All-Russian Collection of Plant Cell Cultures

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The collections of plant cell cultures maintained in vitro are valuable sources of strains with unique ecological and biotechnological traits. Such collections play a vital role in bioresource conservation, science, and industry development. Here is an overview of All-Russian Collection of Plant Cell Cultures at the Institute of Plant Physiology of the Russian Academy of Sciences (IPPRAS). The total collection holdings comprise about 120 cell cultures of medicinal and model plant species. Several plant cell culture strains have been adapted for cultivation in bioreactors from laboratory (5–20-L) to pilot (75-L) to semi-industrial (630-L) scale for the production of biomass with high nutritive or pharmacological value. Some of the strains with proven biological activities are currently used to produce cosmetics and food supplements. Here is also provided a brief information on the current collection composition and major activities, their use in research, biotechnology, and commercial application. The most interesting studies performed with collection strains were highlighted.

Keywords: plant biotechnology ; in vitro collection ; plant cell cultures

1. Plant Cell Culture Collections around the World

Plant cell culture is a unique, artificially created in vitro biological system—a population of constantly proliferating undifferentiated plant cells. Cell cultures maintained on the surface of the solid nutrient medium (callus) or in a liquid medium (cell suspension) often retain the ability of the donor plant to produce specific secondary metabolites of high pharmacological value [1][2]. Rapid growth under sterile controlled conditions and stable biosynthesis of the desired compounds make the cell cultures an attractive alternative to wild and plantation-grown medicinal plants for biomass and phytochemical production [3][4]. Cell cultures lacking organismic controls can also be used as model systems in physiological, biochemical, and molecular studies, i.e., investigating the regulation of cell growth and secondary metabolite biosynthesis, stress signaling, and stress tolerance [3].

Pilot production projects using plant cell cultures were developed in the 1980s–1990s (e.g., [5][6][7][8][9][10][11]). Regrettably, most of them were later closed, facing constraints of high production costs and low content of the desired phytochemicals making such hi-tech production unprofitable or uncompetitive [12][13]. However, due to recent trends toward sustainable and eco-friendly production processes, plant cell cultures are retrieving increasing attention and a new spin [12]. Recent reviews [14][15][16][17] highlighted over 20 companies using plant cell culture-derived substances in their cosmetic products. The concept of cell culture-produced biomass as a component of food supplements was also revived [18][19][20]. Recent studies demonstrated that teupolioside, a biologically active phenylpropanoid glycoside produced from the cell culture of *Ajuga reptans* L., was effective for wound healing and exhibited anti-inflammatory activity in the model of induced colitis [21][22]. Cell culture extracts containing different concentrations of teupolioside have been certified as food supplement ingredients in Europe [23]. Additionally, the commercial production of the anti-cancer drug Taxol© (a trading name of paclitaxel) from the cell cultures of *Taxus* spp. has been known for a long time [1][24].

The induction and maintenance of the cell strains with intensive growth accompanied by high and stable metabolite production is a prerequisite for successful cell-based biotechnology. However, the collections of cell cultures are few and mainly limited to developed countries. The largest and most online visible collections are the Plant Cell Culture Library of the University of Massachusetts Amherst (>1000 plant species, USA, https://www.umass.edu/ials/pccl-database, accessed on 23 March 2023); the cell culture collection of the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures (>80 families, last mentioned in [12]); the VTT Culture Collection; collections from Finland (23 species, [25]); RIKEN BRC Plant Cultured Cell Resources, Japan (32 species, [26]); the cell culture collection of the University of Debrecen, Hungary [27]; and the collection of in vitro plant cell cultures at the Institute of Experimental Botany (Czech Republic, >20 species, [28]). These collections hold cell strains with anti-cancer, antimicrobial, antioxidant, insecticidal, and other properties as well as model cell strains of tobacco, *Arabidopsis thaliana* (L.) Heynh. (wild-type and mutants), and plant species with sequenced genomes.

The All-Russian Collection of Plant Cell Cultures hosted by the Institute of Plant Physiology, Russian Academy of Sciences (IPPRAS) is the oldest and most diverse Russian collection of plant cell cultures [29], with a mandate to receive and deposit cell strains from other institutions for patent purposes.

2. All-Russian Collection of Plant Cell Cultures—Historical Perspective and Current Composition

The first cell cultures in Russia were developed by Prof. Raisa G. Butenko and her research team at IPPRAS in the late 1950s–mid 1960s [30]. These included cell cultures of *Panax ginseng* C. A. Mey., *Rauvolfia serpentina* Benth. ex Kurz, *Dichroa febrifuga* (Lour.) Y. De Smet and C. Granados, *Catharanthus roseus* (L.) G. Don, *Dioscorea deltoidea* Wall., and other medicinal plant species [31][32]. Some of those cultures are still maintained in the active collection by periodic subcultures. The collection composition and use have been recently reviewed [30]. Historically, the collection has been focused on developing and maintaining cell strains accumulating isoprenoid compounds (furostanol glycosides, ginsenosides, taxoids, etc.) [33], although model strains of *Nicotiana tabaccum* L. and *Arabidopsis thaliana* are also present [30]. As of March 2023, the collection holds 43 cell culture strains of 24 plant species as the core collection. Furthermore, 74 strains of 32 plant species are cultured for experimental purposes. The most represented families are Araliaceae, Fabaceae, Lamiaceae, and Taxaceae. The core collection is mostly formed by cell strains producing high quantities of secondary metabolites valuable for human health. These strains have optimized culture conditions and the passport data (growth, cytological, biochemical characteristics, etc.) recorded. The core collection includes, for example, cell culture strains of *Dioscorea deltoidea*, with total content of protodioscin, deltoside and their 25(*S*)-isomers up to 4.6–5.7% of the dry cell weight (DW); *Panax ginseng* and *Panax japonicus* (T. Nees) C.A. Mey. cell strains (ginsenoside and their derivatives up to 3.5% DW); *Tribulus terrestris* L. (total content of furostanol glycosides 0.1% DW); *Polyscias filicifolia* L. H. Bailey and *P. fruticosa* Harms (total content of polysciosides and their derivatives 0.5–3.0% DW). The cell cultures of some species, e.g., *Dioscorea deltoidea*, *Mandragora turcomanica* Mizgir., and *Medicago sativa* L., have been maintained by periodic subcultures since the 1970s or 1980s. The experimental collection contains recently acquired cell strains at different stages of growth optimization, biochemical evaluation, and screening for biological activities. These include, for example, cell cultures of medicinal plants *Sutherlandia frutescens* (L.) W. T. Aiton, *Ajuga turkestanica* (Regel) Briq., *Alhagi maurorum* Medik., *Maackia amurensis* Rupr., *Cladochaeta candidissima* DC., *Alcea kusariensis* (Iljin ex Grossh.) Iljin, and *Panax vietnamensis* Ha and Grushv.

3. Using Plant Cell Culture Strains in the Research

Cell culture strains from the collection have been extensively used as models to study plant cell growth and biosynthesis regulation in isolated cells compared to organized tissues or whole plants. For example, wild-type and mutant cell strains of *Arabidopsis thaliana* were used to study the interaction of ethylene and abscisic acid signaling pathways [34], sodium ion intake and transport [35][36], nitric oxide effects [37], as well as the regulation of zinc homeostasis genes in plant cells [38].

The variety of cell lines developed from different species belonging to the same family (Araliaceae, Fabaceae, Taxaceae) allows the investigation of taxon-related variations in primary and secondary metabolism in the cell cultures. In addition, cell strains developed from different plant parts (explants) or donor plants from different geographical locations and maintained on nutrient media with varied mineral and phytohormonal composition are excellent models to study the intra-specific variations in cell culture properties and the role of explant source and cultivation conditions on cell growth and biosynthesis. Recent studies performed on callus and suspension cell cultures of three yew species (*Taxus baccata* Thunb., *T. canadensis* Marshall, and *T. wallichiana* Zucc.) and two Taxus × media Rehder hybrids originating from different explants and grown in over 20 nutrient media revealed that genotype (the individual plant used for culture induction) was the most significant factor influencing the content and composition of taxoid compounds in cell biomass followed by species and medium formulation [39]. Two callus and two suspension cell lines of *Sutherlandia frutescens* induced from hypocotyl and cotyledon explants had distinct cell morphology but very similar profiles of secondary metabolites that differed from secondary metabolite composition in plant leaves [40]. By contrast, the content of fatty acids (FAs), primarily linoleic and linolenic, in cell cultures was influenced by both the explant origin and growth conditions (light or dark) [40]. In *Alhagi maurorum*, the explant type significantly affected the callus induction rate; in vitro seedlings were a superior explant source compared to ex vitro plants [41].

The stability of growth and biosynthetic characteristics of the cell cultures over time is one of the main questions of interest in biotechnological collections and production companies. The cell culture collection at IPPRAS, with its long-term cultured strains, is well-positioned to be utilized in experiments exploring stability monitoring in cell cultures of different taxa. For example, the cell suspension of *Panax japonicus* maintained by periodic subcultures for over 20 years fully

retained its growth characteristics [30] and produced a broad spectrum of ginsenosides, including protopanaxatriols (Re, Rg_1, Rf), protopanaxadiols (Rb_1, Rb_2, Rc, Rd), ginsenoside R_0, and malonyl-ginsenosides [42]. The main growth parameters recorded during cultivation in the 20-L, 75-L, and 630-L bioreactors remained unchanged for the suspension cell culture of *Polyscias filicifolia* after five years of maintenance by periodic subcultures [43].

4. Biotechnological Application of Plant Cell Strains from the Collection

Before being used in biotechnology, cell strains are assessed following a standard evaluation scheme which includes cytological analysis (cell size, form, level of aggregation), reference photographs, evaluation of growth characteristics, and biochemical (secondary metabolites) analysis [30]. Optional parameters such as chromosome number may be recorded for new strains before deposition in the collection. This information is included in cell strain passports and maintained for future reference. Since 2021, the cultures in the collection have also been screened for antioxidant and antimicrobial activities. Strains with a specific growth rate >0.12 day^{-1} and composed of small-sized (about 50 µm) individual cells or small cell aggregates are preferable for bioreactor cultivation [3][33].

Newly developed cell strains often require optimization of medium composition, including phytohormones, inoculum density, and subculture duration to improve biomass and phytochemical yield. In addition, new strains usually undergo "auto-selection"—a process when highly-proliferating cells tend to survive and predominate in the population. It usually takes one to two years for cell suspensions to stabilize under the optimized conditions, but this period is highly species-dependent. Stably growing strains with high content of the desired metabolites or high biological activities are further tested for bioreactor cultivation using a cascade of bioreactors (20 L–75 L–630 L) in the biotechnological facility of IPPRAS, where culture regimes (periodic or semi-continuous) and conditions (air supply, stirring rate) are further optimized. Large-scale (630-L) bioreactor production has been developed and routinely applied for suspension cell cultures of *Dioscorea deltoidea*, *Polyscias filicifolia*, *Panax japonicus*, and *Taxus wallichiana* [43][44][45][46]. Smaller 20-L or 75-L bioreactors were successfully tested for the cell cultures of *Tribulus terrestris*, *Taxus baccata*, *Polyscias fruticosa*, *Panax vietnamensis*, *Stephania glabra* (Roxb.) Miers, and some other species [39][47][48]. Some cell culture strains of biotechnological interest are presented in **Table 1**.

Several commercial products containing bioreactor-produced cell biomass are currently available in the market. For example, the food additive Vitagmal © is based on dried biomass of a *Polyscias filicifolia* cell culture which had passed the clinical trial and was approved for commercial use in the late 1990s. This phytopreparation was proven to exhibit adaptogenic and anti-teratogenic effects [49]. The cell culture of *Panax ginseng,* strain G1, was distributed to government companies for biotechnological production in the 1980s, but those pilot productions collapsed during the country's economic crisis. In the 2020s, however, the strain was successfully adopted by a new commercial company currently producing a series of cosmetics and food additives on its base (https://cosmevita.ru/collections/, accessed on 24 January 2023).

Table 1. Some representative strains with valuable biotechnological traits from the core of the All-Russian Collection of Plant Cell Cultures.

Cell Strain	Year Strain Induced/Received by Collection	Characteristics
***Dioscorea deltoidea*, strains DM-05 and DM-05-03**	**1972/1985**	**Small-aggregated, rapidly growing cell strains developed through mutagenesis (single and double treatment with N-nitroso-N-methylurea) [50]; super-producer of steroidal glycosides protodioscin and deltoside and their 25(*S*)-isomers [33][51][52], adapted for large-scale bioreactor cultivation [53][54]. The total content of steroidal glycosides 4.6–5.7% DW [52] can be increased up to 13.9% DW in bioreactor production with a high aeration level [33][54]. Extensively used to study the regulation of steroidal glycoside biosynthesis in cell cultures [33]. Bioreactor-produced cell biomass was assessed for elemental composition [46], toxicology [55], and demonstrated positive effects in rats with induced type 2 diabetes mellitus and obesity [55][56].**
***Polyscias filicifolia*, strains BFT-01-95 and Pf-SH**	**1991/1995; 2018/2023**	**Cell strains adapted for large-scale bioreactor cultivation [43] with a total content of polysciosides and their derivatives up to 3% DW. Bioreactor-produced cell biomass of BFT-01-95 has adaptogenic and anti-teratogenic activities, and is currently used in commercial food supplements [49][57].**
***Panax ginseng*, strain G1**	**1959/1985**	**One of the oldest cell strains with stable growth and chromosome number, a producer of ginsenosides. The strain is currently used in the commercial production of several cosmetic products.**

Cell Strain	Year Strain Induced/Received by Collection	Characteristics
***Panax japonicus*, strain 62**	**1995–97/1998**	**Cell strain adapted for large-scale bioreactor cultivation [44] with a total content of ginsenosides (Rg_1, malonyl-Rg_1, Rb_1, malonyl-Rb_1, Rb_2/Rb_3, malonyl-Rb_2/Rb_3, Rd, malonyl-Rd, Rf, R_0, chikusetsusaponin IVa) of 3.46% DW [58]. Bioreactor-produced cell biomass exhibited hypoglycemic and hypocholesterolemic activity in rats with diet-induced obesity [55].**
***Tribulus terrestris*, strain 8**	**2014/2014**	**Cell strain adapted for laboratory bioreactor cultivation with a total content of furostanol glycosides 0.1% DW [48]. Bioreactor-produced cell biomass positively affected rats with induced type 2 diabetes mellitus and obesity [55][56].**

Phytopreparations based on cell cultures of *Dioscorea deltoidea* (strain DM-05-03), *Panax japonicus* (strain 62), and *Tribulus terrestris* (strain 8) exhibited a range of positive effects in rats with induced type 2 diabetes mellitus and obesity [55][56]. The toxicological evaluation of *D. deltoidea* cell biomass [55] and its elemental composition [46] were the first steps toward certification for commercial application.

The collection is constantly acquiring new cell cultures. The priority is given to endemic and endangered medicinal species with proven use in traditional medicine. Most recent examples include the cell cultures of *Sutherlandia frutescens* and *Alhagi maurorum*, which are both medicinal plants of the Fabaceae family and contain both secondary metabolites and a unique composition of FAs [40][59], as well as cell cultures of *Ajuga turkestanica* and *Panax vietnamensis* with high antioxidant potential.

In conclusion, the All-Russian Collection of Plant Cell Cultures holds a valuable gene pool of cell culture strains of high biotechnological value and model strains for research and commercial application. This gene pool is a base for research and cell-culture biotechnology in-house and outside IPPRAS. The collection also provides services to research institutes and commercial companies by depositing cell strains for patent purposes, induction of new cell cultures based on the user's interest, cell culture evaluation, passport development, etc.

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