applied sciences

MDPI

Review

Apium Plants: Beyond Simple Food and Phytopharmacological Applications

Bahare Salehi [1], Alessandro Venditti [2], Claudio Frezza [3], Aysun Yücetepe [4], Ümit Altuntaş [5], Sibel Uluata [6], Monica Butnariu [7], Ioan Sarac [7], Shabnum Shaheen [8], Spyridon A. Petropoulos [9], Karl R. Matthews [10], Ceyda Sibel Kılıç [11], Maria Atanassova [12], Charles Oluwaseun Adetunji [13], Adedayo Oluwaseun Ademiluyi [14], Beraat Özçelik [5,15,*], Patrick Valere Tsouh Fokou [16,*], Natália Martins [17,18,*], William C. Cho [19,*] and Javad Sharifi-Rad [20,*]

1 Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam 44340847, Iran
2 Dipartimento di Chimica, Università di Roma "La Sapienza", Piazzale Aldo Moro 5, 00185 Rome, Italy
3 Dipartimento di Biologia Ambientale, Università di Roma "La Sapienza", Piazzale Aldo Moro 5, 00185 Rome, Italy
4 Department of Food Engineering, Faculty of Engineering, Aksaray University, Aksaray 68100, Turkey
5 Department of Food Engineering, Faculty of Chemical and Metallurgical Engineering, Istanbul Technical University, Maslak, Istanbul 34469, Turkey
6 Department of Food Technology, Inonu University, Malatya 44280, Turkey
7 Chemistry & Biochemistry Discipline, Banat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, 300645, Calea Aradului 119, Timis, Romania
8 Chemotaxonomic Lab., Lahore College for Women University, Lahore 54000, Pakistan
9 Laboratory of Vegetable Production, University of Thessaly, Fytokou Street, 38446 N. Ionia, Magnissia, Greece
10 Department of Food Science, Rutgers University, New Brunswick, NJ 08901, USA
11 Department of Pharmaceutical Botany, Faculty of Pharmacy, Ankara University, Ankara 06100, Turkey
12 Scientific Consulting, Chemical Engineering, UCTM, P.O. Box 1756 Sofia, Bulgaria
13 Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo University, Iyamho, Edo State 300271, Nigeria
14 Functional Foods, Nutraceuticals and Phytomedicine Unit, Department of Biochemistry, Federal University of Technology, Akure 340001, Nigeria
15 Bioactive Research & Innovation Food Manufac. Indust. Trade Ltd., Katar Street, Teknokent ARI-3, B110, Sarıyer, Istanbul 34467, Turkey
16 Antimicrobial and Biocontrol Agents Unit, Department of Biochemistry, Faculty of Science, University of Yaounde 1, Ngoa Ekelle, Annex Fac. Sci, P.O. Box. 812, Yaounde, Cameroon
17 Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
18 Institute for Research and Innovation in Health (i3S), University of Porto, 4200-135 Porto, Portugal
19 Department of Clinical Oncology, Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong, China
20 Zabol Medicinal Plants Research Center, Zabol University of Medical Sciences, Zabol 61615-585, Iran
* Correspondence: beraat.ozc@gmail.com (B.Ö.); tsouh80@yahoo.fr (P.V.T.F.); ncmartins@med.up.pt (N.M.); chocs@ha.org.hk (W.C.C.); javad.sharifirad@gmail.com (J.S.-R.)

Received: 25 July 2019; Accepted: 19 August 2019; Published: 29 August 2019

Abstract: *Apium* plants belong to the Apiaceae family and are included among plants that have been in use in traditional medicine for thousands of years worldwide, including in the Mediterranean, as well as the tropical and subtropical regions of Asia and Africa. Some highlighted medical benefits include prevention of coronary and vascular diseases. Their phytochemical constituents consist of bergapten, flavonoids, glycosides, furanocoumarins, furocoumarin, limonene, psoralen, xanthotoxin, and selinene. Some of their pharmacological properties include anticancer, antioxidant, antimicrobial, antifungal, nematocidal, anti-rheumatism, antiasthma, anti-bronchitis, hepatoprotective, appetizer, anticonvulsant, antispasmodic, breast milk inducer, anti-jaundice, antihypertensive, anti-dysmenorrhea, prevention of cardiovascular diseases, and spermatogenesis induction. The present review summarizes data on ecology, botany, cultivation, habitat, medicinal use, phytochemical composition, preclinical and clinical pharmacological efficacy of *Apium* plants and provides future direction on how to take full advantage of *Apium* plants for the optimal benefit to mankind.

Keywords: *Apium*; botany; medicinal use; phytochemicals; pharmacological properties

1. Introduction

Apium plants belong to the family *Apiaceae* which are mostly aromatic plants. This genus consists of about 20 species of flowering plants that are distributed worldwide [1]. They are medium to tall, biennial and perennial plants which grow up to one meter in height in marshy areas throughout subtropical and temperate regions. The leaves are pinnate or bipinnate with small white flowers (arranged in compound umbels). These plants are cultivated throughout the world for their green leaves, bulbous roots, seeds (fruits), and petioles [2]. The most prominent of this genus is the *Apium graveolens* L., popularly known as celery. There are three main varieties which are: *Apium graveolens* viz. *A. graveolens* var. *dulce* (Mill.) Pers which is known as cultivated celery or simply celery, *A. graveolens* var. *rapaceum* (Mill.) DC. also known as celeriac, root celery or turnip-rooted celery, and *A. graveolens* var. *secalinum* Alef. which is called leaf celery [3,4].

Celery (*A. graveolens*) is a rich source of vitamins, carotene, protein, cellulose along with some secondary metabolites including phenolic acids, flavonoids (mainly quercetin, apigenin, chrysoeriol, luteolin, and their glycosides), and terpenoids. The seed of celery is known for its essential oil (~3% dry weight) with characteristic aroma [5] and it is also rich in limonene, coumarins, furanocoumarins (bergapten), and fatty acids [2]. The essential oil of celery contains about 2%–3% volatile oil containing about 60% limonene, 20%–30% phtalids, and up to 13% β-selinene as its major phytoconstituents [2,6]. Furthermore, the presence of apiol, citric, isocitric, fumaric, sedanic acid, sedanolide, tartaric acid, santalol, and malic acid have been reported [2]. Choline ascorbate and phthalides such as butylphthalide have been isolated from leaves and roots of *A. graveolens*, respectively [7,8]. Apiin was found as the major constituents of the leaves of *A. graveolens* var. *dulce* [9]. However, several factors such as the plant part (leaves, stalk or seeds), geographical location, time and stage of harvest, and postharvest process, are known to influence the phytochemistry of *A. graveolens* [2,10].

The leaves of *Apium* plants have been employed as food and medicine and are rich in bioactive compounds, such as tocopherol and flavonoids [11,12], which underline their therapeutic properties. Indeed, various plant parts such as seeds, leaves, stem, roots, and essential oils are widely applied in traditional medicine to treat several ailments [13] such as hypertension, diabetes [14,15], asthma, gastrointestinal infections, bronchitis, and hepatitis [16]. Furthermore, the celery plant has been reported to possess anti-inflammatory properties and has been proven useful in the treatment of bronchitis and hepatitis [16]. The celery root also exhibits anticonvulsant, analgesic, and anthelmintic effects with brain and gastrointestinal tract stimulating properties [17]. Additionally, celery has reportedly been used for the management of gut diseases, kidney stones, urinary calculi, and visceral spasm in Ayurveda [18].

A. graveolens has found wide application in food production as a flavoring ingredient or spice [1,19] due to its peculiar aroma and essential oil. Essential oils are common constituents of plant foods and spices, with usage spanning several centuries due to their therapeutic effect. Recently, exploitation of these plant oils as alternative natural food preservatives has encouraged research into their antimicrobial and antioxidant activities. The antibacterial effect of the volatile oil from *A. graveolens* has been demonstrated against *Listeria spp* and *Staphylococcus aureus* [20]. Alves-Silva et al. reported on the antimicrobial properties of *A. graveolens* aerial parts essential oil obtained via microwave-assisted hydrodistillation against bacterial, yeast, and molds [21]. Sensitivity of several fungi strains, including

A. niger and *A. flavus*, to essential oil obtained by hydrodistillation of celery have been reported [22]. Similarly, celery methanol extract has shown antibacterial activity against *E. aerogenes, E. cloacae, E. coli, K. pneumoniae*, and *P. stuartii* [23,24]. This antimicrobial activity of its essential oil was linked to the presence of some phytochemicals such as limonene, β-selinene, and sedanolide.

Shanmugapriya and Ushadevi have reported the antibacterial potency of *A. graveolens* seed extract on uropathogens such as *E. coli* and *P. aeruginosa*, as well as their antioxidant properties [25]. The *n*-butanol extract of the seed ameliorated oxidative stress in diabetic rats [26]. *A. graveolens* leaf showed anti-inflammatory properties by reducing nitric oxide production through downregulation of the expression of nitric oxide synthase [9,23]. Many reports support the use of celery in cardiovascular disease prevention, control of blood glucose and lipid, as well as lowering blood pressure [23]. The ability of *Apium* extracts to induce differentiation of supportive cells, such as oligodendrocytes and astrocytes, as well as neuronal stem cells to neurons has been demonstrated [27], which has been attributed to their constituent apigenin [28]. In addition, Chonpathompikunlert et al. showed the neuroprotective effect of *A. graveolens* extract on the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced Parkinsonism by modulating related neurotransmitter pathways, antioxidant activity, and increased number of dopaminergic neurons [29].

The current trend toward exploiting medicinal plants as complementary to synthetic drugs has triggered renewed interest into their therapeutic properties, characterized bioactive constituents, and elucidation of their mechanisms of action, thus, making them viable medicinal supplements. In a similar manner, since the medicinal importance of *Apium* plants is widely documented and validated, efforts should be geared towards increased adoption and commercialization of *Apium* plants materials as functional foods and nutraceutical ingredients.

2. Habitat and Cultivation of *Apium* Plants

2.1. Habitat

The *Apium* genus includes edible plants of the Apiaceae family with green blanched leaf stalks [30]. According to The Plant List, this genus includes 18 verified species most of which are spread worldwide in temperate zones [31]. Today, it is found in South and North America, Southern Europe, Asia and Africa [31]. Most of the species are used as herbs, while today only *A. graveolens* is commercially cultivated for its leaves (celery, smallage), roots (celeriac), seeds, and essential oil [32–36] because of its characteristic smell and health benefits [9]. This plant is a "typical example of man's improvement of a wild species", because it has sustained overall selection during the last few hundred years [10]. Although the *Apium* species are widely distributed in the world, many species are endangered, such as *Apium repens* and *Apium bermejoi*, which have been included recently in the IUCN Red List [37,38]. Moreover, various species of the genus show a great variation in growth habits and they can be found in saltmarshes, wetlands, coastal areas, and aquatic habitats [37,38].

2.2. Botany of Apium Graveolens

A. graveolens is a scapose hemicryptophyte characterized by thin and hollow stems and slim roots [10]. It is a deciduous, erect, herbaceous annual or bionomical herb which grows to a height of 0.5 m to 1 m with a crown of rosulate celery-like pinnate leaves with rhombic leaflets and hollow stalks [30,38]. It has a shallow tape root system, and the stem is branched, succulent, and ridged. The leaflets are ovate to suborbicular three lobs 2–4.5 cm. The flowers are small and creamy white, and the calyx teeth are absulate. The seeds are broad, ovoid to globose in shape, and 1.5–2 mm long and wide [39].

2.3. Cultivation

A. graveolens or celery is the most popular species of *Apium* genus and it includes three distinct varieties or morphotypes, namely, *A. graveolens* var. *dulce* (celery or stalk celery), which is cultivated for its edible stalks, leaves, dried fruits, and seeds; *A. graveolens* var. *rapaceum* (root celery, turnip-rooted celery or celeriac), which is commonly used for it edible fleshy tap roots; and *A. graveolens* var. *secalinum* (smallage or leafy celery) which is common mostly in Asian countries and is used for its aromatic leaves [35]. *A. graveolens* is native to eastern Mediterranean, however, the wide distribution of wild ecotypes of the species makes definition of its origin uncertain [39]. It is usually a biannual plant, which is cultivated as an annual crop, however, annual cultivars also exist which are best suited for dry fruit and seed production [40].

It is very common to use celery in intercropping or mixed cropping systems, in order to increase income and diminish the negative impacts of weeds [41]. However, according to Baumann et al., celery has been proven to be very competitive with other species and more research is required regarding the proper amalgamation of species and plant densities in order to ensure marketable yield and quality [42]. Apart from chemical control, cover crops are also a useful means for weed control in celery crops and they may also improve celery yield and decrease fertilizer inputs [43]. Mulching and low tunneling of celery crops have also been suggested to increase total yield, mostly through the reduction of bolting incidences, and hence elongation of the growing period and an increase in the total number of harvests [44]. Other cultivation practices include biological amendments such as inoculation with arbuscular mycorrhizal fungi which has been proven to be beneficial for celery yield and the production of high-quality stalks [45].

2.3.1. Temperature and Soil Requirements

All varieties of celery, including *A. graveolens,* grow in climate conditions with a long, cool season and monthly mean temperatures of 15–21 °C, and therefore cultivation usually starts during autumn or early winter [36,46,47]. All varieties need abundant moisture during their growing, otherwise their roots can be small and hard. Therefore, they grow best in areas where rainfall or irrigation is assured. They are sensitive to freezing temperatures but can tolerate light frost for a short period of time. Celery plants thrive in soil with a pH of 6.0–6.6 in mineral soils and a pH of 5.5–6.0 in organic soils [36]. However, very low winter temperatures may induce bolting within the first growing year in biennial cultivars and severely affect yield and quality of end products (stalks, leaves, and roots) [46,48]. Such conditions are preferable when plants are meant for seed or dry fruit production where earliness in flowering induction is sought after [48]. Apart from the temperature, the photoperiod and plant growth stage are also important for flowering initiation [47], while according to Pressman and Negbi [49], long days after a chilling period increase bolting incidence and flower stalk elongation. Leafy types are considered more sensitive to freezing temperatures, as well as heat and water stress conditions than root celery [35,36,39]. Regarding soil requirements, they must be fertile and have good water holding properties without being prone to waterlogging. *Apium nodiflorum* lives partially submerged in water at an altitudinal range from sea level to 1200 m and it is found in most of North and South America, Europe, Asia, and North Africa. It is prostrate or ascending with a height of up to 1 m, perennial, and propagates by seeds and stolons. Petioles expand at the base sheathing and the stem and leaves are compact, pinnate, with toothed leaflets [50]. The native habitats of *Apium repens* are represented by lakeshores and shallow spring waters. It also grows in wet grasslands as its other habitat and it lives in flood-prone pastures [51,52].

2.3.2. Propagation

Propagation of plants is carried out by direct sowing of seeds (especially in the case of celeriac) or by transplanting after sowing in seed beds or seed trays. According to Baninasab [53], light exposure and temperatures higher than 20 °C and below 25 °C significantly increased germination rate and the percentage of germinated seeds of wild celery, indicating that soil temperature and exposure of seeds to light are crucial for plant propagation [47,48,54,55]. Seed germination may also be improved by thermal treatment (15 °C) and pre-sowing hydration of seeds followed by a slow drying process [56]. Regarding crop establishment, planting density is essential to the total yield, and distances of 15 × 20 cm and

45 × 40 cm for leafy celery and celeriac, respectively, showed the best results, regardless of the cultivar and irrigation regime [57,58].

2.3.3. Irrigation

Irrigation is crucial for high yields and marketability of vegetable products, especially in leafy vegetables such as stalk celery and smallage [59]. Unless precipitation covers crop needs in irrigation water, lack of water has a severe effect on the total yield and quality of celery, especially under low nitrogen rate regimes [60], while water stress conditions may increase furocumarins content in celery juices [61] and alter essential oil composition in terms of volatile compound content such as limonene and myrcene [62]. The quality of water is also essential and saline water (up to 5.83 dS/m) resulted in a yield reduction of 74% as compared with irrigation using tap water (0.25 dS/m) [63]. Moreover, salinity may affect seed germination, and NaCl concentrations higher than 100 mM may completely inhibit germination of celery cv. Ventura [64]. In contrast, according to other authors [65], celery plants (cv. Utah 52/70 R) grown in soilless hydroponic systems have proven to be tolerant to salinity levels up to 10.5 dS/m since no decrease of dry matter content was observed at this level. Moreover, Pardossi et al. reported that salinity levels up to 10 dS/m and 100 mM of NaCl, respectively, had no significant effect on the growth of celery plants grown in a nutrient film technique (NFT) hydroponic system [66]. Drip irrigation is the most common method used in celery crops, since it allows for higher water use efficiency through the application of lower irrigation volumes and more frequent irrigations that match evapotranspiration and crop stage [67], while the method has also been associated with more economical chemical weed control as compared with other irrigation systems [68]. Moreover, subsurface placement of film stripes in greenhouse environments may increase soil water content through the reduction of deep percolation, and further improve irrigation system efficiency [69].

2.3.4. Fertilization

Fertilization of horticultural crops is very intensive, and a careful management is needed to minimize nutrient losses through leaching. Considering the high total biomass production of celery varieties, the species is considered to be demanding in terms of nutrient requirements. According to Christiansen et al., celeriac has a shallow root system which allows for better nitrogen use efficiency in a soil layer of 0–25 cm depth, whereas, nitrogen (N) depletion is higher in larger depths (0.25–2.5 m) [70]. Although celery and celeriac are considered as moderate nitrate accumulators [71], there are significant differences in nitrogen use efficiency (NUE) between the existing cultivars and unreasonable use of N fertilizers should be avoided in order to avoid excessive nitrates contents. However, suggested rates may differ depending on growing and soil conditions. For example, according to Du et al., the application of 200 kg/ha of N and aerated irrigation of celery crops may improve yield, NUE and soil bacteria, fungi, and actinomycetes abundance [72], while Madrid et al. reported that 25% lower N rates (0.31 g/L of KNO_3) resulted in a similar mineral composition of celery plants, as compared with a control treatment (0.59 g/L of KNO_3) [73]. In a study by Min et al., the highest greenhouse-grown celery plants were reported for application rates between 120–180 kg/ha of N, while additional amounts of N (up to 300 kg/ha of N) were depleted through leaching [74]. Moreover, Kolota et al. reported that pre-plant application of 100 kg/ha of N is efficient for early celeriac production [75]. Regarding potassium (K) fertilization, the results from hydroponic studies showed that an application of 482.7 mg/L significantly increased celery yield, while the type of K was also important for quality since K_2SO_4 increased tip-burn incidences as comparing with KCl [76]. In addition, Li et al. reported that 4–8 mmol/L of K, and 8 mmol/L of Ca and Mg were adequate for optimum growth and development of celery plants [77]. For phosphorus (P) fertilization, Li et al. suggested that application rates within the range of 124 to 248 mg/L along with medium Mg and Ca levels (192 mg/L and 320 mg/L, respectively) were sufficient to cover nutrient requirements of celery plants [77]. Celery is very sensitive to Ca deficiency which results in black heart symptoms and quality loss of the final product and can be controlled through foliar application of Ca in the form of $Ca(NO_3)_2$ or $CaCl_2$ [78]. The species is also susceptible to boron deficiency (brown checking and cracked stem) and toxicity which may severely affect the quality and marketability of the final product. According to Bellaloui and Brown, the sensitivity to these physiological disorders depends on the genotype which could explain the differences in the efficiency of boron translocation from roots to shoots and its further distribution to the aerial parts of the plant [79]. Other physiological disorders include pithiness and pencil stripe in celery stalks and hollow heart in celeriac roots [39].

2.3.5. Harvesting

Harvestable maturity is reached when roots measure a diameter of 5–12 cm depending on the growing conditions. In areas with mild winters, roots might be left in the ground or straw mulched with leaves and harvested as needed. Roots can also be removed and stored in humid sand in a cool place [36]. Harvesting of celery (leafy or turnip-rooted types) is carried out manually, especially when successive harvesting is implemented, or mechanically for large fields when the product is meant for industrial purposes. Although the harvesting date is genotype and growing conditions dependent, early harvests may improve the quality of the end product mostly through the visual appearance (color and texture) and physicochemical composition [80], as well as through the increased content of essential oil in the leaves [81]. Late harvests may increase total yield when a single harvest is implemented, however the overall quality of celery petioles is reduced, especially in terms of tissue texture [82]. The white color of petioles is associated with high quality and increases consumers' acceptance, therefore, various cultivation practices (also known as blanching) are implemented to improve petioles color, including covering plants with pots, tie wrapping the leaves in order to cover the middle of the rosette, and hilling up with soil. Moreover, according to Han et al., the feature of white petiole is also genotype dependent and self-blanching or white stalk cultivars have been developed to cover market needs [83].

2.3.6. Postharvest Treatments

The postharvest process is essential for retaining the quality of the final product, especially for minimally processed food products, such as ready-to-eat fresh-cut salads. Celery is commonly marketed as fresh-cut raw leaves and stalks and additional processes are required for better quality and extended shelf-life of the products. Various postharvest treatments have been proposed to reduce the antimicrobial load and increase the shelf-life of processed celery products, including sanitization with gas plasma treatments [84], heat treatments, edible coating and chemical dipping [85–87], packaging [88,89], modified and controlled atmospheres [88,90–92], and light exposure [93], while most of these treatments have been linked with quality changes [94]. However, preharvest treatments are also pivotal and may define the quality and the shelf-life of the final product. According to Ilić et al., early harvesting combined with washing and cool storage may significantly reduce water losses during prolonged storage of celery [95], while Rossi et al. reported that late harvesting may increase the incidence of cut-end browning in celery without postulating ethylene involvement in this process [96]. Moreover, postharvest washing and cold storage of celeriac roots may significantly decrease the content of nitrates [97]. Nitrogen fertilizer rates may also have an effect on the shelf-life of celery sticks. According to Gómez et al., reducing nitrogen rates by 25% may significantly improve sensory quality and decrease decay incidences and nitrate content [98].

2.3.7. Pests and Diseases

Several diseases and pests, such as leafminers (*Liriomyza* sp.), carrot fly (*Psila rosae*), root-knot nematodes (*Meloidogyne* sp.), celery fly (*Euleia brercolai*), aphids (various species), mites (*Tetranychus* sp.), and cutworms attack celery varieties and can significantly reduce the yield and quality of the final product [39]. The main pathogens that infect celery include aster yellows (phytoplasma) carrot motley dwarf virus (CMDV), celery mosaic virus (CeMV), bacterial blight (*Pseudomonas syringae* pv. *apii* and *Pseudomonas cichorii*), alternaria leaf blight (*Alternaria dauci*), septoria spot (*Septoria apiicola*), cercospora leaf blight (*Cercospora apii*), and cercospora leaf spot (*Cercospora apii*), celery pink rot (*Sclerotinia sclerotiorum* and *S. minor*), black rot (*Alternaria radicina*), crater rot of celery (*Rhizoctonia solani*), crater rot of celery (*Rhizoctonia solani*), fusarium yellows (*Fusarium apii* and *F. apii* f.sp. *pallidum*), and grey mold rot (*Botrytis cinerea*) [39].

3. *Apium* Plants Phytochemical Composition

The chemical composition of *Apium* plants is remarkable. The variability of chemical compounds and the effects, which these substances induce, have been determined with 508 published articles indexed in the PubMed databases and 966 articles indexed in the Web of Science–Core Collection (Clarivate Analytics) databases. The chemical composition of *Apium* plants differs depending on plant part (leaves, seeds or stalks), stage of harvesting, geographical region of production, type and method of preparation of essential oil, and growing conditions such as soil structure and climate [35,99]. The phytochemical composition of the *Apium* plants according to the USDA Nutrient Database/Distribution of Nutrients (raw vegetable), is presented in Table 1.

Table 1. Nutritional value per 100 g *Apium* plants [adapted after http://ndb.nal.usda.gov/ndb/foods].

Nutrients		Value/100 g (Unit)	Nutrients		Value/100 g (Unit)
Energy		78 kJ (18 kcal)	**Amino Acids**	Arg	45 mg
Protein		1.6 g		His	25 mg
Water		88.6 g		Ile	50 mg
Carbohydrate		2.3 g		Leu	75 mg
Fiber total		4.2 g		Lys	75 mg
Glucides	Fructose	100 mg		Met	18 mg
	Sucrose	1710 mg		Phe	45 mg
	Starch	440 mg		Thr	45 mg
	Fiber, total dietary	1.6 g		Trp	12 mg
	Sugars, total	1.83 g		Tyr	25 mg
Lipid		0.3 g		Val	75 mg
Lipids (fatty acids)	Palmitic acids	65 mg	**Minerals** (0.9 g)	Sodium	75 mg
	Stearic acids	4 mg		Potassium	320 mg
	Oleic acids	13 mg		Magnesium	9 mg
	Linoleic acids	155 mg		Calcium	70 mg
	Linoleic acids	17 mg		Manganese	150 µg
	Fatty acids, total saturated	0.042 g		Iron	530 µg
	Fatty acids, total monounsaturated	0.032 g		Copper	20 µg
	Fatty acids, total polyunsaturated	0.079 g		Zinc	310 µg
	Cholesterol	0 mg		Phosphorus	80 mg
	Total lipid (fat)	0.17 g		Chloride	150 mg
Vitamins	Vitamin B_{12}	0 µg		Fluoride	14 µg
	Carotin	15 µg		Iodine	3 µg
	Vitamin A, RAE	22 µg		Selenium	1–10 µg
	Vitamin A, IU	449 IU	**Vitamins**	Vitamin B2	70 µg
	Vitamin E (α–tocopherol)	0.27 mg		Nicotinamide	900 µg
	Vitamin D (D_2 + D_3)	0 µg		Pantothenic acid	510 µg
	Vitamin D	0 IU		Vitamin B6	200 µg
	Vitamin K	100 µg		Folic acid	7 µg
	Vitamin B1	35 µg		Vitamin C	8 mg
Purines		30 mg	**Oxalic acid**		6800 µg

The proximate composition of *Apium graveolens* is shown in Table 2.

Table 2. Proximate nutrient composition of *Apium graveolens* (per 100 g) [2,30].

Constituents	Petioles	Stem	Leaves	Seeds
Energy (K cal)	29	34	64	392
Water (g)	96	95	81.3	6.0
Protein (g)	0.7	0.9	6.0	18.1
Fat (g)	0.1	0.1	0.6	25.3
Carbohydrate (g)	1.2	1.2	8.6	41.4
Vitamin A (IU)	90	120	80	52
Thiamine (mg)	0.03	0.03	Trace	–
Riboflavin (mg)	0.02	0.04	Trace	–
Niacin (mg)	0.3	0.3	Trace	–
Vitamin C (mg)	7	10	6.2	17
Ca (mg)	25	70	23	1767
Fe (mg)	0.3	0.5	6	45
Mg (mg)	10	14	–	440
P (mg)	27	34	14	547
K (mg)	–	–	–	1400
Na (mg)	–	–		160
Zn (mg)	–	–		7

The seeds of *Apium* plants have a moisture content of 5%−11% and, generally, have the following constituents: protein (0.8%), non–volatile oil (5.8%−14.2%), volatile oil (1.5%−3%), total ash content (6.9%−11.0%), cold water extract (5.9%−12.9%), and ash insoluble in acid (0.5%−4.0%). The *Apium* plant leaves and stalk contain, generally, moisture (80.30%−93.5%), fibers (1.4%−1.2%), fat (0.6%−0.1%), protein (0%−0.8%), mineral matter (2.1%−0.9%), iron (0.06%−0.05%), calcium (0.23%−0.3%), phosphorous (0.14%−0.4%), vitamin C (62.6 mg/100 mg), and vitamin A (5800−7500 IV) [100].

A. graveolens includes phtalide glycosides, about 0.2% of furocoumarins, flavonoids and flavonoid glycosides (mainly apigenin, luteolin, chrysoeriol, and quercetin in combination with the respective glycosides) [101]. The *A. graveolens* leaves contain large amounts of antioxidant molecules and are a crucial source of natural dietary flavonoids [9]. The chemical constituents of the root extracts from *A. graveolens* var. *dulce* contain flavonoids, antioxidants, polyacetylenes, coumarins, phthalides (*d*-limonene, selinene, and other related phthalides), neocnidilide, cnidilide, *Z*-lingustilide, senkyonolide, linoleic acid, omega-6 fatty acid, and apiol [102]; and *Apium graveolens* var. *rapaceum* includes butylphthalide and *Z*-butylide nephthalide, cnidilide, *E*- and *Z*-ligustilide, neocnidilide, and senkyonolide [36,102]. Major active constituents of *A. graveolens* are L-3-*n*-butylphthalide, sedanolide, linoleic acid, flavonoids, phenolic compounds, and volatile oil, which are extracted from its various parts including roots, leaves, and seeds [9,32]. It also contains undifferentiated oleic acid (0.065 g), total polyunsaturated fatty acids (0.148 g), 18:2 undifferentiated linoleic acid (0.148 g), lutein + zeaxanthin (1 μg), apigenin (2.4 mg), and quercetin (0.18 mg) per 100 g [39]. Furthermore, it contains valuable vitamins and minerals such as vitamin C, potassium, calcium, sodium, and magnesium [103].

The phytochemical screening of *Apium* plants has quantitatively demonstrated the presence of carbohydrates, alkaloids, glycosides, flavonoids, saponins and steroids, tannins, and the majority macro- and microelements, whereas terpenoids were present in small quantities or even absent. In addition, volatile oils, sesquiterpene alcohols, and fatty acid were conferred. The *Apium* plant contains phenols and furocoumarins [104]. Celery contains 3-butilphtalide. The furanocumarins shown in Figure 1 were found in leaves.

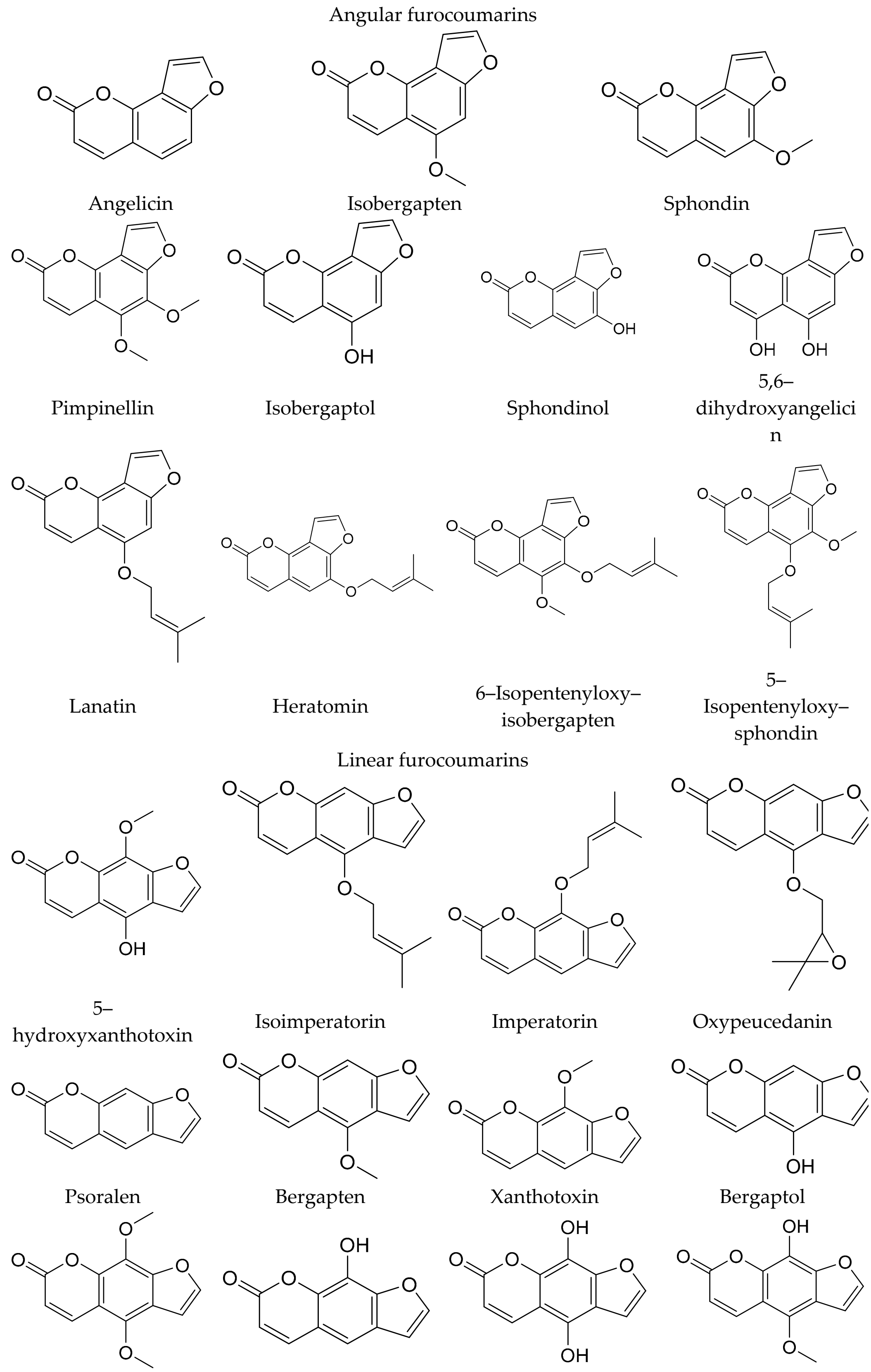


Figure 1. *Cont*.

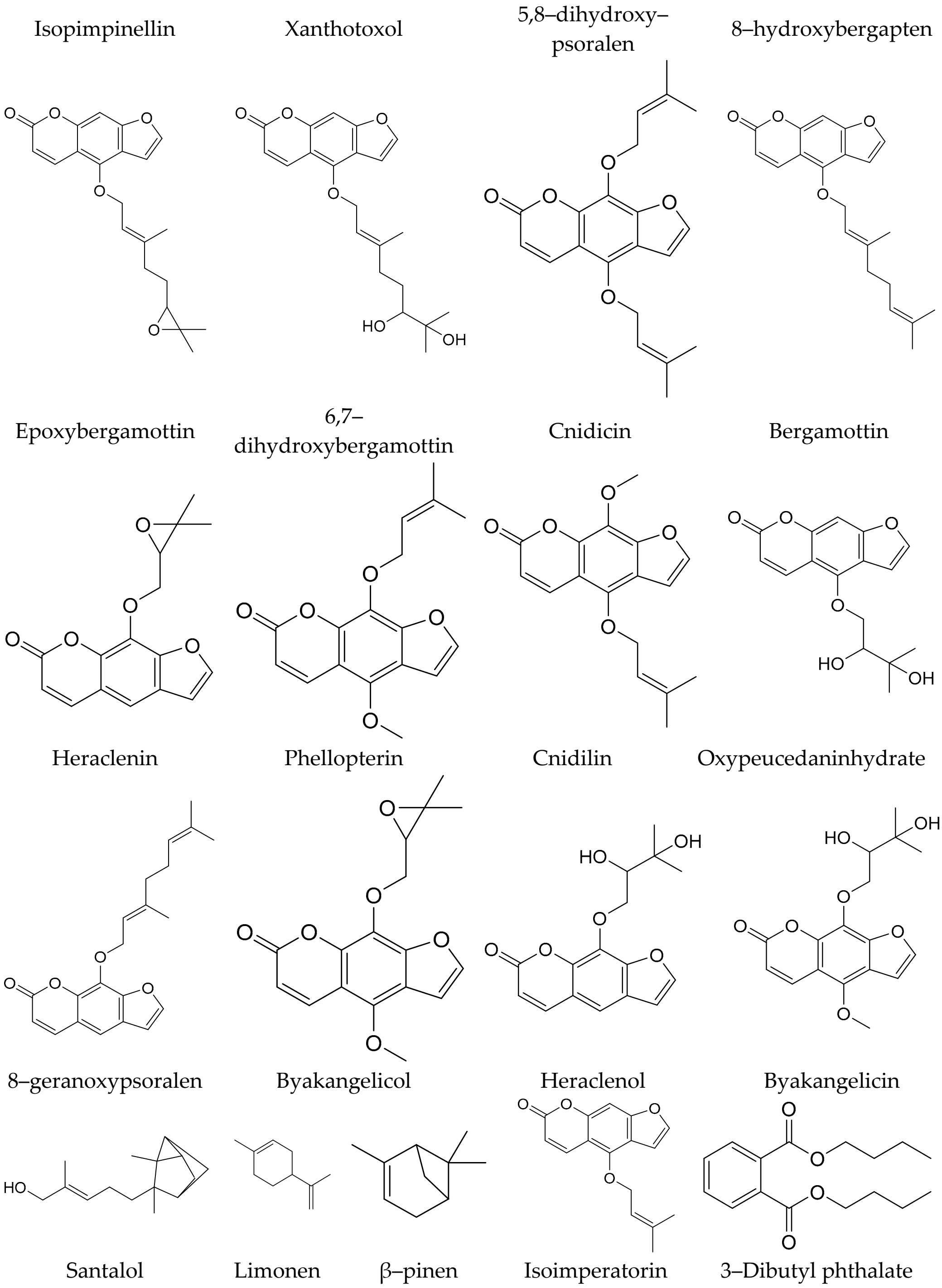
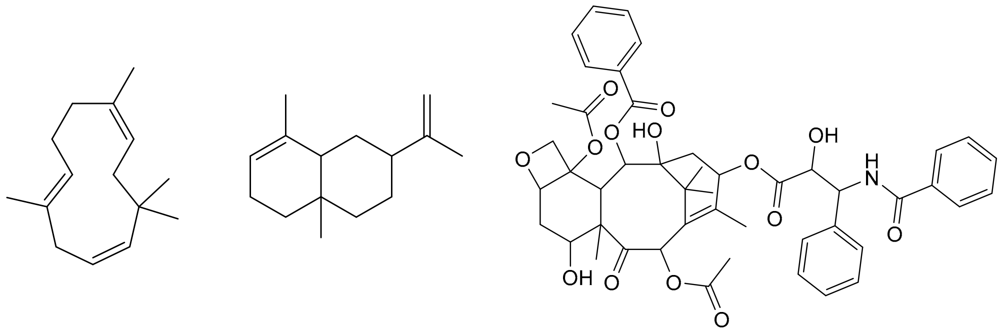


Figure 1. *Cont*.



Humulen Selinen Taxol

Figure 1. Furocoumarins and other phytoconstituents found in *Apium* plant leaves.

The furocoumarins included celerin, psoralen, bergapten, apiumoside, apiumetin, apigravrin, osthenol, isopimpinellin, isoimperatorin, celereoside, and 5- and 8- hydroxy methoxypsoralen [105].

The major constituents from essential oil quantified in *Apium* plant seeds were limonene, coumarines, bergapten, fatty acids, and phthalides. *Z*–ligustilide and *Z*–butylidenephthalide, β–salinene, selinene, apiol, santalol, sedanolide, sedanic acid, citric, isocitric, fumaric, malic and tartaric acids was quantified in *Apium* plant seeds essential oil and oleic, palmitic, palmitoleic, petroselinic, petroselaidic, stearic, myristic, myristoleic acids (all acids have been quantified in fixed oils) [106]. The fatty acids in the oil of *A. graveolens* seed are petroselinic acid (64.3%), oleic acid (8.1%), linoleic acid (18%), linolenic acid (0.6%), palmitic acid (6.9%), stearic acid (1.4%), hexadecenoic acid (0.1%), α-linolenic acid (0.6%), and *cis*-vaccenic acid. *A. graveolens* oil contains 28 compounds belonging to different categories such as terpenes, sesquiterpenes, aromatics, alcohols, oxide, aldehydes, ketones, and esters [107]. The major constituents of celery seed oil are sedanolide, sedanonic anhydride, 3-*n*-butyl phthalide, and other minor phthalides. A series of phthalide derivatives causes the characteristic odor of celery essential oil [108,109].

Apium plants contain many phenolic components (caffeic acid, catechin, catechol, chlorogenic acid, chrysin, rosmarinic acid, ellagic acid, ferulic acid, gallic acid, *p*–coumaric acid, protocatechuic acid, pyrogallol, salycilic acid, and syringic acid), five flavonoids (apigenin, hesperitin, luteolin, quercetrin, apiin, isoquercitrin and chrysin) and three isoflavones (daidzein, genistein, and isorhamnetin) [109]. Other phenolic compounds include tannins, graveobioside A and B, apiin, apigenin, isoquercitrin, and phytic acid [23]. Sedanolide is one of the main flavor compounds [110–112] responsible for the unique aroma of celery [22]. In addition, several phthalides, i.e., sedanenolide and 3-*n*-butylphthalide, are present in remarkable quantity. Quantitatively, *A. graveolens* total phenolic (mg gallic acid equivalent/g) and flavonoid (mg quercetin equivalent/g) content of leaves was found to be 22.7 and 4.08 for ethylacetate, 51.09 and 2.12 for butanol, and 46.40 and 0.77 for water extracts, respectively [113]. Phenolic acids in *A. graveolens* consist mainly of chlorogenic acid (<0.01−55.0 mg), *p*-coumaric acid (<0.01−1.46 mg), and ferulic acid (<0.01−1.04 mg) per g biomass [101].

The overall differences in the chemical compositions for *Apium* plants, both in quantitative and qualitative terms, found in the literature reside in the different ecological factors of territories (the origin of the samples and the genetic composition of the genotypes), the part of the planes taken in the study, the conditioning mode of the vegetal material, and either the method of extraction or the method of analysis used.

4. Traditional Medicinal Uses of *Apium* Plants

Since ancient times, human beings have been faced with disease and discomfort and have struggled to combat these with different approaches. Among all the treatments, herbs are continuously used for the treatment of all the ailments [114]. At the present time, herbal drugs are not in the list of mainline therapies, however, due to unwanted toxicity and side effects, herbal therapy is again gaining momentum. Herbal medicine is now an accepted medicine as a complementary and alternative therapy in combination with the main line therapies in the world [114]. For this reason, the world today is focusing more and more on research in the field of herbal medicine [115–117].

The use of medicinal plants to treat common ailments dates since ancient times and they are preferred due to their many therapeutic properties, lower cost, and reduced side effects [6–11,23,30,118–122]. The use of *Apium* plants in traditional and modern medicine is shown in Table 3.

The medicinal parts of *A. graveolens* used in treatment include (1) leaf of *A. graveolens* var. *secalinum*, (2) stalk of *A. graveolens* L. var. *dulce*, and (3) turnip root of *A. graveolens* var. *rapaceum* [6,107]. Celery is a plant mentioned in the traditional Arab and Islamic medicine with the name "Karafs". According to old literature, it was also called Udasaliyon in Greek [114]. The roots help treatment of liver, spleen dropsy, and jaundice diseases [123].

Celery is used against helminth, joint problems [31], stomach problems (relief of griping pains and flatulence), and spasm, as well as sedative, carminative, diuretic, urinary calculus, urinary antiseptic, kidney stones, emmenagogue, laxative, bronchitis, asthma, osteoarthritis, and arthritic pain [15,103,107,113,114]. It also relieves offensive breath and stimulates the production of semen and libido by its protective role against the sodium valproate [15,23,103,114,124–126] and increases breast milk production [127]. Although no experimental investigation explores its effect on female fertility, its abundance of calcium, magnesium, potassium, and sodium might explain the gender determination [128]. Celery is used as a heart tonic to lower blood pressure [129] and total cholesterol [97] or hyperlipidemia in general [16,103,123,124]. It has important effects such as preserving gastric mucosa, lowering blood pressure, and strengthening the heart. Its root leads to an increase in calcium and a decrease in potassium in the heart tissue [124]. It also has potential benefits related to weight loss or management because it is a low-calorie vegetable [35]. It has a positive effect on the immune system because it contains some vitamins such as vitamin C and vitamin A [103]. Traditionally, *Apium leptophyllum* Pers. prevents tumor, anorexia, vomiting, and colic pain because of its antinephritic, antirheumatic, and carminative properties [101].

Apium plants are popular plants in modern societies as they represent a good alternative to expensive chemical drugs which have many negative effects on human health [30].

Table 3. Use of *Apium* plants in traditional and modern medicine [35].

Use of *Apium*Plants in Traditional Medicine		
Geography	**Plant Fraction**	**Purpose of Use**
Europe, America, Asia	Leaves, stalks, root	Nutrition source
Europe	Roots	Aphrodisiac
Ancient Egypt	Seeds	Medicine
China	Seeds	Arthritis, gout, dizziness
India	Seeds	Diuretic, appetizer
Use of *Apium* Plants in Modern Medicine		
Geography	**Plant Fraction**	**Purpose of Use**
Europe	Fresh plant and seeds	Lower blood pressure, relief anxiety, reduce blood sugar
Western	Seeds	Arthritis, gout, rheumatism, urinary tract problems.
America	Stalks	Anti-high blood pressure, heart disease prevention.
China	Seeds	Arthritis, rheumatism, dizziness, gout, high blood pressure, insomnia, nervousness
India	Seeds	Arthritis, liver protection, urine problems

5. Use of *Apium* Plants in Food Preservation

Celery, as well as many other aromatic and medicinal plants, produces a large array of phytochemicals such as terpenoids, alcoholic compounds, phenols, and essential oils, etc. [130,131] which have uses ranging from the control of metabolic disease to pathogenic microorganisms to food preservation [23,130,132,133]. The antifungal and antibacterial properties of several active constituents and essential oils of *Apium* plants against foodborne microorganisms can be easily served in foods that could provide alternatives to conventional and synthetic bactericides and fungicides [132,133]. Thus, the antimicrobial properties of *Apium* plants enable the possibility of using natural, low-cost, safe, renewable, food grade, and easily biodegradable antimicrobial agents for the preservation of several food products [130]. Consequently, they are important for providing resistance to several pathogens. Some authors have reported that the essential oil of this plant has the potential to act against various bacterial and fungal pathogens due to its composition, which is rich in antimicrobial constituents such as carvone, a-phellandrene, and limonene [130,131].

The antioxidant of celery extracts has also been evaluated both therapeutically and in food preservation [114,120,132,134]. The food industry must continually evaluate the utility of alternative strategies to meet consumer demand for "clean labels" and limit the use of chemical preservatives. The deterioration of the quality of the fats, vegetable oil, and other food systems is associated with lipid peroxidation. For example, the oxidation of lipids in vegetable oils results in chemical changes that impart off-flavor and rancid odor. The use of antioxidants is the most suitable means to stabilize oil, prevent lipid oxidation, and protect oil from free radicals inflicted damages. Mitigation of the oxidation process can be achieved using synthetic antioxidants such as tertiary butylhydroquinone (TBHQ), butylated hydroxyanisole, and butylated hydroxytoluene. An alternative to the use of those synthetic antioxidants is extracts from celery. Celery extracts have demonstrated antioxidant activity and can suitably replace the synthetic antioxidant, TBHQ in canola oil [134,135]. Indeed, essential oil of *Apium* plants has the potential to be used as a substitution for chemical food preservatives like tertiary butyl hydroquinone (TBHQ) and butylated hydroxytoluene (BHT) since it is considered a cancer promoter [130]. However, the method of extraction of the antioxidant compounds must be considered to ensure optimal activity while being simple and cost appropriate.

Admittedly, the greatest application of celery extract (celery powder and celery juice) has been in meat preservation. It can serve as a natural flavoring and can be used as a nitrate replacer in meat products with special significance on their antifungal, antibacterial, and food preservation properties [130,131]. Indeed, Sebranek and Bacus demonstrated that the celery juice or powder and starter culture treatment is an efficient alternative instead of direct addition of sodium nitrite into frankfurter-style cured hams and sausage [136]. The improvement of safety of "naturally cured (no-nitrite-or-nitrate-added)" meats implies a cured cooked meat model system consisting of several natural ingredients (2% salt, 10% water, 80:20 pork, and 150 or 50 ppm ingoing sodium nitrite) that closely looks like the commercial frankfurters that reduced *Listeria monocytogenes* inhibition ($p < 0.05$) in the major part of the uncured meat products (nitrite or nitrate free, with celery powder as the nitrate source) as compared with control samples conventionally produced with direct addition of sodium nitrite [137]. Sodium nitrite is included in the production of cured meat products to provide the characteristic color, flavor, and microbiological safety [138]. Studies have linked the consumption of processed meats containing nitrites to the risk of certain types of cancer [139,140]. In the last decades, the increased demand for nitrite or nitrate-free meat products led many manufacturers to use celery powder, containing a substantial amount of nitrate (celery can contain as high as 1500 ppm to 2800 ppm nitrate or greater than 2500 mg nitrate/kg) in combination with a starter culture to reduce nitrate to nitrite during this process [136,137,141,142]. *Apium petroselinum* essential oil demonstrated antibacterial effects on food spoilage bacteria, *A. faecalis* and *S. dysenteriae* bacteria [142]. Previous studies have also reported that the essential oils and extracts of the *Apium petroselinum* and *A. graveolens* are effective on various bacteria such as *S. dysenteriae*, *E. coli*, and *S. aureus* [143]. Their results suggest that the replacement of synthetic preservatives with the essential oils of these natural healthy compounds can be applied as an alternative way to increase the shelf-life of several special foods [142]. However, to prove its usefulness as a food preservative, the antimicrobial activity of *A. graveolens* essential oil, of known composition, needs to be assessed in specific food products. The effective antimicrobial dose of oil may exceed the sufficient level for flavoring purposes because of its unique taste and aroma [141]. Thus, the use of *Apium* plant oil would probably be limited in food products. Menghini et al. indicated that the essential oil of *Apium nodiflorum* (L.) Lag, which is used as a culinary herb, showed antimicrobial activity against *Helicobacter pylori* with a minimum inhibitory concentration (MIC) of 12.5 µg/mL [144]. *Pseudomonas putida* is one of the most important spoilage bacteria in meat and meat products. Oussalah et al. investigated the effect of several essential oils against *P. putida* to see their antibacterial activity. Oussalah et al. showed that oils which already had proven antimicrobial properties appeared to have little or no effect against the *P. putida* strain. However, the *Apium* plant showed antimicrobial activity at a MIC of 0.8% wt/vol. against *P. putida* [131].

Thus, celery powder and juice are highly compatible sources of nitrite for process meat products due to their mild flavor profile and fairly low vegetable pigment that does not impart the final product flavor [136,141,145]. Indeed, the use of celery juice or powder in processed meat products is widely known [113,119,131,133].

In addition to this, the growth of pathogenic microorganisms including *Listeria monocytogenes*, *Clostridium botulinum*, and *Clostridium perfringens* in processed meats containing celery juice or celery powder has been investigated. Celery juice treatments at both 100 and 200 mg/kg resulted in growth of *L. monocytogenes* similar to that of conventional nitrite at the same concentrations used in ham [145]. The researchers indicated that celery juice may increase the meat product pH which could have an impact on antimicrobial properties of nitrite in some products. The control of *L. monocytogenes* in hams made with pre-fermented celery juice has been demonstrated [146]. The use of natural curing ingredients results in hams that possess *L. monocytogenes* inhibitory properties similar to those in traditionally cured hams. The use of celery juice powder containing preformed nitrite in turkey bologna was shown to have similar antimicrobial properties to the chemical form of nitrite, but it lacked flavor and color [147]. The control of *C. perfringens* in frankfurters containing a natural source of nitrite was effective only when additional natural antimicrobial agent was used [137]. However, the addition of celery powder in processed meat should be limited to around 0.2%–0.4% of the formulation weight since high-level incorporation of celery powder may cause the development of off flavors [148]. Thus, celery powder or concentrate of celery juice was frequently mentioned as ingredients because they are a food plant and their potential contribution as a source of nitrate is very significant [139]. However, the use of celery powder alone, without nitrate reducing bacteria, is less appropriate for producing standard cured meat [143]. Moreover, it would be of interest to investigate the synergistic effects of celery powder rich in natural nitrate and volatile oil on meat preservation.

Overall, the use of celery-based products in the preservation of food will likely expand and might garner greater regulatory oversight that could prevent their use as flavoring ingredients.

6. Pharmacological Properties of *Apium* Plants

6.1. Antimicrobial Activities of Apium Plants

Antibiotics have been critical in the control of microbial infections. The emerging antimicrobial resistance throughout the world [149] emphasizes the research of new treatments. Natural resources, especially plants, are potent candidates for antimicrobial uses. Medicinal plants have a critical role in fulfilling the basic health needs and introduce a new source of natural antibacterial and antifungal agents [150]. Many naturally found compounds, such as essential oils extracted from edible and medicinal plants, herbs, and spices have been shown to possess antimicrobial functionality and serve as a natural antimicrobial agent against a wide range of food spoilage and pathogen microorganisms [130], thus, they have long been traditionally used for centuries due to their antifungal and antibacterial properties. Therefore, essential oil of *Apium* plants can be assumed to be one of the important groups of natural sources for the development of broad-spectrum, safer and cheaper antifungal agents [151]. The main active compounds of these oils are primarily limonene, pinene, and selinene [119,130]. More particularly, phenolic constituents also have been reported to be responsible for these properties [152]. Antimicrobial properties of *Apium* plants have been confirmed in several in vitro studies [109,151–153]. Various epidemiological studies showed that *Apium* plants play a significant role in the prevention of microbial growth with its antibacterial and antifungal effects [119]. Baananou et al. indicated that essential oil and aqueous extract from *A. graveolens* showed antibacterial activity with MIC values of 0.01–0.25 mg/mL [109]. In a study by Asif et al., the antimicrobial activity of the essential oil of this plant was determined in vitro against *Helicobacter pylori* and, consequently, a MIC value of 12.5 mg/mL was obtained [34]. A study by Menghini et al. also revealed the inhibitory activity of *A. nodiflorum* essential oil against *Helicobacter pilori* [143]. Maxia et al. evaluated the antifungal activity of *A. nodiflorum* essential oil and extracts against yeasts, dermatophytes, and *Aspergillus* spp [151]. According to their results, the MIC of the oil showed a variability of inhibition among all the fungi tested. Essential oil of *A. nodiflorum* from different origins showed significant activity against dermatophytes with MIC values ranging from 0.04 to 0.32 μg/mL. The oil for *Aspergillus fumigatus* and *A. flavus* is less effective against *Aspergillus* spp., especially MICs of 2.5 and 5μg/mL [151]. Maxia et al. also indicated that the occurrence of myristicin and dillapiol in essential oil could show a synergistic effect, which may explain the relatively higher antifungal activity against the same strains. These results support the potential application of *A. nodiflorum* essential oil in the treatment of dermatophytosis and candidosis [151]. Moderate antimicrobial activity was shown by *A. graveolens* (leaves) against *Salmonella typhi* that are resistant to most antibiotics [153].

A. graveolens essential oil showed an inhibitory activity against *S. aureus* and different *Listeria* strains, whereas, *E. coli* and several *Salmonella* species remained unaffected. The inhibitory activity was also recorded against several fungal strains with varying efficiency. However, Din et al. indicated that extracts of *A. graveolens* were very effective and showed good activity against *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis,* and *P. aeruginosa* [154]. Baananou et al. showed that the essential oil of *A. graveolens* was strongly inhibitory against *E. coli* and moderately inhibitory against *P. aeruginosa* and *S. aureus* [109]. Din and colleagues performed an experiment to evaluate the antimicrobial activity of *A. graveolens* against several bacterial strains and fungal strains. They reported that all fractions of *A. graveolens* showed good activity against *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis,* and *P. aeruginosa*. It was observed that crude ethanolic fraction of *A. graveolens* exhibited good activity as fraction was effective against *S. typhi* and *B. subtilis* having a MIC value of 0.96 μg/mL and 0.82 μg/mL, respectively, whereas, the same fraction was least effective against *E. coli,* recording MIC values of 17.7 μg/mL. Hexane and methylated spirit showed at par activity while methylated spirit was a slightly less effective inhibitor against *P. aeruginosa* (MIC: 11 μg/mL) [154]. *A. graveolens* was also evaluated against antifungal activity using different strains of fungi. The data showed that the ethanolic fraction of *A. graveolens* was more effective against *A. flavus* having a MIC value of 5 μg/mL followed by hexane fractions (MIC: 12 μg/mL). Similarly, the methylated spirit fraction also proved to be effective against relevant fungal strains followed by the methanolic fractions. It was also noted that the crude ethanolic fraction of *A. graveolens* revealed good activity as compared with other fractions [154].

Rani and Khullar revealed that moderate antimicrobial activity was shown by *A. graveolens* against multidrug-resistant *Salmonella typhi* [155]. Similar results were reported by Shad et al. and Edziri et al. [150,152]. Din et al. also indicated that the ethanolic fraction of *A. graveolens* was more effective against *A. flavus,* followed by hexane fractions. Similarly, the methylated spirit fraction also showed activity against relevant fungal strains followed by methanolic fractions [154]. Momin and Nair reported that the methanolic extract of *A. graveolens* seeds had an inhibitory effect on the growth of *C. albicans* and *C. parapsilasis* at 100 μg/mL [107]. Similarly, Edziri et al. concluded that the methanolic extract of *A. graveolens* had the best antifungal activity against various yeasts such as *C. albicans*, *C. kreussei,* and *C. parapsilosis* with MIC values that varied from 0.08 to 0.31 mg/mL [150,152]. Baananou et al. reported similar results for the antifungal activity of methanolic extract of *A. graveolens* against *Candida* serovars with MIC values ranging between 0.08 and 0.31 mg/mL and with minimum fungicidal concentration values ranging between 0.08 and 0.63 mg/mL [109].

According to the obtained results, which confirmed earlier studies by different authors, the antimicrobial activity of each extract can be varied within each other and that methanol is the best solvent for the extraction of the antimicrobial substances from *Apium* plants as compared with the other solvents [152,156]. Moreover, the development of fractionations of extracts should be carried out for further investigation of their possible use as food preservatives to adopt their promising potential in the food industry [152].

A. graveolens extract antimicrobial activity has been associated with numerous free hydroxyls, limonene, β-selinene, and other compounds that are able to combine with the carbohydrates and proteins in the bacterial cell wall and or the lipophilic character of these compounds, leading to either enzyme inhibition or accumulation in membranes and resulting energy depletion which is associated with their antibacterial properties [130].

In short, *Apium* plants show antifungal and antibacterial activities [109,151,153,154]. In many studies investigating the antimicrobial effect of essential oil or extracts of *Apium* plants, authors generally reported the minimum inhibitory concentration (MIC) of tested samples by using different methods. These methods varied from the agar dilution method to the disc diffusion method [130]. The MIC is defined as the lowest concentration of extract needed to prevent growth of any microorganism [153]. The results of these studies revealed some activity against specific pathogens which varied from none to moderate. It is quite difficult to interpret the obtained data because different antimicrobial tests were used (e.g., disc diffusion and broth microdilution techniques), which were previously shown to provide results that were hard to compare [155].

6.2. Antioxidant Activities of Apium Plants

Flavonoid and phenolic compounds are mostly responsible for the antioxidant activity and they are abundantly found in plants such as *Apium* plants. Many studies have been carried out to demonstrate the antioxidant activity of *Apium* plants both in vitro and in vivo. Many studies reported the antioxidant activity of *Apium* plant seeds, roots, and leaves. *A. graveolens* leaves contain approximately 202 mg/kg flavonoid with 48 mg/kg luteolin and 27 mg/kg chrysoeriol 7-glucosides [157]. Jung et al. extracted the phenolic compound of *A. graveolens* leaves with methanol, partitioned water, ethyl acetate, butanol, and the phenolic contents were determined by Folin-Coicalteu method. In addition, they determined some antioxidant activity in vitro models such as antioxidant capacity by radical scavenging activity using DPPH (α, α-diphenyl-β-picrylhydrazyl), β-carotene-linoleate, reducing power, metal chelating effects, and the phosphomolybdenum method [113]. They showed that the highest phenolic content of the extracts was established in methanol (51.09 mg/g) followed by water extract (46.40 mg/g), ethyl acetate (22.70 mg/g), and butanol extract (19.43 mg/g). In addition, they found that methanol extract had the highest free-radical scavenging capacity followed by water, ethyl acetate, and butanol extract. Their results showed that *A. graveolens* leaves are rich in phenolics and are a good source of antioxidants [113,119]. In another study, Yildiz et al. evaluated the total antioxidant capacity of *A. graveolens* leaves using CUPRAC (cupric ion reducing antioxidant capacity) and ABTS (2,2-azino-bis [3-ethyl-benzothiazoline-6-sulfonate]) methods and they also determined the phenolic compounds with high-performance liquid chromatography (HPLC) [158]. Caffeic acid, p-coumaric acid, and ferulic acid were determined as major phenolic acids, and apigenin, luteolin, and kaempferol were determined as major flavonoids [119,158].

The antioxidant activity of *A. graveolens* was investigated by Din et al. [154]. They also indicated that the total phenolic content was higher in methanolic fraction (63.46 mg GAE/g) followed by ethanol (36.60 GAE/g), and hexane fractions (34.86 mg GAE/g). Similarly, the flavonoid content was high in methanolic extract (56.95 quercetin/g). In addition, they showed antioxidant activity with FRAP assay with 12.48 mM $FeSO_4$ equivalent/L in methanolic fraction [150,154]. The DPPH radical scavenging capacity of the essential oil from the *A. graveolens* leaves was investigated and the results indicated that the essential oil from *A. graveolens* has potential as a natural antioxidant, and thus inhibited the oxidation process [159]. In another study, eleven cultivars of celery were analyzed for their antioxidant activities. Among these eleven cultivars, Shengjie celery had the highest antioxidant activity, whereas, Tropica had the lowest. An extremely significant positive correlation between the antioxidant activity and the contents of total flavonoids, total phenolic acids, or total phenolics was observed in this study. The *A. graveolens* species displayed high antioxidant capacity and high free-radical scavenging activities [134].

Kolarovic et al. investigated the antioxidant activity of celery in rats treated with doxorubicin and also the effect of the celery itself, and its combination with doxorubicin was determined by its antioxidant status [160]. The *n*-butanol extract from *A. graveolens* seed at 60 mg/kg ameliorate lipid peroxidation and its antioxidant properties improved antioxidant enzymes in streptozotocin-induced diabetic rats after 21 days of treatment [26].

6.3. Anticancer Activities of Apium Plants

Cancer is an important health issue throughout the world. Due to the side effects of anticancer drugs, scientists have started to focus on natural products. The discovery of anticancer natural products of plant origin such as vinblastine, vincristine, and podophyllotoxins prompted the research community to explore plant-derived natural products such as flavonoids, terpenes, alkaloids, etc. due to their diverse pharmacological properties including cancer chemopreventive effects. Other *Apium* species also yield similar effects. For example, in a study performed on flavonoidal fractions of *A. leptophyllum* fruits, it was shown that the fractions had chemopreventive potential on 7,12-dimethylbenz[a]anthracene (DMBA) induced carcinogenesis in mice. DMBA is a polycyclic aromatic hydrocarbon, which acts as a procarcinogen and is an ultimate carcinogen after metabolic activation. The activity of the plant might be due to the modulation of cutaneous lipid peroxidation or enhancement of total antioxidant capacity. Flavonoid fractions were also found to be effective in suppressing skin tumor growth at a dose of 20 mg/kg [100].

Combinations of plants with other plant-based natural products are also seen in the literature. For example, *A. graveolens* is known to be present in the herbal-marine mixture called HESA along with *Carum carvi, Penaeus latisculatus,* and other marine products, which are used to improve the quality of life in colon and breast cancer patients in the Near East [161]. Chemoprevention is one of the strategies that can revert or delay the response of carcinogens. Dietary factors contribute to about a third of potentially preventive cancers, long known as preventive effects of plant-based products on tumorigenesis and other chronic diseases [162]. Plants provide important and valuable compounds against this terrifying disease, and therefore using them against cancer and also consuming certain food plants would be beneficial in our fight against cancer.

Several works concerning the in vitro anticancer studies of *Apium* plants are present in the literature, in particular, those regarding both the plant species directly and some compounds previously extracted from *Apium* species. Among the anticancer activity studies on the total species, those concerning *A. graveolens* L. are the most important and well known. Nevertheless, other similar works are present about *A. graveolens* var. *rapaceum* (Mill.) Poir. (unresolved name) and *A. nodiflorum* (L.) Lag.

With respect to *A. graveolens*, its seeds have widely demonstrated its in vitro efficacy as potent anticancer agents. In particular, its crude extracts in *n*-hexane, ethanol, and water showed a concentration-dependent effect on the growth inhibition (GI) of rhabdomyosarcoma cell lines with the *n*-hexane extract as the most efficient one. In fact, the GI percentage for this extract was 68.70% and 81.71% for the concentration of 100 and 200 μg/mL, respectively. Indeed, the GI values for the ethanolic extract and the aqueous extract at the same concentrations were lower, i.e., 59.23% and 63.09% for the former and 56.64% and 61.33% for the latter. An important result from this study was that the power of inhibiting the cell growth started only at concentrations higher than 100 μg/mL. In fact, at lower concentrations, the effects for all three extracts were minimal. On the other hand, all the crude extracts showed a very slight or no effect on the growth inhibition of murine L20B cells, not even reaching GI values of 10% in most cases. All these calculations were made by using cultures containing only the RPMI-1640 medium as a control [163].

Less notable results were observed in three other works. The first one by Octaviani et al. studied the effect of the ethanol extract on the LNCaP prostate cancer cell lines with GI values less than 50% [164]. The second one, by Mencherini and coworkers, studied the effect of the 1:1 ethanol-water extract on

J774.A1 (murine monocyte/macrophage) and HEK-293 (human epithelial kidney) cell lines and gave no inhibition [27]. Lastly, the third one, by Brahmi et al., studied the effect of the H_2O:MeOH extract at only the concentration of 12.5 mg/mL on the SK-N-BE(2)-C (human bone marrow neuroblastoma) and HepG2 (human hepatoblastoma) cell lines against Trolox® used as an antioxidant standard [165].

Indeed, an extremely positive result was achieved by Gao et al. [166] who were the first to discover that the supercritical CO_2 extract of the seeds also possess a very high inhibition on the growth of cultured BGC-823 cells (human gastric cancer). An untreated BGC-823 cell was used as a positive control. The mechanism of the action of this inhibition passes through a concentration- and time-dependent cellular apoptosis via a mitochondria-mediated pathway which represents a total new scenario with respect to the usual pathway as described later for other types of cancer cell lines [166].

With regards to *A. graveolens* var. *rapaceum*, only a partial study has been done. In fact, the data in the literature report only on the anticancer activities of four compounds isolated from the dichloromethane extract of the roots of this species, whereas, no test has ever been performed on the extract obtained from the other plant organs. However, these compounds which belong to the polyacetylenes class showed only modest activity against the investigated cell lines, i.e., CEM-C7H2 (leukemia), U937 (lymphoma), RPMI (lymphoma), and HRT-18 (myeloma) as compared with the positive control, 14-hydroxyhypocretenolide-α-D-glucopyranoside-4′,14′′-hydroxyhypocretenoate. In fact, the general IC_{50} values of these compounds ranged from 30 to above 100 µM as compared with the values of the control which were between 2.59 and 19.2 µM. The only exception was falcarindiol which was shown to be more efficient against CEM-C7H2 having 3.50 µM as an IC_{50} value which was comparable with respect to the control (2.59 µM) [167].

With regards to *A. nodiflorum* (L.) Lag., Maggi et al. collected three different exemplars of this species and studied the anticancer activities of the methanolic extracts of their essential oil against three different cell lines, i.e., A375 (human malignant melanoma), MDA-MB 231 (human breast adenocarcinoma), and HCT116 (human colon carcinoma). In all the experiments, which were repeated three times each, the extracts proved to be effective with IC_{50} values ranging from 3.16 to 17.72 µg/mL. Cisplatin was used as a positive control and was more effective with IC_{50} values which were between 0.48 and 2.79 µg/mL. Thus, *A. nodiflorum* may represent a new possible species to be used against some types of cancer in cases that are not particularly acute [168].

Apium plants have antioxidative and anti-inflammatory properties, which play a vital role in the inhibition of tumor initiation, promotion, and progression [100]. Some of the compounds in the seed of the *Apium* plant have collaborations in the molecular mechanisms and pathways of cellular targets that are considered to have a significant effect on the treatment of human cancers with its anti-inflammatory and analgesic effects [119]. Kolarovic et al. reported on the potential activity of parsley for its anticancer property. In their study, they revealed that the flavonoid apigenin expressed strong antioxidant effects by increasing the activities of antioxidant enzymes and, as a result of this activity, decreased the oxidative damage to the tissues [159]. Moreover, there is a lack of information about peptides from plants of *Apium*. Previously, it had been shown that an antioxidative peptide was already isolated and purified from *A. graveolens*. This purified peptide could possess synergistic antioxidant potential with the other antioxidants, thus, leading to anticancer activity in the fraction of celery extracts [169].

In many in vivo studies, it was shown that perillyl alcohol causes regression of tumors of the pancreas, liver, and breast. Celery seed was injected in wistar rats in the laboratory and had an inhibitive effect on liver carcinoma. A protective effect on the gastric mucosa and it is anti-gastric ulcer was also discovered [119]. *A. graveolens* extract induces apoptosis via Bax and p-53 proteins in the LNCaP human prostate cancer cell line [170].

Zidorn et al. investigated the potential activity of four polyacetylenes against leukemia, lymphoma, and myeloma cell lines. All the polyacetylenes with falcarinol showed at least moderate toxicity to all cell lines. Falcarinol was the most active compound of *Apium* plants and showed significant cytotoxicity against acute lymphoblastic leukemia cell line CEM-C7H2 [157]. Young et al. reported that the polyacetylene falcarinol also showed protective activity against chemically-induced colon cancer development in rats. These compounds of *Apium* plants had a biphasic effect on CaCo-2 cells, with antiproliferative effects at high doses [171]. In addition, the biphasic responses of bioactive polyacetylenes, falcarinol, and falcarindiol on the stress responses in primary myotube cultures were also reported. Preincubation with low concentrations of both polyacetylenes prior to H_2O_2 exposure induced a cytoprotective effect, whereas, higher concentrations had adverse effects [171].

In previous studies, Peng et al. reported that phthalides, such as sedanolide and 3-*n*-butylphthalide, have been shown to possess anticarcinogenic and neuroprotective properties. According to the findings, 3-*n*-butylphthalide inhibits platelet aggregation, reduces neuron apoptosis, improves mitochondrial function, and decreases oxidative damage. These compounds are officially approved for the treatment of stroke patients in China [172]. The efficiency of the protection is very high and quite fast, and also leads to restoration of normal levels of glutathione, ascorbic acid, and glycogen, as well as no increase of the levels of SGOT, SGPT, ALP (liver marker enzymes) and total bilirubin. In this case, one group of seven rats was used as a control, and received only the vehicle for administration, i.e., corn oil. The same protective effect has been observed with the same experimental conditions against other hepatotoxicants [152,168], thus providing this species effective as hepatoprotective. In both these cases, a group of rats was used as control and received the vehicle for administration only.

Moreover, in 2011, Salman et al. discovered that the daily consumption of the fresh leaves and stalks of *A. graveolens* in rabbits that were affected with tumor and already treated with doxorubicin, was able to diminish the severe side effects linked to the assumption of this drug [173]. In fact, doxorubicin (an anthracycline antibiotic) exhibits a high anticancer activity against a broad series of cancer types, i.e., ovarian, breast, lung, uterine, cervical, and soft tissue cancers [174,175] but is also known to have important toxicities, even causing cardiac, hepatic, and hematological damage [176,177]. This interaction was seen at a concentration of 7.5 mg/kg/day per 14 days after comparison with data obtained from the control group that received only 5 mL/kg of 0.9% NaCl solution intraperitoneally four times in 14 days and it was observed to be very effective, acting through an antioxidant pathway [173].

A. graveolens is also one of the three ingredients of HESA-A, an herbal-marine mixture of plant species. This mixture has been shown to have a high antitumor effect on human patients with end-stage metastatic colon cancer after six months of therapy with a great contribution due to *A. graveolens* itself. In fact, HESA-A is able to completely inhibit the growth of cells at the highest concentration of 5.4 mg/mL, whereas, at minor concentrations its effect is somewhat lower. Nevertheless, this mixture does not affect non tumoral cells and acts by following an apoptotic mechanism [178].

Indeed, the methanolic extract of the fruits of *A. leptophyllum* (Pers.) F.Muell. ex Benth. (now synonym of *Cyclospermum leptophyllum* (Pers.) Sprague) have been proven to have a good chemopreventive effect in a dose-dependent manner starting from a concentration of 20 mg/Kg, on DMBA-induced skin cancer cells of Swiss mice. The effect was observed against a control group, and was carried on by the flavonoid components through antioxidant action, and consequently, the normalization of the lipid peroxidation status was observed [100].

6.4. Anti-Inflammatory Effects of Apium Plants

Anti-inflammatory activity studies on *Apium* plants started early. For example, ethanolic extracts of the seeds showed an anti-inflammatory effect against chronic inflammation induced by cotton pellet granuloma. The extract also induced a dose-dependent analgesic protective effect against both thermal stimuli and the writhing syndrome indicating central and peripheral action. These data support the traditional use of these plants for pain and inflammation condition effects [179].

In more recent studies, compounds isolated from *Apium* plants were tested for their anti-inflammatory effect. It was demonstrated that luteolin, a naturally occurring flavone, which has various biological activities, exhibited significant anti-inflammation activity in both acute and chronic inflammatory models. In addition, downregulation of inducible COX-2 expression was an important factor regarding the mechanism underlying its anti-inflammatory activity [175]. In another study, apiin was isolated from the leaves and both apiin and celery extract inhibited in vitro NO release and iNOS expression significantly and in a concentration dependent manner. It is well known that NO production is elevated in inflammatory diseases, and therefore we conclude that the plant has topical anti-inflammatory capability to ameliorate inflammation or other conditions where enhanced expression of iNOS could be observed [9]. The extract can be used alone for its anti-inflammatory effect since aqueous extracts of celery stems have been found to have anti-inflammatory activity in the rat carrageenan foot paw edema model and in mouse ear histamine vascular inflammation [179].

As a result, the plant is demonstrated to have components that possess potent anti-inflammatory effects [180,181]. The anti-inflammatory activity of phytochemicals presents in food merits further study to help those suffering chronic inflammation to ameliorate their inflammatory conditions by offering a proper selection of food [182]. Ovodova et al. studied the anti-inflammatory activity of purified pectin from *A. graveolens* var. Dulce, after oral administration to mice. The findings showed that extracts prevented LPS-induced inflammation. The anti-inflammatory activity of apium pectin suggests a potential health benefit of celery as an alternative for preventing inflammation [183]. Anti-nociceptive and anti-inflammatory effects of *A. graveolens* have been studied previously [154].

6.5. Cardiovascular Effects of Apium Plants

Extracts prepared from the celery plant, or compounds isolated from different parts of the plant, have been studied extensively for a long period for their effects on the cardiovascular system. We can sum these studies up as follows: Increased blood pressure (BP) is one of the important risk factors for coronary heart disease, which is the largest cause of mortality in industrial countries. Hypertension has been termed the silent killer, and if it is untreated, silently damages the blood vessels, heart, brain, and kidneys. Thus, hypertensive patients have increased risk of silent ischemia and unrecognized myocardial infarction. Therefore, regulating blood pressure is of outmost importance among cardiovascular problems [184]. Moghadam et al. conducted a study that confirmed that celery seeds possess a hypotensive effect and this effect was attributable to some hydrophobic constituents, for example, n-butylphthalide (NBP) in this plant [184].

6.6. Central Nervous System Related Effects

Celery plant is known to possess various effects on the central nervous system, and therefore it can be used in the prevention and treatment of various CNS disorders. According to our literature search, celery plant can be used in the following disorders: Alzheimer's disease is the most common form of senile dementia, characterized by progressive memory loss. L-3-*n*-butylphthalide, a pure compound extracted from the seeds of the celery plant, significantly improved microcirculation in pial arterioles, reduced the area of cerebral infarct and inhibited platelet aggregation, improved mitochondrial function and decreased oxidative damage, reduced neural apoptosis and inhibited increases in intracellular calcium levels and the inflammatory response in experimental ischemic animal models. It was also found to alleviate the learning and memory deficits induced by cerebral hypoperfusion in rats. As a result, this compound appears to be promising as a multitarget drug for the prevention and treatment of Alzheimer's disease [185]. This activity of the compound DL-3-*n*-butylphthalide (NBP) was also confirmed in a study by Wang et al., who suggested that NBP alleviates oxidative stress, implicating its potential use in Alzheimer's disease and other forms of dementia [186].

However, not a desired effect, celery plant may lead to some drug interactions that can lead to unwanted results. Celery contains phytoestrogens and these compounds are structurally similar to estrogen making them a commonly utilized herbal supplement for the management of low estrogen states such as menopause. In addition, phytoestrogens also interact with many of the same enzymes as endogenous estrogen including CYP450. Celery also possesses high inhibitory activity directed toward CYP450-2D6, and thus it may change the pharmacokinetics of active substances that are metabolized by these enzymes. For example, in a case report, celery extract usage was believed to lead to the alteration of pharmacokinetics of venlafaxine; the drug was not sufficiently metabolized, and therefore resulted in symptoms of mania [187]. Khalid et al. also reported that the plant might lead to the alteration of the pharmacokinetics, resulting in elevated levels of the venflaxine drug and causing symptoms of mania [187].

A. graveolens extracts have neuroprotective effects in in vitro models and seeds have also been helpful to regulate the nervous system by a combination of effects. It stimulates the sex drive and also produces sedative effects. According to Boonruamkaew et al., methanolic extract of the whole plant was shown to possess antidepressant-like effects in the forced swimming and tail suspension tests. It also had a cognitive-enhancing effect on the Morris water maze and object recognition tests. The plant mediated a potent antidepressant-like effect which involved biochemical changes reducing the MAO-A neurotransmitter system, cognitive-enhancing effects associated with decreased AChE activity, antioxidant pathway related to a decrease of the MDA level, and inhibition percentage of the O_2^- while increasing GPx activity [188]. It has been shown that celery seed extract can be used to regulate the nervous system [30].

6.7. Diabetes Mellitus and Dyslipidemia

Diabetes is a major manifestation of endocrine and metabolism disorders and hyperglycemia and, unfortunately, results in secondary diseases and long-term complications such as nephropathy, neuropathy, retinopathy, and diabetic foot syndrome. In a study by Taskhakori-Sabzevar et al., administration of hexane extract of the seeds of celery significantly reduced water intake and glucose, and cholesterol and triglyceride levels in STZ-induced diabetic rats; it also increased serum insulin, and HDL as compared to the negative diabetic rats [189]. In another study, it was reported that the administration of celery leaf infusion showed significant effect on decreasing the level of blood glucose in rats [190]. However, in another study, the seed extract showed mild antihyperglycemic and antihyperlipidemic effects. The results of these studies are considered important because drugs available for the treatment of diabetes and high blood lipids are associated with side effects, and therefore scientists are focusing on the effectiveness of herbal treatments since they lack side effects [191].

In another study, it has been shown that celery leaf extracts of suspension produce an antipyretic effect. In addition, it has been reported that *Apium* plants produce hepatoprotective, hypocholesterolemic, and anti-inflammatory activities. Aqueous celery extract was also used to decrease total cholesterol level in rats for 8 weeks. On the other hand, aqueous extract of *Apium graveolens* (400 mg/kg) significantly decreased the body weight in obese rats in 40 days as compared to an obesity-induced group [16]. In another study, cafeteria-fed rats were fed daily with 400 mg/kg aqueous extract of *A. graveolens* for 40 days, and the researchers found that glucose, cholesterol, LDL, VLDL, and triglyceride amounts significantly decreased and the HDL cholesterol levels were increased [192].

6.8. Hepatoprotective Effect of Apium Plants

In the Indian medical system, *A. graveolens* seeds were used for the treatment of liver disorders. Singh et al. investigated the antihepatotoxic effect of methanolic extracts of the seeds of the plant [157,173]. Celery plant petroleum ether and methanol extracts of the seeds showed hepatoprotective activity in paracetamol and thioacetamide intoxicated rats. The stimulation of hepatic regeneration resulted in their livers becoming more resistant to damage and toxins. As well, the protective effect of the methanolic extract was further confirmed by histopathological examination [16]. In another and more recent study, seeds of the plant were successively extracted to exhaustion with petroleum ether, acetone, and methanol using the cold percolation method. This methanolic extract showed maximum antihepatotoxic activity against CCL_4-induced hepatotoxicity, which could be related to the methanol soluble particles such as flavone and diterpene. The activity was comparable to that of the standard drug silymarin [157].

The plant can also be used against hepatotoxicity induced by other drugs, as well. For example, carboplatin is an antineoplastic agent with a potent effect, and thus it is being used in the treatment of ovarian cancer recurring following previous chemotherapy and in some other types of carcinogenic developments. However, the substance is reported to lead to renal and hepatic major organ toxicity and also result in peripheral neurotoxicity. Since the seeds of the celery plant are known to be used as hepatoprotective in Turkey, Özbek et al. tested the seeds for their hepatoprotective activity and demonstrated that the administration of carboplatin alone to rats for five consecutive days led to liver damage, however, when carboplatin was combined with the fixed oil obtained from the seeds of the plant, it was observed that liver toxicity could be partially prevented [193].

Acetaminophen is another toxic substance that can manifest harmful effects on humans. In a study performed on a fish species, it was found that for the short-term treatment of efficient flavonoids (rutin, quercetin, and luteolin) rich celery extract could act in multiple ways to preserve the normal functioning of a fish species named *Pangasitus sutchi*. These mechanisms may involve chelating or scavenging the APAP-generated oxyradicals, protecting antioxidant enzymes, preserving hepatocyte structure, promoting antioxidant levels, maintaining normal carbohydrate and lipid metabolism and hepatic ions. Although this study was performed on fish, the authors suggested that flavonoid-rich celery should be included in the diet of humans in case of APAP toxicity [194].

In addition to its direct effect on liver health, the plant can also be used in liver problems associated with other conditions. For example, in a study performed on the livers of rats with adjuvant-induced arthritis in which enzymatic antioxidants are decreased and production of ROS that appear to contribute to oxidative stress in the liver increased, methanolic extract of the whole plant reduced oxidative stress by causing a decrease in the superoxide anion and total peroxide and an increase in the activities of glutathione peroxidase and superoxide dismutase. It was suggested that *A. graveolens* represents a potential beneficial agent for the reduction of liver destruction in arthritis [195].

6.9. Renal Disorders

Hyperuricemia is a predisposing factor for gout since excessive production of uric acid leads to deposition of monosodium uric acid crystals in soft tissues and joints which are associated with gout and is also thought to be associated with a number of clinical disorders including endothelial dysfunction, atherosclerosis, hypertension, coronary artery disease, diabetes, dyslipidemia, and chronic kidney disease. The plant contains furocoumarins (apigravin, celerin, and umbelliferon), flavonoids (apigenin, apiin, kaempferol, and luteolin), phenolic compounds (caffeic acid, *p*-coumaric acid, and ferulic acid), and tannins. Celery essential oil has also been shown to have a series of phthalide derivatives. Antigout activity has been described for phthalide derivatives, phenolic compounds, and tannins. Apigenin, at a dose of 25 mg/kg, also significantly decreased serum uric acid and inhibited liver XO activity by 38.4% in hyperuricemia mice. Luteolin, another major component of celery also reversibly inhibits XO in a comparative manner, by interacting with the primary amino acid residues located within the active site pocket of XO. Therefore, the plant is probably promising in the treatment of hyperuricemia [196].

In another study, it was observed that ethanol and aqueous extracts of the plant showed improvement in the excretion of urinary sodium even after gentamycin induced renal toxicity, and potassium excretion was found to be increased in all treatment groups as compared to a control. The plant has a significant diuretic activity and could be used for this purpose [197]. It has been shown that celery seed extract can help to improve digestion and kidney function [30].

6.10. Reproductive Issues

Reproductive problems are important health issues since they might lead to infertility both in men and in women. Functional foods or nutraceuticals can provide a beneficial alternative in this aspect. Celery plant is also known for its beneficial effects on the reproductive system and when we performed a literature search, we saw that studies were mainly focused on male fertility. In one study, the plant was reported to be listed among the plants that are being used in gynecological disorders in the Ottoman period [198].

Infertility is one of the most common health problems in the world, which involves approximately 15% of couples. Infertility can be present in both genders, but about 50% of infertility is associated with the male factor. Decreased sperm count and motility and deformity of sperm are the most important factors of male infertility. Plasma membrane of sperm is susceptible to oxidative damage due to large amounts of unsaturated fatty acids, finally leading to decreased motility and viability of sperm [23]. The plant may have a direct effect on the male reproductive system, or it may exert a protective effect against various drugs or environmental chemicals.

In a study on the hydroalcoholic extract of celery leaf, it was observed that the extract could increase spermatogenesis in rats, and this effect was more pronounced in higher doses [23]. Similarly, the aqueous extract of the leaves was observed to improve the spermatogenesis process and could be useful for some sperm fertility parameters [126]. In another study, hydroalcoholic extract of the plant was shown to boost spermatogenesis and, as indicated by this study, celery can have a protective effect against substances that cause damage to the testicular structure and spermatogenesis [199].

As for the protective effects of celery, in a study that demonstrated the protective effect of celery seeds against sodium valproate (VPA) used in the treatment of epilepsy, bipolar psychiatric disorders, and migraine, the plant was shown to have a potent protective effect against VPA-induced testicular damage and oxidative stress in rats. The drug is known to disturb the reproductive endocrine function and reduce the quality of semen in epilepsy patients. The protective effect of the plant may be due to its antioxidant property and detoxification capacity [125].

Phthalates, which are used in plastics to impart flexibility to rigid polymers, are also environmental toxic substances that humans are exposed. DEHP (di-(2-ethylhexyl) phthalate) is normally used for the production of storage containers, bags, and waterproof clothing and because it is not covalently bound to the vinyl polymer matrix, it can easily be released from these products into foods, beverages or directly into body fluids. In a study performed on celery oil, it was demonstrated that the oil alleviated testicular damage induced by DEHP and this protective effect can be attributed to its antioxidant properties and the androgenic activities of apigenin, limonene. Celery oil can also decrease the oxidative stress in the testis, protect maturation of spermatozoa, and improve sperm function [200]. In another study performed with the plant, based on the hypothesis that DEHP is rapidly metabolized to mono-(2-ethlyhexyl) phthalate after ingestion which is more toxic for Leydig cells and Sertoli cells as compared with DEHP, administration of the celery oil partially prevented the decrease in body and testicular weights and enhanced epididymal sperm count and serum hormone levels [201]. Apigenin, as the important flavonoid in celery, is a potent antiplatelet agent, and thus a vascular relaxant effect in animals has been demonstrated [202]. It has been shown that ethanol extracts of celery leaves increase spermatogenesis and also improves fertility of rats. In addition, it has been shown that aqueous extract of celery significantly reduced the fat in the blood serum of mice [203]. *A. graveolens* leaves extract were used to examine mice to increase sertoli cells and primary spermatocytes, as well as the improvement of spermatogenesis. However, another study, indicated that the hydroalcoholic extract from *A. graveolens* leaf (150 mg/kg) diminishes FSH level and exerts dependent adverse effect on pituitary in mice [204].

6.11. Osteoarthritis

Osteoarthritis is a major cause of joint pain and disability, resulting in great socioeconomic costs worldwide. A bioactive coumarin called isofraxidin was isolated from *A. graveolens* and it was found that in vivo treatment of isofraxidin not only prevented calcification and erosion of cartilage, as well as the thickening of subchondral bone, but also reduced serum levels of inflammatory cytokines in the mouse osteoarthritis model. Therefore, it can be concluded that isofraxidin has potential in the treatment of osteoarthritis [205].

6.12. Osteoporosis

Methanol extract of fresh roots of the plant was tested against osteoporosis in ovariectomized rats since this animal model has similar pathophysiological mechanism of bone deterioration that is seen especially in women after menopause. Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and, consequently, increased fracture risk. Osteoporosis affects an estimated 75 million people in Europe, USA, and Japan and it is the underlying cause for more than 8.9 million fractures annually. The most common type of osteoporosis is associated with estrogen deficiency in postmenopausal women, and it leads to acceleration of bone resorption and rapid bone loss. Treatment with the extract significantly decreased pain thresholds as compared to control animals. The extract also enhanced BMS (bone mineral density) and improved bone quality. Therefore, it possesses the potential of an effective drug for prevention of possible fracture-induced pain by increasing bone mass density. After supplementation of the extract for a period of 4 weeks in ovariectomized rats pronounced beneficial effects were observed and *Apium* was demonstrated to have the potential as an effective and safe supplementation for retarding osteoporosis development [206].

6.13. Diarrhea

Diarrhea is one of the most important worldwide health issues, particularly affecting people of all ages and resulting in electrolyte loss, dehydration, shock, and sometimes death. Another *Apium* species, *A. leptophyllum*, is traditionally being used in the treatment of diarrhea due to its strong antifungal, antibacterial, and anti-inflammatory properties. Flavonoid fraction of the fruits was shown to exhibit marked reduction in the frequency of diarrhea, the weight and volume of intestinal contents, as well as intestinal transit. In addition, the antidiarrheal effect may be due to the reduction of gastrointestinal motility, inhibition of the synthesis of prostaglandin, and intestinal muscle contraction, all of which are due to the flavonoids that the plant contains [106].

6.14. Hyperthyroid

Hydroalcoholic extract of the leaves of the celery plant is beneficial in the balancing of hyperthyroid. Since abnormalities in the synthesis and release of thyroid hormones may lead to direct or indirect diseases, the plant may be beneficial in increasing the quality of life of humans [207].

6.15. Dandruff

Finally, the plant also has a cosmeceutical effect with its usage against dandruff. Dandruff, in acute or chronic form, is a benign but unsightly scalp disorder affecting 40%–50% of the world adult population, men being two to six times more affected than women. From a preliminary screening, compounds improving barrier permeability functions were identified from marine microorganisms and plants. Some of them belong to the family of phthalides, small compounds widely present in plants and fungi. Senkyunolide-A (SENKY) was extracted from the seeds of the plant and it was concluded that it could be of interest for promoting scalp homeostasis. It reinforced its barrier function and reduced irritation in promoting detoxification and anti-inflammation pathways. When it was applied on the scalp, it significantly reduced the formation of dandruff and soothed the scalp [208].

6.16. Bioactivities of Phytochemicals Identified in Apium spp.

The various activities observed for the extracts are strongly supported by the presence of peculiar phytochemical constituents in both volatile fraction and polar compounds (Figure 2). Sahoo et al. designed an in vivo study to investigate the chemopreventive potential of flavonoid fractions of *Apium* plants (FFAP) on Swiss mice. The co-administration of FFAP with DMBA-treated groups provided significant ($p \leq 0.001$) prevention against skin papilloma and lipid peroxidation statue was normalized as compared to a carcinogenic control. Thus, they suggested that FFAP had chemopreventive potential on DMBA-induced carcinogenesis in mice, which may be due to the modulation of cutaneous lipid peroxidation or enhancement of total antioxidant capacity [95]. Sahoo et al. indicated that FFAP is effective on the enzyme activities of the liver as well as lipid peroxidation, thus, it can possess chemopreventive activity. FFAP was effective in suppressing skin tumor growth especially when a dose of 20 mg/kg was treated, which was probably attributed to anti-lipid peroxidative or antioxidant potential during DMBA tumor induction [100].

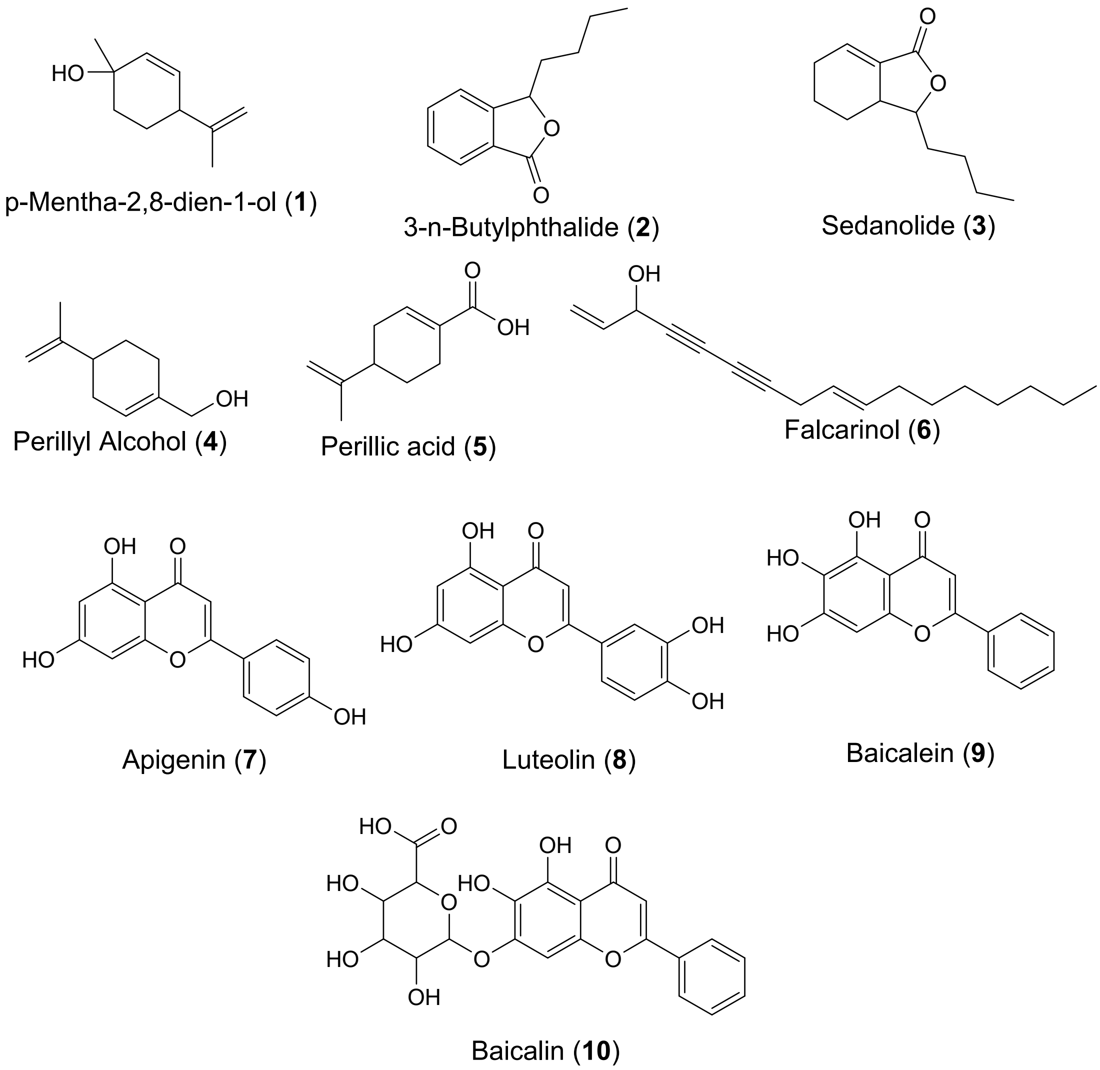


Figure 2. Chemical structure of the most common bioactive ingredients in *Apium* plants.

Gao et al. investigated the antitumor effects of *A. graveolens* extract (AGE) and related mechanisms of apoptosis in human gastric cancer BGC-823 cells [166]. In the study by Gao et al. it was shown that, AGE had an antiproliferation effect on human gastric cancer BGC-823 cells in a dose- and time-dependent manner [166]. The apoptotic rate significantly increased after uptake of AGE with morphological changes typical of apoptosis. The findings indicated that AGE could significantly inhibit the growth and induce apoptosis via the bcl-2 family related mitochondria-mediated pathway of human gastric cancer cell line BGC-823 in vitro. Thus, it would seem to be worth to investigate AGE as a novel natural therapeutic alternative, and the induction of apoptosis by AGE in other cancer cell lines can be the current subject of on-going investigations. [166].

Several studies are available in the literature on the bioactivities of *Apium* constituents. Among these, *p*-mentha-2,8-dien-1-ol (1-methyl-4-prop-1-en-2-ylcyclohex-2-en-1-ol) (1), 3-*n*-butyl-phthalide (3-butyl-2-benzofuran-1(3*H*)-one) (2), and sedanolide (3-butyl-3a,4,5,6-tetrahydro-1(3*H*)-isobenzofuranone) (3) in 20 mg/dose every two days for a total of three doses, resulted to be effective in the induction of synthesis of the detoxifying enzyme glutathione S-transferase (GST) in a female A/J mice model. The GST activity increased 4.5–5.9 and 3.2–5.2 times as compared to the controls. These oil components inhibited the benzo[a]pyrene-induced tumor formation. In particular, the administration of 3-*n*-butyl-phthalide (2) and sedanolide (3) reduced the tumor formation in the order of 68% to 30% and 11%, respectively. Conversely, *p*-mentha-2,8-dien-1-ol (1) produced only a small or no significant reduction of tumor formation [209]. Sedanolide (3) has been reported to be the most active of the phthalides in the reduction of tumors in laboratory animals, i.e., 83% reduction. From the phytochemical standpoint, it is interesting to note that these compounds belong to the monoterpenoid (*p*-mentha-2,8-dien-1-ol) (1) and phthalides (3-*n*-butyl-phthalide and sedanolide) (2 and 3), which are two classes of natural products that are well represented, and to some extent, peculiar, in botanical entities comprised in the Apiaceae family [210,211].

In addition, 3-*n*-butylphthalide (3), was investigated for its neuroprotective potentialities in rat hippocampal neurons and human neuroblastoma SH-SY5Y cells. The results indicated it was an anti-cerebral ischemia agent, and it proved to have therapeutic effects on learning and memory deficits induced by intracerebroventricular infusion and chronic cerebral hypoperfusion. It was shown that 3-*n*-butylphthalide (3) markedly reversed the number of apoptotic cells amyloid-β-induced and, in addition, it significantly decreased the hyperphosphorylation of tau protein [172].

Perillyl alcohol (*p*-mentha-1,8-dien-7-ol) (4), a limonene-type monoterpenoid consisting of a cyclohexene ring substituted by a hydroxymethyl and a prop-1-en-2-yl group at positions 1 and 4, respectively. It is another constituent of *A. graveolens* seed-oil and other essential oils such as those obtained from lavendin, peppermint, spearmint, and cherries. It has been proven to interact with several modulators of cell growth and differentiation. The observed activities included the induction of differentiation, cell cycle arrest in the G1 phase, and apoptosis [212,213]. The effectiveness of this monoterpenoid alcohol as an anticancer agent has been tested in a phase II clinical trial for the treatment of patients with metastatic breast cancer refractory to chemotherapy [214]. It showed a modulation in the regulation of the phosphorylation for several cellular factors in human tumor cells, namely, PKB/Akt, 4E-BP1 and eIF4E/eIF4G [212]. Perillic acid (4-isopropenylcyclohex-1-enecarboxylic acid) (**5**), one metabolite strictly related to perillyl alcohol, showed also antiproliferative activity on non-small cell lung cancer cells (NSCLC, A549, and H520). As well as perillyl alcohol (4), perillic acid (5) by increasing expression of bax, p21. and caspase-3 activity, exerted a dose-dependent cytotoxicity. Dose-dependent sensitization to cisplatin and radiation in cells exposed to these compounds was also observed. Therefore, their use in combination therapy might have a chemotherapeutic value [213].

The polyacetylene falcarinol ((3*R*,9*Z*)-heptadeca-1,9-dien-4,6-diyn-3-ol) (6) is another peculiar phytoconstituent of the *Apium* spp. and more, in general, of several Apiaceae species. It is known to possess an anticancer activity [215–218]. It has been tested in in vitro experiments against many cancer cell lines, namely, L-1210 (leukemia), MK-1 (human gastric adenocarcinoma), B-16 (mouse melanoma), and L-929 (mouse fibroblast-derived tumor cells). It resulted in being most effective against MK-1 cells, showing an ED_{50} value of 0.027 μg/mL [219–221].

There are also more widespread phytoconstituents in celery and in other common foods [222] with interesting bioactivities such as is the case of flavonoids and coumarins. Their mechanism of action is generally due to the antioxidant potentialities, such as in the case of coumarins which prevent the formation of free radicals, hence the damaging of cells. This decreases the mutations incidence thus lowering the potential for cells to become cancerous.

The flavonoid apigenin (5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one) (7) is a widely distributed compound in the plant kingdom. It has also been recognized among the phytoconstituents of *Apium* species. Apigenin (7) was found to inhibit the growth of prostate tumor in athymic nude mice model by down-modulation of several cyclin proteins, namely D1, D2, E, CDK2, CDK4, CDK6, Cip1/p21, and Kip1/p27, after oral administration. The cell cycle of several cell lines (i.e., pancreatic cancer cell Hep G2 HT-29 and MG63) was blocked in G0/G1 or in G2/M phase, thus inducing apoptosis.

A comparison of the spectra for tumor antiproliferation have shown that the flavonoids possess potent antiproliferative activity in the order of luteolin (8), greater than baicalein (9) and finally baicalin (10) [223,224].

Baicalein (5,6,7-trihydroxy-2-phenyl-4*H*-chromen-4-one) (9) proved to inhibit the proliferation of several carcinoma cells (leukemia, hepatoma, breast, and bladder) [225–228], whereas, baicalin (5,6,7-trihydroxyflavone-7-*O*-β-D-glucuronide) (10) resulted in being effective against hepatoma and bladder carcinoma cells. Luteolin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one) (8) has been shown to be active against leukemia, melanoma and carcinoma cells of the pancreas, ovary, kidney, lung, and stomach [229].

7. Clinical Effectiveness of *Apium* Plants in Human

Nowadays, because of their lower side effects and higher effectiveness, medical plants are preferred for the treatment of various illness such as cancer, hypertension, hyperlipidemia, diabetes, cardiovascular, inflammatory diseases, and bronchitis, etc. When we search the literature, we see that numerous clinical studies have been performed on different parts of *Apium* plants and on the bioactive compounds that have been isolated from the species. We also note that these studies have mostly been conducted on *A. graveolens* species, but sometimes, other *Apium* species have been examined. Generally, *Apium* plants can prevent cardiovascular diseases, jaundice, liver and lien diseases, urinary tract obstruction, gout, and rheumatic disorders [160].

7.1. Kidney Inflammation

It has been reported that *Apium* plants have a reducing effect on kidney inflammation [23]. In addition to the positive effect in most cases, a high amount of celery may show a negative effect, especially in a human meal in pregnant women. In one study, the effects of abortion and periods on (bad) pregnant women were investigated. According to the results, the researchers recommended that pregnant women should not eat more celery in their meal, because its high doses can stimulate the uterus [23]. In addition, a study on the effect of creating eczema and allergies in babies during the pregnancy period when their mother ate high amounts of celery was conducted. For this research, they added celery to the meal of pregnant mothers and carried out the allergy test on the babies. The results have shown that a high amount celery in their (mothers') meal may increase the risk of complications [23].

7.2. Gastric Disorders

A. graveolens is known to be used by Unani and Ayurvedic medical practitioners for stomach and kidney disorders. Thus, a study was performed to examine the gastroprotective activity of the methanol extract of the plant and it was demonstrated that the extract was able to inhibit the formation of ulcers induced by different experimental models and it also decreased basal gastric acid secretion. This gastric antiulcer capacity of celery extract could be attributed to its antioxidant properties, resulting in a reduction of the lipid peroxidation and elevation of NP-SH content, in addition to improving the mucus coating of the stomach. These results suggest that the plant might be promising in the prevention of gastric disorders [230]. Functional dyspepsia (FD) is the most common gastrointestinal disorder, accounting for almost 50% of all patients visiting gastrointestinal specialty centers. Celery plant is known to be effective in the digestive system due to its inhibitory effects on gastric ulcers and inflammation. Azimi et al. investigated, in a randomized double-blind trial, a traditional remedy, 500 mg capsules prepared from *A. graveolens* and *Trachyspermum copticom* (AT), and treated patients with functional dyspepsia (FD) in eight weeks [231]. At the end of week four, they determined that the frequency of the symptoms began to decrease and there were significant differences in the frequency of symptoms of functional dyspepsia, and therefore until eight weeks, the frequency of symptoms continued to decrease. The research claimed that the remedy of AT was effective in reducing the frequency of this symptom [231]. The author found that AT was more effective than omeprazole in improving FD symptoms such as postprandial distress syndrome and epigastric pain syndrome [231]. These studies demonstrate that the traditional use of the plant in gastric problems is justified and consuming celery plant may provide additional benefits [114]. However, the study was limited by a small sample size and short follow up period, and therefore cannot be generalizable to all FD patients.

7.3. Central Nervous System Related Effects

The roots of the plant are reported to be a tonic for brain and is being used in Unani medicine. Aqueous extract of the roots was examined for their various effects on the central nervous system and it was found to be effective in Petit-mal epilepsy [17].

Multiple sclerosis is an inflammatory demyelinating disease with no confirmed treatment, and therefore patients tend to use complementary and alternative medicines. On the basis of the anecdotal evidence found in traditional Iranian medicine, MS_{14} is a natural (herbal-marine) product voluntarily used by MS patients. It may have some benefits both on the quality of life and on the symptoms of the patients. This product contains 90% *Penaeus latisculatus* (king prawn), 5% *A. graveolens,* and 5% *Hypericum perforatum.* The drug not only halted the progression of the disease, but also attenuated the inflammation in the central nervous system, indicating that this herbal-marine compound has anti-inflammatory effects [232]. The effectiveness of this Iranian herbal-marine compound combination was further confirmed by another study by Ahmadi et al. in 2010 and the authors concluded that the combination might also be effective in the treatment of other neurodegenerative disorders with the same mechanisms [233].

7.4. Hyperlipidemic Effect

Dietary fat is one of the most important environmental factors associated with the incidence of cardiovascular disease. Plant polyphenols exert cardiovascular benefits by altering concentrations of blood lipid components and a high intake can significantly reduce the risk of mortality from cardiovascular disease. Epidemiological data suggested that foods containing fibers have strong protective effects against major disease risks including cancer, diabetes, cardiovascular diseases, and Alzheimer's disease. Animal and human intervention studies have shown that celery inhibits platelet activation, favorably alters eicosanoid synthesis, suppresses production of proinflammatory cytokines and lipoxygenase activity, stimulates nitric oxide production, and improves endothelial function [234].

Extracts prepared from the seeds of the plant also demonstrated beneficial effects. In a study where the effects of chloroform and aqueous basic fraction of the seeds were examined, it was found that the extract inhibited total cholesterol triglycerides, low-density lipoproteins level, and significantly increased high-density lipoprotein level [235]. Ethanolic extract of the plant was also shown to lower triglyceride levels via inhibition of hepatic cholesterol biosynthesis, increasing fecal bile acid excretion, enhancing plasma lecithin, cholesterol acyltransferase activity, and reduction of lipid absorption in the intestine [236].

8. Conclusions and Future Perspectives

This paper reviewed data on phytochemical composition, distribution, and habitat-cultivation conditions and various pharmacological properties or health effects of *Apium* plants. The medicinal activities of this herb have been previously proven by numerous studies carried out in vitro and in vivo. Therefore, *Apium* plants are considered as important medicinal plants all over the world. As a conclusion, all in vivo and in vitro studies have shown that *Apium* plants have been used to treat many diseases such as cardiovascular disorder, jaundice, liver lien diseases, urinary tract obstruction, gout, and rheumatic disorders in traditional medicine for long time, because leaves, root, seed, and stalk parts of this plant contain many bioactive compounds such as polyphenols, flavonoids, limonene, selinene, coumarin glycosides, vitamin A, and vitamin C.

Overall, numerous information has been gathered concerning celery. If clinical validation is needed, such as that of the spermatogenesis stimulation and protection, most of the clinical studies were poorly designed and involved small sample sizes and short follow up periods. Therefore, commensurable clinical data, including toxicology, are required to support its usefulness.

Author Contributions: All authors contributed equally to this work; B.S., B.Ö., P.V.T.F., W.C.C., N.M., and J.S.-R., critically reviewed the manuscript; all the authors read and approved the final manuscript.

Funding: This research received no external funding.

Acknowledgments: N. Martins would like to thank the Portuguese Foundation for Science and Technology (FCT-Portugal) for the strategic project ref. UID/BIM/04293/2013 and "NORTE2020-Northern Regional Operational Program" (NORTE-01-0145-FEDER-000012).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sowbhagya, H.B.; Srinivas, P.; Krishnamurthy, N. Effect of enzymes on extraction of volatiles from celery seeds. *Food Chem.* **2010**, *120*, 230–234. [CrossRef]
2. Malhotra, S.K. Celery. In *Handbook of Herbs and Spices*, 2nd ed.; Woodhead Publishing Limited: Sawston, UK, 2012.
3. Roslon, W.; Osinska, E.; Gajc-Wolska, J. The influence of raw material stabilization on the quality of celery (*Apium graveolens* L.) leaves. *Acta Hortic.* **2010**, *877*, 201–208. [CrossRef]
4. Mezeyová, I.; Hegedűsová, A.; Mezey, J.; Šlosár, M.; Farkaš, J. Evaluation of quantitative and qualitative characteristics of selected celery (*Apium graveolens* var. Dulce) varieties in the context of juices production. *Potravin. Potr. S. J. F.* **2018**, *12*, 173–179. [CrossRef]
5. Sellami, I.H.; Bettaieb, I.; Bourgou, S.; Dahmani, R.; Limam, F.; Marzouk, B. Essential oil and aroma composition of leaves, stalks and roots of celery (A*pium graveolens* var. dulce) from Tunisia. *J. Essent. Oil Res.* **2012**, *24*, 513–521. [CrossRef]
6. Sarshar, S.S.; Sendker, J.; Qin, X.; Goycoolea, F.M.; Asadi, K.M.R.; Habibi, M.; Bouzari, S.; Dobrindt, U.; Hensel, A. Antiadhesive hydroalcoholic extract from *Apium graveolens* fruits prevents bladder and kidney infection against uropathogenic E coli. *Fitoterapia* **2018**, *127*, 237–244. [CrossRef] [PubMed]
7. Gijbels, M.J.M.; Fischer, F.C.; Scheffer, J.J.C.; Svendsen, A.B. Phthalides in roots of *Apium graveolens* var. rapaceum, *Bifora testiculate* and *Petroselinum crispum*. *Fitoterapia* **1985**, *56*, 17–23.
8. Kavalali, G.; Akcasu, A. Isolation of choline ascorbate from *Apium graveolens*. *J. Nat. Prod.* **1985**, *48*, 495. [CrossRef]
9. Mencherini, T.; Cau, A.; Bianco, G.; Della Loggia, R.; Aquino, R.P.; Autore, G. An extract of *Apium graveolens* var. dulce leaves: Structure of the major constituent, apiin, and its anti-inflammatory properties. *J. Pharm. Pharm.* **2007**, *59*, 891–897. [CrossRef]
10. Kokotkiewicz, A.; Luczkiewicz, M. Celery (*Apium graveolens* var. *dulce* (Mill.) Pers.) Oils. In *Essential Oils in Food Preservation, Flavor and Safety*; Elsevier: Amsterdam, The Netherlands, 2016; pp. 325–338.
11. Ching, L.S.; Mohamed, S. Alpha-tocopherol content in 62 edible tropical plants. *J. Agric. Food Chem.* **2001**, *49*, 3101–3105. [CrossRef]
12. Miean, K.H.; Mohamed, S. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *J. Agric. Food Chem.* **2001**, *49*, 3106–3112. [CrossRef]
13. Perumalraja, R.; Sharief, S.D. Antihyperlipidemic activity of ethanolic extract of celery leaves on rats rattus norvegicus. *Nat. Environ. Pollut. Technol.* **2014**, *13*, 433–436.
14. Covington, M.B. Traditional Chinese medicine in the treatment of diabetes. *Diabetes Spectr.* **2001**, *14*, 154–159. [CrossRef]
15. Syed, S.F.; Rajeev, K.S. Review on the pharmacognostical & pharmacological characterization of *Apium graveolens* Linn. *Indo Glob. J. Pharm. Sci.* **2012**, *2*, 36–42.
16. Singh, A.; Handa, S. Hepatoprotective activity of *Apium graveolens* and *Hygrophila auriculata* against paracetamol and thioacetamide intoxication in rats. *J. Ethnopharmacol.* **1995**, *49*, 119–126. [CrossRef]
17. Ehsanullah, M.; Asif, M.; Asif, S.M.; Amin, K.M. Effects of Bekh-k-Karafs (*Apium graveolens* linn) root on central nervous system. *Anc. Sci. Life* **1990**, *10*, 98. [PubMed]
18. Zhou, Y.; Taylor, B.; Smith, T.J.; Liu, Z.P.; Clench, M.; Davies, N.W.; Rainford, K.D. A novel compound from celery seed with a bactericidal effect against *Helicobacter pylori*. *J. Pharm. Pharmacol.* **2009**, *6*, 1067–1077. [CrossRef]
19. Sowbhagya, H.B.; Sampathu, S.R.; Krishnamurthy, N. Evaluation of size reduction on the yield and quality of celery seed oil. *J. Food Eng.* **2007**, *80*, 1255–1260. [CrossRef]

20. Lis-Balchin, M.; Deans, S.G. Bioactivity of selected plant essential oils against Listeria monocytogenes. *J. Appl. Microbiol.* **1997**, *82*, 759–762. [CrossRef]
21. Alves-Silva, J.M.; Dias dos Santos, S.M.; Pintado, M.E.; Pérez-Álvarez, J.A.; Fernández-López, J.; Viuda-Martos, M. Chemical composition and in vitro antimicrobial, antifungal and antioxidant properties of essential oils obtained from some herbs widely used in Portugal. *Food Control.* **2013**, *32*, 371–378. [CrossRef]
22. Marongiu, B.; Piras, A.; Porcedda, S.; Falconieri, D.; Maxia, A.; Frau, M.A.; Gonçalves, M.J.; Cavaleiro, C.; Salgueiro, L. Isolation of the volatile fraction from *Apium graveolens* L. (Apiaceae) by supercritical carbon dioxide extraction and hydrodistillation: Chemical composition and antifungal activity. *Nat. Prod. Res.* **2013**, *27*, 1521–1527. [CrossRef]
23. Kooti, W.; Ali-Akbari, S.; Asadi-Samani, M.; Ghadery, H.; Ashtary-Larky, D. A review on medicinal plant of *Apium graveolens*. *Adv. Herb. Med.* **2014**, *1*, 48–59.
24. Tankeo, S.B.; Lacmata, S.T.; Noumedem, J.A.; Dzoyem, J.P.; Kuiate, J.R.; Kuete, V. Antibacterial and antibiotic-potentiation activities of some Cameroonian food plants against multi-drug resistant gramnegative bacteria. *Chin. J. Integr. Med.* **2014**, *20*, 546–554. [CrossRef] [PubMed]
25. Shanmugapriya, R.; Ushadevi, T. In vitro Antibacterial and Antioxidant Activities of *Apium graveolens* L. Seed extracts. *Int. J. Drug Dev. Res.* **2014**, *6*, 165–170.
26. Al-Sa'aidi, J.A.; Alrodhan, M.N.; Ismael, A.K. Antioxidant activity of n-butanol extract of celery (*Apium graveolens*) seed in streptozotocin-induced diabetic male rats. *Res. Pharm. Biotechnol.* **2012**, *4*, 24–29. [CrossRef]
27. Wen, T.Q.; Lu, W.; Chen, F.X.; Song, H.S.; Zhao, C.P.; Yu, T. *Apium graveolens* L. accelerating differentiation of neural stem cells in vitro. *J. Shanghai Univ.* **2006**, *10*, 89–94. [CrossRef]
28. Taupin, P. Apigenin and related compounds stimulate adult neurogenesis. *Expert Opin. Ther. Pat.* **2009**, *19*, 523–527. [CrossRef] [PubMed]
29. Chonpathompikunlert, P.; Boonruamkaew, P.; Sukketsiri, W.; Hutamekalin, P.; Sroyraya, M. The antioxidant and neurochemical activity of *Apium graveolens* L. and its ameliorative effect on MPTP-induced Parkinson-like symptoms in mice. *BMC Compl. Alt. Med.* **2018**, *18*, 103. [CrossRef] [PubMed]
30. Fazal, S.S.; Singla, R.K. Review on the pharmacognostical & pharmacological characterization of *Apium graveolens* Linn. *Indo Glob. J. Pharmaceut. Sci.* **2012**, *2*, 36–42.
31. The Plant List. Available online: www.theplantlist.org (accessed on 12 August 2019).
32. Tanasawet, S.; Boonruamkaew, P.; Sukketsiri, W.; Chonpathompikunlert, P. Anxiolytic and free radical scavenging potential of Chinese celery (*Apium graveolens*) extract in mice. *Asian Pac. J. Trop. Biomed.* **2017**, *7*, 20–26. [CrossRef]
33. Wang, S.; Yang, W.; Shen, H. Genetic diversity in *Apium graveolens* and related species revealed by SRAP and SSR markers. *Sci. Hortic.* **2011**, *129*, 1–8. [CrossRef]
34. Asif, H.M.; Akram, M.; Usmanghani, K.; Akhtar, N.; Shah, P.A.; Uzair, M.; Ramzan, M.; Shah, S.M.A.; Rehman, R. Monograph of *Apium graveolens* Linn. *J. Med. Plants Res.* **2011**, *5*, 1494–1496.
35. Malhotra, S. Celery. In *Handbook of Herbs and Spices*; Elsevier: Amsterdam, The Netherlands, 2006; Volume 3, pp. 317–336.
36. Farooqi, A.; Kathiresan, C.; Srinivasappa, K. Agricultural Sciences, India. In *Handbook of Herbs and Spices*; Woodhead Publishing: Cambridge, UK, 2006; p. 313.
37. Burmeier, S.; Jensen, K.A.I. Is the endangered *Apium repens* (Jacq.) Lag. rare because of a narrow regeneration niche? *Plant. Species Biol.* **2008**, *23*, 111–118. [CrossRef]
38. Ronse, A.; Popper, Z.; Preston, J.; Watson, M. Taxonomic revision of European *Apium* L. s.l.: Helosciadium, W.D.J.Koch restored. *Plant. Syst. Evol.* **2010**, *287*, 1–17. [CrossRef]
39. Rubatzky, V.; Yamaguchi, M. Carrot, Celery, and Other Vegetable Umbels. In *World Vegetables: Principles, Production, and Nutritive Values*; Chapman & Hall: New York, NY, USA, 1997; pp. 418–456.
40. Pressman, E.; Shaked, R.; Negbi, M. Germination of seeds of annual and biennial celery (*Apium graveolens*). *Physiol. Plant.* **1988**, *72*, 65–69. [CrossRef]
41. Kumar, R.; Singh, J.; Uppal, S. Intercropping of medicinal and high value crops in autumn sugarcane (*Saccharum* spp. hybrid) for higher productivity and profitability. *Indian J. Agron.* **2015**, *60*, 135–138.
42. Baumann, D.T.; Bastiaans, L.; Goudriaan, J.; van Laar, H.; Kropff, M. Analysing crop yield and plant quality in an intercropping system using an eco-physiological model for interplant competition. *Agric. Syst.* **2002**, *73*, 173–203. [CrossRef]

43. Charles, K.S.; Ngouajio, M.; Warncke, D.D.; Poff, K.L.; Hausbeck, M.K. Integration of cover crops and fertilizer rates for weed management in celery. *Weed Sci.* **2006**, *54*, 326–334. [CrossRef]
44. Jenni, S.; Gamache, I.; Côté, J.C.; Stewart, K.A. Plastic mulches and low tunnels to reduce bolting and increase marketable yield of early celery. *J. Veg. Sci.* **2006**, *12*, 57–73. [CrossRef]
45. Tanwar, A.; Yadav, K.; Prasad, K.; Aggarwal, A. Biological amendments on growth, nutritional quality, and yield of celery. *Intern. J. Veg. Sci.* **2013**, *19*, 228–239. [CrossRef]
46. Alt, C.; Wiebe, H.-J. Flower formation in celeriac (*Apium graveolens* L. var. *rapaceum*) II. Modelling the risk of bolting. *Gartenbauwissenschaft* **2001**, *66*, 46–50.
47. Booij, R.; Meurs, E.J.J. Flowering in celeriac (*Apium graveolens* L. var. rapaceum (Mill.) DC.): Effects of photoperiod. *Sci. Hortic.* **1994**, *58*, 271–282. [CrossRef]
48. Ramin, A.A.; Atherton, J.G. Manipulation of bolting and flowering in celery (*Apium graveolens* L.var. dulce). III.Effects of photoperiod and irradiance. *J. Hortic. Sci.* **1994**, *69*, 861–868. [CrossRef]
49. Pressman, E.; Negbi, M. The effect of day length on the response of celery to vernalization. *J. Exp. Bot.* **1980**, *31*, 1291–1296. [CrossRef]
50. Chorianopoulou, S.N.; Bouranis, D.L.; Drossopoulos, J.B. Oxygen transport by *Apium nodiflorum*. *J. Plant. Physiol.* **2001**, *158*, 905–913. [CrossRef]
51. Mechora, Š.; Čalasan, A.Ž.; Felicijan, M.; Krajnc, A.U.; Ambrožič-Dolinšek, J. The impact of selenium treatment on some physiological and antioxidant properties of Apium repens. *Aquat. Bot.* **2017**, *138*, 16–23. [CrossRef]
52. Rosenthal, G.; Lederbogen, D. Response of the clonal plant *Apium repens* (Jacq.) Lag. to extensive grazing. *Flora-Morphol. Dis. Funct. Ecol. Plants* **2008**, *203*, 141–151. [CrossRef]
53. Baninasab, B. Responses of wild celery (*Apium graveolens*) seeds to light and temperature. *Acta Hortic.* **2011**, *907*, 247–250. [CrossRef]
54. Desai, B.; Kotecha, D.; Salunkhe, P. *Seeds Handbook*; Marcel Dekker Inc. Pub.: New York, NY, USA, 1997.
55. Thomas, T. Is there a circadian germination response to red light in celery (*Apium graveolens* L.) seeds? *Plant. Growth Regul.* **2002**, *37*, 31–35. [CrossRef]
56. Coolbear, P.; Toledo, P.E.; Seetagoses, U. Effects of temperature of pre-sowing hydration treatment and subsequent drying rates on the germination performance of celery seed. *N. Zeal. J. Crop. Hortic. Sci.* **1991**, *19*, 9–14. [CrossRef]
57. Rożek, E. Reaction of leaf celery (*Apium graveolens* L. var. *secalinum*) to planting density and irrigation. *Veg. Crop. Res. Bull.* **2007**, *66*, 69–77.
58. Rożek, E. Effect of plant density and irrigation upon yield and selected technological features of some celeriac (*Apium graveolens* L. var. *rapaceum*) cultivars. *Acta Sci. Pol.-Hortoru.* **2009**, *8*, 79–85.
59. Rożek, E.; Nurzyńska-Wierdak, R.; Dzida, K. Factors modifying yield quantity and quality, as well as the chemical composition of the leaves of leaf celery *Apium graveolens* L. var. *secalinum* grown from seedlings. *Acta Sci. Pol.-Hortoru.* **2012**, *11*, 201–210.
60. Evers, A.; Ketoja, E.; Hägg, M.; Pllami, S.; Häkinnen, U.; Pessala, R. Decreased nitrogen rates and irrigation effect on celery yield and internal quality. *Plant. Food Hum. Nutr.* **1997**, *51*, 173–186. [CrossRef]
61. Kreck, M.; Dietrich, H.; Patz, C.-D.; Ludwig, M.; Paschold, P.J.; Both, S.; Schrenk, D. Characterization of celery juices from different celery cultivars and different irrigation levels. *Dtsch. Lebensm.-Rundsch.* **2006**, *102*, 17–24.
62. Rożek, E.; Nurzyńska-Wierdak, R.; Sałata, A.; Gumiela, P. The chemical composition of the essential oil of leaf celery (*Apium graveolens* L. var. *Secalinum Alef.*) under the plants' irrigation and harvesting method. *Acta Sci. Pol.-Hortoru.* **2016**, *15*, 147–157.
63. Grewal, H.S.; Maheshwari, B.L. Treated effluent and saline water irrigation influences soil properties, yield, water productivity and sodium content of snow peas and celery. *J. Plant. Nutri.* **2013**, *36*, 1102–1119. [CrossRef]
64. Leatherwood, W.R.; Pharr, D.M.; Dean, L.O.; Williamson, J.D. Carbohydrate content and root growth in seeds germinated under salt stress. *J. Am. Soc. Hortic. Sci.* **2007**, *132*, 876–882. [CrossRef]
65. Leonardi, C. Dry matter yield and nitrogen content in celery under salt stress conditions. *Acta Hortic.* **1998**, *458*, 257–261. [CrossRef]
66. Pardossi, A.; Bagnoli, G.; Malorgio, F.; Campiotti, C.; Tognoni, F. NaCl effects on celery (*Apium graveolens* L.) grown in NFT. *Sci. Hortic.* **1999**, *81*, 229–242. [CrossRef]

67. Breschini, S.J.; Hartz, T.K. Drip irrigation management affects celery yield and quality. *HortScience* **2002**, *37*, 894–897. [CrossRef]
68. Ogbuchiekwe, E.J.; Mcgiffen, M.E. Efficacy and Economic Value of Weed Control for Drip and Sprinkler Irrigated Celery. *HortScience* **2001**, *36*, 1278–1282. [CrossRef]
69. Du, Z.; Shao, L.; Ma, M. Deep percolation in greenhouse-cultivated celery using the technique of subsurface film strips placement. *Span. J. Agric. Res.* **2014**, *12*, 519–526. [CrossRef]
70. Christiansen, J.S.; Thorup-Kristensen, K.; Kristensen, H.L. Root development of beetroot, sweet corn and celeriac, and soil N content after incorporation of green manure. *J. Hortic. Sci. Biotechnol.* **2006**, *81*, 831–838. [CrossRef]
71. Derolez, J.; Vulsteke, G. Accumulation of nitrate: A cultivar-linked property with celeriac (*Apium graveolen*s L. var. rapaceum). *Qual. Plant.* **1985**, *35*, 375–378. [CrossRef]
72. Du, Y.; Niu, W.; Zhang, Q.; Cui, B.; Gu, X.; Guo, L.; Liang, B. Effects of nitrogen on soil microbial abundance, enzyme activity, and nitrogen use efficiency in greenhouse celery under aerated irrigation. *Soil Sci. Soc. Am. J.* **2018**, *82*, 606–613. [CrossRef]
73. Madrid, R.; López, M.D.; Barba, E.M.; Gómez, P.; Artés, F. Influence of nitrate fertilizer on macronutrient contents of celery plants on soil-less culture. *J. Plant. Nutr.* **2008**, *31*, 55–67. [CrossRef]
74. Min, J.; Zhao, X.; Wei-Ming, S.; Xing, G.-X.; Zhu, Z.-L. Nitrogen balance and loss in a greenhouse vegetable system in Southeastern China. *Pedosphere* **2011**, 464–472. [CrossRef]
75. Kolota, E.; Osinska, M.; Biesiada, A. Yield of early celeriac in relation to agronomic variables. *Acta Hortic.* **2000**, *533*, 469–473. [CrossRef]
76. Inthichack, P.; Nishimura, Y.; Fukumoto, Y. Effect of potassium sources and rates on plant growth, mineral absorption, and the incidence of tip burn in cabbage, celery, and lettuce. *Hortic. Environ. Biotechnol.* **2012**, *53*, 135–142. [CrossRef]
77. Li, Y.; Wang, T.; Li, J.; Ao, Y. Effect of phosphorus on celery growth and nutrient uptake under different calcium and magnesium levels in substrate culture. *Hortic. Sci.* **2010**, *37*, 99–108. [CrossRef]
78. Olle, M.; Bender, I. Causes and control of calcium deficiency disorders in vegetables: A review. *J. Hortic. Sci. Biotechnol.* **2009**, *84*, 577–584. [CrossRef]
79. Bellaloui, N.; Brown, P.H. Cultivar differences in boron uptake and distribution in celery (*Apium graveolens*), tomato (*Lycopersicon esculentum*) and wheat (*Triticum aestivum*). *Plant. Soil* **1998**, *198*, 153–158. [CrossRef]
80. Guerra, N.; Carrozzi, L.; Goñi, M.G.; Roura, S.; Yommi, A. Quality characterization of celery (*Apium graveolens* L.) by plant zones and two harvest dates. *J. Food Sci.* **2010**, *75*, S327–S332. [CrossRef] [PubMed]
81. Rożek, E.; Nurzyńska-Wierdak, R.; Kosior, M. Efficiency of some agrotechnical treatments in quantity and quality yield modification of leaf celery (*Apium graveolens* L.). *Acta Sci. Pol.-Hortoru.* **2013**, *12*, 227–239.
82. Yommi, A.K.; Gerónimo Di, M.N.; Carrozzi, L.E.; Quillehauquy, V.; Goñi, M.G.; Roura, S.I. Morphological, physicochemical and sensory evaluation of celery harvested from early to late maturity. *Hortic. Bras.* **2013**, *31*, 236–241. [CrossRef]
83. Han, Q.; Wang, S.; Yang, W.; Shen, H. Inheritance of white petiole in celery and development of a tightly linked SCAR marker. *Plant. Breed.* **2012**, *131*, 340–344. [CrossRef]
84. Berardinelli, A.; Pasquali, F.; Cevoli, C.; Trevisani, M.; Ragni, L.; Mancusi, R.; Manfreda, G. Sanitisation of fresh-cut celery and radicchio by gas plasma treatments in water medium. *Postharvest Biol. Technol.* **2016**, *111*, 297–304. [CrossRef]
85. Hernández, A.E.; Julio, C.; Cardozo, M.; Estela, C.; Flores, R.; Andrés, J.; Gómez, P. Application of heat treatment, edible coating and chemical dip as postharvest treatments for the conservation of fresh-cut vegetables. *Acta AgronóMica* **2014**, *63*, 1–10.
86. Viña, S.; Chaves, A.R. Effect of heat treatment and refrigerated storage on antioxidant properties of pre-cut celery (*Apium graveolens* L.). *Inter. J. Food Sci. Technol.* **2008**, *43*, 44–51. [CrossRef]
87. Viña, S.; Osornio, M.M.L.; Chaves, A.R. Quality changes in fresh-cut celery as affected by heat treatment and storage. *J. Sci. Food Agric.* **2007**, *87*, 1400–1407. [CrossRef]
88. González-Buesa, J.; Page, N.; Kaminski, C.; Ryser, E.T.; Beaudry, R.; Almenar, E. Effect of non-conventional atmospheres and bio-based packaging on the quality and safety of Listeria monocytogenes -inoculated fresh-cut celery (*Apium graveolens* L.) during storage. *Postharvest Biol. Technol.* **2014**, *93*, 29–37. [CrossRef]
89. Rizzo, V.; Muratore, G. Effects of packaging on shelf life of fresh celery. *J. Food Eng.* **2009**, *90*, 124–128. [CrossRef]

90. Gómez, P.; Artés-Hernández, F.; Artés, F. Controlled atmosphere effects on sugar content and respiratory activity of green celery. *Acta Hortic.* **2010**, *857*, 31–36. [CrossRef]
91. Radziejewska-Kubzdela, E.; Czapski, J.; Katarzyna, C.; Biegańska-Marecik, R. The effect of pre-treatment and modified atmosphere packaging on contents of phenolic compounds and sensory and microbiological quality of shredded celeriac. *J. Sci. Food Agric.* **2014**, *94*, 1140–1148. [CrossRef] [PubMed]
92. Tamer, C.E.; Çopur, Ö.U.; İncedayi, B.; Vural, H. Evaluation of some quality parameters of minimaly processed celery by quantitative analysis. *J. Food Process. Technol.* **2012**, 1–10. [CrossRef]
93. Zhan, L.; Hu, J.; Lim, L.-T.; Pang, L.; Li, Y.; Shao, J. Light exposure inhibiting tissue browning and improving antioxidant capacity of fresh-cut celery (*Apium graveolens* var. *dulce*). *Food Chem.* **2013**, *141*, 2473–2478. [CrossRef] [PubMed]
94. Yao, Y.; Ren, G. Effect of thermal treatment on phenolic composition and antioxidant activities of two celery cultivars. *LWT—Food Sci. Technol.* **2011**, *44*, 181–185. [CrossRef]
95. Ilić, Z.S.; Sunić, L.J.; Milenković, L. Extended harvest time improves the shelf life of celeriac (*Apium graveolens* var. *rapaceum*) through postharvest treatment and storage conditions. *Acta Hortic.* **2016**, *1142*, 269–276.
96. Rossi, S.; Cools, K.; Terry, L.A. The influence of crop maturity and ethylene on postharvest browning in celery. *Acta Hortic.* **2018**, *1194*, 13–18. [CrossRef]
97. Mirecki, N.; Ilić, Z.S.; Šunic, L.; Rukie, A. Nitrate content in carrot, celeriac and parsnip at harvest time and during prolonged cold storage. *Fresenius Environ. Bull.* **2015**, *24*, 3266–3273.
98. Gómez, P.; Artés, F.; Madrid, R. Nitrogen fertiliser rate and controlled atmospheres effects on the nitrate levels and quality of fresh processed celery sticks. *Acta Hortic.* **2003**, *75*, 1–4. [CrossRef]
99. Manal, A.S.; Naglaa, H.M.H.; Mona, H.M.A. Natural Antioxidant Changes in Fresh and Dried celery (*Apium graveolens*). *Am. J. Energy Eng.* **2015**, *3*, 12–16.
100. Sahoo, H.B.; Das Santani, D.; Sagar, R. Chemopreventive potential of *Apium leptophyllum* (Pers.) against DMBA induced skin carcinogenesis model by modulatory influence on biochemical and antioxidant biomarkers in Swiss mice. *Indian J. Pharmacol.* **2014**, *46*, 531–537. [PubMed]
101. Al Jitan, S.; Alkhoori, S.A.; Yousef, L.F. Phenolic Acids from Plants: Extraction and Application to Human Health. In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, The Netherlands, 2018; Volume 58, pp. 389–417.
102. Al-Moubaraki, A.H.; Al-Howiti, A.A.; Al-Dailami, M.M.; Al-Ghamdi, E.A. Role of aqueous extract of celery (*Apium graveolens* L.) seeds against the corrosion of aluminium/sodium hydroxide systems. *J. Environ. Chem. Eng.* **2017**, *5*, 4194–4205. [CrossRef]
103. Sowbhagya, H. Chemistry, technology, and nutraceutical functions of celery (*Apium graveolens* L.): An overview. *Crit. Rev. Food Sci. Nutr.* **2014**, *54*, 389–398. [CrossRef] [PubMed]
104. Zujovic, Z.; Chen, D.; Melton, L. Comparison of celery (*Apium graveolens* L.) collenchyma and parenchyma cell wall polysaccharides enabled by solid–state (13) C NMR. *Carbohydr. Res.* **2016**, *420*, 51–57. [CrossRef]
105. Jorge, V.; Ángel, J.; Adrián, T.; Francisco, A.; Anuar, S.; Samuel, E.; Ángel, S.; Emmanuel, H. Vasorelaxant activity of extracts obtained from *Apium graveolens*: Possible source for vasorelaxant molecules isolation with potential antihypertensive effect. *Asian Pac. J. Trop. Biomed.* **2013**, *3*, 776–779. [CrossRef]
106. Sahoo, H.; Sagar, R.; Kumar, A.; Bhaiji, A.; Bhattamishra, S. Antidiarrhoeal investigation of *Apium leptophyllum* (Pers.) by modulation of Na+K+ATPase, nitrous oxide and intestinal transit in rats. *Biomed. J.* **2016**, *39*, 376–381. [CrossRef] [PubMed]
107. Momin, R.A.; Nair, M.G. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from *Apium graveolens* Linn. seeds. *Phytomedicine* **2002**, *9*, 312–318. [CrossRef] [PubMed]
108. Sedlacek, J. Is chemo–preventive effect of *Apium leptophyllum* (Pers.) caused only by anti–oxidative property of flavonoids? *Indian J. Pharmacol.* **2015**, *47*, 341–342. [CrossRef]
109. Baananou, S.; Bouftira, I.; Mahmoud, A.; Boukel, K.; Marongiu, B.; Boughattas, N.A. Antiulcerogenic and antibacterial activities of *Apium graveolens* essential oil and extract. *Nat. Prod. Res.* **2013**, *27*, 1075–1083. [CrossRef] [PubMed]
110. Bjeldanes, L.F.; Kim, I.S. Phtalide components of celery essential oil. *J. Org. Chem.* **1977**, *42*, 2333–2335. [CrossRef]
111. Tang, J.; Zhang, Y.; Hartman, T.G.; Rosen, R.T.; Ho, C.T. Free and glycosidically bound volatile compounds in fresh celery (*Apium graveolens* L.). *J. Agric. Food Chem.* **1990**, *38*, 1937–1940. [CrossRef]

112. Pino, J.A.; Rosado, A.; Fuentes, V. Leaf oil of celery (*Apium graveolens* L.) from Cuba. *J. Essent. Oil Res.* **1997**, *9*, 719–720. [CrossRef]
113. Jung, W.; Chung, I.; Kim, S.; Kim, M.; Ahmad, A.; Praveen, N. In vitro antioxidant activity, total phenolics and flavonoids from celery (*Apium graveolens*) leaves. *J. Med. Plants Res.* **2011**, *5*, 7022–7030.
114. Al-Asmari, A.K.; Athar, T.; Kadasah, S.G. An Updated Phytopharmacological Review on Medicinal Plant of Arab Region: *Apium graveolens* Linn. *Pharmacogn. Rev.* **2017**, *11*, 13. [CrossRef] [PubMed]
115. Coelho de Souza, G.; Haas, A.P.S.; Von Poser, G.L.; Schapoval, E.E.S.; Elisabetsky, E. Ethnopharmacological studies of antimicrobial remedies in the south of Brazil. *J. Ethnopharmacol.* **2004**, *90*, 135–143. [CrossRef]
116. Duraipandiyan, V.; Ignacimuthu, S. Antifungal activity of traditional medicinal plants from Tamil Nadu, India. *Asian Pac. J. Trop. Biomed.* **2011**, *2011*, 204–215. [CrossRef]
117. Kalsoom Qureshi, S.J.; Neelam, M.A.; Muhammad, Z.A.; Riffat, J. Anti-Leishmanial, Anti-Fungal, Brine Shrimp Lethality, Anti-Leishmanial and Insecticidal Assay of *Apium graveolens* Lavailable in Khyber Pakhtunkhwa-Pakistan. *Pharma Innov. J.* **2014**, *3*, 51–54.
118. Skalicka-Woźniak, K.; Orhan, I.E.; Cordell, G.A.; Nabavi, S.M.; Budzyńska, B. Implication of coumarins towards central nervous system disorders. *Pharmacol. Res.* **2016**, *103*, 188–203. [CrossRef]
119. Kooti, W.; Daraei, N. A Review of the Antioxidant Activity of Celery (*Apium graveolens* L.). *J. Evid.-Based Complement. Altern. Med.* **2017**, *22*, 1029–1034. [CrossRef] [PubMed]
120. Ghasemi, P.A. *Iranian Medicinal and Aromatic Plants*; Islamic Azad University: Shahrekord, Iran, 2009.
121. Tang, S.; Halliwell, B. Medicinal plants and antioxidants: What do we learn from cell culture and Caenorhabditis elegans studies? *Biochem. Biophys. Res. Commun.* **2010**, *394*, 1–5. [CrossRef] [PubMed]
122. Noori, A.A.M.; Mortazavi, M.; Kalani, N.; Zare Marzouni, H.; Kooti, W.; Ali-Akbari, S. Effect of hydroalcoholic extract of *Rosmarinus officinalis* L. leaf on anxiety in mice. *J. Evid.-Based Complement. Altern. Med.* **2016**, *2016*, NP85–NP90. [CrossRef] [PubMed]
123. Asadi-Samani, M.; Kafash-Farkhad, N.; Azimi, N.; Fasihi, A.; Alinia-Ahandani, E.; Rafieian-Kopaei, M. Medicinal plants with hepatoprotective activity in Iranian folk medicine. *Asian Pac. J. Trop. Biomed.* **2015**, *5*, 146–157. [CrossRef]
124. Kerishchi, P.; Nasri, S.; Amin, G.; Tabibian, M. The effects of *Apium graveolens* extract on sperm parameters and HG hormonal axis in mice. In Proceedings of the 20th Iranian Congress of Physiology and Pharmacology, Hamadan, Iran, 10–14 October 2011.
125. Hamza, A.; Amin, A. *Apium graveolens* modulates sodium valproate-induced reproductive toxicity in rats. *J. Exp. Zool. A Ecol. Genet. Physiol.* **2007**, *307*, 199–206. [CrossRef]
126. Hardani, A.; Afzalzadeh, M.; Amirzargar, A.; Mansouri, E.; Meamar, Z. Effects of aqueous extract of celery (*Apium graveolens* L.). leaves on spermatogenesis in healthy male rats. *Avicenna J. Phytomed.* **2015**, *5*, 113.
127. Esrafil, M.; Maryam, G.; Majid, A.S.; Fatima, A.; Damoon, A.-L.; Najmeh, K.F.; Wesam, K.; Ameneh, H.; Ashraf, A.Z. The Effect of Hydro-Alcoholic Extract of *Apium graveolens* L. Leaf on Delivery Rate in Female Rats, Weight and Gender Ratio of Infants. *Jundishapur J. Nat. Pharm. Prod.* **2017**, *12*, 1–5.
128. Lans, C. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. *J. Ethnobiol. Ethnomed.* **2006**, *2*, 45. [CrossRef]
129. Pandey, A.K.; Kumar, P.; Singh, P.; Tripathi, N.N.; Bajpai, V.K. Essential Oils: Sources of Antimicrobials and Food Preservatives. *Front. Microbiol.* **2017**, *7*, 2161. [CrossRef]
130. Oussalah, M.; Caillet, S.; Saucier, L.; Lacroix, M. Antimicrobial effects of selected plant essential oils on the growth of a *Pseudomonas putida* strain isolated from meat. *Meat Sci.* **2006**, *73*, 236–244. [CrossRef]
131. Hassanen, N.H.; Eissa, A.M.F.; Hafez, S.A.M.; Mosa, E.A.M. Antioxidant and antimicrobial activity of celery (*Apium graveolens*) and coriander (*Coriandrum sativum*) herb and seed essential oils. *Intern. J. Curr. Microbiol. Appl. Sci.* **2015**, *4*, 284–296.
132. Misic, D.; Zizovic, I.; Stamenic, M.; Asanin, R.; Ristic, M.; Petrovic, S.D.; Skala, D. Antimicrobial activity of celery fruit isolates and SFE process modeling. *J. Biomech. Eng.* **2008**, *42*, 148–152.
133. Maleki, M. Effects of celery extracts on the oxidative stability of canola oil under thermal condition. *J. Food Process. Pres.* **2016**, *40*, 531–540. [CrossRef]
134. Yao, Y.; Sang, W.; Zhou, M.J.; Ren, G.X. Phenolic Composition and Antioxidant Activities of 11 Celery Cultivars. *J. Food Sci.* **2010**, *75*, C9–C13. [CrossRef] [PubMed]

135. Jackson, A.; Kulchaiyawat, C.; Sullivan, G.; Sebranek, J.; Dickson, J. Use of Natural Ingredients to Control Growth of *Clostridium perfringens* in Naturally Cured Frankfurthers and Hams. *J. Food Prot.* **2011**, *74*, 417–424. [CrossRef]
136. Bouvard, V.; Loomis, D.; Guyton, K.; Grosse, Y.; Ghissassi, F.; Benbrahim-Tallaa, L.; Guha, N.; Mattock, H.; Straif, K. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol.* **2015**, *16*, 1599. [CrossRef]
137. Cantell, M.; Elliot, C. Nitrates, nitrites and nitrosamines from processed meat intake and colorectal cancer risk. *J. Clin. Nutr. Diet* **2017**, *3*, 27.
138. Xi, Y.; Sullivan, G.A.; Jackson, A.L.; Zhou, G.H.; Sebranek, J.G. Use of natural antimicrobials to improve the control of Listeria monocytogenes in a cured cooked meat model system. *Meat Sci.* **2011**, *88*, 503–511. [CrossRef]
139. Sebranek, J.G.; Bacus, J.N. Cured meat products without direct addition of nitrate or nitrite: What are the issues? *Meat Sci.* **2007**, *77*, 136–147. [CrossRef]
140. Sebranek, J.G.; Jackson-Davis, A.L.; Myers, K.L.; Lavieri, N.A. Beyond celery and starter culture: Advances in natural/organic curing processes in the United States. *Meat Sci.* **2012**, *92*, 267–273. [CrossRef]
141. Chaleshtori, R.S.; Kopaei, M.R.; Salehi, E. Bioactivity of *Apium petroselinum* and *Portulaca oleracea* Essential Oils as Natural Preservatives. *Jundishapur J. Microbiol.* **2015**, *8*, e20128. [CrossRef] [PubMed]
142. Nakhaei, M.M. In vitro anti-bacterial activity of methanolic extract of *Apium petroselinum* L. seed against clinical isolates of *Helicobacter pylori*. *J. Daneshvar Med.* **2010**, *17*, 63–70.
143. Menghini, L.; Leporini, L.; Tirillini, B.; Epifano, F.; Genovese, S. Chemical Composition and Inhibitory Activity Against *Helicobacter pylori* of the Essential Oil of *Apium nodiflorum* (Apiaceae). *J. Med. Food* **2010**, *13*, 228–230. [CrossRef] [PubMed]
144. Alahakoon, A.U.; Jayasena, D.D.; Ramachandra, S.; Jo, C. Alternatives to nitrite in processed meat: Up to date. *Trends Food Sci. Technol.* **2015**, *45*, 37–49. [CrossRef]
145. Horsch, A.M.; Sebranek, J.G.; Dickson, J.S.; Niebuhr, S.E.; Larson, E.M.; Lavieri, N.A.; Ruther, B.L.; Wilson, L.A. The effect of pH and nitrite concentration on the antimicrobial impact of celery juice concentrate compared with conventional sodium nitrite on *Listeria monocytogenes*. *Meat Sci.* **2014**, *96*, 400–407. [CrossRef] [PubMed]
146. Sullivan, G.; Jackson-Davis, A.; Niebuhr, S.; Xi, Y.; Schrader, K.; Sebranek, J.; Dickson, J. Inhibition of *Listeria monocytogenes* Using Natural Antimicrobials in No-Nitrate-or-Nitrite-Added Ham. *J. Food Protec.* **2012**, *75*, 1071–1076. [CrossRef] [PubMed]
147. Djeri, N.; Williams, S.K. Celery juice powder used as nitrite substitute in sliced vacuum-packaged turkey bologna stored at 4C for 10 weeks under retail display light. *Food Qual. Prefer.* **2014**, *37*, 361–370. [CrossRef]
148. Sindelar, J.J.; Cordray, J.C.; Sebranek, J.G.; Love, J.A.; Ahn, D.U. Effects of varying levels of vegetable juice powder and incubation time on color, residual nitrate and nitrite, pigment, pH, and trained sensory attributes of ready-to-eat uncured ham. *J. Food Sci.* **2007**, *72*, S388–S395. [CrossRef]
149. WHO. *WHO Global Strategy for Containment of Antimicrobial Resistance*; WHO: Geneva, Switzerland, 2001.
150. Shad, A.A.; Shah, H.U.; Bakht, J.; Choudhary, M.I.; Ullah, J. Nutraceutical potential and bioassay of *Apium graveolens* L. grown in Khyber Pakhtunkhwa-Pakistan. *J. Med. Plants Res.* **2011**, *5*, 5160–5166.
151. Maxia, A.; Falconieri, D.; Piras, A.; Porcedda, S.; Marongiu, B.; Frau, M.A.; Goncalves, M.J.; Cabral, C.; Cavaleiro, C.; Salgueiro, L. Chemical Composition and Antifungal Activity of Essential Oils and Supercritical CO_2 Extracts of Apium nodiflorum (L.) Lag. *Mycopathologia* **2012**, *174*, 61–67. [CrossRef]
152. Edziri, H.; Ammar, S.; Souad, L.; Mahjoub, M.A.; Mastouri, M.; Aouni, M.; Mighri, Z.; Verschaeve, L. In vitro evaluation of antimicrobial and antioxidant activities of some Tunisian vegetables. *S. Afr. J. Bot.* **2012**, *78*, 252–256. [CrossRef]
153. Rani, P.; Khullar, N. Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant Salmonella typhi. *Phytother. Res.* **2004**, *18*, 670–673. [CrossRef] [PubMed]
154. Din, Z.U.; Shad, A.A.; Bakht, J.; Ullah, I.; Jan, S. In vitro antimicrobial, antioxidant activity and phytochemical screening of *Apium graveolens*. *Pak. J. Pharm. Sci.* **2015**, *28*, 1699–1704.
155. Friedman, M.; Henika, P.R.; Mandrell, R.E. Bactericidal activities of plant essential oils and some of their isolated constituents against *Campylobacter jejuni*, *Escherichia coli*, *Listeria monocytogenes*, and *Salmonella enterica*. *J. Food Protec.* **2002**, *65*, 1545–1560. [CrossRef] [PubMed]
156. Penna, C.; Marino, S.; Vivot, E.; Cruanes, M.C.; Munoz, J.D.; Cruanes, J.; Ferraro, G.; Gutkind, G.; Martino, V. Antimicrobial activity of Argentine plants used in the treatment of infectious diseases. Isolation of active compounds from Sebastiania brasiliensis. *J. Ethnopharmacol.* **2001**, *77*, 37–40. [CrossRef]

157. Ahmed, B.; Alam, T.; Varshney, M.; Khan, S.A. Hepatoprotective activity of two plants belonging to the Apiaceae and the Euphorbiaceae family. *J. Ethnopharmacol.* **2002**, *79*, 313–316. [CrossRef]
158. Yildiz, L.; Baskan, K.S.; Tutem, E.; Apak, R. Combined HPLC-CUPRAC (cupric ion reducing antioxidant capacity) assay of parsley, celery leaves, and nettle. *Talanta* **2008**, *77*, 304–313. [CrossRef] [PubMed]
159. Nagella, P.; Ahmad, A.; Kim, S.J.; Chung, I.M. Chemical composition, antioxidant activity and larvicidal effects of essential oil from leaves of Apium graveolens. *Immunopharmacol. Immunotoxicol.* **2012**, *34*, 205–209. [CrossRef] [PubMed]
160. Kolarovic, J.; Popovic, M.; Zlinska, J.; Trivic, S.; Vojnovic, M. Antioxidant Activities of Celery and Parsley Juices in Rats Treated with Doxorubicin. *Molecules* **2010**, *15*, 6193–6204. [CrossRef]
161. Abu_Darwsih, M.S.; Efferth, T. Medicinal plants from near east for cancer therapy. *Front. Pharmacol.* **2018**, *9*, 56. [CrossRef]
162. Sultana, S.; Ahmed, S.; Jahangir, T.; Sharma, S. Inhibitory effect of celery extract on chemically induced hepatocarcinogenesis: Modulation of cell proliferation, metabolism and altered hepatic foci development. *Cancer Lett.* **2005**, *221*, 11–20. [CrossRef] [PubMed]
163. Al-Jumaily, R.M.K. Evaluation of anticancer activities of crude extracts of *Apium graveolens* L. seeds in two cell lines, RD and L20B in vitro. *Iraqi J. Cancer Med. Genet.* **2010**, *3*, 18–23.
164. Octaviani, C.D.; Lusiana, M.; Zuhrotun, A.; Diantini, A.; Subarnas, A.; Abdulah, R. Anticancer properties of daily-consumed vegetables *Amaranthus spinosus*, *Ipomoea aquatica*, *Apium graveolens*, and *Manihot utilisima* to LNCaP prostate cancer cell lines. *J. Nat. Pharmaceut.* **2013**, *4*, 67–70.
165. Brahmi, N.; Scognamiglio, M.; Pacifico, S.; Mekhoukhe, A.; Madani, K.; Fiorentino, A.; Monaco, P. 1H NMR basedmetabolic profiling of eleven Algerian aromatic plants and evaluation of their antioxidant and cytotoxic properties. *Food Res. Int.* **2015**, *76*, 334–341. [CrossRef] [PubMed]
166. Gao, L.L.; Feng, L.; Yao, S.T.; Jiao, P.; Qin, S.C.; Zhang, W.; Zhang, Y.B.; Li, F.R. Molecular Mechanisms of Celery Seed Extract Induced Apoptosis via S Phase Cell Cycle Arrest in the BGC-823 Human Stomach Cancer Cell Line. *Asian Pac. J. Cancer Prevent.* **2011**, *12*, 2601–2606.
167. Zidorn, C.; Johrer, K.; Ganzera, M.; Schubert, B.; Sigmund, E.M.; Mader, J.; Greil, R.; Ellmerer, E.P.; Stuppner, H. Polyacetylenes from the Apiaceae vegetables carrot, celery, fennel, parsley, and parsnip and their cytotoxic activities. *J. Agric. Food Chem.* **2005**, *53*, 2518–2523. [CrossRef] [PubMed]
168. Maggi, F.; Giuliani, C.; Fico, G.; Ricciutelli, M.; Bramucci, M.; Quassinti, L.; Petrelli, D.; Vitali, L.A.; Cianfaglione, K.; Tirillini, B.; et al. Secondary metabolites, secretory structures and biological activity of water celery (*Apium nodiflorum* (L.) Lag.) growing in central Italy, Plant Biosystems. *An. Int. J. Deal. Asp. Plant. Biol.* **2018**, *1*, 325–335.
169. Yili, A.; Ma, Q.L.; Gao, Y.H.; Zhao, B.; Jun, D.; Aisa, H.A. Isolation of two antioxidant peptides from seeds of *Apium graveolens* indigenous to China. *Chem. Nat. Compd.* **2012**, *48*, 719–720. [CrossRef]
170. Koken, T.; Koca, B.; Koca, T.; Altunbas, K. Apium graveolens extract induces apoptosis via Bax and p-53 proteins in the LNCaP human prostate cancer cell line. *FEBS OPEN BIO* **2018**, *8*, 319.
171. Young, J.F.; Christensen, L.P.; Theil, P.K.; Oksbjerg, N. The Polyacetylenes Falcarinol and Falcarindiol Affect Stress Responses in Myotube Cultures in a Biphasic Manner. *Dose-Response* **2008**, *6*, 239–251. [CrossRef]
172. Peng, Y.; Xing, C.H.; Lemere, C.A.; Chen, G.Q.; Wang, L.; Feng, Y.; Wang, X.L. L-3-n-Butylphthalide ameliorates beta-amyloid-induced neuronal toxicity in cultured neuronal cells. *Neurosci. Lett.* **2008**, *434*, 224–229. [CrossRef] [PubMed]
173. Salman, H.R.; Al-Khafaji, B.A.; Mohammed, N.J. Effect of *Apium graveolens* Leaves and Stalks in Reducing the Side Effects of Doxorubicin in Male Rabbits. *Med. J. Babylon* **2013**, *10*, 46–74.
174. Saalu, L.C.; Osinubi, A.A.; Jewo, P.I.; Ajayi, G.O. An Evaluation of Influence of Citrus paradisi Seed Extract on Doxorubicin-Induced Testicular Oxidative Stress and Impaired Spermatogenesis. *Asian J. Sci. Res.* **2010**, *3*, 51–61. [CrossRef]
175. Pereira, G.C.; Silva, A.M.; Diogo, C.V.; Carvalho, F.S.; Monteiro, P.; Oliveira, P.J. Drug-induced Cardiac Mitochondrial Toxicity and Protection: From Doxorubicin to Carvedilol. *Curr. Pharm. Des.* **2011**, *17*, 2113–2129. [CrossRef] [PubMed]
176. Yilmaz, S.; Atessahin, A.; Sahna, E.; Karahan, I.; Ozer, S. Protective effect of lycopene on adriamycin- induced nephrotoxicity. *Toxicology* **2006**, *218*, 164–171. [CrossRef] [PubMed]
177. Gillick, J.; Giles, S.; Bannigan, J.; Puri, P. Cell death in the early adriamycin rat model. *Pediatr. Surg. Int.* **2002**, *18*, 576–580. [PubMed]

178. Ahmadi, A.; Mohagheghi, M.; Karimi, M.; Golestanha, S.A.; Naseri, M. Anticancer Effects of HESA-A in Patients with Metastatic Colon Cancer. *Integr. Cancer Ther.* **2009**, *8*, 71–74. [CrossRef] [PubMed]
179. Atta, A.H.; Alkofahi, A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. *J. Ethnopharmacol.* **1998**, *60*, 117–124. [CrossRef]
180. Ziyan, L.; Yongmei, Z.; Nan, Z.; Ning, T.; Baolin, L. Evaluation of the anti-inflammatory activity of luteolin in experimental animal models. *Planta Med.* **2007**, *73*, 221–226. [CrossRef] [PubMed]
181. Powanda, M.C.; Raisnford, K.D. A toxicological investigation of a celery seed extract having anti-inflammatory activity. *Inflammopharmacology* **2011**, *19*, 227–233. [CrossRef]
182. Zhu, L.H.; Bao, T.H.; Deng, Y.; Li, H.; Chen, L.X. Constituents from *Apium graveolens* and their anti-inflammatory effects. *J. Asian Nat. Prod. Res.* **2017**, *19*, 1079–1086. [CrossRef] [PubMed]
183. Ovodova, R.G.; Golovchenko, V.V.; Popov, S.V.; Popova, G.Y.; Paderin, N.M.; Shashkov, A.S.; Ovodov, Y.S. Chemical composition and anti-inflammatory activity of pectic polysaccharide isolated from celery stalks. *Food Chem.* **2009**, *114*, 610–615. [CrossRef]
184. Moghadam, M.H.; Imenshahidi, M.; Mohajeri, S.A. Antihypertensive effect of celery seed on rat blood pressure in chronic administration. *J. Med. Food* **2013**, *16*, 558–563. [CrossRef] [PubMed]
185. Peng, Y.; Sun, J.; Hon, S.; Nylander, A.N.; Xia, W.; Feng, Y.; Wang, X.; Lemere, C.A. L-3-n-butylphthalide improves cognitive impairment and reduces amyloid-b in a transgenic model of Alzheimer's disease. *J. Neurosci.* **2010**, *30*, 8180–8189. [CrossRef] [PubMed]
186. Wang, C.-M.; Liang, W.; Ywe, D.T. Comparison of two old phytochemicals versus two newly researched plant-derived compounds: Potential for brain and other relevant ailments. *Evid.-Based Complement. Altern. Med.* **2014**, *2014*. [CrossRef] [PubMed]
187. Khalid, Z.; Osuagwu, F.C.; Shah, B.; Roy, N.; Dillon, J.E.; Bradley, R. Celery root extract as an inducer of mania induction in a patient on venlafaxine and St. John's wort. *Postgrad. Med.* **2016**, *128*, 682–683. [CrossRef] [PubMed]
188. Boonruamkaew, P.; Sukketsiri, W.; Panichayupakaranant, P.; Kaewman, W.; Tanasawet, S.; Tipmanee, V.; Hutamekalin, P.; Chonpathompikunlert, P. *Apium graveolens* extract influences mood and cognition in healthy mice. *J. Nat. Med.* **2017**, *71*, 492–505. [CrossRef]
189. Taskhakori-Sabzevar, T.; Ramezani, M.; Hosseinzadeh, H.; Parizadeh, A.M.R.; Movassasghi, A.R.; Ghorbani, A.; Mohajeri, S.A. Protective and hypoglycemic effects of celery seed on streptozotocin-induced diabetic rats: Experimental and histopathological evaluation. *Acta Diabetol.* **2016**, *53*, 609–619. [CrossRef]
190. Syarifahnur, F.; Amiruddin, R.; Hasan, M.; Karmil, T.F.; Budiman, H. The effect of celery leaves infusa (*Apium graveolens* L.) on reducing level of blood glucose on rat (*Rattus norvegicus*) induced by alloxan. *J. Med. Vet.* **2018**, *12*, 36–39.
191. Abbas, A.H. Antihyperglycemic, antihyperlipidiemic effects of ethanol extracts of *Nigella sativa* and *Apium graveolens* and their combination in streptozocin/high fat diet induced hyperglycemic mice. *World J. Pharm. Pharmaceut. Sci.* **2018**, *7*, 85–117.
192. Vasanthkumar, R.; Jeevitha, M. Evaluation of antiobesity activity of *Apium graveolens* stems in rats. *Int. J. Chem. Pharm. Sci.* **2014**, *5*, 159–163.
193. Özbek, H.; Kösem, M.; Erdoğan, E.; Özgökçe, F. *Sesamum indicum* L. ve *Apium graveolens* L. ekstreleri karboplatin hepatotoksisitesine karşı koruyucu mu? *Genel. Tıp. Derg.* **2004**, *14*, 49–55.
194. Shivashri, C.; Rajarajeshwari, T.; Rajasekar, P. Hepatoprotective action of celery (*Apium graveolens*) leaves in acetaminophen-fed freshwater fish. *Fish. Physiol. Biochem.* **2013**, *39*, 1057–1069. [CrossRef] [PubMed]
195. Sukketsiri, W.; Chonpathompikunlert, P.a.; Tnasawet, S.; Choosri, N.; Wongtawatchai, T. Effects of *Apium graveolens* extract on the oxidative stress in the liver of adjuvant-induced arthritic rats. *Prev. Nutr. Food Sci.* **2016**, *21*, 79–84. [CrossRef] [PubMed]
196. Dolati, K.; Rakshandeh, H.; Golestani, M.; Forouzanfar, F.; Sadeghnia, R.; Sadeghnia, H.R. Inhibitory effects of *Apium graveolens* on xanthine oxidase activity and serum uric acid levels in hyperuricemic mice. *Prev. Nutr. Food Sci.* **2018**, *23*, 127–133. [CrossRef] [PubMed]
197. Ahman, A.; Ishaq, H.; Furqan, M.; Sheikh, D.; Raza, M.L.; Naqvi, B.S.; Mehmood, T. Comparative study of ethanolic and aqueous extracts of *Apium graveolens* L. root with furosemide for its diuretic activity and excretion of urinary metabolites in Wistar rats. *Sci. Int.* **2016**, *28*, 2503–2507.
198. Ögenler, O.; Ün, İ.; Uzel, İ. Medical plants used for treatment of gynecological disorders in Ottomans in the 15th century. *J. Complement. Med. Res.* **2018**, *7*, 171–177. [CrossRef]

199. Kooti, W.; Moradi, M.; Peyro, K.; Sharghi, M.; Alamiri, F.; Azami, M.; Firoozbakht, M.; Ghafourian, M. The effect of celery (*Apium graveolens* L.) on fertility: A systematic revies. *J. Complement. Integr. Med.* **2017**, *15*, 1–12. [CrossRef]
200. Helal, M.A.M. Celery oil modulates DEHP-induced reproductive toxicity in male rats. *Reprod. Biol.* **2014**, *14*, 182–189. [CrossRef]
201. Madkour, N.K. Beneficial role of celery oil in lowering the di(2-ethlyhexyl) phthalate induced testicular damage. *Toxicol. Ind. Health* **2014**, *30*, 861–872. [CrossRef]
202. Zhang, Q.; Zhou, M.M.; Chen, P.L.; Cao, Y.Y.; Tan, X.L. Optimization of Ultrasonic-Assisted Enzymatic Hydrolysis for the Extraction of Luteolin and Apigenin from Celery. *J. Food Sci.* **2011**, *76*, C680–C685. [CrossRef] [PubMed]
203. Ardalani, H. The ethnopharmacological review of medicinal plants in uses hypertension treatment in Iranian complementary medicine. *J. Herb. Drugs* **2016**, *7*, 9–13.
204. Shirani, M.; Heidari-Soureshjani, S.; Yavangi, M. Use of Iranian medicinal plants effective on male fertility indices. *J. Glob. Pharma Technol.* **2016**, *10*, 36–43.
205. Jin, J.; Yu, X.; Hu, Z.; Tang, S.; Zhong, X.; Xu, J.; Shang, P.; Huang, Y.; Liu, H. Isofraxidin target TLR4/MD-2 axis to prevent osteoarthritis development. *Food Funct.* **2018**, *9*, 5641–5652. [CrossRef] [PubMed]
206. Tsakova, A.P.; Surcheva, S.K.; Bankova, V.S.; Popova, M.P.; Peev, D.R.; Popivanov, P.R.; Surchev, K.L.; Ratkova, M.D.; Surchev, L.K.; Vlaskovska, M.V. The effect of *Apium nodiflorum* in experimental osteoporosis. *Curr. Pharmaceut. Biotechnol.* **2015**, *16*, 414–423. [CrossRef]
207. Avcı, G.; Erdoğan, S.M. Tiroid fonksiyon bozukluklarında fonksiyonel besinlerin etkinliği. *Kocatepe Vet. J.* **2017**, *10*, 331–336.
208. Mondon, P.; Ringenbach, C.; Doridot, E.; Genet, V. Reinforcement of barrier function and scalp homeostasis by Senkyunolide A to fight against dandruff. *Int. J. Cosmet. Sci.* **2017**, *39*, 617–621. [CrossRef] [PubMed]
209. Zheng, G.; Zhang, J.; Kenney, P.; Lam, L. Chemoprevention of Benzo [a] pyrene induced forestomach cancer in mice by natural phthlides from celery seed oil. *Nutr. Cancer* **1993**, *19*, 77–86. [CrossRef] [PubMed]
210. Venditti, A.; Frezza, C.; Gatto Agostinelli, V.; Di Cecco, M.; Ciaschetti, G.; Serafini, M.; Bianco, A. Study on the molecular composition of an indigenous Italian species: *Coristospermum cuneifolium*(Guss.) Bertol. *Int. J. Indig. Med. Pl.* **2016**, *48*, 1930–1938.
211. Venditti, A.; Frezza, C.; Salutari, G.; Cecco, M.D.; Bianco, A. Composition of the Essential Oil of *Coristospermum cuneifolium* and Antimicrobial Activity Evaluation. *Planta Med. Int. Open* **2017**, *4*, e74–e81. [CrossRef]
212. Peffley, D.; Sharma, C.; Hentosh, P.; Buechler, R. Perillyl alcohol and genistein differentially regulate PKB/Akt and 4E-BP1 phosphorylation as well as eIF4E/eIF4G interactions in human tumor cells. *Arch. Biochem. Biophys.* **2007**, *465*, 266–273. [CrossRef] [PubMed]
213. Yeruva, L.; Pierre, K.; Elegbede, A.; Wang, R.; Carper, S. Perillyl alcohol and perillic acid induced cell cycle arrest and apoptosis in non small cell lung cancer cells. *Cancer Lett.* **2007**, *257*, 216–226. [CrossRef] [PubMed]
214. Bailey, H.H.; Attia, S.; Love, R.R.; Fass, T.; Chappell, R.; Tutsch, K.; Harris, L.; Jumonville, A.; Hansen, R.; Shapiro, G.R.; et al. Phase II trial of daily oral perillyl alcohol (NSC 641066) in treatment-refractory metastatic breast cancer. *Cancer Chemother. Pharmacol.* **2008**, *62*, 149–157. [CrossRef] [PubMed]
215. Purup, S.; Larsen, E.; Christensen, L. Differential effects of falcarinol and related aliphatic C17-polyacetylenes on intestinal cell proliferation. *J. Agric. Food Chem.* **2009**, *57*, 8290–8296. [CrossRef] [PubMed]
216. Bernart, M.; Cardellina II, J.; Balaschak, M.; Alexander, M.; Shoemaker, R.; Boyd, M. Cytotoxic falcarinol oxylipins from *Dendropanax arboreus*. *J. Nat. Prod.* **1996**, *59*, 748–753. [CrossRef] [PubMed]
217. Cunsolo, F.; Ruberto, G.; Amico, V.; Piattelli, M. Bioactive metabolites from sicilian marine fennel, *Crithmum maritimum*. *J. Nat. Prod.* **1993**, *56*, 1598–1600. [CrossRef] [PubMed]
218. Fujioka, T.; Furumi, K.; Fujii, H.; Okabe, H.; Mihashi, K.; Nakano, Y.; Matsunaga, H.; Katano, M.; Mori, M. Antiproleferative constituents from Umbelliferae plants. V. A new furanocoumarin and falcarindiol furanocoumarin ethers from the root of Angelica japonica. *Chem. Pharm. Bull.* **1999**, *47*, 96–100. [CrossRef]
219. Ahn, B.-Z.; Kim, S.-I. Relation between structure and cytotoxic activity of panaxydol analogs Analogen against L1210 cells. *Arch. Pharm.* **1988**, *321*, 61–63. [CrossRef]
220. Matsunaga, H.; Katano, M.; Yamamoto, H.; Mori, M.; Takata, K. Isolation, determination and antitumor activity. *Chem. Pharm. Bull.* **1989**, *37*, 1279–1281. [CrossRef]
221. Matsunaga, H.; Katano, M.; Yamamoto, H.; Fujito, H.; Mori, M.; Takata, K. Cytotoxic activity of polyacetylene compounds in *Panax ginseng* C. A. Meyer. *Chem. Pharm. Bull.* **1990**, *38*, 3480–3482. [CrossRef]

222. Cherng, J.-M.; Shieh, D.-E.; Chiang, W.; Chang, M.-Y.; Chiang, L. Chemopreventive Effects of Minor Dietary Constituents in Common Foods on Human Cancer Cells. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 1500–1504. [CrossRef] [PubMed]
223. Vo, F.V.; Guthrie, N.; Chambers, A.F.; Carroll, K.K. Inhibition of proliferation of estrogen receptorpositive MCF-7 human breast cancer cells by flavonoids in the presence and absence of excess estrogen. *Cancer Lett.* **1997**, *112*, 127–133.
224. Hirano, T.; Gotoh, M.; Oka, K. Natural flavonoids and lignans are potent cytostatic agents against human leukemic HL-60 cells. *Life Sci.* **1994**, *55*, 1061–1069. [CrossRef]
225. Matsuzuki, Y.; Kurokawa, N.; Terai, S.; Matsumura, Y.; Kobayashi, N.; Okita, K. Cell death induced by baicalein in human hepatocellular carcinoma cell lines. *Jpn. J. Cancer Res.* **1996**, *87*, 170–177. [CrossRef] [PubMed]
226. Choi, S.U.; Ryu, S.Y.; Yoon, S.K.; Jung, N.P.; Park, S.H.; Kim, K.H.; Choi, E.J.; Lee, C.O. Effects of flavonoids on the growth and cell cycle of cancer cells. *Anticancer Res.* **1999**, *19*, 5229–5233. [PubMed]
227. Ikemoto, S.; Sugimura, K.; Yoshida, N.; Yasumoto, R.; Wada, S.; Yamamoto, K.; Kishimoto, T. Antitumor effects of *Scutellariae radix* and its components baicalein, baicalin, and wogonin on bladder cancer cell lines. *Urology* **2000**, *55*, 951–955. [CrossRef]
228. Motoo, Y.; Sawabu, N. Antitumor effects of saikosaponins, baicalin and baicalein on human hepatoma cell lines. *Cancer Lett.* **1994**, *86*, 91–95. [CrossRef]
229. Pettit, G.R.; Hoard, M.S.; Doubek, D.L.; Schmidt, J.M.; Pettit, R.K.; Tackett, L.P.; Chapuis, J.C. Antineoplastic agents 338. The cancer cell growth inhibitory constituents of *Terminalia arjuna* (Combretaceae). *J. Ethnopharmacol.* **1996**, *53*, 57–63. [CrossRef]
230. Al-Howiriny, T.; Alsheikh, A.; Aiqasoumi, S.; Al-Yahya, M.; El Tahir, K.; Rafatullah, S. Gastric antiulcer, antisecretory and cytoprotective properties of celery (*Apium graveolens*) in rats. *Pharmaceut. Biol.* **2010**, *48*, 786–793. [CrossRef]
231. Azimi, M.; Zahedi, M.J.; Mehrabani, M.; Tajadini, H.; Zolala, F.; Baneshi, M.R.; Choopani, R.; Sharififar, F.; Asadipour, A.; Hayatbakhsh, M.M.; et al. Effect of *Apium graveolens* and *Trachyspermum copticom* on clinical symptoms of patients with functional dyspepsia. *Avicenna J. Phytomed.* **2017**, *7*, 554–564.
232. Tafreshi, A.P.; Ahmadi, A.; Ghaffarpur, M.; Mostafavi, H.; Rezaeizadeh, H.; Minaie, B.; Faghihzadeh, S.; Naseri, M. An Iranian herbal-marine medicine, MS14, ameliorates experimental allergic encephalomyelitis. *Phytother. Res.* **2008**, *22*, 1083–1086. [CrossRef] [PubMed]
233. Ahmadi, A.; Habibi, G.; Farrokhnia, M. MS14, an Iranian herbal-marine compounds for the treatment of multiple sclerosis. *Chin. J. Integr. Med.* **2010**, *16*, 270–271. [CrossRef] [PubMed]
234. Tourkostani, R.; Balouni, I.A.; Moselhy, S.S.; Kumosani, T.A. A diet rich fiber improves lipid profile in rats fed on high fat diet. *Turk. J. Biochem.* **2009**, *34*, 105–111.
235. Iyer, D.; Patil, U.K. Effect of chloroform and aqueous basic fraction of ethanolic extract from Apium graveolens L. in experimentally-induced hyperlipidemia in rats. *J. Complement. Integr. Med.* **2011**. [CrossRef] [PubMed]
236. Mahdian, D.; Hosseinzadeh, H. Medicinal plants in treatment of hypertriglyceridemia: A review based on their mechanisms and effectiveness. *Phytomedicine* **2018**. [CrossRef]