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Review Article

In vitro Strategies for the Production of Bioactive Therapeutics from *Caralluma* Species

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ABSTRACT

Bioactive substances that may be used for therapeutic purposes are key sources of supply from medicinal plants. The conventional techniques used for the extraction of these chemicals sometimes need the collection of substantial quantities of plant material from natural habitats. Nevertheless, a significant number of medicinal plant species are under the threat of endangerment as a result of excessive harvesting practices. The use of *in vitro* cell and tissue culture methods presents a viable and sustainable approach to the production of bioactive compounds, eventually reducing the need for over exploitation of the plants from the wild. This is particularly pertinent in the case of the succulent genus *Caralluma*, since it has exhibited the qualities that are anti-diabetic, anti-inflammatory, anti-obesity, and anti-cancer attributed to the endogenous therapeutic compounds like steroidal, pregnane and flavone glycosides. The establishment of cell suspensions, hairy root, and callus cultures of *Caralluma* species has contributed to the efficient production of natural bioactives enabling rapid, sustainable biomass and metabolite beyond whole-plant levels. Elicitation is a dynamic biotechnological tool for the bioaccumulation of secondary metabolites by activation of metabolic pathways stimulated by elicitors. Moreover, the use of *in vitro* methodologies, such as elicitation, may be employed to augment the synthesis of secondary metabolites. This approach aids in the conservation of wild plant populations while simultaneously addressing the growing need for medicines derived from natural products.

Keywords: *Caralluma* species, Pharmacological activities, Therapeutic compounds, *In vitro* cultivation, Conservation.

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INTRODUCTION

Plants are capable of synthesising secondary metabolites, which possess significant bioactivity and have been extensively exploited across several industrial sectors. These compounds are produced through the shikimate, terpenoid, and polyketide pathways.[1] Secondary metabolites are compounds that are not utilised by the plant in their primary metabolism but are produced by the plant in response to defence mechanisms. Wide range of biological properties had shown by secondary metabolites make them essential in the creation of pharmaceuticals. However, the significance of secondary metabolites as therapeutic agents resides in their capacity to serve as primary molecules for drug discovery and their potential to help in the treatment of a wide range of medical disorders, spanning from mild afflictions to severe and potentially fatal illnesses.

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Plant cell culture systems serve as a sustainable reservoir for the production of important pharmaceutical chemicals, perfumes, and colourants. Plant cell, tissue, or organ culture-derived bioactive compounds have significant economic value for various purposes including medicines, flavours, fragrances, pigments, agrochemicals, cosmetics, and food additives. Herbal remedies are often used in the treatment of chronic ailments such as diabetes mellitus, hypertension, hyperlipidemia, osteoporosis, cardiovascular disease, Chronic Obstructive Pulmonary Disease (COPD), asthma, epilepsy, obesity, and other related conditions. These options are favoured because of their wide range of choices, affordability, and high level of safety. The use of herbal medications, including Complementary and Alternative Medicine [CAM], is prevalent among those afflicted with chronic illnesses since herbal remedies lack the adverse effects often associated with traditional pharmaceutical interventions. The presence of bioactive chemicals in medicinal plants has been shown to have the potential to reduce glucose levels by means of insulin-mimicking action, accelerated regeneration of β-cells, or increased glucose absorption. Alkaloids, imidazoline compounds, polysaccharides, flavonoids, and saponins are among the chemicals implicated in these pathways.[2]

Different species belonging to the genus *Caralluma* constitute a wide range of phytochemicals involving glycosides, terpenoids, fatty acids, alkaloids, flavonoids, sterols, saponins, alkaloids, tannins and phenols[3] which are responsible for the therapeutic value of the plant. The therapeutic properties shown by these compounds are investigated by many researchers. Many ethnobotanical studies revealed the medicinal nature of the *Caralluma* in various parts of the world.

The use of *in vitro* production methods has the potential to augment the accumulation of secondary metabolites by the manipulation of diverse parameters, including growing conditions, elicitors, and precursors.[4] This phenomenon has the potential to enhance the production of the targeted phytochemical compounds, hence increasing the viability of their commercialization.[1] Furthermore, the use of *in vitro* production methods facilitates the application of plant transformation methodologies, allowing the synthesis of genetically modified substances, including vaccines and other medicinal agents.[5]

The utilisation of *in vitro* culture offers several advantages, such as the ability to achieve accelerated biomass production, maintain precise control over nutritional and environmental factors, and facilitate year-round cultivation (Figure 1). Uncertainty in the identification and speciation, low yield of bioactive metabolites, and variability of conventional protocols are some of the challenges which can be overcome by *in vitro* culture production.[2]

Scientists are now engaged in the investigation and development of nutraceuticals derived from natural sources, with the aim of improving human health and mitigating any adverse effects.[6] *Caralluma* species possess a wide range of pharmacological activity and exhibit a complex phytochemical composition, making them a useful asset in the exploration and development of new medicinal agents and nutraceuticals. The use of *in vitro* techniques for the synthesis of medicinal compounds derived from *Caralluma* species might effectively help towards the achievement of this objective, as it enables the creation of a regulated environment for the generation of bioactive compounds. This approach has the potential to facilitate the advancement of novel pharmaceuticals and therapeutic interventions by using the pharmacological properties inherent in *Caralluma* species.

Genus *Caralluma*

The taxonomic classification of the genus *Caralluma* defines it within the family Apocynaceae. The family has over 120 species of flowering plants, indicating its considerable size. In 1795, William Roxburgh made an observation on the nomenclature of a certain plant in the Telugu language, identifying it as Car-allum.[7] Succulent branches of this plant may be consumed in their raw state, although possessing a bitter and salty taste. Genus *Caralluma* has gained recognition for its potential anti-obesity properties.[8] This genus encompasses a variety of plant species, notably an Indian variant characterised by a unique and elongated succulent stem adorned with blooms. *Caralluma* plants often exhibit perennial characteristics and possess succulent herbaceous qualities. Furthermore, a significant proportion of these plants are considered edible, assuming various shapes. Additionally, they are used in the culinary process of various pickling methods and the creation of diverse curry dishes.

Typically, plant species classified under the genus *Caralluma* have diminutive caducous foliage. Primarily, these plants are succulent perennial herbs, with some species being documented as edible.[9] The species under consideration exhibit a broad geographical distribution across various regions. These regions include Asia, encompassing countries such as Afghanistan, India, Pakistan, Sri Lanka, as well as Iraq and Iran. Additionally, the species can be found in Africa, specifically in Sudan, Kenya, Ethiopia, and Somalia. Arabian countries, including the United Arab Emirates, Oman, and Yemen, along with the Arabian Peninsula, also serve as habitats for these species. Furthermore, the Canary Islands and Southeast Europe have been identified as additional areas where these species can be found.[10,11]

The *Caralluma* genus has been extensively used in traditional and folk medicine for several common maladies, including colds, coughs, wound healing, and more complex conditions like diabetes, malaria, kidney stones, tuberculosis, snake bite, scorpion sting, skin rashes, scabies, fever, and inflammation.[12-15] Apart from being used in folklore medicine, it has been used in the Unani and Ayurvedic systems of medicine, for the therapeutic management of diabetes and rheumatism.[16] Many tribal communities consider them as a source of sustenance during times of hunger.[17] Additionally, these individuals are also included into the traditional therapeutic practices of their communities.[18] *Caralluma* species have been historically used as an emergency food source in India and Pakistan for many centuries.[19] These plants have been documented as a means of sustenance during times of famine, and no harmful consequences have been noticed so far.[20,21]

Several investigations have demonstrated the phytotherapeutic properties associated with plant extracts derived from several species of *Caralluma* that acted against the progression and acted as anti-alzheimer's, anti-rheumatic, anti-gastrointestinal, hypolipidemic, hepatoprotective, anti-leprosy, anti-protozoan activity, antioxidant, anticancer, antidiabetic, anti-inflammatory, antimicrobial, anti-eczemic, antimalarial and antifungal. [3,22-33]

The therapeutic significance of several species within the *Caralluma* genus is supported by their abundance of pregnane glycosides, flavone and megastigmane glycosides, and diverse esters (Figure 2).[34-36] The presence of pregnane glycosides, stigmasterol, and other phytochemicals in *Caralluma* species suggests a wide range of biological activity.[37-39] Utilisation of pregnane glycoside or an extract of *Caralluma* containing the pregnane glycoside has been patented in the United States for both medical and culinary purposes.[20] Recent studies have reported that the endophytic relationship between fungal strains, *Paecilomyces variotii* and *Epicoccum nigrum* with *Caralluma acutangula* aided in the production of notable quantities of bioactive enzymes such as 1-Aminocyclopropane1-Carboxylate [ACC] deaminase, phosphatases and glucosidases.[40] *Caralluma tuberculata*, a potent ethnomedicinal plant was analysed for their pharmaceutical properties with fourteen distinct solvents and found to have the highest DPPH scavenging activity [36±1%] from water-acetone extract, with a total reducing potential [76.0±1 μg/mg] from ethanol extract, and total antioxidant potential of 92.21±0.70 μg/mg by the acetone extract.[41] Currently, *Caralluma* is receiving significant attention from researchers owing to its possession of a diverse range of immunostimulatory properties, which may be attributed to the presence of numerous endogenous phytochemicals.

Enhancement of secondary metabolites through *in vitro* cultures

The use of *in vitro* methods enables a continuous, environmentally friendly, and cost-effective generation of secondary metabolites.[1] Both traditional and metabolic engineering methodologies are used in order to augment the production and overall yields of secondary metabolites. These strategies exhibit a lack of dependence on meteorological and geographical factors. Metabolite production may be influenced by several factors that include growth conditions, composition of culture medium, and culture environment.

Elicitors have the ability to induce the activation of secondary metabolic pathways in plants, hence promoting plant defence mechanisms and augmenting the synthesis of metabolites. Abiotic elicitors are components derived from non-biological origins. Biotic elicitors are derived from biological sources and may be classified as either exogenous or endogenous. The synthesis of secondary metabolites may be enhanced best by the presence of salicylic acid and methyl jasmonate in plants. Signal transduction pathways are activated by these molecules inside the cell nucleus, ultimately resulting in the production of defence proteins and secondary metabolites. The use of fungal elicitors, such as extracts derived from *Aspergillus niger* and *Saccharomyces cerevisiae*, has been shown to enhance the synthesis of secondary metabolites. Bacterial elicitors, including both Gram-positive and Gram-negative strains, have the capacity to augment the synthesis of secondary metabolites. Another study reported the synthesis and characterization of Chitosan Nanoparticles [CNPs] loaded with Methyl Jasmonate (MJ-CNPs), resulting in enhanced phenylalanine ammonia-lyase enzyme activity as well as increased generation of phenolics and flavonoids.[42]

The initial step in the mechanism of eliciting bioactive compounds involves the identification of the elicitor, a process that frequently occurs at the cellular membrane. These elicitors are perceived via receptor proteins, predominantly Pattern Recognition Receptors (PRRs). Upon detection, an initial stimulus elicits a signalling cascade, frequently involving a swift influx of calcium ions into the cellular environment, wherein Reactive Oxygen Species (ROS) may also be expeditiously generated as an early reaction.[43-45] The commencement of signalling events initiates a sequential activation of protein kinases, resulting in a cascade of phosphorylation. These kinases initiate the activation of diverse downstream components, thereby augmenting the initial signal and guaranteeing the appropriate response. The presence of Mitogen-Activated Protein Kinase (MAPK) cascades is a

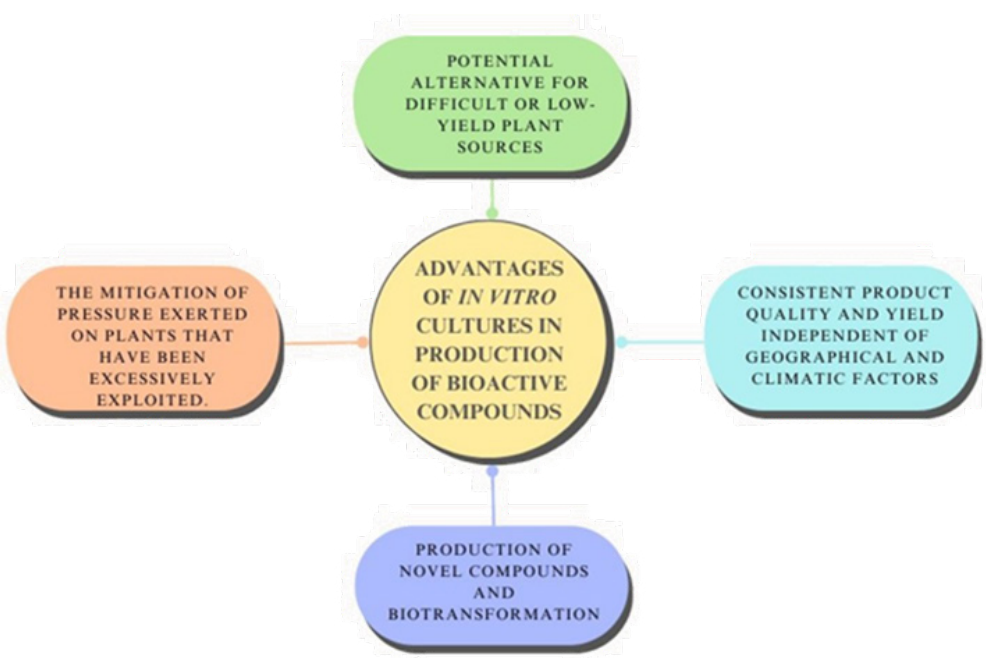

Figure 1: Advantages of *in vitro* production of bioactive compounds from plants.

common characteristic observed in these pathways. In addition to calcium ions and ROS, various secondary messengers, including Nitric Oxide (NO) and cyclic nucleotide monophosphates [such as cAMP and cGMP], are also implicated in the process.[46,47]

These signalling molecules additionally modulate the intracellular reactions and may engage in mutual interactions to achieve a coordinated response. The signal undergoes a series of transfers until it reaches the nucleus, where it exerts an influence on the expression of genes that are linked to the biosynthesis of secondary metabolites. Transcription factors, namely WRKY, MYB, and ERF, undergo activation through either direct means or indirect mechanisms involving the degradation of repressors, as a result of upstream signalling events.[48-50] The aforementioned factors subsequently engage in binding interactions with the promoter regions of specific genes, thereby exerting either augmenting or inhibitory influence on the process of transcription for said genes. Upon the initiation of the pertinent genetic sequences, the biosynthesis of enzymes engaged in the production of secondary metabolites is facilitated. This phenomenon results in an augmented synthesis of secondary metabolites (Figure 3).[51-53]

Metabolic engineering enables the alteration of inherent metabolic processes without any genome changes in order to generate commercially significant metabolites. The process entails the manipulation of metabolic pathways via the use of recombinant DNA technology, resulting in either increased or decreased expression. The production of metabolites encompasses several metabolic routes, one of which is the shikimate pathway. This particular process plays a crucial role in the biosynthesis of phenylpropanoids and aromatic chemicals. The terpenoid pathway plays a crucial role in the synthesis of diverse terpenoids. The polyketide pathway plays a significant role in the production of fatty acids.[1,54,55]

Transcription factors are of the utmost importance in regulating the expression of certain genes. The role of Myeloblastosis viral oncogene homolog [MYB] transcription factors in plants has been recognised as significant in the regulation of metabolic pathways. The regulation of anthocyanin and flavonoid synthesis is governed by the activity of Squamosa-Promoter Binding Protein-Like [SPL] and MYB family proteins. The regulation of artemisinin and gossypol production is mediated by AP2/ERF proteins and GaWRKY1. NAC proteins regulate developmental processes and modulate responses to various environmental stressors. The augmentation of gene expression has been shown to have a positive impact on the accumulation of metabolites in several plant species. The alteration of gene expression in precursor pathways has the potential to enhance the levels of monoterpene and alkaloid compounds.[1]

Elicitor induced secondary metabolite production in *Caralluma* species.

Recent studies on *Caralluma tuberculata* reveal the enhancement of phenols and flavonoids in response to high concentrations of silver nanoparticles along with the plant growth regulators PGR's. Callus growth from the shoot explants [0.5 cm] of *C. tuberculata* inoculated on to the MS media supplemented with 2,4-D [0.5 mg/L]+BA [3.0 mg/L]+sucrose [30 g/L] as carbon source+agar [8 g/L] sub-cultured after 7 weeks onto the same media fortified with silver nanoparticles [AgNPs] [30, 60 and 90

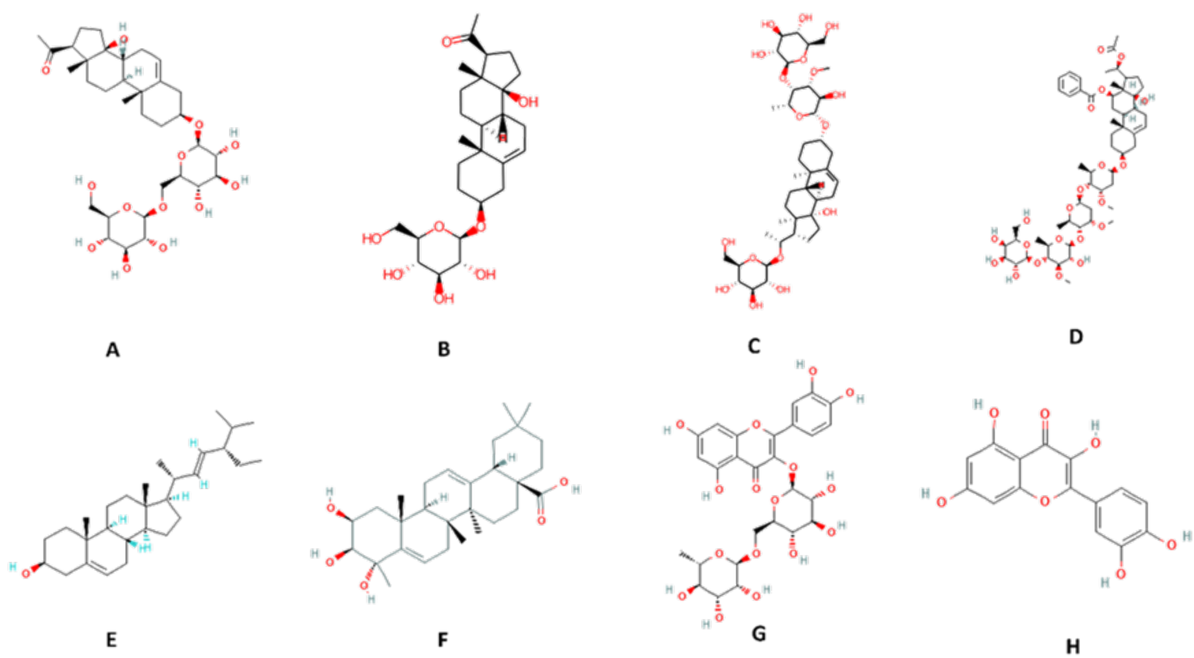

Figure 2: Structures of various bioactive substances found in *Caralluma* species. [A] Carumbelloside I, [B] Carumbelloside II, [C] Carumbelloside III, [D] Russelioside, [E] Stigmasterol, [F] Triterpenoid, [G] Rutin, [H] Quercetin.

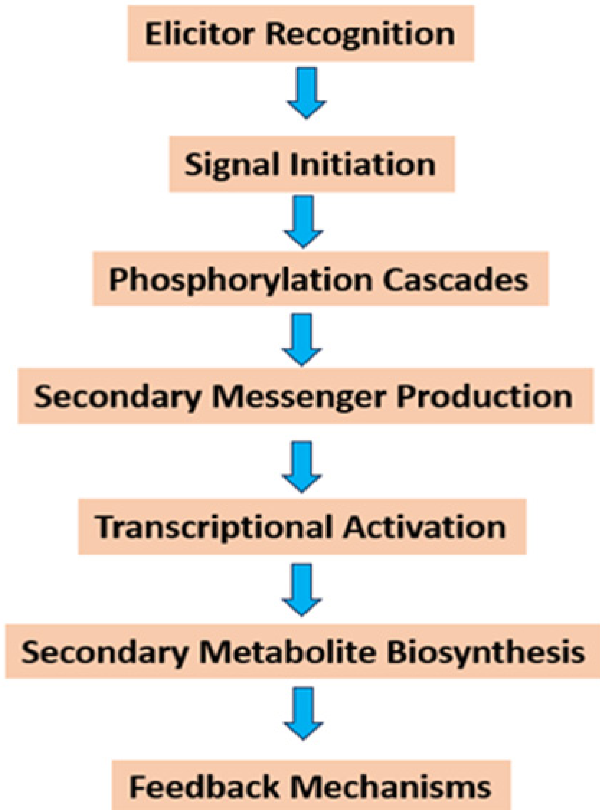

Figure 3: Flow chart representing the mechanism of enhancing secondary metabolites biosynthesis by elicitor treatment.

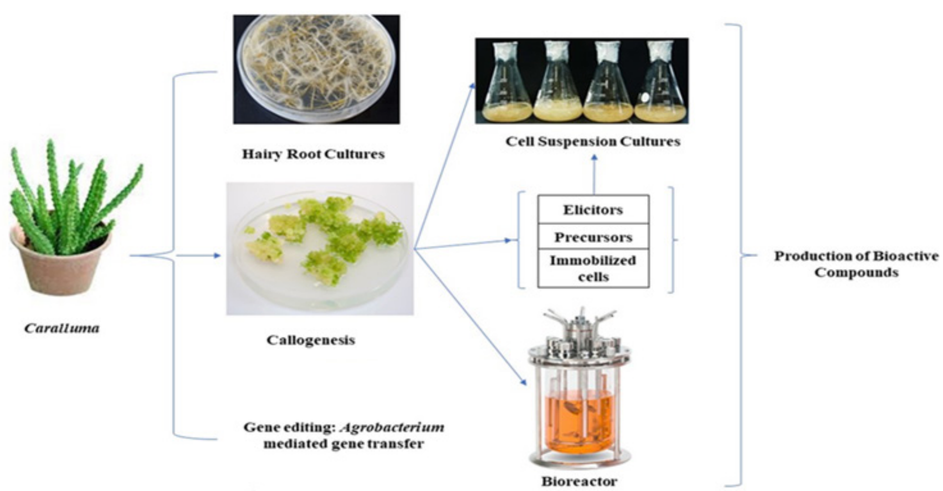

Figure 4: Production of Bioactive compounds in *Caralluma* using different *in vitro* techniques.

µg/L] alone and in combination with PGRs and alone improved the secondary metabolite production. Total Phenolic Content [TPC], Total Flavonoid Content [TFC] and antioxidant activities were analysed after 7 weeks of sub-culturing, among which the callus obtained from AgNPs with 90 µg/L alone resulted in phenolic content [TPC=3.0 mg], flavonoid content [TFC=1.8 mg], PAL activity with 5.8 U/mg and DPPH free radical activity [90%]. The accumulations were higher compared to the AgNPs supplemented in combination with PGRs.[56]

Nanoparticles [NPs] have the potential to function as signalling elicitor chemicals; therefore, they influence both cell growth and the content of secondary metabolites (Figure 4). The exposure of plant cells to NPs results in the occurrence of oxidative bursts and the generation of Reactive Oxygen Species [ROS] within the immediate vicinity of plant cells.[57,58] The cell membrane may be subject to damage by oxidative species. In order to adapt and thrive in a challenging and high-stress environment, plants use many methods to scavenge ROS and activate their machinery associated with the MAPK pathway. Upon initiation of the signalling pathway, the botanical polyphenolic constituents engage in a sequential manner with ROS and effectively eliminate them via a scavenging mechanism. As a result, cellular division is induced subsequent to the cellular response in order to facilitate the average growth and development of plant cells, which is of particular significance in the production of pharmaceutically important secondary metabolites.[56]

CONCLUSION

In vitro culture techniques have unlocked a new frontier for enhancement of therapeutic compounds in medicinal plants, especially in species of *Caralluma*. Despite the limited number of studies conducted in this area, preliminary research has shown promising results, such as the elicitation of bioactive compounds using silver nanoparticles in *C. tuberculata*. This method opened the door to studying other species of *Caralluma* that are said to harbor hundreds of medicinal compounds such as glycosides [pregnane, megastigmane, cardiac], tannins, saponins, flavonoids, terpenoids, and alkaloids.

The significance of these *in vitro* culture methods is not limited to academic research but extends to commercial applications as well. By optimizing the conditions for elicitation, industries involved in pharmaceuticals, nutraceuticals, and food can benefit immensely. It would lead to the mass production of some of the most potent therapeutic compounds with efficiency, thereby providing a viable and sustainable approach that would save the pressures of over-harvesting these plants in their natural habitats.

In conclusion, the use of *in vitro* cultures to enhance medicinal compounds of *Caralluma* species constitutes a new and environmentally friendly approach, which has enormous potential for scientific discovery and commercial exploitation. Further research in this area should focus on identifying the most ideal conditions and elicitation practices that would maximize the biosynthesis of these valuable compounds. Therefore, the knowledge of the *Caralluma* species as a promising source of valuable therapeutic uses is highly important.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NP: Nanoparticles; **ROS:** Reactive Oxygen Species; **ACC:** 1-Aminocyclopropane1-Carboxylate; **DPPH:** 2,2-Diphenyl-1-Picrylhydrazyl; **MAPK:** Mitogen-Activated Protein Kinase; **MYB:** Myeloblastosis; **SPL:** Squamosa-Promoter Binding Protein-Like; **PRRs:** Predominantly Pattern Recognition Receptors; **CNPs:** Chitosan Nanoparticles; **MJ:** Methyl Jasmonate; **cAMP:** Cyclic Adenosine Monophosphate; **CGMP:** Cyclic Guanosine Monophosphate; **NO:** Nitric Oxide; **AgNPs:** Silver Nanoparticles; **PAL:** Phenylalanine Ammonia-Lyase; **PGRS:** Plant Growth Regulators; **COPD:** Chronic Obstructive Pulmonary Disease; **TPC:** Total Phenolic Content; **TFC:** Total Flavonoid Content; **AP2/ERF:** APETALA2/Ethylene Response Factor; **GaWRKY1:** Gibberellin-responsive WRKY1**.**

SUMMARY

Species allied to the genus *Caralluma*, comprises several medicinally important plants exhibiting their therapeutic potential due to presence of numerous bioactive substances. The review paper gives an outline of producing the active metabolites *in vitro* techniques like micropropagation and elicitation by describing the pathways included in enhancing these compounds. Research emphasizes the usage of *in vitro* techniques in fabrication of therapeutically important substances for commercial purposes on a large-scale by reducing the synthetic manufacturing procedures in the synthesizing new drugs.

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