Hazelnuts as Source of Bioactive Compounds and Health Value Underestimated Food

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Abstract
Hazelnut (HN) has found its way into nontraditional foods due to the recognition of its nutritional and nutraceutical properties. Among nut species, hazelnut plays a major role in human nutrition and health because of its special composition of fat (mainly oleic acid), dietary fibre, vitamins (vitamin E), minerals, phytosterols (mainly β-sitosterol), and antioxidant phenolics.

In particular, lipids represent 60% of its dry weight and are mainly represented by triacylglycerols where the main fatty acids are oleic and linoleic acids. Furthermore, HN oil is an exceptional source of specific bioactive compounds as tocopherols, mainly α-tocopherol. Besides a favourable fatty acid profile and high tocopherols content, HNs are also a source of minerals and phytosterols, where potassium and β-sitosterol are the major ones. In addition, the presence of several phenolic antioxidants such as mono- and oligomeric flavan 3-ols has been reported.

HNs represent a very interesting food, and their nutritional and health value need to be further evidenced in intervention trials. In addition, the use of HN by-products as new functional ingredient represents an important challenge for the sector and the food industry.

Introduction
Corylus avellana L., the European HN, is the second most popular nut worldwide just after almonds and production ranges from North Africa and Europe to the Asia Minor and Caucasus region. Countries around the Black Sea account for the majority of production in the world: Turkey (610,264 tons, average for the period 2009–2011), Azerbaijan...
(28,564 tons), and Georgia (20,567 tons). Other important producers are Italy (114,991 tons), the USA (35,079 tons), and Spain (16,988 tons).^1

In Turkey, the principal HN producer providing around 72% of the HN production in the world, the major HN cultivar is Tombul, followed by Çakıldak, Mincane and İncekara, which are located mainly in the provinces of Ordu and Giresun.\(^2\) Italy, the world’s second largest producer, possess numerous traditional cultivars, which are mostly growth in the regions Campania, Latium and Piedmont. Recently, some of the major cultivars (Tonda Romana from Latium, Tonda di Giffoni from Campania and Tonda delle Langhe from Piedmont) obtained the European Community quality stamp for their traditional peculiarity.\(^3\)

Today exists a variety of almost 400 HN cultivars, but only about 20 of them represents the basis of world production. Nut chemical, physical and morphological characteristics are highly dependent on interactions with the environment and genotype, postharvest management and cultural techniques.\(^4\)

Thanks to their sensory properties, HNs are consumed not only as a ripe or “green” fruit but also in a variety of manufactured food such as chocolate spread, cereal bar, cookie, nougat, pastry, ice cream and cooking oil production. HNs are consumed roasted or raw, chopped, intact, or processed into a praline paste; they are typically processed integrally into food products, although HN oil is also frequently used for cooking.\(^5,6\)

Among nuts, HN plays a key role in human nutrition and health because of its special content of macronutrients (lipids and fibre), micronutrients (minerals and vitamins), fat-soluble bioactives (tocols, phytosterols, phytostanols and squalene) and phytochemicals (flavonoids and phenolic and hydroxycinnamic acids).\(^7-9\) A list of each class of nutrients and their quantity is reported in table 1.

Lipids and Fatty Acids
The main nutrient of the HN kernel is the lipid portion, which has the biggest impact on kernel flavour, especially after roasting. For many years the edible vegetable oils composition has been evaluated with the objective to obtain knowledge to improve product quality in terms of flavour, taste, nutrition, storage stability and guaranteeing the legitimacy of the material.\(^10\)

Lipids may constitute more than 60% of the HN kernel dry weight and are constituted of 98.8% triacylglycerols (TAG) and 1.2% polar lipids (PL). Within PL, phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol are present at 56.4%, 30.8% and 11.7%, respectively.\(^11\) Among fatty acids, oleic acid (C18:1n9) is by far the most predominant ranging from 76.7% to 82.8%, followed by linoleic (C18:2n6), palmitic (C16:0), stearic (C18:0) and vaccenic (C18:1n7) acids with mean values of 9.2%, 5.6%, 2.7% and 1.4%, respectively.\(^12\) This is very similar in composition to fatty acids of olive oil and generally recommended for a healthy diet.\(^13\) Moreover, due to the high level of mono-unsaturated fatty acids (MUFA) and tocopherols/tocotrienols content, HN oils have an oxidative stability similar to the value of olive oil, and higher compared to rapeseed oil.\(^14\) As consequence, it is present only a minor increase of the possibly harmful trans fatty acids during the thermal treatment of nuts (roasting) and, although some minor changes occurred in the TAG and fatty acid compositions, the corresponding profiles basically remained identical to that of raw HNs.\(^12\)

Moreover, various studies reported as lipids content increased continuously during the development of the kernel, from 6.38 g/100g dry matter to 68 g/100g dry matter.\(^13,14\) Regarding fatty acids, from early to harvest stage a reducing and an increasing trend in the amount of polyunsaturated fatty acids (from 31 to 10.3 g/100g of oil) and MUFA (from 22 g/100g oil to 79.2 g/100g oil) was detected, respectively. No significant changes were observed in total saturated fatty acids at different maturation stage.\(^14,15\)

From the nutritional viewpoint, various studies have confirmed that a diet with a low amount of saturated fatty acids and high content of MUFA can effectively reduce the risk of coronary heart disease amending blood lipid levels and blood pressure ameliorating metabolic syndrome and insulin sensitivity.\(^16-21\)

Dietary Fibre
In the simple terms, dietary fibre can be considered as a ‘roughage’ material of carbohydrates (beta-glucans,
lignin, cellulose, pectin and hemicellulose) resistant to small intestine digestion, requiring microbiota fermentation situated in the large intestine.\textsuperscript{22,23} Types of dietary fibre may be categorized according to their sources, solubility, fermentability, physiological effects, and they can be obtained from cereals, legumes, fruit and vegetables.\textsuperscript{24-25}

After cereals, nuts are the vegetables most reach in fibre. Among tree nuts, the highest content in dietary fibre were measured in almonds (9.2%), followed by HNs (8.7%), walnuts (6.8%), macadamia nuts (5.5%) and pistachios (4.2%).\textsuperscript{26} Moreover, Silva \textit{et al.}\textsuperscript{27} compared the fibre in six cultivars of HNs harvested in Portugal. The fibre content, expressed as g/100g, ranged from 12.07 to 8.05 for Butler and Merveille de Bollwille varieties respectively, indicating consistent variations of dietary fibre among HN cultivars.

Today, recent and persuasive evidences confirmed that high dietary fibre intake promotes overall health and associates with lower mortality through preventing and mitigating of cardiovascular disease, colon cancer and type 2 diabetes mellitus,\textsuperscript{28} suggesting an adequate intake for the Italian adult in the amount of 25 g/day.\textsuperscript{29} Although the mechanisms that underline the described effects of dietary fibre on health are not well-known, it is supposed to be a consequence of changes in nutrient absorption, production of short chain fatty acids, gut hormones secretion and intestinal viscosity.\textsuperscript{30-32}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{natural_forms_vitamin_e.png}
\caption{Natural forms of vitamin E.\textsuperscript{44}}
\end{figure}

\textbf{Minerals}

Minerals are normally divided into macro-minerals and micro-minerals. Major minerals include Ca, Mg, K, Na, Cl, P and S; while trace minerals are I, Zn, Se, Fe, Mn, Cu, Co, Mo, F, Cr and B. Different plant and animal sources can be consumed to obtain a number of essential minerals for a healthy nutrition.\textsuperscript{33}

In HN, at least a total of 24 minerals have been stated so far with an extremely high variability depending on genotypes, geographical origin, year of harvesting, climate, soil composition, irrigation, use of fertilizer and method of cultivation.\textsuperscript{34,35} Generally, K is the most present mineral with a concentration ranging from 147 mg/100g to 761 mg/100g, followed by P (from 256 mg/100g to 458 mg/100g), Ca (from 65 mg/100g to 328 mg/100g) and Mg (from 34 mg/100g to 335 mg/100g). HNs serve also as an excellent source of trace minerals as Cu (from 0.94 mg/100g to 3.47 mg/100g), Mn (from 1.4 mg/100g to 19 mg/100g), and Se (from 5.5 μg/100g to 60 μg/100g).\textsuperscript{35-40} With regard to the trace minerals, a standard portion of HN (30g) supplies, as percentage of the Population Reference Intake (PRI) or Adequate Intake (AI) for Italian adult males (aged 30-59 years), 31-116% of Cu, 16-211% of Mn, and 3-33% of Se.\textsuperscript{29}

Even though each essential mineral has its own health benefits, Se in particular is an essential trace mineral of central importance to human health. As part of L-selenocysteine, selenium is needed for the
synthesis of selenoproteins, a class of proteins with important functions including skeletal and cardiac muscle function, T-cell immunity, thyroid hormone metabolism and antioxidant defense.\textsuperscript{41}

**Tocols**
Tocopherols and tocotrienols are monophenols having the identical main chemical structure constituted by a long chain attached at 2-position of a chromane ring. Tocotrienols diverge from tocopherols because they have a farnesyl rather than a saturated isoprenoid C16 side chain\textsuperscript{42} and exist as four homologues (α, β, γ, δ) which differ from each other by the number and location of methyl groups in their chemical structures.\textsuperscript{43}

Various nuts have been reported to show significant tocopherols and tocotrienols differences, ranging from approximately 1.6 mg/100g of kernel for macadamia to 32 mg/100g of kernel for black walnut. Among them, α- and γ-tocopherol are the most represented isoforms.\textsuperscript{45} HN oil is an exceptional source of vitamin E, where α-tocopherol being the dominant form with a content up to 41.9 mg/100g extracted oil,\textsuperscript{8,34} corresponding at 96% of total tocols.\textsuperscript{46} Differences in vitamin E content in HN oil depend on the variety and geographical origin, where the Tombul variety grown in Turkey seems to have the highest tocols content.\textsuperscript{41} Moreover, roasting and removal of the pellicle (peeling) have shown to reduce considerably tocopherol content.\textsuperscript{46}

The high α-tocopherol content represents a peculiar characteristic, since of the eight naturally occurring forms, α-tocopherol is the most active homologues retained in human plasma with the highest antioxidant activity.\textsuperscript{47} In addition to its activity as an antioxidant in the prevention of potentially harmful phospholipid oxidation events at plasma membrane,\textsuperscript{48} vitamin E is also involved in various metabolic processes such as regulation of gene expression, cell signalling and immune function.\textsuperscript{49} Moreover, vitamin E forms suppress pro-inflammatory signalling such as STAT3/6 and NF-κB and inhibit eicosanoids catalysed by cyclooxygenase- and 5-lipoxygenase.\textsuperscript{44} Consistent with mechanistic findings, assumption of vitamin E contributes to the prevention of various diseases as cardiovascular, neurodegenerative, non-alcoholic fatty liver diseases and some kind of cancer.\textsuperscript{50}

**Phytosterols and Phytostanols**
HNs are also rich in plant sterols (phytosterols and phytostanols). Phytosterols are comparable in structure to cholesterol, possessing the same basic cyclopentanoperhydrophenanthrene ring structure but differentiating in the side chain at C24 and/or the position and configuration of unsaturated double bonds and the optical rotation at chiral carbons.\textsuperscript{51,52} Phytostanols are produced by hydrogenating phytosterols.

Sterols include a major percentage of the unsaponifiable matter of most vegetable oils and they exist as free sterols and sterol esters of fatty acids. In HN, the total phytosterols content ranges from 133.8 mg/100g to 263 mg/100g of oil. Among them,
β-sitosterol is the major one with a mean percentage of 83.6%, while Δ5-avenasterol and campesterol are the second and the third components of the group with mean values of 6.1% and 5.8%, respectively. Other minor phytosterol/phytostanol found in HN are sitostanol, stigmasterol, cholestenol, campestanol, Δ7-campesterol, Δ5,23-stigmastadienol, Δ5,24-stigmastadienol, clerosterol, Δ7-stigmasterol, and Δ7-avenasterol. The HN oil sterol composition is influenced by agronomic and environmental conditions, crop season, cultivar as well as storage conditions and oil extraction methods. In particular, the percentage of sterol esters ranged from 11% to 75%, mainly depending on the refined process and geographical origin. It is remarkable that sterol esters of Turkish HN oils (either crude or refined) included more than 40%, while they were less than 35% in HN oils from France, Italy and Spain, the lowest values being for roasted crude HN oils (11–16%).

Phytosterols are well-known for their ability of reducing blood cholesterol. In fact, many studies have demonstrated that phytosterols induce clinically significant reductions in low-density lipoprotein cholesterol (LDL-C) levels. In particular, daily dose of 1.5 g - 3 g of phytosterols, phytostanols and their esters have been suggested for lowering total cholesterol (TC) and LDL-C concentration significantly. One of the most suggested mechanisms of action of phytosterols in lowering plasma cholesterol concentration is their capacity to reduce cholesterol absorption at intestinal level. In fact, phytosterols are structurally similar to cholesterol and are assimilated into micelles in the intestinal tract. Since plant sterols are more hydrophobic than cholesterol, they possess a higher inclination for micelles than they have for cholesterol. Consequently, they displace cholesterol from mixed micelles and determine a reduction in the duodenal cholesterol absorption and a higher fecal excretion of cholesterol. Furthermore, in vitro and in vivo studies suggest that phytosterols content in diet promotes a decrease in various cancers including colon, breast and prostate cancer by slowing cell cycle progression, inducing apoptosis, and inhibiting tumor metastasis.

Squalene
Squalene is a highly unsaturated all-trans linear terpenoid hydrocarbon which comports as the biochemical precursor of terpenoids and sterols with their central role in human, animal and plant functions. It is extensively present in nature, and considerable quantities are found in oil from shark and whale liver, wheat-germ, palm, rice bran, olive and amaranth. Among nuts, squalene content was higher in HN > macadamia > peanuts > almonds > walnut, with a value in HN ranging from 93 mg/kg to 885 mg/kg oil, depending by cultivar, environmental conditions, geographical origin, fruit development and the method of squalene extraction. In particular for the latter, squalene contents appeared higher in HN oil extracted with solvent compared to cold pressed one, probably due to higher squalene solubility in hexane.

From a nutritional perspective, squalene has important beneficial effects on health, mainly related to its hypolipidemic, anticancer, antioxidant and detoxifying activity. Enriched squalene diet significantly increased paraoxonase 1 and high-density lipoprotein cholesterol (HDL-C) and reduced oxidative damage in animals. In parallel to its plasma lipids lowering effect, experimental studies have revealed that squalene may efficiently prevent chemically-induced skin, lung
and colon tumorigenesis in rats. The mechanisms implicated for the chemopreventive action of squalene can comprise modulation of carcinogen activation, anti-oxidative activities and inhibition of Ras farnesylation.\textsuperscript{68,69} Furthermore, various \textit{in vivo} and \textit{in vitro} studies suggested that squalene possesses an antioxidant activity, principally acting as radical scavenger, and may protect different biological molecules as DNA, lipids and protein against oxidative stress.\textsuperscript{70-74}

**Phenols**

The health effects of diets rich in fruits and vegetables are due not only to minerals, vitamins and fibre but also to a variety of plant secondary metabolites referred collectively as polyphenols,\textsuperscript{75} to which many biological effects have been attributed.\textsuperscript{76-78} The preponderance of polyphenols in plants exist as glycosides with diverse sugar units at different positions of the polyphenol skeletons and have been categorized by their biological function, source of origin and chemical structure.\textsuperscript{79-80} According to the chemical structures of aglycones, polyphenols may be classified in flavonoids, stilbenes, lignans, flavonoids, hydrobenzoic and hydroxycinnamic acids.\textsuperscript{81}

The presence of several phenolic and hydroxycinnamic acids (sinapic acid, gallic acid, \textit{p}-coumaric acid, caffeic acid, vanillic acid, protocatechuic acid, ferulic acid,\textsuperscript{,}) and flavonoids (catechin, quercetin, myricetin, kaempferol) have been reported in HNs. In particular, the main polyphenolic subclass comprises of mono- and oligomeric flavan 3-ols, which accounts between 34.2 and 58.3\% in HN kernels, with a total phenolic content ranging from 491.2 to 1700.4 mg of gallic acids equivalent/kg.\textsuperscript{82}

Moreover, roasting increase the phenolic content in a time and temperature dependent manner compared to raw HNs.\textsuperscript{83} Numerous epidemiological and nutritional evidences suggest that natural polyphenols play a key role in prevention of cancer,\textsuperscript{84} and in particular Li & Parry have shown that extract of HN roasted skin cultivated in Oregon significantly reduce the proliferation of a human colon cancer cell line.\textsuperscript{85}

<table>
<thead>
<tr>
<th>Table 1. HS Nutrient Composition</th>
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<tbody>
<tr>
<td><strong>Total lipids</strong> &amp; &gt; 60% d.w.</td>
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<tr>
<td><strong>Oleic acid</strong> &amp; 76.7% - 82.8%</td>
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<tr>
<td><strong>Linoleic acid</strong> &amp; 9.2%</td>
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<tr>
<td><strong>Palmitic acid</strong> &amp; 5.6%</td>
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<tr>
<td><strong>Stearic acid</strong> &amp; 2.7%</td>
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<tr>
<td><strong>Vaccenic acid</strong> &amp; 1.4%</td>
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<tr>
<td><strong>Fibre</strong> &amp; 8.05 g/100g - 12.07 g/100g</td>
</tr>
<tr>
<td><strong>K</strong> &amp; 147 mg/100 – 761 mg/100mg</td>
</tr>
<tr>
<td><strong>P</strong> &amp; 256 mg/100g – 458 mg/100g</td>
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<td><strong>Mg</strong> &amp; 34 mg/100g – 335 mg/100g</td>
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<tr>
<td><strong>Cu</strong> &amp; 0.94 mg/100g – 3.47 mg/100g</td>
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<tr>
<td><strong>Mn</strong> &amp; 1.4 mg/100g – 19 mg/100g</td>
</tr>
<tr>
<td><strong>Se</strong> &amp; 5.5 μg/100 – 60 μg/100</td>
</tr>
<tr>
<td><strong>Tocols</strong> &amp; 41.9 mg/100g extracted oil</td>
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<td><strong>Total phytosterols</strong> &amp; 133.8 mg/100g – 263 mg/100g</td>
</tr>
<tr>
<td><strong>Total sterol esters</strong> &amp; 11% - 75%</td>
</tr>
<tr>
<td><strong>\textbf{\textbeta}-Sitosterol</strong> &amp; 83.6%</td>
</tr>
<tr>
<td><strong>\textDelta5-Avenasterol</strong> &amp; 6.1%</td>
</tr>
<tr>
<td><strong>Campesterol</strong> &amp; 5.8%</td>
</tr>
<tr>
<td><strong>Squalene</strong> &amp; 93 mg/kg oil – 885 mg/kg oil</td>
</tr>
<tr>
<td><strong>Total polyphenols</strong> &amp; 0.491 g/kg oil – 1.7 g of gallic acid equivalent/kg</td>
</tr>
<tr>
<td><strong>Flavan 3-ols</strong> &amp; 34.2% - 58.3%</td>
</tr>
</tbody>
</table>
Health Effects of HNs Consumption

Even though a significant number of clinical studies on various tree nuts have been realized, only few studies specifically related to HN have been conducted. In a recent systematic review and bayesian meta-analysis, Perna et al. evidenced that HN-enriched diet is associated with a decrease of LDL-C and TC equal to -0.150 mmol/L and -0.127 mmol/L, respectively, in favour of a HN-enriched diet. More recently, this trend was also confirmed by Deon et al., who reported in adolescents with primary hyperlipidemia a significant effect on serum LDL-C, HDL-C/LDL-C ratio and non-HDL-C. Similar results in the reduction of serum LDL-C were also observed by Santi et al. in healthy volunteers. At the same time, HN consumption was able to decrease LDL oxidation (-15.7%) in normolipidemic healthy volunteers and plasma inflammatory markers such as high-sensitivity C-reactive protein (-35.9%), soluble vascular cell adhesion molecule-1 (-10.6%) and soluble intercellular adhesion molecule-1 (-8.08%) in hypercholesterolemic subjects, compared to a control diet.

Future Directions

At present, considering the world production of HNs, another relevant challenge for the sector could be to turn food processing by-products and wastes into new ingredients. In fact, during processing of HN, by-products arise as waste materials. Among them, none has any commercial value except the HN hard shell, which is currently used as a heating source upon burning. HN wastes could represent functional ingredients to take advantage of to improve nutritional and health value of foods. To do it, comprehensive studies of their chemical composition, physical structure, sensorial properties and nutritional characteristics are necessary.

Conclusion

The expansion of studies and investigations intended to exam the effectiveness of functional nutrients and food components has illuminated many parts of the multifaceted connection between nutrition and health. Despite, we have to take in mind that our diet is based on foods and not on individual compounds. Consequently, it is fundamental to demonstrate that certain nutrients have a positive effect in the prevention of a disease, and to recognize which foods possess them at relevant concentration. Moreover, foods are complex matrices in which those components could have synergistic effects, and bioaccessibility may be influenced by both gastrointestinal conditions and chemical characteristics of the food matrix.

HN is an example of synergism among nutrients that can be transformed into a large variety of products consumed by a wide range of population every day. Studies reported in this review underscore the health-promoting effects of HN nutrients and consumption. At present, more scientific confirmations are needed to regard HNs as functional food, but results are auspicious and there are various elements of great attention that push the researchers to expand the scientific acquaintance about nuts in general and HNs in particular.

Conflict of Interest

The Author reports no potential conflict of interest.

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