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Review

Diet, Polyphenols, and Human Evolution

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Featured Application: The present paper contributes to improve the knowledge about the role of the diet and its functional components in human development and health. The factors analyzed in the present review could also help in understanding dietetic factors mainly associated with neuroprotection.

Abstract: Although diet has contributed significantly to the evolution of human beings, the composition of the diet that has most affected this phenomenon is still an open issue. Diet has undoubtedly participated in the acquisition of the skills that underlie the differentiation of humans from other animal species and in this context the development of the nervous system has played a primary role. This paper aimed to: (1) outline the relationship between diet and human evolution; (2) evaluate how a variation in food consumption may have contributed to the enhancement of cognitive and adaptive capacities. The most widespread diet among the ancient populations that showed the highest levels of civilization (that is well-organized societies, using advanced technical tools, and promoting art and science) was very close to what is now defined as the Mediterranean diet. This suggests that a dietary approach typical of the Mediterranean basin (little meat and some fish; abundant cereals, legumes, fruit, vegetables and wine) significantly increased the intake of antioxidant molecules, including polyphenols, which along with other factors may have modulated the cognitive evolution of humans.

Keywords: polyphenols; human evolution; cognitive evolution; Mediterranean diet

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1. Introduction

Human evolution is the process by which human beings developed on Earth from now-extinct species. *Homo sapiens*, the present human tribe, evolved from *Homo erectus* about 300,000 years ago in Sub-Saharan Africa. Human evolution (see Table 1) lasted millions of years passing through other hominins: *Ardipithecus*, *Australopithecus*, and other species of *Homo* [1–3].

The correlation between diet and human evolution is of great scientific fascination. Although it is generally acknowledged that diet played a critical role in the evolutionary development of the human species, it is unclear which parts of the diet had the greatest impact. Diet was key to acquiring the skills that differentiate humans from other animal species. In this context, the development of the nervous system played a primary role.

Several diets have been hypothesized as the "fuel" of human evolution and this paper critically evaluates their role, focusing on the nervous system.

Table 1. Human evolution and related characteristics [1,2].

Genus/Species	Period	Geographical Area	Other Information
Australopithecines	Around 4.2 to 3–2 × 10^6 years ago	Eastern and southern Africa	Bipedal, small brain, scavenger, use of tools
Homo habilis	2.4–1.4 × 10^6 years ago	Eastern and southern Africa	Nomadic, with large braincase, small face and teeth. Probably the first species making stone tools
H. rudolfensis	Around 1.9–1.8 × 10^6 years ago	Eastern Africa	Very large braincase, long face, large molar and pre-molar teeth
H. erectus	1.89 × 10^6 to 110,000 years ago	Africa, Western and East Asia	Body proportions similar to those of modern humans. Lived on the ground and was able to walk and run. Probably this species produced the first hand-axe, a prehistoric stone tool.
H. heidelbergensis	About 700,000–200,000 years ago	Europe, Eastern and Southern Africa and possibly Asia	Very large brow ridges, large braincase and flatter face. First old human species living in cold regions, used fire and hunted large animals with wooden spears
H. neanderthalensis	About 400,000–40,000 years ago	Europe, and Southwestern to Central Asia	The closest extinct human relative. Big nose, large middle part of the face, short body and large brain. Used sophisticated tools, controlled fire, made and used clothing. Skilled hunters, collected plants as food. Buried their dead.
H. naledi	335,000–256,000 years ago (most recent dating) [a]	South Africa	Not very tall, rather slim, very small brain, perhaps buried their dead
H. floresiensis	Around 100,000–50,000 years ago	Asia (Indonesia)	Short, with small brain, relatively large teeth and feet. Used stone tools, hunted medium-sized animals and may have used fire
H. sapiens (archaic)	300,000 years ago, to present	Evolution from Africa, then worldwide	Compared to earlier humans, *H. sapiens* had a lighter skeleton, large brain, low or no heavy brow ridges and prognathism, smaller teeth. Archaic *H. sapiens* gathered and hunted food and evolved behavior, allowing survival in unfavorable conditions
H. sapiens (modern)			

[a] [3].

2. Diet and the Evolution of the Human Species

Comparing the needs for nutrients of humans to those of other animals, particularly mammals from a qualitative point of view, there are no remarkable differences. However, the type of foods included in the diet can vary quite significantly [4] and there are very clear differences between herbivores, carnivores and omnivores. What most differentiates humans from other animals is the human culture of food, as highlighted by the proliferation around the world of restaurants from many different nations. Human beings tend to retain their eating habits as long as there are no restrictions that force them to have to look for other sources of calories or nutrients, as in the case of famine or moving to other geographical areas where certain foods are not available.

Paleontologists and anthropologists have studied the lifestyles of the human species during evolution, observing that the main driver of changes is the ability to adapt to new conditions [5]. One of these external stimuli is variations in the diet. For example, the discovery of fire, and the ability to control it, shifted the diet from exclusively raw foods to foods that could be cooked. The thermal processing of food, mainly cooking, facilitated an increase in calories by improving the survival and reproductive capacity of the human species [6,7].

It is difficult to date when food was first cooked, which could also have occurred pre-*Homo sapiens* in Africa. The researchers sought to obtain information on the diet by studying the physical and morphological changes that occurred in *Homo* species over the various eras: (1) the type of teeth, which are smaller in modern humans given the greater softness of cooked food; (2) the jaw that became more robust when foods were consumed exclusively raw; (3) the different ways the intestine developed [8,9]. An attempt was also made to correlate the time spent by hominids in activities related to nutrition and the evolution of behavior, but there are no accurate data on this topic [9,10].

More precise information could be derived from the remains of food found in prehistoric sites. However, food is preserved at different levels. For example, fish have very fragile bones that completely disintegrate over time [11].

There have been strong discussions regarding the most suitable diet for humans and how this has varied during evolution. Human beings are usually considered omnivorous, thus making it easy to adapt to different environmental conditions and availability of food.

Some authors believe that primitive hunter–gatherers used a diet that was at least 50% based on fish and meat [12]. Given the arid savannah in which humans first appeared, other research contends that they consumed food of vegetable origin: fruit in the seasons in which it was available, and bulbs [13,14]. In the savannah, foods of animal origin were less available and excessive consumption would still have led to kidney and liver problems, due to the high protein content. Moreover, it is known that humans preferably use carbohydrates and fats for energy purposes and limit the caloric intake from the protein fraction.

Balancing the two opinions, it seems reasonable to think that human beings need an omnivorous diet [15]. In fact, humans synthesize vitamin A from beta carotene, unlike pure carnivores that obtain it preformed from meat. Humans also require vitamin B_{12}, which is obtained exclusively from foods of an animal origin.

2.1. Key Points for the Variation in the Diet in the Ancestors of Modern Humans

The dietary habits of our ancestors have changed and been consolidated over the millennia. However, some events/discoveries have made some transitions much faster. As reported in Table 1, the size and shape of the teeth, the structure of the enamel, and the jaw mechanics are commonly used to identify the type of diet prevalent in the various ancestors of modern humans.

Findings from fossils of ancestral hominids reveal an extraordinary change in eating habits between 4.4 and 2.2 million years ago, i.e., the period dominated above all by Australopithecines (*A. anamensis*, *A. afarensis*, *A. africanus*). The teeth of these hominids were suitable to consume foods with different consistencies: from soft fruits to hard (possibly crumbly) foods. The wide dietetic pattern allowed these species to adapt to different habitats, from the forest to the open savannah [16].

Between 2 and 3 million years ago, hominids had to deal with a substantial reduction in rainfall, which led to a new dietary approach. Given the shortage of fruits due to the drought, the hominids had to turn to meat from hunted animals, as well as tubers and roots, to obtain their necessary energy and nutrients. The consequent need to defend themselves from wild animals, combined with hunting for food, certainly stimulated the sense of "solidarity" between individuals.

2.1.1. The "Discovery" of Fire

A key event that changed the diet of primitive man was the discovery around 400,000 years ago of fire by *H. erectus*, the direct ancestor of modern humans. The still-discussed attribution of the use of fire to *H. erectus* derives from the structure of the related gastrointestinal tract (particularly the colon), which would not have been suitable for a diet based only on raw foods. It thus seems likely that this species cooked food for the first time, so that meat and harder foods (roots and fibrous foods) could be eaten, and the bioavailability of some nutrients (proteins and carbohydrates) increased [17]. In other cases, toxic foods became edible when heat was able to inactivate the toxic molecules [4].

2.1.2. The Advent of Agriculture

The second "revolutionary" event in the history of the human diet was the move to a sedentary life. About 11,000 years ago, in Southeast Asia, humans reduced their nomadic activity to remain in favorable geographical areas to cultivate vegetables. This, in addition to ensuring the availability of food over time, meant that animals were easier to breed [18]. This evolutionary step was facilitated by simpler and more efficient metabolic pathways of glucose. In fact, people from populations with high-starch diets, associated with the advent of agriculture, had on average more amylase 1 (*AMY1*) copies than people who had low-starch diets [4]. A better use of glucose may have aided the development of the nervous system, since in the nervous system, glucose cannot be obtained from non-saccharide precursors.

Clearly, it is difficult to define the composition of the diet of species that lived in very different periods and geographical areas. Many morphological, metabolic and fossil remains give some evidence of the food "chain" through the eras, but to reach more certain conclusions, new and rigorous studies are necessary.

Table 2 provides information on dietary trends, but is not exhaustive regarding the foods available at that time. What we know of the diet of those living from the Iron Age onwards is based on historical documents.

Table 2. Evolution of cultures, main civilizations, and dietetic habits.

Epoch	Period Range	Cultural Stage [a]	Period	Human Evolution/Civilizations	Diet [b]
Pliocene	Start: 5.3×10^6 years ago End 2.58×10^6 years ago			*Australopithecus*	The strong jaw, the flattened teeth and the small pronounced canines indicate a predominantly vegetarian diet.
Pleistocene	Start: 2.58×10^6 years ago End: 11,700 years ago	Paleolithic Period (Old Stone age)	2.50×10^6–10,000 BC	*Homo habilis*, *H. rudolfensis*, *H. erectus*, *H. rudolfensis*, *H. ergaster*, *H. heidelbergensis*, *H. neanderthalensis*, *H. naledi*, *H. sapiens*	Nomadism, food through hunting. (20%) and gathering berries, nuts and roots (80%). *H. erectus* started using fire.
Holocene	Start: 11,700 years ago End: Present	Mesolithic Period (Middle Stone Age)	10,000–8000 BC	*H. sapiens*	
		Neolithic Period (New Stone Age)	8000–3000 BC		Animal husbandry and sedentary cultivation begin (cereals). First attempts to cultivate vines, olives, figs and hazelnuts.
		Copper Age	5000–3000 BC	First State Societies (Egypt, Fertile Crescent, Greece, Crete, Indus Valley, China)	Transition to Bronze Age.
		Bronze Age	3000–1300 BC	Egyptians	Some meat, preserved fish. Prevalence of cereals, milk and derivatives, legumes, fruit, honey, wine and beer.
				Sumerians, Assyrians and Babylonians (Mesopotamia)	Food from both animal and vegetable origin (cereals, legumes, fruits and meat from animal breeding).
				Aegean area civilizations (Minoan and Mycenaean civilizations)	Foods from both animal and vegetable origin (millet, wheat, legumes, fruits and meat from sheep, goat and cattle). Seafood was also important in the Minoan diet.

Table 2. *Cont.*

Epoch	Period Range	Cultural Stage [a]	Period	Human Evolution/Civilizations	Diet [b]
Holocene	Start: 11,700 years ago End: Present	Iron Age	1300–900 BC	Egyptian (Third intermediate period)	See Bronze Age.
				Aegean civilizations (“dark ages”)	See Bronze Age.
				Phoenicians	Food from both animal and vegetable origin (cereals, legumes, fruits and meat from animal breeding, olive oil and wine).
				Others (Persian Empire, Celts, German tribes)	Different dietetic habits.
		Classical Age	900 BC–600 AD	Etruscan culture	Fish in coastal areas, eel, meat (beef, pork, lamb), vegetables, olives and olive oil, cereals and derivatives, cheese, fermented milk, spices, wine.
				Roman Republic/Empire	Cereals and derivatives, legumes, mushrooms, dates, spices, honey, fruit. Some meat and fish. Wine.
				Classical Greece	Cereals and derivatives, cooked and raw vegetables, offal, salads, cheeses, olives, fruit (cherries, strawberries, grapes, figs), olive oil and wine. Some meat and fish.
		Modern Age	Present time		Different habits according to geographical area and cultural/religious group.

[a] Data from: [19]; [b] References in Section 2.1.

2.2. Key Points for the Variation in the Diet in the Ancestors of Modern Man

2.2.1. Neolithic Age

The Neolithic period was a turning point in human evolution due to the establishment of a sedentary life with animal husbandry and land cultivation. In a relative short period of time, *H. sapiens* passed from being a hunter to a breeder of animals. The first examples of the husbandry of cattle, sheep, goats and pigs were in the area of the Fertile Crescent and this extraordinary event for the evolution of man is dated between 13,000 and 10,000 years ago [20]. This transition was also documented in Anatolia in the Pre-Pottery Neolithic period (about 9500–7000 BC) [21].

2.2.2. Bronze Age

During the Bronze Age, some of the most important ancient civilizations developed. Among these, the Egyptian civilization, due to its singularity and level of knowledge, has always fascinated both researchers and the people interested in archeology/ancient history. Egyptian civilization certainly benefited from its favorable geographical position in the Nile Valley, and from the development of agriculture. The floods of the river and their hydraulic knowledge enabled the abundant production of food, the growth in population, and cultural and social development [22]. Knowledge of the diet of the Egyptians is derived largely from images on their tombs. Their diet, which was similar to the Mediterranean diet, included cereals and their derivatives (especially bread), milk and its derivatives, legumes (peas, beans, lentils, etc.) onions, lettuce, cucumbers, fruits, papyrus stalks, and honey. The Egyptians drank wine and beer. Pork and mutton were eaten in moderation, and beef was mostly limited to priests during religious celebrations [23]. Surprisingly, for a people who lived mainly close to the Nile, fish consumption was quite limited. Some species were considered sacred and therefore not consumable, while others were eaten after drying, salting, etc. [24].

Three main civilizations developed in Mesopotamia between 3000 and 600 BC: the Sumerians, Assyrians, and Babylonians. They had a diet based on both animal and plant-based foods. They cultivated cereals (barley and wheat) for both themselves and their animals, and consumed fruit and vegetables (including pomegranate, dates, figs, onions, legumes). They bred sheep, goats and cattle of which they used meat and milk [25].

In the Aegean area, during the Bronze Age, two independent civilizations developed: the Minoans in Crete, and the Mycenaeans in central and southern Greece. The climate was suited to cultivating wheat, barley, olive trees and grapes. Archaeological findings and paintings highlight the consumption of legumes (lentils and peas), nuts, and figs, as well as products derived from the breeding of pigs, sheep, goats, cattle, and deer [26]. Seafood was also important in the Cretan diet, with prevalence of edible mollusks and the occasional use of fish [27].

2.2.3. Iron Age

The duration of the Iron Age varies depending on the geographical area considered. It began when iron tools and weapons were locally more widespread than the bronze equivalents. For some societies, particularly the Greeks, the Iron Age was the start of a period of cultural decline [28]. The most important emerging civilization was that of the Phoenicians, which represented the continuation into the Iron Age of the Canaanite civilization who had already been prosperous in the Bronze Age. The Phoenicians and the Canaanites shared the same area (Lebanon, Syria and Israel), language, and culture. The Phoenicians were above all a people of navigators dedicated to trade.

The Phoenicians consumed high quantities of cereals (wheat, barley) and their derivatives (bread, biscuits), along with vegetables and legumes (peas, lentils, chickpeas, etc.). They ate fruit (apples, pomegranates, almonds, pistachios, dates and figs) and used olive oil as a condiment. The breeding of animals led to a moderate consumption of meat, mainly from cattle, sheep, and poultry. Wine became widespread with the introduction of vines [29,30].

2.2.4. Classical Age

The Etruscan civilization, which developed in Italy in the period between 800 and 300 BC, gave great importance to social events involving the consumption of food and beverage. The Etruscans were not only food producers, but were also importers and exporters. By trading products with other Mediterranean cultures (Phenicia, Spain and African coastal areas), there was no shortage of exotic foods at Etruscan banquets. They consumed beef, lamb and pork, fish (mostly tuna), eggs, cheeses, olives, cereals and their derivatives, and fruit (including grapes and nuts). They flavored their food with honey, spices, and vinegar, and were famous producers/exporters of wine [31].

The diet in Greece and Rome was very similar to the Mediterranean Diet. They ate grains, legumes, vegetables, fruit, milk, cheese, and to a lesser extent fish and meat. Olive oil was the basic condiment. Like the Etruscans, the Greeks and Romans imported cereals, over which there was control by the government. It is believed that their short life expectancy, only 30–35 years, was not due to malnutrition, but to disease and war [32].

3. Role of the Diet in the Evolution of the Brain

The two scientific positions on the prevailing composition of the diet of primitive populations, i.e., vegetables versus meat, also impacts the role that diet played in the development of the nervous system.

H. erectus was the evolutionary stage of the human species for which the main morphological and physiological changes were observed in the whole organism, but particularly in the brain. During the evolution of humans, there was a significant increase in encephalization. The increase in the volume of the neocortex reached 76% compared to the average 16% in other animals [33,34].

Many factors contributed to this increase in encephalization, of which one was diet. The quality of foods along with the activities required to search for them increased the level of socialization, thereby stimulating intelligence and the use of language [35].

The brain and its related cognitive functions require foods that are not only rich in energy, but that are also nutritional. The quality of food was thus key to our evolution. The composition of the food and nutrient bioavailability likely modulated the development of the nervous system. The enhanced ability to use glucose, described in Section 2.1.2, is only one of the possible evolutionary steps. In fact, the increased number of amylase copies aided a more effective use of cereals and starchy foods, which are the basis of the Mediterranean diet [5]. Aiello et al. (1995) argued that the smaller extension of the intestine in "evolved" humans is compatible only with foods with high digestibility and therefore characterized by excellent bioavailability [36].

In other primates, Foley et al. (1991) found that species that eat leaves have smaller brains than those that feed on insects and meat [37]. This situation is somewhat similar to the one occurred in the transition from Australopithecines to genus *Homo*, who introduced foods with a higher nutritional value, such as tubers and meat.

The correlation between diet and human evolution cannot have been limited to just these changes. The introduction of a more enhanced diet (meat, products from agriculture, tubers, etc.) certainly allowed *H. sapiens* to achieve previously unknown objectives. However, it is also clear that the geographical distribution of the human species has shown how new stimuli can be critical in the birth and development of the advanced cultures of the Bronze Age, as illustrated in Table 2. It is therefore interesting to investigate how diet may have affected this phenomenon.

4. Impact of the Diet Composition on Cognitive Functions

How the composition of diet helped the development of civilizations is based on assumptions and recent knowledge related to the influence that certain foods/nutrients have on cognitive abilities. Diet, physical activity and socialization all shape and modify brain functions. Many molecules of dietary origin, with both energetic and functional properties, influence the nervous system, modulating different processes such as neurotransmitter profiles, synaptic transmission, membrane fluidity, and signal transduction [38]. The components of the diet affect human cognitive abilities, both positively and negatively. The molecules that researchers agree on to a greater extent are described below.

4.1. Lipids

The composition of the brain is 77–78% water, 10–12% lipids, 8% proteins, 1% carbohydrates, 2% soluble organic substances, and 1% salt [39]. Excluding water, lipids thus represent 50% of brain. More associations have been found for lipids than for any other components in studies relating to the influence of diet on brain function. The nervous system is the human tissue second in abundance in lipids and diversity in its composition. Some authors have associated the cognitive abilities acquired by human beings through evolution to the multiple functions of lipids in the nervous system: their structural role in biological membranes, participation as bioactive messengers involved in cell signaling and contribution to energy supply [40].

Dietetic lipids can have both a positive and negative influence, as demonstrated in studies performed in humans or laboratory animals. Saturated fatty acids, which are mainly of animal origin, appear to promote a decline in cognitive abilities in elderly subjects [41,42], as well as a reduction in the learning abilities in rodents [43,44].

On the other hand, an adequate intake of omega-3 fatty acids, and in particular docosahexaenoic acid, DHA, seems to improve cognitive abilities in the elderly [38,42,45], including positive results in patients with mood disorders [46].

Studies on the role of DHA in modulating cognitive properties have also identified its importance in the development of the nervous system of children [47,48]. The current trend to supplement bottle feeding products with DHA comes from convincing evidence that a suitable intake of this molecule in infants and toddlers produces positive learning and behavioral outcomes [49]. DHA is present in high concentrations in fish, such as salmon, sardines, anchovies, mackerel and tuna (approximately 500–1900 mg/serving size). The DHA in such fish is beneficial for both the cardiovascular system and cognitive functions [45]. The Mediterranean diet is an excellent source of omega-3 fatty acids, both of vegetable and animal origin, and includes olives and their derivatives, seeds, and fish in smaller quantities.

4.2. Vitamins and Minerals

Several vitamins have been associated with positive effects on cognitive properties; among these are the vitamins of group B (B_6, B_{12} and folates) [50,51] and vitamin D [52]. Antioxidant vitamins (vitamin A, E, C) act against free radicals and thus possibly protect against cognitive decline. Beydoun et al. (2015) correlated the intake of antioxidant vitamins with the cognitive functions in 1274 adults (age: 30–64 years) [53]. They found that a higher intake of vitamin E was associated with better performance in verbal memory/fluency in the whole population and in the psychomotor speed test among women. The positive effects of antioxidant molecules on brain function are further investigated in Section 6.

Vitamin C is an electron donor and shows important physiological roles since it acts as a cofactor for fifteen mammalian enzymes [54]. Interestingly, although vitamin C has an important role in the body, humans have lost its synthetic capacity. Three key reasons have been hypothesized as being the basis of this unusual evolutionary selection: (1) the presence of a high quantity of vitamin C in the diet; (2) its role in selecting young people who had a lower requirement of vitamin C compared to old people so that they survived, thus making reproduction more successful; (3) a more efficient antioxidant defense status [53]. All these aspects could have contributed to human evolution and to the success of Mediterranean diet, in which fruits high in vitamin C are abundant.

How minerals contribute to cognitive functions has mostly been assessed in studies where dietary supplementation is based on vitamin–mineral complexes. Such studies can lead to contrasting results, above all because the evidence depends on the nutritional status of the population considered, the duration of the integration, and the form in which the nutrients are administered, all of which can modify their bioavailability. What can be reasonably concluded is that an adequate intake of vitamins and minerals can help to preserve cognitive abilities in old age, even just in terms of an improvement in mood or in the sensation of physical and mental fatigue [55]. Various minerals have been suggested as possible modulators of cognitive disabilities, e.g., iron both in adults [56] and children [57], selenium [58], and copper [59]. A significant consumption of fruit and other vegetables, rich in vitamins and minerals, by the populations following the Mediterranean-type diet supports the role of this dietary choice in improving the cognitive functions of humans during their evolution.

4.3. Other Molecules

Several approaches based on traditional medicine have (although not always convincingly) highlighted a possible effect of botanical extracts on brain functions (for example *Hypericum perforatum*, *Bacopa monnieri*, *Ginkgo biloba*, etc.), and more recently, the success of dietary supplements with botanical ingredients has further stimulated studies in this area. The evaluation of the effectiveness of plant extracts on the nervous system (as for other systems) requires well-planned studies in humans, in which particular attention must be paid to the product administered (type of extract, abundance of active molecules, etc.). Although very interesting, this topic will not be dealt with in detail as it is beyond the scope of this paper.

Instead, some classes of molecules, commonly known as polyphenols, which have been extensively treated and associated with the health effects of some foods/beverages, are detailed in Section 6 (Polyphenols as protectors of CNS from oxidative stress).

5. Brain and Oxidative Stress

The human brain depends on the availability of oxygen, of which it consumes about 20% of the body's total requirement at rest. A prolonged absence of oxygen can be devastating, as it prevents the synthesis of ATP which is essential for brain activity [60]. Although our nervous system depends on oxygen for the aerobic metabolic processes, it can become dangerous, since oxidative stress can promote neurodegeneration. High concentrations of ROS alter the structure of macromolecules, such as lipids, proteins and nucleic acids. In particular, the oxidation of polyunsaturated fatty acids, which are part of the plasma membrane of neural cells, can cause severe damage.

The production of radicals, in addition explaining the molecular mechanisms underlying "physiological" aging, reveals some steps in the pathogenesis of neurodegenerative disorders [61]. The presence of free radicals, produced within the CNS, becomes extremely dangerous when the body's ability to eliminate them and repair the damage caused by their actions is overwhelmed. When a high production of free radicals is not balanced by antioxidant action, this leads to cognitive decline in the elderly but also has a negative impact even in the early stages of the human life. Different molecular mechanisms could explain how ROS can influence human health. Glutathione is a tripeptide that plays a critical role in maintaining redox balance, i.e., the reduction of oxidative stress, the improvement of metabolic detoxification and the regulation of the function of the immune system. Glutathione depletion in the brain is a common finding in patients with neurodegenerative disorders [62]. Optimizing glutathione levels (in its reduced form) has been proposed as a strategy for health promotion and disease prevention, although causal relationships remain unclear. Clinical research suggests that an adequate diet (rich in phytochemicals) may have important effects on the levels of reduced circulating glutathione, which can in turn translate into health benefits [63].

Another key period for its consequences on brain development is pregnancy, which is characterized by very high metabolic activity. The speed of development makes embryonic and fetal tissues highly sensitive to the presence of oxidative stress and, in the absence of antioxidant protection, ROS may be toxic [64]. Early development needs specific signaling processes in order to regulate cell proliferation. Differentiation must occur at the correct place and the correct time to guarantee the development of a healthy embryo. These pathways are sensitive to changes in the endogenous redox state and are highly sensitive to imbalances between reactive species and antioxidant defenses. The embryonic and fetal brain structures are particularly sensitive to ROS, because they are very rich in polyunsaturated fatty acids, whose oxidation is not always balanced by protective enzymatic activities (superoxide dismutase, catalase, glutathione peroxidase). Furthermore, it has been demonstrated that mitochondria play a critical role in physiological adaptations during pregnancy as observed by the differences in the mitochondrial function of normal and complicated pregnancies. During pregnancy there is an increase in the nutritional requirements necessary to support fetal growth and the metabolism of maternal and fetal tissues. The optimal availability of nutrients regulates mitochondrial metabolism; an excessive intake of macronutrients can lead to oxidative stress and contribute to mitochondrial dysfunction, while micronutrients contribute to optimal mitochondrial processes, as cofactors in energy metabolism and/or as antioxidants. In summary, inadequate consumption of macronutrients and micronutrients can lead to negative pregnancy outcomes, possibly through mitochondrial dysfunction, compromising the energy supply, metabolism, biosynthetic pathways, and the availability of metabolic cofactors that modulate epigenetic processes [65].

Although the antioxidant "patrimony" is normally sufficient to avoid problems, excess ROS can lead to neurological and morphological abnormalities. In fact, with fetuses that have congenital CNS malformations, the amniotic fluid contains biomarkers of oxidative stress [66].

6. Polyphenols and CNS: Protection from Oxidative Stress and Other Functions

The dietary intake of antioxidants, both in the form of food as such and as food supplements has been studied to identify the optimal intake of compounds with anti-oxidizing activity that is able to reduce damage from ROS in the CNS and prevent neurodegeneration. Antioxidant protection is particularly important since the frequency of neurological disorders is increasing due to a longer life expectancy. Many molecules have antioxidant properties and many of these have shown potential CNS benefits (see Section 4). Vitamins A, C, E, beta-carotene, and polyphenols are certainly the most frequently mentioned molecules in this regard.

The term "polyphenols" includes many natural organic substances, which are classified into four classes: flavonoids (including flavones, flavonols, flavanones, isoflavones, anthocyanidins, chalcones, and catechins), stilbenes, lignans, and phenolic acids. The main dietary sources of polyphenols have a vegetal origin [67]. Each group of molecules has its own specific functions and benefits deriving from dietary intake, but the most well-established are their antioxidant and anti-inflammatory properties.

The way polyphenols contribute to neuroprotection is not limited to their antioxidant activity, which is not the only one responsible for the positive effects on human cognitive functions. In fact, the idea that polyphenols act on physiological variables and pathological states solely for their direct antioxidant effects has been accompanied by a growing consensus on the fact that there are also direct interactions with cell signaling pathways [68]. Polyphenols can act at the cellular level either directly or mediated by enzymatic activities, or by modulating the signaling pathways involved in cell survival [64,65]. These processes are critical in the modulation of neurodegeneration, but probably were less involved in the evolution of humans, given the limited life expectancy in the Paleozoic and Mesolithic periods.

The antioxidant efficacy of various molecules depends on the quantity taken with the diet and on the relative bioavailability. Due to their low bioavailability, many polyphenols reach the tissues at a concentration incompatible with the activities found in vitro [69,70]. On the other hand, the efficacy of foods/beverages rich in polyphenols in countering some forms of cognitive degeneration is clear [71,72]. This suggests that the active molecules may be different from those originally present in food or, in other words, that the products of metabolism could be more active. Such products could also be concentrated in certain areas of the organism where they presumably carry out their positive activity [70,73]. Additional in vitro studies, but above all in vivo studies, need to be performed with appropriate experimental protocols to further investigate the antioxidant efficacy of molecules.

7. Could Polyphenols Have Played a Role in Human Evolution?

Considering the numerous factors that have simultaneously contributed to the evolution of the human species, it is difficult to know if polyphenols and other dietary antioxidant compounds have played a critical role.

Although an omnivorous diet seems to be the most suitable for the general well-being of the human body (intake of high-quality proteins, vitamin C and vitamin B_{12}, bioavailable minerals, etc.), a significant leap in evolution occurred when humans started a sedentary life dedicated to agriculture and livestock. The dietary factors that most may have contributed to cognitive development have a mainly vegetable origin e.g., polyunsaturated fatty acids, vitamins and antioxidant molecules. However, fish may also have played a key role, given that they are a source of docosahexaenoic acid. Table 2 shows how *Homo sapiens* (the modern human species) appeared at exactly the same time as sedentary life. This kind of life led to closer social relationships and the cultivation of numerous plants including cereals, fruit trees, vines, olive trees and nuts. These foods and their derivatives (beer, wine) show a good antioxidant activity, which is provided by some vitamins and other active molecules, the most important of which are polyphenols.

Table 3 illustrates the content in polyphenols (per 100 g/mL or portion) and the relative antioxidant activity of some foods present in the Mediterranean diet [74]. Foods have been selected taking into account their presence in the Mediterranean basin in ancient times, excluding those foods or beverages that were introduced relatively recently (tea, coffee, soybean, etc.). The polyphenol contents are also expressed as mg/portion to give a more realistic view of dietary intake. The portions refer to a modern diet, which could be very different from those of ancient times. For example, in Roman times, the volume of wine consumed per adult on a daily basis was well above today's recommendation of 125 mL.

Table 3. Total polyphenol content in some foods (Modified from [74]).

Class of Food	Food	Total Polyphenol Content (mg/100 g or mL)	Serving (g or mL)	Total Polyphenol Content (mg Per Serving)	Total Antioxidant Activity per Serving ^
Berries	Blackberry	260	144	374	821
	Black grape	169	54	91	92
	Green grape	15	54	48	66
	Red raspberry	215	144	310	213
	Strawberry	235	166	390	480
	Sweet cherry	274	145	394	249
		Mean		268	320
Nuts	Chestnut	1215	19	230	524
	Hazelnut	495	28	138	192
		Mean		184	358
Other fruits	Apple	136	110	149	221
	Peach	59	99	59	105
	Pear	17	138	23	149
		Mean		77	158
Fermented beverages	Beer	3.8	574	22	160
	Red wine	101	125	126	269
	White wine	10	125	13	40
		Mean		53.7	156
Olive and derivatives	Black olive	569	15	85	17
	Green olive	346	15	52	24
	Olive oil	62	16	10	8.8
		Mean		49	16.6
Other vegetables	Asparagus	29	75	22	56
	Red onion	168	30	50	31
	White bean	51	35	44	121
		Mean		38.7	69.3
Roots and tubers	Carrot	14	54	7.6	31
	Potato	28	128	36	69
		Mean		21.8	50
Cereals	Whole rye flour	143	20	29	14
	Whole wheat flour	71	20	14	18
		Mean		21.5	16

^ Folin Assay.

8. Discussion

Over the millennia, human beings changed their diet several times and in doing so they increased their potential. With the discovery of fire, the greater extraction of energy from food provided a higher quality diet; the brain increased in size and required even more energy. Humans began to carry out more complex activities, became more organized and managed to move geographically, adapting to each new habitat.

Unsaturated fatty acids, including DHA, are important components of brain structures, but are also a possible preferential target of ROS. These two contrasting aspects of polyunsaturated fatty acids have been identified both during the perinatal period and in old age.

The Mediterranean diet seems to be the most suitable to protect polyunsaturated fatty acids given its powerful antioxidant activity. In fact, the Mediterranean diet predominantly includes fruit and vegetables, seeds, and olives, as well as fish. Some vegetable derivatives, such as olive oil and wine, also play a positive role as they are sources of mono- and polyunsaturated fatty acids (olive oil) and polyphenols (derivatives of grapes and olives). Oleic acid is the main fatty acid of olive oil, which however also contributes significantly of polyunsaturated fatty acids in areas where this oil is the most consumed. This was certainly the situation in old times when other vegetables containing polyunsaturated acids (corn, peanut and soy) had not yet been imported in regions with Mediterranean-like diets (1500–1800 AD).

The introduction in the Mediterranean diet of foods rich in fatty acids of the omega-3 series and in particular in DHA may have been key to the evolution of the nervous system. The Mediterranean-type diet was the most widespread in the period in which the most advanced civilizations appeared (Table 2). These civilizations developed in the Mediterranean basin (Egyptians, Romans, Greek, Phoenician, Etruscan) or in areas with similar climatic characteristics such as Mesopotamia (Assyrians and Babylonians). The climatic conditions certainly promoted a sedentary life, the development of agriculture, and the cultivation of those plants whose fruits over time found a prominent place in the diet. The proximity to the sea of the civilizations in the Mediterranean basin clearly favored the inclusion of fish in the diet. For an interesting review of the historical development of the Mediterranean diet, see Essid [29].

Regarding the evolution of the human brain, diet may have played a fundamental role above all in the perinatal period [75]. Oxidative stress has a well-defined role in brain aging and neurodegenerative disorders [76], but this phenomenon may not have been particularly significant in the period of *H. erectus* when the average lifespan was short [75]. In fact, the average lifespan was 18–20 years in the Paleozoic and Mesolithic eras, 25–35 years at the time of the Egyptian, Roman and Greek civilizations, and really only increased after the mid-nineteenth century [75]. Consequently, the possible role of antioxidant compounds in the evolution of humans seems to be in the embryonic and fetal phase when the nervous system is particularly susceptible to oxidative stress, nutritional restriction, and exogenous agents.

A diet rich in unsaturated fatty acids and antioxidant molecules may have modulated the success of pregnancies, as well as improving embryonic and fetal development. Diet may have been one of the selection factors for the rise of *H. sapiens*, i.e., the species with the highest cognitive skills.

The beginning of sedentary life along with the development of agriculture led to four key objectives: (1) the cultivation of plants whose fruits were used in various ways; (2) the use of vegetables for breeding, which provided foods of animal origin which, although less abundant in the Mediterranean diet, still provide some essential nutrients (proteins of high nutritional value, vitamin B_{12}, etc.); (3) social life facilitating a high level of knowledge even if often with great disparities between the wealthy classes and slaves; (4) the birth of trade fostered by proximity to the sea, which enabled the expansion of the most advanced civilizations and the exchange of goods. Another aspect that could be stressed is that the Mediterranean diet may have contributed over the millennia to maintain health and allow a longer life [77]. This aspect can lead to great benefits in evolution because a longer life may have allowed in the longest-lived Mediterranean subjects the achievement of advanced skills, which in turn could be transmitted to the progeny by stimulating knowledge.

In conclusion, although diet is only one of the evolutionary forces, it may have played the most important selective role in the development of cognitive abilities over the millennia.

Although all forms of nutrients have contributed, it is likely that foods rich in antioxidant molecules, such as some vitamins and polyphenols, played the key role.

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