sustainability

Review

Sustainable Approaches for Biodiversity and Bioprospecting of Citrus

Sony Kumari [1,*], Rony Bhowal [1] and Penna Suprasanna [2,*]

[1] Department of Applied Biology, School of Biological Sciences, University of Science and Technology, Baridua 793101, India
[2] Amity Institute of Biotechnology, Amity University of Maharashtra (AUM), Mumbai 410206, India
* Correspondence: sonykumari_15@yahoo.com (S.K.); penna888@yahoo.com (P.S.)

Abstract: Citrus, belonging to the *Rutaceae* family, is a commercial fruit worldwide, and it is mainly recognized for its nutritional, anti-oxidant, and significant medicinal properties. Citruses are a group of multifaceted fruit crops with a rich traditional knowledge, deeply rooted in ethnic culture, and the fruits have been considered to be health-protecting and health-promoting food supplements since ancient times. The presence of secondary metabolites and their bioactivities has led to the development of new alternative drugs in recent years. Diverse secondary metabolites such as flavonoids, alkaloids, carotenoids, phenolic acids, and essential oils and their high bioactive properties have imparted great value to human health based on their anti-oxidative, anti-inflammatory, anti-cancer, cardiovascular protective, and neuroprotective effects. The indigenous Citrus species of India—mainly Northeast India—have distinctive and valuable genetic traits, such as resistance to biotic and abiotic stress, distinctive aroma, flavor, etc. Hence, these species are considered to be repertoires of valuable genes for molecular breeding aimed at quality improvement. There is a need for awareness and understanding among the citrus-producing countries of the exploitation of biodiversity and the conservation of Citrus for sustainable development and bioprospecting. The current review presents a holistic view of Citrus biodiversity from a global perspective, including phytochemical constituents and health benefits. Advanced biotechnological and genomic approaches for Citrus trait improvement have also been discussed to highlight their relevance in Citrus improvement.

Keywords: citrus; origin; biodiversity; production; functional food; anti-oxidants; post-harvest; quality preservation; mutation breeding; polyploidy; somatic hybridization; transgenesis; genomic editing

Citation: Kumari, S.; Bhowal, R.; Suprasanna, P. Sustainable Approaches for Biodiversity and Bioprospecting of Citrus. *Sustainability* **2023**, *15*, 7731. https://doi.org/10.3390/su15097731

Academic Editor: Pablo Peri

Received: 25 March 2023
Revised: 24 April 2023
Accepted: 25 April 2023
Published: 8 May 2023

1. Introduction

Citruses are among the top fruits in the world, with increasing demand in the international market. They belong to the family *Rutaceae*, and almost all plants of the family have a characteristic aroma from their leaves, aerial shoots, or fruits. Of all fruits, Citrus fruits are among the foremost in the global agroeconomy as both regular foods and food supplements, either fresh or as processed products. Citruses are the fourth most produced crop in the world, with 158,490,986 tonnes produced in the year 2020 [1]. The usefulness of Citrus as a health-protecting and health-promoting food supplement has been known since ancient times, as is evident from its references in sources of traditional knowledge. The traditional wisdom on the benefits of Citrus has been provided by several researchers with respect to various topics such as nutrition, anti-oxidants, and many other bioproperties. While the cultivation of other important fruit crops, such as apple, grape, banana, mango, etc., is restricted to specific climatic and geographical conditions, Citrus has wide adaptability. Unlike other major fruit crops, Citrus has wide genetic diversity (Figure 1), offering an enormous scope of contributions to human health and nutrition.

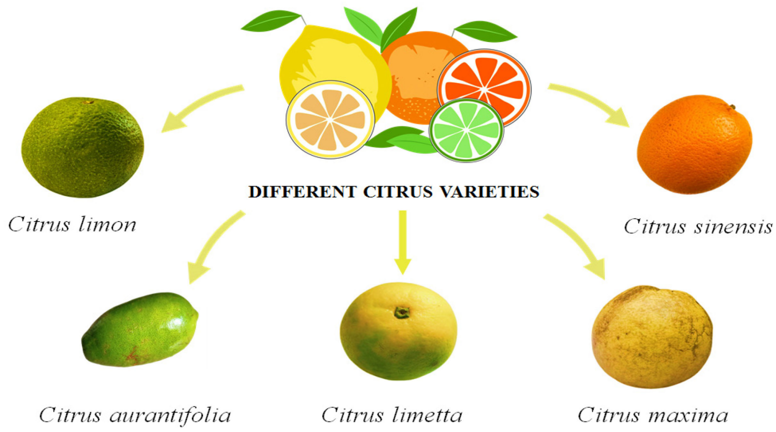

Figure 1. Some *Citrus* species of India [2].

Citruses are evergreen shrubs or small or occasionally medium trees. The leaves are entire, lanceolate in shape, thick, and dark green. Almost all citruses emit a characteristic odor from their leaves, flowers, and fruits. There are approximately 160 genera belonging to the family *Rutaceae*, and Citrus is the most important genus from an economic perspective. There are several systems of Citrus classification which vary widely; the Swingle and Reece (1967) and Tanaka (1977) classification systems are accepted widely, which differentiate based on the number of recognized species [3,4]. Barrett and Rhodes (1967) [5] reported that the true species of Citrus are: Citron (*C. medica* L.), mandarin (*C. reticulata* Blanco.), and pummelo (*C. maxima* (L.) Osbeck). In addition, *C. halimi* was reported as another species [6]. The cultivated species were derived mainly by hybridization between the true species, or closely related genera, followed by natural selection.

The two distinct sub-genera (Eucitrus and Papeda) are well recognized and differ with respect to the morphological features of leaf, flower, and fruit. Sub-genus Eucitrus is the most commercially important and edible species, characterized by a sweet, sub-acidic, sour juice with a pleasant aroma and flavor, free from droplets of oil. On the other hand, the sub-genus Papeda has species whose fruits are not edible and hence are of no economic value except for local uses in ethnic medicine. The fruits of the Papeda sub-genus have pulp vesicles with dense aggregations of droplets of acrid oil that form axile columns, and their juices have a disagreeable, acrid, bitter flavor.

2. Citrus Origin and Domestication

The Citrus term is originated from 'Kedros', a Greek term which denotes trees such as cidar, pine, and cypress. Linnaeus grouped all such fruits under the genus Citrus. It is believed that different groups of Citrus and related genera originated in multiple locations. For instance, *Citrus sinensis* is considered to have its origin in China, whereas Citron (*Citrus medica*) is known to have originated in Indonesia's archipelago and North India [7]. Many Citrus fruits or their progenitors had their origin in northeast India [2], and *Citrus indica* is the most primitive and probable ancestor of the other Citrus species [8]. This observation was based on the discovery of *Citrus indica* in wild condition in forests of Nagaon district (Assam), Meghalaya, and Manipur in India. *Citrus jambhiri* is known to occur in wild conditions in the Siang river basin of Arunachal Pradesh [9].

Citruses and their relatives have their point of the origin in different regions of Asia and Australia [10]. The contribution of Swingle in the origin and diversification of Citrus is considered the main clue for the recognition of new Citrus varieties. Six species of Citrus were recognized; two were native to Papua New Guinea and four were native to Australia [3]. Eremocitrus genus (*E. glauca*) is native to the New South Wales and Queensland deserts (Australia). The Clymenia genus (*C. polyandra*) originated in the Papua New Guinea. Poncirus genus, with deciduous leaves, has its origin in northern China and is tolerant to freezing temperatures (resisting up to −20 °C). Papeda group includes species from different origins; *Citrus micrantha* (Southern islands of the Philippines), *C. latipes* (Northeast India), *C. macroptera* (New Caledonia), *C. celebica* (Indonesian islands), and *C. hystrix* (could be from the Philippines) [3].

A new species, namely, Poncirus (*P. polyandra*), was recognized, showing the properties of tolerating low temperatures, immunity against *Citrus tristeza*, and resistance to *Phytophthora* spp. [11]. It is directly used or crossed with other Citrus species to produce rootstocks for Citrus cultivation. The Citrus species is assumed to be derived from a large area in southeast Asia, probably mountainous regions of southern China and northeast India [12]; it was believed that Yunnan Province could be the origin due to its vast diversity of citruses, and the primary center of origin for the Citrus [13]. Several Citrus species, such as *C. medica*, *C. limon*, *C. aurantifolia*, *C. maxima*, *C. aurantium*, and *C. sinensis*, originated in the south due to a theoretical dividing line running from the northwestern border of India, above Burma, to the Yunnan province of China and then to the south of the island of Hainan [14]. Moreover, *C. reticulata* and other citruses originated north of it. Northeast (NE) India and the Malay and East Indian Archipelago are the origin of Citrons and pummelos [15]. The different types of citruses and their f origins are summarized in Table 1. The broad view of the world-wide origin of Citrus is presented in Figure 2. This covers the various species of Citrus that originated in different locations of the globe, from which they were then migrated and domesticated.

Table 1. Origin of *Citrus* species [7].

Species	**Common Name**	**Center of Origin**
Citrus reticulata Blanco.	Mandarin Orange	Philippines or Cochin China/Secondary center Japan
Citrus sinensis Pers.	Sweet Orange	China/Cochin China
Citrus macroptera Montr.	Satkara	Northeast Region of India
Citrus jambhiri Lush.	Rough Lemon	Possibly India
Citrus indica Tanaka	Indian Wild Orange (Memang Narang)	Northeast Region of India
Citrus limetta Lush.	Sarbati Lime	Tropical Asia
Citrus limon (L.) Burm.	Assam Lemon	East of Himalaya, North Myanmar, South China
Citrus medico L.	Citron	Indonesian Archipelago/North India
Citrus aurantifolia (Christm.) Swingle	Kagzi Lime	Indonesian Archipelago/North India
Citrus karna Raffin.	Karna Khatta	Eastern Region of India
Citrus aurantium L.	Sour Orange	Asia/Cochin China
Citrus megaloxycarpa Lush.	Sishuphal (Bartenga)	Northeast Region of India
Citrus grandis (L.) Osbeck	Pummelo	South East Asia
Citrus ichangensis Swingle	Ichang	Southwest, Central, Western China
Citrus assamensis Dutta and Bhatacharya	Ada Jamir	Northeast Region of India
Citrus latipes (Swingle) Tanaka	Khasi Papeda	Hills of Meghalaya and Nagaland
Citrus limonia Osbeck	Rangpur Lime	India and Sri Lanka

The domestication of plants is the inherited custom of human nature. More than 1500 crops have been domesticated in the past [16]. The domestication of Citrus began independently in different parts of the world. The domestication of Citrus proceeded via the same trend as other plants, i.e., it took place in wild conditions before the domestication by humans began [17]. Interestingly, the currently available commercial varieties are mostly admixtures, which include oranges or lemons, cultivated back around two thousand years by the Romans. Evidence proves that the early cultivation of citron started in India, and of mandarins and other Citrus species, possibly in China. In Yunnan, wide Citrus diversity was observed [15] and in modern citriculture, crossbreeding varieties can partially recover the ancestral phenotypes of the introgressed genomes [18]. The migration of Citrus species via various other means is also a vital contributor to the diversity and domestication of different Citrus varieties. The development of early grafting techniques, such as revealed through the apomictic nature of some Citrus varieties, allowed for the rapid fixation of the genotypes [19]. This was because of the generation of seed clonal individuals, which explains the apomictic nature of commercial Citrus found at the current time [20].

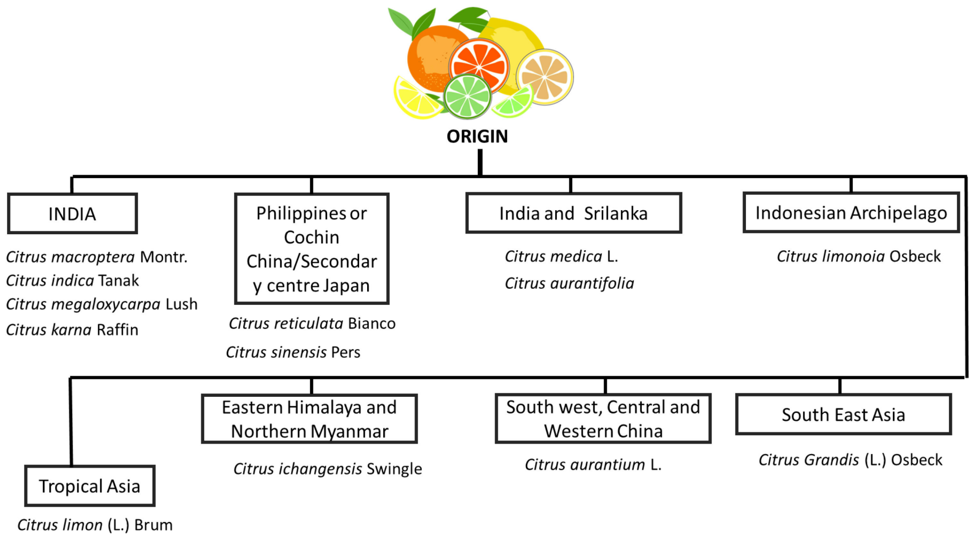

Figure 2. Origin of *Citrus* species [10].

3. Biodiversity

In general, the most marketed varieties worldwide are lemon, orange, mandarin, and grapefruit. Despite being the most crucial horticultural product due to their high level of hybridization during the domestication process, the recent taxonomic classification of Citrus remained unclear and unexplored. Because of its wide adaptability, Citrus rapidly spread and diversified in different parts of the world, though mainly in the West. As per the ancient records of Theophrastus, Citrus reached the Mediterranean region of Europe as early as 310 BC [21]. After dispersal, diversification occurred in the new localities. For instance, some genera of Aurantioideae viz. Afraegle, Aeglopsis, Balsamocitrus, and Citropsisare are native to tropical Africa, while genera such as Microcitrus, and Eremacitrus are native to Australia [22]. Hence, the overall origin of the Citrus genus is Southeast Asia, including South China, Northeast India, Burma. Most commercial cultivation of Citrus is undertaken through vegetative means to maintain quality and genetic uniformity. Moreover, Citrus is propagated through cutting and begins flowering and fruiting early. Citrus plants freely cross between genera, even among those that are closely related to one another. As a result, the plants are extremely heterozygous, and the hybrids created by inter- or intraspecific crosses show a significant amount of variation [23]. Another unique feature of Citrus is polyembryony, i.e., the formation of several embryos in the same seed. Pollination triggers embryo development from nucellar tissue apart from the normal zygotic embryo [24]. Nucellar embryos are more vigorous and have enormous significance in breeding and cultivation since such seedlings can be used as rootstock, which provides robust growth apart from retaining the original genetic complement. Some species of Citrus, such as Pummelo, Tangelo, and Clementine varieties of mandarin, are known to be mono-embryonic [15]. Other mono-embryonic Citrus types include *Citrus indica*, *C. japonica*, *C. maxima*, and *C. medica*. Because of polyembryony, monoembryony, and intercrossing, gene complement in Citrus is highly variable, and very often the distinction between varieties and species becomes blurred. Due to this, diversity assessment in Citrus is complex.

In one of the old records in Northeast (NE) India, there are 17 species and 52 varieties, and 6 probable hybrids [2]; in another report, 17 species and 52 varieties were found [25]. As per exhaustive account, there are 23 species and 68 varieties [26]; *C. macroptera*, *C. juko*, and *C. serotina* belong to the Papeda sub-genus. In NE India, many of the lesser-known citruses are grown and maintained as backyard crops in household gardens. This traditional practice contributes to the conservation of the species. Most Citrus is diploid with chromosome number 2n = 18. It has been found that the chromosome number of different Citrus species, and accordingly, species such as *C. macroptera*, *C. limetta*, *C. karna*, *C. aurantium*, *C. ichengensis*, and *C. assamensis*, are diploid [27]. However, some species have different ploidy levels, such as *C. reticulata* (18, 36; diploid and tetraploid, respectively), *C. sinensis* (18, 27, 36; diplod, triploid, and tetraploid, respectively), *C. limon* (18, 36), *C. medica* (18, 27), *C. aurantifolia* (18, 27), *C. grandis* (18, 36), and *C. limonia* (18, 27, 36). Citruses of the NE region comprise six groups and the citruses of NE India were classified as mandarin, orange, pummelo-grapefruit, acid, papeda, and other minor citruses [7]. The indigenous Citrus species of this region have distinctive and valuable genetic traits such as resistance to biotic and abiotic stress, distinctive aroma, flavor, etc. Hence, they can be considered genetic sources of useful traits for molecular and conventional breeding, as show in Table 2.

Table 2. Useful traits of various *Citrus* species of Northeastern Region, India [26].

Character	Adaptation	Species	Variety
Abiotic	Moisture stress and low fertility.	*C. medica*	Mithajora, soh-manong
	Humid Tropics (very high rainfall)	*C. assamensis*	Ada jamir
	Drought resistance	*C. jambhiri*	Soh-myndong
	Wide adaptability for various types of soils and climates	*C. medica f. limon*	Patilebu
	Water logging and low lying condition	*C. medica f. limon*	Godha patilebu
	Stress conditions of soil and climate	*C. aurantium*	Karun-jamir
	High cold resistance	*C. ichangensis*, *C. laptis*	Ketsa-shuphu
Biotic	Resistance to greening, tolerant to psoriasis and exocortis virus	*C. macroptera*	Tith Kera
	Resistance ton scab, canker, and gummosis	*C. limon*	Assam lemon
	Resistance to greening disease	*C. indica*, *C. laptis*	
Special character	Flavor like ginger of Eucalyptus	*C. assamensis*	Ada jamir
	Flavor like cardamom and more juicy	*C. medica f. limon* *C. macroptera*	Patilebu, Panijamir, Joratenga, Elachi-lebu Satkara
	Prolific bearing	*C. medica f. limon* *C. reticulata*	Kata-jamir, Soh-synteng, Soh-kompriak, Soh-sanikar
	Superior quality albedo (rind)	*C. medica*	Bira-jora
	Fruit quality superior for preparing pickles, chutney, and squash	*C. medica f. aurantifolia*, *C. auruntium*	Abhayapuri lime, Godha-huntera

The domestication and diversification of Citrus reflects the status of Citrus and of the hybrids of various Citrus pure varieties (Figure 3). *C. aurantium* is a product of the natural hybridization of *C. maxima* and *C. reticulata*; in contrast, *C. sinensis* which is a second or third-generation product, is a direct hybrid or backcross between the ancestral taxa, i.e., (*C. maxima* × *C. reticulata*) × *C. maxima* [28]. *C. clementina* is a chance seedling hybrid (*C. deliciosa* × *C. sinensis*), discovered at end of the 19th century in Messerghin [27,29]. The genome is thus an admixture of *C. reticulata* and *C. maxima*; *C. limon* and *C. aurantifolia* are direct hybridization products of *C. aurantium* and *C. medica* and *C. medica* and *C. micrantha*, respectively [30]. New Caledonian and Kaghzi limes have an origin from F2 (*C. micrantha* × *C. medica*) × (*C. micrantha* × *C. medica*). Tahiti limes (seedless), *C. latifolia* (Bearss or IAC), are triploid hybrids of *C. aurantifolia* (diploid pollen) and *C. limon* (haploid ovule). Tanepao, Coppenrath, Ambilobe, and Mohtasseb limes, as well as triploid seedy limes and the Madagascar lemon, have evolved by hybridization of (*C. micrantha* × *C. medica*) × *C. medica* with a diploid gamete from the *C. micrantha* × *C. medica*.

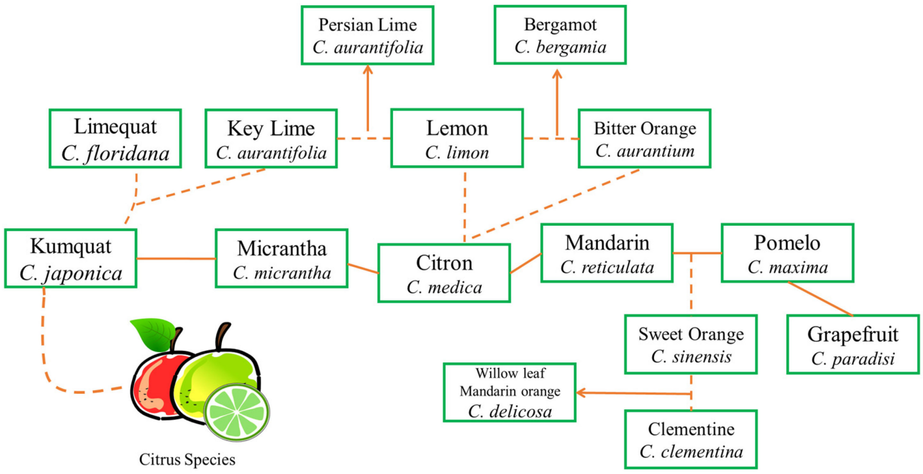

Figure 3. Diversification of *Citrus* species [17].

Due to their independence from external influences, molecular markers such as SSR, SNP, and InDels [31] have greater advantages than phenotypic markers. InDel markers were discovered in a number of Citrus species [32]. It is difficult to assess how these genetic markers relate to physical and chemical characteristics [33]; hence, these markers might not explain variations in flavor profiles. In a recent study, a neighbor-joining method served to explain the diversity of Citrus. As ancestral species, citrus, mandarin, and pummelo represented a diversity pole; nonetheless, interspecific hybrids were found in close proximity [34]. Mosambi and Qicheng, Chanh Giay and Ma Nao Pan and Dalandan mandarins were shown to have close relationships; nevertheless, Pontianak and Nagpur were discovered to be intermediates to mandarins and pummelos. Based on SSR markers, Nagpur was previously described as a mandarin hybrid [35]. SSR [36], SRAP, and ISSR [37] were reported to exhibit low levels of polymorphism in oranges. Similarly, many hybrid accessions from mandarin × mandarin, mandarin × pummelo, or mandarin × tangelo have also been documented in mandarin data [38]. Citrons, rough lemons, and *C. volkameriana* were among the 56 accessions analyzed in citron using SRAP and SSR markers. The similarity levels were 0.70 (for citrons compared to other accessions) [39], 0.65 (for citrons and rough lemons) [40], 0.80 (for lemons and rough lemons compared to *C. volkameriana)* [39], and 0.79 (pummelo and grapefruit by ISSR) [41]. These studies highlight that genetic markers could be highly useful for the analysis of genetic variability among the Citrus varieties.

4. Production and Challenges

Currently, more than 140 countries in the world grow Citrus, and about 70% of the global Citrus production comes from the Northern Hemisphere, particularly Brazil, the US, and countries around the Mediterranean region. Brazil is the world's leading Citrus growing country, followed by China, with a contribution of 18.1% and 17.2% to world production, respectively [42]. Citrus grows well in diverse soil conditions (sandy loam, alluvial soils, clay loam, deep clay loam, or lateritic/acidic soils) and temperature (13 °C to 37 °C). Unlike most other cultivated plants, Citrus species can grow in both acidic and alkaline soils with a pH from 4.0 to 8.0 (optimum range); however, deep soil with pH in the range of 5.5 to 7.5 is most suitable. About 10% of total Citrus production is exported as fresh fruit, of which 62% of the total exports occur in the Northern Hemisphere Mediterranean region [43].

Among all countries, Brazil is leading the world as the top producer of orange and orange juice, followed by China as a tangerines/mandarins and grapefruit producer, and Mexico as a lemons and limes producer (Table 3). The trend of the Citrus market value over the period from 2012 to 2021 showed that average annual value increased at a rate of +3.6%. Out of the total Citrus production in the world (4.43 million tons), India accounts for 4.69%, occupying 0.37 million hectares. Mandarins, sweet oranges, lime, lemons, pummelo, and grape fruit are important. In a recent estimate, the production of Citrus fruits in India has been recorded as 13,200,000 MT/1,034,000 Ha [44], which highlights the production of citruses such as lime/lemon, mandarin, sweet orange, etc. Citrus production ranks third (12.5%) after banana (33.4%) and mango (20.7%) in India [45]. Citrus grows under varied agroecological conditions, from arid and semi-arid areas to the humid tropical conditions of the Northeast India. Species such as *C. ichangensis*, *C. latipes*, *C. indica*, and *C. macroptera* grow in the hilly terrain at altitudes of 1000 to 2700 m, while some species are adapted to submontane tracts at altitudes of 70 m to 1000 m [7].

Table 3. Composition of Citrus fruits [46].

Species	Local Name	Peel (%)	Juice (mL)	Marc (%)	Seed (%)
C. aurantifilia	Lime	20–30	45–48	21–34	0–1
C. aurantium	Bitter orange	27–46	27–37	23–31	5–7
C. grandis	Pummelo	23–24	175	25–37	3–4
C. limon	Lemon	13–24	23–95	13–38	5–7
C. paradisi	Grapefruit	25–39	32–48	18–36	0–3
C. reticulata	Mandarin	35	50%	13	2
C. sinensis	Sweet orange	13–49	25–215	18–41	0–3

The growth of Citrus plants and adaptation is within a wide range of environmental growth conditions. Proper site selection, soil type, irrigation type, water type, pest management, harvesting, marketing, etc., are the key steps involved in Citrus yield and production rate [47]. Agronomic challenges include soil cover system, pest and disease-management, supply of nutrients and organic fertilization, water-management and irrigation, and pruning. The economic challenges involve additional labor-investments, production inputs, production cost yields, know-how, and motivation. In addition, Citrus production is challenged by other external factors which affect plant growth yield and production [48]. For example, temperature, which is the main component of climate, determines Citrus growth and yield. Citrus is an important agricultural and horticultural product of India which provides value addition to economy. Abbas et al. [49] pointed out that the control of the diseases in Citrus can enhance production and thus contribute to achieving health security to manage COVID-19. There is a need to have optimum conditions for Citrus growth to enhance Citrus quality and production.

5. Health Benefits of Citrus

The history of fruits and vegetables is older than human civilization. In the prehistoric ages, human ancestors were hunter-gatherers, and in the course of their migration, their targets forest areas rich in fruit trees and other edible plants, as well as an abundance of animals for hunting. Fruits were possibly the first plant-based food that early man discovered by chance or trial and error in the remote historical past when human evolution was still in progress. Nutraceuticals are such foodstuffs, which, as well as from providing a reasonable amount of calories, also provide sufficient micronutrients and phytochemicals that function as preventive medicine and ward off diseases.

5.1. Chemical Profile

Citrus fruits are a precious resource of secondary metabolites and bioactive compounds. They are beneficial for human health as they can work not only against heart-related diseases, and in treatment of hypertension, but also, as anti-cancerous, anti-inflammation, anti-viral, anti-bacterial, and anti-fungal agents [50]. The enzymes found in Citrus juices act as a remedy for controlling obesity. According to a report, phytochemicals are the natural component found in citrus, mainly in juice, and they play an important role in internal body mechanism, including physiological functions and metabolic changes in the human body [51], as well as in combatting chronic diseases [52] and helping to lower cholesterol, which is useful for diabetes patients [53]. The major chemical composition of Citrus fruits is represented in Figure 4, while, protein (g), fat (g), fibre (g), and minerals (g) are 0.98, 0.47, 0.63, and 0.47, respectively.

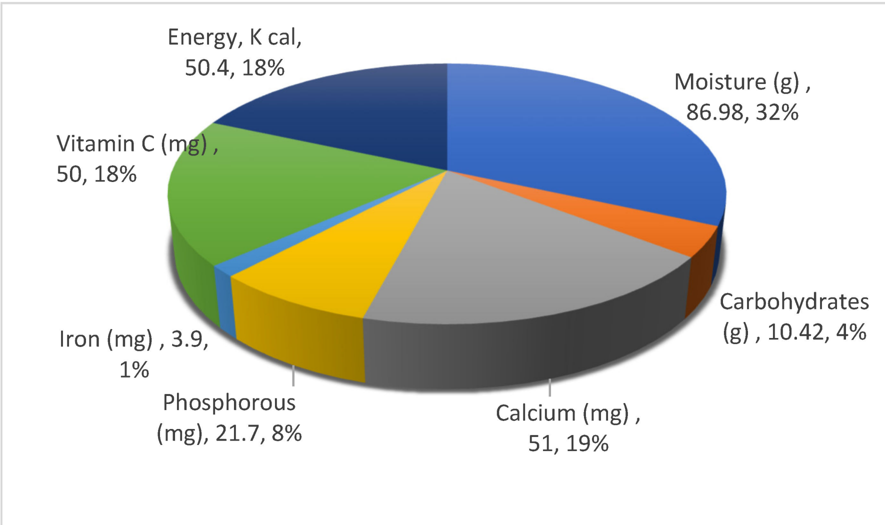

Figure 4. Chemical composition of Citrus (average of different Citrus varieties, content per 100 gm of edible fruit portion) [46].

5.2. Citrus Nutrition and Health Benefits

The fruits are a rich source of phytochemicals and anti-oxidants. The chemical constituents in Citrus perform biological activities conducive to maintaining good health. Table 3 represents the composition of Citrus fruits. The main benefits are anti-carcinogenic [54], cardiovascular [55], hyperglycemia [56], anti-inflammatory, anti-allergic, and analgesic activity [57], anti-microbial activity [53], anti-anxiety, and anti-depressant properties, as well as anti-allergic activity [58] and lipid control [59].

5.3. Citrus Anti-Oxidants: Functional Food Perspective

Citrus fruits are among of the most important global fruits with respect to the maintenance of good health due to the presence of health-related elements and valuable components. The phytochemicals are limonoids, phenolic acids, vitamins, carotenoids, pectins, and fatty acids [60], and the presence of carotenoids, flavonoids, terpenes, limonoids, and many other bioactive compounds provide nutritional and nutraceutical value in Citrus fruits [61]. Phytochemicals can be consumed through fresh fruits or their derived products and have been found to have a wide variety of important biological activities ranging from anti-oxidant, anti-inflammation, anti-mutagenicity, anti-carcinogenicity, and anti-aging activities. The importance of Citrus phytochemicals indicates that the phytochemicals of Citrus have a nutritive value and that they also help in fighting against many disease-causing microorganisms [62]. In addition, phytochemicals provide a pleasant aroma and vibrant color to Citrus fruits. To have a comprehensive idea of the anti-oxidant activity of

Citrus fruits, studies on important chemical components and their role as anti-oxidants are important (see Table 4).

Table 4. Anti-oxidant metabolites and their role found in Citrus.

Compound	Role	References
Flavanones (hesperidin and naringin)	The intestinal fate, bioavailability, intestinal metabolism, and interaction with the gut microbiota	[63]
Flavones	Sources, anti-oxidant, anti-inflammatory, anti-microbial, anti-cancer properties	[64]
Flavonoids	Brain health, minimizing the incidence of inflammatory bowel disease, anti-diabetic potential of 19 Citrus flavonoids, potential in diabetes and diabetic cardiomyopathy, endothelial dysfunction, atherosclerosis, and platelet function	[65–67]
Hesperidin and vitamin C	Antiviral properties against acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	[68]
Naringenin	Antidiabetic properties; combating oxidative stress disorders: cardiovascular disease, diabetes mellitus, neurodegenerative disease, pulmonary disease, cancer, and nephropathy	[69,70]
Nobiletin	Beneficial effects against Alzheimer's disease (AD) and Parkinson's disease (PD)	[71]
Nobiletin,5-demethylnobiletin, and derivatives	Beneficial effects against colon cancer, pharmacokinetics, and bioavailability	[72]
Polymethoxyflavones (PMF)	Biological properties against metabolic disorder, atherosclerosis, inflammation, neuroinflammation, cancer, and oxidation	[73]

Whole fruit, peel, seed, and juice of Citrus are important sources of metabolites, including anti-oxidants such as vitamin C, flavonoids, phenolics, and pectins protecting against free radicals, which are important for human health [74]. Consumption of natural products contributes to reducing the risk of diseases such as metabolic syndrome, neurodegenerative diseases, cardiovascular syndrome, diabetes, cancer, etc. [75]. All of the citrus plant parts contribute to nutritional and nutraceutical properties, as well as anti-microbial, anti-cancer, anti-inflammatory, anti-allergy, and cardiovascular properties (Table 4). Citrus fruit is used and consumed all over the world due to the presence of pharmacological components, for its taste, and also for other health beneficial properties [76]. It is a rich source of alkaloids, coumarins, limonoids, phenols, carotenoides, flavonoids, and other essential oils [77]. This indicates that the phytochemicals in Citrus have great scope for health and pharmaceutical sectors. Citrus fruits are a reservoir and natural source of anti-oxidants, which protect the cells from oxidative stress and damage by neutralizing the free radicals (Figure 5). The bioactive compounds of Citrus play a crucial role in maintaining the immune system and minimizing the risk of various health illnesses.

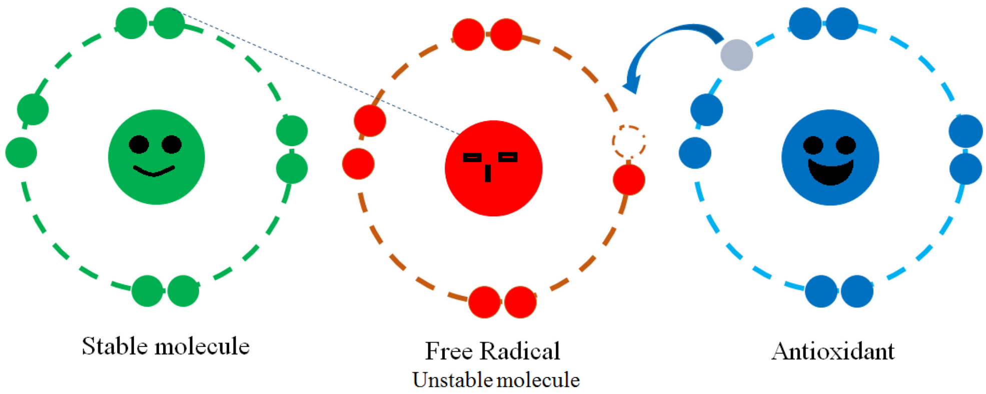

Figure 5. Illustration of the action of Citrus anti-oxidant on free radicals [74].

5.4. Toxicity and Safety Profile of Citrus Metabolites

The effect of Citrus consumption has been studied by using various experimental models, and the toxicity level of Citrus has been determined. Citrus-derived bioactive compounds have been used in various toxicological studies and have been found to show a comparably good safety profile. In a study of toxicity in rats, it was reported that hesperidin from *C. sinensis* peel didn't show any toxicity, similar to flavonoids (nobiletin, tangeretin, and naringin) that have shown a good safety profile [54].

5.5. Medicinal Properties of Citrus

Citrus fruits have several bioactive chemicals that can shield the body from a variety of ailments and, as a result, demonstrate positive effects on health. The medicinal properties of Citrus, including anti-microbial, anti-oxidant, anti-cancer, anti-diabetic properties, are represented in Figure 6.

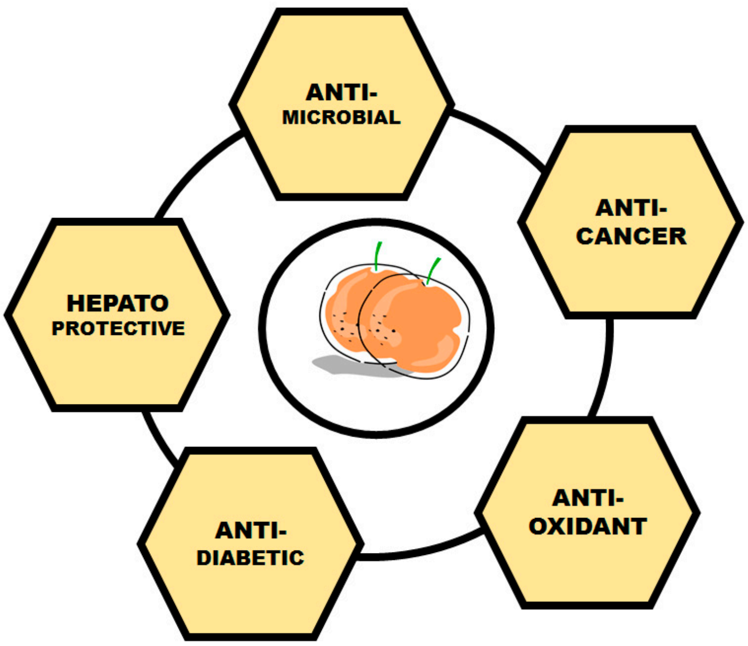

Figure 6. Medicinal properties of Citrus [78].

5.5.1. Anti-Microbial Properties

Microorganisms are the main cause of infection and disease in human beings. The resistance of bacteria against anti-bacterial drugs is the current challenge of globe. Different synthetic chemicals and drugs have been tried as anti-bacterial agents; however, these have side effects. On the other hand, there are several natural phytochemicals with good anti-microbial property and the potential to replace the synthetic drugs. Studies on the search for new natural anti-microbial compounds in plant species are underway [78], and, in this regard, Citrus could be a good example of a plant-based treatment containing anti-microbial and anti-bacterial compounds. Many experiments have validated the activity of Citrus against different pathogenic and non-pathogenic bacteria. Lemon peel extracts have also shown a significant anti-bacterial property [79]. The anti-bacterial property of ethanol and aqueous extracts of Citrus peel has also been reported. The bioactive compounds and extracted oils of Citrus have shown a high anti-fungal property [54]. Essential oils extracted from different varieties of Citrus such as orange, lemon, mandarin, and grapefruit have shown anti-fungal activities against *Aspergillus niger*, *A. flavus*, *Penicillium chrysogenum*, and *P. verrucosum* [80]. The study in *Citrus sinensis* oil was performed to check the hyphal cell wall and diameter characteristics of fungus. It has been reported that oil application reduced the hyphal diameter and hyphal cell wall. The inhibition of conidiophores was also seen [81].

5.5.2. Anti-Cancer Property

Cancer is a dreadful disease which is life threatening, and the condition is characterized by uncontrolled division and proliferation of cells invading nearby cells and tissues. It is a multistep process as it alters the genetic makeup of individual cells, making the normal cells into abnormal cells, which drives the transformation into malignancy [82]. The technique mostly used to treat cancer at the early stage is chemotherapy, but the treatment may cause side effects on normal cells and sometimes fails to control the tumor condition. The best alternative is the use of natural products, which are the sources of bioactive compounds responsible for positive health benefits [83]. Citrus natural products might function as anti-cancer agents since individual components of Citrus, such as vitamins, hesperidin, naringin, tangeritin, limonene, quercetin, tangeretin, nobiliten, etc., all contribute to the anti-cancer property of Citrus [84].

5.5.3. Anti-Oxidant Property

Citrus phytochemicals have the ability to scavenge for the free radicals, thus acting as natural anti-oxidants. Flavonoids, phenols, vitamins, etc., contribute to reducing stress and ageing. Various methodologies are employed to check the anti-oxidant capacity of different parts of Citrus fruits and the common and popular technique employed is the DPPH assay. In a study conducted to assess the DPPH scavenging activity of *Citrus macroptera* peel, the IC50 values were recorded as 87.83 ± 0.012, 237.95 ± 0.005, and 276.11 ± 0.101 µg/mg for aqueous extract, methanol, and aqueous extract, respectively [85]. The nitric oxide scavenging activity also showed a significant IC50 value. In another study, the total flavonoid content (TFC) of *Citrus limetta* fruit peel ethanoic extract was found to be 450 ± 3.46 [86]. Similarly, the content of total phenolic in *Citrus limetta* also showed a higher activity in ethanolic extract than in aqueous extract of Citrus peel. The results revealed that not only is the type of Citrus variety important for anti-oxidant activity, but the solvent extract also.

5.5.4. Anti-Diabetic and Anti-Hypercholesterolemic Properties

The medicinal properties of Citrus also include anti-diabetic and anti-hypercholesterolemic in addition to anti-microbial and anti-oxidant properties. Hesperidin, naringin, flavanoids, vitamin C, and phenolics, the main phytochemicals in Citrus, correspond to anti-diabetic and anti-hypercholesterolemic activities [87]. Hesperidin and naringin act by reducing cholesterol and triglyceride levels by inhibiting HMG-CoA reductase and acetyl-coenzyme A acetyltransferase [88]. Such enzymatic activities have also been shown in orange, which is a source of various bio-active compounds such as hersperidin, narirutin, naringin, and eriocitrin, which are responsible for the anti-diabetic property [89]. The in vivo study of *Citrus medica* [90] and *Citrus limetta* [91] has proved to be useful in lowering blood glucose levels in mice.

5.5.5. Hepatoprotective Properties

Liver damage is the current alarming health condition in human beings. Citrus fruits are beneficial for protection against liver damage. Similar to the anti-microbial and antidiabetic properties of citrus, flavonoids such as naringin and naringenin have also been shown to have a hepatoprotective property [92]. The effect of *Citrus hystri* and *Citrus maxima* as hepatoprotective agents has been studied in albino rats. Both the varieties were found to be effective at the dose concentration of 200 mg/kg [93].

6. Citrus—Bioprospecting and Valorization

Citrus fruits are in high demand as they have several health benefits. The physical properties of Citrus provide them with attractive features; for example, they can be transported to any place worldwide. Because of the high demand, productivity has tremendously increased during the last decade. Many agrifood industries have come up with different ways of processing and preparing useful products from fruits [94]. The valorization of Citrus waste has added a new dimension to food processing industries. The main product of the Citrus industry is juice, which is enjoyed by people of all age groups. Depending upon the variety of citrus, the yield varies along with the co-product after processing. The Citrus co-products include seeds (10%), peel (60–65%), and internal tissues (30–35%) [95]. The co-products are the wastage of any vegetable or fruit juice processing. However, they are rich in bioactive compounds which contribute to several therapeutic properties. In general, the peel waste of Citrus contributes to anti-oxidant, anti-microbial, cardio-protective, anti-inflammatory, anti-diabetic, anti-cancer, and many more health-beneficial properties. It has been found that the biological activity is due to the presence of phytochemicals such as flavonoids, phenolics, vitamins, terpenes, etc., in Citrus waste [96–112]. Some of the important bioactivities of Citrus co-product (peel) are shown in Table 5.

Table 5. Bio-activity of Citrus co-product (peel).

Source	Activity	Reference
Citrus Changshan-huyou	Cardio-protective	[96]
Citrus reticulata		[97]
Citrus unshiu		[98]
Citrus grandis		[99]
Citrus lemon		[100]
Citrus reticulata	Anti-inflammatory	[101]
Citrus sinensis		[102]
Citrus grandis		[103]
Citrus lemon	Anti-diabetic	[104]
Citrus sinensis		[105]
Citrus reticulata		[106]
Citrus reticulata	Anti-cancer	[107]
Citrus reticulata		[108]
Citrus sinensis		[109]
Citrus sinensis		[110]
Citrus junos		[111]
Citrus grandis		[112]

The co-product can be mixed with other raw materials to enhance the bio-activity of the product. Hence, the post-harvest technology involves the shelf life maintenance of the fruit. In addition, the conversion of fruit and its co-product into a useful product can be health beneficial and long lasting. Post-harvest management is vital for consumer acceptance. Citrus production and its processing after harvest is a major prerequisite to increase shelf life while maintaining the quality of Citrus. The appearance of the fruit contributes the most to consumer choice. In this regard, the focus of technologists can be on the consumer preferences, product generation, sustainable packaging, presentation, and marketing.

7. Biotechnological, Mutagenesis and Genomics Approaches for Improvement

Citrus fruits are a commercial fruit worldwide and are mainly popular for their nutritional and anti-oxidant properties; hence, there are large-scale production mandates for fulfilling of the customer demand. Citriculture involves the growth and development of citrus; however, crop production and yield are affected greatly by biotic stresses such as greening, Tristeza, sudden death, canker, etc., and abiotic stresses such as temperature, salinity, drought, etc. [113]. Different approaches, such as conventional breeding, mutation breeding, somatic hybridization, etc., have been used for Citrus improvement. Further, transgenic methods, biotechnological tools, and genetic engineering play a vital role in the genetic manipulation of Citrus for quality improvement.

7.1. Mutagenesis for Induction of Novel Genetic Variability

Classical breeding involves the conventional methods of hybridization and selection, followed by the development of new varieties. Mutation breeding improves both genotypic and phenotypic traits, and has played a vital role in Citrus improvement [114]. Since 1970, 15 mutants of Citrus have been released which comprise mandarins, clementines, sweet oranges, grapefruits, and lemons with individual numbers 6, 6, 2, and 1, respectively [115]. Induced mutation by physical mutagens—for example, by gamma rays and chemical compounds acting as mutagens—enhances the induced genetic variability. Physical mutagen is more popular and 70% of the mutagenesis is by physical agents in plants [116]. The report of Usman and Fatma [117] demonstrated the mutation induction in lime and mandarin crop improvement. In different fruits and vegetables, mutation breeding applications have been evident [117]. It has been reported that also in the case of rough lemon, mutation breeding has its applications [118,119].

There are several natural and commercial breeds, out of which Washington navel and Shamouti represents superior orange mutants (Table 6). However, Marsh, Foster, and Shamber are examples of grapefruit. They originate as bud sports, but Daisy SL, Kinnow SL, Fairchild SL, and Tango are developed through mutation breeding from their seedy parents. Other than these varieties, some important and commercially significant varieties are popular for their better color and seedlessness; for example, Induced mutant Rio Red and Star Ruby. There is a great scope of advancement in Citrus breeding by exploiting modern tools such as molecular markers, Targeting Induced Local Lesions IN Genomes (TILLING), targeted mutagenesis, and CRISPR/Cas9. These technologies have the potential to produce genetically-alerted improved varieties of Citrus and to develop new Citrus varieties with novel attributes.

Table 6. Natural bud and mutation breed mutants of Citrus varieties [120].

Natural Bud Mutants	Mutation Breed Mutants
Washington navel	Daisy SL
Shamouti	Kinnow SL
Marsh	Fairchild SL
Foster	Tango
Shamber	Jin Cheng, Kozan, NIAB Kinnow

7.2. Polyploidy as a Means of Inducing Variability

Polyploidization has shown tremendous scope in the investigation of inheritance patterns in plants as they show higher heterozygosity. In addition, polyploids are more tolerant to stressful environmental conditions and have less inbreeding depression than their diploid progenitors [121]. Polyploidy has been observed in different plants and, in citrus, it was reported that temperature stress, bud pollination, and chromosome doubling can influence polyploidy [122]. Therefore, colchicine was effective in inducing hyperploidy for better breed development in Citrus. Colchicine induces chromosome doubling due to its higher efficacy. Some other methods, such as interploid hybridization [123], unreduced gamete formation [124], and endosperm culture [125] can also induce polyploidy in Citrus. The induction of polyploids of Citrus has also been achieved by the fertilization of the unreduced gametophytes and chromosome-doubling nucellar cells [126].

7.3. Somatic Hybridization

Plant tissue culture is the most efficient tool which can regenerate whole plants, and it has a significant advantage in Citrus as it leads to regeneration, propagation, and improvement. Citrus plants can be regenerated into whole plants through direct or indirect methods of organogenesis and somatic embryogenesis [127]. In the process of in vitro organogenesis, the explants for complete regeneration are mainly epicotyl and internodal stem segments. Some examples of Citrus genotypes where such strategies had been applied include *C. citrange*, *T. citrange*, *P. trifoliata*, Mexican lime, grapefruit, *Swingle citrumelo*, and sweet orange [128]. Somatic embryogenesis has great significance, and the interest is based on its high efficacy of regeneration. The method is utilized to advance genetic variability (nucellar and organelle genomes combination) and to overcome sexual incompatibility. The somatic hybrids can also be developed through the electroporation method by using embryogenic protoplasts and mesophyll protoplasts. The classical breeding method cannot be used for the fusion of Citrus protoplasts which are distantly related; however, the protoplast fusion technique has the potential to develop such breeds. Ohgawara et al. reported the first somatic hybrid of Trovita sweet orange, and *Poncirus trifoliata* [129]. Many such hybrids of Citrus were developed later on by different countries, such as the USA, Japan, and many other countries. Both interspecific and intergeneric triploids of kumquats (*Fortunella japonica*) and *Poncirus trifoliata* were developed by the method of protoplast fusion [130]. Alloplasmic cybrids were developed with polyethylene glycol, which are the result of protoplast fusion of Willow leaf mandarin, Duncan grapefruit, and sweet orange. Endosperm cultures, embryo rescue technique, micrografting, etc., are some of the other methods which are helpful for the development of triploids, shortening the breeding cycle and production of virus-free Citrus plants.

7.4. Transgenic Breeding

Transgenesis allows researchers to cross-breed via the introduction of new genes from unrelated species into the host plant to develop new breeds which are superior and resistant to biotic and abiotic stress conditions. Many techniques have been tried for developing improved varieties in citrus; moreover, success has been reported in the area of the development of disease-resistant plants by *Agrobacterium tumefaciens*-mediated genetic manipulation. The epicotyl explants are the target of T-DNA incorporation [131]; however, it is not used for seedless Citrus plant transformation. Recently, *A. rhizogenes* has been used for *rol* gene expression and for delivering foreign genes to Citrus.

A flexible procedure is required for optimal Citrus transformation, which mainly depends on the timing of seed collection and cultivar variability. The *A. tumefaciens*-mediated transformation method exploits the Citrus leaf as an explant [132], and similar to the direct method of gene transfer in citrus, this method has been useful [133]. The particle bombardment technique was standardized using thin epicotyl sections ofCarrizo citrange (*C. sinensis* × *Poncirus trifoliata*). RNA interference (RNAi), another category of direct gene manipulation in citrus, is a gene silencing phenomenon. The technique, which is popular as a knockdown technology for genetic improvement in plants and has the advantage of efficiency and stability over many other gene manipulation methods, has been useful in pest management [134]. For instance, an intron–hairpin vector carrying full-length genes (*p25*, *p20*, and *p23*) extracted from CTV strain T36 has been used for Mexican lime transformation in order to silence the expression of the genes in CTV-infected cells, and the results showed complete resistance to virus infection.

7.5. Genomic Editing

Several breeding techniques have been developed for gene modification, resulting in successful transformations in Citrus for trait improvement. Trans-grafting and gene editing are examples of advanced technologies for the development of new varieties. Gene editing via genetic engineering is the best tool to create mutations in the Citrus genome. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), associated with Cas9, is a successful tool for genome editing in Citrus, as shown in Figure 7.

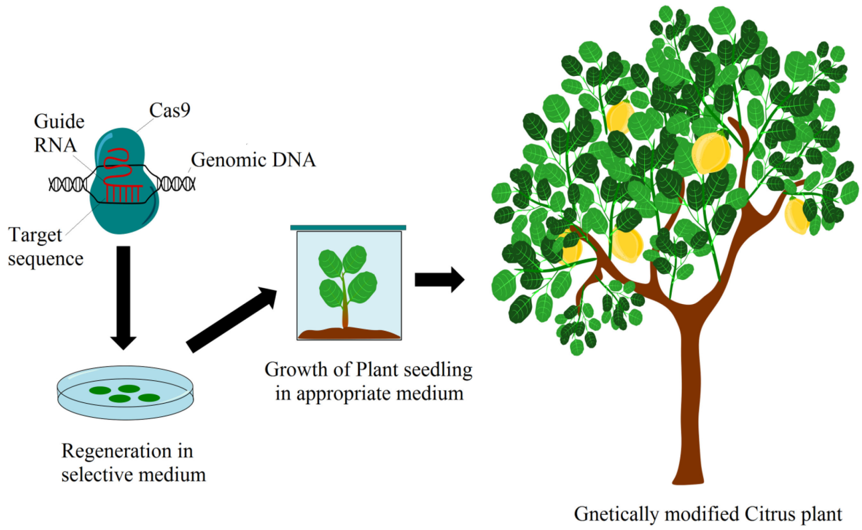

Figure 7. Workflow of CRISPR/Cas9-mediated genome editing in Citrus [135].

Jia and Wang [136] first reported the efficacy of CRISPR in *Citrus sinensis* by editing the phytoene desaturase gene. However, the first trial's efficacy was very low (lower than 5%). A highly efficient CRISPR system for editing the *PDS* gene was later developed [137], which showed that most of the mutations were up to 70% frequency (indels). Editing of *CsLOB1* (*C. sinensis* Lateral Organ Boundaries) was conducted to develop resistance toPthA4 (pathogenicity factor) from *Xanthomonas citri* pv. *citri.* in Citrus canker [138]. In this study, promoter and coding sequences were edited at *CsLOB1* in *C. sinensis* and *C. paradise*, and the genome edited plants exhibited higher mutation rates (23 to 67%) with resistance to canker disease. Homozygous and biallelic canker-resistant Pummelo plants [136], CRISPR editing of *CsWRKY22* in *C. sinensis* that reduced the susceptibility to *X. citri* subsp. *citri* (Wang et al., 2019) [139], *PDS* gene editing in *C. sinensis* plants using embryogenic callus [140], and the editing of LOB1 promoter in Duncan grapefruit by using *SaCas9* are some of the successful examples of genome editing in Citrus.

7.6. Future Prospects

Quality improvement in Citrus is restricted by conventional breeding methods. Therefore, genetic engineering could become a good alternative for crop improvement in order to overcome the constraints of traditional breeding. Genetic modification techniques can be useful in Citrus to develop novel varieties. Nanotechnology can be employed for seamless delivery and to reduce the limitations of other transformation systems. Nanoparticles or nanomaterials can interact with any biomaterial with fine control and precision [141], and can therefore improve the effectiveness of Citrus genetic engineering. There is a need for a more compact CRISPR system, multiple PAM site selection, culture-free GE methods, etc., to move beyond the constraints of the CRISPR/Cas9-mediated genome editing technology [135]. Recent advances in genome editing technology have demonstrated the effectiveness of CRISPR/Cas9 technology in treating Citrus illnesses such as Citrus canker and greening [142]. The public's awareness of the use of modern technologies is a necessary requirement before novel traits and candidate genes can be targeted for quality enhancement in Citrus.

8. Conclusions

Citruses have wide adaptability to diverse agroclimatic and geographical conditions. Citrus fruits are a precious resource of secondary metabolites and bioactive compounds. Diverse secondary metabolites such as flavonoids, alkaloids, carotenoids, phenolic acids, and essential oils and their high bioactive properties have imparted great value to human health based on the anti-oxidative, anti-inflammatory, and anti-cancer properties of Citrus, as well as the cardiovascular protective and neuroprotective effects. Biotechnological approaches have been offered as the best option for developing healthy Citrus plants. Different approaches, such as conventional breeding, mutation breeding, somatic hybridization, etc., have been used for Citrus improvement. The techniques of genetic engineering and genome editing play a vital role in the genetic manipulation of Citrus for disease resistance and quality improvement.

Author Contributions: S.K. and P.S. conceptualized; R.B. and S.K. wrote the manuscript; S.K. and P.S. edited and finalized the manuscript for publication. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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

References

1. Andrade, M.A.; Barbosa, C.H.; Shah, M.A.; Ahmad, N.; Vilarinho, F.; Khwaldia, K.; Silva, A.S.; Ramos, F. Citrus By-Products: Valuable Source of Bioactive Compounds for Food Applications. *Antioxidants* **2023**, *12*, 38. [CrossRef]
2. Barbhuiya, A.R.; Khan, M.L.; Dayanandan, S. Molecular phylogeny of Citrus species in the Eastern Himalayan region of Northeast India based on Chloroplast and Nuclear DNA sequence data. In *Molecular Genetics and Genomics Tools in Biodiversity Conservation*; Springer: Singapore, 2022; pp. 185–201.
3. Swingle, W.T.; Reece, P.C. The botany of Citrus and its wild relatives. In *The Citrus Industry*; Reuther, W., Webber, H.J., Batchelor, L.D., Eds.; University of California Press: Berkeley, CA, USA, 1967; Volume 1, pp. 389–390.
4. Tanaka, T. Fundamental discussion of Citrus classification. *Stud. Citrol.* **1977**, *14*, 1–5.
5. Barrett, H.C.; Rhodes, A.M. A numerical taxonomic study of affinity relationships in cultivated Citrus and its close relatives. *Syst. Bot.* **1976**, *1*, 105–136. [CrossRef]
6. Scora, R.W. Biochemistry, taxonomy and evolution of modern cultivated Citrus. In Proceedings of the International Society of Citriculture VI Congress, Tel Aviv, Israel, 6–11 March 1988; Margraf Pubishers: Kersheim, Germany, 1988; Volume 1, pp. 277–289.
7. Hore, D.K.; and Baruah, U. Status of citriculture in North Eastern Region of India—A Review. *Agric. Rev.* **2004**, *25*, 1–15.
8. Devi, E.J.; Labala, R.K.; Sanabam, R.; Singh, N.S.; Modak, R.; Devi, H.S. New report of *Citrus indica* Yu. Tanaka, a wild progenitor species of citrus from Dailong Forest, Manipur, and recommendation for its conservation. *Genet. Resour. Crop. Evol.* **2022**, *1*, 545–558. [CrossRef]
9. Roy, A.; Das, S.K.; Tripathi, A.K.; Singh, N.U.; Barman, H.K. Biodiversity in North East India and their conservation. *Progress Agric.* **2015**, *15*, 182–189. [CrossRef]
10. Swingle, W.T. *The Botany of Citrus and Its Relatives of the Orange Subfamily Aurantioidae of the Family Rutaceae*; Webber, H.J., Batcheler, L., Eds.; University of California Press: Los Angeles, CA, USA, 1943.
11. Zhang, S.; Chen, J.; Zhang, C.; Zhang, S.; Zhang, X.; Gao, L.; Yang, W. Insights into identifying resistance genes for cold and disease stresses through chromosome-level reference genome analyses of *Poncirus polyandra*. *Genomics* **2023**, *115*, 110617. [CrossRef] [PubMed]
12. Wu, G.A.; Terol, J.; Ibanez, V.; López-García, A.; Pérez-Román, E.; Borredá, C.; Domingo, C.; Tadeo, F.R.; Carbonell-Caballero, J.; Alonso, R.; et al. Genomics of the origin and evolution of Citrus. *Nature* **2018**, *554*, 311–316. [CrossRef]
13. Gmitter, F.G.; Hu, X. The possible role of Yunnan, China, in the origin of contemporary Citrus species (Rutaceae). *Econ. Bot.* **1990**, *44*, 267–277. [CrossRef]
14. Tanaka, T. *Species Problem in Citrus (Revisioaurantiacearum, IX)*; Japan Society for the Promotion of Science: Tokyo, Japan, 1954; p. 152.

15. Nicolosi, E.; Deng, Z.; Gentile, A.; Malfa, S.L.; Continella, G.; Tribulato, E. Citrus phylogeny and genetic origin of important species as investigated by molecular markers. *Theor. Appl. Genet.* **2000**, *100*, 1155–1166. [CrossRef]
16. Meyer, R.S.; Purugganan, M.D. Evolution of crop species: Genetics of domestication and diversification. *Nat. Rev. Genet.* **2013**, *14*, 840–852. [CrossRef]
17. Wu, G.A.; Prochnik, S.; Jenkins, J.; Salse, J.; Hellsten, U.; Murat, F.; Machado, M.A. Sequencing of diverse mandarin, pummelo and orange genomes reveals complex history of admixture during citrus domestication. *Nat. Biotechnol.* **2014**, *32*, 656–662. [CrossRef]
18. Terol, J. A whole genome association study in mandarin hybrids. In Proceedings of the Plant and Animal Genome XXVIII Conference, San Diego, CA, USA, 11–15 January 2020.
19. Mudge, K.; Janick, J.; Scofield, S.; Goldschmidt, E.E. A history of grafting. In *Horticultural Reviews*; John Wiley & Sons: Hoboken, NJ, USA, 2009; Volume 35, pp. 437–439.
20. Wang, X.; Xu, Y.; Zhang, S.; Cao, L.; Huang, Y.; Cheng, J.; Wu, G.; Tian, S.; Chen, C.; Liu, Y.; et al. Genomic analyses of primitive, wild and cultivated citrus provide insights into asexual reproduction. *Nat. Genet.* **2017**, *49*, 765–772. [CrossRef] [PubMed]
21. Kimball, D.A. *Citrus Processing: A Complete Guide*; Springer: Berlin/Heidelberg, Germany, 2012.
22. Ulubelde, M. Turunçgillerintaksonomisi. *Ege Bölgesi Zirai Arastırma Enstitüsü Yayınları* **1985**, *55*, 43.
23. Fatima, B.; Usman, M.; Khan, M.S.; Khan, I.A.; Khan, M.M. Identification of Citrus Polyploids using Chromosome Counts, Morphological and SSR Markers. *Pak. J. Agric. Sci.* **2015**, *52*, 107–114.
24. Das, A.; Mondal, B.; Sarkar, J.; Chaudhuri, S. Genetic resource survey of mandarin orange (*Citrus reticulata* Blanco) in the northeastern Himalayan region of India. *PGR Newsl.* **2005**, *143*, 35–39.
25. Chutia, M.; Bhuyan, P.D.; Pathak, M.G.; Sarma, T.C.; Boruah, P. Antifungal activity and chemical composition of Citrus reticulata Blanco essential oil against phytopathogens from North East India. *LWT-Food Sci. Technol.* **2009**, *42*, 777–780. [CrossRef]
26. Sharma, B.D.; Hore, D.K.; and Gupta, S.G. Genetic resources of Citrus of north—Eastern India and their potential use. *Genet. Resour. Crop. Evol.* **2005**, *51*, 411–418. [CrossRef]
27. Curk, F.; Ollitrault, F.; Garcia-Lor, A.; Luro, F.; Navarro, L.; Ollitrault, P. Phylogenetic origin of limes and lemons revealed by cytoplasmic and nuclear markers. *Ann. Bot.* **2006**, *117*, 565–583. [CrossRef]
28. Federov. *Chromosome Numbers of Flowering Plants*; Otto Koeltz Science Publisher: Konigstein, Germany, 1974.
29. García-Lor, A.; Luro, F.; Navarro, L.; Ollitrault, P. Comparative use of InDel and SSR markers in deciphering the interspecific structure of cultivated citrus genetic diversity: A perspective for genetic association studies. *Mol. Genet. Genom.* **2012**, *287*, 77–94. [CrossRef]
30. Ollitrault, P.; Curk, F.; Krueger, R. Citrus taxonomy. In *The Genus Citrus*; Woodhead Publishing: Sawston, UK, 2020; pp. 57–81.
31. Le Nguyen, K.; Grondin, A.; Courtois, B.; Gantet, P. Next-generation sequencing accelerates crop gene discovery. *Trends Plant. Sci.* **2019**, *24*, 263–274. [CrossRef] [PubMed]
32. Noda, T.; Daiou, K.; Mihara, T.; Nagano, Y. Development of Indel markers for the selection of Satsuma mandarin (*Citrus unshiu Marc*.) hybrids that can be used for low-cost genotyping with agarose gels. *Euphytica* **2020**, *216*, 1–13. [CrossRef]
33. Yi, K.U.; Zhin, K.L.; Oh, E.U.; Kim, S.S.; Kim, H.B.; Song, K.J. Phenotypic and genetic characterization of three different types of Dangyooza (Citrus grandis), Korean landrace citrus. *Hortic. Sci. Technol.* **2021**, *39*, 96–105.
34. Goh, R.M.; Pua, A.; Luro, F.; Ee, K.H.; Huang, Y.; Marchi, E.; Liu, S.Q.; Lassabliere, B.; Yu, B. Distinguishing citrus varieties based on genetic and compositional analyses. *PLoS ONE* **2022**, *17*, e0267007. [CrossRef] [PubMed]
35. Barkley, N.A.; Roose, M.L.; Krueger, R.R.; Federici, C.T. Assessing genetic diversity and population structure in a citrus germplasm collection utilizing simple sequence repeat markers (SSRs). *Theor. Appl. Genet.* **2006**, *112*, 1519–1531. [CrossRef]
36. Novelli, V.M.; Cristofani, M.; Souza, A.A.; Machado, M.A. Development and characterization of polymorphic microsatellite markers for the sweet orange (*Citrus sinensis* L. Osbeck). *Genet. Mol. Biol.* **2006**, *29*, 90–96. [CrossRef]
37. Fang, D.Q.; Roose, M.L. Identification of closely related citrus cultivars with inter-simple sequence repeat markers. *Theor. Appl. Genet.* **1997**, *95*, 408. [CrossRef]
38. Uzun, A.Y.; Yesiloglu, T.; Aka-Kacar, Y.I.; Tuzcu, O.; Gulsen, O. Genetic diversity and relationships within Citrus and related genera based on sequence related amplified polymorphism markers (SRAPs). *Sci. Hortic.* **2009**, *121*, 306–312. [CrossRef]
39. Uzun, A.; Yesiloglu, T.; Polat, I.; Aka-Kacar, Y.; Gulsen, O.; Yildirim, B.; Tuzcu, O.; Tepe, S.; Canan, I.; Anil, S. Evaluation of genetic diversity in lemons and some of their relatives based on SRAP and SSR markers. *Plant. Mol. Biol. Report.* **2011**, *29*, 693–701. [CrossRef]
40. Gulsen, O.; Roose, M.L. Lemons: Diversity and relationships with selected Citrus genotypes as measured with nuclear genome markers. *J. Am. Soc. Hortic. Sci.* **2001**, *126*, 309–317. [CrossRef]
41. Gulsen, O.; Uzun, A.; Canan, I.; Seday, U.; Canihos, E. A new citrus linkage map based on SRAP, SSR, ISSR, POGP, RGA and RAPD markers. *Euphytica* **2010**, *173*, 265–277. [CrossRef]
42. UNCTAD. Citrus Fruits. Market Information in the Commodities Area Website. 2010. Available online: http://www.unctad.org/infocomm/anglais/orange/ (accessed on 1 January 2020).
43. FAOSTAT. Food and Agriculture Organization of the United Nations Report. *World Statistical Yearbook.* 2010. Available online: http://faostat.fao.org (accessed on 1 January 2020).
44. Area and Production of Horticulture Crops for 2018–19 (3rd Advance Estimates). National Horticulture Board; Horticulture Information Service 2019. Available online: https://nhb.gov.in/Statistics.aspx?enc=WkegdyuHokljEtehnJoq0KWLU79sOQCy+W4MfOk01GFOWQSEvtp9tNHHoiv3p49g (accessed on 1 January 2020).

45. Citrus Production in India (MMT). Statista Research Department 2022. Available online: https://www.statista.com/statistics/1038920/india-production-of-citrus-fruits-by-type/ (accessed on 1 January 2020).
46. Anonymous. The Wealth of India. In *Publication and Information Directorate*; CSIR: New Delhi, India, 2002; pp. 657–664.
47. Kilcher, L. *Organic Citrus: Challenges in Production and Trade*; Research Institute of Organic Agriculture (FiBL): Geneva, Switzerland, 2005; Available online: http://orgprints.org/00008124/ (accessed on 1 January 2020).
48. Iglesias, D.J.; Cercós, M.; Colmenero-Flores, J.M.; Naranjo, M.A.; Ríos, G.; Carrera, E.; Ruiz-Rivero, O.; Lliso, I.; Morillon, R.; Tadeo, F.R.; et al. Physiology of citrus fruiting. *Braz. J. Plant. Physiol.* **2007**, *19*, 333–362. [CrossRef]
49. Abbas, G.; Duraid, K.A.; Taey, A.; Saad, S.M.; AL-Azawi, M.; Qureshi, R.A.M.; Jasman, A.K.; Slomy, A.K.; Khan, M.A.; Jabbar, M.A.; et al. Controlling Strategies of Citrus to Increase The Yield in The Country: A step Towards The Fight Against COVID-19. Fourth International Conference for Agricultural and Sustainability Sciences. *IOP Conf. Ser. Earth Environ. Sci.* **2021**, *910*, 012045. [CrossRef]
50. Bhowal, R.; Kumari, S.; Sarma, C.; Suprasanna, P.; Roy, P. Phytochemical Constituents and Bioactivity Profiles of Citrus Genus from India. *Anal. Chem. Lett.* **2006**, *12*, 770–787. [CrossRef]
51. Waseem, A.; Rafia, A. *Citrus: An. Ancient Fruits of Promise for Health Benefits*; IntechOpen Limited: London, UK, 2019.
52. Lücker, J.; El Tamer, M.K.; Schwab, W.; Verstappen, F.W.; van der Plas, L.H.; Bouwmeester, H.J.; Verhoeven, H.A. Monoterpene biosynthesis in lemon (*Citrus limon*). cDNA isolation and functional analysis of four monoterpene synthases. *Eur. J. Biochem.* **2002**, *269*, 3160–3171. [CrossRef]
53. Calomme, M.; Pieters, L.; Vlietinck, A.; Vanden Berghe, D. Inhibition of bacterial mutagenesis by Citrus flavonoids. *Planta Med.* **1996**, *62*, 222–226. [CrossRef] [PubMed]
54. Li, Y.; Kandhare, A.D.; Mukherjee, A.A.; Bodhankar, S.L. Acute and sub-chronic oral toxicity studies of hesperidin isolated from orange peel extract in Sprague Dawley rats. *Regul. Toxicol. Pharm.* **2019**, *105*, 77–85. [CrossRef]
55. Maqbool, Z.; Khalid, W.; Atiq, H.T.; Koraqi, H.; Javaid, Z.; Alhag, S.K.; Al-Shuraym, L.A.; Bader, D.M.; Almarzuq, M.; Afifi, M.; et al. Citrus waste as source of bioactive compounds: Extraction and utilization in health and food industry. *Molecules* **2023**, *28*, 1636. [CrossRef]
56. Shen, W.; Xu, Y.; Lu, Y.H. Inhibitory effects of Citrus flavonoids on starch digestion and antihyperglycemic effects in HepG2 cells. *J. Agric. Food Chem.* **2012**, *60*, 9609–9619. [CrossRef]
57. Ahsan, M.; Maria, N.N.; Tahmida, U.; Jasmin, A.A.; Chowdhury, D.U. Anxiolytic, analgesic and anti-inflammatory effects of Citrus maxima (Burm.) Merr. Seed extract in Swiss albino mice model. *Clin. Phytoscience* **2023**, *9*, 1–9. [CrossRef]
58. Qu, S.S.; Zhang, Y.; Ren, J.N.; Yang, S.Z.; Li, X.; Fan, G.; Pan, S.Y. Effect of different ways of ingesting orange essential oil on blood immune index and intestinal microflora in mice. *J. Sci. Food Agric.* **2023**, *103*, 380–388. [CrossRef] [PubMed]
59. Kurowska, E.; Spence, J.; Jordan, J.; Wetmore, S.; Freeman, D.; Piche, L.; Serratore, P. HDL-cholesterol-raising effect of orange juice in subjects with hypercholesterolemia. *Am. J. Clin. Nutr.* **2000**, *72*, 1095–1100. [CrossRef] [PubMed]
60. Liu, S.; Lou, Y.; Li, Y.; Zhang, J.; Li, P.; Yang, B.; Gu, Q. Review of phytochemical and nutritional characteristics and food applications of *Citrus L.* fruits. *Front. Nutr.* **2022**, *9*, 968604. [CrossRef] [PubMed]
61. Saini, R.K.; Ranjit, A.; Sharma, K.; Prasad, P.; Shang, X.; Girinur, K.; Gowda, M.; Keum, Y.S. Bioactive Compounds of Citrus Fruits: A Review of Composition and Health Benefits of Carotenoids, Flavonoids, Limonoids, and Terpenes. *Antioxidants* **2022**, *11*, 239. [CrossRef]
62. Jerang, A.; Kumari, S.; Borthakur, M.; Ahmed, S. Anatomical and Physiological Responses of Citrus megaloxycarpa Lush.: A Cryptic Species of Northeast India. *Appl. Biochem. Biotechnol.* **2022**, *194*, 382–394. [CrossRef]
63. Stevens, Y.; Van Rymenant, E.; Grootaert, C.; Van Camp, J.; Possemiers, S.; Masclee, A.; Jonkers, D. The Intestinal Fate of Citrus Flavanones and Their Effects on Gastrointestinal Health. *Nutrients* **2019**, *11*, 1464. [CrossRef]
64. Barreca, D.; Mandalari, G.; Calderaro, A.; Smeriglio, A.; Trombetta, D.; Felice, M.R.; Gattuso, G. Citrus Flavones: An Update on Sources, Biological Functions, and Health Promoting Properties. *Plants* **2022**, *9*, 288. [CrossRef]
65. Pontifex, M.G.; Malik, M.; Connell, E.; Muller, M.; Vauzour, D. Citrus Polyphenols in Brain Health and Disease: Current Perspectives. *Front. Neurosci.* **2021**, *15*, 640648. [CrossRef]
66. Musumeci, L.; Maugeri, A.; Cirmi, S.; Lombardo, G.E.; Russo, C.; Gangemi, S.; Calapai, G.; Navarra, M. Citrus fruits and their flavonoids in inflammatory bowel disease: An overview. *Nat. Prod. Res.* **2020**, *34*, 122–136. [CrossRef]
67. Gandhi, G.R.; Vasconcelos, A.B.S.; Wu, D.T.; Li, H.B.; Antony, P.J.; Li, H.; Geng, F.; Gurgel, R.Q.; Narain, N.; Gan, R.Y. Citrus Flavonoids as Promising Phytochemicals Targeting Diabetes and Related Complications: A Systematic Review of In Vitro and In Vivo Studies. *Nutrients* **2020**, *12*, 2907. [CrossRef]
68. Bellavite, P.; Donzelli, A. Hesperidin and SARS-CoV-2: New Light on the Healthy Function of Citrus Fruits. *Antioxidants* **2020**, *9*, 742. [CrossRef]
69. Den Hartogh, D.J.; Tsiani, E. Antidiabetic Properties of Naringenin: A Citrus Fruit Polyphenol. *Biomolecules* **2019**, *9*, 99. [CrossRef] [PubMed]
70. Zaidun, N.H.; Thent, Z.C.; AbdLatiff, A. Combating oxidative stress disorders with citrus flavonoid: Naringenin. *Life Sci.* **2018**, *208*, 111–122. [CrossRef] [PubMed]
71. Nakajima, A.; and Ohizumi, Y. Potential Benefits of Nobiletin, A Citrus Flavonoid, against Alzheimer's Disease and Parkinson's Disease. *Int. J. Mol. Sci.* **2019**, *20*, 3380. [CrossRef] [PubMed]

72. Goh, J.X.H.; Tan, L.T.H.; Goh, J.K.; Chan, K.G.; Pusparajah, P.; Lee, L.H.; Goh, B.H. Nobiletin and Derivatives: Functional Compounds from Citrus Fruit Peel for Colon Cancer Chemoprevention. *Cancers* **2019**, *11*, 867. [CrossRef]
73. Gao, Z.; Gao, W.; Zeng, S.L.; Li, P.; Liu, E.H. Chemical structures, bioactivities and molecular mechanisms of citrus polymethoxyflavones. *J. Funct. Foods* **2018**, *1*, 498–509. [CrossRef]
74. Jayaprakasha, G.K.; and Patil, B.S. In vitro evaluation of the antioxidant activities in fruit extracts from citron and blood orange. *Food Chem.* **2007**, *101*, 410–418. [CrossRef]
75. Lapuente, M.; Estruch, R.; Shahbaz, M.; Casas, R. Relation of Fruits and Vegetables with Major Cardiometabolic Risk Factors, Markers of Oxidation, and Inflammation. *Nutrients* **2019**, *11*, 2381. [CrossRef]
76. Naz, S.; Sajjad, A.; Ali, J.S.; Muhammad, Z. Antioxidative, phytochemical and antimicrobial analysis of juices of eight citrus cultivars grown in Pakistan. *Nat. Resour. Hum. Health* **2022**, *2*, 300–305. [CrossRef]
77. Lv, X.; Zhao, S.; Ning, Z.; Zeng, H.; Shu, Y.; Tao, O.; Xiao, C.; Lu, C.; Liu, Y. Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. *Chem. Cent. J.* **2015**, *9*, 68. [CrossRef]
78. Parekh, J.; Jadeja, D.; Chanda, S. Efficacy of aqueous and methanol extracts of some medicinal plants for potential antibacterial activity. *Turk. J. Biol.* **2005**, *29*, 203–210.
79. Gupta, M.; Gularia, P.; Singh, D.; Gupta, S. Analysis of Aroma Active Constituents, Antioxidant and Antimicrobial activity of C. sinensis, Citrus limetta and C. limon Fruit Peel Oil by GC-MS. *Biosci. Biotech. Res. Asia* **2014**, *11*, 895–899. [CrossRef]
80. Viuda-Martos, M.; Ruiz-Navajas, Y.; Fernández-López, J.; Pérez-Álvarez, J. Antifungal activity of lemon (*Citrus lemon* L.), mandarin (*Citrus reticulata* L.), grapefruit (*Citrus paradisi* L.) and orange (*Citrus sinensis* L.) essential oils. *Food Control.* **2008**, *19*, 1130–1138. [CrossRef]
81. Sharma, N.; Tripathi, A. Fungitoxicity of the essential oil of Citrus sinensis on post-harvest pathogens. *World J. Microbiol. Biotechnol.* **2006**, *22*, 587–593. [CrossRef]
82. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* **2000**, *100*, 57–70. [CrossRef]
83. Sultana, S.; Asif, H.M.; Nazar, H.M.; Akhtar, N.; Rehman, J.U.; Rehman, R.U. Medicinal plants combating against cancer—A green anticancer approach. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 4385–4394. [CrossRef]
84. Gyawali, R.; Kim, K.S. Anticancer Phytochemicals of Citrus Fruits—A Review. *J. Ofanimal. Res.* **2014**, *4*, 85–95. [CrossRef]
85. Nongalleima, K.; Ajungla, T.; Singh, C.B. GCMS Based Metabolicprofiling of Essential Oil of Citrus macroptera Montruz. Leaves and Peel, Assessment OF in Vitro Antioxidant and Anti-inflammatory activity. *Int. J. Pharm. Pharm. Sci.* **2017**, *9*, 107–114.
86. Mohanty, S.; Maurya, A.K.; Saxena, A.J.; Shanker, K.; Pal, A.; Bawankule, D.U. Flavonoids Rich Fraction of Citrus limetta Fruit Peels Reduces Proinflammatory Cytokine Production and Attenuates Malaria Pathogenesis. *Curr. Pharm. Biotechnol.* **2015**, *16*, 554–562. [CrossRef]
87. SoBok, H.; Lee, S.-H.; Park, Y.-B.; Bae, K.-H.; Son, K.-H.; Jeong, T.-S.; Choi, M.-S. Plasma and hepatic cholesterol and hepatic activities of 3-hydroxy- 3-methyl-glutaryl-CoA reductase and acyl CoA: Cholesterol transferase are lower in rats fed citrus peel extract or a mixture of citrus bioflavonoids. *J. Nutr.* **1999**, *129*, 1182–1185.
88. Wilcox, L.J.; Borradaile, N.M.; de Dreu, L.E.; Huff, M.W. Secretion of hepatocyte apoB is inhibited by the flavonoids, naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP. *J. Lipid Res.* **2001**, *42*, 725–734. [CrossRef] [PubMed]
89. Parmar, H.S.; Kar, A. Medicinal values of fruit peels from Citrus sinensis, Punicagranatum, and Musa paradisiaca with respect to alterations in tissue lipid peroxidation and serum concentration of glucose, insulin, and thyroid hormones. *J. Med. Food* **2008**, *11*, 376–381. [CrossRef] [PubMed]
90. Sah, A.N.; Joshi, A.; Juyal, V.; Kumar, T. Antidiabetic and Hypolipidemic Activity of Citrus medica Linn. Seed Extract in Streptozotocin Induced Diabetic Rats. *Pharmacogn. J.* **2011**, *3*, 80–84. [CrossRef]
91. Kundusen, S.; Halder, P.K.; Gupta, M.; Mazumder, U.P.; Saha, P.; Bala, A.; Bhattacharya, S.; Kar, B. Evaluation of Antihyperglycemic activity of Citrus limetta Fruit Peel in Streptozotocin-Induced Diabetic Rats. *Int. Sch. Res. Netw.* **2011**, *2011*, 869273. [CrossRef]
92. Ammar, N.; Hassan, H.A.; Abdallah, H.M.I.; Afifififi, S.M.; Elgamal, A.M.; Farrag, A.R.H.; El-Gendy, A.E.G.; Farag, M.A.; Elshamy, A.I. Protective Effects of Naringenin from Citrus sinensis (var. Valencia) Peels against CCl4-Induced Hepatic and Renal Injuries in Rats Assessed by Metabolomics, Histological and Biochemical Analyses. *Nutrients* **2022**, *14*, 841. [CrossRef]
93. Del Borghi, A.; Moreschi, L.; Gallo, M. Life cycle assessment in the food industry. In *The Interaction of Food Industry and Environment*; Galanakis, C., Ed.; Academic Press: London, UK, 2020; pp. 63–118.
94. Sharma, K.; Mahato, N.; Lee, Y.R. Extraction, characterization and biological activity of citrus flavonoids. *Rev. Chem. Eng.* **2018**, *35*, 265–284. [CrossRef]
95. Bechlin, T.R.; Granella, S.J.; Christ, D.; Coelho, S.R.M.; and Paz, C.H. Effects of ozone application and hot-air drying on orange peel: Moisture diffusion, oil yield, and antioxidant activity. *Food Bioprod. Process.* **2020**, *123*, 80–89. [CrossRef]
96. Ling, Y.; Shi, Z.; Yang, X.; Cai, Z.; Wang, L.; Wu, X.; Ye, A.; and Jiang, J. Hypolipidemic effect of pure total flavonoids from peel of Citrus (PTFC) on hamsters of hyperlipidemia and its potential mechanism. *Exp. Gerontol.* **2020**, *130*, 110786. [CrossRef] [PubMed]
97. Fayek, N.; El-Shazly, A.H.; Abdel-Monem, A.R.; Moussa, M.Y.; Abd-Elwahab, S.M.; El-Tanbouly, N.D. Comparative study of the hypocholesterolemic, antidiabetic effects of four agro-waste Citrus peels cultivars and their HPLC standardization. *Rev. Bras. Farm.* **2017**, *27*, 488–494. [CrossRef]
98. Kang, S.; Song, S.; Lee, J.; Chang, H.; Lee, S. Clinical investigations of the effect of Citrus unshiu peel pellet on obesity and lipid profile. Evid. Based Complement. *Alternat. Med.* **2018**, *2018*, 4341961.

99. Ding, X.; Guo, L.; Zhang, Y.; Fan, S.; Gu, M.; Lu, Y.; Jiang, D.; Li, Y.; Huang, C.; Zhou, Z. Extracts of pomelo peels prevent high-fat diet-induced metabolic disorders in c57bl/6 mice through activating the PPARα and GLUT4 pathway. *PLoS ONE* **2013**, *8*, e77915. [CrossRef] [PubMed]
100. Ashraf, H.; Butt, M.S.; Iqbal, M.J.; Suleria, H.A.R. Citrus peel extract and powder attenuate hypercholesterolemia and hyperglycemia using rodent experimental modeling. *Asian Pac. J. Trop. Biomed.* **2017**, *7*, 870–880. [CrossRef]
101. Chen, X.M.; Tait, A.R.; Kitts, D.D. Flavonoid composition of orange peel and its association with antioxidant and anti-inflammatory activities. *Food Chem.* **2017**, *218*, 15–21. [CrossRef] [PubMed]
102. Gosslau, A.; Ho, C.T.; Li, S. The role of rutin and diosmin, two citrus polyhydroxyflavones in disease prevention and treatment. *J. Food Bioact.* **2019**, *5*, 43–56. [CrossRef]
103. Ibrahim, M.; Amin, M.N.; Millat, M.S.; Raju, J.A.; Hussain, M.S.; Sultana, F.; Islam, M.M.; Hasan, M.M. Methanolic extract of peel of citrus maxima fruits exhibit analgesic, CNS depressant and anti-inflammatory activities in Swiss albino mice. *Biol. Eng. Med. Sci. Rep.* **2018**, *4*, 7–11. [CrossRef]
104. Naim, M.; Amjad, F.; Sultana, S.; Islam, S.; Hossain, M.; Begum, R.; Rashid, M.; Amran, M. Comparative study of antidiabetic activity of hexane-extract of lemon peel (*Limon citrus*) and glimepiride in alloxan-induced diabetic rats. *Bangladesh Pharm. J.* **2018**, *15*, 131–134. [CrossRef]
105. Sathiyabama, R.G.; Gandhi, G.R.; Denadai, M.; Sridharan, G.; Jothi, G.; Sasikumar, P.; Siqueira Quintans, J.d.S.; Narain, N.; Cuevas, L.E.; Coutinho, H.D.M.; et al. Evidence of insulin-dependent signalling mechanisms produced by *Citrus sinensis* (L.) Osbeck fruit peel in an insulin resistant diabetic animal model. *Food Chem. Toxicol.* **2018**, *116*, 86–99. [CrossRef]
106. Ali, A.M.; Gabbar, M.A.; Abdel-Twab, S.M.; Fahmy, E.M.; Ebaid, H.; Alhazza, I.M.; Ahmed, O.M. Antidiabetic potency, antioxidant effects, and mode of actions of Citrus reticulata fruit peel hydroethanolic extract, hesperidin, and quercetin in nicotinamide/streptozotocin-induced wistar diabetic rats. *Oxid. Med. Cell Long.* **2020**, *2020*, 1730492.
107. Duan, L.; Dou, L.L.; Yu, K.Y.; Guo, L.; Bai-Zhong, C.; Li, P.; Liu, E.H. Polymethoxyflflavones in peel of Citrus reticulata 'Chachi' and their biological activities. *Food Chem.* **2017**, *234*, 254–261. [CrossRef]
108. de Oliveira, M.S.; Almeida, M.M.; Salazar, M.L.; Pires, F.C.; Bezerra, F.W.; Cunha, V.M.; Cordeiro, R.M.; Urbina, G.R.; da Silva, M.P.; e Silva, A.P.; et al. Potential of medicinal use of essential oils from aromatic plants. *Potential. Essent. Oils InTech* **2018**, *5*, 1–21.
109. Tajaldini, M.; Samadi, F.; Khosravi, A.; Ghasemnejad, A.; and Asadi, J. Protective and anticancer effects of orange peel extract and naringin in doxorubicin treated esophageal cancer stem cell xenograft tumor mouse model. *Biomed. Pharm.* **2020**, *121*, 109594. [CrossRef] [PubMed]
110. Fan, K.; Kurihara, N.; Abe, S.; Ho, C.T.; Ghai, G.; Yang, K. Chemopreventive effects of orange peel extract (OPE). I: OPE inhibits intestinal tumor growth in ApcMin/+ mice. *J. Med. Food* **2007**, *10*, 11–17. [CrossRef] [PubMed]
111. Kim, S.H.; Shin, E.J.; Hur, H.J.; Park, J.H.; Sung, M.J.; Kwon, D.Y.; Hwang, J.T. Citrus junos Tanaka peel extract attenuates experimental colitis and inhibits tumour growth in a mouse xenograft model. *J. Funct. Foods* **2014**, *8*, 301–308. [CrossRef]
112. Li, S.; Li, F.; Li, H.B.; Deng, G.D.; Ling, W.H.; Wu, S.; Xu, X.R.; Chen, F. Antiproliferative activity of peels, pulps and seeds of 61 fruits. *J. Funct. Food* **2013**, *5*, 1298–1309. [CrossRef]
113. Mendonca, L.B.P.; Badel, J.L.; Zambolim, L. Bacterial citrus diseases: Major threats and recent progress. *Bacteriol. Mycol.* **2017**, *5*, 340–350.
114. Ahloowalia, B.S.; Maluszynski, M.; Nichterlein, K. Global impact of mutation derived varieties. *Euphytica* **2004**, *135*, 187–204. [CrossRef]
115. Rana, M.A.; Usman, M.; Fatima, B.; Fatima, A.; Rana, I.A.; Rehman, W.; Shoukat, D. Prospects of mutation breeding in grapefruit (Citrus paradisiMacf.). *J. Hortic. Sci. Technol.* **2020**, *3*, 31–35. [CrossRef]
116. Mba, C.; Afza, R.; Shu, Q.Y. Mutagenic radiations: X-rays, ionizing particles and ultraviolet. In *Plant. Mutation Breeding and Biotechnology*; Shu, Q.Y., Forster, B.P., Nakagawa, H., Eds.; CAB International: Wallingford, UK, 2012; pp. 83–90.
117. Usman, M.; Fatima, B. Mandarin (Citrus reticulata Blanco) breeding. In *Advances in Plant. Breeding Strategies: Fruits*; Al-Khayri, J.M., Jain, S.M., Johnson, D.V., Eds.; Springer: Cham, Switzerland, 2018; pp. 465–533.
118. Saini, H.K.; Gill, M.I.S. Induction of mutation in rough lemon (*Citrus jambhiri* Lush.) using gamma rays. *J. Hortic. Sci.* **2009**, *4*, 41–44.
119. Maluszynski, M.; Nichterlein, K.; Van-Zanten, L.; Aloowalia, B.S. Officially released mutant varieties—The FAO/IAEA database. *Mutat. Breed. Rev.* **2000**, *12*, 1–84.
120. Williams, T.; Roose, M.L.; Daisy, S.L.; Fairchild, S.L.; Kinnow, S.L. Three New, Very Low-Seeded, Mid Season Irradiated Selection of W. Murcott Mandarin from the University of California Riverside. In Proceedings of the International Citrus Congress, Wuhan, China, 26–30 October 2008.
121. Khalid, M.F.; Hussain, S.; Anjum, M.A.; Ali, M.A.; Ahmad, S.; Ejaz, S.; Ali, S.; Usman, M.; Ehsan, U.H.; Morillon, R. Efficient compartmentalization and translocation of toxic minerals lead tolerance in volkamer lemon tetraploids more than diploids under moderate and high salt stress. *Fruits* **2020**, *75*, 204–215. [CrossRef]
122. Montalt, R.; Prósper, L.; Vives, M.C.; Navarro, L.; Ollitrault, P.; Aleza, P. Breakdown of Self-Incompatibility in Citrus by Temperature Stress, Bud Pollination and Polyploidization. *Agriculture* **2022**, *12*, 273. [CrossRef]
123. Rouiss, H.; Cuenca, J.; Navarro, L.; Ollitrault, P.; Aleza, P. Unreduced megagametophyte production in lemon occurs via three meiotic mechanisms, predominantly second-division restitution. *Front. Plant. Sci.* **2017**, *12*, 1211. [CrossRef] [PubMed]

124. Xie, K.D.; Xia, Q.M.; Peng, J.; Wu, X.M.; Xie, Z.Z.; Chen, C.L.; Guo, W.W. Mechanism underlying 2n male and female gamete formation in lemon via cytological and molecular marker analysis. *Plant. Biotechnol. Rep.* **2019**, *9*, 141–149. [CrossRef]
125. Yanagimoto, Y.; Kaneyoshi, J.; Yamasaki, A.; Kitajima, A. Estimation of polyploidy of embryos and gametes based on polyploidy of endosperm remaining in the citrus seed. *Hortic. Res.* **2018**, *17*, 293–302. [CrossRef]
126. Xie, K.D.; Wang, X.P.; Biswas, M.K.; Liang, W.J.; Xu, Q.; Grosser, J.W.; Guo, W.W. 2 n megagametophyte formed via SDR contributes to tetraploidization in polyembryonic 'Nadorcott'tangor crossed by citrus allotetraploids. *Plant. Cell Rep.* **2014**, *33*, 1641–1650. [CrossRef] [PubMed]
127. Chiancone, B.; Germanà, M.A. Micropropagation of Citrus spp. by organogenesis and somatic embryogenesis. *Methods Mol. Biol.* **2013**, *11013*, 99–118.
128. Ballester, A.; Cervera, M.; Pena, L. Evaluation of selection strategies alternative to nptII in genetic transformation of citrus. *Plant. Cell. Rep.* **2008**, *27*, 1005–1015. [CrossRef]
129. Ohgawara, T.; Kobayashi, S.; Ohgawara, E.; Uchimaya, H.; Ishii, S. Somatic hybrid plants obtained by protoplasm fusion between Citrus sinensis and Poncirustrifoliata. *Theor. Appl. Genet.* **1985**, *71*, 1–4. [CrossRef]
130. Guo, W.W.; Deng, X.X. Intertribal hexaploid somatic hybrid plants regeneration from electrofusion between diploids of Citrus sinensis and its sexually incompatible relative, Clausenalansium. *Theor. Appl. Genet.* **1999**, *98*, 581–585. [CrossRef]
131. Dutt, M.; Grosser, J.W. Evaluation of parameters affecting Agrobacterium-mediated transformation of citrus. *Plant. Cell Tissue Organ. Cult.* **2009**, *98*, 331–340. [CrossRef]
132. Khan, E.U.; Fu, X.Z.; Liu, J.H. Agrobacterium-mediated genetic transformation and regeneration of transgenic plants using leaf segments as explants in Valencia sweet orange. *Plant. Cell. Tissue Organ. Cult.* **2012**, *109*, 383–390. [CrossRef]
133. Chamandoosti, F. Citrus tissue culture with two different approaches. *Int. J. Biosci. Biotechnol.* **2020**, *8*, 19–30. [CrossRef]
134. Yu, X.; Killiny, N. RNA interference-mediated control of Asian citrus psyllid, the vector of the huanglongbing bacterial pathogen. *Trop. Plant. Pathol.* **2020**, *45*, 298–305. [CrossRef]
135. Barbier, F.F.; Dun, E.A.; Kerr, S.C.; Chabikwa, T.G.; Beveridge, C.A. An update on the signals controlling shoot branching. *Trends Plant. Sci.* **2019**, *24*, 220–236. [CrossRef]
136. Jia, H.; Wang, N. Generation of homozygous canker-resistant citrus in the T0 generation using CRISPR-SpCas9p. *Plant. Biotechnol. J.* **2020**, *18*, 1990–1992. [CrossRef]
137. Zhang, F.; LeBlanc, C.; Irish, V.F.; Jacob, Y. Rapid and efficient CRISPR/Cas9 gene editing in Citrus using the YAO promoter. *Plant. Cell. Rep.* **2017**, *36*, 1883–1887. [CrossRef] [PubMed]
138. Jia, H.; Zhang, Y.; Orbović, V.; Xu, J.; White, F.F.; Jones, J.B.; Wang, N. Genome editing of the disease susceptibility gene CsLOB1 in citrus confers resistance to citrus canker. *Plant. Biotechnol. J.* **2017**, *15*, 817–823. [CrossRef]
139. Wang, L.; Chen, S.; Peng, A.; Xie, Z.; He, Y.; Zou, X. CRISPR/Cas9-mediated editing of CsWRKY22 reduces susceptibility to Xanthomonas citri subsp. citri in Wanjincheng orange (*Citrus sinensis* (L.) Osbeck). *Plant Biotechnol. Rep.* **2019**, *13*, 501–510. [CrossRef]
140. Dutt, M.; Mou, Z.; Zhang, X.; Tanwir, S.E.; Grosser, J.W. Efficient CRISPR/Cas9 genome editing with Citrus embryogenic cell cultures. *BMC Biotechnol.* **2020**, *20*, 58. [CrossRef]
141. Wang, J.W.; Grandio, E.G.; Newkirk, G.M.; Demirer, G.S.; Butrus, S.; Giraldo, J.P.; Landry, M.P. Nanoparticle-Mediated Genetic Engineering of Plants. *Mol. Plant.* **2019**, *12*, 1037–1040. [CrossRef]
142. Peng, A.; Chen, S.; Lei, T.; Xu, L.; He, Y.; Wu, L.; Yao, L.; Zou, X. Engineering canker-resistant plants through CRISPR/Cas9-targeted editing of the susceptibility gene Cs LOB 1 promoter in citrus. *Plant. Biotechnol. J.* **2017**, *15*, 1509–1519. [CrossRef] [PubMed]