Almond as a Nutraceutical and Therapeutic agent in Persian Medicine and Modern Phytotherapy: A narrative review

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Abstract:

Sweet almond (*Prunus dulcis* (Mill.) D.A.Webb) is a known nut, which has long been used in several ethno-medical systems, especially in Persian medicine (PM) for its nutritional and therapeutic activities. In this study, we aimed to provide a summary on traditional uses, phytochemistry and pharmacological activities of sweet almond. Thus, we reviewed textbooks of PM and electronic literature on traditional medicine. Moreover, the available data on the usage of sweet almond were searched in electronic databases to find articles on its pharmacological properties and phytochemistry. According to phytochemical investigations, this plant contains macronutrients, micronutrients, essential oils, various phenolic compounds and phytosterols. Current pharmacological studies represent that *Prunus dulcis* has several biological activities including pre-biotic, anti-microbial, antioxidant, anti-inflammatory, anti-cancer, hepatoprotective, cardiometabolic protection, nootropic, anxiolytic, sedative-hypnotic and nervous-improving effects. Further clinical trials and meta-analysis are required to draw a definitive conclusion on the efficacy and therapeutic activities of almond.

KEYWORDS: *Prunus dulcis*, Almond, Nutraceutical, Medicinal plant, Persian medicine, Phytotherapy

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PM, Persian medicine; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; BDNF, brain-derived neurotrophic factor; PPG, postprandial glucose; GLP-1, glycoprotein-1; BMI, body mass index; FBS, fasting blood sugar; apo B, apolipoprotein B; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; ACF, aberrant crypt foci; CRP, C-reactive protein; IL-6, interleukin-6; CCl4, carbon tetrachloride; GABA, Gamma-aminobutyric acid

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1. Introduction

Nutraceuticals are defined as foods or parts of food with medicinal properties that can play an important role in health promotion and disease prevention. In recent years, these food compounds have attracted a great deal of attention because of their safety, nutritional and therapeutic effects (Nasri, Baradaran, Shirzad, & Rafieian-Kopaei, 2014). They can be categorized based on their chemical compositions including terpenoids, phenolic substances, fatty acids and structural lipids, carbohydrates, amino acid-based substances, microbes, and minerals (Keservani et al., 2010). Nuts as a nutraceutical are nutritious healthy foods, which are widely used along due to their medicinal properties. They contain several beneficial compositions, including fats, proteins, and carbohydrates. Nuts are a rich source of certain minerals, vitamins, dietary fiber, nutrient and non-nutrient antioxidants which have therapeutic effects. A number of pharmacological and clinical studies have shown that regular nut consumption can reduce the risk of several diseases in humans (Lamuel-Raventos & Onge, 2017; Rocchetti et al., 2019; Sheorey, Sengupta, & Hinge, 2011).

The name "tree nuts" is referred to dry, edible, one-seeded fruits enclosed in hard outer covering such as almond, walnut and hazelnut (Rusu, Gheldiu, Mocan, Vlase, & Popa, 2018). *Prunus dulcis*, also known as almond or sweet almond, is a well-known tree nut, which belongs to the Rosaceae family (Barreca et al., 2020). According to "The Plant List" *Prunus dulcis* (Mill.) D.A.Webb is considered the only accepted name of the plant, with several synonyms including *Prunus amygdalus* Batsch., *Amygdalus dulcis* Mill., *Amygdalus communis* L., *Prunus amygdalus* var. *dulcis* (Borkh. ex DC.) Koehne and etc. (The Plant List, 2010). Almond and its related species are indigenous to the Mediterranean climate region of the Middle East. Traditional regions of almond cultivation are located around the Mediterranean Sea and southwest Asia in addition to Southwestern Russia and Ukraine, Caucasus, Middle Asia, and Himalaya. Latter it is introduced into North and South America, South Africa and Australia, and was distributed in more than 60 countries (Chalak, 2013). The almond grows in the dry mountainous and desert regions of Central Asia and the Middle East, particularly in Iran. It is cultivated in many countries and top six almond producers in the world are United States, Spain, Iran, Morocco, Turkey and Italy, in ranking order (Simsek et al., 2018; M Zeinalabedini, Khayam-Nekoui, Grigorian, Gradziel, & Martínez-Gómez, 2010). (Figure 1)

Please insert Figure 1 here

Almond tree is a medium-sized one, rarely up to 12 m long, with pale red branches, and its leaves are rectangular. It has aromatic flowers, 19-20 mm long, with light pink to white color. The almond tree starts bearing fruit after three to four years. Almond's fruit has 3.5–4.6 cm long and 2.5-3 cm width (Gruenwald, Brendler, & Jaenicke, 2007) which has four parts: the inner part is kernel or meat, the second part is brown thin cover called the seed coat or almond skin, the third one is the middle shell and the last one is outer shell or almond hull. Among these parts, the kernel has the most nutritional importance. Almond has two types of taste: bitter and sweet. The edible part of the almond is the popular nut, which is considered as enriched nutraceutical food (Frison & Sporns, 2002). It is used in some processed foods such as cookies, cakes, and snack food (Esfahlan, Jamei, & Esfahlan, 2010).

Medicinal uses of *Prunus dulcis* back to ancient times, which its various medicinal purposes are described in traditional and folklore medicine of different countries in details. In Persian medicine (PM) textbooks, almond was known as "*Lawz*" or "*Badam*". In some other countries such as Turkey, India, Afghanistan, Pakistan, and Tajikistan, "*Badam*" is also the common name for this plant (Mehrshad Zeinalabedini, Sohrabi, Nikoumanesh, Imani, & Mardi, 2012). According to the PM literature, almond has been used for the treatment of some brain disorders, respiratory and urinary tract problems (Rhazes, 2005; Avicenna, 2005). Additionally, modern pharmacological studies represent that *Prunus dulcis* has several biological activities, including pre-biotic, antimicrobial, antioxidant, anti-inflammatory, anticancer, laxative, hepatoprotective, cardiometabolic protection, nootropic, anxiolytic, sedative, hypnotic, and nervous-improving effects (Chen, Lapsley, & Blumberg, 2006).
In the present study, we aimed to review pharmacological activities, safety, adverse events and clinical applications of sweet almond as a nutraceutical and therapeutic agent based on both PM and modern phytotherapy. This information may shed light on beneficial approaches in designing future clinical trials.

2. Methods

In this review, we surveyed the most famous ancient PM textbooks such as *Al-Qānūn fī al-Tibb* (The Canon of Medicine) by Avicenna, *Al-Hawi fi al-Tibb* by Rhazes and the most comprehensive traditional medicine pharmacopeias e.g., *Makhzan al-Adviah, Al-Shamil fi al-Sina'a al-Tibbiya* and *Tohfah al-Momenin*, and also published literature, according to the keywords of "*Lawz*" or "*Badam*" to find traditional uses and medicinal properties of almond. Moreover, electronic databases including PubMed, Scopus, Google Scholar, and Web of Science were searched for studies evaluating the phytochemical components, pharmacological activity and therapeutic uses of sweet almond. Data were collected with a focus on review articles, *in vivo* and *in vitro* studies. The keywords included: "almond", "sweet almond", "almond seeds", "*Prunus dulcis*", and "*Prunus amygdalus*". The results were reviewed and concluded in this paper.

3. Results and Discussion

3.1. Bioactive compounds of almond

Several compounds have been identified in sweet almond, which are comprised of phytochemical groups such as macronutrients (fat, protein and carbohydrate), micronutrients (minerals and vitamins), essential oils and phytochemicals like various polyphenols. Table 1 and 2 provide a summary of the nutrients and bioactive compounds of almond. Chemical structures of the major phytochemicals that have been isolated from *Prunus dulcis* are shown in Figure 2.

3.1.1. Fat and fatty acid content of almond

Nutritionally, lipids are the major ingredients in almond and make up more than 50% of the dry weight of the kernels. Almond lipids are consist of monounsaturated fatty acids (MUFAs) mainly oleic acid (ω9) 62%, polyunsaturated fatty acids (PUFAs) mainly linoleic acid (ω6) 24%, and saturated fatty acids i.e., palmitic acid, stearic acids and arachidic acid (Zhu, Wilkinson, & Wirthensohn, 2015). These healthy fats can prevent constriction of blood vessels and reduce blood cholesterol levels and hypertension (Venkatachalam & Sathe, 2006).

3.1.2. Proteins and amino acids

After lipids, proteins are the major chemical components of almond. The main proteins in almond are globulin and albumin. Almond is a rich source of amino acids, which build the structure of proteins (Alasalvar & Shahidi, 2008). Leucine, phenylalanine, and tyrosine (as essential amino acids), glutamic acid, arginine, and aspartic acid (as non-essential amino acids) are found in almond (Yada, Lapsley, & Huang, 2011).

3.1.3. Minerals nutrient

Similar to other plants, the mineral content of almond can be altered by many environmental factors and agronomic practices (Yada et al., 2011). Calcium, copper, iron, magnesium, manganese, potassium, phosphorus, selenium, sodium and zinc are the mineral elements of almond (United States Department of Agriculture, 2016). The calcium content of almond is higher than other nuts. The magnesium in almond plays an important role in decreasing blood pressure by maintaining a balance of calcium and potassium. Copper plays a key role in hematopoiesis. The selenium prevents cell damage by producing selenoproteins as antioxidant enzymes (Alasalvar & Shahidi, 2009). In fact, owing to these components, almond plays an important role in the regulation of blood pressure, bone and teeth development, nerve stimulation growth, the activity of sex hormones and muscles' function (Yada, Lapsley, & Huang, 2011).

3.1.4. Vitamins

Almond is a good source of different types of B-complex vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6) and folate. In addition, almond is one of the richest sources of vitamin E. The alpha, beta, gamma and delta-tocopherol and tocotrienol are eight forms of vitamin E. Alpha (α) tocopherol is the major form of tocopherol found in almond (Ahmad, 2010; Çelik et al., 2019)**.** Owing to the antioxidant activity of vitamin E, it has an effective role in the prevention and treatment of different disease (Rizvi, Raza, Faizal Ahmed, Abbas, & Mahdi, 2014)**.**

3.1.5. Phenolic compounds

Prunus dulcis is a source of polyphenols and phytosterols. Almond's polyphenols are mainly concentrated in the skin. After consumption of almond, its polyphenols are recognized as xenobiotics are degraded by body tissues and gut microbiota; therefore, polyphenols have less bioavailability than almond's macronutrients (Garrido et al., 2010; Manach, Scalbert, Morand,

Rémésy, & Jiménez, 2004). Studies have shown that polyphenols have protective effects against diseases such as cardiovascular diseases, diabetes mellitus, cancer, osteoporosis, neurodegenerative diseases, and aging (Graf, Milbury, & Blumberg, 2005). Polyphenols of almond consist of phenolic acids (caffeic acid, ferulic acid, P-coumaric acid and Vanillic acid), flavonoids (anthocyanidins, isoflavones, flavonols, flavanols, flavanones), stilbenes, lignans, hydrolysable tannins, condensed tannins or proanthocyanidins and phytoestrogens. Almost 130 different polyphenols have been identified in almond. Among these components, tannins and flavonoids are the most biologically active components (Alasalvar & Shahidi, 2008; Bolling, 2017; United States Department of Agriculture, 2016).

The condensed tannins which known as proanthocyanidins, are the most abundant class of polyphenols in this nut. Almond proanthocyanidins consist of mainly (−)-epicatechin and (+)-catechin, with lower amounts of (−)-epiafzelechin. Almond interflavan bonding is B- and A-type but seems to be mainly B-type. B-type interflavan bonding has carbon–carbon bonds at C4→C6 or C4→C8. A-type bond is either C2→C7 with either C4→ C6 or C4→ C8, or C2→ C5 with C4→C6 bonds. In addition to almond proanthocyanidin polymers, B-type (procyanidin B1, B2, B3, B5, B7) and A-type dimers, B-type oligomers, and mixed B-/A-type oligomers have also been identified. (Pérez-Jiménez & Torres, 2012). Stilbenes is found in almond's meat and skin but has mainly accumulated in almond's skin. Resveratrol-3-β-glucoside (Polydatin) has been identified in almond's skin (7.19–8.52 μg per100 g of almond). Piceatannol + oxyresveratrol was recognized in almond blanch water (0.19–2.55 μg per100 g of almond) (Xie & Bolling, 2014). Gallotannins, ellagitannins, and phlrotannins are hydrolysable tannins in almond. Because these components are hydrolyzed, they can release gallic acid, ellagic acid, and phloroglucinol. Lignans are a small class of almond's polyphenols. Socoisolariciresinol lariciresinol >cyclolariciresinol _ (+)-pinoresinol > (+)-sesamin > (+)-syringaresinol > (−)-7-hydroxymatairesinol > (−) matairesinol_7 hydroxysecoisolariciresinol are the components of this class, which are isolated by hydrolytic method (Kuhnle et al., 2008). Flavonols, anthocyanins (cyanidins), flavanols, flavanones and flavan 3-ols are the identified flavonoids in almond. Among these, flavonols are the most abundant class (from 87 to 135 mg per 100 g of almond). This group includes kaempferol, quercetin, isorhamnetin and their 3-*O*-glucosides, rutinosides, galactosides and morin. Flavan 3-ols include (+)-Catechin, dihydrocaffeamperfrol, and (−)-epicatechin are more abundant. Biodicrochroxetine, galucatacin gallate, epicycin galactose and epicatchin glycoses has less abundance. Main flavanones of almond are Naringenin and its 7-*O*-glucoside, derivatives in whole almond and eridicytol-7-*O*-glucoside mainly exist in almond skin and blanch water (~3 mg per 100 g of almond).

Hydroxycinnamic acids, chlorogenic acid, hydroxybenzoic acids, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, ferulic acid, 5-hydroxybenzoic acid, caffeic acid, neochlorogenic acid, sinapic acid and cryptochlorogenic acid are some of the known phenolic acids in almond (ranging from 5 to 12 mg per 100 g of almond) (Barreca et al., 2020; Milbury, Chen, Dolnikowski, & Blumberg, 2006). Biochanin A is the most abundant (~25 μg per 100 g of almond) and genistein, daidzein, glycitein and formononetin are the isoflavones that derivative of almond, which were identified by high-performance liquid chromatography-mass spectrometry (HPLC-MS) and gas chromatography-mass spectrometry (GCMS) (Mandalari et al., 2010).

3.1.6. Carbohydrates

Carbohydrates of almond are classified into two categories, including digestible and indigestible. The sugars, starch polysaccharides and some sugar alcohols are digestible and can provide a source of energy. Non-starch polysaccharides, which are known as dietary fiber, are indigestible but have beneficial effects on human health (Mandalari et al., 2010; Yada et al., 2011).

Please insert Figure 2 here

3.2. Nutritional functions

Nutrients are compounds in dietary sources, which are essential to health and growth. There are six major essential nutrients, including proteins, lipids, carbohydrates, vitamins, minerals and water. Among them, carbohydrates, lipids, proteins and water are categorized as macronutrients, which are needed in a larger amount for the body. Vitamins and minerals, as micronutrients, are needed in small doses. Nuts are known as rich sources of nutrients with health benefits and have been a part of the daily diet worldwide since thousands of years ago (Musa-Veloso, Paulionis, Poon, & Lee, 2016). Almond, as a tree nuts, is a healthy nutrient-dense snack that is a rich source of essential nutrients such as proteins, MUFAs, dietary fibers, vitamins and minerals. Thus almond-rich daily diet can maintain body health and also ameliorate satiety. Almond may modify body adiposity and reduce excess fat depositions. Therefore, almond, as a component of a healthy diet, can supply many essential nutrients and promote health and body function properly (Gama, Wallace, Trueman, & Bai, 2017; St-Onge, Campbell, & RoyChoudhury, 2020). There are various forms of almond snack to be used in the daily diet. Almond's kernel can be consumed as whole, raw, roasted, salted or blanched almond. It can be prepared as almond milk. Almond oil can be also used in edible form. (Dikariyanto, Berry, Francis, Smith, & Hall, 2020). It is shown that one cup of unsweetened almond milk can be used as a substitute for dairy milk, meanwhile, it contains lower calorie and higher levels of trace minerals such as iron and zinc compared with the cow's milk. In addition, nutritional value of almond milk is higher than other plant-based milk products like soy milk (Al Tamimi, 2016; Alozie Yetunde & Udofia, 2015). Moreover, almond can be a good snack because it can make satiety feeling due to its constituents such as fiber, proteins and fats. Researches have shown that almond milk may be an efficacious substitute for children with cow's milk protein allergy due to some active principles (Salpietro et al., 2005).

3.3. Pharmacological effects

3.3.1. Traditional uses of almond in PM textbooks

According to the basic principles of PM, any object in the world is made of quadratic elements: soil, water, fire and air and the combination of these four elements cause different qualities in objects. This specific quality is called temperament "*Midzaj*". Each herb like other objects has a specific temperament. It has been shown that there is a relevance between the temperament of an herb and its major chemical compounds such as phenolic compounds, alkaloids and essential oils. Therefore, each herb performs some particular functions in the body (Ardekani, Rahimi,

Javadi, Abdi, & Khanavi, 2011; Rahimi & Ardekani, 2013). The fruit of the almond tree, which is known as *"Lawz*" in PM, is temperate in hot and cold nature and these features lead to the lowest complications when it is used as a therapeutic agent, therefore, almond is considered as a great nutraceutical also based on PM (Nafis, 2000). In the PM manuscripts, *Prunus dulcis*is is an important nutraceutical and medicinal plant and several therapeutic properties have been claimed for it (Tonkaboni, 2007). In the viewpoint of PM, almond has a tonic effect on the brain and nervous system. Moreover, its tonic effect will increased if is consumed with candy. It is believed that almond can improve all the brain functions. Also, this plant has been reported to be a memory enhancer and has mild sedative activity; therefore, almond has been mostly used for neurological diseases such as amnesia and insomnia and can improve visual acuity (Gorji, Moeini, & Memariani, 2018). Almond has been applied in obstructive diseases of liver and spleen and has analgesic effects. It has also laxative activity. Roasted almond can act as a gastric tonic. Almond's seed milk with sugar has some beneficial properties for respiratory diseases such as cough and may soften the throat by humidifying the respiratory tract. Almond acts as an aperient agent and is useful in intestinal and bladder ulcers and also can relieve dysuria. It produces semen and increases sexual desire (Aghili Khorasani, 2011; Avicenna, 2005). Therapeutic applications of sweet almond in PM literature have shown in Table 3.

3.3.2. Information from modern phytotherapy

Various preclinical and clinical studies also some reviews and meta-analysis have been carried out on pharmacological activities of different parts of almond. We explain the pharmacological effects which have yet noticed in the investigations. Pharmacological activity, main involved compounds, mechanisms of action, experimental model and the dosage related to each activity example were shown in table 4.

3.3.2.1. Antioxidant activity

Several studies have indicated antioxidant and free radical-scavenging activities of almond. Natural antioxidants, including vitamins, minerals, carotenoids and polyphenols are divided into two groups, nutrient (*e.g*. vitamins) and non-nutrient (*e.g*. phenolics) in which non-nutrient ones are stronger than nutrient antioxidants. Almond contains these two antioxidant groups (Alasalvar & Shahidi, 2009). It has been shown that almond is a rich source of phenolic acids and flavonoids. The presence of high contents of phenolic compounds may be attributed to the antioxidant activities (Milbury, Chen, Dolnikowski, & Blumberg, 2006). These compounds, in addition to free radical-scavenging properties, have metal-chelating activities (Wijeratne, Abou-Zaid, & Shahidi, 2006). *In vitro* studies show that the flavonoids in almond provide a high level of cytoprotection against cell death due to oxidative stress (Milbury, Chen, Dolnikowski, & Blumberg, 2006). Moreover, almond consumption has a protective effect on stress-oxidation and DNA damage in smokers (X. Jia et al., 2006).

3.3.2.2. Prebiotic activity

Many aspects of human health are associated to the intestinal microbiota composition and their functions, which include the protection against pathogens, promotion immune homeostasis and responses. These functions have positive effects on the gastrointestinal function and colon health. High dietary quality has a great impact on intestinal microbiota diversity (Mai & Draganov, 2009).

Almond seeds as the main source of prebiotics can increase *Bifidobacteria* and *Eubacterium* populations, which subsequently increase the concentration of butyrate (Rocchetti et al., 2019). Administration of raw and roasted almond to rats can regulate their intestinal microbiome. The underlying mechanisms comprise beneficial bacterial stimulation, harmful bacterial inhibition, modification of bacterial enzymes' activity, and metabolic activity improvement (Z. Liu, Wang, Huang, Zhang, & Ni, 2016).

Almond and its skin consumption increase the activity of β-galactosidase enzyme, which is produced by beneficial colonic bacteria. The impairment of β-galactosidase can interfere with the metabolism of unabsorbed carbohydrates such as those seen in Crohn's disease and ulcerative colitis. Moreover, the prebiotic effects of almond can decrease the activity of harmful enzymes of pathogenic bacteria such as *Clostridium*, *Shigella* and *Veillonella,* which are known as mutagenic and carcinogenic agents (Z. Liu et al., 2014). It has been shown that almond intake can increase butyrate-producing bacteria and enhance positive changes in microbiota such as fungal microbiota (Ukhanova et al., 2014).

Findings of a clinical trial study on healthy adult men and women showed that the use of different types of almond (e.g. natural almond, dry roasted almond, or chopped almond) have different effects on microbial community composition (Holscher, Taylor, Swanson, Novotny, & Baer, 2018). Polysaccharides and polymerized polyphenols seem to have the prebiotic effects. After consumption of the nut like almond, these components reach the colon as intact substrates for colon microbiota. Polysaccharide fermentation process by microbiota produces butyrate, which makes changes in gene expression and regulates the hormonal operation; therefore, they act as the main nuts' product by microbiota. This mechanism can explain some beneficial prebiotic effects of nuts in the human (Lamuel-Raventos & Onge, 2017).

3.3.2.3. Anxiolytic activity

In an animal study, the anxiolytic effects of almond have been evaluated. It has been demonstrated that almond in the daily dose of 1600 mg/kg can reduce stress to the same extent of diazepam (Sahib, 2014). Anti-anxiety effects of almond may result from the presence of flavonoids, phenolic acids and some essential amino acids such as tryptophan. Moreover, dietary flavonoids have been reported as potential for prevention of neurodegenerative disorders (Gul, Saleem, Haleem, & Haleem, 2019; Karim et al., 2018; Sahib, 2014). Lower levels of antioxidant activity, have been reported in people with anxiety and depressed mood; accordingly, antioxidant effects of plants such as almond can improve anxiety and depression. Furthermore, omega-3 fatty acids in almond are also involved in the improvement of anxiety-related disorders (Saki, 2018).

3.3.2.4. Sedative and hypnotic activity

Almond have several therapeutic effects on brain function. Sedative and hypnotic effects of almond have been considered in an animal study. It has been demonstrated that an aqueous extract of almond can be significantly effective in sleep time prolongation and NREM sleep duration. Moreover, those amino acids which are available in almond such as glycine, glutamine, arginine and ornithine can act as an amino acid neurotransmitter; therefore, they play an important role in excitation and inhibition of synapses (Abdollahnejad et al., 2016; Dwivedi, Singh, Malik, & Jawaid, 2012).

A recent study in some students was demonstrated that sweet almond had a significantly impact on reducing insomnia and improving quality of sleep (Ghafarzadeh, Sadeghniiat-Haghighi, Sadeghpour, Akbarpour, & Amini-Behbahani, 2019).

3.3.2.5. Memory and cognition enhancing effects

Several cohort studies have reported that daily nut intake has a prominent effect on cognitive function in older people (Nooyens et al., 2011; O'Brien et al., 2014). The exact mechanism of almond effects on the memory and cognitive performance in human subject is still unclear; however, according to several human and animal studies, there are a few hypotheses which explain these effects (Gorji et al., 2018).

It has been shown that the almond intake can reduce post-lunch dip and improve cognitive ability, especially memory and attention due to the high content of unsaturated fat and low levels of carbohydrates (Dhillon, Tan, & Mattes, 2017).

Some evidence has shown that the brain-derived neurotrophic factor (BDNF) was increased after a nut-enriched diet. This is considered as a potential mechanism of action for improving cognitive and memory disorders; also BDNF deficiency leads to neurodegenerative disorders such as Alzheimer's disease (Sánchez-Villegas et al., 2011).

The use of overnight soaked almond together with vitamin E were effective on improving learning and memory in rodent models. This effect is likely to be further enhanced by the inhibition of acetylcholinesterase in the brain by vitamin E; however, other mechanisms of almond effects on dementia and Alzheimer's disease may be involved (Arslan, Ahmed, & Gilani, 2017; Gorji et al., 2018). The effect of vitamin E on prevention of dementia and Alzheimer's disease has been recognized (Fata, Weber, & Mohajeri, 2014). The anti-acetylcholinesterase activity of almond has been considered in other animal studies as an anti-amnesia mechanism, which along with the antihypercholesterolemic effect of almond, can prevent the production of amyloid plaque causing Alzheimer's disease (Kulkarni, Kasture, & Mengi, 2010)

Another animal study has also shown an improvement in memory and learning after almond consumption, which are increasing the levels of tryptophan monoamines and serotonergic interactions in the brain (Haider, Batool, & Haleem, 2012).

It has been demonstrated that almond consumption is effective in prevention of senile memory disorders (scopolamine-induced amnesia) in mice models by reducing oxidative stress and producing cholinergic effect (Batool et al., 2016; Batool, Tabassum, Siddiqui, & Haider, 2018).

3.3.2.6. Hepatoprotective effects

The presence of some components, including unsaturated fatty acids, tocopherols and phenolic compounds can be attributed to the hepatoprotective activities of almond. In an animal study, the hepatoprotective mechanisms of almond oil against carbon tetrachloride (CCL4) induced liver damage have been demonstrated. These mechanisms include increasing the activity of antioxidant enzymes, blocking the oxidative chain reaction, and inhibiting the lipid peroxidation processes (X.-Y. Jia et al., 2011). Procyanidins from almond skin as a phenolic polymer, have a hepatoprotective activity that leads to protection of cells against chemical-oxidative stress and cancer in the *in vitro* and *in vivo* studies. Increasing of expression and activity of the liver antioxidant enzymes by almond skin can reduce the acute acetaminophen-induced hepatotoxicity in mice model (Truong et al., 2014).

3.3.2.7. Anti-inflammatory activity

Nuts such as almond are also considered anti-inflammatory food, which contain some components, including magnesium, L-arginine, MUFAs, PUFAs, antioxidants and dietary fibers (Casas-Agustench, Bulló, & Salas-Salvadó, 2010).

There are different results about anti-inflammatory effects of almond in various studies. In a randomized, controlled, crossover feeding study on healthy individuals, a high almond diet could decrease serum E-selectin and C-reactive protein (CRP) but had no effect on interleukin-6 (IL-6) or other inflammatory markers (Rajaram, Connell, & Sabaté, 2010). Although almond supplementation could significantly improve CRP parameter in patients with diabetes, it had no effect on the blood lipid profile or IL-6 in these patients (Gulati, Misra, & Pandey, 2017; Hou et al., 2018). In an *in vitro* study, it is shown that almond oil extract has anti-inflammatory properties and could inhibit the expression and formation of inflammatory mediators in macrophages (Müller et al., 2019).

3.3.2.8. Anti-microbial activity

Recent evidence suggests that phenolic compounds and flavonoids have antimicrobial properties through a strong binding with microbial proteins and glycoproteins; thus the presence of these components can elucidate the antibacterial activity of almond. Pyrogallol, ethylgallate and p-hydroxybenzoic acid are phenolic compounds isolated from almond seeds that have been shown to have strong antibacterial activity against Gram-positive and Gram-negative bacteria (Bolling, 2017; Dhingra, Kar, Sharma, & Bhasin, 2017; G Mandalari et al., 2010). Moreover, the extract of blanched almond could inhibit growth of *Escherichia coli*, *Serratia marcescens*, and *Streptococcus mutans* colonies (Smeriglio et al., 2016). Almond skin extracts also showed potent antibacterial activity *against Salmonella enterica*, *Listeria monocytogenes*, and *Staphlococcus*

aurus (G Mandalari et al., 2010). Administration of almond oil had an inhibitory effect on *Staphylococcus aureus* and *Bacillus subtilis* and showed a potent antifungal activity (Rizwana, 2018).
Polyphenols, which are available in almond skin, are effective against *Helicobacter pylori*. So, these compounds are suggested to be used in antibiotic combinations for the treatment of resistant strains (Bisignano et al., 2013)

3.3.2.9. Anti-cancer activity

Some studies have demonstrated cytotoxic activities of almond and its fractions against several human cancers. It is believed that almond can be considered as a new drug in the management of cancerous tumors. Adding almond or its oil to the rats' diet could significantly decrease the aberrant crypt foci (ACF) and colonic cell turnover (Davis & Iwahashi, 2001).
According to the findings of an *in vitro* study unsaturated fatty acids in almond oil, especially oleic acid, have antiproliferative and anti-cancer effects due to decreasing of signaling molecules, which play important roles in the proliferation and differentiation of colon cancer cells. Therefore, almond oil may have protective effect against proliferation of tumors (Mericli et al., 2017). Ethanolic extracts of amygdalin from almond have antitumor activity in oral cancer cells. This cytotoxic effect is caused by the release of hydrocyanic as a secondary metabolite (Sireesha, Reddy, Reginald, Samatha, & Kamal, 2019). Furthermore, acid-soluble polysaccharides from almond skin have a significant cytotoxic activity against cancer cells (Dammak et al., 2018).

3.3.2.10. Cardiometabolic protective activity

There are some components in almond, which have protective effects in metabolic disorders and also are useful for cardiovascular protection (Alasalvar & Bolling, 2015; Sheorey et al., 2011). Metabolic syndrome, as a cardiovascular risk factors, is characterized by hyperlipidemia, high blood pressure, elevated blood glucose and adiposity. These conditions may be potentially improved by almond consumption (Kamil & Chen, 2012). Diets containing almond are rich of MUFAs and PUFAs, which have shown cardioprotective effects (Alasalvar & Bolling, 2015). MUFAs principally oleic acid, can ameliorate endothelial dysfunction. On the other hand, PUFAs have anti-atherosclerotic effects by inhibition of thrombotic and inflammatory pathways. Also, PUFAs intake can result in weight loss (Al Tamimi, 2016; Bhardwaj et al., 2018).
A recent systematic review and meta-analysis of randomized controlled trials demonstrated that total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and HDL-cholesterol were significantly decreased with almond consumption. In addition, the almond diet could reduce body weight and apolipoprotein B (apo B) concentration. It was shown that TC, LDL-C and apo B concentration were affected more than other parameters in almond intervention group. Finally, it was concluded that some effects of almond were dose-dependent. Furthermore, TC, diastolic blood pressure (DBP), fasting blood glucose (FBG) and body weight were significantly reduced after consumption of more than 42.5 g of almond per day (Lee-Bravatti et al., 2019).

There are two potential mechanisms which are involved in the almond effects on biomarkers of cardiometabolic risk. The first one is the effect of almond on lipid profile and hypertension due to weight reduction. The other mechanism is the competition between β-sitosterol, as a component of almond, and the cholesterol for absorption in the gastrointestinal tract (Alasalvar & Bolling, 2015; Lee-Bravatti et al., 2019).

Almond can reduce central adiposity, which is considered as an important cardiometabolic risk factor. When almond is consumed in regular diet, bodyweight is intact, whereas it can promote weight loss in hypocaloric diet (Berryman, West, Fleming, Bordi, & Kris-Etherton, 2015; Foster et al., 2012; Tan & Mattes, 2013).

Almond intake may help decrease body fat composition, especially in the truncal area (Dhillon, Tan, & Mattes, 2016).

In addition, using one cup of almond milk can significantly reduce in body mass index (BMI) and central adiposity (Al Tamimi, 2016).

Almond intake improves glycemic control and can reduce fasting blood sugar (FBS) and postprandial glucose (PPG) in patients with type 2 diabetes. Unsaturated fatty acids in almond have beneficial effects on glucose metabolism. They stimulate secretion of glycoprotein-1 (GLP-1) and increase insulin sensitivity due to exposing the glucose receptor on the surface of cells. Soluble fiber in almond slows down the absorption of carbohydrates and also decrease PPG (Gulati, Misra, & Pandey, 2017).

It seems that almond is a low glycemic index food, which help to promote insulin responses slowly and is useful for glucose metabolism. Consumption of almond before the meals (preload consumption) specially reduces central adiposity and enhances the glucose control (Crouch & Slater, 2016; Y. Liu et al., 2017).

A summary of the therapeutic effects of sweet almond according to the modern phytotherapy and PM and also its nutritional functions are presented in Figure 3.

Please insert Figure 3 here

3.4. Allergy and Toxicity

Almond has several health benefits and is used in many products in the world food industry (Costa, Mafra, Carrapatoso, & Oliveira, 2012).

Food allergy is a social health problem; therefore, an accurate prevalence evaluation is required**.** Allergy to tree nuts has a prevalence of 1%. Almond proteins may cause allergenicity in susceptible people because of some allergenic proteins (Giuseppina Mandalari & Mackie, 2018). Although eight groups of allergenic proteins have been recognized in almond, including Pru du 1, Pru du 2, Pru du 2S albumin, Pru du 3, Pru du 4, Pru du 5, Pru du 6, Pru du γ-conglutin (Costa et al., 2012), little clinical information is available on this group of proteins (Weinberger & Sicherer, 2018). The first allergens introduced in almond was amandin (Pru du 6); it is a major storage protein that has been known as the main allergen (Giuseppina Mandalari & Mackie, 2018). There is not a true prevalence known about allergic reactions to tree nut and the available

prevalence rates reported in literature are controversial. Further studies are needed in different populations to figure out an accurate allergic prevalence rate to almond. Besides, gold standard methods like food challenge test should be performed in studies to assess almond allergy (McWilliam et al., 2015).

In sweet almond the amounts of toxic phytochemicals are reported very low, while bitter almond, in addition to its various health benefits has serious adverse and toxic effects (Moradi, Heidari-Soureshjani, Asadi-Samani, & Yang, 2017). The edible plants belong to the Rosaceae family are contained chemical compounds namely cyanogenic glycosides. During processing, chewing and digestion of the food crop, hydrolysis of cyanogenic glycosides occurred, which led to the production of cyanide (Bolarinwa, Oke, Olaniyan, & Ajala, 2016). High exposure to cyanide in humans may leads to cyanide poisoning, which is characterized by nausea, vomiting, diarrhea, dizziness, weakness and literally death (Burns, Bradbury, Cavagnaro, & Gleadow, 2012). The amounts of cyanide in bitter almond (1062 ± 148.70 mg/kg) are almost 40 times higher than the few levels detected in sweet one (25.20 ± 8.24 mg/kg) (Chaouali et al., 2013). It can be explained that amygdalin content of bitter almond also mainly exceeds its amount in the sweet one, (265 mg CN^{-1}/100 g) and (2 mg CN^{-1}/100 g) respectively (Dicenta et al., 2002). Actually, the enzymatic hydrolysis of amygdalin is the source of cyanide content in bitter almond. The acute lethal dose for oral consumption of cyanide is described to be 0.5– 3.5 mg/kg. Therefore, eating of 50 bitter almonds in adults and about 5 to 10 of them in children are considered fatal (Chaouali et al., 2013). Moreover, bitter almond poisoning has been confirmed in a human study. A 5-year-old boy, ingested about 10 bitter almonds was diagnosed with generalized tonic-clonic seizure. His main symptoms were neurological manifestations include dizziness, confusion and complicated later by seizures and coma (Mouaffak et al., 2013).

Reviewing of current literatures demonstrate that there are no serious adverse effects, toxic reactions or contraindications to the consumption of sweet almond. However, further animal and human studies are needed to verify the potential adverse effects of sweet almond.

4. Conclusion

Prunus dulcis (Mill.) D.A.Webb (almond or sweet almond) is a medicinal herb, which has been used since ancient time. In the present study, we reviewed its traditional uses, phytochemistry, pharmacology, and toxicity from the viewpoint of PM and modern phytotherapy.

Almond is one of the most popular three nuts, which is nutritionally dense and low in calories. Sweet almond as a nutraceutical and functional food, has high biological value and health benefits; therefore, it can be considered a medicinal plant for the treatment of a number of diseases. Also, based on the PM manuscripts, several therapeutic properties are claimed for almond. (Figure 3) Some of these therapeutic effects are confirmed by recent studies; hence in modern literature, almond has been applied for the treatment of neurodegenerative disorders and gastrointestinal function improvement (Rusu et al., 2018). Various studies have revealed that sweet almond has many biological activities including antioxidant, anticancer, anti-

inflammatory, antibacterial, pre-biotic, anxiolytic, sedative-hypnotic, nootropic, metabolic disorder protective and hepatoprotective.

Based on PM, almond can improve all neurological functions. This benefit may be compatible with recent results about anxiolytic, sedative, nootropic and neurodegenerative improvement effect of almond. Almond is rich in PUFAs, choline, essential amino acids and tryptophan as brain enhancers, α-tocopherol, and other flavonoids work as antioxidants; so they can play an essential role in the prevention and treatment of neurodegenerative disorders. In the PM manuscripts, it is mentioned that almond has beneficial effect on some hepatic disorders. In the recent years, a number of studies have demonstrated its hepatoprotective properties as well.

Based on PM literature, almond is mentioned as a useful drug for intestinal ulcers. Studies have shown that almond can affect inflammatory processes in the intestine; therefore, it may be beneficial for the treatment of inflammatory bowel diseases (IBD). Moreover, it can reduce the production of pro-inflammatory cytokines in the colon (Giuseppina Mandalari et al., 2011). There are some therapeutic effects for almond such as antitussive effect and softening of throat, which have not yet studied. However, owing to almond's anti-inflammatory properties and high content of fatty acids, these therapeutic applications of almond may be justified.

On the other hand, there are some other therapeutic effects of almond based on PM that are not studied recently and cannot be also explained by any of known mechanisms of almond compounds. These benefits include improvements of urinary ulcers, dysuria, renal diseases, sexual desire problems, and visual acuity disorders.

Dyslipidemia as a metabolic disorder is improved by consumption of almond, but beneficial effects of almond on TC, DBP, FBG levels and body weight are dose-dependent. These factors are significantly reduced if almond is consumed at the daily dose of >42.5 g. This is equivalent to 35 almond or a 1.5 handful of almond. This dosage is similar to that mentioned in the PM literature. Almond can control oxidative stress, body weight, adiposity, glucose homeostasis and then improve metabolic and cardiovascular function. Moreover, almond is considered a part of heart-healthy diet (Lee-Bravatti et al., 2019). In addition, low glycemic index and special effect on body fat disturbance and adiposity may lead to weight control during calorie-restricted diets. From the viewpoint of PM, almond digestion in stomach progresses a little slowly, so it is advised to be eaten before the meals; also, almond consumption with sugar helps its digestion and leads to proportional weight gain and growth (Hollis & Mattes, 2007; Tonkaboni, 2007).

Some allergic reactions with almond have been recorded because of some protein constituents of almond, especially amandine; however, there are not enough evidence to provide conclusive allergic risk assessment (Kalita et al., 2018), Also there is not a true prevalence of almond allergenicity and no serious adverse effects or toxic reactions by consumption of this nut, therefore, it is considered as a safe nutraceutical in non-allergic individuals.

Reviewing of current literatures show that there are widespread researches reported various pharmacological activities of almond, however, insufficient evidence was demonstrated by *in vivo* and *in vitro* studies about some therapeutic aspects of almond. Therefore, further studies

such as clinical trials are recommended to investigate various beneficial effectiveness and safety of ingestion of this nutraceutical.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Nutrient compositions of sweet almond as listed in USDA National Nutrient Database for Standard References,release 28

Proximates	**One value per 100 grams**
Water	4.41 g
Energy	579 Kcal
Protein	21.15 g
Total lipid	49.93 g
Fatty acids (total saturated)	3.802 g
Fatty acids (total monounsaturated)	31.551 g
Fatty acids (total polyunsaturated)	12.329 g
Cholesterol	0 mg
Carbohydrate (by difference)	21.55 g
Fiber (total dietary)	12.5 g
Sugars (total)	4.35 g
Minerals	
Calcium	269 mg
Iron	3.71 mg
Magnesium	270 mg
Phosphorus	481 mg
Potassium	733 mg
Sodium	1 mg
Zinc	3.12 mg
Vitamins	
Folate, DFE	44 µg
Vitamin E (alpha-tocopherol)	26.63 mg
Niacin	3.618 mg
Vitamin B-6	0.137 mg
Riboflavin	1.138 mg
Thiamin	0.205 mg

Table 2. Bioactive compounds in sweet almond as listed in USDA National Nutrient Database for Standard References, release 28

Compounds			Mean value (mg/100 g)
Phenolic acids	Protocatechuic acid		0.26
	Vanillic acid		0.17
Flavonoids	Anthocyanidins (Cyanidin)		2.46
	Flavan-3-ols	Epicatechin	0.59
		Epigallocatechin	2.60
		Catechin	1.28
		Gallocatechin 3-*O*-gallate	0.46
	Flavonols	Isorhamnetin	2.64
		Kaempferol	0.39
		Quercetin	0.36
	Flavanones	Eriodictyol	0.25
		Naringenin	0.43
		Naringenin-*O*-glucoside	0.16
	Proanthocyanidins	Dimers	9.26
		Trimers	7.63
		4-6mers	27.42
		7-10mers	28.16
		Polymers	80.26
Phytosterols	Stigmasterol		4
	β-sitosterol		130
	Campesterol		5
Total Polyphenols			287.90

Table 3. Therapeutic applications of sweet almond in PM literature. (*Rhazes, 2005; Avicenna, 2005; Tonkaboni, 2007; Aghili Khorasani, 2011)*

Body organs	Therapeutic applications	Application form
Central nervous system	Tonic effect on the brain and nervous system Improve all the brain functions Memory enhancer Mild sedative activity Used for neurological diseases such as amnesia and insomnia Analgesic effects	Almond kernel with candy
Visual system	Improve visual acuity	Eating kernel or apply it in form of kohl
Respiratory tract	Antitussive effect Soften the throat by humidifying the respiratory tract Aperient agent	Almond milk with sugar or with sugar and butter
Gastrointestinal tract	Tonic effects on stomach/ laxative activity Useful in intestinal ulcers Useful in obstructive diseases of liver and spleen	Roasted almond with sugar or common fig
Urinary tract	Useful in bladder ulcers Amelioration of dysuria Tonic effect on kidneys	Almond jam

Table 4. Pharmacological activities of almond in *in vitro* and *in vivo* studies.

Pharmacological activity	Main involved compounds	Mechanisms of action	Experimental model	Dosage and the used part of almond	Ref.
Antioxidant activity	Polyphenols	Cause main level of cytoprotection	*In vitro*	-	Milbury, Chen, Dolnikowski, & Blumberg, 2006
	Flavonoids	Free radical scavenging, metal chelating activities	*In vitro*	1 mg/ml of whole seed and 0.5 mg/ml of brown skin and green shell cover/methanol extraction	Wijeratne, Abou-Zaid, & Shahidi, 2006
Prebiotic activity	Flavonoids, lignans, phenolic acids	Production a wide range of phenolic metabolites in colon	*In vitro*	-	Rocchetti et al., 2019
	PUFAs, Fibers	Different changes in the microbial community composition of gastrointestinal microbiota with different form of almond	*In vivo*	42 g/day each of whole almonds, whole roasted almonds, roasted chopped almonds, almond butter and control group	Holscher, Taylor, Swanson, Novotny, & Baer, 2018
	Peptides, amino acids, fatty acids, dextrin, oligosaccharides, fibers	Promotion the growth of *Lactobacillus acidophilus* (La-14) and Bifidobacterium, inhibition the growth of Enterococcus	*In vivo* (rats) *In vitro*	3 ml of raw almond slurry, or 3 ml of roasted almond	Z. Liu, Wang, Huang, Zhang, & Ni, 2016
	Polyphenols, Fibers	Provoke fecal *bifidobacteria* & *lactobacilli* populations Increase the activity of β-galactosidase enzyme, decrease the activity of enzymes of pathogenic bacteria	*In vivo*	Daily roasted almonds (56 g), almond skins (10 g)	Z. Liu et al., 2014

	-	Increase concentration of butyrate modifying gut microbiota composition	*In vivo*	1 or 3 servings/d of almonds	Ukhanova et al., 2014
Anxiolytic activity	Flavonoids, phenolic acids, some essential amino acids (like tryptophan)	Effect on central nervous system and benzodiazepine (BZD) receptors, bind with high affinity BZD site of Gamma-aminobutyric acid (GABA) receptors	*In vivo* (mice)	Almond at doses of 800 and 1600 mg/kg	Sahib, 2014
Sedative and hypnotic activity	Amino acids (like glutamine)	Decrease in the core body temperature, inhibitory actions of spinal cord interneurons, increases the production of GABA, stimulate detoxification of the liver	*In vivo* (rat)	Almond at doses of 100, 200, 400 mg/kg	Abdollahnejad et al., 2016;
Memory and cognition enhancing effects	Various antioxidants	Reduce oxidative stress	*In vivo* (rat)	400 mg/kg almond suspension	Batool, Tabassum, Siddiqui, & Haider, 2018
	Vitamin-E	Acetylcholinesterase inhibitory actions in the brain	*In vivo* (rodent)	Soaked almond in different dose (3, 6 and 12 g/kg)	Arslan, Ahmed, & Gilani, 2017
	Choline	Produce cholinergic effect	*In vivo* (rat)	400 mg/kg almond suspension	Batool et al., 2016
	Tryptophan, choline, PUFAs	Increase the levels of tryptophan monoamines and serotonergic interactions in the brain	*In vivo* (rat)	Suspension of 80 mg of crushed almond	Haider, Batool, & Haleem, 2012
	Omega-3 fatty acids	Anticholinesterase activity in the brain, antihypercholesterolemic effect	*In vivo* (rat)	Suspension of almond at three doses of 150, 300 and 600 mg/kg/day	Kulkarni, Kasture, & Mengi, 2010
Hepatoprotective effects	Procyanidins	Increase the expression and activity of the liver antioxidant enzymes	*In vivo* (mice)	Procyanidin extraction of almond skin (100g)	Truong et al., 2014

	Unsaturated fatty acids, tocopherols and phenolic compounds	Increase the antioxidant enzymes activity, reduce oxidative stress, inhibit the lipid peroxidation processes	*In vivo* (rat)	Almond oil at 14 and 21 ml/kg	X.-Y. Jia et al., 2011
Anti-inflammatory activity	Polyphenols	Inhibit the expression and formation of inflammatory mediators in macrophages	*In vitro*	-	Müller et al., 2019
	MUFAs, polyphenols, flavonoids	Decrease serum E-selectin, reduce oxidative stress	*In vivo*	High-almond diet (68 g/d per 8386 kJ)	Rajaram, Connell, & Sabaté, 2010
Anti-microbial activity	Phenolic compounds, flavonoids	Reduce oxidative stress, strong binding with microbial proteins and glycoproteins	*In vitro*	-	Dhingra, Kar, Sharma, & Bhasin, 2017
	Flavonoids	Inhibit lipid peroxidation, reduce oxidative stress	*In vitro*	-	Smeriglio et al., 2016
	Polyphenols	Activity against *Helicobacter pylori*	*In vitro* and *In vivo*	Natural almond skin (range, 64 to 128 µg/ml), natural skin post gastric digestion (range, 128 to 512 µg/ml), and natural almond skin post gastric plus duodenal digestion (range, 256 to 512 µg/ml): the minimum inhibitory concentration	Bisignano et al., 2013
	Polyphenols	Interactions with various bacteria	*In vitro*	Methanolic extraction of natural almond skin (5 g)	Mandalari G et al., 2010
Anti-cancer activity	Amygdalin	Causes apoptosis in oral cancer cells	*In vitro*	50 µg/ml of ethanolic extracts of amygdalin	Sireesha,et al., 2019

				from almond (maximum efficacy)	
	Acid soluble polysaccharides	Exhibit cytotoxicity activity against cancer cells	*In vitro*	-	Dammak et al., 2018
	Unsaturated fatty acids	Decrease of signaling molecules for cell proliferation	*In vitro*	-	Mericli et al., 2017
	Unsaturated fatty acids	Affect prostaglandin and cyclooxygenase-2 and bile acid/cholesterol metabolism in colon cancer	*In vivo*	200 g of whole almond per kilogram of total diet or the equivalent of this diet of almond meal and almond oil	Davis & Iwahashi, 2001
Cardiometabolic protective activity	PUFAs	Anti-atherosclerotic effects by inhibition of thrombotic and inflammatory pathways and improving endothelial dysfunction	*In vivo*	Almond diet (provided 7.6% energy)	Bhardwaj et al., 2018
	Unsaturated fatty acids, fibers	Stimulate secretion of GLP-1 and increase the insulin sensitivity, slow down the absorption of carbohydrates	*In vivo*	Raw almonds in diet (20% of energy intake)	Gulati, Misra, & Pandey, 2017
	Unsaturated fatty acids	Modify body fat percentages, affect the metabolism of glucose and lipid	*In vivo*	56 g of almonds	Y. Liu et al., 2017
	MUFAs principally oleic acid	Ameliorate endothelial dysfunction and reduce the BMI and central adiposity	*In vivo*	One cup (240 ml) of almond milk	Al Tamimi, 2016
	Unsaturated fatty acids	Reduce visceral fat	*In vivo*	An almond enriched diet (15% of energy from almond)	Dhillon, Tan, & Mattes, 2016
	Unsaturated fatty acids, fibers	Reduce central adiposity, enhance the glucose control and insulin response	*In vivo*	Half ounce (12) of dry-roasted almonds	Crouch & Slater, 2016

	Unsaturated fatty acids, fibers, phytosterols	Reduce LDL-C and central adiposity	*In vivo*	1.5 oz. of almonds/day	Berryman, West, Fleming, Bordi, & Kris-Etherton, 2015
	α-tocopherol, MUFAs	Reduce postprandial serum glucose responses and hunger	*In vivo*	43 g of almonds/day	Tan & Mattes, 2013
	Unsaturated fatty acids	Affect very low-density lipoprotein (VLDL) metabolism	*In vivo*	56 g of almonds/day	Foster et al., 2012