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## The Caucasian flora: a still-to-be-discovered rich source of antioxidants

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### ABSTRACT

Cellular redox homeostasis is a state of balance between the formation of Usually Reactive Oxygen and / or Nitrogen Species (ROS/RNS), endogenous antioxidant defence systems, and exogenous dietary antioxidants. The disturbance of redox homeostasis, by the overproduction of endogenous ROS/RNS, may increase the risk of development of so-called civilisation diseases. The solution seems to be either the increased production of endogenous or consumption of exogenous antioxidants. Plant-borne antioxidants act via different chemical and molecular mechanisms, such as decreasing the level of oxidative damage in cells directly by reacting with ROS/RNS or indirectly – by inhibition of the activity and expression of free radical generating enzymes or by enhancing the activity or expression of intracellular antioxidant defence enzymes. Despite the fact that the Caucasian flora is rich of health promoting edible/medicinal plants, recent studies concerning the biological activity of these plants are very scarce. This review is summarising the state-of-art on the health-promoting potential of plants representing the Caucasian flora, whose antioxidant capacity have been investigated in various *in vitro* models.

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### The significance of redox homeostasis

In 19<sup>th</sup> century, the French physiologist Claude Bernard (1813–1878) pointed out the relevance of maintenance of “the *milieu* interior” or “the interior environment,” as important for good health of every living organism. The maintenance of intracellular homeostasis may be a way to prevent or even cure some diseases [1]. This concerns also redox homeostasis, which can be disrupted easily by reactive species derived from oxygen (Reactive oxygen species – ROS), Nitrogen (Reactive Nitrogen Species – RNS), Sulphur (Reactive Sulfur Species – RSS), or Selenium (Reactive Selenium Species– RSeS) [2–5].

Reactive species are produced in different parts of the cell (e.g. plasma membranes, chloroplasts, mitochondria, peroxisomes, endoplasmic reticulum, apoplasts, and cell walls) under both normal and stress conditions (e.g. microbial infections, extensive exercise, or the influence of pollutants/toxins, different types of radiation) [6]. Mitochondria represent one of the major endogenous sources of oxidising agents with their

mitochondrial electron transport chain and NADPH oxidase (NOx) reaction. Nonmitochondrial sources of free radicals include microsomal cytochrome P<sub>450</sub> enzymes, the Fenton reaction, peroxisomal *beta*-oxidation and the phagocytic cell respiratory burst [7]. In some cases, cellular “redox cascades” are also triggered, resulting, for instance, in the formation of RSS [2,3]. Overproduction of reactive species evokes the stressful status of cells commonly referred to as “Oxidative Stress.” (OS).

However, ROS play a dual role in cell metabolism, depending on their concentration. At low or moderate concentrations, they serve as secondary messengers in intracellular signalling cascades, whereas at high concentrations, they may cause different kinds of damage to biomolecules [8]. Not surprisingly, healthy cells maintain an equilibrium between the formation and utilisation of ROS/RNS which can be disturbed by the formation of reactive species, which in time results in enhanced of cell damage [9].

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Redox homeostasis in the organism can be re-established by the action of intracellular antioxidant molecules, proteins and enzymes, and also by the intake of dietary antioxidants [10]. In tissues, both cells and the extracellular matrix respond to an insult of ROS by activating multiple additional internal enzymatic defence mechanisms, which assist in the quenching of ROS and their derivatives. The non-enzymatic antioxidants are represented by molecules, which possess the ability to inactivate different reactive species. Together with small molecule antioxidants, metal scavengers, and redox active proteins, they provide a first line of defence against ROS [11].

Mammalian antioxidant defence systems are not limited to endogenous antioxidants [12]. Dietary antioxidants such as vitamins (vitamin E and vitamin C) carotenoids, polyphenols (flavonoids, phenolic acids, lignans and stilbenes), and some minerals (Zn, Se, Mn and Cu) can affect the activity of endogenous antioxidants. Endogenous and exogenous antioxidants may act synergistically in order to maintain or re-establish the redox homeostasis of the organism [13]. These considerations lead us to the question, if a balanced diet composed of the “best ingredients” found around the globe may be helpful to prevent civilisation diseases.

### Plant-derived antioxidants

Plants contain various antioxidant mechanisms to maintain their own redox homeostasis. Similar to animal cells, plant cells can produce both, enzymatic and non-enzymatic antioxidants. Catalases, superoxide dismutase (SOD), peroxidases, and some other enzymes, which are included in the ascorbate-glutathione cycle, such as ascorbate peroxidase, monodehydroascorbate reductase, dehydroascorbate reductase, and glutathione reductase, belong to the enzymatic antioxidants found in plants [8]. These enzymes are supported by nonenzymatic plant antioxidants, such as ascorbate, glutathione (GSH), carotenoids, tocopherols, anthocyanins, and diverse phenolic compounds [14]. In fact, plant-based antioxidants are highly effective in controlling the level of ROS/RNS as they can also modulate enzymatic activities [15].

The most abundant group of plant-derived substances with antioxidant properties are polyphenols [16,17]. In order to evaluate their antioxidant activity, a range of experimental models are commonly employed, from simple chemical methods (e.g. ferric reducing antioxidant power (FRAP), 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS), and 1,1-diphenyl-2-picrylhydrazyl (DPPH) tests) through biologically more relevant

cellular-based assays, such as the cellular antioxidant activity assay, to the most accurate animal models and clinical trials in humans. *In vitro* studies are common, because they are relatively simple, fast and inexpensive, still these studies do not consider metabolic, biochemical, and other physiological parameters [17,18]. *In vivo* studies are performed mainly in prokaryotic and eukaryotic cells or laboratory animals and studies involving clinical trials remain scarce [18].

Simple chemical assays are most popular for the preliminary evaluation of antioxidant activity of plant extracts and their bioactive constituents. The majority of the *in vitro* tests represents redox-linked colourimetric assays. Polyphenols provide an ideal chemical structure for scavenging free radicals because of their phenolic hydroxyl groups, which can donate a hydrogen atom or an electron to a free radical. Furthermore, they can also count on an extended conjugated aromatic system to delocalise unpaired electrons [19].

Nonetheless, the *in vitro* and *in vivo* effectiveness of polyphenols as antioxidants is still a matter of debate, and, moreover, human studies on this topic are extraordinarily scarce, also when compared to those in animals. Another problem is the bioavailability of polyphenols. Their potential health benefits in humans and in animal models depend on absorption, distribution, metabolism, and elimination. The most common polyphenols present in the human diet are not necessarily the most active within the body, either because of their lower intrinsic activity or because they are poorly absorbed from the intestine, highly metabolised, or eliminated rapidly [20,21].

Despite these apparent drawbacks, diets rich in antioxidants are frequently the focus of epidemiological studies, which aim to correlate certain dietary habits and local peculiarities with the maintenance of health and prevention of certain diseases. Nowadays, these studies are often motivated by demographical changes or ageing of the population [22]. The “NutRedOx” network (EU COST Action 16112) is one fine example of this approach of “healthy living and ageing via healthy lifestyle and healthy eating” [23,24]. The facts – and myths – surrounding the famous “Mediterranean Diet” is another story [25–28]. Interestingly, the focus on such local diets often moves or follows behind the global market, which, in theory, enables the design of particularly attractive new diets with selected ingredients from across the world. It is therefore hardly surprising that culinary and scientific experts are nowadays increasingly joining forces to sample – and investigate – diets and dietary ingredients from various places.



**Table 1.** Content of total phenols in Armenian grapes.

Variety	Skin phenolic content (mg/kg CE* of grape FW*) ( $\pm$ SD)	Seed phenolic content (mg/kg CE* of grape FW*) ( $\pm$ SD)
<b>Aboriginal grapes</b>		
Tchilar	494.13 $\pm$ 17.72	504.68 $\pm$ 16.78
Garandmak	1296.63 $\pm$ 15.53	418.43 $\pm$ 13.10
Mskhali	494.97 $\pm$ 19.22	480.40 $\pm$ 7.27
Arevik	699.9 $\pm$ 19.92	243.07 $\pm$ 9.40
Qrdikhaghogh	552.27 $\pm$ 16.09	85.87 $\pm$ 5.10
Mormor	272.47 $\pm$ 15.12	295.38 $\pm$ 12.78
Hakobivordi	372.13 $\pm$ 15.94	493.86 $\pm$ 31.08
Krhagikarchevan	1244.87 $\pm$ 16.62	185.33 $\pm$ 17.55b
Kakhet	1251.50 $\pm$ 15.01	620.33 $\pm$ 10.4
Meghrivahravar (Shireyi)	506.73 $\pm$ 12.42b	297.11 $\pm$ 11.03
Sali	1005.77 $\pm$ 12.32	150.34 $\pm$ 11.03
Sevkrop	1105.94 $\pm$ 12.57	127.03 $\pm$ 4.70
<b>Interspecific and intraspecific hybrids</b>		
Vardananq	953.80 $\pm$ 11.47	274.51 $\pm$ 10.1
Narekaci	681.53 $\pm$ 14.73	362.15 $\pm$ 16.00
AyvazyaniVardabuyr	333.77 $\pm$ 16.67	173.32 $\pm$ 9.37
Itsaptuk	569.03 $\pm$ 13.98	283.20 $\pm$ 12.78
Parvana	279.57 $\pm$ 14.84d	200.27 $\pm$ 13.31
Hayastan	264.77 $\pm$ 5.65 cd	165.54 $\pm$ 9.18
Hayastaniquyry	186.53 $\pm$ 11.17	247.58 $\pm$ 16.92
Tzeni	234.57 $\pm$ 14.03b	149.01 $\pm$ 1.03
Shahumyani	154.00 $\pm$ 17.51	75.08 $\pm$ 14.19
Anahit	436.80 $\pm$ 11.41	288.44 $\pm$ 31.06
Berqanush	1355.57 $\pm$ 17.13	534.79 $\pm$ 17.76
Arevshat	210.70 $\pm$ 8.30	102.30 $\pm$ 8.13
Arazi	204.67 $\pm$ 13.01	161.85 $\pm$ 12.56
Aygezard	160.60 $\pm$ 16.14	85.87 $\pm$ 5.10
Armenia	512.57 $\pm$ 13.80	137.58 $\pm$ 12.69
Hayreniq	712.77 $\pm$ 12.05	394.61 $\pm$ 18.42
Charenci	802.80 $\pm$ 13.32	176.56 $\pm$ 12.00
Nali	554.57 $\pm$ 13.14	127.72 $\pm$ 12.59
Megrivahravar (semiwild)	887.00 $\pm$ 12.10	725.24 $\pm$ 17.72
<b>Wild grape samples</b>		
Wild grape Megrivahravar	1160.17 $\pm$ 17.44	1263.29 $\pm$ 10.82
Wild grape 1	2911.50 $\pm$ 11.38	2385.29 $\pm$ 14.72
Wild grape 2	527.03 $\pm$ 16.18	648.89 $\pm$ 17.82
Wild grape 3	944.94 $\pm$ 18.54	489.27 $\pm$ 12.63
Wild grape 4	328.20 $\pm$ 18.97	325.51 $\pm$ 14.63
Wild grape 5	339.47 $\pm$ 18.52	372.98 $\pm$ 14.42
Wild grape 6	838.67 $\pm$ 10.59	349.86 $\pm$ 12.70
Wild grape 7	911.67 $\pm$ 15.91	597.76 $\pm$ 14.07
Wild grape 8	2118.30 $\pm$ 15.77	1819.19 $\pm$ 17.47

CE\*: catechin equivalent; FW\*: fresh weight.

## The botanical diversity of the Caucasian flora

Within this context, the Caucasus, and here regions in Armenia and Georgia appear to be particularly rich in such health promoting edible or medicinal plants. Armenia is positioned at the junction of several biogeographical zones. These areas are characterised by amazing botanical diversity, with approximately 3600 plant species in Armenia alone. In Armenia, these biogeographical zones are closely linked, which results in relatively few endemic species of Armenian flora. Overall, 123 endemic plant species are described, a fraction which represents just 3% of the total Armenian flora, which overall is very rich in plants with pharmacological significance [29]. These plants are commonly employed in traditional medicine for the prevention and treatment of various diseases from Amirdovlat Amasiatsi(XX-

YY), the 15<sup>th</sup> century Armenian physician, for instance, demonstrated a preference for wild-growing plants as a source of drugs. He recommended the use of saffron, mandrake and hashish as pain-relieving and sleep-inducing drugs [30,31]. Despite this promising botanical richness, there is only limited literature published in recent years related to the biological activity of plants belonging to the Armenian flora.

## Armenian grapes and wine production

Among the Armenian plants described as being rich in antioxidants, grape (*Vitis vinifera*) features prominently. Armenia is considered a homeland of viticulture and earliest "wine culture". Recent archaeological excavations in the Areni-1 cave complex (South-Eastern Armenia) (Latitude: 39.730361°N Longitude:



**Table 2.** Content of phenols in Georgian grapes.

№ wine	Region	Total phenols, mg/kg CE	Catechine, mg/kg	Flavonoids mg/kg GAE*	Antioxidant activity, mg (IC <sub>50</sub> of 0.1 mM DPPH)
Colikouri	Adjara Keda	686.0 ± 20.58	42.35 ± 1.27	220.2 ± 6.61	24.3 ± 0.73
Colikouri	Adjara Kobuleti	633.4 ± 19.0	37.96 ± 1.14	220.8 ± 6.62	25.2 ± 0.76
Cicka	Adjara Kobuleti	611.0 ± 18.33	40.0 ± 1.20	272 ± 8.16	27.6 ± 0.83
Klarjuli	Adjara Kobuleti	488.88 ± 14.67	33.81 ± 1.01	170 ± 5.10	29.1 ± 0.87
Krachuna	Adjara Kobuleti	405.8 ± 12.17	32.5 ± 0.98	109 ± 3.27	30.1 ± 0.9
Qutaturi	Adjara Kobuleti	386.68 ± 11.6	35.78 ± 1.07	105 ± 3.15	28.05 ± 0.84
Colikouri	Samegrelo Martvili	499.7 ± 14.99	37.8 ± 1.13	161.3 ± 4.84	26.5 ± 0.8
Colikouri	Samegrelo Martvili	497.8 ± 14.93	36.9 ± 1.11	159.7 ± 4.79	27.2 ± 0.82
Colikouri	Samegrelo Martvili	476.6 ± 14.30	33.0 ± 0.99	145.9 ± 4.38	37.1 ± 1.11
Colikouri	Imereti Bagdadi	845.0 ± 25.35	45.25 ± 1.36	380 ± 11.40	22.4 ± 0.67
Cicka	Imereti Bagdadi	653.22 ± 19.60	44.85 ± 1.35	392 ± 11.76	22.3 ± 0.67

GAE\*: gallic acid equivalent.

45.203722°E) have revealed important artefacts and installations, which suggest wine production dating back to around 4000 BC [32].

Armenian grape cultivars were selected traditionally for thousands of years and the resulting variability of hybrids was extended further by cross-breeding. Currently, viticulture is one of the most important branches of the Armenian agriculture and the production of wine and brandy provides an important contribution to the country's economy. In three ampelographic collections, 140 grape cultivars are preserved, among them 125 are local accessions and 15 are varieties of foreign origin. Around 70 local varieties are old autochthonous cultivars. The areas of distribution of wild grapevine (*Vitis vinifera* ssp. *sylvestris*) in Armenia have recently declined sharply. Still, many wild populations are still growing in Southern Armenia [33].

### Antioxidant activity of grape cultivars

In recent years, polyphenols present in such grapes have been of scientific and applied interest. The grape skin and seeds both are rich in phenolic compounds and flavonoids. Their content in grapes depends on the variety of grapevine and is also influenced by viticultural and environmental factors, such as altitude and soil conditions; Aroutiounian, *et al.* for example, evaluated the total phenolic content and antioxidant properties of a large number of Armenian aboriginal varieties, interspecific and intraspecific hybrids and wild species with different genetic background and geographic origin (Table 1) [33].

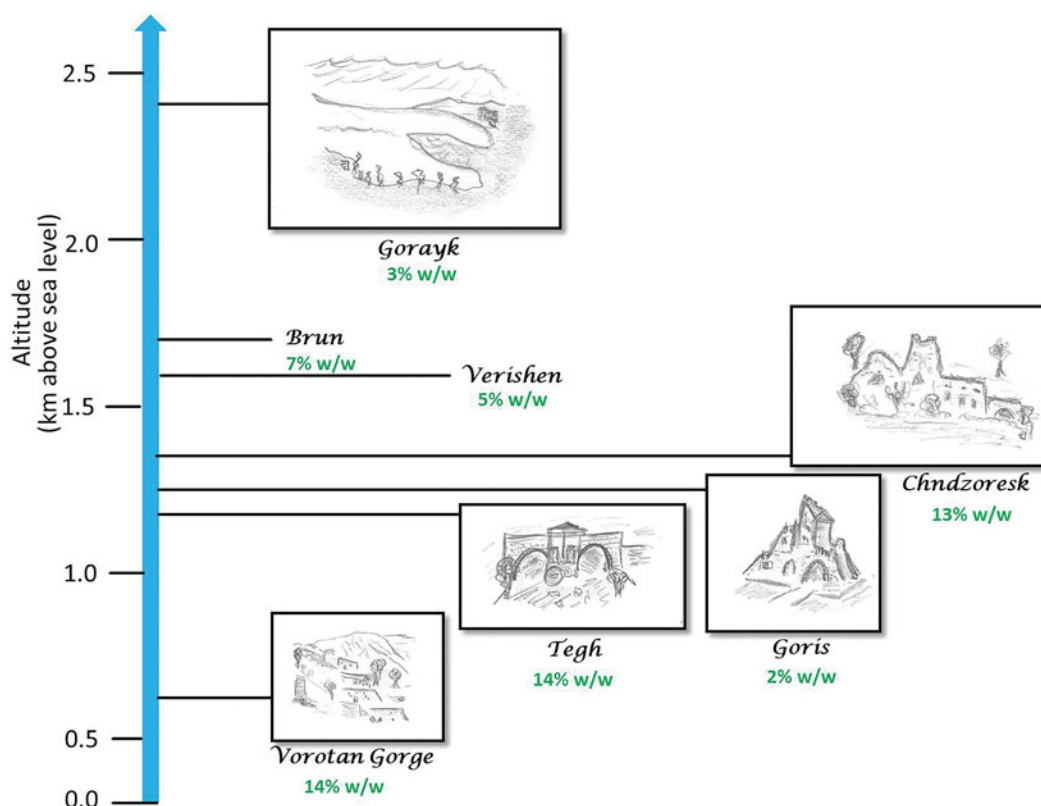
The results on Armenian grapes are also reflected by grapes grown in neighbouring Georgia. Here, 14 samples of dry grapes, titrated acidity, and active acidity of five species of white grapes, i.e. Tsoolikouri, Tsitska, Klarjula, Krakhuna, and Kutaturi, were studied, spread across three regions of Western Georgia – Adjara, Imereti, and Samegrelo [34]. Different spectrophotometric assays were employed to determine the total

phenolic and total flavonoid content and antioxidant activity (Table 2). Due to the variety of grapes, differences between the content of biologically active compounds on the one side and the activities in the antioxidant activities on the other were observed. These parameters were directly proportional and the studies were therefore able to identify specific varieties of grapes, such as the Tsoolikouri and the Tsitska, grown in Opcha (Imereti) and Keda (Adjara), as particularly high in antioxidant activity [35].

### Antioxidant activity of wine

The antioxidant activities of grapes are reflected in corresponding activities of wine. The content of phenolic compounds and antioxidant properties of wines produced of five varieties of white grapes were studied in Adjara, Imereti, and Samegrelo. A range of phytochemicals, including (-)epicatechin, quercetin-3-glucoside, quercetin-3-rhamnoside, quercitrin-3-glucuronide, and procyanidin B2 were identified by ultra performance liquid chromatography – mass spectrometry (UPLC-MS). With the help of the spectral methods, the total amount of phenols, catechins, and flavonoids was defined in the wines of all five varieties of grapes and their antioxidant properties were established (0.01 mM DPPH 50% inhibition). It was observed that wines produced from Tsoolikouri and Tsitska grapes contain high amount of phenolic compounds and are characterised by antioxidant activity [35,36].

Together, the research conducted on wines and grapes grown and produced in Armenia and Georgia revealed apparent differences among the cultivated varieties and wild species with respect to their total phenolic content and antioxidant activity [37,38]. These differences imply that biological activity, and not simply taste, may represent an important “seal of quality” for these natural products and produce. Notably, the high antioxidant activity in grapes is not limited to juice. Skin and seeds are also rich in antioxidant components,



**Figure 1.** The influence of altitude on antioxidant capacity of the plants from the *Lamiaceae* family (sketch was provided by prof. C. Jacob).

and rather than “going to waste” by vermicomposting, could be turned into valuable new products for the food industry, for instance in form of additives and baking [39,40]. Additionally, medical and also agricultural and cosmetic applications may be considered [41,42].

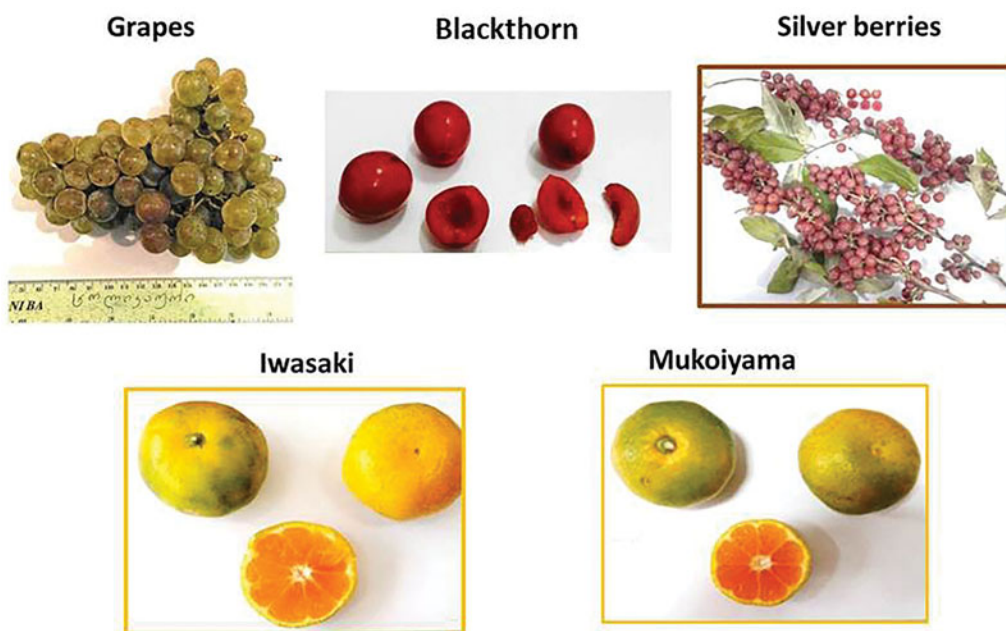
### Antioxidant activity of plant extracts

Another medicinally important family of Armenian plants on which there is some scientific literature concerning antioxidant activity is represented by the *Lamiaceae* family. Hayrapetyan *et al.* demonstrated that the antioxidant activity of *Thymus serpyllum* L. depends on the altitude of cultivation [43]. The highest amount of antioxidants was found in ethyl acetate extracts of thyme growing in the Vorotan Gorge (14% w/w, 650 m a.s.l.), while the same activity of *T. serpyllum* growing in other places, such as the old city of Goris (2% w/w, 1250 m a.s.l.), the village Verishen (5% w/w, 1600 m a.s.l.), the gorge in the village Brun (7% w/w, 1700 m a.s.l.), the gorge in the village Chndzoresk (13% w/w, 1350 m a.s.l.), the gorge in the village Tegh (4% w/w, 1200 m a.s.l.), and the village Gorayk (3% w/w, 2400 m a.s.l.) was lower [43]. These findings are particularly

stimulating as they demonstrate that antioxidant content is not simply a property of a given plant species, it also depends decisively on a number of environmental factors, from the temperature, humidity, and soil to altitude. In this particular case, the plants grown at higher altitude were frequently lower in antioxidants (Figure 1).

Such a correlation may be due to the fact that the conditions of growth at higher altitude are generally harsher and plants therefore produce less secondary metabolites, including antioxidants. Then again, these plants are also exposed to higher stress levels and this, in turn, may also increase the production of protective substances, explaining that certain plants found at higher altitude are actually more stress resistant and also richer in certain phytochemical than their counterparts found at lower altitudes.

Similarly, in a study conducted in neighbouring Georgia, several plants including *Elaeagnus* L., *Prunus spinosa* L., *Iwasaki*, *Mukoiyama* and *Tiagara Unshiu* were chosen to determine the content of the phenols in the Georgian flora. It turned out that the highest amount of phenols and antioxidant activity was recorded at 120 m a.s.l., and was relatively low at 80 m a.s.l. The amount of phenols in silverberry (*Elaeagnus* L.)



**Figure 2.** The influence of altitude on antioxidant capacity of the plants from the Lamiaceae family (sketch was provided by professor C. Jacob).

differed with the altitude from the sea level between 1863.3 mg/100 g to 2336.59 mg/100 g (fresh berry). Antioxidant activity was observed to vary around 16.4 mg (50% inhibition of 0.1 mM DPPH solution is produced). In another plant endemic to Georgia, *P. spinosa* L., the amount of phenols again differed according to the area of cultivation and ranged from 331.0 mg to 114.9 mg/100 g. Antioxidant activity was somewhere around 25.11 mg. As for Georgian tangerines, the total amount of phenols varied between 0.364 mg and 0.474 mg/ml (in juice). The highest value radical scavenging activity among the samples was found in the tangerines Tiaxara Unshiu (80.05 mg) and Iwasaki (74.45 mg), with lower activities in samples of Mukoiyama and Clemenules, that is, 79.9–191.72 mg (Figure 2) [44,45].

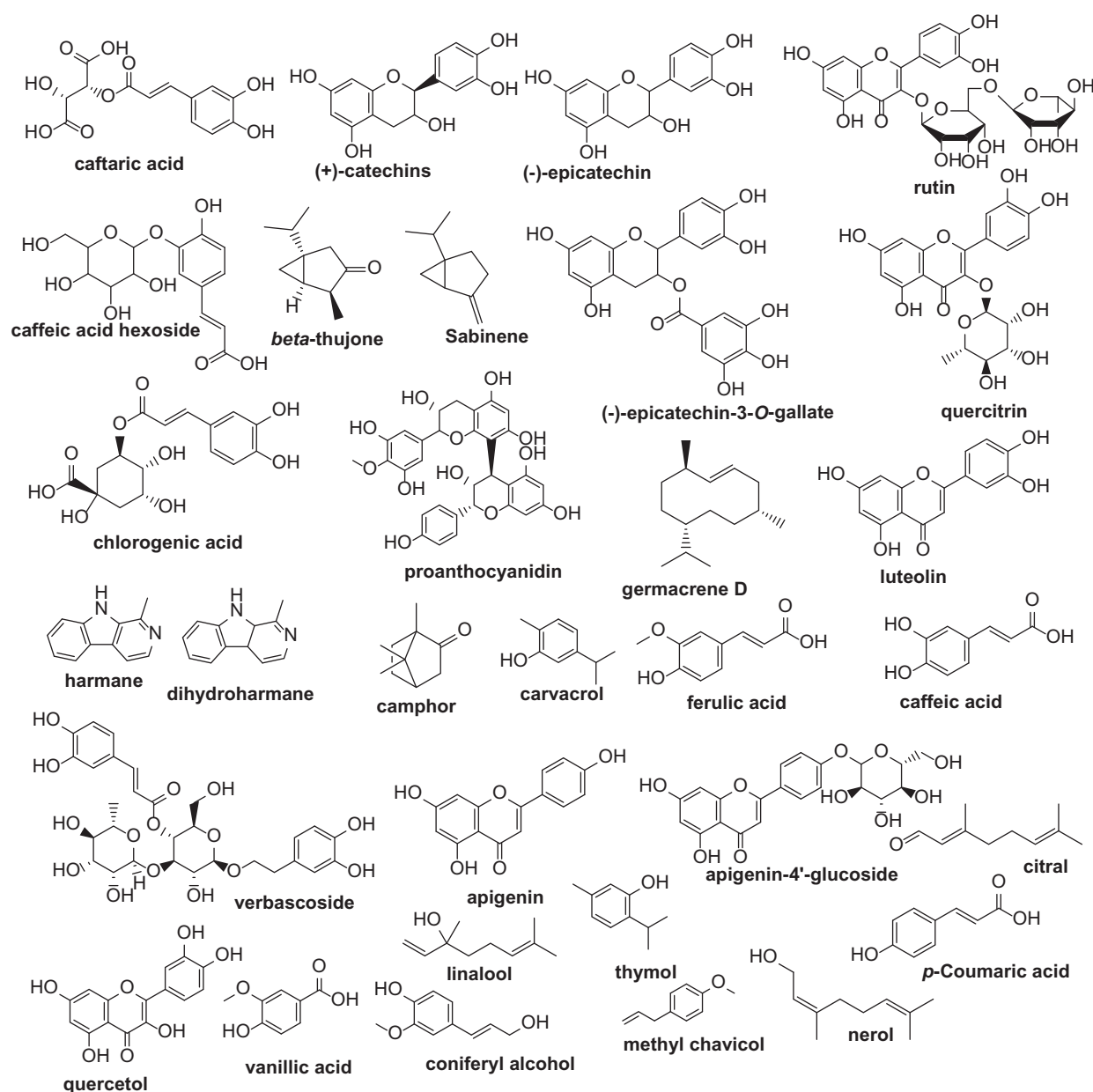
Once again, these findings underline the impact of environmental factors on the composition and activity of such plants. Armenia – and its neighbour Georgia – are Caucasian countries with varying altitude, and height clearly matters.

Another Armenian Highland plant of the *Lamiaceae* family, *Ajuga genevensis* and its isolated culture, also exhibited high antioxidant activity, estimated by photo-chemoluminescent analysis [46]. Some authors compared the antioxidant potential of *Teucrium polium* varieties of the wild plants and determined some flavonoids (e.g. apigenin), flavonoid glycosides (e.g. apigenin-4'-glucoside), and phenylpropanoid glycosides (e.g. verbascoside) [47].

Similarly, plants of the genus *Artemisia* possess excellent biological activities, such as antioxidant, antimicrobial, anticancer and are employed widely in medicine, cosmetics and food production. Around 300 species of this genus have been reported and 16 are described as part of the Armenian flora [48]. Thus, Babayan *et al.* were able to demonstrate that *Artemisia vulgaris* L., *A. fragrans* Willd., *A. absinthium* L., and *A. splendens* Willd. collected from the Aragatsotn region (1500–1600 m a.s.l.) during the flowering period displayed high antioxidant potential, although the radical scavenging activity depended on the specific conditions of the extraction method [49]. Vardapetyan *et al.* presented a comparative analysis of phenolic component and radical scavenging activity of extracts of *Crataegus laevigata*, *Plantago major*, and *Artemisia absinthium* plants growing in Armenia. The authors demonstrated a direct relationship between the content of quercetin and the antiradical activity of selected ethanol extracts obtained from these plants [50].

Climatic and environmental changes also increase stress levels in plants, including the formation of a variety of free radicals, which plants have to deal with in order to survive. Since the chemical composition, that is, chemotype, and biological activity of substances obtained from the plants belonging to the same species may vary significantly, depending on the variety of cultivars, environment, elevation, and cultivation methods, it is essential to study examples of these plants growing in other regions. For instance, according to





**Figure 3.** Structures of a range of phytochemicals identified in grapes, *A. genevensis*, *O. basilicum* species, *T. serpyllum* L. silver-berry, *P. spinosa* L., *T. polium*, and *Artemisia* species (see the text for details).

Avetisyan *et al.*, the dominant constituent of *Ocimum basilicum* var. *purpureum* (purple basil) growing at high altitude Armenian landscape (1600 m a.s.l.) is methyl chavicol (estragole), whereas the major component for the other variety of the same species, *O. basilicum* var. *thyriflora* (Thai basil) is linalool [51]. At the same time, the chemical composition of *O. citriodorum* hybrid plant differed from the first two basil varieties, grown at the same area. This variety contains a significant amount of the aldehyde citral, with another prevalent constituent being nerol, a monoterpene alcohol. The authors stated that essential oil from the *O. basilicum* var. *thyriflora*

displayed the highest ability to neutralise free radicals. The relevant chemical structures of these important phytochemicals are provided in Figure 3.

To recapitulate, a major share of plants found within the Armenian flora exhibits considerable antioxidant potential. Nonetheless, these plants – and their antioxidant potential – still have not been investigated fully. They should be considered as part of more comprehensive investigations to identify particularly promising plants with equally promising antioxidant activities and to identify the potential mechanisms and modes of actions associated with them.



## Conclusions

Since the turn of the Millennium, a considerable amount of scientific data has been published concerning the antioxidant potential of plants. Some researchers suggest that approximately 60% of plant species investigated could possess medicinal value, including a large number of plants displaying antioxidant activity. Plants are able to synthesise and accumulate enzymatic antioxidants during their metabolism. Among these substances, tocopherols, ascorbic acid, glutathione, poly-phenols, and other low molecular weight components – which act via different mechanisms on and in the human body – take the centre stage.

Almost all plants studied demonstrate some antioxidant activity in *in vitro* assays. Still, due to the complexity of biological systems, such activities may not translate directly into action within more complex organisms. In fact, antioxidants of plant origin may act via multiple mechanisms, there could be issues related to the limited bioavailability, and the presence or absence of transition metal ions and co-antioxidants may also interfere. As a consequence, information obtained in *in vitro* assays may not be extrapolated directly to *in vivo* studies as plant-originated antioxidants have to pass through a number of physiological-metabolic processes and interact with co-antioxidants and transition metal ions.

As the investigations of different varieties of grapes and thyme in Armenia and Georgia have demonstrated, the composition of antioxidants and activities associated with them may vary considerably, between different subspecies and as a result of environmental factors, including altitude.

Despite the considerable amount of literature available today, there is – literally – a vast field to cultivate, in research, nutrition, agriculture, and medicine. Such studies need to focus on the detection of new plants with antioxidant potential, including those from the Caucasian landscapes. At the same time, the mechanisms, modes of action, and applications under both, *in vitro* and *in vivo* conditions, have to be considered.

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## Author contributions

All authors contributed equally in writing the manuscript.

## Disclosure statement

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## References

- [1] Bernard C. Lectures on the phenomena common to animals and plants. Hoff HE, Guillemin R, Guillemin L, translators. Springfield (IL): Charles C. Thomas; 1974.
- [2] Giles GI, Tasker KM, Jacob C. Hypothesis: the role of reactive sulfur species in oxidative stress. *Free Radic Biol Med.* 2001;31:1279–1283.
- [3] Giles GI, Jacob C. Reactive sulfur species: an emerging concept in oxidative stress. *Biol Chem.* 2002;383:375–388.
- [4] Giles GI, Nasim MJ, Ali W, et al. The reactive sulfur species concept: 15 years on. *Antioxidants.* 2017;6:38.
- [5] Jawad Nasim M, Ali W, Dominguez-Alvarez E, et al. Reactive selenium species: redox modulation, antioxidant, antimicrobial and anticancer activities In: Jain VK, Priyadarsini KI, editors. *Organoselenium compounds in biology and medicine: synthesis, biological and therapeutic treatments.* London (UK): The Royal Society of Chemistry; 2018. Chapter 10, p. 277–302.
- [6] Poljsak B, Šuput D, Milisav I. Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. *Oxid Med Cell Longev.* 2013;2013:956792.
- [7] Gilca M, Stoian I, Atanasiu V, et al. The oxidative hypothesis of senescence. *J Postgrad Med.* 2007;53:207–213.
- [8] Trchounian A, Petrosyan M, Sahakyan N. Plant cell redox homeostasis and reactive oxygen species In: Gupta DK, Palma JM, Corpas FJ, editors. *Redox state as a central regulator of plant-cell stress responses.* Cham (Switzerland): Springer International Publishing; 2016. p. 25–50.
- [9] White PAS, Oliveira RCM, Oliveira AP, et al. Antioxidant activity and mechanisms of action of natural compounds isolated from lichens: a systematic review. *Molecules.* 2014;19:14496–14527.
- [10] Lubrano V, Balzan S. Enzymatic antioxidant system in vascular inflammation and coronary artery disease. *WJEM.* 2015;5:218–224.
- [11] El-Bahr SM. Biochemistry of free radicals and oxidative stress. *Sci Int.* 2013;1:111–117.



- [12] Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenous non-enzymatic antioxidants in the human body. *Adv Sci Pol.* 2018;63:68–78.
- [13] Jacob C. Redox signalling via the cellular thiolstat. *Biochem Soc Trans.* 2011;39:1247–1253.
- [14] Zujko ME, Witkowska AM, Waśkiewicz A, et al. Estimation of dietary intake and patterns of polyphenol consumption in Polish adult population. *Adv Med Sci.* 2012;57:375–384.
- [15] Ahmad P. Oxidative damage to plants: antioxidant networks and signaling. London, UK: Academic Press; 2014.
- [16] Kapravelou G, Martínez R, Andrade AM, et al. Improvement of the antioxidant and hypolipidaemic effects of cowpea flours (*Vigna unguiculata*) by fermentation: results of in vitro and in vivo experiments. *J Sci Food Agric.* 2015;95:1207–1216.
- [17] Avello MA, Pastene ER, Bustos ED, et al. Variation in phenolic compounds of *Ugni molinae* populations and their potential use as antioxidant supplement. *Rev Bras Farmacognosia.* 2013;23:44–50.
- [18] Lin DR, Xiao MS, Zhao JJ, et al. An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. *Molecules.* 2016;21:1374.
- [19] Rubió L, Motilva MJ, Romero MP. Recent advances in biologically active compounds in herbs and spices: a review of the most effective antioxidant and anti-inflammatory active principles. *Crit Rev Food Sci Nutr.* 2013;53:943–953.
- [20] Dai J, Mumper RJ. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. *Molecules.* 2010;15:7313–7352.
- [21] Kuznierewicz B, Piasek A, Bartoszek A, et al. The optimisation of analytical parameters for routine profiling of antioxidants in complex mixtures by HPLC coupled post-column derivatisation. *Phytochem Anal.* 2011;22:392–402.
- [22] Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 2004;79:727–747.
- [23] Wilson DW, Nash P, Buttar HS, et al. The role of food antioxidants, benefits of functional foods, and influence of feeding habits on the health of the older person: an overview. *Antioxidants.* 2017;6:81.
- [24] Cost. Personalized Nutrition in aging society: redox control of major age-related diseases: COST Association COST Action CA16112; 2016. [cited 2018 Feb 22]. Available from: [http://www.cost.eu/COST\\_Actions/ca/CA16112](http://www.cost.eu/COST_Actions/ca/CA16112)
- [25] Tur JA, Jacob C, Chaimbault P, et al. Personalized nutrition in ageing society: redox control of major-age related diseases through the NutRedOx Network (COST Action CA16112). *Free Radic Res.* 2019 [cited Feb 22]; [8p.]. doi:10.1080/10715762.2019.1572890
- [26] Gil A, Ortega RM, Maldonado J. Wholegrain cereals and bread: a duet of the Mediterranean diet for the prevention of chronic diseases. *Public Health Nutr.* 2011;14:2316–2322.
- [27] Aguilera Y, Martín-Cabrejas MA, González de Mejía EG. Phenolic compounds in fruits and beverages consumed as part of the Mediterranean diet: their role in prevention of chronic diseases. *Phytochem Rev.* 2016;15:405–423.
- [28] Gil A. Bread and the Mediterranean diet: a duet for the prevention of chronic diseases. *Ann Nutr Metab.* 2017;71:1358–1358.
- [29] Meryem P, Havva S. Mediterranean diet in prevention of chronic diseases. *Int J Med Res Health.* 2017;6:36–39.
- [30] Protection TMon. First national report to the convention on biological diversity incorporating a country study on the biodiversity of Armenia. National report. Convention of biological diversity. 1999; p. 1–104.
- [31] Sanjian AK. AMIRDOVLAT‘AMASIATS‘I. *Encyclopaedia Iranica*; 2012. [Cited 2019 Feb 20]. Available from: <http://www.iranicaonline.org/articles/amirdovlat-amasiatsi>
- [32] Anassian HS. Armenian bibliography: Vth-XVIIIth centuries I. *Cols.* 1959; p. 650–675.
- [33] Barnard H, Dooley AN, Areshian G, et al. Chemical evidence for wine production around 4000 BCE in the Late Chalcolithic near Eastern Highlands. *J Archaeol Sci.* 2011;38:977–984.
- [34] Aroutiounian R, Nebish A, Margaryan K, et al. Armenian grapevines: cytoembryological, morphological and chemical analysis. *Vitis.* 2015;54:139–142.
- [35] Kharadze M, Djaparidze I, Vanidze M, et al. Chemical composition and antioxidants of 14 varieties of white grape spread in Western Georgia. *Glob J Curr Res.* 2018;6:31–35.
- [36] Kharadze M, Djaparidze I, Shalashvili A, et al. Phenolic compounds and antioxidant properties of some white varieties of grape wines spread in Western Georgia. *Bull Georgian Natl Acad Sci.* 2018;12:103–109.
- [37] Kharadze M, Japaridze I, Kalandia A, et al. Anthocyanins and antioxidant activity of red wines made from endemic grape varieties. *Ann Agrar Sci.* 2018;16:181–184.
- [38] Aroutiounian R, Nebish A, Melyan G, et al. Phenotypic profiles of Armenian grape cultivars. *BIO Web Conf.* 2015;5:01011.
- [39] Margaryan K, Melyan G, Vardanyan D, et al. Phenolic content and antioxidant activity of Armenian cultivated and wild grapes. *BIO Web Conf.* 2017;9:02029.
- [40] Griffin S, Sarfraz M, Farida V, et al. No time to waste organic waste: nanosizing converts remains of food processing into refined materials. *J Environ Manage.* 2018;210:114–121.
- [41] Nistor E, Dobrei A, Dobrei A, et al. Grape pomace in sheep and dairy cows feeding. *J Hortic For Biotech.* 2014;18:146–150.
- [42] Zacharof M. Grape winery waste as feedstock for bio-conversions: applying the biorefinery concept. *Waste Biomass Valor.* 2017;8:1011–1025.
- [43] Hayrapetyan SA, Vardanyan LR, Vardanyan RL. Antioxidant activity of Creeping thyme (*Thymus serpyllum* L.) in cumene oxidation reaction. *Proc YSU.* 2013; 2:23–31.
- [44] Uzun A, Çelik B, Karadeniz T, et al. Assessment of fruit characteristics and genetic variation among naturally



- growing wild fruit *Elaeagnus angustifolia* accessions. Turk J Agric For. 2015;39:286–294.
- [45] Farzaei MH, Bahramsoltani R, Abbasabadi Z, et al. A comprehensive review on phytochemical and pharmacological aspects of *Elaeagnus angustifolia* L. J Pharm Pharmacol. 2015;67:1467–1480.
- [46] Sahakyan N, Petrosyan M, Trchounian A. Comparative analysis of chemical composition and biological activities of *Ajuga genevensis* L. in in vitro culture and intact plants. Int J Biol Biomol Agric Food Biotechnol Eng. 2016;10:322–326.
- [47] Galstyan H. Standardization of felty germander (*Teucrium polium* L.) by natural phytoestrogens: phenylpropanoid and flavonoid glycosides. New Armenian Med J. 2014;8:53–58.
- [48] Gabrielian E, Xirau JV. New data about the genus *Artemisia* L. (Asteraceae) in Armenia. Willdenowia. 1996;26:245–250.
- [49] Babayan A, Petrosyan M, Sahakyan N, et al. The radical scavenging activity of some species of *Artemisia* genus, represented in Armenian flora. Biol J Armenia. 2017;1:96–99.
- [50] Vardapetyan H, Hovhannisyan D, Tiratsuyan S, et al. Quercetin content and antioxidant activity of Armenian *Crataegus laevigata*, *Plantago major* and *Artemisia absinthium* plants extracts. J Exp Biol Agric Sci. 2014;2:220–225.
- [51] Avetisyan A, Markosian A, Petrosyan M, et al. Chemical composition and some biological activities of the essential oils from basil *Ocimum* different cultivars. BMC Complement Altern Med. 2017; 17:60.

