



Assessment of pharmaceutically important phenolic compounds in fungal crude extracts of native endophytes

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Abstracts

In the present study, we observed the potential of our earlier isolated endophytic fungi viz., *Nigrospora oryzae* strain SUBL33, *Alternaria alternata* strain SUBL51 and *Aspergillus terreus* strain SUBL206 for the production of seven industrially and pharmaceutically important phenolic compounds named gallic acid, *p*-coumaric, caffeic acid, chlorogenic acid, ferulic acid, quercetin and kaempferol. The high-performance thin-layer chromatography (HPTLC) and high-performance liquid chromatography (HPLC) methods were used for the simultaneous determination of the aforementioned phenolic compounds in fungal crude extracts (FCEs). The percent amount of these aforesaid phenolic compounds in FCEs were found in significant amount. In conclusion, this study shows that we can simultaneously produce large amounts of phenolic compounds with pharmaceutical and industrial potential from a single microorganism in a short frame of time, which will lessen our reliance on other sources like plants and consequently reduce their over-depletion in an economical and environmentally friendly way.

Keywords – Endophytic fungi – Fungal crude extracts – HPLC – HPTLC

Introduction

In living organisms, aerobic metabolisms lead to the production of reactive oxygen species (ROS) as a byproduct (Juan et al. 2021). Though ROS play a crucial role in the defense response to both biotic and abiotic stress and are also involved as a signaling molecule for the regulation of various biological processes, their over-production causes damage to cellular materials and toxicity in plants (Dvořák et al. 2021, Mansoor et al. 2022). In humans, excessive ROS production causes various diseases, including cancer, Alzheimer's, ageing, heart disease, etc. (Singh et al. 2019, Hajam et al. 2022). Therefore, antioxidant radical scavenging is compulsory for living beings to mitigate the consequences caused by the over-production of ROS.

Many phenolic compounds have been reported to have antioxidant, antimicrobial, anticancer, anti-ageing, and other pharmacological properties (Rahman et al. 2022). Due to this, in the living system, phenolics have various biological effects as nutritional supplements for health promotion and disease prevention. In living beings, these phenolic compounds play a crucial role in diminishing the over-production of ROS (Świątek et al. 2019). Due to the aforementioned

properties, the demands for polyphenol-rich foods and beverages continuously increase in many industries (pharmaceuticals, foods, beverages, cosmetics, etc.) with increasing interest from consumers (Rathod et al. 2023).

Endophytic fungi are colonizing in a plant without causing any damage to the host and are found ubiquitously within all examined plants. Like their host plants, they can independently produce secondary metabolites. It is believed that they produce these substances by co-evolution or gene transfer from host plants to endophytes (Kumari et al. 2023, Ebadi et al. 2024). Therefore, bioactive molecules from endophytic fungi may deserve attention. The earlier study reported that endophytes are an excellent reserve for discovering new bioactive compounds (Soni et al. 2021). To date, more than 20000 substances are known to be produced by endophytes, and out of them, 51% bear a novel structure, whereas most of them have some biological activity (Segaran & Sathiavelu 2019, Tsipinana et al. 2023). These biological activities include antimicrobial, anti-parasitic, antioxidant, neuroprotective, antiviral, anticolinesterasic, antineoplastic, cytotoxic and immune-suppression properties (Ascêncio et al. 2014).

Phenolic compounds are reported as secondary metabolites of fungal endophytes. These are seemingly the antioxidant components and have been widely studied as the primary free radical scavenging molecules (Siriwach et al. 2012, Świątek et al. 2019). Therefore, it is necessary to explore the hush-hush of fungal endophytes with respect to their phenolics and antioxidant components. Based on the aforementioned information, in the present study, an attempt has been made to explore those endophytic fungi that would be able to produce industrially and pharmaceutically important phenolic compounds. Moreover, the effort was also made for the simultaneous identification of pharmaceutically and industrially important different types of phenolic compounds in endophytes Using HPLC and HPTLC. The identification of polyphenols using UV-V is spectrometer (Jankulovska et al. 2023), HPLC (Stoenescu et al. 2022), and HPTLC (Niranjan et al. 2017) has been reported earlier in plant systems.

Material & Methods

General chemicals and instruments used for phenolic analysis

The CAMAG (Muttentz, Switzerland) HPTLC system was equipped with a LinomatIV applicator, CAMAG TLC Scanner 3, and integrated software winCATS version 1.4.3 was used for HPTLC analysis. HPLC (model-Prominence) of Shimadzu (Japan) synchronised with detector (PDA SPD M 20), dual pump system (LC-20AD) autosampler with cooler (SIL-20 AC) and Shimadzu RP-C18 column (250 × 4.6 mm and 5 µm pore size) was used for HPLC analysis. The Standard of phenolics was purchased from Sigma Aldrich, India, while chemical solvents used in HPLC and HPTLC analysis were procured from Merck, India.

Fungal isolation, culturing and preparation of fungal crude extracts

Three endophytic fungi named *Nigrospora oryzae* strain SUBL33, *Alternaria alternata* strain SUBL51 and *Aspergillus terreus* strain SUBL206 (Genbank accession numbers MH071153, MH071155 and MH071154, respectively) were previously isolated from *Bacopa monnieri* and taken for study. Fungal culturing and preparation of fungal crude extracts (FCEs) for further experiments were done following the method described earlier (Soni et al. 2021).

Analysis of Phenolic Compounds by HPTLC

The analysis of phenolic compounds in FCEs using HPTLC was performed by following a HPTLC protocol described by Niranjan et al. (2017). HPTLC was performed on pre-coated silica gel HPTLC plates (Merck, India) 60 F254 (20 × 20 cm) with a 0.20 mm layer thickness. Sample and standard bands of 6-mm wide were applied to the plate under a flow of N₂ gas, 11.3 mm apart, and 10 mm from the bottom edge, starting 8 mm from the edge of the HPTLC plate with Linomat IV applicator. The linear ascending development was carried out in a CAMAG twin-trough chamber (20 × 10 cm), which was pre-saturated with 25-mL mobile phase toluene-ethyl acetate-

formic acid (13:11:2) at room temperature ($25 \pm 2^\circ\text{C}$) for 30 min. The length of the chromatogram run was 8 cm, and the TLC plates were air-dried in the fuming hood with adequate ventilation before scanning. Quantitative evaluation of the plate was performed in absorption mode at 282 nm, using a slit width of 6×0.45 mm at data resolution 100 μm per step and scanning speed at 10 mm s^{-1} with a computerized TLC Scanner 3, furnished with winCATS software version 1.4.3 at 282 nm. Quantification of the compounds in FCEs was performed by using pure gallic acid, chlorogenic acid, caffeic acid, p-coumaric acid, ferulic acid, quercetin, and kaempferol (Sigma-Aldrich, USA) as external standard.

Analysis of phenolic compounds through HPLC

All 7 aforementioned phenolic compounds were also analysed by HPLC (model-Prominence) of Shimadzu (Japan) synchronised with detector (PDA SPD M 20), dual pump system (LC-20AD) and autosampler with cooler (SIL-20 AC). Separations of the metabolites were achieved on the Shimadzu RP-C18 column (250×4.6 mm and 5 μm pore size). Gradient elution of the mobile phase was performed to resolve the peaks of metabolites. The mobile phase used for separation was prepared from acetic acid (1%, v/v) in HPLC-grade water (component A) and acetonitrile (component B). The elution of solvent B was from 18 to 36% in 0.1 to 15 min; and from 36 to 50% in 15 to 40 min, with a flow rate of 0.6 mL/min. The data were integrated by Shimadzu Lab solution software, and the results were obtained in triplicate by comparison with the standards. Before analysis by HPLC, all samples and solutions were filtered through 0.45 μm Nylon filters (Millipore). For the identification of blank peaks, a plain mobile phase was used as a control. The detection was made at 254 nm. Data acquisition and computation were performed using lab solution software.

Results

The FCEs of *Nigrospora oryzae* strain SUBL33, *Alternaria alternata* strain SUBL51, and *Aspergillus terreus* strain SUBL206 were subjected to both HPTLC and HPLC for analysis of phenolic compounds. The band of HPTLC (Fig. 1) as well as the spectra of both HPTLC and HPLC (Fig. 2 and Fig. 3, respectively) revealed that all the endophytes produced significant concentrations of phenolic compounds. Among them, *Aspergillus terreus* strain SUBL206 was found to be produced maximum amount of chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, Kaempferol and quercetin. However, the quercetin was detected in significant concentration only in HPTLC analysis. Moreover, the gallic acid and quercetin (in HPLC result) was reported to be produced maximum in *Nigrospora oryzae* strain SUBL33 and *Alternaria alternata* strain SUBL51, respectively. Further, the percent amount of phenolic compounds detected by both aforesaid methods are depicted in Table 1.

Discussion

In our earlier study, we found that the endophytic fungi, isolated from leaves of *Bacopa monnieri* viz., *Nigrospora oryzae* strain SUBL33, *Alternaria alternata* strain SUBL51 and *Aspergillus terreus* strain SUBL206 produced significant concentrations of bioactive saponin (triterpene)- bacoside and withanolide; which were estimated through HPLC (Soni et al. 2021). We also tried to check the phenolic compounds in the FCEs of the aforementioned endophytes by qualitative biochemical colour-based methods, which are less sensitive and repeated experiments give variable results (Soni et al. 2021). In this study, we examined the potential of aforementioned endophytes for the production of seven bioactive phenolic compounds viz., gallic acid, chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, quercetin and kaempferol using HPLC and HPTLC method. The presence of both types, including triterpene and phenolic compounds, in our isolated fungi, indicated that the acetate/mevalonate pathway, which is responsible for the synthesis of both phenolic and triterpene (saponin) may be driven in aforementioned isolated strains.

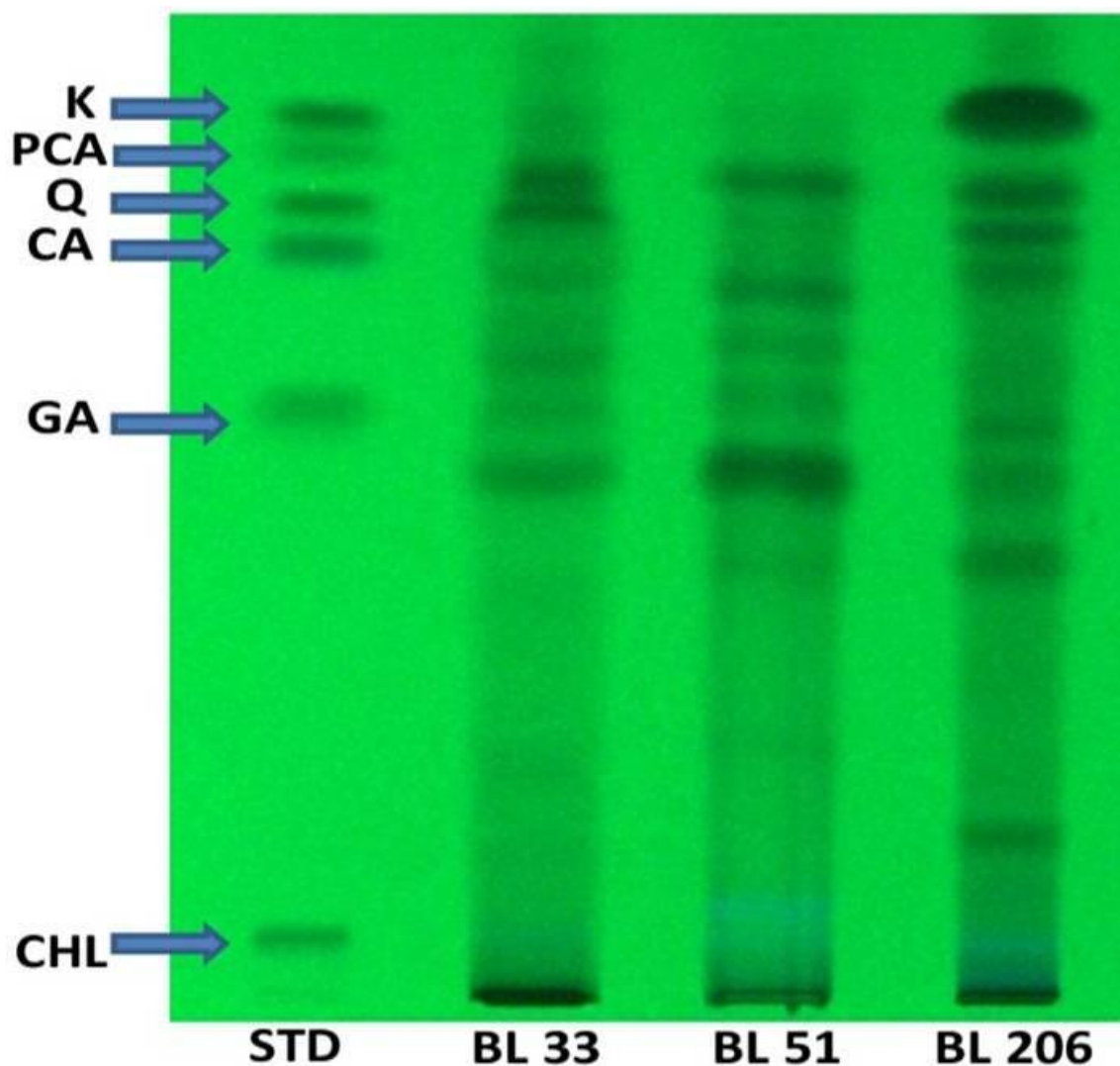


Fig. 1 – Fingerprint profiles of STD, standards [Mixture of chlorogenic acid (CGA), gallic acid (GA), caffeic acid (CA), p-coumaric acid (PCA), ferulic acid (FA), quercetin (Q) and kaempferol (K)]; BL33, FCE of *Nigrospora oryzae* strain SUBL33; BL51, FCE of *Alternaria alternata* strain SUBL51; BL206, *Aspergillus terreus* strain SUBL206 on silica gel 60 F254 HPTLC plates.

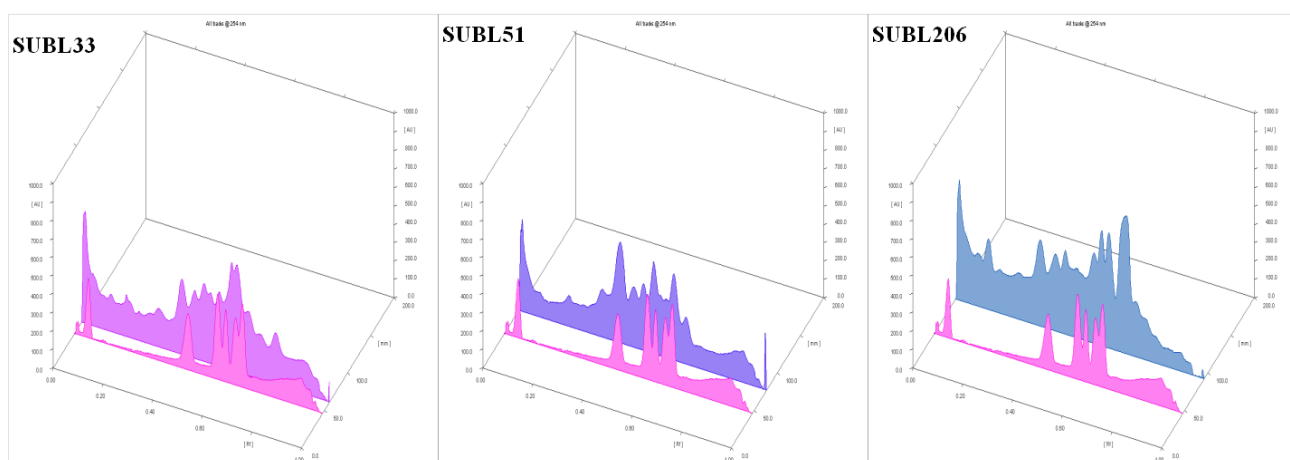


Fig. 2 – 3D overlaid chromatograms of standard along with SUBL33 (Crude extract of *Nigrospora oryzae* strain SUBL33); SUBL51 (Crude extract of *Alternaria alternata* strain SUBL51); SUBL206 (Crude extract of *Aspergillus terreus* strain SUBL206).

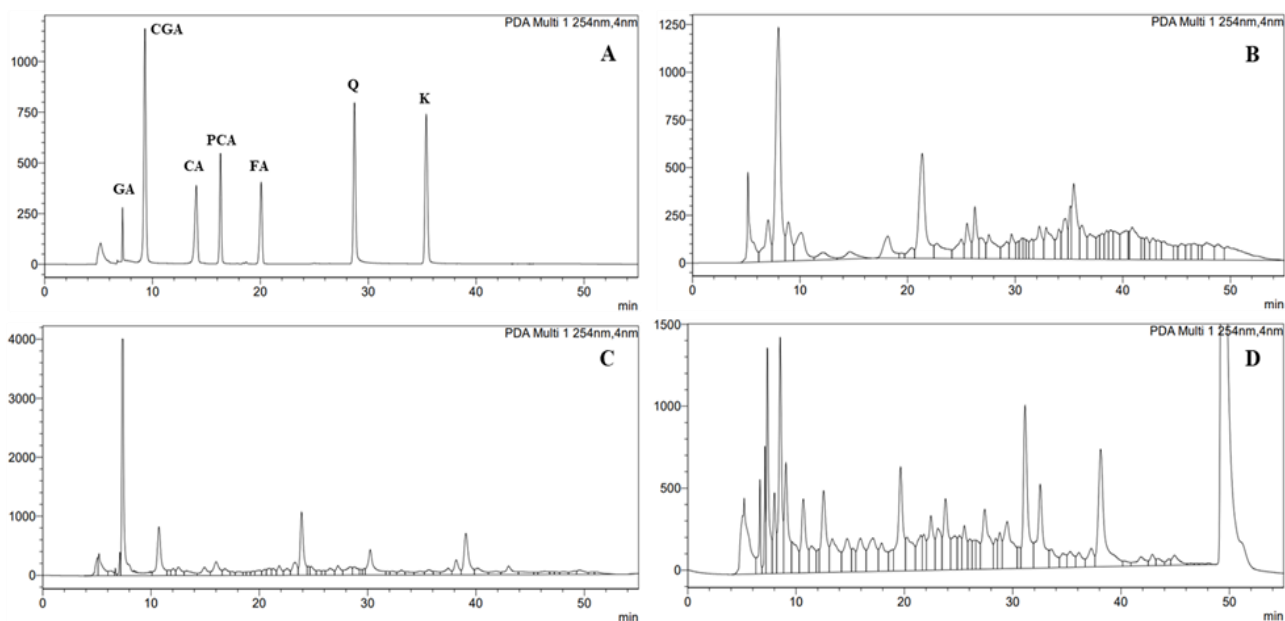


Fig. 3 – HPLC chromatograms of (A) standards [Mixtures of gallic acid (GA), chlorogenic acid (CGA), caffeic acid (CA), p-coumaric acid (PCA), Ferulic acid (FA), quercetin (Q) and kaempferol (K)] (B) Crude extract of *Nigrospora oryzae* strain SUBL33 (C) Crude extract of *Alternaria alternata* strain SUBL51 (D) Crude extract of *Aspergillus terreus* strain SUBL206.

Table 1 Amount (%) of phenolic compounds in fungal crude extract of endophytes

Phenolic compounds	SUBL33		SUBL51		SUBL206	
	HPLC	HPTLC	HPLC	HPTLC	HPLC	HPTLC
Gallic acid	2.33	2.21	0.82	0.78	1.62	1.71
Chlorogenic acid	0.30	0.29	0.11	0.15	0.70	0.68
Caffeic acid	0.31	0.35	0.23	0.19	1.63	1.49
Coumaric acid	0.35	0.40	1.06	0.97	1.12	1.23
Ferulic acid	0.25	excluded	0.36	excluded	1.18	excluded
Quercetin	0.41	0.39	0.81	0.91	0.09	1.24
Kaempferol	0.77	0.70	0.20	0.25	1.03	0.96

This previous finding of other researchers revealed that the different genera of endophytic fungi can produce a number of bioactive phenolic compounds viz., protocatechuic acid, coumaric acid, caffeic acid, chlorogenic acid, p-hydroxybenzoic acid, protocatechuic acid, gallic acid, ferulic acid, rosmarinic acid, caffeic acid, m-coumaric acid, alternarienoic acid, apigenin, rutin, luteolin, kaempferol, camptothecin, quercetin, coumarin, talaroflavone, altenuene, altenuisin, alternariol, alternariol-5-O-methyl ether etc. and/or their derivatives (Qi et al. 2009, Govindappa et al. 2015, Ebada et al. 2016, Pan et al. 2017, Das et al. 2017, Abonyi et al. 2018, Eze et al. 2019, Kaur et al. 2020, Shaaban et al. 2021, Parvandi et al. 2021, Mazumder et al. 2021, Mohinudeen et al. 2021, Rochín-Hernández et al. 2022, Elbermawi et al. 2022, Ashoka & Shivanna 2023, Gupta et al. 2023, Ebadi et al. 2024).

The genus *Aspergillus* is one of the significant contributors to the secondary metabolites of fungal origin. This genus has over 180 species. They produce a broad range of structurally heterogeneous secondary metabolites such as phenolics, alkaloids, terpenoids, xanthenes, steroids, polyketide compounds, etc. (Vadlapudi et al. 2017, Ibrahim et al. 2023, Yu et al. 2021, Bai et al. 2023). Even after investigations spanning several decades, this genus nevertheless continues to yield metabolites with new structures and interesting biological activities (Vadlapudi et al. 2017, Yu et al. 2021). The phenolic compounds identified in this study that were produced by *Aspergillus sp.* concurred with the earlier findings by other researchers. In a previous study, Kaur

et al (2020) found that the endophytic fungi *Aspergillus fumigatus* isolated from *Moringa oleifera* produced phenolic compounds viz., caffeic acid, quercetin and Kaempferol. In another study, the research conducted by Abonyi et al. (2018) also accounted for ferulic acid in the crude extract of *Aspergillus sp.* Similarly, an investigation conducted by Danagoudar et al. (2017) reported the presence of ferulic acid together with other phenolic compounds viz., p-coumaric acid and cinnamic acid in culture extract of *Aspergillus austroafricanus* isolated from *Zingiber officinale* rhizomes. Bose and Gowrie (2017) determined gallic acid in culture extract of endophytic *Aspergillus sp.* isolated from *Casuarina junghuhniana* Miq. Mazumder et al. (2021) observed chlorogenic acid in the crude extract of the endophyte *Aspergillus niger*.

Endophytic *Alternaria* spp. were also reported earlier to produce many phenolic compounds such as rosmarinic acid, rutin, luteolin, apigenin, quercetin, ferulic acid, gallic acid, camptothecin, kaempferol, Coumarin, protocatechuic acid, p-hydroxybenzoic acid, caffeic acid, m-coumaric acid, talaroflavone, alternarienoic acid, altenuene, altenuisin, alternariol, alternariol-5-O-methyl ether etc. and/or their derivatives (Qi et al. 2009, Govindappa et al. 2015, Parvandi et al. 2021, Mohinudeen et al. 2021, Elbermawi et al. 2022, Ashoka & Shivanna 2023, Gupta et al. 2023, Ebadi et al. 2024). In this study, we also observed that *Alternaria sp.* produced phenolic compounds (Table 1). We found that the concentration of quercetin was significantly found to be much higher among the observed endophytic fungi. Our observation is in line with the findings of other researchers. Parvandi et al (2021) found that the endophyte *Alternaria tenuissima* SBUp1 isolated from *Ferula assa-foetida* capable of producing quercetin along with some other bioactive phenolic compounds like rosmarinic acid, rutin, luteolin, apigenin and ferulic acid. In a recent study, Ebadi et al. (2024) isolated endophytes *Alternaria alternata* and *A. tenuissima* produced gallic acid, caffeic acid, and coumaric acid along with other phenolic compounds either alone or with both types of endophytes. We also observed the chlorogenic acid in FCEs of *A. alternata*. This might be the first report on the production of chlorogenic acid by *A. alternata*.

In this study, gallic acid, an important phenolic compound was found to be produced maximum by *Nigrospora oryzae* strain SUBL33 among the observed endophytes. The production of gallic acid might be reported first time in *Nigrospora oryzae*. There are only a few reports available concerning to production of phenolic compounds by *Nigrospora oryzae*. Earlier, Ebada et al (2016) noticed phenolic compounds viz., quercetin monoglycosides which is a derivative of quercetin produced by *Nigrospora oryzae*.

The extracellular phenolic compounds produced by these fungi can be an alternative source of medicinal plants. This study concludes that we can produce a bulk quantity of industrially and pharmaceutically important phenolic compounds simultaneously from a single microorganism in a short period and consequently reduce the dependency on other sources like plants and ultimately trim down their over depletion in an eco-friendly and cost-effective manner.

Author Contributions

SKS conceived and designed the experiment. SKS performed the microbiological part of the work. AN performed High-performance liquid chromatography and High-performance thin-layer chromatography and analyzed the results. SKS, IA, SKD and IV wrote the MS draft. SKS edited and finalized the MS

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Consent for publication

All authors read and approved the manuscript.

Compliance with ethical standards

This article does not contain any studies with animals or human participants performed by any of the authors.

Conflict of interest

The authors declare that they have no competing interests.

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