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Cleavage of mangiferin by *Acinetobacter* SM902 isolated from *Mangifera indica* rhizosphere: Production of norathyriol and other phenolic compounds

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ABSTRACT

Norathyriol is one of the xanthone aglycone synthesized through the shikimate pathway, and it serves as a precursor of mangiferin in plant metabolism. In microbial metabolism, however, it can appear as a product of mangiferin degradation. Norathyriol plays an importante role as an anti-inflammatory, anticancer, and antioxidant agent. In comparison with chemical synthesis, the use of microorganisms capable to metabolize mangiferin has advantages, since it does not require strong acids or phenolic reagents. The aim of this study was to produce norathyriol from mangiferin using a bacterial strain SM902 isolated from the rhizosphere of *Mangifera indica* (mango). The strain was identified, and its ability to degrade mangiferin was analyzed. Rhizosphere and bulk soil samples of *M. indica* were inoculated into synthetic medium containing mangiferin as the only carbon source, and the bacterial isolates were screened. Strain SM902 was identified as *Acinetobacter* sp. through 16S rRNA gene sequencing. Photoluminescence excitation analysis confirmed the production of norathyriol as a biotransformation product. In addition, the SM902 extract was examined by ultra-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight mass spectrometry in MSE mode (UPLC-QTOF-MSE), allowing the characterization of monogalloyl-glucose, homomangiferin, tetrahydroxyxanthone-C-hexoside dimer and its isomers as additional products from mangiferin biotransformation. This is the first report of an aerobic Gram-negative bacterium able to metabolize mangiferin, producing norathyriol and other phenolic compounds with potential pharmacological relevance. Further studies are still necessary to identify the metabolic pathway involved in this process.

1. Introduction

Between all the classes of plant's secondary metabolites, phenolic compounds are among the most studied, playing key roles in growth, reproduction, and defense against environmental stresses [1,2]. In addition to their physiological functions in plants, they have gained considerable attention due to their potential health benefits in humans. A specific class of phenolic compounds, the xanthones, stand out for their wide range of biological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer effects [3,4].

Mangiferin (1,3,6,7-tetrahydroxyxanthone-C-2-β-D-glucoside, MGF) is a C-glucosyl xanthone first isolated from *Mangifera indica* and now reported in more than 17 plant families, such as Gentianaceae, Rubiaceae, Fabaceae, and Iridaceae [5–9]. In *M. indica*, MGF is considered one of the major phenolic constituents, commonly found in leaves, roots, bark, and fruit extracts [10–12]. In recent years, MGF has attracted growing interest due to its broad pharmacological profile, including antioxidant [13], antidiabetic [14], and anticancer activities [15].

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However, its low oral bioavailability (ca. 1.2 %) has limited its pharmaceutical application [16].

In vivo studies suggest that mangiferin undergoes extensive metabolism, with at least 30 derivatives formed after oral administration in animal models [17]. Among these, norathyriol (1,3,6,7-tetrahydroxyxanthone, NRT), the aglycone product of MGF deglycosylation, has demonstrated biological properties that are sometimes even more potent than those of MGF itself, particularly in antidiabetic and anti-inflammatory assays [18–21]. This has led to the hypothesis that MGF may act as a prodrug, with NRT being the main bioactive form [22].

Due to its pharmacological relevance, there is an increasing interest in novel synthetic routes exploration for norathyriol. One example of that is the acid hydrolysis of MGF, which remains the most accessible approach, but typically requires harsh conditions, including strong acids (e.g., HCl/phenol mixtures) and high temperatures, which are neither environmentally friendly nor compatible with large-scale applications [23–25].

Biocatalysis offers an alternative route, enabling C—C and C—O bond transformations under mild conditions with high selectivity [26,27], as opposed to current synthetic routes. While literature reports evidence of anaerobic bacteria from human gut microbiota capable of perform the deglycosylation of mangiferin, resulting into norathyriol [28–30], the potential of aerobic soil microorganisms in this transformation remains unexplored.

Here, we report the isolation and screening of an aerobic bacterial strain, isolated from soil and rhizosphere samples of *M. indica*, with the capacity to convert mangiferin into norathyriol. As mangiferin has a native fluorescence propriety, as well as its metabolites, we developed a fluorescence-based screening approach to detect active microbial cultures. Additionally, the biotransformation products were analyzed by ultra-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight mass spectrometry (UPLC-ESI-QTOF-MSE), providing insight into microbial pathways involved in mangiferin metabolism.

Our findings highlight a new microbial platform for the mild and selective biotransformation of a complex natural product, potentially expanding the set of strategies for green production of bioactive xanthones.

2. Experimental section

2.1. Chemicals

The reagent MGF was extracted and purified according to Barreto et al. (2008) [12]. All other reagents used were of analytical grade.

2.2. Bacterial strain

The *Acinetobacter* sp. strain SM902 used in this study was isolated from a rhizosphere sample of *Mangifera indica*, collected at the Beraba farm, Ceará state, Brazil (coordinates 4°11′54″S, 38°04′58″W), from where ten soil samples and rhizospheres were collected for cultivation and isolation of microorganisms. For each assay, 5 g of soil or 3 g of rhizosphere were inoculated into Nutrient Broth, composed of 3.0 g of yeast extract and 5.0 g of peptone per liter, adjusted to pH 7.0, for 24 h, at 240 rpm and 30 °C. After that, the cultures were left to rest for decantation of solid particles and an aliquot of 1.0 mL was used for serial dilution in 0.9 % (*w/v*) NaCl solution. The dilutions 10^{-5}, 10^{-6} and 10^{-7} were plated in duplicate using the spread plate technique on ATGE medium, which consisted of 15.0 g of agar, 5.0 g of tryptone, 1.0 g of glucose, and 2.5 g of yeast extract per liter. After 24 h, well-isolated colonies with distinct morphologies were picked to prepare pure culture. The cultures were preserved in glycerol and stored at −80 °C. The nucleotide sequence data of strain SM902 have been deposited in the NCBI GenBank database under the accession number [SUB15687137].

2.3. Screening of microorganisms capable of metabolizing mangiferin

The isolates were reactivated from stock and cultured in ATGE medium at 37 °C for 18 h to obtain isolated colonies. Then, the colonies were cultivated in TGE medium which contained, per liter, 5.0 g of tryptone, 1.0 g of glucose, 2.5 g of yeast extract and a pH equal to 7.0 for 24 h at 150 rpm, incubated at 30 °C using a Tecnal® incubator, model TE-420. After incubation, 30 µL of the culture was transferred, in duplicate, to 96 well plates containing 1 mM of mangiferin (MGF) in a modified mineral medium (MM) [31]. The MM medium was prepared with, per liter, 5.0 g of yeast extract, 2.7 g of NaCl, 1.0 g of $(NH_4)_2SO_4$, 6.0 g of Na_2HPO_4, 3.0 g of KH_2PO_4, 0.6 g of $MgSO_4{\cdot}7H_2O$, and adjusted to pH 7.0. The medium was sterilized at 110 °C for 15 min, then supplemented with 0.1 % (*v/v*) of a micronutrient solution composed of 10.95 g of $ZnSO_4.7H_2O$, 5.0 g of $FeSO_4.7H_2O$, 1.54 g of $MnSO_4.H_2O$, 0.39 g of $CuSO_4.5H_2O$, 0.25 g of $Co(NO_3)_2.6H_2O$, and 0.17 g of $Na_2B_4O_7.10H_2O$, per liter, sterilized at 0.22 µm membrane filtration, with final volume of 200 µL. The cultures grew by 48 h at 150 rpm, incubated at 30 °C. The absorbances were measured before and after cultivation, at 630 nm in a microplate reader (ThermoPlate, São Paulo, Brazil). The microorganism that presented better growth, SM902, was selected for the subsequent experiments.

2.4. DNA extraction of SM902 strain

The genomic DNA of the SM902 strain was extracted using a Cetyltrimethylammonium Bromide (CTAB) protocol with modifications [32]. At the end of the extraction, the obtained DNA was eluted in 50 µL of Tris-HCl (pH 8.4) with 20 µg/L of RNAse. DNA sample quality was evaluated using a Nanodrop® ND-1000 spectrophotometer (NanoDrop, Wilmington, DE, USA).

2.5. Molecular identification of SM902 strain

The 16S rRNA gene was amplified by polymerase chain reaction (PCR) with the universal bacterial primers 27F and 1525R [33], performed in a final volume of 25 µL containing 100 ng of genomic DNA (template), 20 mM of Tris-HCl (pH 8.4), 50 mM of KCl, 3.0 mM of $MgCl_2$, 0.2 mM of each dNTP, 0.5 µM of each primer and 1.0 unit of Taq DNA polymerase (MBI Fermentas Inc., USA). The amplification was performed in an Eppendorf Mastercycler® ep gradient S thermal cycler (Hamburg, Germany) programmed for an initial denaturation step (4 min at 94 °C) followed by 35 cycles of 1 min at 94 °C, 1 min at 55 °C, 2 min at 72 °C and a final extension of 10 min at 72 °C. PCR product was analyzed by 1 % (*w/v*) agarose gel electrophoresis, stained with SYBR® Safe DNA (Invitrogen, USA) and purified by ethanol precipitation protocol and resuspended in ultrapure water. The sample was sequenced by Macrogen Inc. (South Korea) using the primers 27F, 1492R, 518F, and 800R. Partial sequences were used to generate consensus using the Geneious Prime® (v2020.1.2), and the sequence was analyzed and compared with others deposited in GenBank using the Basic Locl Alignment Search Tool- Blast [34].

2.6. Cultivation of SM902 strain on mangiferin

The SM902 strain was pre-inoculated in TGE medium for 18 h at 150 rpm and 30 °C. After cultivation, the grown cells were inoculated in MM with 1 mM of MGF for 24 h, also at 150 rpm and 30 °C. The culture was centrifuged at 9000*g* for 15 min at 4 °C (Sigma 6–15, UK) and the precipitated cells were washed three times in NaCl 0.9 % (*w/v*) solution, followed by resuspension in saline and density adjusted to 0.150 ± 0.020 using a spectrophotometer (Genesys™ 6, USA) at 600 nm. The biomass was incubated in MM with 1 mM of mangiferin for 48 h, at 150 rpm and 30 °C. After that, the samples were centrifuged at 9000*g*, for 15 min at 4 °C and cell free supernatants were used for analyzes.

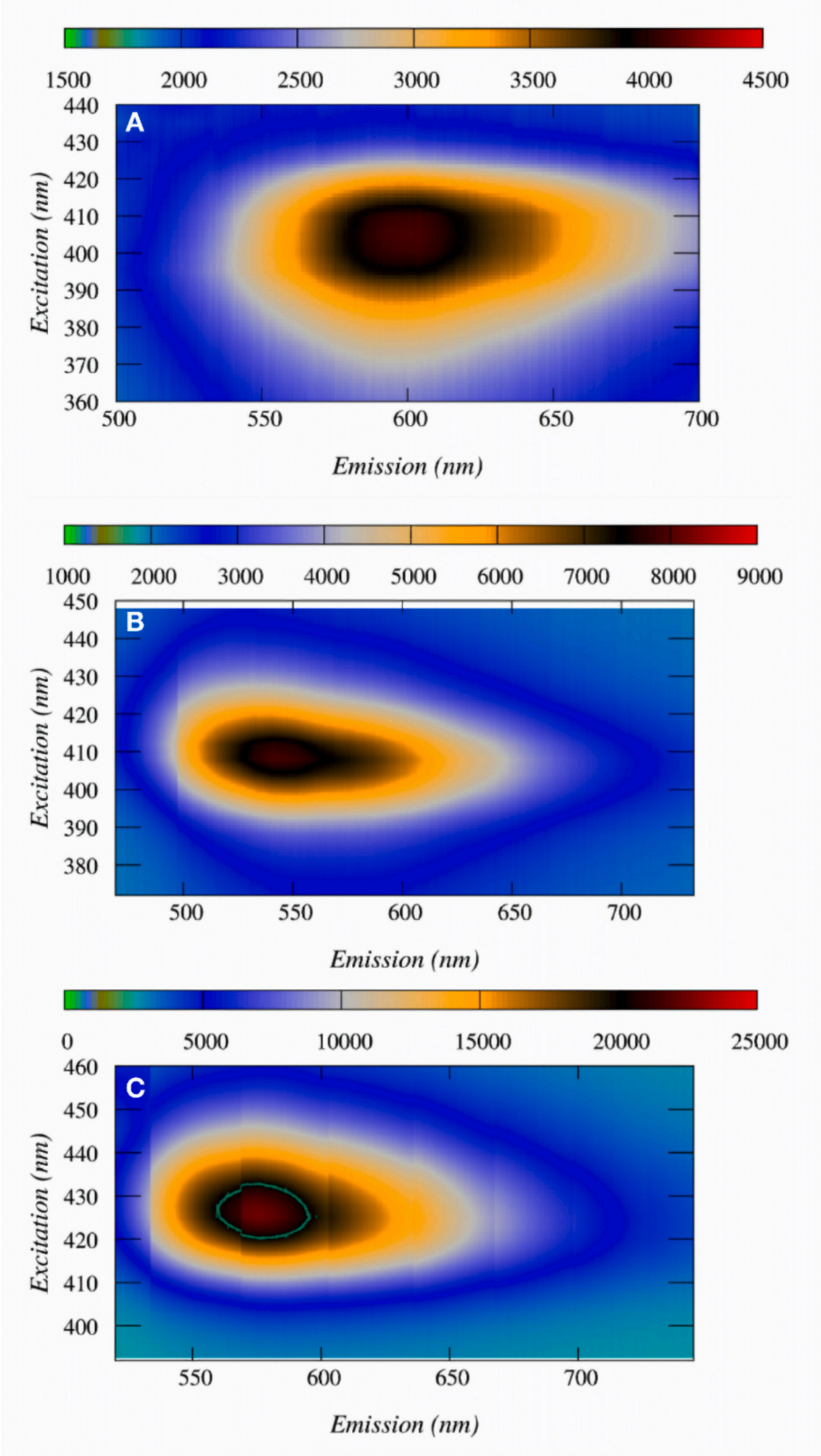

Fig. 1. Excitation-emission maps obtained through Photoluminescence Excitation. **A** and **B** shows fluorescence signatures of mangiferin and norathyriol, respectively. **C** represents byproducts resulted from cultivation of SM902 strain in 1 mM of mangiferin.

2.7. Photoluminescence Excitation (PLE) analysis

The energy gap between the highest occupied and lowest unoccupied electronic levels is a critical parameter determining the electronic, optical, redox, and transport (electrical) properties of a material [35]. Photoluminescence excitation (PLE) maps [36] were acquired using a Horiba Nanolog fluorometer cooled by liquid nitrogen, equipped with a xenon light source and InGaAs detector. The maps were recorded in the excitation range from 300 to 600 nm and emission range from 300 to 700 nm. The resolution in the excitation and emission range was 0.5 and 1 nm, respectively. The analyzes were repeated in triplicate.

2.8. UPLC-ESI-QTOF-MS^E analysis

The biomass of SM902 previously grown in MM containing 1 mM of MGF for 48 h was lysed by sonication and the cell extract was re-incubated in 1 mM MGF for 48 h at 150 rpm, 30 °C. The extract was centrifuged and the supernatant was analyzed by UPLC-ESI-QTOF-MS^E analysis.

The analysis was performed on Waters UPLC system (Waters, Milford, MA, USA) coupled with a Waters UPLC BEH C18 column (150 × 2.1 mm, 1.7 μm) at 40 °C using a mobile phase composed of formic acid-aqueous solution containing 0.1 % (A), and acetonitrile with 0.1 % formic acid (B). The elution of 5 μL of injected sample was performed at a flow rate of 0.4 mL/min under gradient: on the first-time interval (0–15 min), concentration of B increased from 2 to 95 %, adjusted to 100 % between 15.1 and 17 min, then lowered to 2 % between 17.1 and 19.1 min. The MS analysis was achieved on a Waters Xevo G2-S Q-TOF mass spectrometer (Waters, Milford, MA, USA) equipped with ElectronSpray Ionization (ESI) source in both the positive and negative ion mode. For this analysis, the source temperature was set to 120 °C and the desolvation temperature to 350 °C, with a cone gas flow of 350 L h^{-1}. The extraction cone was operated at 0.5 V with a 2.6 kV of capillary voltage, a mass range of 110–1180 *m/z* was scanned on ESI-(−) mode, and the mass spectrometer operated with MSE centroid programing using a tension ramp (20 to 40 V). Leucine enkephalin was used as lock mass. The instrument was controlled by Masslynx 4.1 software (Waters Corporation).

3. Results and discussion

Both mangiferin (MGF) and norathyriol (NRT) presents as compounds with a polyphenolic framework and extended conjugation. Thus, they also exhibit intrinsic fluorescence properties which allows their detection, and even differentiation, via photoluminescence-based techniques such as fluorescence spectroscopy. Known for its molecular selectivity and high sensitivity, the use of fluorescence spectroscopy to monitor transformations between compounds whose structure is related (like the xantones under study in this work) is favorable. Although MGF and NRT share the same xanthone core, the presence or absence of the C-glycosidic moiety introduces subtle but significant and detectable differences in their photophysical behavior.

Taking advantage of those differences, photoluminescence excitation (PLE) analysis was employed to distinguish MGF and NRT based on their distinct fluorescence decay profiles. Upon photon absorption, each molecule is excited to a higher electronic state and then relaxes back to the ground state, releasing energy and emitting a photon whose wavelength and intensity are influenced by the electronic structure and compound's conformation. On PLE, a resulting excitation-emission matrix (EEM) is obtained, yielding a molecular fingerprint allowing relatively precise identification [37,38].

The isolation process of microorganisms from soil and rhizosphere samples of *Mangifera indica* resulted in 40 bacterial strains isolated, from which strain SM902 demonstrated superior growth when cultivated in medium containing MGF as the sole carbon source. Partial sequencing (1348 bp) of its 16S rRNA gene revealed 100 % identity with sequences from *Acinetobacter nosocomialis* and *Acinetobacter calcoaceticus*, leading to its classification as *Acinetobacter* sp. *Mangifera indica* is known to accumulate mangiferin as a major bioactive compound in its tissues and root exudates, enriching the rhizosphere with this substrate. Microorganisms inhabiting this niche are therefore naturally exposed to mangiferin and more likely to develop specific metabolic pathways for its cleavage. Within this context, the genus *Acinetobacter*, composed of Gram-negative, strictly aerobic bacilli from the class Gammaproteobacteria, is commonly found in terrestrial and aquatic ecosystems [39], which includes rhizospheres, with remarkable metabolic adaptability, including the degradation and mineralization of aromatic compounds and other xenobiotics [40] and the ability to degrade phenolic compounds and other aromatics [41–43], supporting their potential as biocatalysts in environmental and industrial contexts.

When cultured with MGF, strain SM902 was able to biocatalyze the transformation of the substrate into NRT. This conversion was confirmed by comparing the fluorescence signature of the culture supernatant with those of authentic MGF and NRT standards. The MGF standard showed a characteristic emission maximum at 600 nm with excitation at 405 nm (Fig. 1A), while NRT exhibited a distinct emission peak at 540 nm with excitation at 410 nm (Fig. 1B). Analysis of the cell-free supernatant from the SM902 culture revealed a dominant emission peak at 540 nm, matching that of NRT (Fig. 1C), thus confirming the formation of the aglycone.

To the best of our knowledge, this is the first report of an aerobic soil bacterium capable of cleaving the C—C bond of a C-glucosyl xanthone under mild cultivation conditions. Unlike previously described anaerobic transformations involving human gut microbiota, this finding expands the known repertoire of microbial strategies for xanthonoid metabolism and suggests the presence of yet-undescribed enzymatic systems in *Acinetobacter* species that may be harnessed for biotechnological applications. This work also highlights the usefulness of fluorescence-based techniques as rapid and non-destructive tools for monitoring biotransformation of polyphenolic compounds.

To our knowledge, no previous studies have reported the use of excitation emission matrix (EEM) fluorescence spectroscopy for the simultaneous characterization of mangiferin (MGF) and its aglycone, norathyriol (NRT). Most fluorescence-based analyses of mangiferin rely on single-wavelength emission or excitation spectra [39,40,44,45], which limit the scope of structural information available. In contrast, EEM spectroscopy provides multidimensional data that reflect subtle variations in molecular conformation, environment, and substitution pattern. The resulting spectral fingerprints offer a more informative and sensitive approach for distinguishing structurally related polyphenols. We emphasize that this strategy is particularly valuable for tracking biotransformation processes in complex biological systems.

Until now, microbial deglycosylation of MGF into NRT has been reported exclusively in the context of mammalian gut microbiota. Several studies have detected NRT in the feces of rats, pigs, and humans after oral administration of MGF or MGF-rich plant extracts, indicating in vivo microbial cleavage of the C—C glycosidic bond [46–48]. Hasanah et al. (2021) [48] isolated a bacterium from mouse intestine, identified as *Bacillus* sp. KM7-1, capable of converting MGF to NRT. Regarding humans, Sanugul et al. (2005) [9] isolated a strain with similar capability under anaerobic conditions, named *Bacteroides* sp. MANG, from a mix of human fecal bacteria. In this study, others strains representing common gut genera including *Bifidobacterium*, *Lactobacillus*, *Escherichia*, and *Clostridium* did not catalyze this transformation, suggesting that MGF-deglycosylating activity is relatively rare, even among specialized anaerobic populations.

The present study is the first to report an aerobic bacterium—identified as *Acinetobacter* sp. strain SM902—capable of catalyzing this transformation. This genus is widely distributed in soil and aquatic environments, and several species are known to possess metabolic versatility, including the degradation of phenolic and aromatic compounds [49–52]. The ability of *Acinetobacter* SM902 to biotransform

Table 1
Proposed of metabolites obtained from mangiferin biotransformation using SM902 cell extract by UPLC-ESI-QTOF-MS/MS.

Compound	Retetion time (min)	$[M-H]^-$	MS/MS fragment ions relative abundance (%)	Empirical formula	Error (ppm)	Putative name
1	1.29	331.0661	211, 169	$C_{13}H_{16}O_{10}$	1.2	Monogalloyl-glucose
2	2.14	841.1487	823, 751, 733, 703, 631, 601	$C_{38}H_{33}O_{22}$	2.4	Tetrahydroxyxanthone-*C*-hexoside dimer
3	2.52	841.1492	823, 751, 733, 703, 631, 601	$C_{38}H_{33}O_{22}$	0.7	Tetrahydroxyxanthone-*C*-hexoside dimer isomer I
4	3.01	841.1460	823, 751, 733, 703, 631, 601	$C_{38}H_{33}O_{22}$	0.8	Tetrahydroxyxanthone-*C*-hexoside dimer isomer II
5	3.27	421.0761	331, 301, 271, 259	$C_{19}H_{18}O_{11}$	2.1	Mangiferin
6	3.55	435.0932	315, 301, 271	$C_{20}H_{19}O_{11}$	1.1	Homomangiferin

MGF into NRT under aerobic conditions represents a novel strategy for producing NRT via microbial biocatalysis, without the need for anaerobic cultivation or human-derived microbial consortia.

This is particularly relevant given the growing evidence that NRT possesses significantly higher oral bioavailability than MGF [49]. For instance, in a pharmacokinetic study, Han et al. (2010) [19] shows that MGF oral bioavailability was as low as 1.2 %, while the value to NRT was equal to 30,4 % [53]. Therefore, the in vitro conversion of MGF to NRT by strain SM902 may have important implications for enhancing the bioavailability and biological effects of mangiferin-derived therapeutics.

In addition to NRT, further biotransformation products were observed in the cell-free supernatant of SM902 cultures incubated with MGF. Analysis by ultra-performance liquid chromatography coupled with high-resolution electrospray ionization quadrupole time-of-flight mass spectrometry (UPLC-ESI-qTOF-MSE) revealed multiple secondary metabolites, likely formed via partial hydrolysis or oxidative cleavage of the xanthone scaffold. Identification was based on retention time, accurate mass, and MS/MS fragmentation patterns. Fig. S1 displays the total ion chromatogram (TIC) from the SM902 extract (negative mode), while Table 1 summarizes the proposed identities and molecular formulas of the detected compounds. These findings indicate the presence of multiple enzymatic activities in SM902, with potential utility in the selective modification of bioactive polyphenols for pharmaceutical or nutraceutical applications.

Spectral data obtained from the SM902 cell-free extract were compared with reference profiles reported in the specialized literature for a series of structurally related phenolic compounds. These include mono-galloyl-glucose (1, Fig. S2) [31,54], tetrahydroxyxanthone-C-hexoside dimers (2, Fig. S3; 3, Fig. S4; and 4, Fig. S5) [31,55], mangiferin (5, Fig. S6) [54,55], and homomangiferin (6, Fig. S7) [56]. The identification of these compounds was based on a combination of retention times, high-resolution mass measurements, and fragmentation patterns obtained via UPLC-ESI-qTOF-MSE analysis.

Like norathyriol, these phenolic compounds are of pharmacological interest due to their potential therapeutic applications. For example, mono-galloyl-glucose is a precursor of hydrolyzable tannins and represents a key pharmacophoric unit in compounds with documented anticancer activity [55,56]. Homomangiferin, a C-glucosyl xanthone structurally analogous to mangiferin but with an additional hydroxyl group on the sugar moiety, has been cited in several patents for its potential use in the treatment of metabolic syndromes including cardiovascular disease, diabetes, obesity, and hyperuricemia as well as neurological disorders such as post-stroke depression [57,58].

In contrast, the isomeric forms of the tetrahydroxyxanthone-C-hexoside dimers identified in this study have not yet been associated with any specific biological activity. However, given their structural similarity to bioactive xanthones, further investigation into their pharmacological potential may be warranted.

4. Conclusions

This study presents the first report of an aerobic bacterial strain, isolated from the rhizosphere of *Mangifera indica*, capable of metabolizing mangiferin into norathyriol and other phenolic derivatives with potential pharmacological relevance, including compounds not previously described in the literature. The strain, designated SM902 and identified as *Acinetobacter* sp., is likely well-adapted to the specialized chemical environment of the mango root microbiome, where mangiferin is naturally produced and exuded.

These findings not only expand the known biological routes for C-glycoside cleavage under aerobic conditions but also highlight the biocatalytic potential of rhizospheric bacteria in the structural modification of bioactive natural products. Further investigations are warranted to elucidate the enzymatic pathways and genetic determinants underlying this biotransformation, which may contribute to the development of sustainable microbial platforms for the production of high-value xanthone derivatives.

CRediT authorship contribution statement

Gabrielly O. Silva: Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. **Manoel L. Alves-Neto:** Writing – original draft, Visualization, Methodology. **Francisco L. da Silva:** Writing – review & editing, Visualization, Validation, Software. **Maria T.S. Trevisan:** Writing – original draft, Resources, Investigation, Conceptualization. **Edy S. Brito:** Writing – original draft, Conceptualization. **Samuel P.D. Marques:** Writing – original draft, Methodology. **Carlos L. Cesar:** Software, Resources, Methodology. **Vânia M.M. Melo:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Davila Zampieri:** Writing – review & editing, Validation, Resources, Methodology, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2025.109099.

Data availability

Data will be made available on request.

References

[1] M. Naczk, F. Shahidi, Extract and analysis of phenolics in food, J. Chromatogr. A 1054 (2004) 95–111, https://doi.org/10.1016/j.chroma.2004.08.059.
[2] A.R. Tapas, D.M. Sakarkar, R.B. Kakde, Flavonoids as nutraceuticals: a review, Trop. J. Pharm. Res. 7 (3) (2008) 1089–1099. https://www.ajol.info/index.php/tjpr/article/view/14693.
[3] F. Shahidi, M. Naczk, Phenolics in Food and Nutraceuticals, 2nd ed., CRC Press, Taylor & Francis Group, Boca Raton, 2003 https://doi.org/10.1201/9780203508732.
[4] J.S. Negi, V.K. Bisht, P. Singh, M.S.M. Rawat, Joshi GP (2013) naturally occurring Xanthones: chemistry and biology, J. Appl. Chem. 621459 (2013) 1–9, https://doi.org/10.1155/2013/621459.
[5] M. Sekar, Molecules of interest-mangiferin-a review, Annu. Res. Rev. Biol. (2015) 307–320, https://doi.org/10.9734/ARRB/2015/12669.
[6] P.R. Kshirsagar, N.B. Gaikwad, S. Panda, H.V. Hegde, S.R. Pai, Reverse phase-ultra flow liquid chromatography-diode array detector quantification of anticancerous and antidiabetic drug mangiferin from 11 species os Swertia from India, Pharmacogn. Mag. 12 (2016) S32, https://doi.org/10.4103/0973-1296.176105.
[7] P. Talamond, L. Mondolot, A. Gargadennec, Hamon S. De Kochiko, A. Fruchier, C. Campa, U.S. Patent 12/936,859, 2011.
[8] E. Joubert, M. Manley, M. Botha, Use of NIRS for quantidication on mangiferin and hesperidin contents of dried green honeybush (*Cyclopia genistoides*) plant material, J. Agric. Food Chem. 54 (15) (2006) 5279–5283, https://doi.org/10.1021/jf060617l.
[9] K. Sanugul, T. Akao, Y. Li, N. Kakiuchi, N. Nakamura, M. Hattori, Isolation of a human intestinal bacterium that transform mangiferin to norathyriol and inducitibily of the enzyme that cleaves a *C*-glucose bond, Biol. Pharm. Bull. 28 (9) (2005) 1672–1678, https://doi.org/10.1248/bpb.28.1672.
[10] S. Iseda, On mangiferin, the coloring matter of mango (*Mangifera indica* Linn.). IV. Isolation of 1,3,6,7-tetrahydroxyxanthone and the skeletal structure of mangiferin, B Chem. Soc. Jpn. 30 (1957) 625–629, https://doi.org/10.1246/bcsj.30.625.
[11] J. Rodríguez, D. Di Pierro, M. Gioia, S. Monaco, R. Delgado, M. Coletta, S. Marini, Effects of a natural extract from *Mangifera inidica* L, and its active compoud, mangiferin, on energy state and lipid peroxidation of red blood cells, Biochim. Biophys. Acta, Gen. Subj. 1760 (9) (2006) 1333–1342, https://doi.org/10.1016/j.bbagen.2006.04.005.
[12] J.C. Barreto, M.T. Trevisan, W.E. Hull, et al., Characterization and quantitation of polyphenolic compounds in bark, kernel, leaves, and peel of mango (*Mangifera indica* L.), J. Agric. Food Chem. 56 (14) (2008) 5599–5610, https://doi.org/10.1021/jf800738r.
[13] L. Zhang, M. Wang, Growth inhinitory effect of mangiferin on thyroid cancer cell line TPC1, Biotechnol. Bioprocess Eng. 23 (2018) 649–654, https://doi.org/10.1007/s12257-018-0212-x.
[14] A.K. Singh, V. Raj, A.K. Keshari, et al., Isolated mangiferin and naringenin exert antidiabetic effect via PPRAy/GLUT4 dual agonistic action with strong metabolic regulation, Chem. Biol. Interact. 280 (2018) 33–44, https://doi.org/10.1016/j.cbi.2017.12.007.
[15] L.W. Rocha, I.J.M. Bonet, C.H. Tambeli, F.M. de-Faria, C.A. Parada, Local administration of mangiferin prevents experimental inflammatory mechanical hyperalgesia through CINC-1/epinephrine/PKA pathway and TNF-α inhibition, Eur. J. Pharmacol. 830 (2018) 87–94, https://doi.org/10.1016/j.ejphar.2018.04.030.
[16] P.S. Sellamuthu, P. Arulselvan, B.P. Muniappan, S. Fakurazi, M. Kandasamy, Magiferin from Salacia chinensis prevents oxidative stress and protects pancreatic β-cell in streptozotocin-induced diabetic rats, J. Med. Food 16 (8) (2013) 719–727, https://doi.org/10.1089/jmf.2012.2480.
[17] O. Benard, Y. Chi, Medicinal properties of mangiferin, structural features, derivative synthesis, pharmacokinetics and biological activities, Mini-Rev. Med. Chem. 15 (7) (2015) 582–594, https://doi.org/10.2174/1389557515666150401111410.
[18] H. Liu, K. Wang, Y. Tang, et al., Structure elucidation of in vivo and in vitro metabolites of mangiferin, J. Pharmaceut. Biomed. 55 (5) (2011) 1075–1082, https://doi.org/10.1016/j.jpba.2011.03.012.
[19] D. Han, C. Chen, C. Zhang, Y. Zhang, X. Tang, Determination of mangiferin in rat plasma by liquid-liquid extraction with UPLC-MS/MS, J. Pharmaceut. Biomed. 51 (1) (2010) 260–263, https://doi.org/10.1016/j.jpba.2009.07.021.
[20] C. Hou, Theorical study of antioxidative ability and antioxidative mechanism of norathyriol in solution, Comput. Theor. Chem. 1028 (2014) 87–91, https://doi.org/10.1016/j.comptc.2013.11.023.
[21] J. Li, M. Malakhova, M. Mottamal, et al., Norathyriol suppresses skin cancers induced by solar ultraviolet radiation by targeting ERK kinases, Cancer Res. 72 (1) (2012) 260–270, https://doi.org/10.1158/0008-5472.can-11-2596.
[22] F.N. Ko, C.N. Lin, S.S. Liou, T.F. Huang, C.M. Teng, Vasorelaxation of rat thoracic aorta caused by norathyriol isolated from Gentianaceae, Eur. J. Pharmacol. 192 (1) (1991) 133–139, https://doi.org/10.1016/0014-2999(91)90079-6.
[23] C.M. Teng, F.N. Ko, J.P. Wang, C.N. Lin, T.S. Wu, C.C. Chen, T.F. Huang, Antihaemostatic and antithrombotic effect of some antiplatelet agents isolated from Chinese herbs, J. Pharm. Pharmacol. 43 (9) (1991) 667–669, https://doi.org/10.1111/j.2042-7158.1991.tb03561.x.
[24] J.P. Wang, S.L. Raung, C.N. Lin, C.M. Teng, Inhibitory effect od norathyriol, a xanthone from *Tripterospermum lanceolatum*, on cultaneous plasma extravasation, E. J. Pharmacol. 251 (1) (1994) 35–42, https://doi.org/10.1016/0014-2999(94)90440-5.
[25] F. Wang, J. Yan, Y. Niu, et al., Mangiferin and its aglycone, norathyriol, improve glucose metabolism by activation of AMP-activated protein kinase, Pharm. Biol. 52 (1) (2014) 68–73, https://doi.org/10.3109/13880209.2013.814691.
[26] L. Hu, H. Hu, W. Wu, X. Chai, J. Luo, Q. Wu, Discovery of novel xanthone derivatives as xanthine oxidase inhibitors, Bioorg. Med. Chem. Lett. 21 (13) (2011) 4013–4015, https://doi.org/10.1016/j.bmcl.2011.04.140.
[27] S. Ahn, H. Yun, Y.T. Han, An improved C-deglycosylation of mangiferin to norathyriol, Org. Prep. Proced. Int. 50 (2018) 91–94, https://doi.org/10.1080/00304948.2017.1405336.
[28] H. Ding, Y. Zhang, C. Xu, D. Hou, J. Li, Y. Zhang, W. Peng, K. Zen, C. Zhang, X. Jiang, Norathyriol reverses obesity- and high-fat-diet-induced insulin resistance in mice through inhition of PTP1B, Diabetologia 57 (10) (2014) 2145–2154, https://doi.org/10.1007/s00125-014-3315-8.
[29] J. Guo, C. Xu, R. Xue, W. Jiang, B. Wu, C. Huang, Cytotoxic activities of chemical constituents from rhizomes of *Anemarrhema asphodeloides* and their analogues, Arch. Pharm. Res. 38 (2015) 598–603, https://doi.org/10.1007/s12272-014-0431-4.
[30] J.L. Adrio, A.L. Demain, Microbial enzymes: tools for biotechnological process, Biomolecules 4 (1) (2014) 117–139, https://doi.org/10.3390/biom4010117.
[31] T. Beelders, D. De Beer, M.A. Stander, E. Joubert, Comprehensive phenolic profiling of Cyclopia genistoides (L.) vent. By LC-DAD-MS and –MS/MS reveals novel xanthone and benzophenone constituents, Molecules 19 (8) (2014) 11760–11790, https://doi.org/10.3390/molecules190811760.
[32] G.C. Allen, M. Flores-Vergara, S. Krasynanski, S. Kumar, W.F. Thompson, A modified protocol for rapid DNA isolation from plant tissues using cetyltrimethylammonium bromide, Nat. Protoc. 1 (2006) 2320–2325, https://doi.org/10.1038/nprot.2006.384.
[33] D.J. Lane, 16S/23S rRNA Sequencing, in: E. Stackebrandt, M. Goodfellow (Eds.), Nucleic Acid Techniques in Bacterial Systematic, John Wiley and Sons, New York, 1991, pp. 115–175.
[34] S.F. Altschul, T.L. Madden, A.A. Schäffer, J. Zhang, Z. Zhang, W. Miller, D. J. Lipman, Gapped BLAST and PSI-BLAST: a new generation of protein database search programs, Nucleic Acids Res. 25 (17) (1997) 3389–3402, https://doi.org/10.1093/nar/25.17.3389.
[35] J.L. Bredas, Mind the gap!, Mater. Horiz. 1 (2014) 17–19, https://doi.org/10.1039/C3MH00098B.
[36] Z. Zhao, M. Gonsior, J. Luek, et al., Picocyanobacteria and deep-ocean fluorescent dissolved organic matter share similar optical properties, Nat. Commun. 8 (2017) 15284, https://doi.org/10.1038/ncomms15284.
[37] J.R. Lakowicz, Principles of Fluorescence Spectroscopy, Springer Science & Business Media, New York, 2006, https://doi.org/10.1007/978-0-387-46312-4.
[38] W. Becker, Flourescence lifetime imaging-techniques and applications, J. Microsc. 247 (2) (2012) 119–136, https://doi.org/10.1111/j.1365-2818.2012.03618.x.
[39] G. Conéjéro, M. Noirot, P. Talamond, J.L. Verdeil, Spectral analysis combined with advanced linear unmixing allow for histolocalization of phenolics in leaves of coffee trees, Front. Plant Sci. 5 (2014) 39 (https://doi:103389/fpls.2014.00039).
[40] Z.Q. Feng, C.G. Sun, J.Z. Zheng, Z.B. Hu, D.Z. Mu, W.F. Zhang, Optimization of spray-drying conditions and pharmacodynamics study of theophylline/chitosan/β-cyclodextrin microspheres, Dry. Technol. 33 (2014) 55–65, https://doi.org/10.1080/07373937.2014.935857.
[41] Y. Liu, W. Wang, S.B. Shah, G. Zanaroli, P. Xu, H. Tang, Phenol biodegradation by *Acinetobacter radioresistens* APH1 and its application in soil bioremediation, Appl. Microbiol. Biotechnol. 104 (2020) 427–437, https://doi.org/10.1007/s00253-019-10271-w.
[42] M.E. Kuc, et al., Efficient biodegradation of phenol at high concentrations by *Acinetobacter* biofilm at extremely short hydraulic retention times, J Water Process Eng 47 (2022) 102781, https://doi.org/10.1016/j.jwpe.2022.102781.
[43] L. Yang, T. He, M. Chen, M. Zhang, L. Yang, C. Zheng, C. Wang, Excellent phenol removal ability of Acinetobacter guillouiae BY18 under different inorganic nitrogen conditions, Environ. Technol. Innov. 35 (2024) 103694, https://doi.org/10.1016/j.eti.2024.103694.
[44] H. Lin, J. Lan, M. Guan, F. Sheng, H. Zhang, Spectroscopic investigation of interaction between mangiferin and bovine serum albumin, Spectrochim. Acta A Mol. Biomol. Spectrosc. 73 (5) (2009) 936–941, https://doi.org/10.1016/j.saa.2009.04.025.

[45] H. Lin, R. Chen, X. Liu, F. Sheng, H. Zhang, Study on interaction of mangiferin to insulin and glucagon in ternary system, Spectrochim. Acta A Mol. Biomol. Spectrosc. 75 (5) (2010) 1584–1591, https://doi.org/10.1016/j.saa.2010.02.023.
[46] H. Liu, B. Wu, G. Pan, L. He, Z. Li, M. Fan, L. Jian, M. Chen, K. Wang, C. Huang, Metabolism and pharmacokinetics of Mangiferin in conventional rats, Pseudo-germ-free rats, and Streptozotocin-induced diabetic rats, Drug Metab. Dispos. 40 (11) (2012) 2109–2118, https://doi.org/10.1124/dmd.112.045849.
[47] C. Bock, W. Ternes, The phenolic acids from bacterial degradation of the mangiferin aglycone are quantified in the feces of pigs after oral ingestion of an extract of Cyclopia genistoides (honeybush tea), Nutr. Res. 30 (5) (2010) 348–357, https://doi.org/10.1016/j.nutres.2010.05.005.
[48] U. Hasanah, K. Miki, T. Nitoda, H. Kanzaki, Aerobic bioconversion of C-glycoside mangiferin into its aglycone norathyriol by an isolated mouse intestinal bacterium, Biosci. Biotechnol. Biochem. 85 (4) (2021) 989–997, https://doi.org/10.1093/bbb/zbaa121.
[49] D. Bunt, M. Schwalbe, F. Hayeeawaema, S.A. Aidy, Gut microbiota-mediated conversion of mangiferin to norathyriol alters short chain fatty acid and urate metabolism, Gut Microbes 17 (2025) 1, https://doi.org/10.1080/19490976.2025.2508422.
[50] P. Bhatt, Y. Huang, H. Zhan, S. Chen, Insight into microbial applications for the biodegradation of pyrethroid insecticides, Front. Microbiol. 11 (2019) 1758, https://doi.org/10.3389/fmicb.2019.01778.
[51] J. Lin, V. Sharma, R. Milase, N. Mbhense, Simultaneous enhancement of phenolic compound degradations by Acinetobacter strain V2 via a step-wise continuous acclimation process, J. Basic Microbiol. 56 (6) (2016) 627–634, https://doi.org/10.1002/jobm.201500263.
[52] Z. Liu, W. Xie, D. Li, Y. Peng, Z. Li, S. Liu, Biodegradation of phenol by Bacteria strain Acinetobacter Calcoaceticus PA isolated from phenolic wastewater, Int. J. Environ. Res. Public Health 13 (3) (2016) 300, https://doi.org/10.3390/ijerph13030300.
[53] X. Guo, M. Cheng, H. Pei, Z. Shi, S. Chen, H. Liu, H. Shi, Z. Xu, X. Tian, C. Huang, Absorption, metabolism, and pharmacokinetics profiles of norathyriol, an Aglycone of Mangiferin, in rats by HPLC-MS/MS, J. Agric. Food Chem. 66 (46) (2018) 12227–12235, https://doi.org/10.1021/acs.jafc.8b03763.
[54] J.E. Ramirez, R. Zambrano, B. Sepúlveda, M.J. Simirgiotis, Antioxidant properties and hyphenated HPLC-PDA-MS profiling of Chilean Pica mango fruits (*Mangifera inidica* L. Cv. Piqueño), Molecules 19 (1) (2014) 438–458, https://doi.org/10.3390/molecules19010438.
[55] L. Formentini, P. Arapistas, M. Pittelli, M. Jacomelli, V. Pitozzi, S. Menichetti, A. Romani, L. Giovannelli, F. Moroni, A. Chiarugi, Mono-galloyl glucose derivatives are potente poly(ADP-ribose) glycohydrolase (PARG) inhibitors and partially reduce PARP-1-dependent cell death, Br. J. Pharmacol. 155 (8) (2008) 1235–1249, https://doi.org/10.1038/bjp.2008.370.
[56] K. Tikoo, M.S. Sane, C. Gupta, Tannic acid ameliorates doxorubicin-induced cardiotoxicity and potentiates its anti-cancer activity: potencial role of tannis in cancer chemotherapy, Toxicol. Appl. Pharmacol. 251 (3) (2011) 191–200, https://doi.org/10.1016/j.taap.2010.12.012.
[57] L. Song, W. Zhang, X. Gao, X. Yang, Mango leaf extract and application thereof. Patent CN103768112, 2012.
[58] W. Zhang, Z. Yang, Y. Gong, X. Gao, L. Song, X. Yang, Application of 3-methoxyl mangiferin in prepraring medicine used for treationg post-stroke depression. Patent CN103191141, 2012.

Glossary

MGF: Mangiferin
NRT: Norathyriol
HA: Hydrochloric acid
SM902: Acinetobacter sp. strain
MM: Mineral medium
CTAB: Cetyltrimethylammonium bromide
PCR: Polymerase chain reaction
PLE: Photoluminescence excitation
TIC: Total ion chromatogram