An Assay on Mechanisms of the Anti-Fibrotic Effects of Honey

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Abstract

Fibrosis is a consequence of diverse continual compensation of various connective tissue in the body. That results in the formation of extracellular matrix that is why it forms a sandwiched between matrix and deterioration. It is well resolute and articulated as scarring and as of particular cell lines fibrosis is developed, such conditions are known as a fibroma. Immune cells produce several factors like cytokines, chemokines, etc. that serves as the best factors which affects the inflammation. A variety of synthetic and herbal drugs are accessible in the market that are specially designed for the treatment of fibrosis. Throughout the remedies, honey is one of the most common and easily available ingredient of our kitchen that contains numerous enzymes, vitamins, organic acids, flavonoids, phenolic acids, amino acids, and volatile components. These phytochemicals are responsible for different pharmacological activities including anti-fibrotic effect. In this chapter, we focused on mechanisms of the anti-fibrotic effects of honey and we conclude that how honey inhibits the inflammatory cytokines, chemokines, and other factors viz. PDGF, IL-4, TGF-β, and interleukin-13. These biomarkers are incorporated with proliferation and causes activation of myofibroblast cells. Balance for the extracellular matrix degradation and its synthesis helps determine ECM homeostasis. At last, these immune cells, endothelial or epithelial cells lead

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to apoptosis, proliferation, and repair at the damage site, resulting in the healing of the wound and showed a strong anti-fibrotic effect.

Keywords

Honey · Fibrosis · Anti-fibrotic effect · Extracellular matrix · Chemokines

5.1 Introduction

Nowadays numerous herbal preparations are used by the physicians for the treatment of different diseases due to various side effects of allopathic preparations. The research is going on in search of natural drugs having less or minimal side effects. In this journey, we can't forget the name of honey as it is used for the preparation of various ancient Egyptian and Greeks along with numerous Unani, Ayurvedic, Naturopathic, and Traditional Chinese preparations (Eteraf-Oskouei and Najafi 2013; Miguel et al. 2017). Honey is naturally sweet and viscous food product prepared by honey bees with the help of nectar obtained for flowers.

It is determined by color and odor. Light color honeys have high value of marketed price as compare to darker one. Sweetness of honey is due to presence of monosaccharides, glucose, and fructose. Rest of constituents are various enzymes, vitamins, organic acids, flavonoids, phenolic acids, amino acids, and volatile components (Alqarni et al. 2014).

Fibrosis can be defined as the development, overgrowth, hardening, and/or scarring of additional connective tissue (fibrous) in any part of the human body especially organ or tissue which has a role in a reactive process (Birbrair et al. 2014). When we focus on fibrosis we found that there is a deposition of large amount of components, especially at the matrix portion behind it (Glick et al. 2010; Wynn 2011). It is well determined and expressed as scarring and from specified cell lines fibrosis is developed, such conditions are known as fibroma (Birbrair et al. 2014). When chronic inflammation is developed in the body then, at last, it is referred to fibrosis due to various stimuli, especially immune reactions, allergic reactions, persistent infections, radiations, and various tissue damages. Recent facts show that there are several novel pathogenic mechanism that plays a critical role in the progression and reverse establishment of fibrosis (Wynn 2011). There are different types of fibrosis depending on the organ they are present. Some of them are enlisted in Table 5.1.

5.1.1 Diagnosis

It can be diagnosed with the help of computerized tomography images of fibrosis, gross pathology of fibrosis, histopathology of fibrosis, X-rays of fibrosis, etc. (Sica et al. 2019).

Table 5.1 Major organs affected by fibrosis, types of fibrosis, and possible contributing factors

Organ	Type of fibrosis	Possible contributing factors	References
Liver	Cirrhosis Bridging fibrosis	Viral hepatitis, hepatocellular carcinoma, schistosomiasis, and alcoholism	Dwivedi and Jena (2018), Li et al. (2017)
Lung	Cystic fibrosis, replacement fibrosis, focal fibrosis, diffuse parenchymal lung disease, idiopathic pulmonary fibrosis, radiation-induced lung injury	Sarcoidosis, silicosis, drug reactions, rheumatoid arthritis, systemic sclerosis, and idiopathic pulmonary fibrosis	Rockey et al. (2015) Borthwick et al. (2013)
Kidney	Renal fibrosis Cystic fibrosis Nephrogenic systemic fibrosis	Chronic kidney diseases, diabetes and hypertension	Rockey et al. (2015), Li et al. (2017)
Heart	Atrial fibrosis Endomyocardial fibrosis Old myocardial infarction	Cardiac fibrosis, hypertrophic cardiomyopathy, heart attack, hypertension, atherosclerosis and arrhythmia	Eddy (2000) Li et al. (2017)
Eye	Subretinal fibrosis, Epiretinal fibrosis	Macular degeneration, retinal and vitreal retinopathy	Li et al. (2017)
Skin	Keloid (skin fibrosis) Nephrogenic systemic fibrosis	Hypertrophic scars, systemic sclerosis, scleroderma, multiple cancers, and pulmonary arterial hypertension	Li et al. (2017)
Pancreas	Pancreatic fibrosis	Autoimmune and hereditary causes	Wynn (2011)
Intestine	Crohn's disease	Inflammatory bowel disease and pathogenic organisms	Wynn (2011)
Brain	Glial scar	Alzheimer's disease and AIDS	Li et al. (2017)
Bone marrow	Myelofibrosis	Chronic myelogenous leukemia, Myelodysplastic syndrome and aging	Li et al. (2017)
Others	Arthrofibrosis (knee, shoulder, other joints) Dupuytren's contracture (hands, fingers) Mediastinal fibrosis (soft tissue of the mediastinum) Peyronie's disease (penis)	Surgical complications, scar tissues, chemotherapeutic drug-induced fibrosis, radiation-induced fibrosis, and mechanical injuries	Parish and Rosenow (2002), Li et al. (2017)

5.1.2 Physiology

In case of fibrosis, myofibroblast is the cellular mediator. These fibroblasts serve as initial collagen developing cells and upon maturation, they produce mesenchymal, endothelial, and epithelial cells. Cellular mediators were activated with the help of various mechanisms, especially paracrine signals developed from various macrophages and lymphocytes. Myofibroblast secretes autocrine factors and pathogen species produce pathogen-associated molecular patterns (PAMPS). These

PAMPS then interacts with recognition receptors, chemokines, cytokines, monocytes, chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 β (MIP-1 β).

Cytokines that are present in human body are transforming growth factor-beta 1 (TGF-β1) and interleukins (IL). Growth factors are platelet-derived growth factors (PDGF) and angiogenic factors are vascular endothelial growth factor (VEGF), caspase, acute-phase proteins, and peroxisome proliferator-activated receptors (PPARs). Rennin angiotensin aldosterone II acts as a manager of fibrosis and targeted for drugs which were used for the treatment of fibrosis.

5.1.3 Prevalence and Incidence

There are several studies reported for the evaluation of incidence and effectiveness of fibrosis. According to different agencies, the most afferent data range from 4.6 to 7.4 cases/100,000 and 13 to 20 cases/100,000 for females and males, respectively (Flume et al. 2009). On the basis of earlier data, it is understandable that in Europe, fibrosis affect near about 7500 people. There is an unknown concept for the incidence and prevalence of the fibrosis, that is why geographical and racial factors influenced it most (Kim et al. 2015). Level of prevalence is increased nowdays due to strong optimization of latest diagnostic methods and lifestyle increment.

5.1.4 Prognosis and Etiological Causes

The prognosis of fibrosis is underprivileged and the survival rate is only 2–3 years after its diagnosis (Kim et al. 2015). Delay in progression leads to chronic respiratory failure. In rest of cases, there are periods of comparable stability with particular worsening in complications and sometime death also. In small number of patients, the duration of disease is very short with fast progression. Generally average rate of survival is 2–5 years as determined in symptoms (Raghu et al. 2011).

The etiological causes of fibrosis are not well determined due to diagnostic complications. As this disease occurs due to various predetermined factors like genetic, environment, immunological, and others; that plays an important role in the etiology of fibrosis. Genetic mutation is one of the most effective alterations that maintain the length of telomeres. Fibrosis is commonly due to the presence of various surfactants like mucin 5B promoter region and protein C gene. It is determined that there is no well-established genetic test to carry out predisposition for fibrosis (Wu et al. 2018). Apart from genetic, environmental factors also a predominant risk factor for the development of fibrosis. Examples like exposure of silicon, steel, brass, lead, farming, smoking, and wooden houses (Cystic Fibrosis Trust 2014). Some studies also determine that gastroesophageal reflux, autoimmune diseases, and immunosuppressive therapy are major and effective risk factors for progression and predisposition of fibrosis (Ng and Moore 2016; Michael et al. 2015; Abdalla et al. 2009). The other factors like radiology and histology are also well-

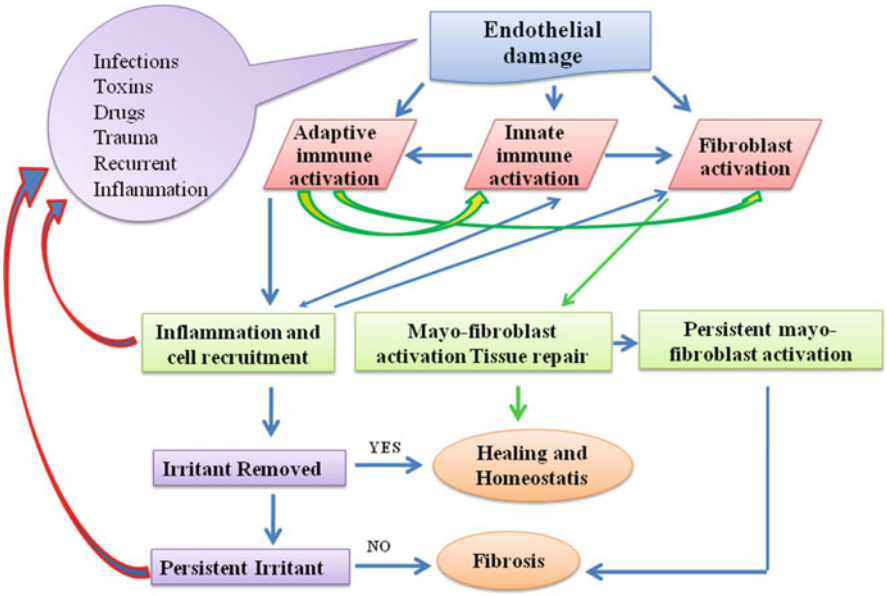

Fig. 5.1 Diagrammatic representation of how honey acts in the pathogenesis of fibrosis

established manifestation of fibrosis along with the factors associated with connective tissue create fibrosis (Al-Momani et al. 2016).

5.1.5 Pathogenesis

Fibrosis is the pathological result of normal wound healing process. Generally, when injuries generated at that time endothelial and epithelial cells are destroyed and release pro-inflammatory cytokines with the help of cascade coagulation and immune cell replacement (Darby and Hewitson 2007). The most important of them are macrophages and neutrophils. Tissue damage and dead cells are removed by the determined immune cells due to acute inflammation (Klingberg et al. 2013). At the same time, these immune cells produce several factors like cytokines, chemokines, which serve as best factors that affected inflammation. The other factors are like growth factors viz. PDGF, IL-4, TGF-β, and interleukin-13 which are incorporate a limited amount of proliferation and activation of myofibroblast cells (Wynn and Vannella 2016). Myofibroblasts were derived from various multiple cells like epithelial cells, bone marrow cells, and epithelial endothelial mesenchymal transitional cells. These cells are properly related to various blood vessels except resident fibroblast. Precursor cells such as pancreatic stellate cells (PSC) and hepatic stellate cells (HSC) may also develop myofibroblastic phenotype in the liver and pancreas.

Therefore, myofibroblast may achieve the balance for the extracellular matrix (ECM) degradation and its synthesis is helpful in determining ECM homeostasis. At last, these immune cells, endothelial, or epithelial cells lead to apoptosis, proliferation, and repair at the damage site, resulting in healing of wound (Darby et al. 2014; Ghosh et al. 2013) (Fig. 5.1).

5.2 Factors Affecting the Progression of Fibrosis

5.2.1 Extracellular Factors

Most of the extracellular factors associated with fibrosis are ligands that bind with receptors, like growth factors and cytokines. In endocrine signaling pathways, autocrine and paracrine are the factors which target distant cells and adjacent cells (Gabbiani 2003). They instead bind to specific cell membrane receptors which activate intracellular signaling, culminating in cellular level pro-fibrotic responses. Various extracellular factors, particularly enzymes which are effective for their property such as metalloproteinases matrix (MMPs), can diminish ECM to prevent excessive level of accumulation (Vettori 2012).

5.2.2 Growth Factors

These are the large protein molecules that trigger the proliferation and growth of various cells. They are released by different cells to produce cellular responses as well as fibroblast proliferation (Kendall and Feghali-Bostwick 2014; Marvig et al. 2015). Transforming growth factor beta (TGF-β) is the chief determinant which plays an important role in fibrogenesis by regulating cell growth through small mothers against decapentaplegic (Smad) (Scales and Huffnagle 2013). Along with that, it also causes the overexpression of α-hallmark muscle actin (α-SMA) myofibroblast. However, TGF-β signaling responds to collagen I and III gene transcription contributing to ECM accumulation (Luchetti et al. 2014). Platelet-derived growth factor (PDGF) can induce the hematopoietic stem cell derived proliferation and collagen expression. Hepatocyte growth factors (HGF) are also responsible for fibrosis which helps reduce overexpression (Fan et al. 2018). In case of inflammatory type of wound healing process, excessive level of cytokines especially chemokines are released by the immune cells which include neutrophil, T cells, and macrophages. When we compare growth factors to that of cytokines, it acts as a transmitter for the cell signaling and results in increased immunological response of cell and ultimately leads to inflammation in cells. Chemokines having the property to migrate into liver and there they produce fibrosis (Gressner and Gressner 2008). Interleukin 6 is also reported as agent that moves various tissue conservation via signal transducer and transcription activator 3 that type of signaling pathway in some peritoneal type of fibrosis to a chronic inflammatory state (Luchetti et al. 2014).

5.2.3 Broad Range of Proteins/Peptides

Wide range of protein and peptides are other extracellular variables that differentiate myofibroblast with growth factor. For example, during embryonic growth and responds to defect through Snail and Twist's inhibition of epithelial-cadherin signal. Hh signaling pathway epigenetic regulation refers to biliary level of fibrosis along with that it is also associated with liver fibrosis. The up determinant type of signaling was well reported in an ample supply of β catenin in either fibrotic kidney. The pathways control epithelial-to-mesenchymal transition (EMT) induced genes like Twist, LEF 1, which aggravates disorder (Van Mourik 2017).

5.2.4 Matrix Metalloproteinases (MMPs)

Extracellular endopeptidases (laminins, fibronectin, proteoglycans, and collagens) are the factors that degrade the ECM metalloproteinase tissue inhibitors (TIMPs) can also function as MMPs inhibitors. To maintain the homeostasis, MMPs and TIMPs modulate the system either by development of fibrosis or cell injuries. It can be in balance position by the activation of various latent immune cells and some myofibroblast (Barr et al. 2018).

5.2.5 Intracellular Factors

Intracellular factors also modulate and relocate the expression of some extracellular factors, such as cytokines and growth factors. Certain inflammatory pathways and metabolize them from cells to enhance immune responses. In addition, epigenetic factors function as a new way of manipulating gene expression correlated with fibrosis (Xu et al. 2016).

5.2.6 Nuclear Receptors

These types of receptors are located in the cytoplasm and nucleus. They receive various signals from intercellular ligands to bind with specific receptor inside the DNA and regulate genetic expression (Rieger et al. 2015). Some examples are like proliferator-activated receptor γ (PPAR-γ), peroxisome which may completely and directly manage and regulate type I collagen gene expression and can block TGF β signaling pathways. Other receptors are also found in nucleus like farnesoid-X receptor (FXR) which can exhibit an fibrotic protecting effect via the reduction of various proliferation type of cholangiocytes and subsequent reduction in TGF β (Manley and Ding 2015). The strong activation of FXR which can also decrease and diminish a series of strong type of profibrotic factors especially including α-SMA, collagens, TIMP-1, and MMP-2 (Ali et al. 2015).

5.2.7 Multiple Kinases

There are different intracellular kinase which serves as a reservoir in the inflammatory process like TNF-α, epidermal growth factors, and TGF-β. They initiate the mitogen-activated protein kinase pathway (MAPK). Among all of them, TNF-α activates another important deterministic mammalian target of rapamycin (mTOR). This mTOR receptor causes activation of transcription factor β-1 and decreases the accumulation of collagen and fibrosis (Afroz et al. 2016a, b).

5.2.8 Galectin-3/Lysyl Oxidase Homolog 2 (LOXL2)/Oxygen Species (ROS)

There are such factors influencing either extra/intracellular mechanisms of fibrosis, particularly species with galectin-3, reactive oxygen species (ROS), and homologous lysyl oxidase. Tissue damages, cell damage, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activities will produce ROS. The ligand binding oxygen species targets the paptides and triggers TGF-β signals, whereas inteacellular oxidative stress in human body targets p53 cells. That causes apoptosis and activation of mitochondrial caspase inside the cells. So far as galectin-3 is involved, extracellular type of galectin-3 which can induce apoptosis in T type of cells performs as well-defined dual activity in and outermost side of cells (Tzou et al. 2014). The LOXL2 variable is usually considered as extracellular enzymes, which then in reaction to excessive pressure promotes the production of collagen and crosslink with collagen fibers. Moreover, intracellular type of LOXL2 has been well reported to induced EMT in the development of carcinoma. On such basis, the targets involved in these mechanisms will have to be reexamined and their possible functions determined in fibrosis type of treatment across tissues and organs (Table 5.2; Aydin and Akcali 2018).

5.3 A Honey Boon for a Human Being

Honey is a historic item whose background can be directly attributed 8000 years in Europe but still has popular being used as a popular food product (Alvarez-Suarez et al. 2014). Unlike the other traditional food items, honey also has its cultural importance and symbolic significance in certain communities, which has led its effectiveness as therapeutic agent. Overall, honey is a result arising from any insects that store nectar in hives, but perhaps the item produced by honeybees, the subfamily Apis, is usually referred to as honey (Kwakman et al. 2010). Honey in the severe form is generated via a process of network rehashing and evaporation ability to concentrate in the beehive. Honey continues to develop within beehives as the main bee food in wax honeycombs. Honey's deep taste derives from the very high sugar content of fructose and glucose (Jull et al. 2015). The organic mechanism is derived from indicating that honey contains many biochemical and biochemical compounds.

Table 5.2 List of targeting factors for prognosis of fibrosis

Group	Target or mechanism type	Target or mechanism	Organs	References
Targeting intracellular factors				
Enzymes	mTOR	mTOR complex 1/2	Liver, kidney, Lung, heart, Skin, gut	Li et al. (2017)
Nuclear receptors	PPAR	PPAR-γ	Liver, kidney, Lung, heart, Pancreas, skin	Gao and Bataller (2011)
Other proteins	Intracellular TGF-β signaling	SMAD2/3	Liver, kidney, Lung, heart	Verrecchia and Mauviel (2007)
Epigenetics	miRNA	miR-21		Li et al. (2017)
Targeting extracellular factors				
Growth factors	Extracellular TGF-β signaling TGF-β	TGF-β	Liver, kidney, Lung, heat, Pancreas, skin	Biernacka et al. (2011)
Cytokine	Interleukin	IL-13	Liver, kidney, Lung, heart, pancreas, Skin, gut	Borthwick et al. (2013)
MMP/TIMP	MMP/TIMP	MMP-2/ MMP-9/ TIMP-1	Liver, kidney, Lung, skin, Heart, pancreas	Gieseck et al. (2018)
Other proteins and peptides	Endothelin	ET-1 receptor	Liver, kidney, Lung, heart, Skin, gut	Fan et al. (2012)

Honey from its natural state is commonly used as fresh produce. Honey can also be used in many baking procedures and goods where natural tartness is supplied. Honey's physiological structure is that its base is water having high osmolality. That is why pathogens do not develop in honey, their biological source means that they might exhibit bacteria and microorganism spores along with highly poisonous types such as *Clostridium botulinum*, some of the most toxic substances known to mankind (Rybak-Chmielewska 2003). The many substances and growth factors used in honey have led in their use for medical purposes (Fig. 5.2). Various variety of honey with their specification is given in Table 5.3.

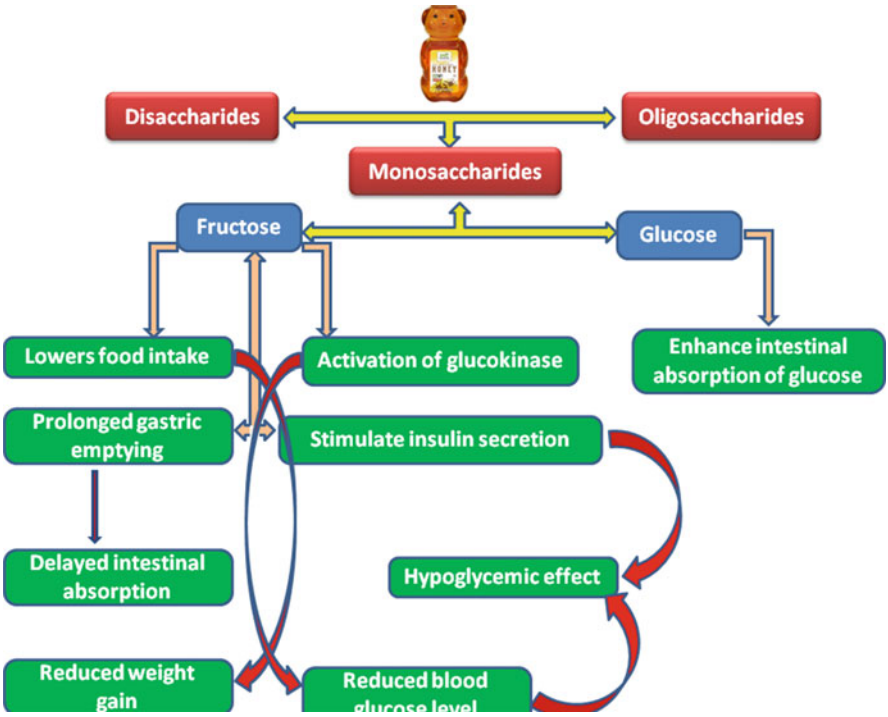

Fig. 5.2 Different uses and health benefits of honey for human beings

5.4 Adulteration of Honey

As the need for any food item is increased as well as its supply is less in that case suppliers opt for adulteration process. The production and cost of honey depend upon weather and harvesting condition. It is subjected to two types of adulteration:

1. Indirect.
2. Direct.

5.4.1 Indirect

Indirectly honey is adulterated by proving factory sugar to the honeybees at natural breeding stage. Such indirect adulteration is very difficult to detect. For discrimination between pure and impure, several chromatographic techniques are used. These chromatographic techniques are useful only when there is an adulteration between 10 and 40% (Siddiqui et al. 2017).

Table 5.3 Different types of honey with their specifications

Type of honey	Specification	Reference
Acacia honey	Most popular honey Identification: light and clear Taste: floral Fructose concentration is high to retain in the liquid state Popular in diabetics	(Muhammad et al. 2016)
Alfalfa honey	Majority production in Canada and the United States Light in color Made from purple–blue blossoms Taste and aroma: mild floral Used for backing purpose	(Akbari et al. 2020)
Aster honey	Light color Honey Extracted from Midsouth region and the United States The thick and smooth consistency Crystallize faster than other honey Used as a natural sweetener	(Akbari et al. 2020)
Avocado honey	Extracted from California avocado blossoms Dark-colored honey Buttery flavor	Almasaudi et al. (2017)
Basswood honey	Found throughout North America Most popular for biting taste White color and exceptional malleability quality Produced from cream-colored basswood blossoms	Sporns et al. (2007)
Beechwood honey	Known as Honeydew Found in New Zealand Produced by aphids on the bark of beechwood tree Used as a syrup for pancakes Regular consumption increase body immunity, better digestive system, high nutritional value	Popek (2002)
Blueberry honey	Pleasant flavor Produced in New England Extracted from white flowers of blueberry bush Light amber-colored	Akbari et al. 2020
Bluegum honey	Eucalyptus honey species Grows in South Australia and Tasmania Dense texture and amber color	Lu et al. (2014)
Buckwheat honey	Strongest and darkest honey Produced in Minnesota, Ohio Rich source of iron and other essential nutrients Antioxidant property	Popek (2002)
Clover honey	Most widely available and popular honey Produced across Canada and New Zealand Classic one because of pleasant and floral sweet taste	Almasaudi et al. (2017)
Dandelion honey	Relatively strong honey Widely produced in New Zealand Bears dandelion aroma considered a medicinal herb in China, Tibet, India due to its healing nature	Cooper et al. (1999)

(continued)

Table 5.3 (continued)

Type of honey	Specification	Reference
Eucalyptus honey	Produced in Australia and California Strong medicinal honey variety Used for cold and headaches The herbal flavor and a slight aftertaste of menthol	(Akbari et al. 2020)
Fireweed honey	Obtained from a tall herb grown in open woods of north-west United States Light color Sweet and complex at the same time The smooth, delicate and buttery taste	Sherlock et al. (2010)
Heather honey	Strongest and most pungent flavors Amber in color and a rich source of protein Almost bitter	(Akbari et al. 2020)
Iron bank honey	Eucalyptus floral variety with bold taste Extracted throughout the year in eastern Australia	Sommeijer (1999)
Jarrah honey	Dark- amber eucalyptus variety Caramel aftertaste An effective remedy for wounds, burns, skin allergies	Lu et al. (2014)
Leatherwood honey	Obtained from leatherwood blossom Available in Southwest region Tasmania, Australia Unique taste and strong flavor Known as Tasmanian honey	Shukrimi et al. (2008)
Linden honey	Light yellow color The very delicate and fresh woody scent Medically rich verities Sedative properties help immensely in cases of anxiety and insomnia Used for treatment of cold, cough, and bronchitis	Gupta and Sharma (2009)
Macadamia honey	Sourced in Australia Floral nectar of Macadamia Nut tree Deep in color with a complex aroma and has a subtle nutty flavor	Kasiotis et al. (2014)
Manuka honey	Produced in New Zealand coastal areas Collected from the flower of Tea Tree bush Rich antibacterial, effectively treating stomach ulcers sore throat, indigestion, and acne and pimples	Avila et al. (2018)
Orange blossom honey	Combination of citrus sources Light in color and mild flavor with a fruity scent Obtained from Spain and Mexico	Bobiş et al. (2018)
Pinetree honey	Mainly comes from Greece Slightly bitter taste with a strong aroma Rich minerals and proteins	Abdulrhman et al. (2013)
Sourwood honey	Light color, caramel kind of taste Sweet and nutty	Kadirvelu and Gurtu (2013)
Sage honey	Heavy bodied Sage honey Produced in California Packed with the property of granulate Delightful taste	Bahrami et al. (2009)

(continued)

Table 5.3 (continued)

Type of honey	Specification	Reference
Tupelo honey	Most premium honey Southern gold tupelo honey Produced in southeastern US swamps Granulating like quality	Umesh et al. (2008)

5.4.2 Direct

Inclusion of other substances in honey is termed as clear adulteration. This type of adulteration is detected by the means of characterization of physical and chemical properties. S86 honey is the example of that type of characterization which requires extensive sample preparation and complex analytical equipment along with it is a time-consuming process. This type of adulteration can be characterized by the help of modern analytical techniques such as nuclear magnetic resonance and calorimetric analysis (Siddiqui et al. 2017; Padovan et al. 2003).

5.5 The Pharmacological Effect of Honey

5.5.1 Antioxidant Activity

A lot of diseases are due to the generation of reactive oxygen species, which are generated during the metabolism. The antioxidants are the agent that intercepts free radicals prior to they get damage. Darkness of honey is directly proportional to its antioxidant activity; hence, we can say that darker the honey, richer the source of antioxidants. Honey is an ample source of phenolic compounds and flavonoids, which act as a reservoir for antioxidant activity. These compounds act as an antioxidant due to its donating ability of hydrogen ion and electrons, which result in the generation of free radical as a consequence due to oxidative stress (Afroz et al. 2016a, b).

5.5.2 Antimicrobial Property

The dynamic cause of antimicrobial property of honey is due to the presence of glucose oxidase enzyme and the physical properties of honey. Rest factors are increase osmotic pressure; down pH; protein in less amount; increase in reducing sugar, carbon, and nitrogen ratio; viscosity; and other phytochemical constituents present in the honey (Abd Jalil et al. 2017; Allen et al. 1991).

5.5.3 Antibacterial Property

The antibacterial effect of honey is due to its property to release the peroxide ion commencing due to glucose oxidation to form gluconolactone and gluconic acid in the existence of oxidase enzyme. This activity was called peroxide activity and constitutes, at variable extent, the mode of action of some honey (Henriques et al. 2006).

5.5.4 Antiviral Property

The antiviral property of honey owes due to the presence of flavonoids (chrysin, acacetin, and apigenin). Several researches suggest that honey can inhibit the human immunodeficiency virus (HIV) either due to the activation via inhibiting the transcription of virus. Chrysin a constituent of honey shows activity against herpes simplex virus (type 1). One study suggests that the chrysin and apigenin have significant antiviral activity against HIV-1 in acutely infected H9 lymphocytes. Apigenin also exhibited antiviral activity against the influenza virus (H3N2) in vitro (Liu et al. 2008).

5.5.5 Anticancer

Honey shows its anticancer property by the potent inhibition on the progression of malignant cells. Its inhibitory action on malignant cell proliferation, tumor, and cancer is due to arrest in cell cycle; commencement of mitochondrial pathway; increase in the permeability of mitochondrial cell wall, apoptosis, and reduction in the development of cancer cells (Erejuwa et al. 2014).

5.5.6 Anti-Inflammatory/Immunomodulatory Activities

Honey is a protective agent, due to its chemical composition especially the phenolic content (Al-Waili and Boni 2003), it shows anti-inflammatory property which is proven by research from in vivo (Fernandez-Cabezudo et al. 2013), in vitro models (Bilsel et al. 2002) and also from the clinical trials (Leong et al. 2012). The presence of flavonoids and phenolic compounds leads to the suppression of cyclooxygenase-2 (COX-2) by altering its pro-inflammatory property (Viuda-Martos et al. 2008). Honey regulates the protein as well as other agents like ornithine, tyrosine, and nitric oxide. In the tissue culture, honey shows increase in natural killer cells and other hemocytoblast (Yaghoobi et al. 2013).

5.5.7 Wound Healing

Experimental research illustrated the use of honey upon wound healing due to the presence of several bioactive products having several activities such as germicidal, protease inhibitor activity, immune modulators, and antiaging. Honey releases the cytokines which work in the tissue repairing process. It also causes the activation of immune system which ultimately prevents the human body from infections (Yaghoobi et al. 2013).

5.5.8 Antidiabetic

Some research suggests the use of honey in diabetes due to its antioxidant property. Apart from its antioxidant property, it also causes a decline in the production of reactive oxygen species, which plays an important key role in the management of diabetes. Data from a research suggest that in a trial with patients of both types of diabetes, the honey-treated group shows a drastic decline in the glycemic index as compared with glucose. The honey-treated group in diabetic patient shows a significant decline in plasma glucose level as compared with dextran-treated group (Rao et al. 2016).

5.5.9 Neuroprotective

Honey shows protective effect on nerves due to the presence of polyphenols. Act by quenching the ROS, which is an important cause of neurotoxicity and deposition of proteins. Polyphenolic contents of honey contradict the oxidative stress, apoptotic effect, and neuroinflammation due to ischemia injury. These polyphenols also play an important role in the memory enhancement (Azman et al. 2018).

5.5.10 Cardioprotective

Honey shows its cardioprotective effect due to the presence of certain constituents viz. flavonoids, phenolic compounds, and vitamin C. The mechanism of action behind this protective role is vasodilation, decrease in coagulation of blood, and by decreasing the level of low-density lipoprotein (LDL) level (Afroz et al. 2016a, b). A number of constituents like caffeic acid, quercetin, phenethyl ester, kaempferol, galangin, and acacetin in honey are responsible for its pharmacological effect as a cardioprotective agent (Rao et al. 2016).

5.5.11 Anti-asthmatic

As listed in the above statement that honey works as a potent anti-inflammatory agent due to the presence of phenolic agents and flavonoids. These agents are also responsible for its preventive effect in asthmatic patients. Some studies on animals show that honey treats unrelieved bronchitis and bronchial asthma. Honey when inhaled at a specific dose cures goblet cell hyperplasia due to the secretion of mucus (Srivastav et al. 2011).

5.6 Pharmacokinetics of Honey

The physical and chemical characteristics of honey specimens were calculated (water content, color, and pH). The second component of honey is water (20%) by weighing and honey's pH is no more than 5. Honey varieties were seen as no diverse in terms of pH and fluid content. The preliminary color of examined honey varies according to several variables such as flower form and its duration (from the period of fermentation to date of the study). Honey the Siam weed flower is noticed to have had the highest color. Although longan and dual-floral honey have the same color spectrum, with the exception of pH 7, which would be induced by the fermentation date discrepancy (Zaworra et al. 2019). Maillard reaction rate and product character are calculated by the chemical nature, along with percentage of water, pH, temperature, and its composition. The essential kinetic variables in reaction of Maillard are temperature and water content. During this analysis, under specific condition, the temperature effect was examined. Therefore, honey water content was steady (Karl-Fischer titrations). For quality control, European Union used hydroxyl methyl furfural (HMF) as a chemical indicator. HMF composition is only affected by temperature. Kinetic studies have tracked the consequences of sugar and amino acid on the time, by the means of bright and dark environments with temperatures from 25 to 85 °C. The kinetic variables were extracted from not only product formation (HMF), as well as from declines in molecules (reduction of sugars and amino acids). From the temperatures test, it is mentioned in literature that carbohydrates and amino acids decreased by 55 and 85% simultaneously by changing the temperature from 25 to 85°. On the other hand, there has also been a substantial increase in HMF content. The reactions show first-order kinetics with amino acids and for HMF it shows zero-order kinetics which determines honey kinetics (Zhang et al. 2018a, b).

5.7 Possible Mechanisms of Honey and Its Components as Anti-fibrotic Agent

The literature review on medicinal properties of honey includes its application as a potent anti-fibrotic agent. There are different types of honey that have their own health benefits; among all, the *manuka honey* is well known for its medicinal

properties. It protects against apoptosis, intracellular ROS production, oxidative damage, mitochondrial dysregulation, and cell differentiation by activating the signaling pathway of adenosine monophosphate-activated protein kinase (AMPK) or nuclear factor erythroid 2 related factor 2 (Nrf2) or antioxidant response elements (ARE). Apart from that it also modifies different antioxidant biomarkers viz. superoxide dismutase (SOD), catalase, and glutathione (GSH) (Alvarez-Suarez et al. 2016). A research on manuka honey suggests that it can inhibit the epidural fibrosis subsequent to laminectomy. Treatment with propolis shows a significant decline ($p < 0.05$) in the rate of fibrosis (epidural). It is well reported for its wound healing property and now the result of this study shows that manuka honey can reduce the development of post-laminectomy epidural fibrosis in rats by stimulating TNF α production in macrophages through the toll-like receptor (Gunaldi et al. 2014). One more work on manuka honey shows that in a concentration ($\leq$10% w/v) along with antibiotics (colistin and tobramycin) it restrains cystic fibrosis development along with the respiratory tract infection (Jenkins et al. 2015). Tonks et al. 2003 suggested that manuka honey stimulates the production of TNF-α in macrophages via toll-like receptor (Tonks et al. 2001). Hence we can say that manuka honey can be used as a possible alternative to treat resistance related to antibiotics in case of cystic fibrosis.

The medicinal qualities are not restricted with manuka only but the other varieties of honey also have tremendous pharmacological effects. As per Afrin et al. (2019), it was reported that *strawberry tree honey* ROS generation by suppressing Nrf2-ARE and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) signaling pathways and it also induce damage of cellular macromolecules and decreased antioxidant enzyme activities. *Kanuka honeys* work as an anti-inflammatory agent by affecting the toll-like receptors (TLR1/TLR2) signaling pathway. This effect is possibly due to the presence of phenolic contents in honey (Tomblin et al. 2014). Some reports suggest that honey works as an anti-fibrotic agent by modulating the inflammatory responses along with that it causes proliferation of fibroblasts and epithelial cells. Another study on *buckwheat honey* proposed that different activities are due to the presence of phenolic constituents in it which are most effective in reducing ROS levels (van den Berg et al. 2008).

A study was performed to examine the consequences of honey on both the early detection of the composition of postlaminectomy chronic inflammation in the adult Sprague–Dawley rat model. The results of this study show that honey can act as an anti-inflammatory agent by reducing edema and an amount of exudates by downregulating the inflammatory process. Such a downregulation of excessive inflammatory biomarkers works as a possible target for the prevention of peridural fibrosis and an impact on wound healing without leakage in the brain fluid (Farrokhi et al. 2011) (Fig. 5.3).

Apart from honey as a whole, the individual photochemical also have their own pharmacological properties. A large number of constituents have been reported in honey-like vitamins, minerals, flavonoids, phenolic acid, and many more. The promising anti-fibrotic effects of honey are reported in human as well as in different models of fibrosis possibly due to the presence large amount of flavonoids and phenolic acids. *Apigenin*, a constituent from honey, shows antiproliferative and anti-

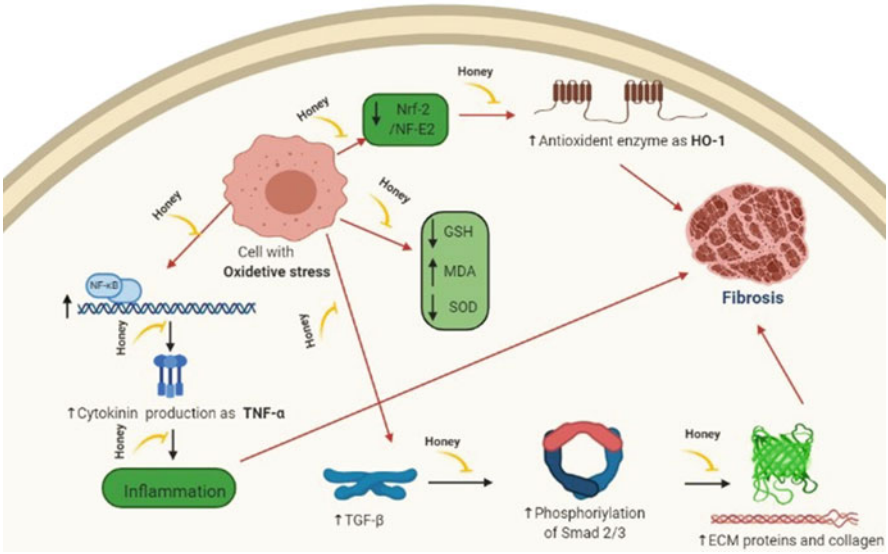

Fig. 5.3 Modulation of various pathways involved in the anti-fibrotic mechanism of honey and its components

inflammatory properties. It suppresses the proliferation and induces apoptosis in pancreatic stellate cells, which reduces the PSCs mediated fibrosis in chronic pancreatitis (Chen et al. 2014). Mrazek et al. (2015) suggest that it reduces the level of parathyroid hormone-related protein (PTHrP) and subsequently elevates the level of protein matrix collagen and fibronectin in PSC. It also causes proliferation of nuclear antigen in cells, TGF-β, and IL-6. It also protects lung fibrosis induced by bleomycin by inhibiting the elevated level of MPO, TGF-β, TNF-α, and collagen (Chen and Chen 2016). Apigenin at a dose of 20 mg/kg attenuates the oxidative stress and fibrosis by decreased transforming growth factor-β1, fibronectin, and type IV collagen. It causes a significant prevention of MAPK activation that ultimately inhibits the inflammatory biomarkers (Malik et al. 2017). It shows its anti-fibrosis action via suppression of MAPK-NF-κB-TNF-α and TGF-β1-MAPK-fibronectin pathways (Qiao et al. 2020). *Hesperidin* is naturally occurring flavanone glycosides that attenuate the liver fibrosis by downregulation of α-SMA and collagen both in vivo and in vitro. Derivative of hesperidine also inhibits fibrosis by inhibiting the activation and proliferation of PGDF via targeting Wnt/β-catenin signaling pathway (Lin et al. 2015). It also exerts protective effect on both lung and liver fibrosis by reducing the obstruction induced due to injury as well as by deposition of ECM and fibronectin in a mouse model. Furthermore, it significantly suppressed EMT, as evidenced by decreased expression of α-smooth muscle actin and E-cadherin. It also prevents the progression of bile duct ligation induced liver fibrosis via inhibiting level of TNF-α, IL-6, collagen, fibrosis indicators (laminin, hyaluronic acid, and

hydroxyproline via TGF-β1/Smad pathway (Kong et al. 2018). It also inhibits the cardiac fibrosis in post diabetic rat model by blocking NF-κB signaling pathway (Yin et al. 2017). *Rutin* is a polyphenolic flavonoid that ameliorates renal fibrosis in nephrectomized animal by its anti-oxidation property along with inhibiting TGFβ1-smad signaling (Han et al. 2015). It also protects hepatic fibrosis induced by bile duct ligation through the reduction in α SMA and Smad. It causes downregulation of NF-κB and TGF-β/Smad signaling, probably via interference of extracellular signal-regulated kinase activation and/or enhancement of nuclear factor erythroid 2 (NF-E2) related factors 2 (Nrf2), hemeoxygenase-1 (HO-1), and AMP-activated protein kinase activity (Pan et al. 2014). One study suggests that it inhibits the ECM by decreasing the level of collagen and fibronectin. It is possible because of the anti-inflammatory property of honey that works by inhibiting the TGF-β1/Smad3 signaling pathway (Wang et al. 2016). *Quercetin* suppressed the TNF-α, IL-1β, and IL-6, thiobarbituric acid reactive substances (TBARS), and reduced GSH level. It may also attenuate the pulmonary fibrosis via anti-inflammation and anti-oxidative properties (Baowen et al. 2010). The anti-inflammatory and anti-fibrotic mechanism is regulated by NF-κB and MAPK signaling pathways (Wang et al. 2017). In a dose-dependent manner, it inhibits fibrotic markers and downregulates the overexpression of TGF-β. Along with that, it causes stimulation of collagen, fibronectin, IL-1β, and MMPs (Yoon et al. 2012). The major role as anti-fibrotic is played by the possible reduction in α-SMA-matrix-and Smad 2/3 activity. Quercetin also attenuated bile duct ligation induced oxidative stress, leukocyte accumulation, nuclear factor (NF)-κB activation, and pro-inflammatory cytokine production (Lin et al. 2014). *Isorhamnetin* is a constituent from honey that protects against hepatic fibrosis by inhibiting TGF-β1 in HSC by blocking the ROS generation through activation of Nrf2 (Yang et al. 2016). It also inhibits collagen and expression of α-SMA in pulmonary fibrosis induced by bleomycin (Zheng et al. 2019). Data of a study show that it reduces collagen production in HSC cells, through inhibiting extracellular-signal-regulated kinase (ERK) signaling pathway (Lee et al. 2008). Another study suggests that it protects liver fibrosis by inhibiting the HSC, ECM, and autophagy via the downregulation of TGF-β1-mediated Smad3 and MAPK signaling pathways (Liu et al. 2019). *Myricetin* inhibits the activation of HSC in an animal model of liver fibrosis induced by carbon tetrachloride. It acts by suppressing α SMA and collagen deposition by inhibiting the phosphorylation of Smad2 and MAPK (Geng et al. 2017). It also reduces the secretion of inflammatory cytokines by activating Nrf2/HO-1 pathway by strengthening the anti-oxidative stress (Zhang et al. 2018a, b). Another research shows that it also inhibits the macrophage and hence protecting the hepatic fibrosis in mice model (Yao et al. 2020). *Pinocembrin* is a flavonoid that improves the oxidative stress by increasing the level of glutathione level and superoxide dismutase along with reduction in malondialdehyde. It also stimulates the nuclear factor erythroid -2 (NF-E2) and its related factor 2 (Nrf2). It also induces hemeoxygenase-1 (HO-1) enzyme, TNF-α, and different biomarkers (α-SMA and collagen) of fibrosis. It also inhibits the TGF-α/Smad signaling pathway by downregulation of TGF-α and p-Smad2/3 (Stine et al. 2018). *Galangin* shows its anti-fibrotic mechanism by attributing the

antioxidant action and inhibition of HSCs proliferation and collagen gene expression. Wang et al. (2013) reported that it causes downregulation of the overexpression of α-smooth muscle actin (α-SMA) and transforming growth factor 1 (TGF-β1) by removing the free radicals and inhibiting hepatic stellate cells activation and proliferation. Its mechanism may be related to the upregulation of MMP1, downregulation of TIMP1, and promotion of collagen degradation (Wang et al. 2013). *Luteolin* causes significant inhibition of PDGF and TGF β1, whereas it stimulates the Smad pathway (Jie et al. 2014). Another study suggests that luteolin at a dose of 10 mg/kg suppresses the neutrophil infiltration as well as TNF-α and IL-6 elevation. It also inhibited TGF-β1-induced α-SMA, type I collagen, and vimentin expression in primary cultured mouse lung fibroblasts (Chen et al. 2010). *Kaempferol* suppresses skin fibrosis by reducing the amount of ROS, number of myofibroblasts, T-cells, macrophages, inflammatory/pro-fibrotic cytokines including IL-6, TGF-β, and TNFα (Sekiguchi et al. 2019). Kaempferol significantly inhibits collagen synthesis and causes the activation of HSCs by downregulating the Smad2/3 phosphorylation in a dose-dependent manner (Xu et al. 2019). *Chrysin* modulates the ECM and tissue inhibitors of metalloproteinase 1 (TIMP) or modulation of MMP rebalance and decrease collagen deposition in a dose-dependent manner (Balta et al. 2018). It also causes the downregulation of phosphatidylinositol-3-kinase (PI3K)/Akt/Nrf2 and ERK/Nrf2 pathway (Gao et al. 2013). *Acacetin* is a flavonoid compound that shows significant decline in fibrotic markers by targeting the MAPK and PI3K/Akt signaling pathways (Chang et al. 2017). It alleviates myocardial fibrosis via TGF-β1/Smad3 signaling pathway (He et al. 2020).

Other flavonoid components from honey such as pinobanksin and 12-acetoxyviscidone show reduced cardiac fibrosis by downregulating the expression of fibrosis factors (collagen, MMPs, TGF-β1, and p-Smad2/3) which coincided with the upregulation and expression of silent information regulator 1 (SIRT1) in the hearts of rats with myocardial infarction (Wang et al. 2018).

Apart from the flavonoids, some phenolic acids are also present in honey that also plays an important role in the mechanism of anti-fibrosis. *Gallic acid* is the phenolic acid which is present in high concentration in honey and shows its anti-fibrotic action by attenuating the irregular deposition of collagen. It shows a potent inhibitory action on fibrosis when it is coadministered with advanced glycated end products possibly due to its mechanism of upregulation of profibrotic genes and ECM (Umadevi et al. 2014). It attenuates bleomycin-induced fibrosis due to the presence of high amount of antioxidants present in it. It also results in an increased level of collagen, malondialdehyde (MDA), and different cytokines (TNF-α and IL) as well as ameliorates total thiol content, glutathione peroxidase (Nikbakht et al. 2015). One of the recorded data shows that it has progression on hepatic fibrosis through reduction in the proliferation of HSC (El-Lakkany et al. 2019). Gallic acid prevents cardiac fibrosis via regulating c-Jun N-terminal kinase (JNK2) signaling and Smad3 binding activity (Ryu et al. 2016). *Ellagic acid* at the dose of 60 mg/kg body weight can use a significant decrease in the expression of fibrotic markers in alcohol-induced toxicity either by creating a balance between MMP/TIMP or by blocking the activation of PSC (Devipriya et al. 2007). It shows its anti-fibrotic

mechanism by inhibiting the level of IL and TNF-α induced activation in MAPK (Masamune et al. 2005). It also prohibits the overproduction of ROS in PSC along with a response in modification of TGF-β1 and PDGF (Suzuki et al. 2009). It also inhibits the degenerative changes in hepatocytes by increasing their survival in prolonged culture (Buniatian 2003). *Caffeic acid* shows its anti-fibrotic effect by modifying the level of TGF-β1, TNF-α, and PGE2 level. It also prevents pulmonary fibrosis by balancing pro-fibrotic or anti-fibrotic contents (Larki-Harchegani et al. 2013). It also suppresses the formation of myofibroblast and collagen in a human dermal model case (Mia and Bank 2016). It is suggested by the researcher that phenethyl ester of caffeic acid prevents the induction of fibrosis induced by bleomycin due to its potent action as free radical scavenger along with high contents of antioxidants present in that (Ozyurt et al. 2004). Zaeemzadeh et al. (2011) suggest that at a dose of 5 μmol/kg, caffeic acid shows potent anti-fibrotic effect. It attenuates fibrosis via inhibition of TGF-β1/Smad3 pathway and AKT/mTOR signaling pathways in HSC (Yang et al. 2017; Prasetyo et al. 2019). *Tannic acid* is a natural polyphenol from honey which acts as a potent anti-fibrotic agent for the treatment of pulmonary fibrosis induced by bleomycin in fibroblast culture. It inhibits TGF-β, which is induced by the overexpression of collagen and smooth muscle α-actin as well as force generation by primary cultured human lung fibroblasts (Reed et al. 2019).

After a lot of discussion on the anti-fibrotic action of honey and its components along with their possible mechanism, we came on the conclusion that honey and its components can work as a potent anti-fibrotic agent and can be used for the future prospective.

5.8 Future Prospective

No pharmacotherapy so far has received specific suggestions for the treatment of fibrosis, as is clear from the 2015 guidelines. The major side effect of synthetic drugs taken by fibrosis patients is these drugs produce severe comorbid conditions which can't cure. The environment for the management of fibrosis is clearly on fake grass and the stability of the disease (i.e., worsening of the disease and development of the fibrosis). From the above descriptive study, it is clear that honey has numerous health benefits viz. antioxidants, anxiolytics, anticonvulsant, antinociceptive, and antidepressant activity. Due to its properties, it improves the fibrosis's antioxidant status. Several studies of honey supplementation indicate that the polyphenol compounds present in honey show its anti-fibrotic effect. Polyphenol components of honey quench natural reactive oxygen species causing toxicity to nerves and aging along with protein deposition. The knowledge includes assessing the effects of fresh honey and its constituents in various fibrosis disorders, as well as researching the biochemical effects of honey on mitochondrial dysfunction, cell death, and necrobiosis. In addition, studying the actual cell signaling cascades related with synaptic plasticity may provide honey for more precise therapeutic interventions. It is also necessary to determine the honey outcome on plasticity under regular and

disease circumstances. More consideration should be given to the neural circuits and receptors involved in the fibro pharmacological effects of honey.

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