European Journal of Cardiovascular Medicine
Print ISSN: 2042-4884 |E-**ISSN:** 2042-4892
Language: Multilingual
Origin: United Kingdom
Website: https://www.healthcare-bulletin.co.uk/ **Volume 13 Issue: 3 - 2023**
Research Article **Open Access**

Alleviate COPD using Liquorice and Asafoetidaenriched foods by combating AGE-RAGE axis

Dr. Sharadendu Bali[1]; Dr. Randhir Singh[2]; Asfia Khan[3]

Abstract: *Advanced Glycation End Products (AGEs) are formed in the lungs either spontaneously or as a result of the insult due to cigarette smoke. These AGEs have deleterious effects due to their pro oxidant and inflammatory actions. The AGEs can interact with the receptor for AGE, called RAGE, triggering various kinase pathways that activate transcription factor NF-κB (nuclear factor kappa B). This, in turn, leads to the production of several inflammatory substances and promoters. Impeding the formation of AGEs and inhibiting the AGE-RAGE axis can prove beneficial in down regulating the inflammatory process, leading to favourable outcomes.*
Asafoetida and liquorice are two such herbs that can significantly impede the AGE-RAGE-NF-κBaxis, which plays a key role in the pathogenesis of chronic obstructive pulmonary disease (COPD). These herbs have the potential to improve symptoms and lung function in patients suffering from this condition..

Keywords: Licorice in COPD, Asafetida, AGE inhibition, Herbs in COPD, Herbal RAGE blockade, Smoking and COPD

AFFILIATIONS
[1]*Professor General Surgery, Adesh Medical College and Hospital,Shahbad Markanda, Kurukshetra. Haryana, India.136135*
[2]*Associate Professor, Department of Pharmacology, Central University of Punjab, VPO, Ghudda, Bathinda, Punjab 151401*
[3]*M.Phil, Hamdard University, Karachi*

CORRESPONDINGAUTHOR
Dr. Sharadendu Bali

INTRODUCTION

Glycyrrhizaglabra (Liquorice, Mulethi in Hindi) has been extensively utilized in diverse traditional medicinal systems due to its wide-ranging therapeutic properties. These properties include protection against peptic ulcers, demulcent effects, expectorant properties, antitussive capabilities, and purgative effects [1,2]. Liquorice(also spelt as licorice) has been especially valued in various ancient cultures, including Assyrian, Egyptian, Chinese, Indian, Greek, and Roman, for its therapeutic benefits in managing respiratory tract disorders. These disorders include cough, hoarseness of voice, sore throat, bronchitis, asthma, and tonsillitis, with liquorice roots and rhizomes being commonly used for this purpose. Today, licorice powder and extract continue to be highly regarded for their efficacy in treating conditions such as sore throat, cough, and bronchial catarrh [3,4]. Asafoetida (Heeng in Hindi), is used in traditional medicine as well as in culinary staple in India, Pakistan, Afghanistan, and Iran. Extracted from the Ferula species, this oleo-gum resin has a range of pharmacological properties including expectorant and antispasmodic actions, which are particularly advantageous for the respiratory system [5]. Some researchers attribute the oil's elimination through the lungs as part of its effectiveness against diseases like asthma, bronchitis, and whooping cough [5,6,7].

Glycation is a non-enzymatic, spontaneous chemical process characterized by the interaction between reducing sugars, including glucose and fructose, and free amine groups present in biological macromolecules such as proteins, lipids, and nucleic acids [8]. This reaction leads to the covalent attachment of sugar moieties to macromolecules, culminating in the generation of intricate structures known as Advanced Glycation End Products (AGEs) [8]. These potentially harmful molecules pose a significant risk to human health. They can alter the structure and function of proteins within our bodies, leading to cellular damage and even cell death [9]. RAGE, or receptor for advanced glycation end products, is a type of pattern recognition receptor (PRR) that binds with a variety of advanced glycation products (AGEs) [10]. The membrane-bound receptor, also known as membrane RAGE (mRAGE) or full-length (fl)RAGE, is a multi-ligand receptor and is considered a crucial mediator in immune responses and chronic inflammation [11]. RAGE basal levels are high in pulmonary tissue, particularly in human airways [12]. RAGE is also present in pro-inflammatory cells such as neutrophils, macrophages, monocytes, and T and B lymphocytes [10]. Blocking the formation of AGEs and the actions of RAGE are potential therapeutic targets in several lung disorders including chronic obstructive lung disease (COPD). In this respect, Asafoetida and liquorice can prove very beneficial.

Traditional Use of Mulethi (Glycyrrhizaglabra) and Heeng (Asafoetida)in respiratory disorders

Licorice has found extensive use in traditional Chinese, Korean and Indian medicine to alleviate and prevent conditions such as cough, phlegm, dyspnea, spasms, and pain, owing to its antitussive, expectorant, and anti-inflammatory properties. In Ayurveda and Siddha practices, the roots and rhizomes of licorice are the primary parts utilized for medicinal purposes. The powder and extract derived from licorice have been employed as carminatives and for the treatment of various respiratory tract disorders, including cough, sore throat, bronchitis, bronchial catarrh, asthma, and tonsillitis [13,14]. Glycyrrhizaglabra showcases antitussive, demulcent, and expectorant properties, aiding in the reduction of upper respiratory tract congestion and enhancing tracheal mucus secretion [15,16]. It is also widely utilized in Ayurvedic medicine due to its anti-inflammatory properties [17,18]. In traditional Korean medicine, Glycyrrhizaglabra has found application as a cough reliever and as an agent with immuno-modulatory and anti-inflammatory, and detoxifying properties. Key components of liquorice, such as Glycyrrhizic acid (GA) and flavonoids, have displayed promise as complementary or alternative treatments in asthma due to their anti-asthmatic, anti-allergic, anti-inflammatory, and anti-oxidative activities [16,19].

A**safoetida** also has a long history of traditional use in various ancient cultures for the treatment of several diseases, with respiratory illnesses being a common indication [7]. In India, asafoetida has been employed for the symptomatic treatment of angina pectoris and asthma [20]. In Ayurveda, asafoetida is regarded as a valuable remedy for conditions like whooping cough, pneumonia and bronchitis in children. Ayurvedic medicine administers a hot water extract of dried asafoetida resin, orally as an expectorant for chronic bronchitis [5,7]. It is also recognized as a pulmonary stimulant, antispasmodic, and carminative [21]. It is known to stimulate the mucous membranes, specifically in the alimentary tract, thereby alleviating conditions like flatulent colic. In Pakistan and Saudi Arabia, dried asafoetida is used medicinally for whooping cough, asthma, and bronchitis [22]. In Iranian folk medicine, asafoetida is used as a medicine for the treatment of asthma [23]. In Fiji, the dried gum is taken for whooping cough [22]. In ancient Rome, it was employed as a culinary spice [24]. It is also used for tuberculosis and persistent cough. The aromatic constituents are believed to underpin its substantial pharmacological and clinical activities, particularly in conditions like hysteria, spasmodic afflictions, and advanced stages of respiratory illnesses in children [6,7].

In Afghanistan, a hot water extract of dried gum is consumed orally to manage whooping cough [5]. Traditional remedies for children's cold and cough in India and Thailand involve incorporating asafoetida into a strong-smelling paste and hanging it in a bag around the sick child's neck. In certain regions like Khyber Pakhtoon Khwa, Pakistan also, Asafoetida is used as a preventative measure against seasonal, bacterial, and viral illnesses, including respiratory infections. This is achieved by hanging a bag of Asafoetida around the neck or attaching it to the arm, underscoring its historic link to respiratory health [6,7]. In summary, licorice and asofoetida, , with their rich history of usage in traditional medicine systems, offer a wide range of potential benefits for the respiratory system, functioning as expectorant, antitussive, and anti-inflammatory agents. Their extensive use in diverse cultures and well-documented therapeutic effects underscore their potential in managing various respiratory conditions.

Advanced Glycation Endproducts (AGEs) formation and role in Cellular Signaling

AGEs are known to influence various signaling pathways via cell membrane receptors. These signaling pathways include the nuclear transcription factor (NF-κB), mitogen-activated protein kinase (MAPK), and signal transducer and transcriptional activator (STAT) pathways. The presence of AGEs has been linked to the progression of numerous metabolic disorders, including atherosclerosis, diabetes, and Alzheimer's disease [9]. The formation of AGEs is a multifaceted, two-stage process. In the initial phase, reducing sugars interact with free amino groups in proteins and nucleic acids, yielding unstable Schiff base adducts. These adducts subsequently rearrange into more stable Amadori products, known as early glycation products (see Figure 1). A minor fraction of Amadori products undergo direct conversion to AGEs through the irreversible processes of oxidation or hydrolysis, facilitated by the Hodge pathway.
The majority of Amadori products are transformed into AGE precursors, including glyoxal, methylglyoxal, and 3-deoxyglucosone, via oxidative cracking, dehydration, or cyclization. These α-dicarbonyl compounds form covalent bonds with proteins and other structural components, generating stable AGEs [25, 26]. Additional pathways, such as the Wolff, sorbitol, and other pathways, also produce AGE precursors, further contributing to the formation of AGEs in biological systems [9].

AGE Accumulation and AGE-RAGE Interactions: Implications for Oxidative Stress and Inflammation

Despite their chemical differences, AGEs have similar biological effects, with higher molecular weight AGEs exhibiting greater pathogenic potential. Upon accumulation, AGEs activate cellmembrane receptors such as scavenger receptors and the multiligand receptor for advanced glycation end products (RAGE). RAGE activation stimulates stress-

and inflammation-related pathways, including extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. Concurrently, transcription factors, such as activating protein-1 (AP-1) and NF-κB, are engaged, provoking the expression of multiple pro inflammatory molecules [9] (Figure 1).

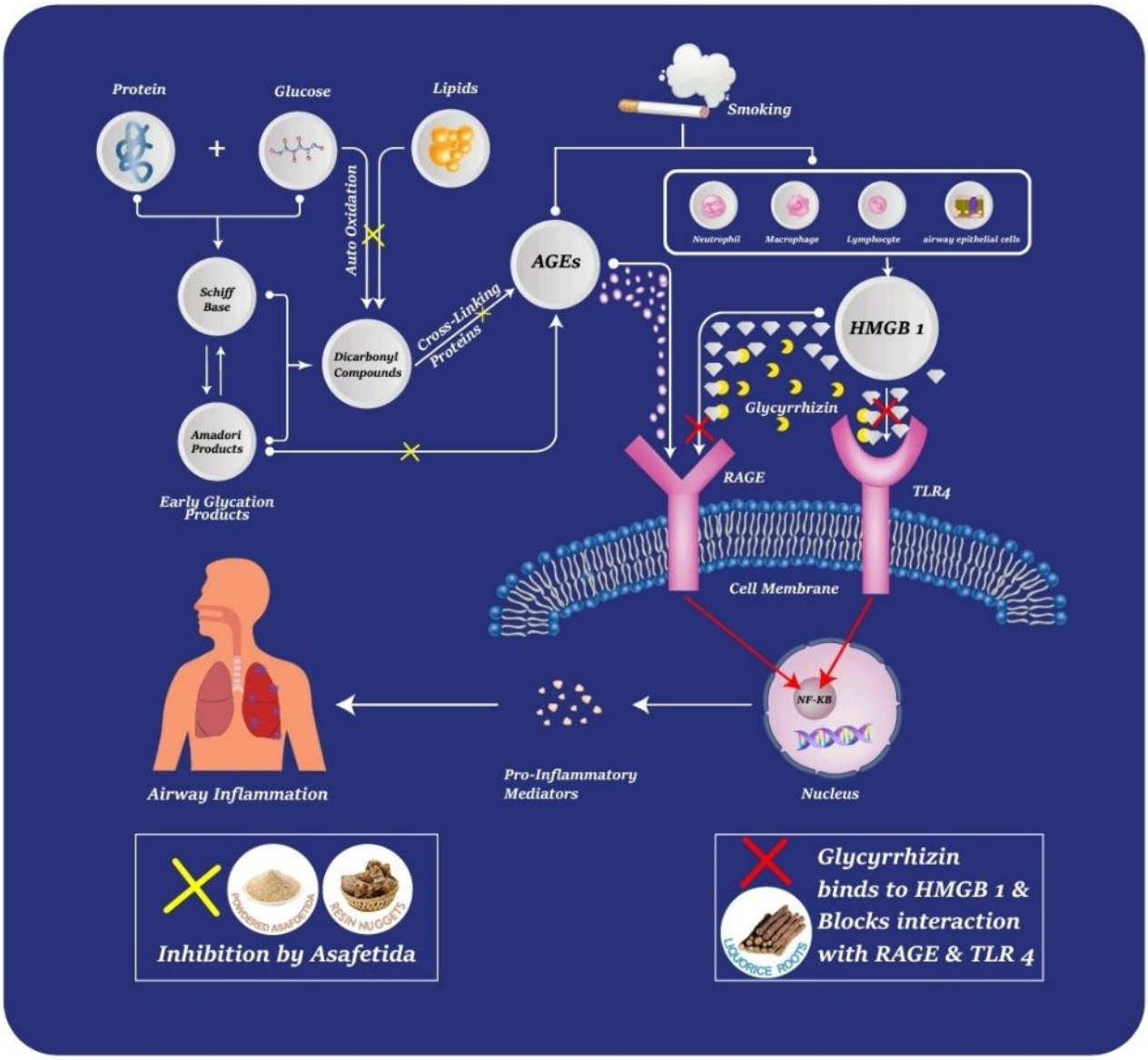

Figure 1. Shows the AGE-RAGE axis and the points of inhibition by asafetida and liquorice. While asafetida acts by blocking the formation of AGEs at several stages, glycyrrhizin in liquorice acts by binding to HMGB1 which prevents the interaction of HMGB1 with the RAGE and TLR receptors.

Furthermore, RAGE activation prompts endoplasmic reticulum (ER) stress, culminating in inflammation or apoptosis. AGE accumulation within the ER disrupts canonical protein folding, whereas AGE-induced cross linking of mitochondrial proteins impedes adenosine triphosphate (ATP) synthesis and enhances oxidative free radical production. These pathways perpetuate a self-reinforcing cycle of intracellular damage, compromised cellular function, and eventual cell death, ultimately resulting in aging and the manifestation of diverse age-related chronic diseases [9].

When RAGE binds with AGEs, it increases the production of reactive oxygen species (oxidative stress) by activating NADPH oxidase [27]. Additionally, it enhances the expression of pro-inflammatory cytokines (IL and TNF) [28], leading to various pathological conditions such as Alzheimer's disease [29], cardiovascular disease [30], cancer [31,32], diabetes mellitus [33], inflammation [34], and diabetic nephropathy [35]. RAGE has been considered a potential

biomarker of various pathological conditions and has been demonstrated as a potential therapeutic target in numerous diseases.

Pathological Role of AGEs in COPD

AGEs have been implicated in the development and progression of various lung diseases, including chronic obstructive pulmonary disease (COPD). A study on healthy individuals aged 50-64 revealed a significant association between AGE accumulation and lung function decline, as measured by skin auto fluorescence (SAF). The findings suggest that AGEs may contribute to lung parenchyma changes, impairing lung function [36]. Moreover, the proinflammatory AGEs molecules can alter the extracellular matrix, with the Receptor for Advanced Glycation End Products (RAGE) mediating some effects. A study using formalin-fixed lung tissue from bronchial carcinoma patients revealed increased AGEs and RAGE staining intensity in the airways and alveolar walls of COPD patients compared to controls. The findings suggest that the RAGE-AGEs interaction may contribute to COPD pathogenesis [37].

Furthermore, oxidative stress is a critical factor in the pathogenesis of COPD, and recent studies highlight the connection between oxidative stress and protein glycation. Elevated oxidative stress can increase protein glycation via auto-oxidative glycation. A research study involving 11 non-diabetic COPD patients found reduced whole-blood glutathione levels and increased lipid peroxide and fructosamine levels. These findings confirm the presence of oxidative stress and enhanced protein glycation in COPD, suggesting that **antioxidant therapy could be a valuable addition to COPD treatment regimens** [38]. Also, AGEs accumulation in COPD patients contributes to tissue damage through direct effects or binding to RAGE. The study found higher skin auto fluorescence (AFR) and lower plasma sRAGE (soluble form of RAGE) levels in COPD patients, correlating with decreased lung function. Results suggest that the protective mechanism of sRAGE as a decoy receptor is impaired in COPD, with AGEs accumulating differentially across body compartments [39]. Another study reported that COPD is linked to systemic inflammation and oxidative stress, which may contribute to the formation of AGEs. In a study involving 88 COPD patients and 55 control subjects, Gopal et al found that specific AGEs in the circulation and AFR are increased in COPD patients. The findings suggest that AGEs are involved in COPD pathophysiology [40].

To sum up, AGEs have been implicated in the pathogenesis of COPD through their association with systemic inflammation, oxidative stress, and impaired lung function. Increased formation and accumulation of AGEs in response to smoking and oxidative stress may cause local tissue damage directly or by binding to the RAGE. These findings support the potential use of antioxidant therapy as part of the treatment regimen for COPD patients.

Blockade of the AGE-RAGE Interaction: Therapeutic Potential

RAGE blockers in use

Blocking the interaction of AGEs with RAGE is a powerful approach to attenuate RAGE-mediated immuno-inflammatory diseases. FPS-ZM1 is a small RAGE blocker that inhibits the binding of RAGE with the V-domain and Aβ1-42, and it is used to treat Alzheimer's disease [29].Similarly, several studies show that cognitive decline and neurodegenerative disorders can be reduced by inhibiting the RAGE interaction with Aβ [41], which induces oxidative stress in endothelial and neural cells [42]. A small peptide (S100P) acts as a RAGE antagonist and suppresses inflammation and growth of cancer cells by blocking its interaction with AGEs ligands [43]. The potent RAGE antagonists Azeliragon, Papaverine, Emetine, and Fluorine-18 treat numerous RAGE-associated disorders [44,45]. Certain herbs also contain potential compounds that act as RAGE inhibitors and are used to treat numerous diseases [46]. Liquorice is one such powerful herb, in which the phytoconstituent glycyrrhizin is a potent inhibitor of RAGE.

Role of blocking RAGE in lung disorders

Aging and Smoking are the two major culprits that enhance the risk of COPD [47]. Cigarette smoke delivers toxins, particularly glycotoxins (precursors of AGEs), to the alveolar environment, making COPD worse [48] (Figure 1). Furthermore, RAGE over expression stimulates NO (nitric oxide) synthase activity and increases NO level, whereas glutathione (antioxidant) decreases; as a result, the activation of pro-inflammatory factors NF-kB increases eventually leading to chronic inflammation [49]. Various studies claim that lung diseases are linked with RAGE expressions, such as asthma, acute lung injury, respiratory distress syndrome, cystic fibrosis, interstitial lung disease, lung cancer, broncho-pulmonary dysplasia, and COPD [50]. These conditions can potentially be improved by suppressing the expression of RAGE. For example, RAGE inhibition improves lung ischemia [4], neutrophilic asthma [51], attenuates lung injury [52], cigarette-smoke-induced-lung epithelial cell damage [53] and inhibits the growth of cancer cells [32]. Blocking RAGE proves beneficial in fighting lung diseases, particularly COPD (Chronic Obstructive Pulmonary Disease). Several studies show that pharmacologic RAGE blocking can be a protective methodology for treating cigarette smoke-induced lung injury [54, 55]. An inhibitor, FPS-ZM1, can reduce lung inflammation and reverse emphysema [56].

Role of HMGB1 antagonists in COPD

The high-mobility group box 1 (HMGB1) is a nuclear protein that when released extra cellularly, acts as a pro-inflammatory cytokine. By binding to receptors like RAGE, HMGB1 can promote inflammation and contribute to disease progression in various pulmonary conditions, including asthma and COPD [57]. The protein consists of 215 amino acid residues (with a molecular weight of 25-30 kDa) with two DNA-binding domains that are homologous in nature (box A: amino acid 1-79; box B: amino acid 89-162), along with a long acidic C-terminal tail that is negatively charged (amino acid 186-215) [58][Fig 2].

The C-terminal acidic domain of HMGB1 also acts as a transcriptional activator [59]. The B-box of HMGB1 can trigger pro-inflammatory signals after extracellular stimulation, and the A-box demonstrates antagonistic effects [60]. The biological functions and activity of HMGB1 are influenced by the interactions with various receptors, intracellular partners, and extracellular partners. The residues 89-108 of HMGB1 bind to Toll-like receptor (TLR) 4, increasing the pro-inflammatory signaling [60], while the residues 150-183 play an important role in cell migration [61] and inflammation by interacting with the receptor for advanced glycation end products (RAGE).

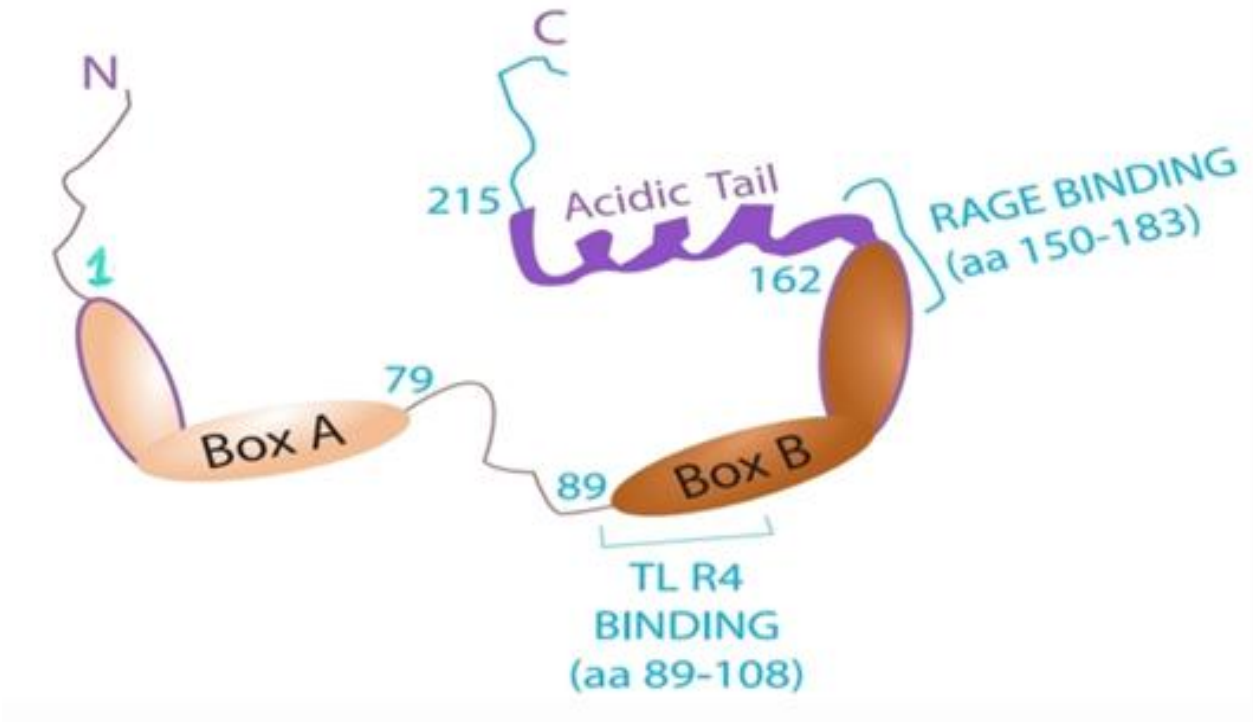

Figure 2. The structure of the HMGB1 protein.

The binding of HMGB1 with RAGE receptors causes a series of reactions, and progressively induces airway inflammation in COPD [62]. Upon interaction with RAGE, it activates signaling pathways and stimulates the production of chemokines such as TNF-α & IL-8 [63], and cytokines [64] that cause oxidative stress and inflammation. Glycyrrhizin is the natural HMGB1-antagonist that binds to this protein and suppresses its expression [65]. Okuma et al found that Glycyrrhizin binds to HMGB1 but not RAGE ; the formation of this glycyrrhizin-HMGB1 complex prevented HMGB1 from binding to RAGE in vitro [66]. Hu et al demonstrated that administration of glycyrrhizin reduced the expression of HMGB1, TLR4 and RAGE in an animal model [67].Glycyrrhizin has also been suggested to inhibit HMGB1 release, resulting in inhibition of the pro inflammatory cytokine-like activity of this protein. Thus, blocking or inhibiting the expression of HMGB1, RAGE, AGEs, and other inflammation-induced receptors like TLR4 is a powerful protective therapy against COPD.

Asafoetida: A Versatile Spice with Culinary and Medicinal Significance

Asafoetida (Hing or heeng) is the dried latex (oleo-gum resin) derived mainly from tap roots or rootstocks of various Ferula species such as F. narthex, F. foetida , F. rubricaulis , F. alliacea , and F. asafoetida. Asafoetida is known as an effective remedy to treat whooping cough, bronchitis, asthma, stomachache, ulcer, epilepsy, intestinal parasites, antispasmodic, and common digestive disorders [68,69].

Phytochemistry and pharmacological actions

The **sesquiterpenecoumarins** that have been isolated from asafetida are: feselol, ligupersin A, asacoumarin A, 8'-O-acetyl-asacoumarin A, 10'R-karatavacinol and 10'R-acetyl-karatavacinol, farnesiferol A, gummosin and badrakemone, fnarthexone and fnarthexol [70,71], Three known coumarin derivatives, conferol (3), conferone (4), and umbelliferone (5), were also isolated from the plant Ferula narthex [71].

The compound 10′-R-acetyl-karatavacinol from Ferula narthex showed significant inhibition of α-glucosidase in vitro. In the 15-lipoxygenase inhibition assay, 10′-R-karatavacinol showed high level of 15-lipoxygenase inhibition, demonstrating potent anti-inflammatory properties [72]. Asafetida also displays remarkable antioxidant activity, which can be attributed to its effective constituents such as monoterpenes, flavonoids, and phenolic components, known for their antioxidant properties and their ability to inhibit lipoxygenase activity [73].

Crude root extracts of Ferula narthex showed a significant antibacterial effect against P.aeruginosa, E. coli ,S. typhi and S. pneumoniae, and moderate antifungal activity against M. canis [71]. In a study conducted by Saleem in 2001, the effect of asafoetida in early carcinogenesis was investigated. The findings indicated that **asafoetida is a potent antioxidant** and can provide protection against free radical mediated diseases such as carcinogenesis [74].The significant anti-glycation actions of ferula sesquiterpenecoumarins are described below.

Ameliorative Effect of Asafetida in COPD

Antiglycation Activity

Several phytochemicals present in Ferula narthex exhibit significant anti-glycation activity. In the BSA-glucose (bovine serum albumin-glucose) test, the sesquiterpenecoumarin Ligupersin A displayed potent anti-glycation activity, even surpassing the positive control aminoguanidine. Meanwhile, in the BSA-MGO (methylglyoxal) assay, another sesquiterpenecoumarin called 8'-O-acetyl-asacoumarin A displayed significant anti-glycation activity, although it was less active compared to aminoguanidine. The antiglycation activity of these ferula phytochemicals was due to both oxidative and non-oxidative modes of inhibition [75]. By inhibiting glycation and the production of advanced glycation end products, asafoetida can prevent the damaging effects of AGEs and the consequences of the AGE-RAGE interaction.

Anti-inflammatory activity

Ferula narthex also contains Fukanemarin B (1), fukanefuromarin E (2), and fukanefuromarin F. These compounds have been shown to suppress the expression of the NO synthetase gene, thus inhibiting the nitric oxide (NO) production in vitro in a murine macrophage-like cell line (RAW264.7) [76]. Nitric oxide (NO) is a signalling molecule that plays a key role in the pathogenesis of inflammation.

Umbelliprenin is one of the major bioactive components found in Ferula asafoetida. It has been reported that synthetic umbelliprenin exhibits anti-inflammatory and **lipoxygenase inhibitory activity** [77]. Lipoxygenase is involved in the catalyzation process converting arachidonic acid found in membrane phospholipids into leukotriene pro-inflammatory mediators, which can lead to diseases such as asthma and chronic obstructive pulmonary disease (COPD). Therefore, the suppression of lipoxygenase has been considered beneficial in the treatment of these conditions [78, 79, 80].

Upon examining the anti-inflammatory activity of umbelliprenin using the carrageen in mouse paw edema model, it was reported that umbelliprenin suppressed the inflammation process by up to 39% , which is a significant result [78]. Umbelliprenin from Ferula persica has been identified as a strong **inhibitor of matrix metalloproteinases,** along with some other sesquiterpenecoumarins present in asafetida. Since matrix metalloproteinases plays a significant role in various pathological diseases, these**sesquiterpenecoumarins** are potential natural agents for the treatment of malignant and inflammatory disorders [81].

In an open randomized clinical study, the effectiveness of Hingu-Pippali Yoga, a herbal formulation containing asafetida (Heeng) and Pippali (Piper longum), on lung dysfunction was assessed. The trial group received the authenticated and standardized test drug twice a day in a dose of 250 mg for 28 days, along with honey and sugar. Lung function tests with a spirometer and a haemogram were conducted before starting the treatment and at the end of the study to evaluate the results. The trial group showed significant reduction in subjective parameters such as, cough, rhinitis and dyspnea. Pulmonary Function Tests demonstrated a significant increase in lung capacity in the trial group. Furthermore, there was a significant reduction observed in eosinophil count and ESR (erythrocyte sedimentation rate). Hingu-pippali yoga was found to be effective in reducing the respiratory disorder caused by air pollution and enhanced the lung capacity of subjects [82].

Licorice in the Treatment of COPD

Licorice (Glycyrrhizaglabra) is a small perennial herb belonging to the Fabaceae family. Its roots are widely used in the health, pharmaceutical, and food industries worldwide [1]. Licorice contains a variety of components, including amino acids, proteins, simple sugars, polysaccharides and mineral salts (calcium, iron, phosphorus, sodium, potassium, zinc, copper, magnesium, silicon, selenium, manganese). It also contains starches, pectins, resins, gums, and sterols [83]. Moreover, licorice serves as a source of oestrogens, tannins, glycosides, coumarins, phytosterols, and vitamins (B1, B2, B3, B5, E, and C [83]. Additionally, several biological compounds such as flavonoids, triterpenes, and saponins (associated with sweet flavor) have also been discovered in licorice [84].

The primary active components of liquorice are **Glycyrrhizin (GL) and glycyrrhetinic acid**. [85]. The pharmacological effects of both glycyrrhetinic acid and glycyrrhizin are the same since glycyrrhizin undergoes metabolic processes to be converted into glycyrrhetinic acid [86]. These bioactive substances, along with other active ingredients present in Licorice roots such as flavonoids, isoflavonoids, and glycyrrhizic acid have shown excellent effects in the regulation of respiratory functions, immuno-regulation, antiinflammation, antineoplastic, and hepatoprotection. Isoliquiritin is known for its anti-asthmatic, anti-diabetic, anti-atherogenic, anti-cancer, anti-microbial, anti-inflammatory, and antispasmodic properties [2, 87].Moreover, licorice is also utilized in the treatment of cognitive impairment, Alzheimer's disease, and dementia [88].

Glycyrrhizaglabra has exhibited effectiveness in inhibiting airway constriction, eosinophil infiltration, airway remodelling, hyper-reactivity, and airway inflammation [89]. Research has provided evidence that Glycyrrhizin (GL) and glycyrrhetinic acid are effective in reducing the expression of inflammatory mediators [90]. The protective effects of these bioactives against lung inflammation make them suitable candidates for the treatment of lung diseases associated with inflammation. Another component, **Isoliquiritigenin**, a natural flavonoid extracted from licorice roots, has demonstrated strong anti-inflammatory and antioxidant properties. The impact of isoliquiritigenin was investigated against cigarette smoke-induced COPD in a mice study. The results revealed that isoliquiritigenin reduced inflammatory cytokines and the infiltration of inflammatory cells. By regulating the NF-κβ and Nrf2 signalling pathways, isoliquiritigenin provides protection against COPD induced by cigarette smoke [91].

Studies have demonstrated the inhibitory effects of glycyrrhizic acid (GA) on the inflammatory response in Acute lung injury (ALI) [92]. Qu et al., conducted a study in 2019 to investigate the effects of Glycyrrhizic acid (GA) on lipopolysaccharide (LPS) induced ALI in mice. The study suggested that GA is capable of inducing autophagy through the PI3K/AKT/mTOR path way to ameliorate ALI by suppressing the secretion of inflammatory factors including TNF-α, IL-1β, and HMGB1 [93]. Furthermore, GA has been found to substantially reduce the levels of TGF-β1 in the lungs while protecting mice from lung injury caused by thoracic irradiation [94]. Thoracic irradiation leads to a significant increase in the expression of TGF-β1, proteins, Smad2, and Smad3 mRNA. It also increases mRNA levels of Smad7 in lung tissue. GA counteracted the elevated expression of Smad2, and Smad3 mRNA, TGF-β1, and proteins in lung tissue, and did not affect the mRNA expression of Smad7. These findings indicate that GA possesses the ability to prevent pneumonia caused by radiation exposure. This effect is associated with its ability to inhibit the activation of the TGF-β1/Smads signaling pathway [94].

Chen et al. in 2021 investigated the effect of licorice on chronic obstructive pulmonary disease (COPD) and concluded that the Mitogen-activated protein kinase (MAPK) signalling pathway is a crucial target of the primary ingredients of licorice in protecting against COPD symptoms [95]. A KEGG enrichment analysis showed that the MAPK signaling pathway was involved in the mediating activity of licorice [95]. The MAPK (Mitogen-Activated Protein Kinase) pathway serves as a key regulator in stress, inflammation, differentiation, functional synchronization, apoptosis, and cell proliferation. MAPK signal pathways play an important role in oxidative stress and inflammation reactions [96].

DISCUSSION

Chronic obstructive lung diseases, especially prevalent among smokers, have become increasingly common in the general population . The rising pollution levels in larger cities have also contributed to the growing incidence of COPD worldwide [97]. The link between COPD and cardio-vascular disorders emphasizes the need to find simple measures to prevent and manage these conditions. In this regard, use of asafetida and liquorice in everyday meal dishes can prove to be highly beneficial and cost-effective. Asafetida also known as *heeng*, is a commonly available spice in India. Interestingly, despite being the world's largest consumer of this spice, India does not produce it within its large and geographically diverse landmass. As a result, India imports the entire asafetida quantity of asafoetida consumed from central Asian countries [98].

The popularity of *heeng* in Indian cuisine can be attributed to the principles enshrined in Ayurveda, the traditional Indian system of medicine. Ayurveda classifies Asafoetida as a substance that alleviates *Vata* disorders. As a consequence of the advocacy in Ayurvedicformulations, *heeng* is commonly used to provide relief from intestinal

bloating and aids passage of flatus per rectum. Asafetida, in its original form has a very powerful and concentrated aroma, which is why it needs to be diluted considerably with starch before being marketed and used [99].

Advanced glycation end products (AGEs) are indeed significant contributors to the pathogenesis of COPD [37]. Blocking the production of AGEs by asafetida is a crucial factor in ameliorating COPD. Additionally, asafetida's anti-oxidant and anti-inflammatory activities also contribute to alleviating COPD. The lipoxygenase inhibitory activity of asafetida is particularly significant in this context, as it helps reduce the generation of leukotrienes [77]. Leukotrienes play a central role in asthma and COPD through three primary mechanisms: promoting inflammation, inducing bronchoconstriction, and stimulating mucus production [100]. Among these, cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are identified as the most significant broncho-constrictors, leading to airway obstruction associated with asthma [101]. Leukotrienes promote the inflammatory process by attracting white blood cells to the lungs, increasing mucus production and causing swelling of the lung lining by facilitating fluid accumulation. Blocking the formation of leukotrienes is therefore crucial in alleviating the symptoms of COPD [102].

The advantages of using asafetida go beyond relieving symptoms of COPD, as it may have a role in reducing the risk of developing lung cancer in COPD patients. The mechanisms of chronic inflammation in COPD and carcinogenesis overlap, suggesting that herbs with inhibitory effects on carcinogenesis might offer therapeutic benefits for COPD [74]. In this regard , the study conducted by Saleem in 2001, assessing the role of asafetida in early carcinogenesis is significant. Saleem applied a single dose of TPA (The phorbol ester 12-*O*-tetra-decanoylphorbol-13-acetate), a known tumor promoter topically to mice skin. This application resulted in a significant reduction in cellular antioxidant levels, induced ornithine decarboxylase (ODC) activity, rate of DNA synthesis and hydrogen peroxide levels in mice skin. All of these are early biomarkers of carcinogenesis. However, pretreating the animals with asafoetida recovered the antioxidant levels and reversed the induced ODC activity and DNA synthesis significantly. These findings demonstrated that asafetida acts as a potent antioxidant and can provide protection against early stages of carcinogenesis [74].

Glycyrrhizaglabra, commonly known as licorice or Mulethi, is primarily used in the industrial production of food additives, sweetening agents, and flavours [103]. It is a popular flavouring component in various food products, including candies, chewing gum, ice cream, soft drinks, and baked goods [84]. Licorice contains several phytoconstituents that exhibit anti-oxidant and anti-inflammatory activities. Notably, glycyrrhizin has the ability to bind to HMGB1 and block the activation of RAGE by HMGB1, providing anti-inflammatory effects. Additionally, liquorice demonstrates anti-glycation activity, further enhancing its potential to reduce inflammation in COPD [104,105].

COPD is characterized by exacerbations caused by repeated respiratory infections, which cause further deterioration in lung function. **In this context ,** Glycyrrhizaglabra has demonstrated significant antibacterial activity against various bacterial strains in vitro [106.107,108,109]. **Additionally,** extracts of Glycyrrhizaglabra and glycyrrhizic acid have shown potential inhibitory effects against several viruses, including herpes simplex, hepatitis A, B, and C, and influenza virus [110]. Glycyrrhizic acid has also been found to inhibit virus multiplication and disrupt virus particles [111]. These anti-bacterial and anti-viral activities of liquorice make it highly beneficial in preventing repeated bouts of respiratory infections in patients of COPD. Moreover, the polysaccharide fractions of Glycyrrhizaglabra can stimulate macrophages, potentially enhancing immune response. Glycyrrhizaglabra is also suggested to relieve upper respiratory tract congestion by promoting bronchial mucosa secretion, which can aid in the treatment of bronchial cough, catarrh, and sore throat [112].

Recommended dishes in which to use Heeng and Mulethi

Asafetida is commonly used in savory dishes, particularly in Indian cuisines, to add a unique and pungent flavor. It is commonly employed in sauces, curries, meatballs, and pickles. Often referred to as the "food of gods", or "Devil's dung", asafoetida is a popular condiment in Indian vegetarian cooking [113]. It is also included in various spice mixtures to enhance the taste of dishes. On the other hand, licorice is mostly employed as a flavoring agent in desserts and mousses, offering a sweet and pleasant taste. It is widely used in various confectionary products, including candies and sweets. In addition to its culinary uses, licorice also holds medicinal value and is extensively utilized in traditional herbal medicine.

Indeed, Liquorice or mulethi is commonly used in Europe as flavor agent in confectionery. It possesses a sweet taste that is approximately 30-50 times sweeter than sucrose, which is why it is called Yastimadhu in Sanskrit. This natural sweetness makes it an ideal ingredient for use in custards, cakes and puddings. Additionally a pinch of powdered liquorice can be added to most sweets to enhance theirflavor while providing potential health benefits. In traditional remedies, small pieces of raw mulethi sticks can also be slowly sucked to provide relief from sore throat and coughs. This natural remedy has been used for its soothing properties and potential benefits in alleviating throat irritation and cough symptoms.

Conclusion

COPD is a highly prevalent respiratory disorder worldwide. Excessive free radical and AGE production in the body and lungs have been implicated in the pathogenesis and further clinical deterioration of patients suffering from this condition. The sesquiterpenecoumarins present in asafetida , and the glycyrrhizin in liquorice roots have been found useful in decreasing oxidation processes and blocking the actions of AGEs. These actions of these two herbs can prove useful in ameliorating COPD and preventing worsening of symptoms. Both liquorice and asafetida can easily be incorporated into our daily dietary regimen, and provide a savory and pleasant way to alleviate the symptoms of COPD.

REFERENCES

1. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBP. Liquorice (Glycyrrhizaglabra): a phytochemical and pharmacological review. Phytother Res. (2018) 32:2323–39. doi: 10.1002/ptr.6178
2. Wahab, S.; Ahmad, I.; Irfan, S.; Siddiqua, A.; Usmani, S.; Ahmad, M.P. Pharmacological Efficacy and Safety of Glycyrrhizaglabra in the treatment of respiratory tract infections. Mini-Rev. Med. Chem. 2021, 21.
3. Armanini, D., Fiore, C., Bielenberg, J., &Ragazzi, E. (2005). Licorice (Glycyrrhizaglabra). Encyclopedia of Dietary Supplements, Coates P (ed.). Marcel Dekker Inc.: New York, 391-399. https://books.google.com/books?hl=en&lr=&id=Sfmc-fRCj10C&oi=fnd&pg=PA391&dq=traditional+uses+of+glycyrrhiza+glabra+lung&ots=lQJK0zuxEG&sig=zOSXLw3Wj3eVtc3Ic6Z-V3KJg_Y
4. Sharma, A., LaPar, D., Stone, M., Zhao, Y., Kron, I., &Laubach, V. (2013). Receptor for advanced glycation end products (RAGE) on iNKT cells mediates lung ischemia–reperfusion injury. American Journal of Transplantation, 13(9), 2255-2267. (PubMed &Scoup)
5. Shah, N. C., &Zare, A. (2014). Asafoetida (Heeng): The well-known medicinal-condiment of India & Iran. The Scitech Journal, 1(4), 30-36. https://www.researchgate.net/profile/Amirreza-Zarekarizi/publication/370492659_Asafoetida_Heeng_The_Well_Known_Medicinal_Condiment_of_India_Iran/links/6452d8c65762c95ac36ebc8c/Asafoetida-Heeng-The-Well-Known-Medicinal-Condiment-of-India-Iran.pdf
6. Mahendra, P., &Bisht, S. (2012). Ferula asafoetida: Traditional uses and pharmacological activity. Pharmacognosy reviews, 6(12), 141–146. https://doi.org/10.4103/0973-7847.99948https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3459456/
7. MiladIranshahy; MehrdadIranshahi (2011). Traditional uses, phytochemistry and pharmacology of asafoetida (Ferula assa-foetida oleo-gum-resin)—A review. , 134(1), 0–10. doi:10.1016/j.jep.2010.11.067 https://sci-hub.mksa.top/10.1016/j.jep.2010.11.067
8. Twarda-Clapa A, Olczak A, Białkowska AM, Koziołkiewicz M. Advanced Glycation End-Products (AGEs): Formation, Chemistry, Classification, Receptors, and Diseases Related to AGEs. Cells. 2022 Apr 12;11(8):1312. doi: 10.3390/cells11081312. PMID: 35455991; PMCID: PMC9029922.
9. Song Q, Liu J, Dong L, Wang X, Zhang X. Novel advances in inhibiting advanced glycation end product formation using natural compounds. Biomed Pharmacother. 2021 Aug;140:111750. doi: 10.1016/j.biopha.2021.111750. Epub 2021 May 26. PMID: 34051615. https://pubmed.ncbi.nlm.nih.gov/34051615
10. Yan, S. F., Yan, S. D., Ramasamy, R. & Schmidt, A. M. Tempering the wrath of RAGE: an emerging therapeutic strategy against diabetic complications, neurodegeneration and inflammation. Annals of medicine 41, 408-422, 10.1080/07853890902806576 (2009).
11. Hudson, B. I. et al. Blockade of receptor for advanced glycationendproducts: a new target for therapeutic intervention in diabetic complications and inflammatory disorders. Archives of biochemistry and biophysics 419, 80-88 (2003).
12. Morbini, P. et al. The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease? Mod Pathol 19, 1437-1445 (2006).
13. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological Effects of Glycyrrhizaglabra (Licorice): A Review. Phytother Res. 2017 Nov;31(11):1635-1650. doi: 10.1002/ptr.5893. https://sci-hub.mksa.top/10.1002/ptr.5893
14. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, Kandasamy G, Vasudevan R, Ali MS, Amir M. Glycyrrhizaglabra (Licorice): A Comprehensive Review on Its Phytochemistry, Biological Activities, Clinical Evidence and Toxicology. Plants. 2021; 10(12):2751. https://doi.org/10.3390/plants10122751https://www.mdpi.com/2223-7747/10/12/2751
15. Hasan, M. K., Ara, I., Mondal, M. S. A., &Kabir, Y. (2021). Phytochemistry, pharmacological activity, and potential health benefits of Glycyrrhizaglabra. Heliyon, 7(6). https://www.cell.com/heliyon/pdf/S2405-8440(21)01343-8.pdf
16. Kim, S. H., Hong, J. H., Yang, W. K., Geum, J. H., Kim, H. R., Choi, S. Y., ... & Lee, Y. C. (2020). Herbal combinational medication of Glycyrrhizaglabra, Agastacherugosa containing glycyrrhizic acid, tilianin inhibits neutrophilic lung inflammation by affecting CXCL2, interleukin-17/STAT3 signal pathways in a murine model of COPD. Nutrients, 12(4), 926. https://www.mdpi.com/2072-6643/12/4/926

17. Thakur, A. K., & Raj, P. (2017). Pharmacological perspective of Glycyrrhizaglabra Linn: A mini-review. J. Anal. Pharm. Res, 5(5), 00156. https://www.researchgate.net/profile/Dr-Ajit-Thakur/publication/322269263_Pharmacological_Perspective_of_Glycyrrhiza_glabraLinn_a_Mini-Review/links/60ba20b7458515218f8d6182/Pharmacological-Perspective-of-Glycyrrhiza-glabraLinn-a-Mini-Review.pdf
18. Sharma, D., Namdeo, P., & Singh, P. (2021). Phytochemistry& pharmacological studies of glycyrrhizaglabra: A medicinal plant review. Int. J. Pharm. Sci. Rev. Res, 67(1), 187-194. https://www.researchgate.net/profile/Priyanka-Namdeo-2/publication/351480408_Phytochemistry_Pharmacological_Studies_of_Glycyrrhiza_glabra_A_Medicinal_Plant_Review/links/60dc2917a6fdccb745f48291/Phytochemistry-Pharmacological-Studies-of-Glycyrrhiza-glabra-A-Medicinal-Plant-Review.pdf
19. Xiaoying W, Han Z, Yu W,Glycyrrhizaglabra (Licorice): Ethnobotany and Health Benefits. DebasisBagchi,Sustained Energy for Enhanced Human Functions and Activity, Academic Press,2017,Pg 231-250. https://doi.org/10.1016/B978-0-12-805413-0.00014-4
20. Srinivasan K. Spices as influencers of body metabolism: an overview of three decades of research. Food Research International, Volume 38, Issue 1, 2005, Pg. 77-86, https://doi.org/10.1016/j.foodres.2004.09.001
21. Kapoor LD, Ed. 2001. Handbook of Ayurvedic Medicinal Plants. Washington, D.C., CRC Press.
22. Ross IA. 2005. Medicinal plants of the world : chemical constituents, traditional, and modern medicinal uses. Totowa, N.J., Humana Press.
23. Zargari A, Ed 1996. Medicinal Plants, Tehran University Publications, Tehran
24. Appendino G, Maxia L, Bascope M, Houghton P J, Sanchez-Duffhues G, Munoz E, et al. 2006. A meroterpenoid NF-kappaB inhibitor and drimanesesquiterpenoids from Asafetida. J Nat Prod, 69: 1101-1104
25. Brownlee, M. (2000). Negative consequences of glycation. Metabolism, 49(2), 9-13.
26. Thornalley, P. J. (1998). Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. Cellular and molecular biology (Noisy-le-Grand, France), 44(7), 1013-1023.
27. Daffu, G., Del Pozo, C. H., O'Shea, K. M., Ananthakrishnan, R., Ramasamy, R., & Schmidt, A. M. (2013). Radical roles for RAGE in the pathogenesis of oxidative stress in cardiovascular diseases and beyond. International journal of molecular sciences, 14(10), 19891-19910. (PubMed &Scoup)
28. Prasad, K., & Mishra, M. (2018). AGE–RAGE stress, stressors, and antistressors in health and disease. International Journal of Angiology, 27(01), 001-012. (PubMed &Scoup)
29. Deane, R., Singh, I., Sagare, A. P., Bell, R. D., Ross, N. T., LaRue, B., . . . Deane, R. J. (2012). A multimodal RAGE-specific inhibitor reduces amyloid β–mediated brain disorder in a mouse model of Alzheimer disease. The Journal of clinical investigation, 122(4), 1377-1392. (PubMed &Scoup)
30. Yamagishi, S.-i., Nakamura, K., & Matsui, T. (2009). Regulation of advanced glycation end product (AGE)-receptor (RAGE) system by PPAR-gamma agonists and its implication in cardiovascular disease. Pharmacological Research, 60(3), 174-178. (PubMed &Scoup)
31. Allmen, E. U. v., Koch, M., Fritz, G., &Legler, D. F. (2008). V domain of RAGE interacts with AGEs on prostate carcinoma cells. The Prostate, 68(7), 748-758. (PubMed &Scoup)
32. Logsdon, C. D., Fuentes, M. K., Huang, E. H., &Arumugam, T. (2007). RAGE and RAGE ligands in cancer. Current molecular medicine, 7(8), 777-789. (PubMed &Scoup)
33. Ramasamy, R., Yan, S. F., & Schmidt, A. M. (2005). The RAGE axis and endothelial dysfunction: maladaptive roles in the diabetic vasculature and beyond. Trends in cardiovascular medicine, 15(7), 237-243. (PubMed &Scoup)
34. Ramasamy, R., Vannucci, S. J., Yan, S. S. D., Herold, K., Yan, S. F., & Schmidt, A. M. (2005). Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology, 15(7), 16R-28R. doi:10.1093/glycob/cwi053(PubMed &Scoup)
35. Tabrez, S., Al-Shali, K. Z., & Ahmad, S. (2015). Lycopene powers the inhibition of glycation-induced diabetic nephropathy: A novel approach to halt the AGE-RAGE axis menace. Biofactors, 41(5), 372-381. (PubMed &Scoup)
36. Zaigham S, Persson M, Jujic A, Frantz S, Borné Y, Malinovschi A, Wollmer P, Engström G. Measures of lung function and their relationship with advanced glycation end-products. ERJ Open Res. 2020 Jun 1;6(2):00356-2019. doi: 10.1183/23120541.00356-2019. PMID: 32523964; PMCID: PMC7261968. https://pubmed.ncbi.nlm.nih.gov/32523964/
37. Wu L, Ma L, Nicholson LF, Black PN. Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD. Respir Med. 2011 Mar;105(3):329-36. doi: 10.1016/j.rmed.2010.11.001. Epub 2010 Nov 26. PMID: 21112201. https://pubmed.ncbi.nlm.nih.gov/21112201/
38. Parija M, Bobby Z, Kumar V, Saradha B. Oxidative stress and protein glycation in patients with chronic obstructive pulmonary disease. Indian J PhysiolPharmacol. 2005 Jan;49(1):95-8. PMID: 15881865. https://pubmed.ncbi.nlm.nih.gov/15881865/
39. Hoonhorst SJ, Lo Tam Loi AT, Pouwels SD, Faiz A, Telenga ED, van den Berge M, Koenderman L, Lammers JW, Boezen HM, van Oosterhout AJ, Lodewijk ME, Timens W, Postma DS, Ten Hacken NH. Advanced glycationendproducts and their receptor in different body compartments in COPD. Respir Res. 2016 Apr 26;17:46. doi: 10.1186/s12931-016-0363-2. PMID: 27117828; PMCID: PMC4847335. https://pubmed.ncbi.nlm.nih.gov/27117828/

40. Gopal P, Reynaert NL, Scheijen JL, Engelen L, Schalkwijk CG, Franssen FM, Wouters EF, Rutten EP. Plasma advanced glycation end-products and skin autofluorescence are increased in COPD. EurRespir J. 2014 Feb;43(2):430-8. doi: 10.1183/09031936.00135312. Epub 2013 May 3. PMID: 23645408. https://pubmed.ncbi.nlm.nih.gov/23645408/
41. Deane, R., Du Yan, S., Submamaryan, R. K., LaRue, B., Jovanovic, S., Hogg, E., . . . Yu, J. (2003). RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain. Nature medicine, 9(7), 907-913. (PubMed &Scoup)
42. Yan, S. D., Stern, D., Kane, M. D., Kuo, Y.-M., Lampert, H. C., &Roher, A. E. (1998). RAGE-AB interactions in the pathophysiology of Alzheimer's disease. Restorative neurology and neuroscience, 12(2-3), 167-173. (PubMed &Scoup)
43. Arumugam, T., Ramachandran, V., Gomez, S. B., Schmidt, A. M., & Logsdon, C. D. (2012). S100P-Derived RAGE Antagonistic Peptide Reduces Tumor Growth and MetastasisRAP Inhibits RAGE Tumor-Promoting Functions. Clinical cancer research, 18(16), 4356-4364. (PubMed &Scoup)
44. Sabbagh, M. N., Agro, A., Bell, J., Aisen, P. S., Schweizer, E., &Galasko, D. (2011). PF-04494700, an oral inhibitor of receptor for advanced glycation end products (RAGE), in Alzheimer's disease. Alzheimer disease and associated disorders, 25(3), 206. (PubMed &Scoup)
45. Yoshizawa, K., Takeuchi, K., Nakamura, T., Ukai, S., Takahashi, Y., Sato, A., . . . Tanuma, S. i. (2021). Antinociceptive activity of the novel RAGE inhibitor, papaverine, in a mouse model of chronic inflammatory pain. Synapse, 75(3), e22188. (PubMed &Scoup)
46. Cui, L., Cai, Y., Cheng, W., Liu, G., Zhao, J., Cao, H., . . . Liu, T. (2017). A novel, multi-target natural drug candidate, matrine, improves cognitive deficits in Alzheimer's disease transgenic mice by inhibiting Aβ aggregation and blocking the RAGE/Aβ axis. Molecular neurobiology, 54, 1939-1952. (Scoup)
47. Smith, M. C., &Wrobel, J. P. (2014). Epidemiology and clinical impact of major comorbidities in patients with COPD. International journal of chronic obstructive pulmonary disease, 871-888. (PubMed &Scoup)
48. Cerami, C., Founds, H., Nicholl, I., Mitsuhashi, T., Giordano, D., Vanpatten, S., . . . Bucala, R. (1997). Tobacco smoke is a source of toxic reactive glycation products. Proceedings of the National Academy of Sciences, 94(25), 13915-13920. (PubMed &Scoup)
49. Chen, L., Wang, T., Guo, L., Shen, Y., Yang, T., Wan, C., . . . Wen, F. (2014). Overexpression of RAGE contributes to cigarette smoke-induced nitric oxide generation in COPD. Lung, 192, 267-275. (Scoup)
50. Oczypok, E. A., Perkins, T. N., &Oury, T. D. (2017). All the "RAGE" in lung disease: The receptor for advanced glycationendproducts (RAGE) is a major mediator of pulmonary inflammatory responses. Paediatric respiratory reviews, 23, 40-49. (PubMed &Scoup)
51. Zhang, F., Su, X., Huang, G., Xin, X.-F., Cao, E.-H., Shi, Y., & Song, Y. (2017). sRAGE alleviates neutrophilic asthma by blocking HMGB1/RAGE signalling in airway dendritic cells. Scientific Reports, 7(1), 14268. (PubMed &Scoup)
52. Blondonnet, R., Audard, J., Belville, C., Clairefond, G., Lutz, J., Bouvier, D., . . . Fournet, M. (2017). RAGE inhibition reduces acute lung injury in mice. Scientific reports, 7(1), 1-13. (PubMed &Scoup)
53. Lee, H., Lee, J., Hong, S.-H., Rahman, I., & Yang, S.-R. (2018). Inhibition of RAGE attenuates cigarette smoke-induced lung epithelial cell damage via RAGE-mediated Nrf2/DAMP signaling. Frontiers in Pharmacology, 9, 684. (PubMed &Scoup)
54. Shapiro, S. D. (1999). The macrophage in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 160(supplement_1), S29-S32. (PubMed &Scoup)
55. Hogg, J. C., Chu, F., Utokaparch, S., Woods, R., Elliott, W. M., Buzatu, L., . . . Coxson, H. O. (2004). The nature of small-airway obstruction in chronic obstructive pulmonary disease. New England Journal of Medicine, 350(26), 2645-2653. (PubMed &Scoup)
56. Lee, H., Park, J.-R., Kim, W. J., Sundar, I. K., Rahman, I., Park, S.-M., & Yang, S.-R. (2017). Blockade of RAGE ameliorates elastase-induced emphysema development and progression via RAGE-DAMP signaling. The FASEB Journal, 31(5), 2076. (PubMed &Scoup)
57. Zhao Y & Li R. HMGB1 is a promising therapeutic target for asthma, Cytokine, Volume165,2023,156171, http://doi.org/10.1016/j.cyto.2023.156171
58. Lee SA, Kwak MS, Kim S, Shin JS. The role of high mobility group box 1 in innate immunity. Yonsei Med J. (2014) 55:1165–76. 10.3349/ymj.2014.55.5.1165
59. Banerjee S, Kundu TK. The acidic C-terminal domain and A-box of HMGB-1 regulates p53-mediated transcription. Nucleic Acids Res. 2003 Jun 15;31(12):3236-47. doi: 10.1093/nar/gkg412. PMID: 12799451; PMCID: PMC162246.
60. Li J, Kokkola R, Tabibzadeh S, Yang R, Ochani M, Qiang X, Harris HE, Czura CJ, Wang H, Ulloa L, Wang H, Warren HS, Moldawer LL, Fink MP, Andersson U, Tracey KJ, Yang H. Structural basis for the proinflammatory cytokine activity of high mobility High expression of group box 1. Mol Med. 2003 Jan-Feb;9(1-2):37-45. PMID: 12765338; PMCID: PMC1430376.

61. Huttunen, H.J., C. Fages, J. Kuja-Panula, A.J. Ridley, and H. Rauvala. 2002. Receptor for advanced glycation end products-binding COOH-terminal motif of amphoterin inhibits invasive migration and metastasis. Cancer Res. 62:4805–4811.
62. Ko, H. K., Hsu, W. H., Hsieh, C. C., Lien, T. C., Lee, T. S., & Kou, Y. R. (2014). High expression of high-mobility group box 1 in the blood and lungs is associated with the development of chronic obstructive pulmonary disease in smokers. Respirology, 19(2), 253-261. (PubMed &Scoup)
63. Fiuza, C., Bustin, M., Talwar, S., Tropea, M., Gerstenberger, E., Shelhamer, J. H., &Suffredini, A. F. (2003). Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. Blood, The Journal of the American Society of Hematology, 101(7), 2652-2660. (Scoup)
64. Park, J. S., Arcaroli, J., Yum, H.-K., Yang, H., Wang, H., Yang, K.-Y., . . . Tracey, K. J. (2003). Activation of gene expression in human neutrophils by high mobility group box 1 protein. American Journal of Physiology-Cell Physiology, 284(4), C870-C879. (PubMed &Scoup)
65. Le, Y., Wang, Y., Zhou, L., Xiong, J., Tian, J., Yang, X., . . . Sun, Y. (2020). Cigarette smoke-induced HMGB1 translocation and release contribute to migration and NF-κB activation through inducing autophagy in lung macrophages. Journal of cellular and molecular medicine, 24(2), 1319-1331. (PubMed &Scoup)
66. Okuma, Y.; Liu, K.; Wake, H.; Liu, R.; Nishimura, Y.; Hui, Z.; Teshigawara, K.; Haruma, J.; Yamamoto, Y.; Yamamoto, H.; et al. Glycyrrhizin inhibits traumatic brain injury by reducing HMGB1-RAGE interaction. Neuropharmacology 2014, 85, 18–26.
67. Hu Z, Xiao M, Cai H, Li W, Fang W, Long X. Glycyrrhizin regulates rat TMJOA progression by inhibiting the HMGB1-RAGE/TLR4-NF-κB/AKT pathway. J Cell Mol Med. 2022 Feb;26(3):925-936. doi: 10.1111/jcmm.17149. Epub 2021 Dec 24. PMID: 34953035; PMCID: PMC8817133.
68. Takeoka G. Volatile constituents of Asafoetida. In: Takeoka G.R., Guntert M., Engel K.-H., editors. Aroma Active Compounds in Foods. American Chemical Society; Washington, DC: 2001. pp. 33–44.
69. Lee C.L., Chiang C.L., Cheng L.H., Liaw C.C. Influenza A (H1N1) antiviral and cytotoxic agents from Ferula asafoetida. J Nat Prod. 2009; 72:1568–1572.
70. Ramadan, N. I., & Al Khadrawy, F. M. (2003). The in vitro effect of Assafoetida on Trichomonasvaginalis. Journal of the Egyptian Society of Parasitology, 33(2), 615–630. https://pubmed.ncbi.nlm.nih.gov/14964671/
71. Bashir, S., Alam, M., Ahmad, B. and Aman, A., 2014. Antibacterial, anti-fungal and phytotoxic activities of Ferula narthex Boiss. Pak J Pharm Sci, 27(6), pp.1819-25. https://www.academia.edu/download/35826913/Paper-12_2.pdf
72. Amin, A., Hanif, M., Rafey, A., Zaib, S., Bakhsh, S., Ramzan, M., Zaman, A., Rehman, F.U., Iqbal, J. and Pieters, L., 2020. Sesquiterpenecoumarins from Ferula narthex 15-LOX, α-Glucosidase inhibition and molecular docking studies. RevistaBrasileira de Farmacognosia, 30(1), p.12-17. https://idp.springer.com/authorize/casa?redirect_uri=https://link.springer.com/article/10.1
73. Bagheri, S. M., Hedesh, S. T., Mirjalili, A., &Dashti-R, M. H. (2016). Evaluation of Anti- inflammatory and Some Possible Mechanisms of Antinociceptive Effect of Ferula assafoetida Oleo Gum Resin. Journal of evidence-based complementary & alternative medicine, 21(4), 271–276. https://doi.org/10.1177/2156587215605903https://pubmed.ncbi.nlm.nih.gov/26427790/
74. Saleem, Mohammad, AftabAlam, and Sarwat Sultana. "Asafoetida inhibits early events of carcinogenesis: a chemopreventive study." Life sciences 68, no. 16 (2001): 1913-1921. https://www.sciencedirect.com/science/article/abs/pii/S0024320501009778
75. Amin, Adnan, Emmy Tuenter, Paul Cos, Louis Maes, VassilikiExarchou, Sandra Apers, and Luc Pieters. "Antiprotozoal and antiglycation activities of sesquiterpenecoumarins from Ferula narthex exudate." Molecules 21, no. 10 (2016): 1287. https://www.academia.edu/download/76754645/4.pdf
76. Motai T, Kitanaka S. Sesquiterpenecoumarins from Ferula fukanensis and nitric oxide production inhibitory effects. Chem Pharm Bull (Tokyo). 2004 Oct;52(10):1215-8. doi: 10.1248/cpb.52.1215. PMID: 15467238.
77. Iranshahi, Mehrdad&Askari, M. &Sahebkar, A. &Hadjipavlou-Litina, Dimitra. (2009). Evaluation of antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the prenylatedcoumarinumbelliprenin. Daru. 17. 99-103.
78. Peters-Golden, M., & Henderson, W. R. (2007). Leukotrienes. New England Journal of Medicine, 357(18), 1841–1854. doi:10.1056/nejmra071371
79. Dwyer JH, Allayee H, Dwyer KM, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med. 2004;350:29–37.
80. Bamoniri, Abdolhamid&Mazoochi, Asma. (2009). Determination of bioactive and fragrant molecules from leaves and fruits of Ferula assa-foetida L. growing in central Iran by nano scale injection. Digest J Nanomaterials Biostructures. 4.
81. Shahverdi AR, Saadat F, Khorramizadeh MR, Iranshahi M, Khoshayand MR. 2006. Two matrix metalloproteinases inhibitors from Ferula persica var. persica. Phytomedicine 13: 712– 717.

82. Bhosale S, Kapgate S. Effect of Hingu-Pippali Yoga, a Herbal Formulation in Respiratory Disorders Caused by Air Pollution in Traffic Police–A Pilot Study. Asian Journal of Water, Environment and Pollution. 2015 Jan 1;12(2):99-106.
83. Wang, Q. , Qian, Y. , Wang, Q. , Yang, Y.-f. , Ji, S. , Song, W. , … Ye, M. (2015). Metabolites identification of bioactive licorice compounds in rats. Journal of Pharmaceutical and Biomedical Analysis, 115, 515–522.
84. Rizzato, G. , Scalabrin, E. , Radaelli, M. , Capodaglio, G. , & Piccolo, O. (2017). A new exploration of licorice metabolome. Food Chemistry, 221, 959–968.
85. El-Saber Batiha, G.; MagdyBeshbishy, A.; El-Mleeh, A.; Abdel-Daim, M.M.; Prasad Devkota, H. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of Glycyrrhizaglabra L. (Fabaceae). Biomolecules 2020, 10, 352.
86. Kowalska, A. and Kalinowska-Lis, U. (2019), 18β-Glycyrrhetinic acid: its core biological properties and dermatological applications. Int J CosmetSci, 41: 325-331. https://doi.org/10.1111/ics.12548
87. Mitscher, L.A.; Park, Y.H.; Clark, D.; Beal, J.L. Antimicrobial agents from higher plants. antimicrobial isoflavanoids and related substances from Glycyrrhizaglabra L. var. typica. J. Nat. Prod. 1980, 43, 259–269.
88. Sharma, S.; Sharma, S.; Chourasia, R.; Pandey, A.; Rai, A.K.; Sahoo, D. Chapter 2—Alzheimer's disease: Ethanobotanical studies. In Naturally Occurring Chemicals Against Alzheimer's Disease; Academic Press: Cambridge, MA, USA, 2021; pp. 11–28. ISBN 978-0-12-819212-2.
89. Hocaoglu, A.B.; Karaman, O.; Erge, D.O.; Erbil, G.; Yilmaz, O.; Bagriyanik, A.; Uzuner, N. Glycyrrhizin and long-term histopathologic changes in a murine model of asthma. Curr. Ther. Res. Clin. Exp. 2011, 72, 250–261.
90. Wang CY, Kao TC, Lo WH, et al.. Glycyrrhizic acid and 18β-glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF-κB through PI3K p110δ and p110γ inhibitions. J Agric Food Chem 2011;59:7726–33.
91. Yu, D.; Liu, X.; Zhang, G.; Ming, Z.; Wang, T. Isoliquiritigenin inhibits cigarette smoke-induced COPD by attenuating inflammation and oxidative stress via the regulation of the Nrf2 and NF-κβ signaling pathways. Front. Pharmacol. 2018, 9, 1001.
92. Zhao H, Zhao M, Wang Y, Li F, Zhang Z. Glycyrrhizic acid prevents sepsis-induced acute lung injury and mortality in rats. J HistochemCytochem. 2016;64:125–137.
93. Qu L, Chen C, He W, Chen Y, Li Y, Wen Y, Zhou S, Jiang Y, Yang X, Zhang R, Shen L. Glycyrrhizic acid ameliorates LPS-induced acute lung injury by regulating autophagy through the PI3K/AKT/mTOR pathway. Am J Transl Res. 2019 Apr 15;11(4):2042-2055. PMID: 31105816; PMCID: PMC6511780.
94. Chen, J., Zhang, W., Zhang, L., Zhang, J., Chen, X., Yang, M., ... & Hong, J. (2017). Glycyrrhetinic acid alleviates radiation-induced lung injury in mice. Journal of Radiation Research, 58(1), 41-47.
95. Chen, C., An, J., Shen, G., & Shen, Y. (2021). Potential Pharmacodynamic Mechanism of the Main ingredients in Licorice for Chronic Obstructive Pulmonary Disease. bioRxiv, 2021-08.
96. Guan R, Wang J, Li D, Li Z, Liu H, Ding M, Cai Z, Liang X. Hydrogen sulfide inhibits cigarette smoke-induced inflammation and injury in alveolar epithelial cells by suppressing254 PHD2/HIF-1alpha/MAPK signaling pathway[J]. INT IMMUNOPHARMACOL. 2020;81:105979.
97. Duan RR, Hao K, Yang T. Air pollution and chronic obstructive pulmonary disease. Chronic Dis Transl Med. 2020 Jul 11;6(4):260-269. doi: 10.1016/j.cdtm.2020.05.004. PMID: 33336171; PMCID: PMC7729117.
98. Alluri A. Asafoetida: The Smelly Spice India loves but never grew [Internet]. BBC; 2020 [cited 2023 Jun 3]. Available from: https://www.bbc.com/news/world-asia-india-54617077
99. Attokaran M. Natural food flavors and colorants. John Wiley & Sons; 2017 Mar 20.
100. Cuzzo B, Lappin SL. Physiology, Leukotrienes. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526114/
101. Montuschi P. Role of Leukotrienes and Leukotriene Modifiers in Asthma. Pharmaceuticals (Basel). 2010 Jun 2;3(6):1792-1811. doi: 10.3390/ph3061792. PMID: 27713330; PMCID: PMC4033953.
102. Usery, J. B., Self, T. H., Muthiah, M. P., & Finch, C. K. (2008). Potential Role of Leukotriene Modifiers in the Treatment of Chronic Obstructive Pulmonary Disease. Pharmacotherapy, 28(9), 1183–1187. doi:10.1592/phco.28.9.1183
103. Mukhopadhyay, M. , &Panja, P. (2008). A novel process for extraction of natural sweetener from licorice (Glycyrrhizaglabra) roots. Separation and Purification Technology, 63(3), 539–545.
104. Siddiqui MA, Rasheed S, Saquib Q et al. In-Vitro dual inhibition of protein glycation, and oxidation by some Arabian plants. BMC Complementary and Alternative Medicine (2016) 16:276 DOI 10.1186/s12906-016-1225-7
105. Alvi SS, Nabi R, Khan MS et al. Glycyrrhizic Acid Scavenges Reactive Carbonyl Species and Attenuates Glycation-Induced Multiple Protein Modification: An In Vitro and In Silico Study. Oxidative Medicine and Cellular Longevity Volume 2021, Article ID 7086951, 14 pages https://doi.org/10.1155/2021/7086951
106. Sultana S., Haque A., Hamid K., Urmi K.F., Roy S. Antimicrobial, cytotoxic and antioxidant activity of methanolic extract of Glycyrrhizaglabra. Agric. Biol. J. N. Am. 2010;1:957–960. doi: 10.5251/abjna.2010.1.5.957.960. https://www.researchgate.net/profile/Kaiser-Hamid/publication/265813074_Antimicrobial_Cytotoxic_and_Antioxidant_Activity_of_methanolic_extract_of_Glycyrr

hiza_glabra/links/541c39b40cf241a65a0bcb5e/Antimicrobial-Cytotoxic-and-Antioxidant-Activity-of-methanolic-extract-of-Glycyrrhiza-glabra.pdf

107. Sedighinia F, SafipourAfshar A, Soleimanpour S, Zarif R, Asili J, Ghazvini K. Antibacterial activity of Glycyrrhizaglabra against oral pathogens: an in vitro study. Avicenna J Phytomed. 2012 Summer;2(3):118-24. PMID: 25050240; PMCID: PMC4075669. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4075669/

108. Irani M, Sarmadi M, Bernard F, Ebrahimi Pour GH, Shaker Bazarnov H. Leaves Antimicrobial Activity of Glycyrrhizaglabra L. Iran J Pharm Res. 2010 Fall;9(4):425-8. PMID: 24381608; PMCID: PMC3870067. https://pubmed.ncbi.nlm.nih.gov/24381608/

109. Krausse R, Bielenberg J, Blaschek W, Ullmann U. In vitro anti-Helicobacter pylori activity of Extractumliquiritiae, glycyrrhizin and its metabolites. J AntimicrobChemother. 2004 Jul;54(1):243-6. doi: 10.1093/jac/dkh287. Epub 2004 Jun 9. PMID: 15190039. https://pubmed.ncbi.nlm.nih.gov/15190039/

110. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003 Jun 14;361(9374):2045-6. doi: 10.1016/s0140-6736(03)13615-x. PMID: 12814717; PMCID: PMC7112442. https://pubmed.ncbi.nlm.nih.gov/12814717/

111. Arora R., Chawla R., Marwah R., Arora P., Sharma R.K., Kaushik V., Goel R., Kaur A., Silambarasan M., Tripathi R.P., et al. Potential of complementary and alternative medicine in preventive management of novel H1N1 Flu (Swine Flu) pandemic: Thwarting potential disasters in the bud. Evid. Based Complement Alternat. Med. 2011;2011:1–16. doi: 10.1155/2011/586506. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2957173/

112. Kuang Y, Li B, Fan J, Qiao X, Ye M. Antitussive and expectorant activities of licorice and its major compounds. Bioorg Med Chem. 2018 Jan 1;26(1):278-284. doi: 10.1016/j.bmc.2017.11.046. Epub 2017 Dec 2. PMID: 29224994. https://pubmed.ncbi.nlm.nih.gov/29224994/

113. Ravindran, P. N., Pillai, G. S., &NirmalBabu, K. (2004). Under-utilized herbs and spices. Handbook of Herbs and Spices, 53–103. doi:10.1533/9781855738355.1.53