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A Systematic Review on Biological Activities of Polyphenols from Almonds.

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ABSTRACT:

Almonds provide excellent nutrients and have been linked to several potential health advantages for a diversified diet. The bioactive polyphenolic compounds found in almonds have recently sparked an interest. The pharmaceutical and healthcare sectors are paying close attention to polyphenols because of their potential. Anthocyanins, flavanols, flavonols, stilbene, phenolic acids, proanthocyanins, and hydrolysable are among the most important polyphenolic compounds in almonds because they have numerous biological activities, including antiviral, antimutagenic, anti-inflammatory, and anticancer properties. This review highlights current knowledge on the bioactivities of almond phenols. Polyphenol extraction, isolation, and identification methods from almonds, as well as bioavailability and potential toxicity, are also covered.

KEYWORDS: almonds; polyphenols; bioactivities; antioxidant activity; Immunomodulatory; anti-viral activity; antimicrobial effect.

1. INTRODUCTION:

Traditionally considered a source of vital nutrients, almonds (*Prunus dulcis L.*) (almond or sweet almond), from the family Rosaceae, are now in high demand as healthy food, with rising consumer and producer interest [1]. Almonds' nutritional value is influenced by several variables, including environmental and genetic ones. As a result, studies investigating the impact of various variables on almond quality were also included. Almond consumption has been linked to many therapeutic and health-protective advantages in epidemiological research [2,3]. Almonds' macro-and micronutrient composition is related to their consumption's beneficial effects on health [3]. Because of its chemical components, which include fatty acids, phenolics, vitamin E, and sucrose, almonds are considered to provide health benefits [4]. Almonds have an excellent nutritional profile that includes vitamins E and B2 as well as minerals, particularly copper, manganese, and magnesium (riboflavin) [4,5].

Studies have indicated that bioactive substances such phenolic compounds (flavonoids and phenolic acids) and terpenoids are present in almond by-products (of the kernel, peel, and shell) (sterols and triterpenoids). These by-products are rich in antioxidants for reducing oxidative processes, also as a natural antibacterial, prebiotic, and antiviral substances [5]. This almond kernel stands out for its beneficial properties for both health and industry. However, the presence of flavonoids and phenolic acid in its by-products, like skin, shell, hull, makes them stand out for usage in dietary and pharmaceutical formulations [4,5]. The almond's quality, characteristics, and shelf life are all influenced by the concentration of polyphenols at the lipid contact with the environment [4]. The skins of almonds contain a high concentration of polyphenols, which can be removed by blanching. Even though blanching reduces the polyphenol content of almonds, it is frequently done for commercial reasons [6]. Almond skins' dry weight is between 0.2 and 0.8 percent flavonoids and other polyphenols [2]. The fibre and polyphenol content of almonds may serve as a substrate for microbial fermentation in the gut, assisting in the control of intestinal microflora [7]. Almond seeds exhibited the potential to be used as a novel source of prebiotics [8]. Many promising bioactivities have emerged in recent years, including hypolipidemic, hypoglycaemic, immunostimulant, antioxidant, and nootropic activity of almonds have been reported [2] .Because of their biological effects, such as their anticancer, antiviral, antimutagenic, and anti-inflammatory properties, flavonoids, which are secondary metabolites of polyphenols, have received much research [8]. The most common flavonoids are (+)-catechin, (-)-epicatechin, kaempferol, and isorhamnetin, the latter as 3-O-rutinoside or 3-O-glucoside [9].

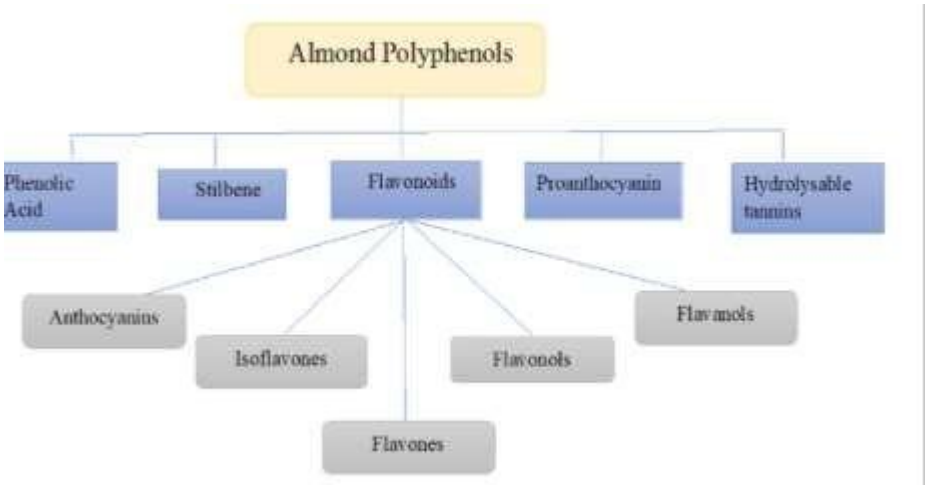


Fig.1. Classification of phenolic components isolated from Almonds

This review summarises current knowledge on almond phenolic bioactivities. Polyphenol extraction, isolation, and identification methods from almonds are also covered, also their bioavailability and potential toxicity.

2.The Phenolic Compound Distribution in Almonds:

The skin of almonds have total phenolic content of 50-75%., which includes aldehydes, makes it a rich source of the following: flavanones, phenolic acids, hydroxybenzoic acids, flavan-3-ols, isoflavones, and flavonol glycosides biphenyl propane derivatives, lignans, and anthocyanins Procyanidins, phenolic compounds, and (cyanidin and delphinidin) isolated from acids, as well as hydrolysable tannins from ripening nuts.

Table 1: The bioactive phenolic content of *Prunus amygdalus* in various parts

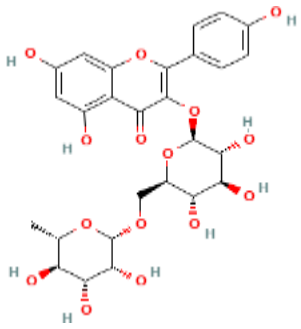
Resources	Type of secondary metabolite	Phytoconstituents	References
Kernel	Hydroxybenzoic acids	Protocatechuic acid,	12,13
	Hydroxycinnamic acids	Ferulic acid, Caffeic acid, Sinapic acid	14 14 14
	Anthocyanidin and procyanidin	Procyanidin B2, Delphinidin, Cyanidin	15 13 15,13
	Flavanol glycosides	Kaempferol-3-Orutinoside	16
	Flavonol aglycones	Kaempferol, Quercitrin	15 13
	Sterols	Stigmasterol, B-sisterol	19
Skin	Hydrobenzoic acid	Protocatechuic acid Vanillic acid p-Hydroxybenzoic acid	13 20 20
	Hydroxycinnamic acid	Sinapic acid Ferulic acid Caffeic acid	14 14 14
	Flavanol glycosides	Kaempferol-3-Orutinoside Kaempferol-3-Oglucoside Isorhmnetin-3-O-rutinosoide Isorhamnetin-3-Oglucoside Quercetin-3-Oglucoside	13 18,12 16,13 16,13 20,13

	Flavanone glycoside	Naringenin-7-Oglucoside Eriodictyol-7-Oglucoside	12,18 12,18
	Flavonol aglycones	Kaempferol, Quercetin Quercitrin	17 16 13
	Sterols	Stigmasterol, B-sisterol	19
Hull	Hydroxycinnamic acids	Ferulic acid, Sinapic acid, Caffeic acid	14 14 14
	Flavonol glycosides	Isorhamnetin-3-Oglucoside	12,13

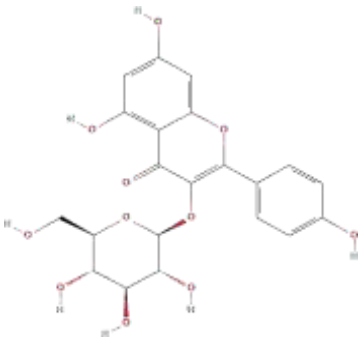
Extraction, Purification, and Identification of Phenolic Compounds from Almonds:

Conventional extraction methods for extracting antioxidants from almond skin often involve macerating with a solvent at room temperature for days or using high temperatures for several hours at reflux [20,21]. For the isolation of phenolic chemicals from almond skin by-products, a microwave-assisted extraction (MAE) process was developed. MAE was carried out using a modified M1711N domestic microwave oven. [23]. The effect of almond skin weight, microwave power, and irradiation time on total phenolic content was studied using a three-level, three-factor Box-Behnken design (TPC) [21,22].

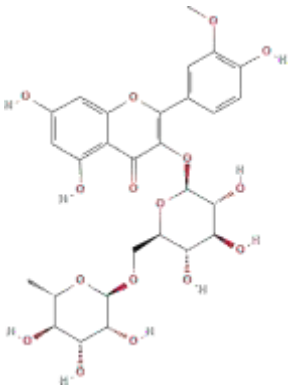
According to earlier reports, the blanching procedure causes the polyphenol content of the blanched water to rise while the phenol content of blanched almond skins falls [19,20]. The number of OH functional groups in the molecule decreases, the phenolic compound becomes more hydrophobic and has less solubility in boiling water. As a result, these substances may have a stronger affinity for an organic phase, such as ethanol, during MAE. [28]. Compounds in almond skin cultivars with more than seven OH groups in their molecules isorhamnetin-3-O-rutinoside, kaempferol-3-O-rutinose, isorhamnetin-3-O-glucoside, and quercetin-3-O-rutinoside were found in higher concentrations, followed by catechin, epicatechin, and naringenin-7-O-glucoside with only five OH groups. The Folin-Ciocalteu colorimetric method was used to determine the TPC of almond skin extracts in triplicate. [24]. TPC was expressed as milligrammes of quercetin equivalent (QE) per gramme of dry almond skin, with quercetin serving as the reference standard (25 1000 mg/kg). The total flavonoid content was determined using HPLC-ESI-MS/MS. [24]. The quantity of each flavonoid in the extracts from the investigated cultivar of almonds skin. In terms of flavonoid profiles,almond skin cultivars showed significant variances; Acetate and phenylalanine in plants are converted into flavonoids via the shikimate pathway [21].Many chemical structures of phenolic compounds from almonds have been reported in the literature. Figure 1 depicts the chemical structures of a few important phenolic compounds.



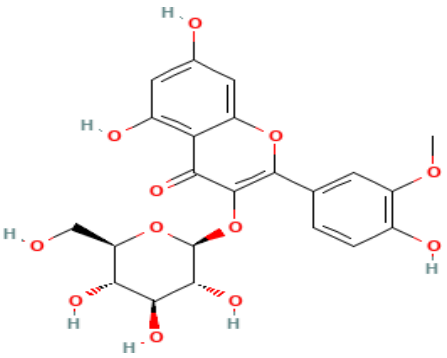
Kaempferol-3-Orutinoside



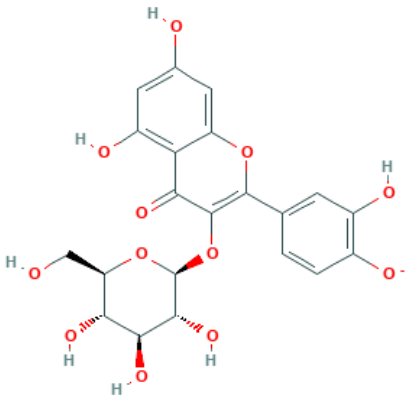
Kaempferol-3-Oglucoside



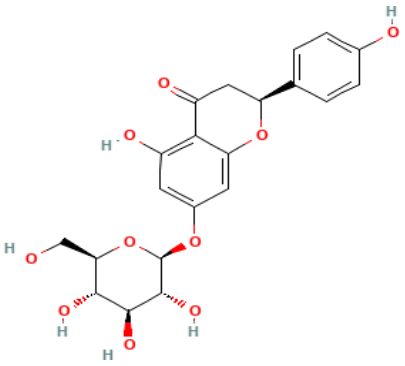
Isorhamnetin-3-O-rutinoside



Isorhamnetin-3-Oglucoside



Quercetin-3-Oglucoside



Naringenin-7-Oglucoside

Bioavailability and metabolism of Almond Components :

Almonds are high in polyphenols, which are metabolised impressively after consumption. The bioavailability of these compounds has a significant impact on both the matrix's ability to promote health and the health of its co-products and derivatives. Polyphenol breakdown may result in the formation of a wide range of metabolite classes, many of which may have more intriguing biological properties than dietary natural precursors. [4].

Almonds include several substances that perform impressive biological activities. They are abundant providers of vitamins, minerals, secondary metabolites, fatty acids, carbohydrates (primarily dietary fiber), proteins, and amino acids [3,4]. There are also studies on the bioavailability of almond polyphenols in humans after consuming whole almonds or their crude extracts. The preliminary investigation conducted in which they defined and evaluated the polyphenols and their metabolites found in the plasma and urine of healthy human participants who ate almond peel polyphenols [23]. identified O-methyl glucuronide, O-methyl sulfate, sulfate, and glucuronide derivatives of (epi)catechin, the glucuronide conjugates of isorhamnetin and naringenin, and the sulfate conjugates of isorhamnetin, along with conjugates of hydroxyphenyl Valero lactones and several products. According to the literature, almond skins, a byproduct of industrial blanching, could be used as prebiotics and that the presence of polyphenols in them did not interfere with bacterial fermentation. [13].

3. Reported activities of almond polyphenols:

Almond is a member of the Rosaceae family and is high in nutrients due to phytochemicals such as phenolic compounds, phytosterols, flavonoids, phenolic acids, vitamins, and fatty acids. The most prevalent polyphenols preserved in extract, including catechin, epicatechin, kaempferol-3-O-rutinoside, isorhamnetin-3-O-rutinoside, and naringenin, are thought to have antibacterial characteristics [11]. Almond skin fractions have antimicrobial activity against L. monocytogenes and Staph. Aureus, and natural skins have antimicrobial activity against Gram-negative bacteria. Enterica Salm. [12].

Antibacterial Activity:

A possible source of organic antimicrobials is almond skin. Regardless of the bacterial genotype, almond skin polyphenols were efficacious in vitro against H. pylori [14]. A variety of food-borne diseases are resistant to almond shells. Blanched skins, a leftover from the processing of almonds, may contain natural antimicrobials [26,27]. The broth microdilution method was used to determine the minimum inhibitory concentrations (MICs) of NS and BS, as well as the pure flavonoid components naringenin, catechin, protocatechuic acid, epicatechin, and isorhamnetin-3-O-glucoside, according to CLSI. [27]. Almond skin purified components could be used as natural antibacterial agents in food systems, extending the shelf life of processed foods. [28]. The highest antibacterial ability of NS can be related to its flavonoids, which are present in 10-fold greater amounts than in BS. However, the combination of several polyphenols preserved by this by-product may be the cause of the activity exhibited by BS [29,30].

Antioxidant activity :

Antioxidant activity is defined as a compound's ability to prevent oxidative degradation, such as lipid peroxidation (LPO)[31]. These fruits' hulls and shells were used to make the methanolic extracts, and the total phenolic and flavonoid content was determined using the Folin-Ciocalteu method.. At different concentration levels, the extracts' ability to reduce and scavenge radical nitrite, hydrogen peroxide, and superoxide was examined [9]. Flavan-3-ols, flavonols, and flavanone glycosides were found to have the greatest impact on the antioxidant capacity of the almond skins studied. [31,32]. It was demonstrated that LPO alters the integrity, fluidity, permeability, and functional loss of bio membranes and generates potentially toxic products. [32]. The findings show that roasting, without considering other factors; the method demonstrated is the most appropriate method of industrial processing almonds to obtain almond skin extracts with the highest antioxidant content (economic, technological, safety, and so on) [33,34]. It has been demonstrated that oven drying enhances the antioxidant capacity of blanched almond skins. In comparison to blanched almond skins, roasted almond skins had higher phenolic contents (total polyphenols were 3.4–6.0 times higher and proanthocyanidins were 1.9–2.8 times higher, respectively) [33]. The antioxidant potential of almond skins, on the other hand, has been confirmed to be primarily due to the presence of phenolic compounds, and the phenolic levels vary depending

on the method used to remove the almond skin. [32,33]. To determine the relationship between the number of phenolic compounds and the antioxidant capacity of almond skins, linear regression analysis was used to compare total polyphenol values and proanthocyanidins against ORAC values (n = 9) [34].

Antiviral Activity:

In peripheral blood mononuclear cells, the antiviral activity of natural almond skins against herpes simplex virus type 2 (HSV-2) has been established 20,21. For those who have HSV, frequent outbreaks can have a severe psychological and social impact. Furthermore, HSV lesions offer a straightforward method for HIV infection during sexual activity [35]. Type 1 immunity, also known as the proinflammatory host response, is required as the initial line of defense against viral infections [35,36]. Activation of mononuclear cells limits viral infection by inducing an antiviral state in nearby cells (via IFNs) or destroying virus-infected cells (via TNF-). [22]. The effects of NS therapy on IL-10 and IL-4 production by infected PBMC are unexpected because they appear to contradict its known antiviral action. However, the primary regulating factors of the observed antiviral activity, IL-12, IFN-, and TNF-, were noticeably generated [23]. Additionally, uninfected PBMC treated with NS produced significant levels of IFN-, IL-12, TNF-, IL-10, and IL-4 [36,37]. The findings strongly suggested that inhibiting inflammatory cytokines like IFN- and IL-12 did not increase IL-4 and IL-10 production, but rather decreased. In light of this, we could hypothesise that in the absence of IL-12 and IFN-, other biological mediators (such as type III IFNs and IL-18), either directly induced by almond skins or indirectly induced by other paracrine stimuli induced by almond skins, contribute to the down-regulation of IL-4 and IL-10.[38].

Immuno-stimulant Action :

According to a study, almonds can produce a variety of cytokines, such as interleukins (IL12), interferon (INF-), INF-gamma, and tumor necrosis factor (TNF-), among others. Literature suggests that almonds could greatly improve peripheral blood mononuclear cells' immune surveillance against the Herpes simplex virus type 2 (HSV-2) and other viral infections [39].

Table 2: Reported activities and effects of phenolic compound

Reported activity	Present Polyphenols	Effect	References
Antimicrobial Activity	naringenin, catechin, protocatechuic acid, epicatechin, and isorhamnetin-3-O-glucoside	i]flavonoids from almond skins are effective against a range of food-borne pathogens ii] antimicrobial activity against (gram-positive) L.monocytogenes and Staph. Aureus, (Gram-negative)Salm. enterica	11
Antioxidant Activity	flavan-3-ols, flavonols, and flavanone glycosides	1] Presence of high levels of flavonoids 2] by scavenging ROS	17
Antiviral Activity	flavonols, flavan-3-ols, hydroxybenzoic acids and flavanones	decreasing the inflammatory response supported by helper T (Th)1 cell	12,13

Conclusions and Future Directions:

The pharmaceutical and healthcare industries are paying close attention to polyphenols because of their potential for antibacterial and antiviral action in vitro. The utilization of polyphenols derived from natural sources could be the foundation of a novel antiviral and antibacterial strategy. Purified almond skin components may be employed in food systems as natural antibacterial agents, prolonging the shelf life of processed foods. A potential source of organic antimicrobials is almond skin. An extensive review of the literature on Prunus amygdalus polyphenols revealed that these plants contain numerous dietary supplements as well as active novel medicinal agents with significant antioxidant, antimicrobial, and antiviral activity, among other things. These activities distinguish this medicinal plant as a distinct candidate for writing a review and providing useful information to researchers. The current study found that almond skins polyphenols are effective against a variety of food-borne infections, including ROS and HSV. More research is required to truly understand the mechanisms involved in these interactions.

REFERENCES :

1. Esfahlan AJ, Jamei R, Esfahlan RJ. The importance of almond (Prunus amygdalus L.) and its by-products. Food chemistry. 2010 May 15;120(2):349-60.

2. Musarra-Pizzo M, Ginestra G, Smeriglio A, Pennisi R, Sciortino MT, Mandalari G. The antimicrobial and antiviral activity of polyphenols from almond (Prunus dulcis L.) skin. Nutrients. 2019 Oct 3;11(10):2355.

3. Barreca D, Nabavi SM, Sureda A, Rasekhian M, Raciti R, Silva AS, Annunziata G, Arnone A, Tenore GC, Süntar I, Mandalari G. Almonds (Prunus dulcis Mill. DA webb): A source of nutrients and health-promoting compounds. Nutrients. 2020 Mar 1;12(3):672.

4. Ibourki M, Bouzid HA, Bijla L, Aissa R, Ainane T, Gharby S, El Hammadi A. Physical fruit traits, proximate composition, fatty acid and elemental profiling of almond [Prunus dulcis Mill. DA Webb] kernels from ten genotypes grown in southern Morocco. OCL. 2022;29:9.
5. Tabasum Fatima, Nazia Nissar, Bazila Naseer, Syed Zameer Hussain. "Health benefits of almonds." J Med Plants Stud 2018;6(2):228-231.
6. Garrido I, Monagas M, Gómez- Cordovés C, Bartolomé B. Polyphenols and antioxidant properties of almond skins: influence of industrial processing. Journal of Food Science. 2008 Mar;73(2):C106-15.
7. Yada S, Huang G, Lapsley K. Natural variability in the nutrient composition of California-grown almonds. Journal of food composition and analysis. 2013 Jun 1;30(2):80-5.
8. Garcia-Perez P, Xiao J, Munekata PE, Lorenzo JM, Barba FJ, Rajoka MS, Barros L, Mascoloti Sprea R, Amaral JS, Prieto MA, Simal-Gandara J. Revalorization of almond by-products for the design of novel functional foods: An updated review. Foods. 2021 Aug 6;10(8):1823.
9. Liu Z, Wang W, Huang G, Zhang W, Ni L. In vitro and in vivo evaluation of the prebiotic effect of raw and roasted almonds (Prunus amygdalus). Journal of the Science of Food and Agriculture. 2016 Mar;96(5):1836-43
10. Ruchi Singh, Syed Misbahul Hasan, Akash Ved and Om Prakash "An update on phytochemicals, nutritional composition, and pharmacological significance of prunus amygdalus batch: a comprehensive review" IJPSR (2022), Volume 13, Issue 4
11. Rao, Hari & Lakshmi, (2012). "Therapeutic Applications of Almonds (Prunus amygdalus L): A Review." Journal of Clinical and Diagnostic Research. 6. 130-135.
12. Mandalari, G.; Tomaino, A.; Arcoraci, T.; Martorana, M.; Lo Turco, V.; Cacciola, F.; Rich, G.T.; Bisignano, C.; Saija, A.; Dugo, P. "Characterization of polyphenols, lipids and dietary fiber from skins of almonds (Amygdalus communis L.)" J. Food Comp. Anal. 2010, 23, 166–174.
13. Mandalari, G.; Faulks, R.M.; Bisignano, C.; Waldron, K.W.; Narbad, A.; "Wickham M.S. In vitro evaluation of the prebiotic properties of almond skins (Amygda communis L.)."FEMS Microbiol. Lett. 2010, 304, 116–122
14. Monagas M, Garrido I, Lebron-Aguilar R, Bartolome B, and Gomez-Cordoves C: "Almond skins as a potential source of bioactive polyphenols." J Agr Food Chem 2007; 55: 8498–8507
15. Wijeratne SSK, Abou-Zaid MM, and Shahidi F: "Antioxidant polyphenols in almond and its coproducts" J Agr Food Chem 2006; 54: 312–318.
16. Siriwardhana SKW, Amarowicz R and Shahidi F: "Antioxidant activity of almonds and their by-products in food model systems." J Am Oil Chem Soc 2006; 83: 223– 230
17. Amarowicz R, Troszynska A, and Shahidi F: "Antioxidant activities of almond seed extract and its fractions". J Food Lipids 2005; 12: 344–358.
18. Frison-Norrie S and Sporns P: "Identification and quantification of flavonol glycosides in almond seed coats using MALDI-TOF mass." J Agr Food Chem 2002; 50: 6818–6822.
19. Sang S, Lapsley K, Jeong WS, Lachance PA, Ho CT, and Rosen RT: "Antioxidative phenolic compounds isolated from almond skins (Prunus amygdalus Batsch)." J Agric Food Chem 2002; 50(8): 2459-2463
20. Hughey, C. A.; Januszewicz, R.; Minardi, C. S.; Phung, J.; Huffman, B. A.; Reyes, L.; Wilcox, B. E.; Prakash. A. " Distribution of almond polyphenols in blanch water and skins as a function of blanching time and temperature." Food Chem. 2012, 131, 1165−1173
21. Biesaga, M.; Pyrzynska, K. "Stability of bioactive polyphenols from honey during different extraction methods." Food Chem. 2013, 136, 46−54
22. Urpi-Sarda, M.; Garrido, I.; Monagas, M.; Gómez-Cordovés, C.; Medina-Remón, A.; Andres-Lacueva, C.; Bartolomé, B. "Profile of plasma and urine metabolites after the intake of almond [Prunus dulcis (Mill.) D.A. Webb] polyphenols in humans." J. Agric. Food Chem. 2009, 57, 10134–10142.
23. Liu, Y.; Hwang, H.J.; Kim, H.S.; Park, H. "Time and Intervention Effects of Daily Almond Intake on the Changes of Lipid Profile and Body Composition among Free-Living Healthy Adults." J. Med. Food 2018, 21, 340–347
24. Bolling, B. W.; Dolnikowski, G.; Blumberg, J. B.; Chen, C.-Y. O. " Polyphenol content and antioxidant activity of California almonds depend on cultivar and harvest year". Food Chem. 2010, 122, 819−825.
25. (Milbury, P. E.; Chen, C.-Y. C.; Dolnikowski, G. G.; Blumberg, J. B. " Determination of flavonoids and phenolics and their distribution in almonds." J. Agric. Food Chem. 2006, 54, 5027−5033
26. Valdés A, Vidal L, Beltrán A, Canals A, Garrigós MC. "Microwave-Assisted Extraction of Phenolic Compounds from Almond Skin Byproducts (Prunus amygdalus): A Multivariate Analysis Approach." J Agric Food Chem. 2015 Jun 10;63(22):5395-402

27. Singleton, V. L.; Rossi, J. A. "Colorimetry of total phenolics with the phosphomolybdic-phosphotungstic acid reagent." Am. J. Enol. Vitic. 1965, 16, 147

28. Bisignano, C.; Mandalari, G.; Smeriglio, A.; Trombetta, D.; Pizzo, M.M.; Pennisi, R.; Sciortino, M.T. "Almond Skin Extracts Abrogate HSV-1 Replication by Blocking Virus Binding to the Cell." Viruses **2017**, 9, 178

29. Chen CY, Blumberg JB. "In vitro activity of almond skin polyphenols for scavenging free radicals and inducing quinone reductase." J Agric Food Chem. 2008 Jun 25;56(12):4427-34..

30. Mandalari G, Bisignano C, D'arrigo M, Ginestra G, Arena A, Tomaino A, Wickham MS. Antimicrobial potential of polyphenols extracted from almond skins. Letters in applied microbiology. 2010 Jul;51(1):83-9.

31. Taguri, T., Tanaka, T. and Kouno, I. (2004) "Antimicrobial activity of 10 different plant polyphenols against bacteria causing food-borne disease." Biologic and Pharmac Bulletin

    27, 1965–1969.

32. Bisignano C, Filocamo A, La Camera E, Zummo S, Fera MT, Mandalari G. "Antibacterial activities of almond skins on cagA-positive and-negative clinical isolates of Helicobacter pylori." BMC Microbiol. 2013 May 9;13:103.

33. Davidson, P.M. and Parish, M.E. (1989) "Methods for testing the efficacy of food antimicrobials." Food Technol 43,148–155.

34. V. Roginsky and E. A. Lissi, Food Chemistry, 92, 235 (2005).

35. E. Niki, Free Radical Biology and Medicine, 47, 469 (2009).

36. I. Garrido; M. Monagas; C. Gómez-Cordovés; B. Bartolomé (2008). "Polyphenols and Antioxidant Properties of Almond Skins: Influence of Industrial Processing." 73(2)

37. Van de Perre, P.; Secondly, M.; Foulongne, V.; Ouedraogo, A.; Konate, I.; Huraux, J.M.; Mayaud, P.; Nagot, N. "Herpes simplex virus and HIV-1: Deciphering viral synergy. Lancet Infect." Dis. 2008, 8, 490–497

38. Arena, A.; Bisignano, C.; Stassi, G.; Mandalari, G.; Wickham, M.S.; Bisignano, G. "Immunomodulatory and antiviral activity of almond skins." Immunol. Lett. 2010, 132, 18–23.

39. Arena, A.; Bisignano, C.; Stassi, G.; Filocamo, A.; Mandalari, G. Almond Skin Inhibits HSV-2 Replication in Peripheral Blood Mononuclear Cells by Modulating the Cytokine Network. Molecules 2015, 20, 8816–8822

40. Alcami A. "Viral mimicry of cytokines, chemokines, and their receptors." Nat Rev Immunol 2003; 3:36–50.

41. Adriana Arena; Carlo Bisignano; Giovanna Stassi; Giuseppina Mandalari; Martin S.J. Wickham; Giuseppe Bisignano (2010). "Immunomodulatory and antiviral activity of almond skins."132(1-2), 18–23.

42. Arena A, Gugliandolo C, Stassi G, Pavone B, Iannello D, Bisignano G, et al. "An exopolysaccharide produced by Geobacillus thermodenitrificans strain" B3-72:

43. Tramice A, Arena A, De Gregorio A, Ottanà R, Maccari R, Pavone B, Arena N, Iannello D, Vigorita MG, Trincone A. Facile Biocatalytic Access to 9- Fluorenylmethyl Polyglycosides: Evaluation of Antiviral Activity on Immunocompetent Cells. ChemMedChem: Chemistry Enabling Drug Discovery. 2008 Sep 15;3(9):1419-26.