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Medicinal and aromatic plants in the omics era: application of plant breeding and biotechnology for plant secondary metabolite production

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Abstract: Human being has strong and historic connections with plants to fulfill food, feed, and shelter. Moreover, human uses plants as medicine for the treatment of various diseases. Plants are chemical factories for the biosynthesis of the huge number of secondary metabolites (SMs) that are directly used as a medicine or indirectly used in the development of commercial pharmaceutical drugs. Their improvement through classical breeding remains a difficult struggle for plant breeders. Hence, rapidly advancing research on the plant omics era has accelerated our understanding of the complex structure of SMs synthesis in medicinal and aromatic plants (MAPs). In addition, sequencing technologies and the completion of several genome sequences of MAPs have opened numerous opportunities for fine mapping and gene characterization. The accessibility of these technologies together with research of quantitative trait loci (QTL) and candidate genes for key characteristics such as SMs content and biologic activity and resistance to biotic and abiotic stresses pave the way for the development of new strategies for the improvement of MAPs. To explore the knowledge of SMs in MAPs, several reviews have been published over the last three decades for researchers with advanced knowledge of plant biotechnology. However, this review has offered a summary of the recent developments, limitations, and future potential in molecular breeding of MAPs species and their application to plant breeding.

Key words: Genomics, transcriptomics, plant tissue culture, QTL, GWAS

1. Introduction

Since ancient times, people have been discovering nature mainly plants in search of new drugs. This has contributed to the use of many medicinal and aromatic plants (MAPs) with healing properties to cure various diseases. Still, more than 80% of the world's population relies on plants or plant-derived compounds to meet their main health care requirements (Laloo et al., 2021). Remarkably, more than 25% of drugs prescribed today contain at least one compound of plant basis (Sin et al., 2018). Therefore, the importance of MAPs is consistently preserved.

The application of omics approaches such as genomics, transcriptomics, and metabolomics to MAPs have supported the development of phytomedicine. Such studies have helped in elucidating the genes and proteins involved in the biosynthesis of significant secondary metabolites (SMs) (Mehta and Hasija 2018; Chakraborty, 2018). Screening plants for their potential therapeutic chemicals is interesting, but it is an immense task since there are more than 422,000 plant species available (Schippmann et al., 2006). Thus, scientists are conducting genome-level studies to identify the genes responsible for making a wide variety of bioactive compounds. Understanding these gene-protein-metabolite networks can open up better opportunities for increasing the production of important specialized metabolites through conventional as well as advanced plant biotechnology techniques.

2. Classification and utilization of secondary metabolites

MAPs have strong phyto-constituents which are responsible for their therapeutic properties (Zengin et al., 2022). In addition to primary metabolites such as nucleic acids, proteins, fats, and carbohydrates, SMs are synthesized in much smaller quantities (Pagare et al., 2015). Initially, SMs were thought of now as waste materials with no functions. However, it has been understood that SMs have important functions in plants such as adaptation, defense, survival, and maintenance of their production (Yang et al., 2018; Ramawat and Goyal, 2020).

SMs can be divided into the following chemically defined groups; terpenoids, phenolics, nitrogen-containing, and sulfur-containing compounds. They are

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synthesized by following different synthesis pathways starting with photosynthesis; shikimic acid for phenols, tannins, aromatic alkaloids; acetate-malonate for phenols and alkaloids; pentose for glycosides, polysaccharides, mevalonic acid, and methyl erythrose phosphate for terpenes, alkaloids, and steroids (Trenchard et al., 2015, Shirley et al., 2019). Terpenoids consist of more than 23,000 recognized structures, the most common category of active compounds in plants. The volatility of terpenoids offers a way for communication with other organisms such as neighboring plants, pollinators, and herbivores (Cheng et al., 2007). Their functions underlies agricultural applications ranging from finding alternative methods of pest control to the production of flavors and fragrances. Menthol, linalool, artemisinin, geranyl pyrophosphate, limonene, citral, camphor, pinene, eucalyptol, bisabolol, farnesol embrene, kahweol, taxadiene, cafestol, and sclareol are some of the terpenes that are important for the quality of agricultural products.

Alkaloids are SMs containing basic nitrogen atoms. They also contain several associated compounds with neutral and weakly acid properties. Alkaloids have a wide range of structural variations, and there is no single classification system. The majority of alkaloids are toxic in nature and serve as a defense against microbial infection and herbivorous attacks. Some alkaloids have been utilized as insecticides, such as nicotine salts and anabasine (Casanova 2002; Zammit et al., 2014). Additionally, alkaloids exhibit a wide variety of pharmacological properties such as antimalarial (quinine), antiasthma (ephedrine), anticancer (homoharringtonine), and analgesic (morphine) (Dixit et al., 2021). There is also a sulfur-containing class of secondary metabolites such as alliin and defensins. These components are directly or indirectly engaged in plant defense systems against microbial diseases.

Phenolic compounds derived from plants are one of the largest groups of SMs. Polyphenols are more than 8,000 different compounds that have been identified so far (Mustafa et al., 2020). Polyphenols can be subdivided into two classes: flavonoids and nonflavonoids. They are widely distributed in plants and perform many functions such as producing yellow, red, or blue pigmentation in petals. In addition, flavonoids are involved in ultraviolet filtration and symbiotic nitrogen fixation in higher plants (Kabera et al., 2014). They can also function as chemical messengers, physiological regulators, and inhibitors of cell cycles. The tannins are the phenolics that precipitate proteins. They consist of various groups of oligomers and polymers. With the exception of some high molecular weight structures, tannins are water-soluble compounds (Doss et al., 2022). They are usually divided into two groups: hydrolyzable tannins and condensed tannins.

Alkaloids are used more as drugs (e.g., source of morphine for poppy plants), terpenoids are used more as aroma (e.g., source of menthol for peppermint plants), and phenolic substances are used more as antioxidants (e.g., source of rosmarinic acid for rosemary plants) (Baydar, 2005). Essential oils, alkaloids, glycosides, steroids, saponins, balms, resins, waxes, natural rubber, dyes, and others are irreplaceable products that bring great benefits to people.

3. Extraction, determination, and biological activity of secondary metabolites

A number of extraction methods have been developed for the extraction of SMs. Apart from soxhlet and clevenger extractions methods, more sophisticated extraction technologies such as supercritical-fluid extraction, accelerated solvent extraction (or pressurized solvent extraction), microwave-assisted extraction, and ultrasound-assisted extraction are widely used. Generally, chromatographic or spectrophotometric techniques are used for the determination of SMs. Chromatography is the most common analysis technique used to separate the compounds based on the differences in their speed of movement between two different phases (Prebihalo et al. 2018). Thin-layer chromatography (TLC), high-pressure liquid chromatography (HPLC), and gas chromatography (GC) are the most common chromatography techniques (Sharma et al., 2022). The spectrophotometric method is based on how much light is transmitted (absorbing) from a solution in certain spectra (Morris, 2015). Parallel to the intensity of the solution or the amount contained in the substance, the amount of light that cools the solutions in the spectral meter changes. By measuring the intensity of light that can pass through the solution, the amount of the target substance in the solution is quantitatively calculated.

Secondary metabolites (SMs) are not only important for the plant's defense signaling pathways but they are also known to have biological activities. They have a variety of biological activities such as antioxidant, anticancer, antimicrobial, antigenotoxic, antihyperlipidemic, antidepressant, anxiolytic, anticonvulsant, anticataractogenic, antinociceptive, antiinflammatory, antidiabetic, antitussive, aphrodisiac, antiplatelet, antivenin, hypotensive (Singh et al., 2018). These activities are determined by different methods. For example, there are two general types of assays widely used for different antioxidant studies. One is an assay associated with lipid peroxidation assays. Other assays are associated with electron or radical scavengings, such as DPPH, ABTS, FRAP, FOX, FTC, and ACA. In addition, for determining antimicrobial activity, there are many in vitro lab techniques but agar well diffusion, spot-on-lawn, disc diffusion, and fluorescence-based assays are generally preferred by the researchers.

4. Genetic resources and classical breeding of MAPs

It has been reported that nearly 72,000 species are used for medicinal purposes (Schippmann et al., 2006). However, only 500 of these 72,000 medicinally important plants are included in various pharmacopeias. The Turkish flora is made up of 11,707 plant taxa belonging to 167 families and 3649 of these taxa are endemic (Güner et al., 2012). Hundreds of plant species that grow natively in Turkey, especially endemic ones, have very high medicinal and aromatic potential.

Tropical regions are the richest in terms of MAPs genetic resources, while the number of species decreases towards the poles. Most MAPs growers still use wild types or local varieties that have not undergone selection (Wang et al., 2020). However, numerous research studies have been carried out for the successful breeding of MAPs using classical breeding methods such as recurrent selection, single seed descent (SSD), pedigree, backcross method, gamete selection, sib mating, half sib mating, bridge crossing, distant hybridization to achieve a wide range of objectives (Pank et al., 2006). The primary breeding efforts have been to improve the tolerance of these plants to various environmental conditions and increase resistance to various biotic and abiotic challenges. Big challenges to the breeders were to develop varieties from mixed populations. Despite all of the challenges, the greatest advantage of MAPs to the breeders is the presence of a high level of genetic variation that can be used for varietal development in a short period of time, even with a simple selection method. Conservation of MAPs in different gene banks is vital, especially for plant breeding. The accession number of ninety-one medicinal and aromatic species conserved across 109 seed genebanks is presented in Table 1. As a conservation strategy all across the world, medicinal plant species are held in different collection countries (Figure 1) and the main conservator institutions of medicinal and aromatic plant accessions are presented in Figure 2. This conservation makes a great contribution to the improvement of MAPs through breeding.

Wild plant populations and landraces are the most important resources that contain higher genetic diversity compared to their improved cultivars. Most of the MAPs cultivars in the world were developed from populations, landraces, or introduction materials by mass, pure line, or clonal selection methods (Baydar, 2005). For example, in Turkey, many of the registered cultivars of MAPs such as cumin, coriander, anise, fennel, fenugreek, black cumin, buckwheat, flax, and sesame are purified by selection from populations (Baydar, 2005). Moreover, in MAPs, many new cultivars were obtained through interspecific and intraspecific hybridization. The majority of poppy and tobacco cultivars in Turkey were improved by combination hybridization (Baydar, 2005). Today, widely grown lavandin (*Lavandula* × *intermedia*) is hybrid of *Lavandula latifolia* × *Lavandula angustifolia* subsp. *pyrenaica*. The hybrid lavandin (*Lavandula* × *intermedia*) has more flower and essential oil yield compared to the other two types and this has significantly narrowed the agriculture of lavender (*Lavandula angustifolia*). In addition, in order to form the genetic variation, physical or chemical mutagens are used in mutation breeding. For example; an increase in the level of steroidal sapogenin (diosgenin) in *Trigonella corniculata* was detected with the application of dimethyl and diethyl sulfate (Jain and Agrawal 1987). Furthermore, *Papaver somniferum* variety which is nonnarcotic (opium less and alkaloid free) was developed through mutagenesis (Kolakar et al., 2018). As another example, Baydar et al. (2021) created a large variation in flower color and number of petals by applying gamma rays at doses of 0, 100, and 200 Gy of radioactive Cobalt-60 to the seeds of the oil rose plant (*Rosa damascena*) in Turkey.

Another method used in the breeding of MAPs is the utilization of polyploidy. For instance, the essential oil ratio of many species such as mint (*Mentha* sp.), lavender (*Lavandula* sp.), and clary sage (*Salvia sclarea*) is increased by the advanced ploidy level (Jordanov et al., 1995; Moetamedipoor et al., 2022). Of the various degrees of ploidy obtained through the use of colchicine in *Papaver somniferum*, contains higher levels of morphine (Mishra et al., 2010). Autotetraploid seeds of datura (*Datura stramonium*) and henbane (*Hyoscyamus niger*) contain about twice as many alkaloids as diploid ones, particularly for scopolamine and hyoscyamine alkaloids (Berkov, 2001).

5. Biotechnological techniques in MAPs

Secondary metabolite production is an imperative technique having an immense commercial application. More than 50 products based on extracts from plant cell cultures have been made as mentioned by Eibl et al. (2018). However, there remain significant obstacles to the commercial synthesis of high-value chemicals from these sources (Ochoa-Villarreal et al. 2016). Plant cell, tissue, or organ culture is an important and potential technique for the commercial fabrication of highly significant secondary metabolites from plants based upon requirement and demand (Aasim et al., 2014, 2018a). The final outcome from cell/tissue cultures is the rapid proliferation rate (Rao and Ravishankar, 2002) and production of specific therapeutic phytochemicals equivalent to or more than the whole plant (Ncube and Staden, 2015) grown under field conditions (Rao and Ravishankar 2002). On the other hand, different approaches like strain development, the use of different cell lines, and media optimization can be applied for the enrichment of secondary metabolites (Sarin 2005; Aasim

Table 1. Accession number of ninty-one medicinal and aromatic species conserved across 109 seed genebanks (www.genesys-pgr.org).

English name	Latin name	Accessions	English name	Latin name	Accessions	English name	Latin name	Accessions
Alchemilla	*Alchemilla* spp.	72	Black bryony	*Dioscorea communis*	16	Dog-rose	*Rosa canina*	45
Onion	*Allium cepa*	7826	Echinacea	*Echinacea* spp.	339	Rosemary	*Rosmarinus officinalis*	509
Garlic	*Allium sativum*	4027	Giant fennel	*Ferula communis*	75	Red sorrel	*Rumex acetosella*	35
Marsh mallow	*Althaea officinalis*	110	Fennel	*Foeniculum vulgare*	158	White willow	*Salix alba*	15
Maryam's flower	*Anastatica hierochuntica*	19	Gentian	*Gentiana lutea*	60	Greek sage	*Salvia fruticosa*	123
Dill	*Anethum graveolens*	1319	Ginkgo	*Ginkgo biloba*	15	Sage	*Salvia officinalis*	423
Angelica	*Angelica archangelica*	139	Liquorice	*Glycyrrhiza glabra*	122	Savory	*Satureja* spp.	571
Absinthium	*Artemisia absinthium*	108	Hop	*Humulus lupulus*	1704	Golden thistle	*Scolymus hispanicus*	20
Sweet wormwood	*Artemisia annua*	16	Henbane	*Hyoscyamus niger*	133	Milk thistle	*Silybum marianum*	139
Belladonna	*Atropa belladonna*	16	St. John's-wort	*Hypericum perforatum*	703	Yellow mustard	*Sinapis alba*	1572
Borage	*Borago officinalis*	134	Iris	*Iris* spp.	1372	Stevia	*Stevia rebaudiana*	7
Brown mustard	*Brassica juncea*	4649	Jasmine	*Jasminum* spp.	56	Trumpet tree	*Tabebuia* spp.	57
Black mustard	*Brassica nigra*	726	Laurel	*Laurus nobilis*	16	Feverfew	*Tanacetum parthenium*	60
Marigold	*Calendula officinalis*	324	Lavender	*Lavandula spp.*	822	Dandelion	*Taraxacum officinale*	52
Hemp	*Cannabis sativa*	1523	Summer snowflake	*Leucojum aestivum*	19	Yew	*Taxus* spp.	99
Caper bush	*Capparis spinosa*	46	Lily	*Lilium* spp.	370	Wall germander	*Teucrium chamaedrys*	45
Shepherd's purse	*Capsella bursa-pastoris*	112	Goji berry	*Lycium chinense, Lycium barbarum*	16	Thymbra	*Thymbra* spp.	103
Pepper	*Capsicum annuum*	20753	Chamomile	*Matricaria spp.*	193	Thyme	*Thymus* spp.	690
Cassia	*Cassia* spp.	247	Melissa	*Melissa officinalis*	194	Lindens	*Tilia* spp.	185
Bright eyes	*Catharanthus roseus*	38	Mint	*Mentha* spp.	1753	Fenugreek	*Trigonella foenum-graecum*	1212
Centella asiatica	*Centella asiatica*	7	Catnip	*Nepeta cataria*	51	Huflattich	*Tussilago farfara*	71
Vetiver	*Chrysopogon zizanioides*	13	Tobacco	*Nicotiana tabacum*	9179	Nettle	*Urtica dioica*	120
Cinnamon	*Cinnamomum spp.*	9	Black cumin	*Nigella* spp.	298	Bilberry	*Vaccinium myrtillus*	158
Coffee	*Coffea arabica*	1837	Basil	*Ocimum* spp.	1447	Valerian	*Valeriana officinalis*	161
Autumn crocus	*Colchicum autumnale*	130	Sahlep	*Orchis mascula, Orchis militaris*	7	Vanilla	*Vanilla* spp.	23
Coriander	*Coriandrum sativum*	1490	Oregano	*Origanum*	714	White hellebore	*Veratrum album*	17
Shafron	*Crocus sativus*	143	Opium poppy	*Papaver somniferum*	4547	Periwinkle	*Vinca minor*	11
Cumin	*Cuminum cyminum*	108	Wild rue	*Peganum harmala*	72	Ginger	*Zingiber officinale*	2
Curcuma longa	*Curcuma longa*	4	Blackpepper	*Piper nigrum*	17	Jujube	*Ziziphus jujuba*	222
Datura	*Datura* spp.	606	Mayapple	*Podophyllum peltatum*	4		Total	78515
Digitalis	*Digitalis* spp.	468	Sumac	*Rhus* spp.	277			

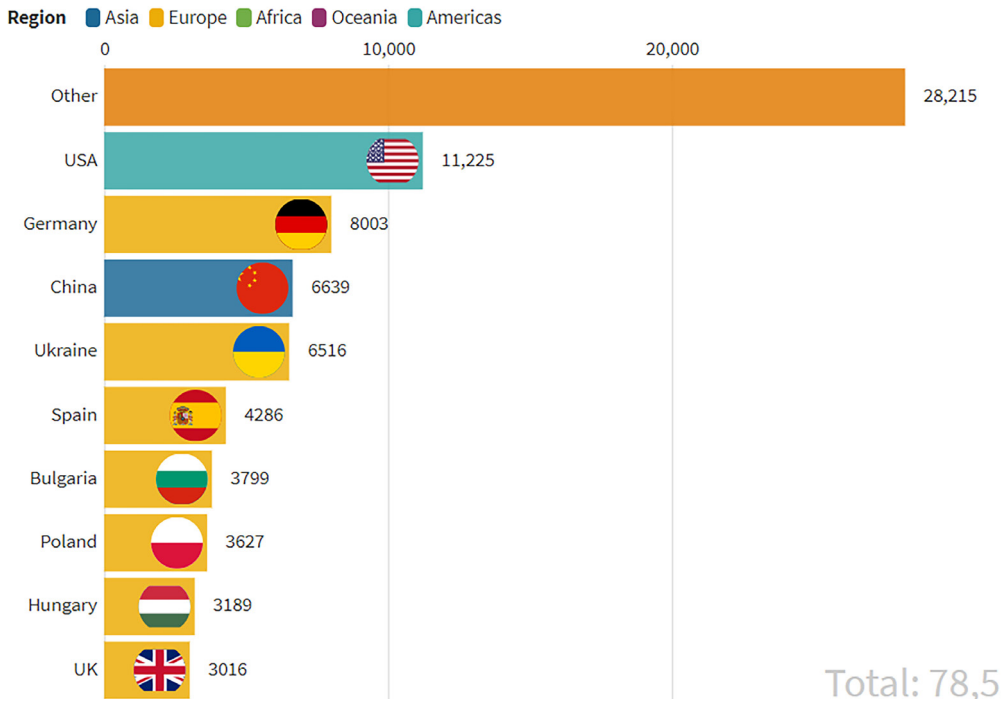

Figure 1. The main conservator countries of MAP accessions. Data accessed through Genesys Global Portal on Plant Genetic Resources, www.genesys-pgr.org, 2021-06-15.

et al., 2019). Plant tissue culture techniques offer an efficient and high-yielding technique for the production of these metabolites at the commercial level without the influence of external factors like geographical and seasonal variations (Aasim et al., 2018b; Iqbal and Ansari, 2019). Therefore, it is also possible to alter the concentration of the secondary metabolite and also possible to obtain the unique compounds from the parent plant which is not possible with traditional techniques (Naik and Al-Khayri, 2016). The classical plant tissue culture techniques include organ culture, callus culture, hairy root culture, and bioreactors. On the other hand, it is also possible to manipulate the potential of SMs by using novel techniques like the use of precursors (Koul et al., 2020), and in vitro elicitation (Śliwińska et al., 2021), endophytes, and metabolite engineering (Iqbal and Ansari 2019).

Precursors are biotic or abiotic agents that can be used in the chemical reactions for the production of other compounds and can be used in plant tissue culture (Karuppusamy 2009). The most commonly used precursors are fungus, yeast extract, polysaccharides, chitosans, meja, and amino acids. Some of the commonly used precursors include methyl jasmonate (Baek et al., 2020), sodium nitroprusside (Koul et al., 2020; Mahendran et al., 2021), calcium pantothenate, and cholesterol (Koul et al., 2020).

The application of biotic (microbes) and abiotic (physical, chemical) elements in plant tissue culture can lead to certain morphological and physiological changes in plants, and this process is known as "elicitation". The process of elicitation can be done in three different ways (i) exposing explants to elicitor followed by in vitro culture, (ii) no exposure of explants to elicitor followed by in vitro culture supplemented with different elicitor, and (iii) by exposing explants to elicitor followed by in vitro culture containing elicitor. The main objective of the elicitation is the existence, perseverance, and effectiveness of in vitro cells/tissues/organs (Kiong et al., 2005; Karuppusamy, 2009). The selection of an appropriate elicitor is highly significant and these elicitors are certain biological or nonbiological agents that trigger the protection and stress-generated reactions in plants (Radman et al., 2003; Kumar and Shekhawat, 2009).

Biotic elicitors are generally molecules originating from either pathogen or host (plants, insects or pathogens, or living organisms like fungi) and generally induce defense responses (phytoalexin accumulationhypersensitive response) in plant tissue (Angelova et al., 2006). The frequently used biotic elicitors include different polysaccharides like pectin, chitosan (Baque et al., 2012), chitin, dextran (Gadzovska Simic et al., 2014), oligogalacturonic acid (Hu et al., 2003), excerpt of microbes like Chitin (Dawande et al., 2020), glucans (Klarzynski et al., 2000) and glycoproteins (Yang et al., 2009), use of different cultured cells (fungal elicitors) like *Phytophthora cinnamoni* (Bais et al., 2002), yeast extract (Zaker et al., 2015), animal hormones like Melatonin (Coskun et al., 2019), and amino acids like glutamic acid (Ampofo and Ngadi, 2021).

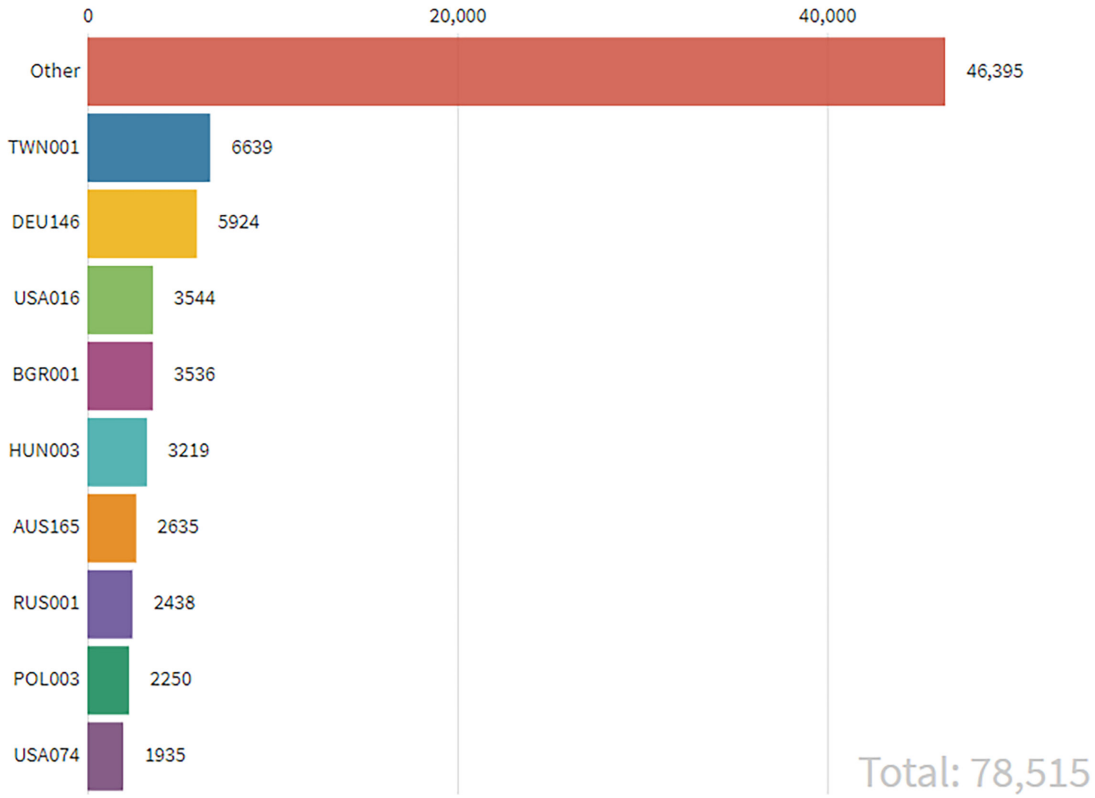

Figure 2. The main conservator institutions of medinal and aromatic plant accessions. Data accessed through Genesys Global Portal on Plant Genetic Resources, www.genesys-pgr.org, 2021-06-15. (TWN001 • World Vegetable Center, Taiwan, DEU146 • Genebank, Leibniz Institute of Plant Genetics and Crop Plant Research, Germany, USA016 • Plant Genetic Resources Conservation Unit, Southern Regional Plant Introduction Station, University of Georgia, USDA-ARS, United States, BGR001 • Institute for Plant Genetic Resources 'K.Malkov', Bulgaria, HUN003 • Institute for Agrobotany, Hungary, AUS165 • Australian Grains Genebank, Department of Economic Development Jobs Transport and Resources, Australia RUS001 • N.I. Vavilov Research Institute of Plant Industry, Russia, POL003 • Plant Breeding and Acclimatization Institute, Poland • USA074 • US Nicotiana Germplasm Collection, United States).

Abiotic elicitors are physical or chemical agents or compounds used for in vitro elicitation of different medicinal plants. The most commonly employed physical elicitors under in vitro conditions includes light and temperature. Light is a vital factor that affects the production of SMs. Different light sources used for in vitro elicitation include rays like UV (Nazir et al., 2020) or exposing explants to different LEDs lights (Kapoor et al., 2018) or light combinations (Khurshid et al., 2020). Temperature is another physical factor employed for in vitro elicitation (Naik and Al-Khayri 2016) by exposing cultured explants or shoots to thermal shocks/stress (Karakas et al., 2020), etc. Besides that, osmotic stresses, salinity, or drought induction are other physical factors applied for SMs fabrication. Some of the examples of osmotic stress elicitors include the application of proline (Gupta et al., 2015), PEG (Yamaner et al., 2013), and sucrose (Zobayed et al., 2007).

Chemical elicitors are used more prominently with a wide array of compounds with their subsequent impact as elicitors. Among these chemical elicitors, metal salts, metaloins, nanoparticles, and hormonal elicitors are most widely accepted. The application of metals (heavy metals and salts) to plants induces metabolic changes which in turn affect the production of different metabolites due to certain enzymes inhibition (Nasim and Dgir, 2010). These include the use of elicitors like $CuSO_4$ for Andrographolide contents in *Andrographis paniculata* (Dawande et al., 2020). Use of $CdCl_2$ in *Allium sativum* for Alliin, sugar, protein, and proline contents (Malik et al., 2020), reserpine and ajmalicine in *Rauvola serpentina* (Zafar et al., 2020), and stigmasterol in *Abutilon indicum* (Rao et al., 2021) have also been documented. Other heavy metals like Ca, Mg, Mn, Zn, Cu, Fe, Co in *Beta vulgaris* have also been applied as chemical elicitors for betalain (Savitha et al., 2006).

Nanoparticles of different origins are gaining popularity as a chemical elicitor for SMs and some of the examples of NPs include ZnO NPs, CuO NPs, CoO NPs; Ag NPs, Cu NPs (Fatima et al., 2020), and TiO_2 (Al-oubaidi and Kasid, 2015). Although the application of NPs as an elicitor revealed a positive impact on yielding maximum metabolites, the nanotoxicity impact of NPs on secondary metabolites production has also been documented (Jamshidi et al., 2016; Javed et al., 2017).

Plant growth regulators like salicylic acid (SA) or jasmonates like jasmonic acid (JA) or methyl jasmonate (MeJa) are the most preferred chemical elicitors in vitro (Koca and Karaman, 2015; Kahveci et al. 2021; Assaf et al. 2022). Some of the examples include the impact of SA and JA on Hypericin and Hyperforin in *Hypericum hirsutum and H. maculatum* (Coste et al., 2011) and Bacoside in *B. monnieri* (Koul et al., 2020), and Phenylethanoid and Glycoside contents in *Rehmannia glutinosa* by SA (Piatczak et al., 2016). It was also evident from the results that the concentration used in these studies varied from 1 mg/L to 300 mg/L depending on the genotype. MeJA has been used at a relatively higher rate of 50 mg/L and above (Inyai et al., 2021) for the elicitation of different SMs. However, some studies have mentioned the application of MeJa at the relatively low rate of 0.11–0.33 mg/L in *Pueraria candollei* var. Mirica (Rani et al., 2020) and 5–25 mg/L for *Andrographis paniculata* (Dawande et al., 2020).

6. Genetic engineering

Identification and characterization of the underlying genes responsible for metabolite synthesis and modification is a prerequisite for increasing metabolite production or engineering genes found in homologous or heterologous systems (Pickens et al., 2011). It is now possible to profile thousands of genes at once as a result of advances in sequencing technologies (Sun et al., 2021). Commonly, the objective is to boost the level of production of specific compounds in MAPs or to transfer a pathway to other organisms (Satish et al., 2019).

Two broad techniques have been used to improve the synthesis of one or more compounds. First, methods have been used to alter the expression of gene(s), so overcoming specific rate-limiting steps in the metabolic pathway, disabling competitive metabolic pathways, and reducing the catabolism of the target product. Second, regulatory genes that control several biosynthetic genes have been altered. Many research activities involving the overexpression of different pathway genes have been carried out, with the goal of producing new flower colors (Nishihara, 2011). In another example, RNA interference technology was used to make decaffeinated coffee, and the expression of one of the genes (theobromine synthase) was suppressed. The caffeine content of these transgenic plants was reduced by 70% (Ogita et al., 2003). In some circumstances, a metabolite may be hazardous to humans in one form, or in other circumstances, it may be less present in its natural product. Using genetic engineering approaches, these metabolites can be transformed into either a nonharmful or more effective chemical derivative.

Several attempts have been reported on genetic information in MAPs. In saffron (*Crocus sativus*) Rubio-Moraga et al. (2008) isolated four CCD genes. Then, they detected the expression pattern in which CsCCD1a showed a constant expression and CsCCD1b was expressed especially in stigma tissue. However, only CsCCD4a and CsCCD4b expressed cooperatively throughout stigma formation, resulting in the highest levels of carotene and ionone release. Similarly, in saffron, the CCD4 genomic DNA regions were isolated and analyzed by Ahrazem et al. (2010). In the saffron flower specifically in pollen, CCD4a promoter sequence was found appropriate to initiative GUS expression.

7. Medicinal plant in OMICS era

Omics use interdisciplinary fields of biology, such as genomics, transcriptomics, proteomics metabolomics, and ionomics to analyze different types of molecules on a large scale through high-throughput technologies (Blankenburg et al., 2009). These technologies are automated allowing fast, accurate and detailed analysis of huge numbers of samples in a very short period (Porter and Hajibabaei 2018). The sequencing of the genomes and transcriptomes is possible with minimal expenditure of time and money using bioinformatic approaches. Besides their contribution to the identification of gene controlling metabolites, they have also allowed us to investigate their indigenous effects inside cell lines.

7.1. Genomics of MAPs

The genetic profiling of each crop species is supportive of plant breeding activities. Previously, molecular markers such as RAPD, AFLP, and ISSR were often applied for breeding purposes. Besides morphological, anatomical, and chemical markers, the genetic diversity of medicinal plant species could be efficiently authenticated with recent developments like SCAR, Loop-mediated isothermal amplification (LAMP), and DNA barcoding. In addition, DNA sequences and fingerprints could be used to develop a reference library in the future (Ganie et al., 2015). Next-generation sequencing (NGS) and third-generation sequencing (TGS) are also easier and cheaper than older sequencing methods, and they can be done much faster than older sequencing methods like Maxam-Gilbert sequencing and Chain-termination.

7.1.1. Quantitative trait locus (QTL) mapping

QTL mapping research should be expanded since it is one of the most practical approaches to disclose the heredity of

SMs and scan the complete genome to discover the QTLs regulating characteristics linked with SMs production in MAPs. For instance, in *Artemisia annua,* Graham et al. (2010) reported QTL map which explains a significant part of the variation in key traits that control artemisinin yield. Artemisinin is the key component in the acceptance and commitment to therapy of malaria and the demand is expected to increase in the near future. In another study, Celik et al. (2016) analyzed 103 Turkish landraces and 15 cultivars of the opium poppy (*Papaver somniferum* L.) for the identification of QTLs controlling morphine content and they found one SSR and three AFLP loci significantly linked with morphine content. There is no doubt that the whole detected markers provide preliminary information for marker-assisted trait selection in plant breeding. In addition, extensive QTLs data of MAPs obtained from earlier studies are presented in Table 2.

7.1.2. Genome-wide association studies (GWAS)

The ever-increasing market demand for MAPs forces plant breeders and biotechnologists to create novel cultivars with improved qualitative and quantitative traits. In nature, there is enough genetic diversity for a wide number of MAPs species to have different yields and secondary metabolite compositions. Many of the genes involved in various stages of secondary metabolite biosynthesis pathways have been described. Furthermore, genetic inheritance research in some MAPs revealed the qualitative and quantitative character of the genes involved in these syntheses. According to Pichersky (1999) a dominant gene, LIS encoding linalool synthase in *Clarkia breweri* and a related dominant gene in *Mentha aquatica* regulate the accumulation of linalool and exhibit monogenic inheritance. GWAS success stories in numerous crop species have sparked heated debate. On the other hand, the emergence of NGS and other genotyping technologies has significantly increased the possibilities of extremely rapid marker creation, allowing for genome-wide screening of markers in unsequenced and uncharacterized MAPs. For example, Otto et al. (2017) used genotyping-by-sequencing (GBS) in chamomile to assess the genetic structure of the cultivated varieties-populations and to conduct a genome-wide association study (GWAS) to identify linked markers associated with flowering time and alpha-bisabolol content. GBS analysis identified 6495 high-quality SNP-markers in the panel of 91 *Matricaria recutita* and 4 *Matricaria discoidea* plants as an outgroup, grown in the greenhouse in Gatersleben, Germany. *M. recutita* turned out to be differentiated from the outgroup, as various cluster and main coordinate analyzes with the SNP markers showed. Chamomile genotypes of the same origin shared a high degree of genetic similarity. Flowering time analysis revealed that diploids flowered earlier than tetraploids, while alpha-bisabolol analysis revealed some tetraploid genotypes with high content. GWAS analysis discovered SNPs associated with flowering time (9) and alpha-bisabolol (71) that were highly significant. GWAS data open the path for future studies on the genetics of chamomile traits, the identification of marker-trait associations, and the development of reliable markers for plant breeding activities. For example, Fan et al. (2020) discovered the markers associated with the ginsenoside synthesis pathway, dry root weight, and stem thickness in *Panax notoginseng* by using SNP markers. As another example, in *Nicotiana tabacum* L., Tong et al. (2020) sequenced the whole genome of an intraspecific recombinant inbred line population, including an F1 generation and its parents. To create the genomic map, 45,081 markers were described, spanning a genetic distance of 3486.78 cM. This high-density genetic map will be contributed to QTL identification, gene localization, GWAS, and marker-assisted breeding in tobacco.

7.1.3. Kompetitive allele specific PCR (KASP)

KASP is one of the Uniplex SNP genotyping platforms and has become a global benchmark technology. It generates over a million data points annually for crop improvement purposes. Jang et al. (2020) sequenced the complete mitogenome of ginseng based on long-read data from the Nanopore sequencing platform in *Panax ginseng* C. A. Mey. They found 278 variants (213 SNPs and 65 InDels). Furthermore, 10 KASP markers were developed from 10 SNPs. The genotypes of 59 Korean ginseng were reliably identified using these markers, and mitogenome diversity was elucidated. These markers identified the genotypes of 59 Korean ginseng genotypes and mitogenome diversity. Ginseng breeding will benefit from the full mitogenome sequencing and 10 KASP markers. With another example, Ruzicka et al. (2021) used KASP to analyze the comfrey plant, which was developed using a next-generation sequencing approach. The plants were grouped into six distinct genetic clusters. Rosmarinic acid was not associated with any of the clusters, while a cluster was significantly different for some compounds, including allantoin and globoidan A. Similarly associated with a particular genetic cluster was low PA levels, which could become a valuable gene pool for minimizing PA levels through breeding.

7.1.4. Genome editing

Genome editing has lately offered plant breeders and biotechnologists a new tool for making precise and large-scale changes to plants that are not possible using traditional genetic engineering approaches. So far, only a few studies have shown that genome editing in MAPs may be used for secondary metabolic engineering (Jansing et al., 2019). For this aim, CRISPR/Cas (clustered regulatory interspaced short palindromic repeats), TALENs (transcription activator-like effector nucleases), and ZFNs

Table 2. Several SMs related QTLs/markers in medicinal and aromatic plants.

Species	Trait	Gene/QTL	Marker System	Marker	Linkage group	Reference
Salvia miltiorrhiza	Salvianolic acid b content	3 QTL	53 SSR, 38 SRAP, and 2 ISSR	Between DSSR-540 and DSSR-98	LG7	(Li et al., 2019)
	Lithospermic acid content	2 QTL		DSSR-140 and DSSR-77	LG2 and LG4	
	Rosmarinic acid	1 QTL		Between DSSR-540 and DSSR-98	LG7	
Nicotiana tabacum	Total alkaloids	-	AFLP, SSAP, and ISSR markers	EA30	LG2	(Julio et al., 2006)
	Nicotine			PA41	LG2	
	Polyphenols			PC33	LG14	
				DHCTTS	LG3	
	Anabasine			EA27	LG14	
				PA9	LG4	
	Anatabine			HAGTSA1	LG4	
	Nornicotine			EA28	LG3	
				DEA35	LG14	
	Nicotine	*qNIC1-1*	-	M4E12-250–M4E12-240	LG1	(Li et al., 2011)
		qNIC1-2		U829-720–M2E16-295	LG1	
Allium cepa	Anthocyanin synthesis	*qAS7.1*	HRM Markers	T25488.1_1462-i39918_357-HRM	LG7	(Choi et al., 2020)
	Anthocyanin content	*qAC4.1*		T57513.1_314-T53764.1_356	LG4	
		qAC4.2		T84695.1_220-i32123_1465-HRM	LG4	
Papaver somniferum	Morphine content	-	Genomic SSR	psgSSR853	-	(Celik et al., 2016)
			AFLP	E-ACA + M-CAG-63		
				E-ACC + M-CAC-146		
				E-AGC + M-CTA-138		
Capsicum annuum	Oleoresin content	*Qole.iivr-2.1*	39 SSRs, 1 SCAR, and 5RAPD marker	CAMS-373-HpmsE006	LG2	(Dwivedi et al., 2014)
		Qole.iivr-3.3		HPMSE-027-CAMS-122	LG3	
Camellia sinensis	Anthocyanin content	*qOPC03a_2015*	SNPs	dm58	LG03	(Xu et al., 2018)
		qOPC08a_2015		f7O7	LG08	
		qOPC08b_2015		fl 360	LG08	
		qOPC08c_2015		df710	LG08	
	Caffeine content	*qCAFlla_2014*		dm870	LG11	
		qCAFUb_2015		f983	LG11	

Table 2. (Continued).

Stevia rebaudiana	Reb A (%TSG)	*qPRAs.2.1*	SSR markers	4013A	LG2	(Vallejo et al., 2021)
		qPRAh.2.1		4013A	LG2	
	Reb D (mg/g)	*qRDs.1.1*		2SS3A	LG1	
		qRDh.1.1		1460A	LG1	
		qRDs.6.1		3546A	LG6	
		qRDh.6.1		3546A	LG6	
	Reb D (>TSG)	*qPRDs.6.1*		3546A	LG6	
		qPRDh.6.1		3546A	LG6	
	Stevioside	*qSTH.5.1*	SNPs	Contig_20_2310420	LG5	(Bahmani, 2021)
		qSTS.5.1		Contig_20_2310420	LG5	
		qSTG.5.1		Contig_20_2310420	LG5	
	Reb A	*qRAH.5.1*		Contig_148_756211	LG5	
		qRAS.5.1		Contig_148_756211	LG5	
		qRAG.5.1		Contig_20_2310420	LG5	
	Reb B	*qRBH.5.1*		Contig_1993_192020	LG5	
		qRBH.5.2		Contig_20_2310420	LG5	
	Reb D	*qRDH.5.1*		Contig_20_2310420	LG5	
		qRDS.5.1		Contig_20_2310420	LG5	
		qRDG.5.1		Contig_1621_108763	LG5	
	Total steviol glycosides	*qTSGsG.6.1*		Contig_578_275761	LG6	
		qTSGsG.6.2		Contih_2287_26230	LG6	
		qTSGsG.6.3		Contig_146_1129026	LG6	
	Reb A	*qPRAH.5.1*		Contig_199_465228	LG5	
		qPRAS.5.1		Contig_199_465228	LG5	
		qPRAG.5.1		Contig_20_2310420	LG5	
	Reb D	*qPRDH.5.1*		Contig_199_465228	LG5	
		qPRDS.5.1		Contig_199_465228	LG5	
		qPRDG.5.1		Contig_199_465228	LG5	
		qPRDG.5.2		Contig_1439_177475	LG5	

(zinc-finger nucleases) are now artificially engineered.

According to Wilson and Roberts (2014), the CRISPR/Cas9 system is one of the most recent and promising gene modification approaches, allowing plant metabolic engineering by altering multiple genes in the same region of the chromosome and generating smart variations in the plants. In recent years, the number of research papers on the CRISPR/Cas9 system use has steadily grown in MAPs. Li et al. (2016) and Ma et al. (2015) used this system to silence the major gene of the tanshinone metabolic pathway and inhibit the rosmarinic acid synthase gene (SmRAS), in *Salvia miltiorrhiza*. Feng et al. (2018) reported the inhibition of farnesyl pyrophosphate synthase (FPS) enzyme activity by a targeted mutation in gene Dzfps in *Dioscorea zingiberensis*, which resulted in 1.6 times less squalene content than wild type plants. These findings provide fresh insight into genome editing of MAPs and offer breeders a new tool for precision breeding.

Alagoz et al. (2016) used the type II CRISPR/SpCas9 system to knock out the 4′OMT2 in opium poppy (*Papaver somniferum* L.), a gene that regulates the biosynthesis of benzylisoquinoline alkaloids. They showed that the biosynthesis of benzylisoquinoline alkaloids (e.g., morphine, thebaine) was significantly reduced in the transgenic plants. Furthermore, they observed a novel uncharacterized alkaloid only in CRISPR/Cas9 edited plants. Therefore, the applicability of the CRISPR/Cas9 system demonstrated for the first time for MAPs to regulate BIA metabolism and biosynthesis.

7.2. Transcriptomics of MAPs

The word "transcriptome" refers to the entire collection of ribonucleic acid (RNA) molecules that are expressed in a particle unit, including tissue, cell, or organism (Milward et al., 2016). Medicinal plant transcriptomic research has become the most active area of medicinal plant genomic research in the last few years. Transcriptome analysis provides interesting and helpful data regarding the activation or expressions of the genes (Wang et al., 2015). Transcriptomics research on medicinal plants can help scientists to understand better gene function and regulatory mechanisms as well as improve methods of cultivation and breeding selection for better production. In the field of molecular biology, transcriptome-sequencing technology (TST) is widely used for sequencing methods (Sun and Wei, 2018). High-throughput transcriptome sequencing studies in MAPs are presented in Table 3.

Xu et al. (2014), during their experiment, used the high-throughput transcriptome IGA-II (Illumina GA-II) sequencing technology to study the Amur grape (*Vitis amurensis* L.) and resulted a total of 6850 transcripts participated in thermos regulation. This finding opens the way for further research into Vitis species' cold tolerance mechanisms and the genes implicated in the cold stress regulation network. Liu et al. (2015) analyzed the transcriptome of *Panax notoginseng* adventitious roots and discovered 17% transcript changes in adventitious roots compared to common roots, as well as twenty-one genes involved in ginsenoside production. Pragati et al. (2018) conducted a study on Aloe vera to sequence the transcriptome in leaf and root samples. They used IPE (Illumina paired-end) sequencing technology and reported 221,792 and 161,733 transcripts from leaf and root with 113,062 (root) and 141,310 (leaf) uni-genes. Sixteen (16) genes linked to the biosynthesis of carotenoids, lignin and anthraquinone, and saponins were identified during the study. Another study was performed by Guo et al. (2018) on *Paeonia suffruticosa* commonly called "tree peony" for transcriptome sequencing. They found drought resistance-related 81,725 uni-genes in *P. suffruticosa* Plant. Their study provides information on drought stress during the early flowering stage of the plant and also provides information about the hormone signaling, metabolic pathways, and reproductive system's interaction.

Singh et al. (2017) applied IPE sequencing technology to sequence the Nag chhatri plant (*Trillium govanianum*) transcriptome and found a total of 69,174 transcripts and identified a series of genes. Biosynthesis of steroid saponins and other secondary metabolite pathways were recognized during the study. This discovery provided assets for genetic manipulation for the pinpointing of potentially biological dynamic metabolites and can help in developing functional related molecular marker resources. Furthermore, Loke et al. (2017) during his research sequenced the transcriptome of *Polygonum minus* L. commonly known as "kesum" and attained the 188,735 transcripts. They also study the metabolic pathway of identified genes in the root and leaf tissues of the plant. Li et al. (2016) sequenced the transcriptome of a flowering shrub named *Callerya speciose* L. by using the Illumina sequencing method and reported 161,926 uni-genes with 4538 differential gene expression (DEGs) in the studied plant. DEGs linked to light signaling, cell wall loosening, and starch synthesis could be connected with the development of storage roots. Hou et al. (2018) planned a study on the medicinal plant *Cornus officinalis* and applied next-generation sequence (NGS) technology to study the transcriptome of leaf and fruit tissues of *C. officinalis*. During the study, they identified 56,392 uni-genes and 4585 significant DEGs. Among the DEGs, upregulated genes are 1392 and 3193 genes are downregulated. Furthermost DEGs are related to the regulation of secondary metabolism and terpenoid biosynthesis. Understanding plant genes and biosynthetic pathways are provided by this. The compound rosmarinic acid biosynthesis in *C. officinalis* is a multifunctional phenolic biologically active compound with different antiviral and antibacterial activities. Li et al.

Table 3. High-Throughput Transcriptome Sequencing study in MAPs.

Species	Sequencing platform	Tissue	Uni-genes	Medicinal compounds	Reference
Salvia miltiorrhiza	Illumina's HiSeq 2000	Roots and leaves	58,085	phenylpropanoids and terpenoids	(Li et al., 2020)
Prunus armeniaca	Illumina HiSeq 4000	-	116,957 and 31,360	-	(Wang et al., 2020)
Angelica sinensis	Illumina HiSeq X ten	Root	25,463	-	(Feng et al., 2020)
Polygonatum cyrtonema Hua (P. cyrtonema)	Illumina	Leaf, root, and rhizome	164,573	Polysaccharide	(Wang et al., 2019)
Arisaema heterophyllum Blume	Illumina HiSeq 4000	Root, tuber, and leaf	35,686, 43,363, and 47,783	Flavonoids	(Wang et al., 2018)
Artemisia argyi	RNA sequencing	Leaf, root, and stem	99,807	Terpenoids	(Liu et al., 2018)
Ginkgo biloba	Illumina	-	37,625	Flavonoids	(Wu et al., 2018)
Pinellia ternata	Illumina HiSeq 2000	Leaves and root	89,068	Benzoic Acid and Ephedrine	(Zhang et al., 2016)
Atractylodes lancea	Illumina	Leaves and root	62,352	Terpenoids	(Ahmed et al., 2016)
Panax ginseng	454	Leaves, roots, and flowers	107340	Triterpene saponins	(Jayakodi et al., 2014)
Gentiana rigescens	Illumina Hiseq2000	Root	76,717	Terpenoid biosynthesis	(Zhang et al., 2015b)
Astragalus chrysochlorus	Illumina	Leaves and root	59,656	Secondary metabolites and carbohydrate metabolism	(Cakır et al., 2015)
Panax japonicus	Illumina	Root	66,403	Triterpenoid saponin	(Zhang et al., 2015a)
Chinese wolfberry	Illumina	Leaves	61,595	Carotenoid	(Wang et al., 2015)
Glycyrrhiza uralensis	Illumina RNA-Seq	Root	43,882	Putative cytochrome P450 enzymes and putative vacuolar saponin transporters	(Ramilowski et al., 2013)
Macrotyloma uniflorum	Illumina sequencing technology	Root	21,887	Threonine protein	(Bhardwaj et al., 2013)
Panax quinquefolius	454	Root	41,623	Ginsenoside	(Wu et al., 2013)
Rhodiola algida	Illumina	Leaves, fruits, and root	82,664	-	(Zhang et al., 2014)
Isatis indigotica	454	Flowers, leaves, stems, and roots	36,367	Indole, terpenoid, and phenylpropanoid	(Chen et al., 2013)
Litsea cubeba	Illumina HiSeq 2000	Flower buds, full open flowers, young leaves, leaf buds, and fruits	285	terpene synthase	(Han et al., 2013)
Lycium chinense	Illumina HiSeq 2000	Leaves, fruits, and root	56,526	phenylpropanoid, chlorogenic acid	(Zhao et al., 2013)
Lotus corniculatus	Illumina/Solexa sequencing	Flowers, pods, leaves, and roots	45,698	flavonoid biosynthesis	(Wang et al., 2013)

Table 3. (Continued).

Hypericum perrforatum	Illumina HiSeq 2000	Roots, stems, leaves, and flowers	2,291	Type III polyketide synthases	(He et al., 2012)
Digitalis purpurea	454	Leaf, stem,	23,532	Cardiac glycosides	(Wu et al., 2012)
Paeonia suffruticosa	454	Flower buds	23,652	Various	(Gai et al., 2012)
Ricinus communis	Illumina	Seed, leaf,	75,090	Lipids	(Brown et al., 2012)
Punica granatum	Illumina	Fruit peel	9,839	Phenolic, flavonoids	(Ono et al., 2012)
Bupleurum chinense	454	Root	24037	Saikosaponins	(Sui et al., 2011)
Panax ginseng	454	Root	31741	Ginsenosides (triterpene saponins)	(Chen et al., 2011)
Panax notoginseng	454	Root	30852	Triterpene saponins	(Luo et al., 2011)
Glycyrrhiza uralensis	454	Root, stem, leaf	27,229	Flavonoid, ginkgolides	(Lin et al., 2011)
Camptotheca acuminata	454	Leaf	30,358	Terpenoid, indole alkaloid, camptothecin	(Sun et al., 2011)
Fraxinus spp.	454	Phloem plug	58,673	NS	(Bai et al., 2011)
Taxus cuspidata	454	Leaf	20,557	Paclitaxel, taxanes	(Wu et al., 2011)
Siraitia grosvenorii	Illumina	Fruit	43,891	Mogrosides (triterpene saponins)	(Tang et al., 2011)
Ginkgo biloba	454	Leaf	22,304	Tanshinone, salvianolic	(Lin et al., 2011)
Panax quinquefolius	454	Root	31,088	NS flavonoids	(Sun et al., 2011)
Epimedium sagittatum	454	Leaf	76,459	Glycyrrhizin	(Zeng et al., 2010)
Glycyrrhiza uralensis	454	Root, stem, leaf	27,229	Flavonoid, ginkgolides	(Li et al., 2010a)
Salvia miltiorrhiza	454	Root	18,235	NS	(Li et al., 2010b)
Salvia sclarea	454	Calyx	45,822	Lycopodium alkaloids	(Legrand et al., 2010)
Huperzia serrata	454	Leaf, root	36,763	NS	(Luo et al., 2010)
Phlegmariurus carinatus	454	Leaf, root	31,812	Lycopodium alkaloids	(Luo et al., 2010)

(2017) examined the transcriptome of the medicinal plant *Dracocephalum tanguticum* and identified 151,463 uni-genes. Thoroughly, 22 rosmarinic acid-related biosynthetic genes were anticipated that provide a reference for destiny studies on biosynthetic genes associated with rosmarinic acid in this plant species.

Yuan et al. (2018) investigated the biosynthesis paths of flavonoids and relevant precursors using NGS technology to perform de novo transcriptome sequencing and analysis of *Abrus mollis* leaves. In the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, the unigenes with their important enzymes in the biosynthesis of phenylpropanoid, phenylalanine, isoflavonoids, and flavonoids were studied. Their findings will aid in the discovery of isoflavonoid and flavonoid production mechanisms in *A. mollis* leaves, as well as biological regulatory studies. Fu et al. (2019) sequenced the transcriptome of *Dysphania schraderiana* flower and leaf tissues for the first time using Illumina Hiseq4000 and discovered 40142 uni-genes. There are 2579 genes that are expressed differentially in flowers and leaves among the 40,142 uni-genes and were included in future enrichment analysis. This research has cleared the way for further research into *D. schraderiana*'s physiological processes and secondary metabolite production. Dinh et al. (2020) used a new transcriptomics sequence technique "Illumina HiSeq 4000 sequencing platform" to investigate the transcripts from the stem, leaves, and roots of a medicinal plant *Populus alba* commonly called silver poplar. 11343 EST-SSRs primers were optimized and 101 primers were selected from 7774 primer pairs for polymorphism confirmation. Among the 101 primer pairs, 20 primers showed high polymorphism. These results were important for the restoration, conservation, and better management approaches of *Populus alba*.

Wang et al. (2020) Exclude highlighted words applied NGS tools for transcriptome sequencing of *Gastrodia elata* and recognized 33,322 uni-genes. Among the 33322, 5.85% uni-genes confined at least one (01) SSR marker. The AG/CT reappearance keynote was the most common in SSRs with 21.67% detections. The conclusion of this present study represents a deeper appreciation of molecular mechanisms and basics of internal metabolism, growth, and improvement of *G. elata* medicinal plant. Lade et al. (2020) studied the genetic variation of 96 *Tinospora cordifolia* medicinal plants from different locations in India and recognized 7611 SSRs from 26,8149 transcripts of *T. cordifolia*. The maximum variation was found in Tc131, 31, 129, 38, 16, 59, 60, 17, 106 and 130. The following markers TCSSR-37, TCTSSR-92, SSR-18, TCTSSR-59, TCTSSR-126, and TCTSSR-123 showed high potential for genetic variation. Hina et al. (2020) applied the Illumina technology and de novo assembly against the two Menispermum species for transcriptome sequencing. A total of 78,921 uni-genes were obtained and 521 polymorphic EST-SSRs were detected that showed high transferability against the Menispermum species. Their study concluded that newly designed marker will be helpful for further Menispermum genetics studies. He et al. (2020) analyzed SSR sites in *Paeonia lactiflora* using microsatellite software and discovered 86,195 uni-genes, with 21,998 SSR sites spread across 17,567 uni-genes. Forty-five primers showed high polymorphism out of 100 randomly selected primers. These highly polymorphic primers were used for clustering sixteen *P. lactiflora* varieties. These newly developed markers will be helpful for further *P. lactiflora* genetic study. Shah et al. (2020) performed a de novo transcriptome analysis of *Lantana camara* leaves and roots using transcriptome sequencing techniques. In leaf and root tissues, a total of 72,877 and 513,985 unigenes were found, with 229 and 943 genes engaged in phenylpropanoic acid production, respectively. For the treatment of fever and sore throat, *Tetrastigma hemsleyanum* extract is utilized as a broad-spectrum antibiotic substance. Liao et al. (2020) used comparative transcriptome analysis to find 26 cytochrome P450 and 17 uridine diphosphate glycosyltransferase candidate genes relevant to triterpene saponin production in Entada phaseoloides root, stem, and leaf tissues. The findings aided in the functional genomics of triterpene, saponin biosynthesis research.

Bains et al. (2019) sequenced the leaf transcriptome of *Saussurea lappa* using NGS technology and discovered transcripts encoding proteins involved in flavonoid and sesquiterpene production. These discoveries will help the researchers learn more about this plant's functional genomics. Learn to investigate the response of *Artemisia argyi* to abiotic stress, Rastogi et al. (2019) performed transcriptome sequencing of leaves under drought, waterlogged, cold conditions, and salt stress. The plants were the most sensitive to cold stress of all the tested pressures. Eugenol production was likewise lowered by the abiotic stress treatments. Yan et al. (2020) analyzed the metabolome and transcriptome of *Tetrastigma hemsleyanum* green and purple leaves. In the leaves, a total of 4211 transcripts and 209 metabolites were found to be differently expressed, with sixteen compounds revealed to be substantially related with fourteen transcripts implicated in the anthocyanin biosynthesis pathway. Because of the sesquiterpene lactones it produces, this has a lot of therapeutic potentials.

8. Conclusions

The understanding of biochemistry of MAPs-based secondary metabolite synthesis has been increased in recent years with the development of omics approaches. The advent of DNA markers, which has helped to detect QTLs along the chromosomes controlling for these biomolecules, is one of the series' important breakthroughs. Moreover,

the development of MAPs confronts numerous obstacles, including gene knockdown, irregular gene expression due to a complicated gene network, and a limited or no rise in the concentration of desired SMs up to the commercialization level. Therefore, the future of MAPs for human health depends on the application of multidisciplinary approaches right from the basics of biology, ethnobotany, and conservation biology to the current omics. It is obvious that these multidisciplinary approaches consist of combining traditional methodologies, omics, marker-assisted selection, and artificial intelligence technologies in compound design and production.

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