxide formation will be affected by the interaction of enzymes resulting in altered antibacterial activity (Brudzynski 2006). The source of catalase is purely botanical. It mainly comes from pollen grains. A small amount is also extracted by honey from nectar of plant. Their functions differ according to their origin (Huidobro et al. 2005). Water and free oxygen are formed by the action of catalase on hydrogen peroxide (Keilin and Hartree 1938). It is completely a redox reaction. Association of glucose oxidase and catalase was described by Weston (2000) in which he interpreted how they both affect the antibacterial activity. He proposed that low level of catalase produces high level of hydrogen peroxide and so do high level of glucose oxidase (Weston 2000). It was observed during study that antibacterial activity is reduced upon adding catalase (Adcock 1962). So, the main players associated with bacterial activity are glucose oxidase and the production of hydrogen peroxide. Non peroxidase activity is seen to be responsible for anti-bacterial activity other than previously described features of honey (Simon et al. 2009). Even in the absence of hydrogen peroxide honey and catalase perform antibacterial activity. Because of this feature these types of honeys is known as non-peroxidase honey (Atrott and Henle 2009). Flavonoids and simple phenolic compounds are observed in honey and there is possibility that they may have some role in antibacterial activity (Albaridi 2019). There are some other compounds that are seen to be having role in non-peroxidase activity of honey like methyl glyoxal (MGO) and methyl syringate (MSYR) (Kato et al. 2012). These two compounds are predominantly observed in honey from Manuka tree. Such honey is known as Manuka honey. Dihydroxyacetone (DHA) give rise to the production of MGO (Grainger et al. 2016). Bees that collect nectar and pollen from Manuka tree harbor more DHA as its level is high in Manuka tree (Williams et al. 2014). As the level of MGO increases in Manuka honey, its antibacterial capacity increases. MGO concentration in manuka honey is about 800mg/kg. it is 100 times more amount of MGO found in other honey types (Wallace et al. 2010). This reveals that Manuka honey is highly antibacterial rather than other types due to its MGO content (Johnston et al. 2018). DHA is the main parent molecule which gives rise to MGO. So even after

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harvesting or in hive concentration of MGO tends to increase (Hossain et al. 2022). Certain conditions are required for formation of MGO and warm temperature in one of them. Too hot or too cold an environment stops that conversion (Adams et al. 2008). Royalisin, also termed as bee defensin-1 is an anti-bacterial newly identified peptide that is found in Revamil source (RS) (Kwakman et al. 2010). Standardized greenhouses are used to provide adequate environment for RS honey. Honeybee hemolymph also contains that peptide in its head, thoracic gland, and royal jelly (Casteels-Josson et al. 1994). Royalisin has high antibacterial capacity, but it is only limited to gram positive bacteria like *S. aureus, B. subtilis* and *Paenibacillus larvae* (Kwakman and Zaat 2012). Royalisin has not been observed in Manuka honey till now but is readily identifiable in RS honey (Kwakman et al. 2011). This proves that botanical origin also affects the compounds that are present in honey and so does its antibacterial capacity (Baltrušaitytė et al. 2007). Different factors playing part in the antibacterial property of honey are illustrated in Fig. 1.

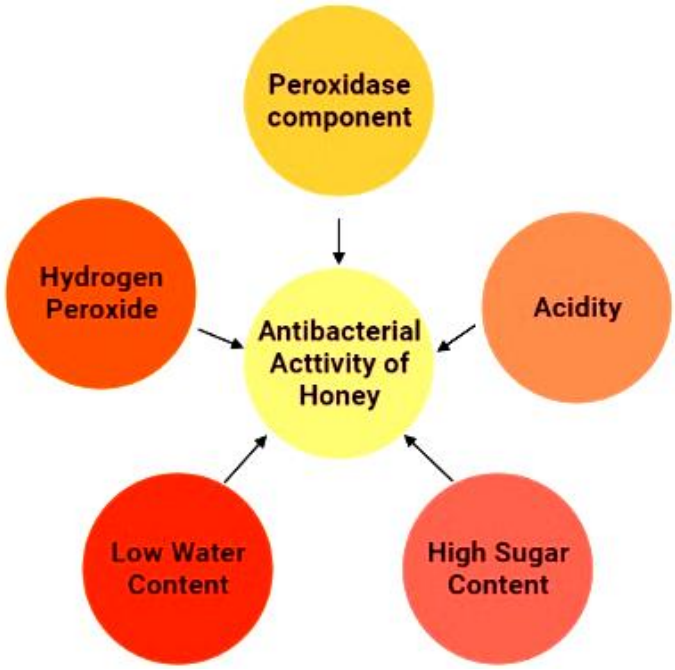

Fig. 1: Properties of honey contributing to antibacterial activity of honey (Drawn by BioRender App).

3. Honey as an Antiviral agent

Honey characteristics are extensively explored on the basis of an antibiotic and antifungal agent (Israili 2014). Anti-viral character of honey still needs to be studied well as we are lagging research in that aspect. This will help in the treatment and prevention of viral diseases. In 1996, an *in vitro* study was done on Vero cell line that was of monkey kidney cells. Infection was given via Rubella virus and was kept for incubation for 4 days (Zeina et al. 1996). Without any sort of cytotoxicity, 1mL of honey was sufficient to kill 1mL virus. Concentration ranges for honey were 1:1 to 1:1000. For viruses it was 10 to 10^9 (Al-Hatamleh et al. 2020). Honey also proved its antiviral activity against Herpes Simplex Virus (HSV) with a concentration of 500µg/mL. it reduced the virus upto level of 100 µg/mL (Hashemipour et al. 2014). HSV causes skin lesions that are recurrent in nature, and they can be treated by honey. Antiviral characters of Manuka and clover honey are proved against Varicella Zoster virus in In-vitro conditions (Shahzad and Cohrs 2012). A study was done to check the antiviral effects of different types of honey. Manuka honey proved to be the best among them as an antiviral against H1N1 influenza virus. Influenza virus was incubated in Madin-Darby canine kidney, a type of Vero cell line (Watanabe et al. 2014). Mixing garlic and ginger in honey also enhanced the antiviral activity of honey against the influenza A virus. Its effect against virus is like an antiviral standard drug, Amantadine (Vahed et al. 2016). The mode of action was revealed by In-vitro study. Honey garlic and ginger stops the division of virus in mononuclear cells of human peripheral blood and promote the proliferation of cells (Vahed et al. 2016). The two pathways that are primarily involved in killing the virus are described below.

3.1. Myeloid Differentiation Factor 2 (MD-2)/ Toll-Like Receptor 4 (TLR4) Pathway

TLR4 interacts with MD-2 to activate the immune response of the host upon the entry of pathogen into the cell. These TLR4 receptors are transmembrane in nature (Mukherjee et al. 2016). They are primarily present on cells from myeloid lineage like dendritic cells (DCs), monocytes and macrophages. However, they can be present on any other cell (Vaure and Liu 2014). Previously it was believed that when a gram-negative bacterium binds hydrophobic

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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pockets of MD-2 activate MD-2/TLR4 signaling pathway. Lipopolysaccharide (LPS) was considered responsible for binding to MD-2 (Mazgaeen and Gurung 2020). After extensive study it was observed that viruses also have the tendency to activate the MD-2/TLR4 signaling pathway (Olejnik et al. 2018). Ebola virus proved to have ability to attach with hydrophobic pocket of MD-2. This binding was done through glycoproteins (GP) of the RNA present in Ebola virus (Okumura et al. 2010). This signaling starts the production of cytokines that are pro inflammatory and anti-inflammatory in nature (Escudero-Pérez et al. 2014). In a study it was revealed that T-lymphocyte death and severity of infection was also associated with GP of Ebola virus (Iampietro et al. 2017). Similar results were shown in the case of Vesicular Stomatitis Virus. Fusion proteins of Respiratory syncytial virus, dengue virus nonstructural proteins also adapt the same pathway of MD-2/TLR4 activation (Rallabhandi et al. 2012; Modhiran et al. 2015). Extensive inflammatory response in also seen in the case of SARS-Cov-2 (Tay et al. 2020). S Proteins infects the T cells by process of membrane fusion (Wang et al. 2020). It eventually leads to death due to lymphocytopenia (Zheng et al. 2020; Zeng et al. 2020). It is still unknown if T-lymphocyte upon getting infection by SARS-Cov-2 can multiply or not. Nonstructural proteins associated with SARS-Cov-2 are made from cleavage of 3 structural GPs and polyproteins (Astuti 2020). This proves that the activation of MD-2/TLR4 is partially responsible for the acute inflammatory response in patients suffering from SARS-Cov-2. A direct relation between SARS-Cov-2 and activation of MD-2/TLR4 is not reported yet. The steps involved in the MD-2/TLR4 pathway are shown in Fig. 2.

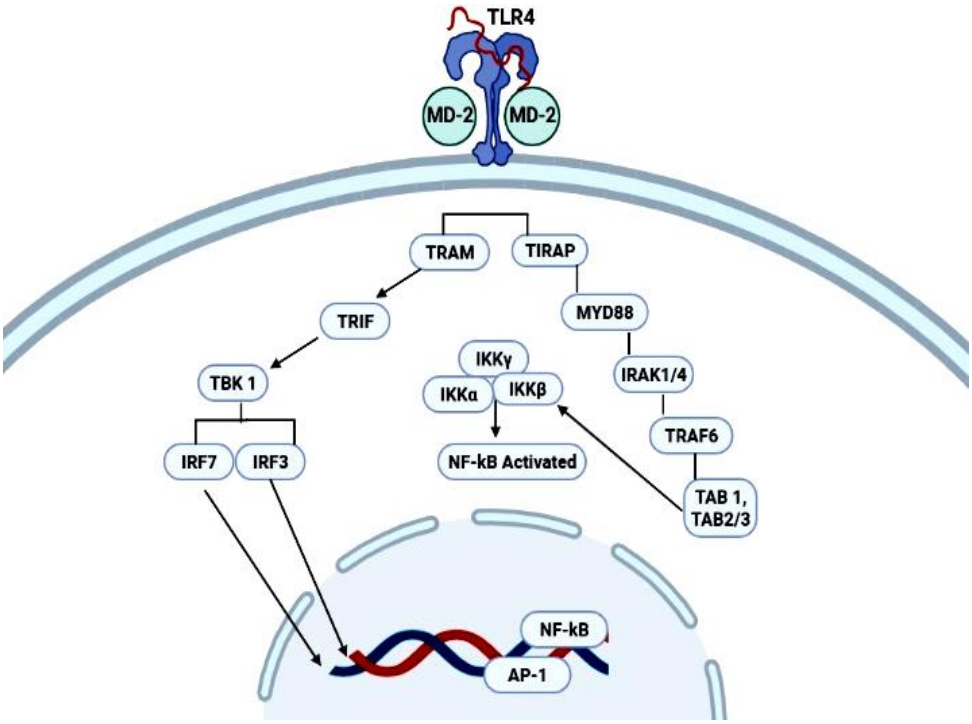

Fig. 2: Illustration of MD-2 pathway (Drawn by BioRender App).

As illustrated previously immune response is stimulated by MD-2/TLR4 signaling. Viral proteins activate the MD-2/TLR4 signaling pathway by attaching to MD-2 hydrophobic pockets (Miyake 2004). Cytoplasm has 2 signaling molecules. One is Myd88 and the other one is TIR domain having an adaptor molecule that produces interferon-β (TRIF) via TRAM that is TRIF related adaptor molecule. Myd88 utilizes interleukin-1 receptor associated kinases 1 and 6 (IRAK1/4) members, TNF receptor-associated factor 6 and Transforming growth factor beta-activated kinase 1 complex to start two major transcription factors. I kappa B kinase complex activates nuclear factor kappa B and mitogen-activated protein kinases (MAPK) activate the Activator protein-1 (AP-1) (Feng and Chao 2011). Cytokine expression and response to any infection is controlled by gene expression via nuclear factor kappa B and AP-1. Transcription factors like Interferon regulatory factor 3 (IRF3) and Interferon regulatory factor 7 (IRF7) are activated by TRIF/TRAM through TANK binding kinase 1 (TBK1). TBK1 manages the innate immune response (Awasthi 2014).

3.2. Nitric Oxide Pathway

Nitric Oxide (NO) is an alternative pathway by which honey kills the virus and proves to have antiviral potential. Physiologically, nitric oxide acts as neurotransmitter in many instances (Al-Waili et al. 2004; Al-Waili et

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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al. 2006). Honey tends to increase its level. It is also observed that in pathological conditions such as viral infections (Mehta et al. 2012) NO is a remedy. In the early 1990s it was proposed that NO boost innate immunity, so the researchers tried to discover its anti-viral potential (Reiss and Komatsu 1998). In 1998 the antiviral effect of NO was reviewed on DNA and RNA viruses. OBL21 neuronal cell line was infected using murine coronavirus (M-CoV) (Lane et al. 1997). Upon addition of NO, replication of the virus was blocked. In another study upon Japanese encephalitis virus (JEV) it stopped the RNA synthesis, viral protein builds up and release of virus from the infected host cell (Lin et al. 1997). The exact mechanism by which NO kills the virus is still unclear. There is a huge gap in study especially regarding RNA viruses. It is assumed that it may target enzymes (Saura et al. 1999). It stops the viral replication mechanism and kills the virus. In 2005, It was observed by the scientists that in infected E6 Vero cell line replication of SARS-CoV was inhibited by NO. That NO was produced by NO synthase enzyme (Åkerström et al. 2005). SARS-CoV replication was inhibited by NO donor S-nitroso-N-acetyl penicillamine (SNAP). This inhibition was dose dependent from 100 µM to 400 µM. (Akaberi et al. 2020) 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide Assay (MTT assay) was used to identify any cytotoxic changes but there was none.

It is hypothesized that mode of action still need to be discovered. According to this mechanism MD-2/TLR4 signaling pathway is involved intracellularly. This activates MAPK and NFkB that in turns activate Nitric oxide synthase 2 (NOS2) gene (Van'T Hof and Ralston 2001). NOS2 associated mRNA will start production of NOS enzyme that will convert l-arginine (Arg) and l-citrulline (Cit) with help of NADPH and oxygen into NOS enzyme (Braulio et al. 2004). This enzyme is present in 3 forms, neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) and is responsible for the production of NO. They are present in different types of cells and their expression is also dependent on different cellular types. In a viral infected cell, viral protease enzyme will be inhibited by NO. It will prevent the viral polyproteins from cleaving. This will render the virus unable to synthesize viral RNA and will eventually inhibit the replication of virus (Al-Hatamleh et al. 2020). NO induced antiviral pathway is further illustrated in Fig. 3.

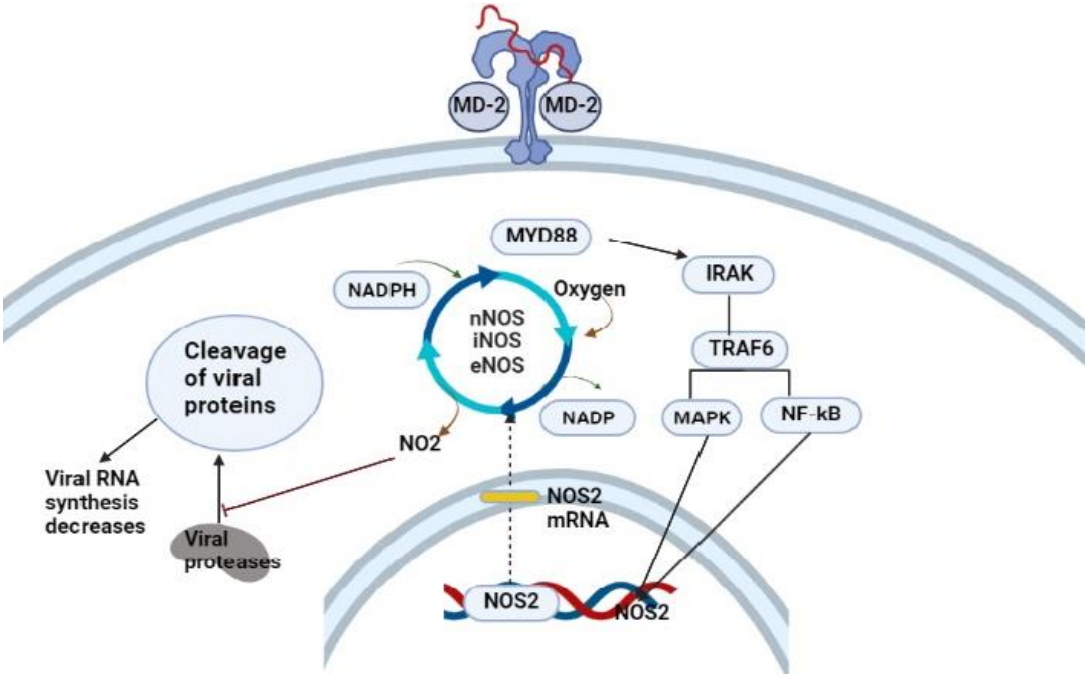

Fig. 3: Schematic illustration of NO2 Pathway (Drawn by BioRender App).

Patients having idiopathic pulmonary arterial hypertension in the infection course due to COVID-19 were subjected to NO inhalation treatment. Inhalation dose started from 20 ppm of NO and gradually decreased to 10, 5 and 0ppm in 11 days. Duration of inhalation was 12-14 hours per day that were reduced to 2-3 hours per day (Zamanian et al. 2020). Patients showed excellent effects and recovered from the infection without medical care. This report does not define the presence of nucleic acid test of SARS-CoV-2 after regaining health. So, it is not sure that NO can be used as treatment of SARS-CoV-2, or it was just stopping the progressive phases of the disease. Therefore, further case studies and investigations are ongoing whether inhaled NO can be considered as treatment of COVID-19 or not (Alvarez et al. 2020).

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4. Honey as an Anti-Allergic agent

Honey contains certain compounds like phytochemicals that are proven to be antiallergic in nature (Aw Yong et al. 2021). The amount and type of phytochemicals differ significantly in different types of honey like manuka, gelam and tualang. Chrysin, kaempferol, quercetin and apigenin are phenols and polyphenols (Bodor et al. 2021). Their level is high in honey, and it gives certain medicinal properties to honey. However, the anti-allergic property of honey isn't investigated properly, and research is lagging in this aspect. Different pathways to inhibit allergic reactions were demonstrated by scientists during their research. In rats, peritoneal mast cells are inhibited by gallic acid to release intracellular calcium, histamine and proinflammatory cytokine by editing the activity of MAPKs and Nuclear factor kappa B. β-hexosaminidase and cytokines release are also suppressed via kaempferol, an anti-allergic compound present in honey (Lee et al. 2010). In another study β-hexosaminidase was inhibited by caffeic acid and p-coumaric acid in RBL2H3 cell lines. This all process was IgE mediated (Zhu et al. 2015). Compounds like hyacinthin and luteolin require further investigation to prove its anti-allergic activity (Aw Yong et al. 2021). Possible association of all these molecules also needs to be studied.

5. Honey as an Anti-Fungal Agent

Fungal infections are increasing day by day in the community and there is no ideal anti-fungal that claims to eliminate the infection. Due to this reason many scientists have started to work on traditional medicine and its active compounds responsible for eradicating disease (Scorzoni et al. 2017). Honey is in limelight due to its anti-fungal properties. Azoles are considered effective against fungal diseases (Whaley et al. 2017) but there are some reports of development of resistance to the drug especially in cases of *Candida auris* species (Whaley et al. 2017; Jeffery-Smith et al. 2018). In this way all other four classes of anti-fungal drugs have their pros and cons. Some develop toxicity related issues, mode of administration, unavailability of drug in immunocompromised patients while some develop resistance of anti-fungal agent (Groll and Grist 2009; Perlin et al. 2015). Biofilms of certain species of fungus are also targeted by some types of honey along with the antifungal property i.e., *Ziziphus jujuba* honey (Ansari et al. 2013). Osmotic effect is responsible for anti-fungal effect of honey (Yupanqui Mieles et al. 2022). However, some scientist claimed that even when the honey aquatic content is more and osmolality is less, honey has the tendency to kill fungi, thus this killing feature is not attributed to the osmotic effect. Candida species were checked against four types of honey, and they proved their anti-fungal effect (Irish et al. 2006). In another study 6 Iranian monofloral types and one multifloral type of honey were used against 11 fungal strains. Candida specie that was fluconazole resistant and susceptible, both were targeted by honey (Katiraee et al. 2014). Polyphenols, hydrogen peroxide and acidity contribute to the anti-fungal activity and there is a huge variation in these contents. This difference of contents is attributed to the origin of honey. Several volatile and phenolic compounds give rise to anti-fungal activity. Estragole is responsible for anti-fungal activity in Agastache honey. Several benzaldehydes and 2,4-ditert-butylphenol acts against *Aspergillus*, *Dermatophytes*, *Candida albicans* and *Trichophytons* are present in honey (Anand et al. 2019). Acetanisole was reported to be a major anti-fungal compound in honey extracted from *Leptospernum* origin. Super Manuka is extracted from *Leptospermum polygalifolium*. Principle compound in super manuka is methyl 3,5-dimethoxybenzoate, it is responsible for killing *Candida albicans* (Arai et al. 2002). *P. vulgaris* is killed via nonanal, linalool and acetanisole. These compounds are also seen in *Leptospermum* originated honey (Kubo et al. 1995). Benzyl cinnamate, caffeic acid, methyl cinnamate, and terpenoids are aromatic compounds that give rise to antifungal property of honey, especially high content of propolis in honey has quite high anti-fungal property (Israili 2014).

6. Honey as an Antioxidant Agent

Reactive oxygen species are produced via metabolic reactions occurring in a biological system. They are harmful and cause oxidative stress. This oxidative stress results in a number of problems like impaired glucose tolerance, insulin resistance is developed dure to problematic signaling pathway to insulin and dysfunction of β-cell. Defaulted insulin receptor and substrate-1 leads to hyperglycemia and results in organ failure (Amos et al. 1997). Phenolic compounds are responsible for the antioxidant activity of honey (Alshammari et al. 2022). They tend to promote the secretion of enzymes that are antioxidant in nature such as catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, peroxiredoxin and glutathione reductase (Moniruzzaman et al. 2012). These enzymes are responsible for neutralizing the reactive oxygen species (ROS). Sources of ROS are explained in Fig. 4. Neutralizing these species leads to enhanced immune system. Ferric Ion Reducing Antioxidant Power, 2,20-azino-bis-3-ethylbenzothiazolin-6-sulphonic acid (ABTS) and 2,2-diphenyl-1-picrylhydrazyl assay (DPPH) are the mostly used methods by which antioxidant capacity is determined in honey, at least two methods should be adapted to decrease the chances of false positive or false negative result (Alvarez-Suarez et al. 2009).

7. Honey as an Anti-Inflammatory Agent

Honey is considered as an anti-inflammatory agent which plays two roles. One is it lowers the proinflammatory cytokines production and down regulate the transcription factors of inflammation i.e., MAPK and Nuclear factor

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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kappa B. Secondly it does help in manufacturing cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) that are inflammatory mediators (Schieber and Chandel 2014). Honey is accepted by many scientists to be involved in anti-inflammatory activity by altering the levels of iNOS, ornithine decarboxylase, (COX-2) and tyrosine kinase (Waheed et al. 2019). Cancer is also treated by honey due to its protective ability and immune modulation. There is a sugar present in honey, named NOS, it is reported to boost the immune system. When swelling and inflammation persist in a cell it leads to disastrous results. In different Clinical trials, animal models and cell cultures, study was done on the anti-inflammatory role of honey (Shamala et al. 2000). It was proven that honey lowers inflammation in all these groups of study. Proinflammatory enzyme and cytokines are the factors which initiate the process of inflammation. COX-2 helps in the conversion of arachidonic acid into a prostaglandin that is responsible for inflammation. Hence arachidonic acid helps in inflammation and eventually carcinogenesis (Federico et al. 2007). These all are suppressed by means of phenolic compounds present in honey.

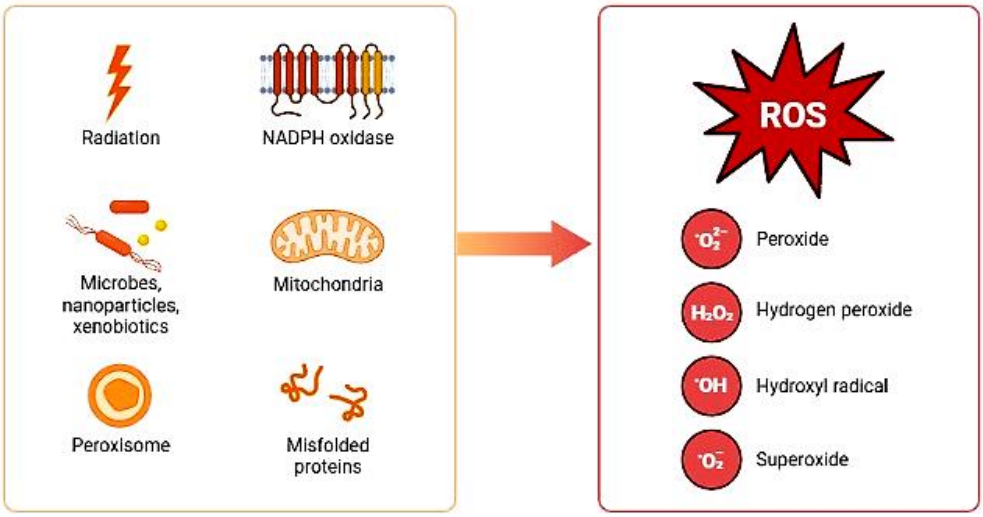

Fig. 4: Sources of Reactive oxygen species generation (Drawn by BioRender app).

8. Honey as an anti-cancer agent

Honey is tested in many living tissues and different cancer cell lines for its anti-cancerous activity. It was tested in breasts, renal, endometrial, prostate (Samarghandian et al. 2011; Othman 2012), and colorectal cancers (Afrin et al. 2017). The effectiveness of honey was also checked against cancers of oral cavity (Porcza et al. 2016) and cervical cancers (Fauzi et al. 2011). Polyphenols present in honey play a vital role in anticancer activity. Techniques like DPPH and FRAP are adapted to measure the intensity of anticancer activity in honey. Phenolic constituents and flavonoids give honey a remarkable anticancer effect (Moniruzzaman et al. 2012). Cell cycle is composed of four different phases named M, G1, G2 and S phase. They are highly regulated events and in each step cell growth can be analyzed (Williams and Stoeber 2012). Protein kinase is responsible for regulating these phases of the cell cycle. It becomes dysregulated due to any issue it results in the formation of cancer (Pichichero et al. 2010). Honey exhibit character to affect the proliferation of cells. In Wistar rat tumor cell line a solution of honey and aloe vera was tested and it proved to down regulate the expression of Ki67-LI (Samarghandian et al. 2017). Honey constituents like phenols and flavonoids were reported to arrest the cancerous cell cycle at G0/G1 phase in cancerous cell lines (Afroz et al. 2016). Anticancer effects of honey are proven to be time and dose dependent by MTT and Trypan blue exclusion assay (TBEA) techniques (Yang et al. 2013). Experimentally in lungs cancer cell lines, honey has proven to stop the cell cycle (Gogvadze et al. 2006). Chrysin is an anticancer compound in honey. It has proven its antiproliferative capacity in human cells and murine melanoma. It arrested the cell cycle at G0/G1 phase (Afroz et al. 2016).

Anticancer effect of honey also involves mitochondrial pathway and cause the death of cancerous cells. Cytochrome C is a protein located in the inner membrane space of mitochondria. When there is any sort of stress these proteins are released and take part in the death of the cell (Ren et al. 2012). Honey can also release these proteins by means of flavonoids. Honey has the ability to release cytotoxic mediators (Jaganathan and Mandal 2010). Mitochondrial proteins are leaked via Mitochondrial outer membrane permeabilization (MOMP) into the cytosol and causes the death of the cell by these mediators. This was observed in colon cancer cell HCT-15 and HCT-29, where Indian honey reduce the membrane potential of mitochondria and induced MOMP. Quercetin, a flavonoid, is responsible for causing MOMP which further aggravates the situation. Cell death eventually occurs

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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(Nassar and Blanpain 2016). Apoptosis is a natural pathway to prevent cancer. If this apoptotic pathway is disturbed and cell is dividing continuously it will eventually lead to cancer. Induction of apoptosis is the main principle in anticancer therapy (Safarzadeh et al. 2014). Apoptosis is further divided into three levels. In initiation phase, death inducing signals increase the proapoptotic signal transduction. Then second stage is effector stage in which mitochondria is involved in inducing cell death. Deprivation phase is the last phase. It involves nuclear and cytoplasmic modifications such as contraction of chromatin, disintegration of genetic material and tissue blebbing (Andersen and Becker 2005). Caspase 8 is mostly involved in apoptosis along with mitochondrial pathway (Angst et al. 2013). Caspase 3 gets activated and antiapoptotic proteins are suppressed via natural honey. Bcl-2 is replaced by Bax that is proapoptotic in nature.by means of quercetin (Yaacob et al. 2013). Honey exhibit safe form of cell death occurring due to chemotherapy rather than using toxic compounds. It is a potent natural anticancer agent.

9. Honey as an Immunity Booster Agent

Honey is known for its immune booster capacity for decades. It helps in better proliferation of B and T lymphocytes (Abuharfeil et al. 1999). It maintains production of monocytic pro inflammatory cytokines and enhances the phagocytic pathways (Tonks et al. 2003). Sometimes it also blocks these pro inflammatory cytokines from expressing themselves. These features are the principle of antioxidant capacity of honey and performs immunomodulatory role (Miguel et al. 2017), and oxidative stress is prevented or managed as shown in Fig. 5. Phenolic compounds are playing the key role in performing this activity (Kek et al. 2014). Main task for being an antioxidant is to scavenge the free radicals present in the biological system. Cell maturation as well as immune system, requires free radical to perform its killing function. They are required at a limited level, and they are manufactured by endogenous along with exogenous sources (Al-Hatamleh et al. 2020). Production of free radicals more than required amount is damaging to cell. Free radicals are highly reactive it alters the DNA and other constituents present in cells (Wu and Cederbaum 2003). These free radicals are neutralized via antioxidants. Antioxidants are electron donors. They donate electrons to free radicals and make them stable compounds (Tan et al. 2002).

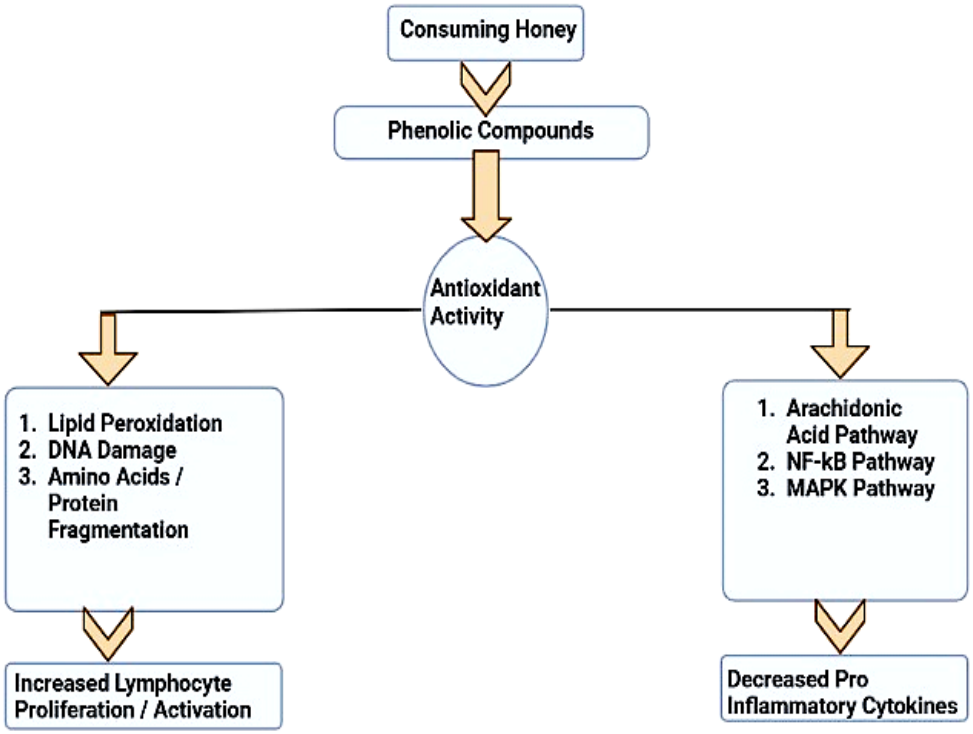

Fig. 5: Pattern of antioxidant capacity of honey (Drawn by BioRender App).

10. Honey as an Anti-Diabetic Agent

Honey has shown lower glycemic level rather than artificially made honey by means of added sugar or sucrose (Akhtar and Khan 1989). Research was done in rat. Scientists also reported that upon feeding honey to rats, there was a significant reduction in the level of HbA1c. A significant increase in level of HDL cholesterol has also been observed, while other lipids gave same results which were fed sucrose diet or sugar free diet in rats (Molan 2001). Comparison was done in honey and fasting over blood glucose level and body weight, which was significant.

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Diabetes was experimentally induced in some animals for research purposes (Erejuwa et al. 2010). Beneficial effects were seen with the use of honey. In Alloxan induced diabetic experiments over rats, honey shown anti hyperglycemic response. The same response was recorded by another scientist in rats who were induced diabetes via STZ (Adesoji and Oluwakemi 2008). In many research studies, the anti-hyperglycemic effect of honey was seen. In STZ induced diabetic rats, by administering honey and combination of honey and metformin, triglycerides level along with VLDL decreased and HDL level increased (Erejuwa et al. 2011). This positive anti hyperglycemic response of honey along with lipid level exerted by honey is still under study. May be fructose is the key player which is reducing the level of glucose in blood (Kwon et al. 2008). Study was done on rodents by inducing diabetes in them. They show evidence of reduction in blood glucose level via fructose. Possible mechanisms that cause this antidiabetic effect may include reduction in the feed intake (Thibault 1994), reduction in the absorption of intestinal contents (Kellett et al. 2008) and prolonged emptying time of stomach (Moran and McHugh 1981). Liver is responsible for storing glucose as glycogen and fructose content of honey has been reported to regulate the glucokinase activity in the hepatocytes (Van Schaftingen and Vandercammen 1989). A reduction in insulin level along with peripheral glucose is observed when fructose is infused in the duodenum of dog (Watford 2002). It also increased its hepatic storage and uptake. Fructose absorption is promoted by the glucose which is present in honey and due to its elevated delivery to liver, its hepatic actions are promoted (Fujisawa et al. 1991). Liver plays a vital role in the management of glycaemia and is one of the three Musketeers that have role in regulation of glucose, other two are skeletal muscles and the pancreas (Klip and Vranic 2006). Fructose also blocks the phosphorylase activity of liver. This helps in increased breakdown of glycogen to glucose along with increase in the synthetic pathway. It also elevates hepatic glucose phosphorylation (Youn et al. 1987). The presence of glucose and fructose in honey acts synergistically in liver (Regan et al. 1980). In one study it was observed that low level of fructose is beneficial for diabetes treatment while high content of fructose has the opposite effect (Wei et al. 2004). Increased consumption of fructose leads to increase in weight gain, altered lipid metabolism, increased fat deposition in viscera and insulin resistance (Malik et al. 2006). This concern is not attributed to honey but to a diet that contain excessive fructose content (Tappy and Lê 2010).

11. Future Aspect

There are certain challenges involved for the use of honey as a medicinal drug. The quality of honey, its potency and formulation of dosage of honey as a drug is a critical step. Lack of standardization of honey for clinical use make it difficult to prescribe honey as a medicine. Quantification of honey and its medicinal properties are highly dependent on chemical composition of honey and its extraction method. Storage methods and conditions along with adulterants alter the chemical composition and are responsible for altered medicinal properties. Till today there is no research done to check honey if it can be used as an antimicrobial and antiviral agent. The properties of honey are quite variable among its type and there is no study regarding the use of honey as a drug. Lack of research is the reason due to which one cannot prescribe a dose of honey with confidence. Efficacy comparison between conventional medicine and honey is not available regarding its antiviral property. These parameters need to be addressed properly through research so that honey can be used in clinical practice. Pharmacists need to make medicine via extracting these natural compounds from honey and dose must be quantified for its use. Immuno-boosting capacity of honey will be helpful in discovering the treatment of immunodeficient diseases such as AIDS. Honey constituents need to be investigated thoroughly and dosage formulation must be addressed so that it can be practically applied in clinics for the treatment of diseases.

12. Conclusion

Honey has unique features regarding health benefits and physicochemical properties. Different constituents of honey and its physical properties play vital roles in the medicinal activity of honey. High sugar content, peroxidase and non-peroxidase activity, viscosity, and low water content along with flavonoid and phenolic compounds makes honey a wonder drug. Antiviral activity is primarily involved for the growing interest of scientists due to corona virus recent pandemic. Therapeutic aspect of honey can be proven as a novelty in the field of medicine if properly investigated. These approaches of honey can bring up new treatment methodologies if the deficiency of research will be fulfilled. It will open a new era of discoveries in health and disease cure with advanced studies. It will end up making certain products that will help in treating the uncurable diseases.

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ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
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