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A REVIEW ON *CYDONIA OBLONGA* MILLER AS AN HERBAL MEDICINE

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Abstract:

Almost all parts of medicinal plant Cydonia oblonga Mill., known as "Quince" belonging to Rosaceae family, such as seeds, buds, leaves, fruit and peel are used to prevent or treat several ailments such as cancer, diabetes, hepatitis, ulcer, respiratory, and urinary infections, etc. It is rich in useful secondary metabolites such as phenolics, pectin, steroids, flavonoids, terpenoids, tannins, sugars, organic acids, glycosides and essential oils with a wide range of pharmacological activities like cardiovascular, hypoglycemic, nephro, hepato and UV-protective, aphrodisiac, antioxidant, anti-allergic, anti-atherosclerotic, antimicrobial, antibacterial, antifungal, antihypertensive, hypolipidemic, diuretic, antidiarrheal, antidepressant, antispasmodic, and anti-inflammatory effects. It is used as a single drug or as an ingredient in various formulations such as syrup, extract, confection, semisolid preparations and pill. This review focuses on detailed investigations of pharmacological and phytomedicinal attributes of the plant, from past to present, which are reported in Books and Scientific Journals.

Keywords: ***Quince, Cydonia oblonga, Herbal Medicine, Pharmacological Effects.***

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INTRODUCTION:

Plants are not only a dietary source for both human beings and animals but also safe herbal medicines. Whereas enormous number of plants possess medicinal effects, herbal medicines have been traditionally used to treat various ailments in Islamic, Iranian, Mesopotamia, Unani, Chinese, and Indian Ayurveda systems of therapies [1] [2] [3] [4] [5]. For instance, in traditional Indian folk medicines, more than 25,000 plant based drug formulations have been reported [6]. World Health Organization has also scheduled over 21,000 plant species used around the world for therapeutic and medicinal purposes [7]. Nowadays, tendency to herbal medicines for treatment of different diseases is growing rapidly and this curing experience of plants can be supported by many scientific evidences [8] [9] [10] [11] [12]. In response to new challenges in health care, researchers are also trying to isolate active phytochemicals from plants [10] [13]. During the recent years, a modest number of studies have investigated the efficacy of traditional herbal medicines using modern methodology and favorable outcomes have been achieved raising the possibility for the revival of herbal remedies [14].

Cydonia oblonga Miller, known as Quince, a plant of family *Rosaceae* is conventionally popular for its medicinal, nutritional, and ornamental uses [15] [16] [17] [18]. Table I summarizes general specifications of this plant. The major parts of this plant which have been used medicinally are leaves, fruit and seeds and its efficacy has been tested in several experimental or clinical studies so that, no significant side effect or contra indication related to consumption of products of Quince has been reported so far. A brief review of medical literature revealed that preparations from different parts of Quince act like stimulant for heart and brain and have some positive effects in the medical treatment of various conditions, including cardiovascular diseases and cancer, cough, bronchitis, bronchial asthma, nausea, fever, diarrhea, stomachache, cystitis, constipation, hemorrhoids, diabetes, vomit and hypertension [19] [20] [21] [22] [23]. Moreover, several studies have been conducted to evaluate antioxidant and anti-proliferative properties of Quince. The plant also contains an enzyme, phenol peroxidase, which decolorizes carcinogenic aromatic dyes in industrial waste water [24] [25]. In this review, after mentioning Geographical and Historical Background and uses in Islamic Comments and Iranian Traditional Medicine, available references dealing with the biological activities of Quince plant have been reviewed and the pharmacological importance of it, has been highlighted.

Table I: General Specifications of *Cydonia oblonga* Mill. (Quince).

Synonyms [26]	*Cydonia oblonga* Mill., *Cydonia vulgaris* Pers., *Cydonia maliformis* Mill., *Cydonia lusitanica* Mill., *Pyrus cydonia* L., *Cydonia cydonia* var. *lusitanica* (Mill.) Pers., *Cydonia oblonga* f. *lusitanica* (Mill.) Rehder, *Cydonia vulgaris* var. *lusitanica* (Mill.) DC.
Names in Different Languages [27] [19] [28] [29]	**Arabic**: Sefarjal; **Azari:** Heyva; **Chinese**: Wen po; **English**: Quince; **French**: Cognassier, Coing, Coigner; **German:** Quitte, Quittenbaum; **Greek:** Strythion; **Hindi:** Bihi; **Italian:** Cotogno, Melo Cotogno, Pero Cotogno; **Persian**: Beh; **Portuguese**: Marmelo, Marmeleiro; **Russian**: Ajva; **Spanish**: Membrillero, Membrillo; **Swedish**: Kvitten; **Turkish:** Ayva.
Classification [27] [30] [19]	**Kingdom:** Plantae; **Subkingdom**: Tracheobionta; **Superdivision**: Spermatophyta; **Division:** Magnoliophyta; **Class:** Magnoliopsida; **Subclass**:Rosidae; **Order:** Rosales; **Family:** *Rosaceae*; **Subfamily:** Maloideae, Spiraeoideae, Amygdaloideae; **Tribe:** Pyreae, Maleae; **Subtribe:** Pyrinae, Malinae; **Genus:** Monotypic, *Cydonia* Mill.; **Species:** *Cydonia oblonga* Mill.
Varieties [31] [32]	Pyriformis (Pear-Shaped); Maliformis (Apple-Shaped); Lusitanica (Lusitanian or Portugal Quince with Broader Leaves and Larger Fruits). The apple-shaped fruits have harder flesh with more astringent taste as compared to pear-shaped.
Main Constituents [33] [34] [35] [36] [37] [18] [23] [38] [39] [40] [24] [25] [41] [42] [43]	**Plant:** Essential Oils, Phenolic Compounds, Acids, Tannins, Tetracyclic Sesterterpenes, Ionone Glycosides, Pectin, Quercetin and Kaempferol Heterosides, including: **Seeds:** Sterols, Triterpenes, Tannins, Phenolics, Organic Acids, Amino Acids. **Leaves:** Aromatic Aldehyde, Fatty Acid, Phenolics, Oxygenated Monoterpene, Sesquiterpene Hydrocarbon. **Fruits:** Water, Vitamin A, B, C, Protein, Phenolics, Sugars, Pectin, Acids, Carbohydrates, Lipids, Fibre and Minerals (N, Na, K, Ca, Mg, P, Fe, Cu, Zn and Mn).

Geographical Distribution and Production [27] [44] [45] [46]	**The Center of Origin:** Western Asia and Caucasian Region (Iran, Turkey, Armenia, Azerbaijan, Southwestern Russia, Turkmenistan, Western and Eastern Ante-Caucasus, Daghestan, Eastern and Southern Transcaucasia, Talysh). **Now:** Worldwide. **Important World Producers:** Turkey (25%), and China, Iran, Argentina, and Morocco (each produce less than 10%).
Description [46] [19] [31] [20] [47] [28] [45] [48]	It is the sole member of genus *Cydonia*, a multi-stemmed spineless shrub or small tree with tomentose buds, petioles, leaves, and fruit. It is grown and cultivated in grounds or gardens under warm temperature and grows up to 8 m in height and 5 m width. The bark is smooth and brown approaching to black. The young branches are covered with pale greyish wool, flowers are pink or white, squat fat fruits are bright yellowish and shape ranges from round to pear-like, usually pear-shaped. The fruit is a fragrant, astringent taste pome with large numbers of plano-convex seeds arranged in two vertical rows, acquiring 7–12 cm length, 6-9 cm diameter, with pleasant flavor and aroma. Leaves are ovate to oblong, dusky green above and whitish underneath, about 5 cm across and 6-11 cm long. The solitary white flowers are 4-5 cm across, have 5 petals, 20 or more stamens, 5 styles, an inferior ovary with many ovules and are borne on current season of growth. Bloom time overlaps with that of apples, usually at the beginning of April to mid-April in the central latitudes of the Northern Hemisphere.

Geographical and Historical Background

The name of the *Cydonia* genus is derived from the name of a region Kydonia in the northwestern Coast of Crete Greece, where this tree has been cultivated since the ancient times. In older Greek ritual these fruits were offered in wedding as they symbolized fertility [49]. Geographically, In Italy, Quince leaves have been utilized in folk medicine for the cure of diverse skin as well as cardiovascular diseases. However, in Portugal, decoctions or infusions of leaves are consumed in traditional medicine due to their antitussive antipyretic, antidiarrheal, and sedative properties [18] [50]. In Iran as well as other areas of the Middle East, the dried up pits of the fruit are used to cure cough and sore throat. The fruit pits are immersed in water and the viscous product is then drunk like cough medicine. It is considered safe for children, as it is alcohol free. In Afghanistan the Quince seeds are boiled and consumed for curing pneumonia. In Chinese medicine, the stem bark is used as astringent for ulcers, and the fruits are utilized for their carminative, peptic, antivinous, and astringent qualities. A prominent formulation, Gencydo® containing aqueous Quince extracts and lemon juice has been used for treatment of allergic rhinitis and asthma in Europe [51] [52]. Quince-made paste is much admired in European countries, mostly in Spain as well as in parts of Latin America. This saccharine, sweet-smelling, akin to jelly confection is cut into pieces and frequently serves up along a spicy cheese. Quince is used in several salty and sweet dishes, and is recurrently cooked with lamb in Armenia [53]. In different areas of France, especially Angers, it was utilized as pear rootstock before 1500 years. The French people were growing Quince plants from the healthy cuttings and layering in stool beds by the early 1600s. France supplies major rootstocks to entire world [36].

Traditionally different parts of plants such as roots, flowers, fruits, leaves, and seeds have been used frequently to get rid of various complications because of their secondary metabolites such as tannins, terpenoids, alkaloids, *etc*. [54] [55]. About *Cydonia oblonga* Mill., the fruits were traditionally used as astringent, antiseptic, hepatoprotective, cicatrising, anti-inflammatory; for treatment of diarrhoea, dysentery, hepatic disorders, leucorrhoea, haemoptysis, uterine haemorrhages, and wounds. The quite ripe raw fruits were good for those who spit blood or are troubled with hemorrhage. The juice of raw Quinces has been sovereign remedy for the swollen spleen, dropsy and the difficulty of taking breath. The seeds were traditionally used as demulcent, astringent and emollient for the treatment of gastro intestinal (GI) disorders such as gum problems, canker sores, intestinal colic, dysentery, constipation, diarrhea, and respiratory tract disorders including asthma, bronchitis, sore throat, rhinitis and cough. The seed mucilage has also been used for healing dermal wounds. Traditionally, the leaves were used as astringent and antiseptic and leaf decoction has been used to cure nervousness, dysuria, insomnia, cough, cold abdominal cramps, diarrhea, fever, and hyperglycemia. The fresh or dried flowers were effective for inflamed eyes. The roots were used as charmed against Scrofula. Quince extracts have been conventionally utilized as dietary supplements in addition to medical treatment for inflammatory diseases and infections [12] [28] [56] [57] [31] [58] [56] [59] [60].

Uses in Islamic Comments and Iranian Traditional Medicine (ITM)

Regarding Quince, there are different narrations from Islam Prophet Muhammad: “Eat Quince because it purifies the heart, it's very good for lungs and clean them”; “Eat Quince to refresh your soul”; “Feed your pregnant women on Quince, it cures the diseases of the heart and makes the babies beautiful.”; “Anyone who breaks his fast with Quince for three days, his mind will be opened; his patience and knowledge will expand, and will be safe from tricks and deceptions of the devil” [61]; “Quince gives relaxation to heart, generosity to miser, and braveness to coward” [62]; “Eat Quince, because it strengthens the mind and weak heart, cleans the stomach, improves the courage, makes the coward brave, relieves the heaviness from chest, and makes the baby beautiful” [63] [64]. The effects of eating Quince, as stated by Imam Ali, are as follows: (a) Strengthens weak heart, (b) Causes increase in weight, (c) Cleans the stomach, (d) Increases reason, and (e) Makes a man courageous. Imam Baghir also said: “Quince relieves the grief of stricken”. According to Imam Sadiq: “A pregnant woman should eat Quince to improve complexion and beauty of baby and it may smell good”; “Whosoever would have a Quince as the first thing in the morning, God

will bless his tongue with wisdom for a period of forty days"; "Quince makes sorrow depart from the sad people in the same way as one's hand cleans one's sweat". Also, Imam Reza said: "Eating Quince treats eye darkness and strengthens your mind" [65] [61] [66].

Moreover, Iranian traditional medical practitioners have described several properties of Quince. In Iranian Traditional Medicinal Books such as "Makhzan-al-Advia" and "Tuhfat-al-mu'minin", it is mentioned about Quince that: Sweet ones are refresher, diuretic, tonic for hearts, minds and stomach, meanwile increasing joy of soul. Sour ones are stronger than the sweet ones in strengthening the warm stomach, its high consumption is laxatives and its extract is beneficial to relieve hangover, puke, thirst, strengthen the stomach and urination. Meles ones' properties are close to the two other ones. Smelling all kinds of Quince is refresher, strengthener of soul's strengths and terminative of nausea. Eating especially sweet ones is useful for recreation, eliminating obsession, headache, nasal discharge and strengthening the liver, stomach and its mouth, fixing their weaknesses, stimulating appetite, preserving the fetus from abortion, eliminating halitosis, preventing vapors to reach the brain and heart, drunken state, nausea, puke, boredom, suffocation, jaundice, materials' flux into stomach, diarrhea, inflammation and pain at the mouth of the stomach [67] [68]. Moreover, Ibn Sina said in "The Canon of Medicine": baked Quince is more useful. Quince and its flowers and oil are astringent. Quince is nourishing organs and prevents the flow of materials and excreta to the viscera. It is benefical for hangover and puke, and relieves thirst. Drinking its syrup strengthens the stomach, prevents the flow of excreta into it, strengthens fallen appetite and eliminates nausea and vomit [4]. It has also relaxing effects so that, drinking a teaspoon of brewed leaf of Quince with honey or blooms of bitter Orange in the morning, treats anger. Moreover, drinking 30 mg/l brewed blooms of both Quince and bitter Orange is a good sedative [62]. In the other reference Books including "Eksir-e Azam", "Qarabadin-e Kabir" and "Qarabadin-e Salehi", such the terms has also reported [69] [70] [71].

Pharmacological Effects

The several pharmacological effects of Quince's different parts which are summarized as below have been described in the next sections:

Fruit: Pomes of Quince have hard acidic flesh with high flavor, and raw fruits are not agreeably eatable due to its stiffness, acrimony and astringent properties. Therefore, they are widely used in food industry in the form of jam "marmalade", jelly, preserves, supplement to main dishes and for flavoring pies, as a source of pectin that protects colonal damage in irritable bowel syndrome (IBD) and peptic ulcer [19] [72] [20] [73]. Quince fruit is recognized as a good, cheap and important dietary source of health-promoting compounds such as phenolics, due to its biologically active constituents which are characterized by their antioxidant, anti-carcinogenic, antimicrobial, anti-inflammatory, anti-allergic, anti-ulcerative and hypoglycemic properties [28] [43] [42]. It has protective effect against oxidative hemolysis of human erythrocytes [74].

Seeds: Seeds of the plant are traditionally utilized for the treatment of diarrhea, cough, dysentery, sore throat, constipation, bronchitis, intestinal colic and constipation [58] [56]. Quince seeds contain sterols, triterpenes, and tannins as active phytochemicals that account for its antidiarrheal activity [40]. The presence of different phenolics, organic acids, and amino acids has also been described in Quince seeds [41]. Quince seed mucilage has a wound healing activity too [75].

Leaves: Quince leaf extract has been found effective against diabetes, cancer, and hemolysis [76] [77] [78] [79]. Quince leaves have been used, after decoction or infusion, in folk medicine for their sedative, antipyretic, antidiarrheic and antitussive properties and for the treatment of various skin diseases [18]. Anticancer characteristics of the Quince leaf have been reported in recent investigations [38] [78]. Quince leaves have reducing capacity and 2, 2-diphenyl-1-picrylhydrazyl (DDPH) radical scavenging activity [80]. It has been suggested that leaves from Quince can be used as an immense natural and inexpensive source of bioactive compounds with major antioxidative properties along with other mechanisms of action. By modulating various cardiovascular risk factors such as atherosclerosis, smoking, endothelial dysfunction, hypertension, diabetes and hyperhomocysteinaemia, Quince leaf extract may have relevance in the prevention and treatment of different pathological states of ischemic, inflammatory and hypertrophic heart disease [81].

Antidiabetic Effects

An experiment conducted by Koutba and Morsy (2012) showed that the extract of the unripe fruit of Quince has a number of biological active components including sorbitol, quinic acid, pvinylphenol and cyclopropanecarboxylic acid. The last two components might be implicated in alpha amylase inhibition and in turn have hypoglycemic effect [82]. Aslan *et al.* (2010) studied the antidiabetic effect of Quince leaves hydro-ethanolic extract along with three herbal remedies used in Turkish traditional medicine on normal and streptozotocin induced diabetic rats. There was no significant effect on normal rats after intake of 2 g/kg glucose. However, a considerable reduction in the blood glucose levels of diabetic rats was observed at a time period of 0 to 3 h. The beneficial effect of the extract (250 or 500 mg/kg dried extract) was the same as a standard antidiabetic drug (tolbutamide, 100 mg/kg) and there was no significant difference between glucose levels of the extract and tolbutamide treated rats. The antioxidant activity of the Quince extract was evaluated by glutathione (GSH) and thiobarbituric acid reactive substance (TBARS) contents of kidney, liver and heart of diabetic rats. As a result, there was no significant decrease in GSH contents of diabetic and non-diabetic rats, while significant decreases were observed in TBARS of heart tissue of diabetic rats when compared with diabetic control group. The low dose oral administration of Quince extract (250 mg/kg) revealed a slight and non-significant decrease on kidney TBARS, whereas the higher dose (500 mg/kg) showed significant

decrease in TBARS content of kidney ($p < 0.01$) and blood glucose level (33.8%) in streptozotocin induced diabetic rats after 5 days. Accordingly, long term use of Quince is recommended in type II diabetic patients to protect against the complications of diabetes mellitus [77]. In another study, Quince fruit aqueous extract was evaluated for its potential to overcome complications associated with diabetes. The extract at once daily dose of 80, 160 and 240 mg/kg body weight for 6 weeks was orally administered to male Sprague–Dawley rats in which diabetes was induced by single intraperitoneal dose of streptozotocin (60 mg/kg) dissolved in citrate buffer (1 mL, pH 4.5). The results clearly demonstrated that Quince fruit extract successfully reduced total cholesterol level, serum triglycerides, ALT, AST ALP, HDL, LDL, urea, and creatinine [83].

Antioxidant and Anti-hemolytic Effects

Currently, it has been established that different ailments such as Parkinson's disease, Alzheimer's, cancer, arteriosclerosis, diabetes, and arthritis are associated with generation of free radicals that cause hemolysis [84]. In this regard, Rahimi *et al.* (2010) reported that the phenolic composition of Quince has the strongest antioxidant effects among its other extracts and provides clear evidence of its medicinal importance [85].

Silva *et al.* (2004) carried out qualitative and quantitative analysis of Quince fruit collected from different regions of Portugal and evaluated their antioxidant potential using DPPH assay. The antioxidant activity of Quince fruit seed, peel, pulp and jam methanolic extracts were fractionated into a phenolic and organic acid fractions and analyzed by high-performance liquid chromatography/diode array detection and HPLC/UV. Antiradical activities of the extracts and fractions were evaluated by a micro-assay using 1,1'-diphenyl-2-picrylhydrazyl. It was observed that the phenolic fractions possessed stronger antioxidant and free radical scavenging activity than the organic acid fractions and the whole methanolic extracts, while the organic acid extracts were the weakest in terms of antiradical activity of Quince fruit and jam. The evaluation of the antioxidant activity of methanolic extracts showed that peel extract exerted the highest antioxidant capacity. The IC_{50} values of Quince peel, pulp, and jam extracts were correlated with the caffeoylquinic acids content. Among the phenolic fractions, the seed extract was the one that exhibited the strongest antioxidant activity [86].

Similarly, in another study, Magalhaes *et al.* (2009) isolated phenolics of methanolic extract of Quince fruit seed, peel, and pulp using HPLC/UV and evaluated their free radical scavenging abilities using 2,2'-diphenyl-1-picrylhydrazyl (DPPH) assay to show the antioxidant activities of extracts specially for preventing oxidative hemolysis of human erythrocytes induced by 2,2-azobis (2-amidinopropane)-dihydrochloride (AAPH). There was a lag time of 2 h, due to endogenous antioxidants of erythrocytes. The IC_{50} values of peel and pulp extracts were 695 and 652 mg/ml, respectively, which were observed after 3 h of incubation. The group used radical scavenging activities of ascorbic acid and 5-O-caffeoylquinic acid as reference compounds. The EC_{50} values for seed, peel and pulp were 12.2, 0.8 and 0.6 mg/ml of methanolic extract, respectively [74]. The EC_{50} value of seed extract in this study was higher than that of a previous work (2 µg/ml) in [87]. This observation could be due to natural variability, maturity stage of the fruits and edapho-climatic conditions [19]. The EC_{50} values of free radical scavenging activities of ascorbic acid and 5-O-caffeoylquinic acid were 8.1 and 15.1 µg/ml, respectively. Considering the total caffeoylquinic acid contents of the extracts, that is, 0.8, 2.6 and 1.5 µg/ml, for seed, peel and pulp, respectively. Peel and pulp extracts showed similar DPPH free radical scavenging activities (EC_{50} of 0.8 and 0.6 mg/ml, respectively), while seed extract presented much lower antioxidant potential (EC_{50} of 12.2 mg/ml). So, under the oxidative action of AAPH, pulp and peel extracts showed significant antioxidant ability and protection of the erythrocyte membrane from hemolysis greater than seed extract, in a time- and concentration-dependent manner. The antiradical activities of the extracts were much higher than standard antioxidants, possibly due to additive and synergistic effects of pheytochemicals. The total caffeoylquinic acid contents of the extracts were correlated ($r = 0.989$) with the antioxidant activities. The correlation coefficient of total phenolic compounds with the antioxidant activity was 0.913 which supports the previous hypothesis in [41] dealing with the more responsibilities of caffeic acid derivatives for antioxidant activity of Quince fruit [74].

Papp *et al.* (2013) compared phenolic profile and antioxidant potential of Quince peel and fruit of 12 different cultivars and inferred that fruit is a rich source of phenolics with strong antioxidant activity. The cultivars such as "Champion", "De Husi", and "Konstantina polyi" were found best for scavenging free radicals. The analysis of phenolic contents of aqueous alcoholic extracts using Folin–Ciocalteu reagent depicted appreciable amounts of phenolics (8.55 mg GAE/g FW) in fruit [88]. Similarly, antioxidant potential of Tunisian Quince fruit peel and pulp predicted that peel has higher radical scavenging activity than pulp. The radical scavenging potential of the extracts was determined and compared with that of synthetic antioxidants. The stronger properties corresponded to those obtained from peel material with a 70-80% inhibitory effect on DPPH radicals [42]. Alesiani *et al.* (2010) tested the DPPH radical-scavenging capacity, superoxide radical-scavenging activity, and total antioxidant capacity of 59 isolated phytochemicals from Quince peels. The most active antioxidants were quercetin and quercetin 3-O-rutinoside [89].

Costa *et al.* (2009) evaluated the antioxidant and anti-hemolytic potential of Quince leaf methanolic extract using three different assays (Folin-Ciocalteu reducing capacity; the ability to quench the stable free radical 2,2'-diphenyl-1-picrylhydrazyl (DPPH); and the ability to inhibit the 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH)-induced oxidative hemolysis of human erythrocytes) and compared the results with those of green tea extract [76]. In this study, phenolic profile of Quince leaf was evaluated using HPLC/UV showing 5-*O*-caffeoylquinic acid as its major component. The results of Folin-Ciocalteu test on the

reducing capacity of methanolic extracts of 12 Quince leaf samples collected from different places in northern and central parts of Portugal in June and October of 2008 with the mean value of 227.8 ± 34.9 g of 5-O-caffeoylquinic acid/kg dry leaf which was more than that of green tea with the mean value of 112.5 ± 1.5 g of 5-O-caffeoyl Quince acid/kg dry leaf. So, major phenolic compound 5-O-caffeoylquinic acid in Quince leaf extract caused significantly higher reducing power than green tea and leads it to act as defensive or therapeutic agent against radicals. In the second set of experiments, DPPH free radical scavenging activity of Quince leaf and green tea methanolic extracts were investigated and the EC_{50} mean value of 21.6 ± 3.5 and 12.7 ± 0.1 µg/ml were found, respectively. The difference was statistically significant ($p<0.005$) revealing that the leaf extract of Quince exhibited comparable ability to

reduce DPPH free radicals with that of green tea with half maximal effective concentrations. Considering high phenolic content of Quince leaf in comparison with peel, pulp and seed, more antioxidant activity of leaf (EC_{50} of 21.6 µg/ml) is expected in which the EC_{50} values were 600, 1700 and 2000 µg/ml, respectively for peel, pulp and seed. Anti-hemolytic activity of Quince leaf was also compared with that of green tea. Both methanolic extracts significantly protected the erythrocytes from hemolysis induced by AAPH as dose dependant manner after a lag time of 2 h. The IC_{50} mean values were 30.7 ± 6.7 and 24.3 ± 9.6 µg/ml, respectively for Quince leaf and green tea extracts in which statistically no significant difference was observed ($p>0.25$) [76]. Moreover, in another study, the quantitative assessment of TPC was found to be 235.66 GAE/g (gallic acid equivalent) and 17.6 QE/g (quercitin equivalent) in methanolic extract of Quince leaves. The antioxidant capacity of Quince leaf extract (IC_{50} = 36.5 µg/mL) was found almost similar to standard with BHT (38.4 µg/mL) [90].

The antioxidant effects of lipophilic Quince Wax Extract (QWE) and a Quince Aqueous Fermented Extract (QAFE) were also studied including their radical scavenging and reductive power as well as their anti-lipoperoxidative properties. QAFE effectively scavenged DPPH free radicals (ID_{50} = 68.8 µg/ml) and successfully prevented the formation of thiobarbituric acid reactive species at very low concentration (ID_{50} = 73.7 µg/ml). However, QWE was more effective than QAFE at preventing the production of superoxide radicals (ID_{50} = 48.9 µg/ml) [91].

Total phenolic compounds of Quince seed was reported as 104.35 mg/g dry seed and the antioxidant activity of 64.25% for scavenging of DPPH free radicals [92]. Hamauzu *et al*. (2005) measured total phenolic content of Quince fruit by Folin-Ciocalteu method resulting 302 mg/100 g which was five times more than that of apple fruit (61 mg/100 g), and higher than a previous report in [87], in which the mean value of 26.8 mg/100 g was reported, probably because of different extraction procedures employed in these works [93]. They reported the IC_{50} of 12.1 for the antioxidant activity for SDS/LHAAPH system and EC_{50} of 7.5 for DPPH radical scavenging activity of Quince fruit. Quince fruit extract at the concentration of 0.5 mg/ml inactivates the influenza viruses, most probably because of the existence of procyanidins. The antioxidant functions of Quince phenolic extracts were superior to that of chlorogenic acid and ascorbic acid, evaluated in both the linoleic acid peroxidation system and the DPPH radical scavenging system [93].

Antimicrobial, Antibacterial and Antifungal Effects

The resistance of microorganisms to antibiotics urges the researchers to discover new phytomedicines from plants which have been used traditionally for curing different ailments [94] [95] [96] [97]. In one such attempt regarding a common pathogenic bacterial strain, the *in vitro* anti-*Helicobacter pylori* activity of 33 substances, juices and plant extracts and 35 of their combinations including Quince juice (10%) were tested using an agar diffusion method on Columbia blood agar media (ZOI 11 mm). A synergistic effect in antibacterial activity of Quince juice was observed with bilberry, cranberry juice, black choke berry, red currant juice, green tea, and sweet flag rhizome. Quince juice demonstrated the strongest anti-*H. pylori* activity followed by cranberry juice [98]. Acetone and aqueous extracts of Quince fruit peel and pulp depicted antimicrobial activity due to presence of chlorogenic acid 5-*O*-caffeoylquinic along with other phenolic components. Quince peel extract was the most active one and showed significant decrease in bacteria growth with minimum inhibitory and bactericide concentrations in the range of 102-5 x 10^3 µg polyphenol/ml. It appeared that chlorogenic acid is regarded as the major component acting in synergism with other components of the extracts to exhibit their total antimicrobial activities [42]. Anti-influenza viral activities of Quince fruits' phenolic extract was also studied and showed on the hemagglutination inhibition test [93].

The antibacterial effects of Quince fruit and seeds' ethanolic, acetonic and aquatic extracts were also studied on some dermatic bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Quince seeds extracts showed more antibacterial effects compared with Quince fruit ones and ethanolic extract of Quince seeds was the most effective extract. However, the aquatic extracts didn't show any antibacterial effects [99]. After that, these extracts were studied on bacteria *Escherichia coli*, *Klebsiella pneumonia*, *S. aureus*, and *Enterobacters aerogenes*. Similarly, the results showed that the ethanolic extract of seeds was the most efficient one while, aqueous extracts were the least effective ones in preventing the growth of bacteria. Moreover, *E. coli* was the most sensitive bacterium to the extracts, and aqueous extracts only showed antimicrobial effects against *E. aerogenes* [100]. Moreover, the antifungal effects of Quince leaves' ethanolic and acetonic extracts against *Aspergillus niger* were studied. The results showed that the Quince extracts inhibited the growth of *A. niger* while ethanolic extract was more effective than acetonic ones [101]. A similar study also conducted by Alizadeh et al. (2014) to evaluate antifungal effects of Quince leaf's extracts [102].

In another study, the ethanolic extract of Quince seeds was dissolved in dimethylsulfoxide (DMSO) to obtain the final concentrations of 500, 250, and 125 mg/ml, and the agar well diffusion method was used to determine antibacterial activity of the extract. Six millimeter diameter wells were punched in to the agar and filled with 0.1 ml of each extract. Solvents were used as negative control. The extract exhibited antibacterial activity against *S. aureus* (ZOI 12 mm) at 500 mg/ml (sensitive to all concentrations while the sensitivity increased directly with increasing the concentration), *S. epidermidis* (ZOI 15 mm) at 500 mg/ml and *K. pneumonia* (ZOI 8 mm) at 250 mg/ml concentrations. *E. coli* and *Moraxella* were resistant to this ethanolic extract [103]. Zsivanovits *et al.* (2013) investigated antibacterial effects of Quince fruit variety *Konstantina polyi* extract, against foodborn pathogenic bacteria strains *S. aureus*, using rapid automated bacterial impedance technique (RABIT) [104]. The basic principle involved in this technique is to assess the changes in electrolyte composition of nutrient media by growing bacteria [105]. The inhibition in growth of *S. aureus* by Quince fruit extract was assessed comparing integrated area under impedimetric growth curves in different medias i.e. culture media containing only distilled water, culture media containing citric acid and distilled water, and culture media containing Quince fruit extract that were found to be 1,256,014.0 ± 56,474.4, 1,005,672.0 ± 32,851.3, and 800,389.5 ± 137.9, respectively, clearly showing antibacterial activity of Quince fruit extract [104].

The antimicrobial activity of Quince leaves extracts against different microorganism strains was also investigated. In a study, it was performed by diffusion method in dishes with disks embedded at the concentrations of 100, 200 and 400 mg/ml fruit decoction and crude extract of Quince leaves, against six bacteria. The crude extract of leaves showed antibacterial activity which partially inhibited the growth of *Streptococcus agalactiae* [21].

Effects on Respiratory and Gastrointestinal Disorders

As mentioned before, various parts of Quince plant have been used to cure respiratory disorders such as asthma, cough, and bronchitis [56] [58]. In this regard, the results of Janbaz *et al.* (2013) study showed that the crude extract of Quince seeds produced atropine sensitive spasmodic effects in isolated ileum of guinea-pig and rabbit jejunum preparations. In rabbit jejunum, this extract also showed relaxant activity at slightly higher concentrations (0.1-10 mg/ml). When analyzed on rabbit jejunum pre-contracted with K^+ (80 mM), the plant extract (0.003-10 mg/ml) produced relaxation. A rightward shifting of Ca^{++} dose-response curves along with decline in the maximum response was observed after pretreatment with the extract (0.003-0.01 mg/ml), which was similar to the effect of verapamil. The crude extract of Quince seeds (0.01-10 mg/ml) relaxed carbachol (1 μM) and K^+ (80 mM)-induced contractions of isolated rabbit tracheal preparations, similar to the effect produced by verapamil [106].

Minaiyan *et al.* (2012) attempted to treat IBD by studying the effect of Quince juice (QJ) and Quince hydroalcoholic extract (QHE) on UC induced by TNBS (trinitrobenzene sulfonic acid) in male Wistar rats. Rats were grouped (n = 6) and fasted for 36 h before colitis induction. TNBS was instilled into the colon with a hydroalcoholic carrier and then treatments were made for 5 days starting 6 h after colitis induction, with different doses of QJ (200, 400, 800 mg/kg) and QHE (200, 500 & 800 mg/kg) orally, QJ (400 mg/kg) and QHE (200 and 500 mg/kg) intraperitoneally. Macroscopic and histopathologic assessments revealed that the colon tissue was removed and tissue damages were scored by both QJ and QHE like standard, dexamethasone. Although, the examined doses of QJ and QHE were apparently effective to reduce the extent of UC lesions, only the greatest ones (500 and 800 mg/kg) resulted in significant alleviation. Weight/length ratio as an illustrative of tissue inflammation and extravasation was also diminished with Quince treatments while the results correlated with macroscopic and histopathologic evaluations. These data suggest that QJ and QHE were effective to diminish inflammation and ulcer indices in this murine model of acute colitis [73]. In another study, as reviewing the effective traditional treatments of IBD, Rahimi *et al.* (2010) have introduced Quince fruit and peel *in vitro* [85]. The phenolics like chlorogenic acid and flavonoids such as quercetin, rutin, and kaempferol present in Quince fruit are also helpful to repair the colon damage with IBD due to their antioxidant and anti-inflammatory potential [107] [108] [109] [110].

Quince fruit preparations reduced the gastrointestinal propulsion and inhibited castor oil-induced diarrhoea in mice [33]. Quince fruit also contains pectin in significant amounts which protects colon damage in colitis by triggering colonal cell proliferation [111] [112]. In a double blind clinical study, the effect of Quince syrup in alleviating gastro-esophageal reflux disease (GERD) symptoms in children (5–18 years old) was assessed. Quince syrup and omeprazole was administered orally to children at dose of 0.6 and 1 cc/kg/day in Quince group and omeprazole group, respectively. After 4 and 7 weeks of therapy, age related questionnaires were filled to assess intensity of symptoms, and cumulative symptoms score (CSS) was compared with that of initial base line. A significant reduction of CSS was noticed in Quince group as compared to control group suggesting usefulness of Quince syrup in GERD [113]. Tansaz *et al.* (2013) also observed the effect of antigastro-esophageal reflux of fruit extract of Quince. They have done a pilot study on selected 5 infants who had reflux without any response to routine management. After a month, they observed that the four of 5 infants showed significant changes in the symptoms of reflux such as vomiting, cough, agitation and low appetite. They had soft defecation with the extract, and they concluded that Quince is a good remedy for infant's reflux more probably because of its astringent property, which can reinforce the sphincter and inhibit the reflux [114].

Cardiovascular Effects

Quince has been used in traditional medicine to treat or prevent cardiovascular diseases. In a study, it was observed that ethanolic extract of Quince leaves and fruit at dose of 80 and 160 mg/kg body weight lowered blood pressure after 4 weeks while captopril (25 mg/kg) after 2 weeks.

After 8 weeks, blood pressure was similar in captopril (167 ± 7) and ethanolic extract (166 ± 4) treated rats as compared with model rats (193 ± 7). The effect of aqueous extracts (20, 40, and 80 mg/kg dose) of Quince leaves and fruit increased clotting (1.44, 2.47, and 2.48) and bleeding times (2.17, 2.78, and 3.63) as compared to aspirin (1.91 and 2.58), respectively. The mortality reduction with extracts (27, 40, and 53%) due to pulmonary embolus was promising as compared to aspirin (47%). Thrombolysis was also increased with Quince aqueous extracts (45, 55, and 63%) as compared to aspirin (56%). The results proved the potential use of Quince for prevention of thrombosis and to decrease risks of cardiovascular disorders [115].

The effect of ethanol leaf extracts of Quince (COM) was also studied on hypertension and on biomarkers associated with blood pressure control, such as angiotensin-II (AII), plasma renin activity (PRA), apelin-12 (A), endothelin (ET) and nitric oxide (NO), compared to captopril. Two-kidney one-clip (2K1C) Goldblatt model rats were divided randomly into six groups: sham, model, captopril 25 mg/kg, COM leaf extract 80, 160 and 320 mg/kg. Drugs were administered orally daily for eight weeks. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before treatment and every 2 weeks. Blood and kidney samples were collected after the last treatment to measure AII, PRA, A, ET and NO. Renal hypertensive rats (RHR) had increased blood pressure, AII, A, PRA, ET and decreased NO. Treatment with captopril reduced blood pressure, AII, A, PRA, and ET, though not quite to normal values. COM leaf extracts significantly and dose-dependently reduced blood pressure, AII, A, RA and ET, whereas NO was increased. The effects of COM extracts on blood pressure and biomarkers were dose-dependent and at the highest dose, it produced effects similar to those of captopril [116].

Moreover, the effects of *Cydonia oblonga*. (COM) fruit and leaf extracts on blood pressure and rheology were studied in renal hypertensive rats (RHR). Daily doses of 80 and 160 mg/kg aqueous or ethanol extracts of COM fruit or leaves, or 25 mg/kg captopril were given orally once daily for 8 weeks. Blood pressure was measured before treatment and every 2 weeks thereafter. Blood rheology was tested after 8 weeks. Model rats had higher blood pressure than sham, 8 weeks after the procedure (systolic blood pressure 193 ± 7 vs. 138 ± 8 mmHg, $p < 0.05$). Those treated with captopril had decreased blood pressure within 2 weeks but that did not return to the level found in the sham group at 8 weeks (167 ± 7, $p < 0.05$ vs. model). With the COM extracts, the effect on blood pressure was notable after 4 weeks. At 8 weeks blood pressure was similar with captopril and with 160 mg ethanol leaf extract (166 ± 4, $p < 0.05$ vs. model), it was the most effective of the extracts. Model rats had higher blood viscosity and lower erythrocyte deformability than sham. Captopril had little effect on blood rheology; whereas COM extracts reduced whole blood viscosity and improved erythrocyte deformability to levels approaching those found in sham [117].

Abliz *et al.* (2012) also investigated the antihypertensive effect of Quince on renovascular hypertensive rats. 60 hypertensive rats were randomly divided into 6 groups as model, captopril control, Quince high, medium and low three-doses, and sham operation for 8 weeks. Blood pressure of rats was measured every two weeks, resulting that the Quince and Captopril groups had significantly lower amounts than ($p < 0.05$) the model group; and the Ang II levels of renal tissue in Quince high, medium and low dose groups were lower than the model group ($p < 0.05$) [118]. It was observed in one study that phenolics particularly 5-*O*-caffeoyl quinic acid present in Quince leaves had immense cardio protective potential as it captured ROS [81]. The flavonoids, quercitin, and kaempferol-3-*O*-glucoside (astragalin) and kaempferol-3-*O*-rutinoside in Quince leaves are also cardioprotective [19].

Hypolipidemic and Kidney Protecting Effects

Hypercholesterolemia as a malfunction of glomerulus, which causes renal injury, proteinuria, glumerulosclerosis, and masangial cell damage, can be eliminated using antioxidants [119]. Whereas the renal protective effect of antioxidants as lipid lowering agents in hypercholesterolemia has been well-established in different literatures such as [119] and [120], and Due to the presence of phenolics in Quince fruit and leaves with antioxidant effects, renoprotective potential of Quince leaves decoction in hypercholesterolemic rabbits has been evaluated in white New Zealand male rabbits divided into three groups by Jouyban *et al.* (2011) [79]. Before feeding with normal diet for 6 weeks, group I was fed with high cholesterol diet and group II was administered high cholesterol diet with Quince leaf decoction for 6 weeks whereas group III was treated as control group. After this diet, all animals were shifted to their normal diet for another 6 weeks. At the end of this study (12 weeks), urine samples from all groups were collected and ratio of urine protein to creatinine was calculated. All animals were sacrificed to assess the kidney damage due to high cholesterol diet and observed that Quince leaf decoction has significantly prevented renal injury in hypercholesterolemic rabbits that might be due to antioxidant activity of phenolics present in Quince [79].

Khademi (2009) investigated the effects of hydromethanolic extract of Quince leaf on the lipid profile of rabbits fed with cholestrol enriched diet (2% w/w). Her observations showed that the lipid lowering activity of Quince extract is the same as that of atorvastatin [121]. Khademi *et al*. (2013) studied the comparative effects of atorvastatin and Quince leaf extract on atherosclerosis. The results indicated the lipid-lowering activities of Quince leaf analogous to atorvastatin and it can probably serve as a new possible natural product for atherosclerosis management [122].

In a study, Quince leaf extract successfully reduced level of total cholesterol (TC), low density lipoproteins (LDL), serum triglycerides (TG), liver stenosis and increased high density lipoproteins (HDL) and lipoprotein lipase (LPL). The extract inhibited the activity of ALT, AST and LPS, whereas activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), and hepatic lipase (HL) was increased in hyperlipidemic rats after 56 days of

treatment. The results were comparable with simvastatin except increased LPL and HL Quince leaf extract [123].
The effects of Quince total flavonoids (TF) from leaves and fruit on the blood lipid and antioxidant potentials were studied using hyperlipidaemic rat models. Compared with the hyperlipidaemic model group, TF significantly reduced serum TC, TG, LDL-C ($p < 0.01$), ALT and AST ($p < 0.01$ or $p < 0.05$) and increased HDL-C ($p < 0.05$ or $p < 0.01$). TF also reduced MDA ($p < 0.01$ or $p < 0.01$) (6- 114). Mirmohammadlu *et al.* (2015) demonstrated that Quince fruit aqueous extract successfully reduced total cholesterol level, serum triglycerides, ALT, AST ALP, HDL, LDL, urea, and creatinine in diabetic male rats [83].

Antidiarrheal Effects
Aqueous-methanolic of seeds was studied for its spasmolytic/spasmodic activity in isolated rabbit jejunum and guinea pig ileum. It was observed that seeds extract produced slight prokinetic effect at lower concentrations (0.003–0.03 mg/mL) with EC_{50}-value (0.73 mg/mL) and induced muscle relaxation. Moreover, the extract successfully eliminated the KCl induced smooth muscle spasm in rabbit jejunum (EC_{50} 0.86 mg/mL) similar to that of verapamil, a calcium channel blocker. The plant extract also induced atropine sensitive spasmodic effect on isolated ileum of guinea-pig at concentration of 1–10 mg/mL which is about 31.22 ± 3.7% of control, acetyl choline (0.3 μM). This spasmodic effect is attributed to activation of muscarinic receptors, in the gut by the extract like that of acetyl choline. Thus, Quince extract contains spasmodic constituents that relieve constipation. However, plant extract is needed in slightly higher concentration (1–10 mg/mL) for spasmodic effect than spasmolytic action [106].

Spermatogenesis, Aphrodisiac and Genoprotective Effects
Whereas raised blood cholesterol and serum lipids results in male infertility, the effect of Quince leaves decoction on protection of testes and restoration of spermatogenesis has been studied in hypercholestrolemic rabbits by Ashrafi *et al*. (2013) [124]. Hypercholesterolemia was induced with high cholesterol diet before administering leaf decoction (100 mL) for 12 weeks. The histopathology of testes showed an increase in intertubular connective tissues and thickening of tunica albuginea in all animals of untreated group however histological picture of treated group was comparable with that of control. The mean Johnsen's score of untreated group (4.20 ± 1.92) was also lower than treated (7.33 ± 0.52) and control group (7.05 ± 0.07). The study ended with conclusion that Quince leaves decoction had protective effect on spermatogenesis [124], like administering of lipid-lowering agents to protect the testes and reproductive function during hypercholesterolemia [125] [126].

Aslam and Sial (2014) conducted experiment on Wistar rats. They used hydroalcoholic extract of the fruits of Quince. The purpose of study was to assess the aphrodisiac activity. They observed that after administration of the extract mounting frequency and the mating performance of the rats increased highly significantly. The extract also influenced the behavior of treated animals in comparison to non-treated rats in a notable way, making them more fascinated to females [127].

Mobarakeh *et al.* (2015) evaluated genoprotective potential of aqueous and hydroalcoholic extracts of Quince fruit against genotoxic effect of methyl methane sulfonate (MMS) on human hepatoma cells (HepG2 cells) using comet assay. For this purpose, HepG2 cells were incubated with 100 μM concentration of MMS for 1 h, followed by incubation with Quince extracts (10, 50, 100, and 500 μg/mL) for 2 h. It was revealed that tail length, %DNA contents in tail and tail moment of HepG2 was significantly decreased in both aqueous and hydroalcoholic extracts showing genoprotective effect of Quince fruit [128].

Immunological and Anti-allergic Effects
The effects of the combined *Citrus medica* ssp. Limonum *efructibus*/Quince *efructibus* (each 0.01 g/ml), and separate products of Citrus (0.01 g/ml) and Quince (0.01 g/ml) were investigated on the immunological pathways involved in seasonal allergic rhinitis (SAR). Peripheral blood mononuclear cells (PBMCs) from five healthy and five grass pollen allergic donors were isolated and analyzed *in vitro* after polyclonal and allergen-specific stimulation of T cells in the presence of the three extracts. The analyses demonstrated acceptable cell survival with no signs of toxicity. Citrus mainly had a selective effect on reducing allergen-specific chronic inflammatory (TNF-α; Citrus compared to Quince and Citrus/Quince: −87.4 ($p<0.001$) and −68.0 ($p<0.05$), respectively) and Th2 pathway activity (IL-5; Citrus compared to Quince: −217.8 ($p<0.01$)); while, both Quince and Citrus/Quince mainly affected the induction of the allergen-specific Th1 pathway (IFN-γ; Quince and Citrus/Quince compared to Citrus: 3.8 ($p< 0.01$) and 3.0 ($p<0.01$), respectively). Citrus and cydonia demonstrated different working mechanisms in the treatment of SAR and the combination product did not demonstrate larger effects than the separate preparations [129].

Gencydo®, a combination of Lemon (*Citrus limon*) juice and Quince fruit extract is used traditionally to treat allergic rhinitis or asthma. In a research, it was evaluated for its anti-allergic effects which were reported on the patients earlier by 1- Baars and De Bruin (2005). They observed that Gencydo® caused reduction of histamine, IL-8, and TNF-α release from mast cells induced by Immunoglobulin-E (IgE) and phorbolmyristate acetate (PMA/A23187) in allergic disorders. Furthermore, Gencydo® also blocked eotaxin release from human bronchial epithelial cells. The study supported the use of Gencydo® for the treatment of allergic reactions [52].

In a three-way-crossover study in 18 healthy male and female subjects aged from 20 to 49 years, the influence of a 1% and 3% solution of a standardized composition of *Citrus* Limon succus, and extract from Quince fructus (Gencydo®) on the intranasal mucociliar clearance was investigated after multiple administration. Neither after intranasal administration of the 1% and 3% Citrus/Quince solution nor after placebo solution, was found a

prolongation of the perception time. It could be concluded that there was no measurable influence of the test products on the intranasal ciliar function [130].

Shinomiya *et al*. (2009) investigated the anti-allergic effects of hot-water extract of Quince fruit using *in vivo* and *in vitro* tests. The release of β–hexosaminidase was reduced significantly after addition of 50, 100 and 200 µg/ml of hot-water extract to cell culture without any changes in the proliferation and viability of the cells suggesting the inhibited degranulation process. They studied the development of atopic dermatitis-like skin lesions in mice, serum levels of IgE and the release of β–hexosaminidase from rat basophilic leukemia cell line. The results showed that atopic dermatitis like signs appeared on the face, ear, nose, neck and dorsal skin of mice in control group after three weeks, whereas the severity scores of the signs in Quince treated mice were significantly low. The IgE levels of control and Quince treated animals with 5% hot-water Quince extract orally were 1635 ± 289 and 994 ± 205 ng/ml in which the difference was statistically significant ($P<0.01$). Quince hot-water had an inhibitory effect on type I allergy by suppressing IgE production and IgE-mediated degranulation. These properties are due to presence of low molecular weight polyphenols in Quince fruit [131].

To compare the efficacy and safety of two routes of administration (nasal spray versus subcutaneous injections) of Citrus/Quince in seasonal allergic rhinitis, a randomized comparative clinical trial with two parallel groups was carried out. After a one- or two-week wash-out period, 23 patients were randomized, to a 6-week treatment period and the immunological and symptom severity changes and safety were evaluated. Both routes of administration were safe, they demonstrate immunological and clinical effects, with larger inflammatory and innate immunological effects of the nasal spray route and larger allergen-specific clinical effects of the subcutaneous route [132].

In another study by Kawahara and Iizuka (2011), concentrated and freeze dried of Quince fruit hot water extract was found effective against IgE stimulated late phase allergic reactions of mast cells. The effect of the extract was investigated on IGE-dependent late phase immune reactions of mast cells on a well-established mast cell like model, that is, basophilic leukemia cell line (RBL-2H3). This group showed the effects of the extract on the expression of interleukin-13 and tumor necrosis factor α on RBL-2H3 cells in which the expressions were reduced in a dose-dependent manner. Concerning the findings of Passante *et al.* (2009) in [133] stating that the RBL-2H3 cells are not fully representatives of the mast cells and basophils, Kawahara and Iizuka (2011) also reported the following results of the effects of Quince extract treatment: (1) Suppression of histamine release from mouse bone marrow-derived mast cells (BMMCs) without any change in their proliferation and viability; (2) Significant inhibition of IGE and antigen induced interleukin-13 and tumor necrosis factor α in BMMCs; (3) Alleviating leukoterine C4 release; (4) Lowering porstaglandin D2 levels; (5) Suppression of the expression of cyclooxygenase 2 (COX-2) without any change in COX-1 expression [134].

The anti-allergic properties of preparations from *Citrus medica* Lemon and Quince, used in anti-allergic pharmaceutical products, were investigated. Preparations were analyzed with respect to their impact on the degranulation capacity from basophilic cells as well as mediator release from activated human mast cells *in vitro*, including IL-8 and TNF- α secretion. The results showed that the degranulation of basophilic cells was diminished only in the presence of Citrus, and this effect was compared to the synthetic drug azelastine. Furthermore, Citrus and Quince both inhibited the production of IL-8 and TNF-α from human mast cells, and additive effects were observed at low concentrations [135].

A randomized single blinded placebo controlled study was also conducted to evaluate the effects of combined Unani formulations in allergic rhinitis (Nazla Haar) with special reference to the eosinophils in nasal smear. Forty subjects diagnosed with allergic rhinitis were selected and randomly divided to two groups so that, test group was obtained the decoction of Quince, Zizyphus jujube, Cordia dichotoma with syrup of viola odorata, and the placebo controlled group was obtained sugar syrup orally. The effect of the study was assessed based on the subjective parameters (rhinorrhoea, sneezing, nasal congestion, itchy nose, mouth or throat, lacrimation, post nasal drip and headache) in three follow ups and the objective parameter nasal smear for eosinophils (NSFE) at baseline and at the end of the treatment. The test group showed a significant improvement in reducing the number of eosinophils in allergic rhinitis patients as compared to the placebo group [136] [137].

Anti-inflammatory Effects

The anti-inflammatory effect of polyphenolic extract from the Tunisian Quince was investigated. Lipopolysaccharide (LPS) treatment of human THP-1-derived macrophages stimulated secretion of the pro-inflammatory cytokine TNF-α and the chemokine IL-8. Quince peel polyphenolic extract inhibited these changes in a dose-dependent manner. Concomitantly, Quince polyphenols enhanced the level of the anti-inflammatory cytokine IL-10 as well as IL-6 secreted by LPS-treated macrophages. The increase in IL-6 secretion that occurred when Quince polyphenols were associated with LPS treatment was partially responsible for the polyphenols-mediated inhibition of TNF-α secretion. Biochemical analysis showed that Quince polyphenols extract inhibited the LPS-mediated activation of three major cellular pro-inflammatory effectors, nuclear factor-kappa B (NF-κB), p38MAPK and Akt [138]. Anti-inflammatory activity of Quince leaf ethanolic extract was also reported by Ahmed and Bastawy (2014) [139]. Ethanolic extract of Quince leaves was administered orally at concentrations of 25, 50, and 100 mg/kg 1 h prior to topical administration of arachidonic acid (2%) to each ear and 0.1 mL of carrageenan injection to sub-planer region of paw for induction of paw edema. Quince leaf extract effectively alleviated symptoms of carrageenan induced paw edema and arachidonic acid induced ear edema in rats [139].

Wound Healing Effects

Traditionally, Quince seeds mucilage has been used as folk remedy for wound healing [140]. The effect of Quince seed mucilage on proliferation of human skin fibro blasts was evaluated by Ghafourian *et al*. (2015) to study the mechanism of wound healing. Different concentrations (50, 100, 200, 400 µg/mL) of mucilage were applied to human skin line culture and effect of mucilage was observed after 12, 24, 48, and 72 h. The investigations cleared that Quince mucilage geared up proliferation of human skin fibroblasts after 48 h even at low concentration (50 µg/mL) as studied using microculturetetrazolium assay [59]. In another study, evaluation of ethanolic extract of Quince seeds for healing second degree burn wounds was carried out on mice showing that 1% ointment of Quince seed extract produced 99.5% of wound healing as compared to sulfadiazine standard (92.97%) [141]. Similarly, Quince seeds methanolic and acetonic extracts, and silver nanoparticles of mucilage were found effective against wounds infected with *S. aureus* [100]. The effectiveness of Quince seeds mucilage for skin wound healing has also been justified applying 5, 10, and 20% Quince seeds mucilage cream (QMC) in eucerin base on skin wounds of white Iranian rabbits. QMC (20%) cream healed wounds completely in 13 day treatment [142]. Dermal patches of Quince mucilage were prepared and evaluated for mechanical, microstructural, antioxidant, anti-bacterial, physical, and thermal parameters by incorporation of 1, 1.5, and 2% v/v oregano essential oils [143]. Fekri *et al*. (2008) analyzed moisture content, percentage yield, proteins, and ash contents of mucilage. The moisture content, percentage yield, proteins, and ash contents were found to be 4.38, 10.97, 20.9, and 8.24%, respectively [144]. Wound healing activity of Quince leaves was also shown by Sabale *et al*. (2012) [145]. In a double blind clinical trial, Mousavi *et al*. (2006) reported effective topical wound healing containing Quince seed mucilage 10% for 34 patients referred to dermatology clinic for benign lesions to biopsy or surgery [146].

Hemmati *et al*. (2012) investigated the healing effect of Quince seed mucilage on the skin lesions induced by T-2 toxin. The rabbits were divided into five groups; group 1: receiving the poison as positive control, group 2: receiving eucerin as negative control, groups 3 to 5: receiving 5, 10, and 15% mucilage treatment. A solution of T-2 toxin (83 mg/ml) in methanol was prepared and 12 µl were applied on skin twice with 24 h interval. On the day eight, erythema and inflammation were observed in groups 1, 2 and 3, but the complete healing of the skin damage by 10 and 15% guince seed (groups 4 and 5) was observed and normal skin with grown hairs was the outcome of treatment with Quince seed mucilage. They proposed the following possible mechanisms of healing effects of Quince seed mucilage: (1) preventing impaired protein synthesis by T-2 toxin; (2) acting as a hindrance between T-2 toxin and skin along with dropping water evaporation; (3) acting as antioxidant and growth factor; (4) affecting fibroblast activities and enhancing collagen production; (5) enabling the construction of granulation tissue and promoting blood circulation; (6) counter balancing dermal toxicity of the toxin [75].

Anti-proliferative and Anticancer Effects

The anti-proliferative properties of Quince leaf and fruit (pulp, peel, and seed) was investigated against human kidney and colon cancer cells. Quince leaf and fruit extracts exhibited distinctive anti-proliferative activities. The extracts from Quince leaf showed concentration-dependent growth inhibitory activity toward human colon cancer cells (IC_{50} = 239.7 ± 43.2 microg/ml), while no effect was observed in renal adenocarcinoma cells. The seed extracts exhibited no effect on colon cancer cell growth, whereas a strong anti-proliferative efficiency against renal cancer cells was observed for the highest concentration assayed (500 microg/ml) [78]. This is a valuable finding since renal cell carcinoma is highly resistant against current chemotherapeutic agents [147]. Moreover the cytotoxic effects of lipophilic Quince wax extract (QWE) and an aqueous fermented one (QAFE) against human HepG2, A549, and HeLa cell lines were evaluated. The two preparations exerted a different effect on the proliferation of the three tested cell lines. Noteworthy, QAFE was almost always more active than QWE but, sometimes, its effects seemed to be strongly dependent on exposure time [91]. Alesiani *et al*. (2010) investigated the anti-proliferative activities of the isolated phytochemicals from Quince peels against murine melanoma B16-F1 cells in which the most active phytochemical to inhibit the growth of melanoma cells was ursolic acid with the IC_{50} of 10.2 µM [89].

UV Protective Effects

The putative role of Quince (*Cydonia oblonga*) leaf extract in protection and/or alleviation of the negative impacts of UVA on some biochemical and hematological variables was studied in economically important African catfish. A significant ($p<0.05$) decrease in the red blood cell counts, hemoglobin and hematocrit were recorded in the groups exposed to UVA compared to the control groups. Exposure to UVA induced marked red cell shrinkage (increased mean cell hemoglobin concentration) and showed an elevation in mean cell volume and mean cell hemoglobin in the blood of the exposed fish compared to the control. A significant ($p<0.05$) reduction in the total white blood cells was also recorded in the exposed fish compared to the control. The biochemical parameters (blood glucose, total plasma protein, blood cholesterol, plasma creatinine, aspartic amino transferase and alanine amino transferase) were also exhibited a significant increase in the blood of fish exposed to UVA. Methanolic extract of Quince leaf before ripening of the fruits had the ability to prevent hematotoxic stress induced by UVA and resulted in enhancement of the immune system of catfish represented by significant ($p<0.05$) increase in the number of white blood cells and lymphocytes of the catfish. Quince extract also protected the red blood cells and biochemical parameters from UVA effects [38].

Toxic and Side Effects

Health risks or side effects following the proper administration of designated therapeutic dosages of Quince plant have not ever been recorded. However, because Quince mucilage is prepared from the whole seeds, and/or

the whole seeds are taken internally, the cyanogenic glycosides such as amygdalin and prunasin are credited with a slight toxicological relevance. Large quantity of Quince fruit seeds are dangerous to ingest, especially in case of breast-feeding, because the seeds have nitriles, which are commonly present in seeds of the *Rosaceae*. In stomach, the enzymes and stomach acid both hydrolyze nitriles and ultimately produce hydrogen cyanide which is a poisonous volatile gas and the seeds are prone to be toxic if excess amount is consumed [32] [33].

CONCLUSION:

Since ancient times, different parts of *Cydonia oblonga* Mill., have been traditionally used to treat a spread spectrum of diseases. Recent scientific studies about the pharmacology and chemistry of this plant have proven the presence of many beneficial compounds and the claims of traditional system of medicine for this plant via *in vivo* and *in vitro* tests. This plant is an excellent and inexpensive natural resource of metabolites with remarkable biological properties which possesses significant medicinal and ethnobotanical uses. Whereas, chemical and synthetic compounds have many demerits and side effects, more clinical researches are needed to explore its medicinal effects in order to introduce its different compounds as standard drugs for various disorders and diseases.

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The Authors announce that they have no conflict of interest.

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