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REVIEW ARTICLE

Plant stem cells and their applications: special emphasis on their marketed products

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Abstract
Stem cells are becoming increasingly popular in public lexicon owing to their prospective applications in the biomedical and therapeutic domains. Extensive research has found various independent stem cell systems fulfilling specific needs of plant development. Plant stem cells are innately undifferentiated cells present in the plant's meristematic tissues. Such cells have various commercial uses, wherein cosmetic manufacture involving stem cell derivatives is the most promising field at present. Scientific evidence suggests anti-oxidant and anti-inflammatory properties possessed by various plants such as grapes (*Vitis vinifera*), lilacs (*Syringa vulgaris*), Swiss apples (*Uttwiler spatlauber*) etc. are of great importance in terms of cosmetic applications of plant stem cells. There are widespread uses of plant stem cells and their extracts. The products so formulated have a varied range of applications which included skin whitening, de-tanning, moisturizing, cleansing etc. Despite all the promising developments, the domain of plant stem cells remains hugely unexplored. This article presents an overview of the current scenario of plant stem cells and their applications in humans.

Keywords Plant stem cells · Stem cell extract · Cosmetics · Skincare · Anti-ageing

Introduction

Plant stem cells are innately undifferentiated cells present in the meristematic tissues, providing them vitality and a steady supply of precursor cells which later differentiate into various parts or tissues (Batygina 2011). The two vital sources of stem cells in plants are apical and lateral meristematic tissues (Dodueva et al. 2017). The characteristic features of these cells are self-renewal and ability to create differentiated cells (Xu and Huang 2014). Plant stem cells do not undergo the process of ageing and senescence, they undergo differentiation to form specialized and unspecialized cells. These in turn have the potential to develop into any organ or tissue. Therefore, plant stem cells are termed as totipotent cells. Such cells have the potential to regenerate and thereby result in the formation of new organs in the lifetime of a species (Dinneny and Benfey 2008).

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Plant stem cells are a form of adaption but due to their immobility, it is difficult for plants to counteract dangerous and stressful stimuli. It has been hypothesized that stem cells help plants for surviving harsh external conditions thus preserving the plant life (Sena 2014). These cells are differentiated on the basis of their action (Table 1) (Crespi and Frugier 2008; Kretser 2007; Sablowski 2007; Verdeil et al. 2007; Vijan 2016) or location (Table 2) (Bäurle and Laux 2003; Byrne et al. 2003; Stahl and Simon 2005).

Propagation of plant stem cells in culture

Some of the important factors contributing towards the maintenance of stem cells in plants are known. These include the signals transmitted from the microenvironment and epigenetic control of stem cells in a manner similar to that in mammals (Weigel and Jürgens 2002). Mature plant stem cells consist of totipotent stem cells that are capable of regeneration into a whole new plant. The technique of plant tissue culture is focused on the process of plant stem cell propagation resulting in either the formation of a whole new plant or tissue or specific types of single cells in the culture for the purpose of harvesting

Table 1 Types of stem cells on the basis of their action

Multipotent	Pluripotent	Totipotent	Unipotent
Comprise of all basic functions	Known as 'True stem cells'	Capable of giving rise to any type of cell	Capable of differentiating only across one lineage
Unspecialized cells	Ability to differentiate to form any kind of stem cell	Have the same function in plants as those in animals	Found in mature tissues and possess the lowest potential of differentiation
Capable of self-renewal for long durations	Capable of generating sparse, distinct cells inside the body	Can be obtained from roots and shoots of growing tips	Can differentiate into only a single type of cell
Undergo differentiation to produce specialized cells		Play an important role in growing diameter of trunks as well as branches of woody plants	Bear property of self-renewal
Form limited quantities of differentiated diverse cells			

plant metabolites (Sang et al. 2018). This technique is used to standardize the production of plant material under sterile conditions, independent of environmental constraints. Nearly all plant tissues can be used to initiate tissue culture (Takahashi and Suge 1996). Tissue material obtained for culture is called an explant, whose cut surface provides the necessary area for new cells. This is akin to a wound healing reaction. The cells further dedifferentiate, losing distinctive features of normal plant cells to create a colourless cell mass called callus, wherein the stem cells are comparable to those in the meristematic regions. Callus cells are cultured as individual cells or small cell clusters in a liquid culture for higher yield (Imseng et al. 2014; Pavlovic and Radotic 2017; Perez-Garcia and Moreno-Risueno 2018). Various steps and techniques involved in the process of propagation and extraction of stem cells from plants are shown in Fig. 1.

Potential of plant stem cells

Emerging trends in cosmetics include anti-ageing creams consisting of plant-based complexes derived from *Mirabilis jalapa* and the Indian gooseberry fruit *Phyllanthus emblica* (Choi et al. 2015). In addition to these, certain peppermint-based haircare products are also derived employing the technique of plant cell culture (Barbulova and Apone 2014). Some products consist of a combination of plant and human stem cell-based constituents, wherein tropoelastin is the constituent derived from human embryonic stem cells. Many cosmetic manufacturers claim the use of stem cell technology in their products (Schmid et al. 2008). Professional skincare cosmetics consist of active derivatives of extracts from plant stem cells and not live plant stem cells. Thus, the claimed effects such as smooth and firm skin are due to the presence of antioxidants in plant extracts (Schmid et al. 2008). Significant plant components such as anti-oxidant and anti-inflammatory compounds are found in various plants like grapes (*Vitis vinifera*), lilacs (*Syringa vulgaris*), and Swiss apples (*Uttwiler spatlauber*). Cosmetics containing these extracts are capable of exhibiting a photo-protective action against UV rays induced damage (Reisch 2009). Fruit-based antioxidant compounds like anthocyanin and curcumin are found in grapes and turmeric respectively, whereas apple stem cells are considered to be rich in phytonutrients such as carotenoids and flavonoids (Prhal et al. 2014). Several other botanical sources are currently being developed as cosmetic products, such as—tomatoes (*Solanum lycopersicum*), orchard apples (*Malus domestica*), ginger (*Zingiber officianale*), cloudberries (*Rubus chamaemorus*), edelweiss (*Leontopodium nivale*), and argan buds (*Argania*

Table 2 Types of stem cells on the basis of location

Stem cell niche in shoot tip	Stem cell niche in root tip
Found in dome-shaped organ called shoot apical meristem Has organizing centre which is responsible for the maintenance of the stem cell Stem cells divide into new cells on their own and transit-amplifying cells (group of intermediate cells produced before cell differentiation) by asymmetric division Transit-amplifying cells-play an important role in retaining activity of the cell and accumulate to give to new organs Upper region of shoot apical meristem with stem cell niche-forms central zone of the center This region has slower rate of cell division which reduces the probability of producing mutations Peripheral zone is situated around the central zone, where cell division is more rapid	Different from stem cell niche in shoot tips in their structural arrangement Small amount of organizing cells are surrounded by different types of plant stem cells These centres rarely undergo cell division, so called as Quiescent centres These cells divide in an asymmetrical manner Form stem cells on their own and also form differentiated root cells without forming transit-amplifying cells Stem cells present on the tip side of the root cap are sloughed off in a continuous manner and serves the key role of protecting the stem cell niche

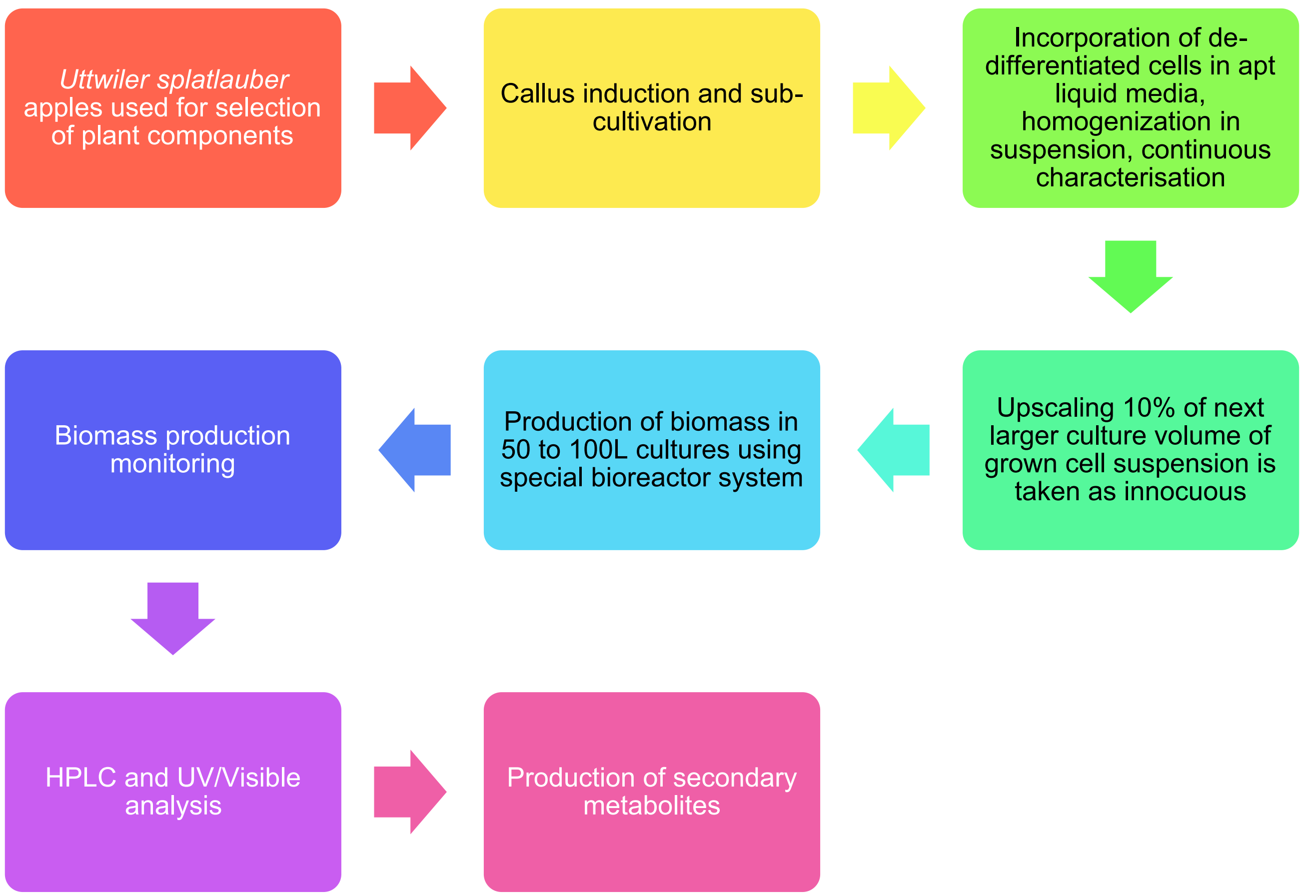

Fig. 1 Schematic representation of the stepwise process of isolation of stem cells from Swiss apples (*Uttwiler splatlauber*)

spinosa) etc. (Georgiev et al. 2018; Tito et al. 2011; Fu et al. 2001).

Comparison between plant and animal stem cells

Stem cells are a group of undifferentiated cells, capable of forming a variety of specialized cells—thus acting as a master key. Such cells are imperative for growth and tissue generation. In mammals, the biggest drawback of stem cells is that specialized cells are unable to return to their original undifferentiated state. This limitation is overcome in case of plant stem cells which are capable of reverting to their original state without any external manipulation. Plants undertake a natural reprogramming process in order to replenish their stem cells (Heidstra and Sabatini 2014).

Even though the proteins in mammalian stem cell systems and plant stem cell systems vary in nature, major similarities can be observed in the way they interact with each other. For example, the process in which stem cells strengthen or weaken each other (Zubov 2016; Greb and Lohmann 2016).

Animal cells are vulnerable to reverting back to a stem cell state as a result of external manipulation. However, the process involves steps like increasing concentration of specific proteins which make it extremely delicate and complex. By gaining a better insight of the reasons leading to easy manipulation of plant cells in comparison to animal cells, the clinical potential of cell reprogramming in humans can be improved (You et al. 2014). Mathematical formulas can be utilized as an effective tool to perform the analysis of interactions occurring between proteins during the course of evolution of stem cells, as well as the interactions taking place between the proteins and genes linked to the process of stem cell formation (Sablowski 2004) (Fig. 2).

Plant stem cells v/s plant stem cell extracts

Many cosmetic manufacturers assert that their products contain stem cells, when in reality they contain stem cell extracts and not live stem cells. Terminology is an important factor in terms of the claims made by cosmetic manufacturers. In order to gain an insight into the ‘plant stem cell’ claim made by manufacturers, understanding of ingredients in cosmetic products is required. This may involve the use of stem cells extracted from primitive cells (Lohmann 2008).

Various skincare products and cosmetics manufacturing companies are marketing their products with the claim of using stem cell technology for different purposes. One such example is of Image Skincare which has a series of products like anti-ageing serums, lightening creams, lightening cleansers and lotions (Draelos, 2012). Furthermore, certain stem cell products like Dermaquest Stem cell 3D HydraFirm serum, Peptide eye firming serum etc. are marketed with the affirmation of containing stem cells derived from plants such as gardenia (*Gardenia jasminoides*), Echinacea (*Echinacea purpurea*), lilac (*Syringa vulgaris*)and orange (*Citrus sinensis*) (Barbulova and Apone 2014).

Scientific evidence from research-based data on plant stem cells used in skincare shows their potential as skin protective, anti-ageing and anti-wrinkle agents. However, stem cells used in cosmetic formulations are already dead. Extracts from stem cells fail to act in the same way as the active stem cells. The affirmed benefits of smooth and firm skin occur due to the presence of other beneficial plant products such as antioxidants and active extracts from stem cells. In order to obtain all the authentic and positive outcomes from stem cells and to let them work as per their described applications in skincare products, they are required to be incorporated as active cells and should remain so in the cosmetic formulations (Reisch 2009).

Applications

Protecting human stem cells

Cells extracted from blood present in the umbilical cord are an ethically accepted source of stem cells of human origin. The extract of stem cells from the *Uttwiler spatlauber* species was studied and observed for its effect on the growth of stem cells obtained from umbilical cord blood in two different studies. The first study was designed to observe the effect of extracted cells on proliferative activity of human stem cells. It was observed that the effect was concentration dependent. The second experiment was carried out by keeping the stem cells in a stressed environment using the irradiation technique with a UV light as the source of suitable wavelength. It was concluded that 50% of the cells cultured in the growth medium alone died, whereas the cells which were cultured in the presence of an extract of stem cells from *Uttwiler spatlauber* were found to have experienced only a small loss in terms of their viability (Schmid et al. 2008).

Reversing signs of senescence in fibroblast cells

Senescence is described as a natural process in which after dividing 50 times (approx.), the cell loses its ability to undergo any further divisions. However, senescence may also occur earlier in the life cycle of a cell life as a result of an underlying trauma such as a corrective response to damaged cellular DNA. Premature senescence can be considered an atrocity especially when it hits stem cells because they are imperative for the process of tissue regeneration. A cellular model for demonstrating and preventing premature senescence was developed based on fibroblast cells. Following treatment with Hydrogen Peroxide for a period of 2 h, typical signs of senescence were observed in the cells. This model was developed in order to establish the anti-senescence activity of the extract of stem cells from *Uttwiler spatlauber* (Fig. 3) (Schmid et al. 2008).

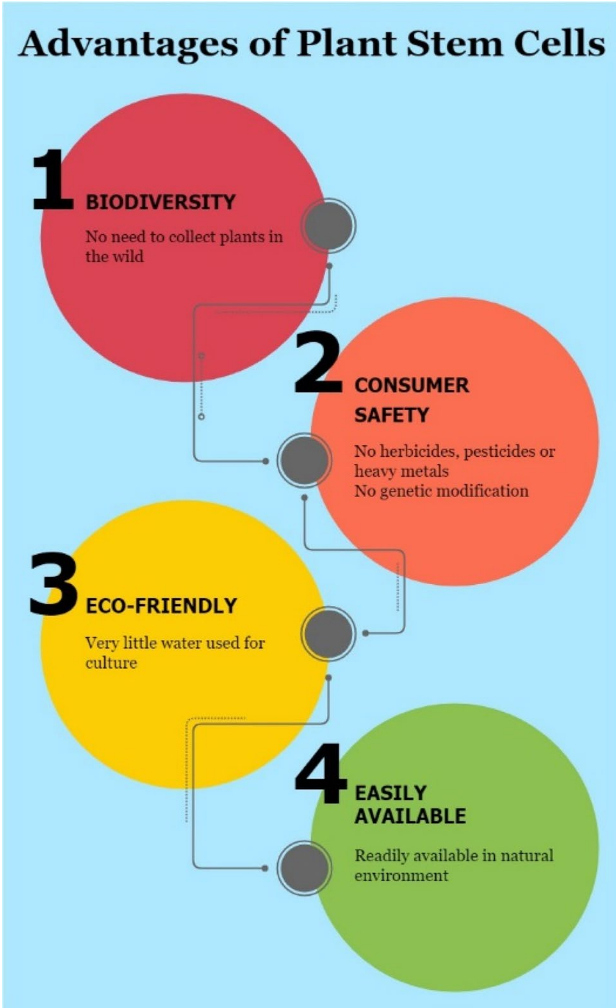

Fig. 2 Diagram consisting of the advantages possessed by plant stem cells and their extracts over animal derived counterparts

Retarding senescence in isolated hair follicles

Follicles of human hair are isolated by the process of micro-dissection from fragments of skin that are left behind after the facelift surgery procedure. For this purpose, follicles which exist in their anagen phase are used. Hair follicles can be compared to a system of mini-organs which mimics the natural model of co-culture of stem cells of epidermal and melanocyte origin as well as differentiated cells. These follicles are preserved in a growth medium wherein they are allowed to elongate for a period of 14 days, following which the follicle cells either enter the stage of senescence or undergo the process of apoptosis i.e. programmed cell death. Due to the lack of blood circulation, the isolated hair follicles are unable to live and grow for a longer duration of time. However, isolated hair follicles are tested in order to determine the activities which are responsible for causing a delay in the process of necrosis (Fig. 4) (Schmid et al. 2008; Nishimura et al. 2005).

Anti-wrinkle effect

The anti-wrinkle activity of *PhytoCellTec™ Malus domestica* was established during a clinical trial which was conducted in a time duration of 4 weeks. A cream constituting a 2% *PhytoCellTec™ Malus domestica* extract was administered two times in a day on crow's feet. The depth of the wrinkle was analyzed using the PRIMOS system after set time intervals in order to determine the effect of the cream. Digital photographs of the crow's feet area were taken prior to administration of the cream and compared with those taken at the end of the study. The application of *PhytoCellTec™Malus domestica* cream was reported to markedly reduce the depth of the wrinkle after a period of 2 weeks and then 4 weeks. The effect can be demonstrated effectively by creating 3D pictures of the subjects for comparison. The anti-wrinkle activity can also be observed by means of digital photographs (Fig. 5) (Schmid et al. 2008; Sengupta et al. 2018).

Marketed products

Stem cell extracts obtained from plants through various extraction techniques are currently being used both for the production of routine cosmetic products (used by consumers on daily basis) as well as for professional care cosmetic products. These are whitening agents such as arbutin, an active constituent obtained from the plant *Catharanthus roseus* and various phytological pigments such as safflower and saflorin obtained from *C.tincorius*. Stem cells obtained from a rare species of apple cultivated in Switzerland have been observed to possess excellent storage properties. This extract of the cultured apple stem cells was obtained following an extraction process involving plant cell lysis under high pressure homogenization (Oh and Snyder 2013; Trehan et al. 2017).

The cosmetic company Mibelle AG Biochemistry in Buchs, Switzerland has conducted experiments wherein human fibroblast cells were incubated and characteristic symptoms of cDNA damage were induced in these cells cultured in a 2% extract of *Uttwiler spatlauber* stem cells. These stem cells were capable of reversing the process of ageing of skin fibroblast cells by causing an up-regulation of various genes essential for the proliferation and growth of the cells and also stimulating expression of required antioxidant enzyme known as haemeoxygenase-1. This experiment has also established the effectiveness of enhancing the lifespan of stem cells derived from the umbilical cord blood and increasing the viability

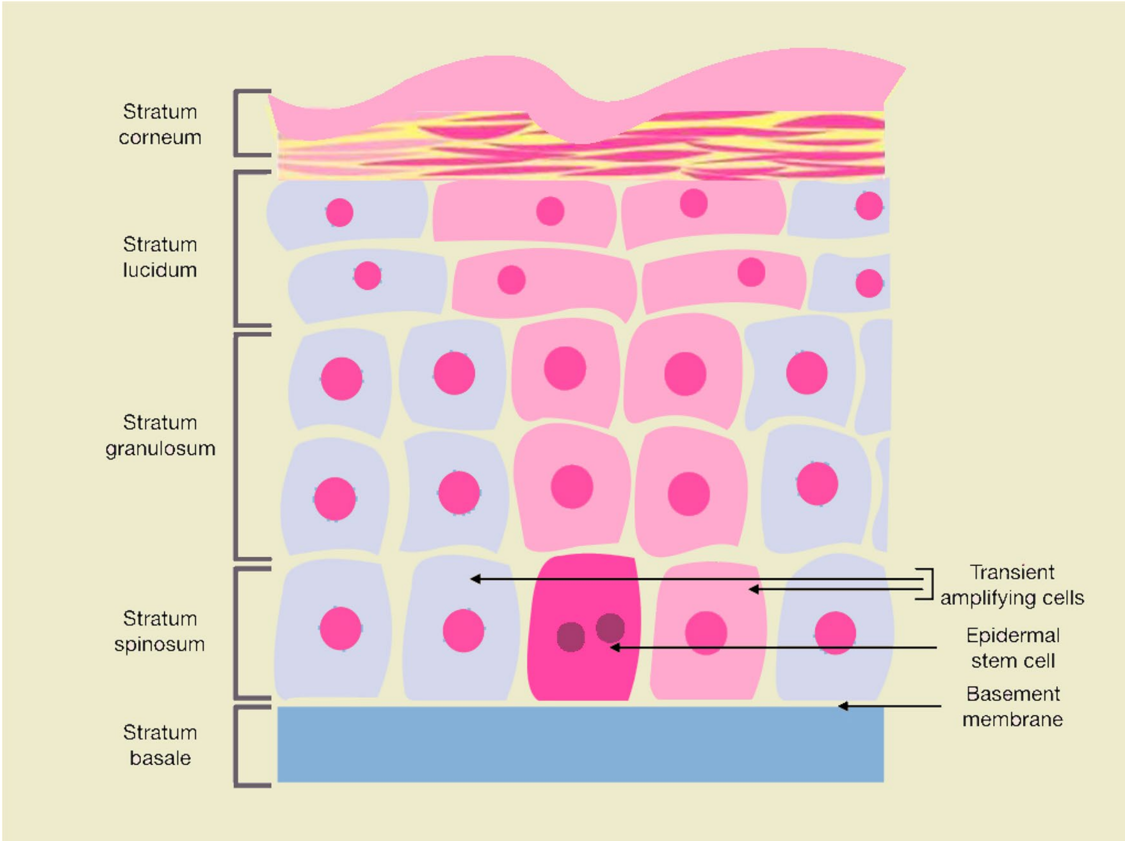

Fig. 3 Diagrammatic representation of cells from the epidermal layer of skin leading to the formation of transient amplifying cells which in turn differentiate to form stratified layers of the skin—thus causing renewal or replenishment of the various skin layers on application of stem cell based formulation

of isolated human hair follicles (Schmid et al. 2008). Another product developed by using a competent production method involved cloudberry (*Rubus chamaemorus*) cells. In this case bioreactors from entrenched callus and suspension cultures of *Rubus chamaemorus* had been used wherein, Murashige and Skoog were the mediums opulent in phytohormones such as kinetin and α-naphthalene acetic acid. The cloudberry cell products obtained by this method were capable of being used as raw material in the cosmetic manufacturing industry on a large scale. This standardized process was a prospective technique for sustainable manufacturing of fresh cells or cell fraction extracts, isolated compounds having potent biological activities, freeze dried cell products, fragrance or colouring agents etc. (Martinussen et al. 2004).

Stem cells cultured from tomato (*Lycopersicon esculentum*) cells were found to possess tremendous potential in terms of protecting skin from adverse effects caused due to toxicity of heavy metals. A hydrophilic cosmetic active ingredient was manufactured from liquid cultures of *L.esculentum* with comparatively higher concentrations of certain components such as flavonoids and phenolic acids like rutin, coumaric, protocatechuic and chlorogenic acids. This extract of tomato stem cells had a higher content of antioxidants and chelating agent phytochelatins which are responsible for chelation of heavy metals. This in turn captures the metals and prevents potential damage to cellular materials and organelles. It was also observed that the extract obtained by this method displayed other phenomenal applications in the area of skincare cosmetics for the purpose of supporting healthy skin growth and maintenance (Tito et al. 2011).

Refined ginger (*Zingiber officinale*) consists of active cells of plants by achieving a particular biotechnological mix of plant cell dedifferentiation and a plant cell culture which is responsible for controlling the synthesis of active molecules inside the cell. In a clinical study performed by the manufacturer, it was observed that women indicated signs of improvement in 50% of their skin structure as a result of pore reduction and a mattifying effect. This effect was enhanced by a consequent reduction in shininess in their skin and also a significant reduction of sebum. An increase in the synthesis of elastin fibres in the skin was observed in in vitro tests which consequently reduced the rate of sebum production (Trehan et al. 2017).

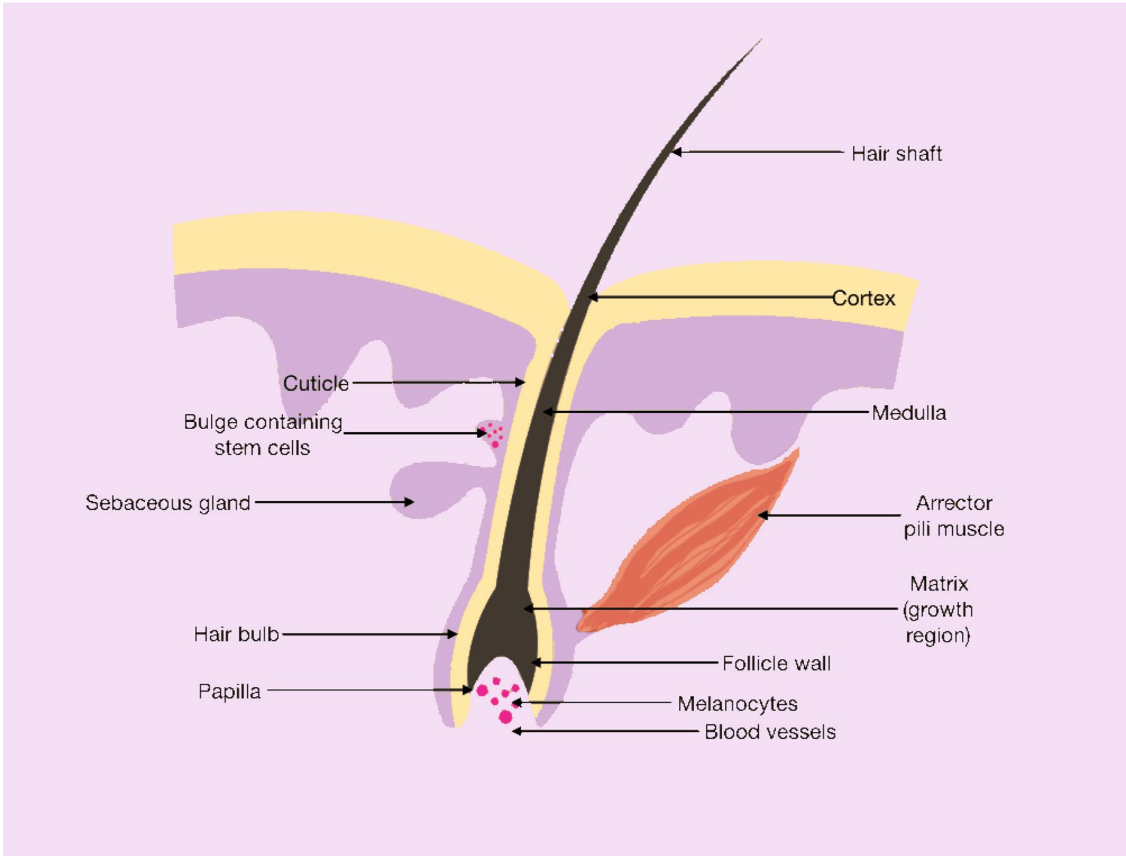

Fig. 4 Diagrammatic representation of a hair bulb containing multipotent stem cells which are responsible for creating lineages in various neighboring parts of the hair bulb such as the epidermal layer, sebaceous gland and hair follicle—thereby initiating the renewal process

The Institute of Biotechnological Research examined the protective and potent anti-collagenase as well as hyaluronidase activity of an anti-ageing component obtained from stem cell extracts of edelweiss (*Leontopodium alpinum*). It is rich in leontopodic acids A and B, which are responsible for exhibiting a strong and potent antioxidant effect on skin (Trehan et al. 2017).

The patented stem cell technology given by XtemCell utilizes the active plant cells from a rare and organic nutrient-rich plant in order to be able to create new cells which are highly pure and nutrient rich. The patented technology promises high concentrations of lipids, proteins, amino acids and phytoalexins as a result of the extraction process in contrast to conventional chemical extraction techniques. In clinical studies performed by the manufacturer it was established that the active cells used in XtemCell products were absorbed in the outermost cells of the epidermis almost instantly; thereby allowing prompt renewal of the skin cells, increasing nutrient absorption, and enhancing the amount of filaggrin proteins in the skin. These are responsible for protecting the skin from any further damage caused by sun exposure and ageing (Trehan et al. 2017).

Global market

Plant stem cell-based cosmetics are regarded as one of the most diverse and ambitious market consisting of large number of manufacturers having high stake and prominent brand names related to the cosmetic industry. Dominating names in this market are: Mibelle group of industries, L'Oreal cosmetics, Estee Lauder, Channel 21, Christian Dior, Clinique cosmeceuticals, MyChelle Dermaceuticals, Juice Beauty, and Intelligent Nutrients (Oh and Snyder 2013).

Key movements in the cosmetic market include the following:

- Increasing demand for plant stem cell-based cosmetics in the tropical regions as a result of exposure to harmful UV rays and a consequent increase in the risk of ageing (Blanpain and Fuchs 2006).
- Desire for nutrients which can be directly absorbed through the membrane of the skin for meeting the nutritional and hydration requirements of the skin by

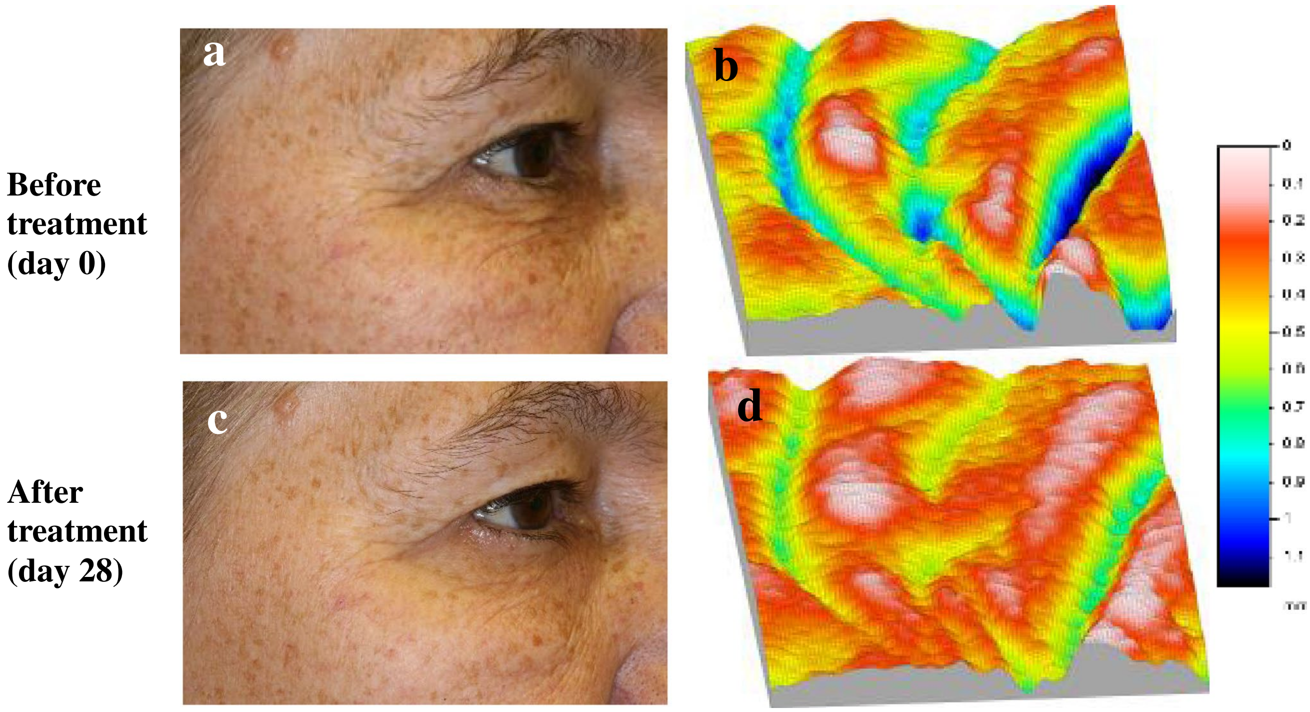

Fig. 5 3D and digital images of the crow's feet area depicting a comparison of the area before (**a**, **b**) and after treatment (**c**, **d**) using a cream containing 2% *PhytoCellTech*™ *Mallus domestica* extract; wherein it can be observed that the depressions in the skin reduce significantly after treatment. [Image from research paper titled 'Plant stem cell extract for longevity of skin and hair', originally published in *International Journal for Applied Science* in May 2008. Used with permission of the author Dr. Schmid of Mibelle Biochemistry, Switzerland]

creating increased demand of plant stem cell-based cosmetics (Barthel and Aberdam 2005).

- In the last few decades, aesthetics, anti-ageing and other procedures were concentrated around women only. However, recent commercially available cosmetic products have also targeted the male population (Trehan et al. 2017).

Conclusion and future prospects

Plant stem cells and related technology are imminent subjects in therapeutic as well as cosmetic industries. Plant stem cells have a wide range of applications in both fields however, their true potential still remains unexplored due to a lack of scientific evidence and large variety of flora available for experimental purposes. The use of plant extracts and their parts such as fruits, flowers, leaves, stems, roots, etc. is established in the field of cosmetics and pharmaceuticals since ancient times. Application of plants and their extracts in cosmetics is thus widespread and the products formulated have a wide range of applications such as whitening, de-tanning, moisturizing, cleansing etc. Various recent developments in the field of plant and human stem cells are being considered important milestones in the search for vital sources of human tissue renewal. Generally, human skin cells renew themselves in a continuous process in order to protect the body against injuries, infections and damage due to the phenomenon of dehydration. With increasing age of stem cells, a decrease in their healing capacity is observed along with accelerated degeneration of the tissues present in the skin. Therefore, the protection and supportive maintenance of stem cells is imperative to healthy skin.

Manufacturing firms are rapidly introducing products employing plant stem cell technology. Such products typically help in protecting skin stem cells from various kinds of damage, particularly ageing. The propensity for the development of skincare products based on plant stem cell extracts is an emerging trend at present due to the vast potential of plant stem cells which are able to develop into different types of cells. Presently various forms of plant stem cells and the products derived from their extracts are commercially accessible to the cosmetic industry. Plant constituents have been found to have a sufficient amount of plant stem cells as well as other therapeutically relevant plant products such as phytohormones and antioxidants. The rich biodiversity present on our planet has a lot of potential for use. Their components and constituents have remained unexplored and unexploited to be used as a source of plant stem cells and utilized in the cosmetic industry for various purposes.

Despite all these promising developments in the area of plant stem cells and their varied applications, it is not yet clear if the plant derived extracts and those from stem cells have ethnicity specific effects on humans. If so, it may help finding the host factor regulating all beneficial traits of stem cell technology. It will prove to be a highly rewarding proposition if the genes responsible for conferring the beneficial traits of stem cells on humans are identified. This would hasten the process of natural healing, achieving yet another goal of the healthcare system.

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Author contributions SA, CS and MS have written the manuscript. MS has supervised the work and MS and MU edited the Manuscript.

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Compliance with ethical standards

Conflict of interest The authors ascertain no conflict of interest.

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