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LC-MS/MS-GUIDED METABOLITE PROFILING AND ALPHA-GLUCOSIDASE INHIBITORY ASSESSMENT OF *Erythrina subumbrans* ETHANOLIC EXTRACTS

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ABSTRACT

Erythrina subumbrans is a medicinal plant traditionally used for diabetes treatment. One effective strategy in managing postprandial hyperglycemia is alpha-glucosidase inhibition, which encourages the exploration of natural inhibitors from medicinal plants. This study aims to investigate the alpha-glucosidase inhibitory activity of *Erythrina subumbrans* ethanolic leaf extract and identify its bioactive constituents using LC-MS/MS. The leaves were authenticated, extracted by maceration with ethanol, and subjected to phytochemical screening, alpha-glucosidase inhibitory assay, and LC-MS/MS profiling. Qualitative screening confirmed the presence of flavonoids, tannins, saponins, and alkaloids, all known for antidiabetic potential. In vitro testing revealed significant alpha-glucosidase inhibition, with an IC_{50} value of 15.98 µg/mL. Metabolite profiling identified 18 compounds, predominantly flavonoids and isoflavonoids. Among them, Sophoraflavanone B and 3′-hydroxyformononetin were notable due to prior evidence of antidiabetic and antioxidant properties. The extract's activity is likely driven by the synergistic effects of these compounds. Method validation showed acceptable reliability for compound identification. These findings align with the ethnomedicinal use of *Erythrina subumbrans* and suggest its potential as a source of natural alpha-glucosidase inhibitors. This study represents the first combined report of LC-MS/MS metabolite profiling and alpha-glucosidase inhibitory activity for this species.

Keywords: *Erythrina Subumbrans*, Alpha-Glucosidase Inhibition, Metabolite Profiling, Flavonoid Compounds, Antidiabetic Activity.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and/or impaired insulin secretion. This condition represents one of the most pressing global health concerns, with its prevalence increasing at an alarming rate each year.[1,2] According to the 2021 report from the International Diabetes Federation (IDF), approximately 537 million adults aged 20–79 years worldwide are living with diabetes.[3] This number is projected to rise to 643 million by 2030 and further to 783 million by 2045.[4] T2DM is often accompanied by severe complications such as nephropathy, retinopathy, neuropathy, and cardiovascular diseases. These complications significantly contribute to increased morbidity, mortality, and healthcare expenditures on a global scale.[5] One therapeutic approach to control postprandial hyperglycemia in T2DM is by inhibiting the enzyme alpha-glucosidase.[6] This enzyme plays a critical role in the hydrolysis of complex carbohydrates into glucose in the small intestine. Although synthetic alpha-glucosidase inhibitors like acarbose, miglitol, and voglibose are widely used, their utility is often restricted by gastrointestinal side effects.[7,8] These include flatulence, diarrhea, and abdominal discomfort, prompting the search for safer natural alternatives.[9] Medicinal plants have long served as a valuable reservoir of bioactive secondary metabolites with diverse pharmacological properties. Compounds such as flavonoids, alkaloids, tannins, saponins, and phenolics are commonly found in these

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plants and have demonstrated promising antidiabetic effects.[10,11] *Erythrina subumbrans* (Hassk.) Merr., commonly referred to as dadap serep, is traditionally used in ethnomedicine across various cultures. Prior phytochemical investigations have shown that species within the Erythrina genus are rich in bioactive constituents, particularly flavonoids and alkaloids.[12,13] These compounds are known to exhibit antidiabetic, antioxidant, and anti-inflammatory activities.[14,15] Despite its widespread traditional use, the scientific validation of *Erythrina subumbrans* as an antidiabetic agent remains limited. This underscores the need for a systematic study to investigate its pharmacological potential. In this research, *Erythrina subumbrans* leaves will be botanically authenticated prior to extraction. Ethanol extraction via maceration will be employed to obtain the crude extract.[16] Subsequently, qualitative phytochemical screening will be conducted to determine the presence of relevant secondary metabolites. To evaluate the biological activity of the extract, an in vitro alpha-glucosidase inhibition assay will be carried out, accompanied by the determination of IC_{50} values to quantify its potency.[17] In addition, comprehensive metabolite profiling of the extract will be conducted using Liquid Chromatography–Mass Spectrometry/Mass Spectrometry (LC-MS/MS). This analytical approach aims to identify and characterize the key bioactive compounds responsible for the observed effects.[18] The integration of phytochemical screening and bioactivity assays will provide a robust understanding of the extract's therapeutic potential. The study is expected to generate scientific evidence supporting the traditional use of *Erythrina subumbrans* in diabetes management. Moreover, the identification of active metabolites could contribute to the development of novel herbal-based antidiabetic agents. Natural inhibitors with fewer side effects offer a compelling alternative to current pharmaceutical therapies. The use of LC-MS/MS also enhances the precision and depth of metabolite characterization. Ultimately, this research provides a foundation for further pharmacological and clinical exploration. It aligns with the growing demand for safe, effective, and plant-based interventions in chronic metabolic disorders.

EXPERIMENTAL

Plant Material and Identification

Fresh leaves of *Erythrina subumbrans* were collected from the West Java region of Indonesia during the vegetative phase to ensure optimal metabolite content. The collected plant material underwent taxonomic verification at the Jatinangor Herbarium, Plant Taxonomy Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Padjadjaran. Identification was performed through detailed morphological comparison with authenticated voucher specimens stored in the herbarium collection. Expert botanists confirmed the species identity, ensuring botanical accuracy for subsequent experimental procedures. A formal certificate of plant identification was obtained as official documentation of species authentication. The authenticated plant specimen was assigned a specific voucher number and deposited in the herbarium for long-term reference and record-keeping. This verification step is crucial for maintaining scientific rigor and ensuring the reproducibility of phytochemical and pharmacological studies. Accurate identification of plant species forms the foundation for credible bioactivity investigations. Misidentification could lead to erroneous results and compromise the validity of the research outcomes.[19] Therefore, botanical authentication was prioritized to support the reliability and integrity of this study on *Erythrina subumbrans*.

Extraction via Maceration

Fresh leaves of *Erythrina subumbrans* (15 kg) were collected and rinsed thoroughly with clean water to eliminate soil particles and surface contaminants. Leaves showing signs of damage or decay were removed through careful wet sorting to ensure sample quality. The clean leaves were then dried in an oven at 37 °C to protect thermolabile bioactive compounds from degradation. After drying, a secondary sorting process was conducted to discard any remaining substandard material and ensure uniformity. The dried leaves were ground into coarse powder using a mechanical grinder to facilitate solvent penetration during extraction. A total of 1000 g of the powdered simplicia was subjected to extraction using 10 liters of 70% ethanol. The maceration process was carried out at room temperature for 24–48 hours with intermittent stirring to enhance mass transfer. The mixture was filtered, and the maceration procedure was repeated three times using fresh solvent to maximize the extraction yield. The combined filtrates, totaling approximately 30 liters, were concentrated under reduced pressure using a rotary evaporator at 40–50 °C. The resulting thick

crude extract was weighed to determine the percentage yield and stored in an airtight container at 4 °C until further use.[20]

Phytochemical Screening

Qualitative phytochemical screening was performed on the ethanolic extract of *Erythrina subumbrans* to detect the presence of major classes of secondary metabolites. Standard phytochemical tests, including colorimetric and precipitation reactions, were employed following established protocols. These tests aimed to identify alkaloids, flavonoids, tannins, saponins, phenolics, glycosides, and terpenoids commonly found in medicinal plants. Each class of metabolite was detected using specific reagents that produce characteristic color changes or precipitate upon reaction with target compounds. For instance, the presence of alkaloids was confirmed using Mayer's and Dragendorff's reagents, while flavonoids were identified through the Shinoda test. Tannins were determined by the ferric chloride test, and saponins were observed through persistent frothing in water. The ethanolic extract showed positive results for alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoids, suggesting a chemically diverse profile. However, glycosides were not detected in the qualitative screening under the conditions used. The presence of these bioactive compounds supports the potential therapeutic relevance of the plant in traditional medicine.[21]

***In-vitro* Alpha-Glucosidase Inhibitory Assay**

The alpha-glucosidase inhibition assay was performed using a modified version of the standard microplate method to evaluate the antidiabetic potential of the extract. The assay was carried out in a 96-well plate by mixing 50 µL of phosphate buffer (100 mM, pH 6.8), 10 µL of alpha-glucosidase enzyme solution (1 U/mL), and 20 µL of test samples or the standard inhibitor acarbose at various concentrations. The mixture was incubated at 37 °C for 15 minutes to allow enzyme-substrate interaction. Following this, 20 µL of the chromogenic substrate 4-nitrophenyl β-D-glucopyranoside (5 mM) was added to initiate the reaction. After a further 20-minute incubation at 37 °C, the reaction was stopped by adding 50 µL of 0.1 M sodium carbonate to each well. The amount of p-nitrophenol released, which indicates enzymatic activity, was measured at 405 nm using a Multiskan microplate reader (Thermo Scientific). Each sample was tested in triplicate, and the results were expressed as mean percentage inhibition. The percentage of enzyme inhibition was calculated using the formula: Inhibition (%) = (1 − A/B) × 100, where A is the absorbance of the test sample and B is the absorbance of the control (without inhibitor). This method enables a reliable screening of alpha-glucosidase inhibitors and provides essential data for IC_{50} determination.[22]

Metabolite Profiling via LC–MS/MS

The identification of bioactive compounds in *Erythrina subumbrans* extract was carried out using Liquid Chromatography–Mass Spectrometry/Mass Spectrometry (LC-MS/MS), an advanced analytical technique widely applied in phytochemical research. This method integrates three primary components, namely ion source, mass analyzer, and detector, to enable the precise detection and characterization of secondary metabolites. Prior to analysis, the extract samples underwent solid-phase extraction (SPE) to eliminate interfering substances and concentrate target analytes. The purified samples were then introduced into the LC-MS/MS system under controlled analytical conditions. Electrospray ionization (ESI) was used as the ionization method to generate molecular ions in solution, which is essential for subsequent mass spectrometric analysis. The ions were separated based on their mass-to-charge (m/z) ratios by the mass analyzer, facilitating accurate identification of compound structures.[23] The resulting spectral data were processed and matched against reference libraries to determine the identities of the major constituents. Identified metabolites included phenolics, flavonoids, alkaloids, and terpenoids, many of which are known for their antioxidant and antidiabetic activities. These findings offer crucial insights into the phytochemical profile of *Erythrina subumbrans* and its potential therapeutic benefits.

RESULTS AND DISCUSSION

Phytochemical Extraction and Screening

Phytochemical screening of the ethanolic extract of *Erythrina subumbrans* successfully identified several classes of secondary metabolites, as shown in Table-1. The extract tested positive for alkaloids, flavonoids, saponins, tannins, quinones, and steroids/triterpenoids. These findings indicate that the extract possesses a chemically diverse profile with multiple potentially active constituents. Alkaloids are nitrogen-containing

compounds often associated with various pharmacological effects, including the modulation of enzyme activity.[24] The presence of flavonoids suggests the potential for antioxidant and enzyme-inhibitory activity relevant to metabolic disorders.[25] Saponins, identified in the extract, are known for their ability to reduce surface tension and disrupt membranes, which may enhance antimicrobial or metabolic modulation properties.[26] Tannins, detected in this screening, are polyphenolic compounds that can form complexes with proteins and metal ions. Quinones, also present, are known for their redox activity and may contribute to electron transfer or oxidative stress regulation.[27] Steroids and triterpenoids were also found, compounds which are often associated with anti-inflammatory and hormonal activities.[28] The combination of these metabolite groups reflects a strong foundation for the extract's bioactivity in pharmacological testing.

Table-1: Qualitative Phytochemical Profile of *Erythrina subumbrans* Extract

Compound Test	Result
Alkaloids	+
Flavonoids	+
Saponins	+
Tannins	+
Quinones	+
Steroids/Triterpenoids	+

The identification of these six metabolite classes confirms the presence of a broad range of bioactive constituents within the *Erythrina subumbrans* extract. Each group of metabolites plays a distinct role in biological systems, which could translate to multi-targeted therapeutic effects. For example, the coexistence of alkaloids and polyphenols supports both enzyme inhibition and free radical scavenging mechanisms. The presence of saponins and triterpenoids can enhance the pharmacodynamic profile through membrane modulation and anti-inflammatory effects.[29] Quinones contribute further through redox cycling and interactions with cellular signaling pathways.[30] These multiple components may act additively or synergistically in a therapeutic context. Importantly, all detected metabolites are commonly found in medicinal plants with documented efficacy in traditional systems. Their presence in *Erythrina subumbrans* supports the empirical use of this plant for various ailments. The comprehensive phytochemical profile observed reflects the richness of the extract and its potential relevance to therapeutic applications. These results form a strong preliminary indication of the pharmacological promise of *Erythrina subumbrans* as a natural product resource.

In-vitro Evaluation of Alpha-Glucosidase Inhibitory Activity

Table-2 shows that the ethanol extract of *Erythrina subumbrans* exhibited alpha-glucosidase inhibitory activity with an IC_{50} value of 15.98 µg/mL, indicating moderate potency compared to the standard inhibitor acarbose, which recorded a much lower IC_{50} of 0.01 µg/mL. Although the extract's inhibitory capacity was relatively weaker, the result demonstrates its potential role in regulating carbohydrate metabolism.

This inhibitory effect suggests that compounds present in the extract are capable of interacting with the active site of the alpha-glucosidase enzyme, thereby preventing substrate cleavage. alpha-glucosidase plays a critical role in hydrolyzing terminal, non-reducing 1,4-linked alpha-glucose residues from oligosaccharides, making its inhibition a valuable therapeutic target in managing type 2 diabetes.[31] Slower carbohydrate breakdown leads to a delayed absorption of glucose into the bloodstream, helping to avoid sudden spikes in postprandial blood sugar levels.

The observed inhibition is likely attributable to the synergistic action of multiple phytochemical constituents, particularly flavonoids, saponins, and tannins, which are known to possess enzyme-modulating properties. These classes of compounds can act by binding to the enzyme surface, altering its conformation, or competing with the substrate.

Furthermore, previous studies on similar plant extracts from the Erythrina genus support the likelihood of antidiabetic effects through enzymatic inhibition.[32] The moderate IC_{50} value obtained here is promising, particularly for a crude extract without fractionation or purification. These findings highlight the value of natural product screening as an entry point into developing safer enzyme inhibitors.

Despite its lower potency compared to acarbose, the *Erythrina subumbrans* extract offers an alternative with potentially fewer adverse effects. Acarbose, though clinically effective, often causes gastrointestinal discomfort due to undigested carbohydrates reaching the colon.

Table-2: In Vitro Alpha-Glucosidase Inhibitory Activity of *Erythrina subumbrans* Extract

Sample	Alpha-Glucosidase Inhibitory IC_{50} (µg/mL)
Erythrina subumbrans ethanol extract	15.98
Acarbose	0.01

The use of plant-based inhibitors may reduce such risks, as many natural constituents act more gently on the digestive tract. This is particularly important for long-term management of diabetes, where treatment adherence is crucial.[33] The presence of flavonoids in the extract may contribute to both enzyme inhibition and complementary antioxidant effects, offering dual therapeutic benefits. Tannins and saponins may further reinforce the inhibitory activity through their ability to form complexes with proteins or disturb membrane functions. The extract's ability to inhibit alpha-glucosidase in vitro supports the hypothesis generated from phytochemical screening results. Moreover, the data provide a rationale for further fractionation and bioassay-guided isolation to identify the most active constituents. While the current IC_{50} value suggests moderate activity, future optimization could enhance efficacy through purification or formulation strategies. Thus, the alpha-glucosidase inhibition profile of *Erythrina subumbrans* reinforces its traditional usage and supports its development as a natural-based antidiabetic agent.

Metabolite Profiling Using LC-MS/MS

Metabolite identification in the ethanolic extract of *Erythrina subumbrans* was successfully carried out using LC-MS/MS, as visualized in the Total Ion Chromatogram (TIC) under negative ion mode (Fig.-1). Each peak in the chromatogram represents a compound eluted from the chromatographic column at a specific retention time (RT). The varying peak intensities on the y-axis indicate the relative abundance of the detected ions. The highest peak was observed at RT 3.49 min, corresponding to 3-(4-hydroxy-2,5-dimethoxyphenyl)-3,4-dihydro-2H-1-benzopyran-7-ol. Additional significant peaks appeared around RT 7.46 min and 10.09 min, identified as 5,7-dihydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)chromen-4-one and Sophoraflavanone B, respectively. The diverse RT distribution and peak intensity demonstrate the complexity and richness of bioactive metabolites within the extract. The use of negative ion mode enhances detection sensitivity for phenolic and flavonoid compounds. This TIC serves as a foundational reference for compound annotation and supports the qualitative metabolite analysis. These analytical insights provide a detailed chemical fingerprint crucial for phytopharmaceutical exploration.

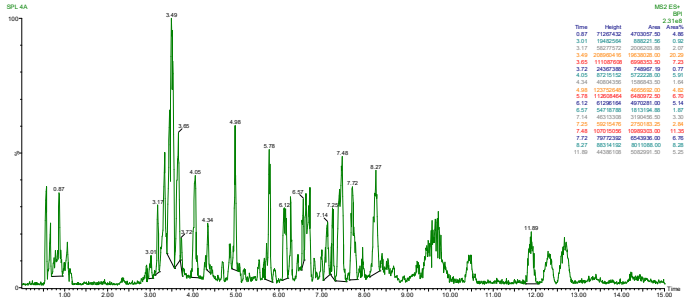

Fig.-1: Total Ion Chromatogram (TIC) of *Erythrina subumbrans* Ethanol Extract in Negative Ion Mode

Table-3 lists a total of 18 annotated compounds from the *Erythrina subumbrans* extract, based on RT, measured m/z values, molecular formulas, and relative composition percentages. The most abundant compound was 5,7-dihydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)chromen-4-one at 11.35%, followed by Sophoraflavanone B at 8.28%, and Tectorigenin at 8.02%. Many of these compounds belong to the flavonoid and isoflavonoid classes, which are well-known for their antioxidant, antidiabetic, and anti-inflammatory properties. Lespedezaflavanone B and Isomixanone were detected at lower percentages (0.92% and 2.07%, respectively), yet remain pharmacologically relevant. The presence of structurally unique metabolites such as 7,11-dimethoxy-indolo[7a,1-a]isoquinoline-8-carboximidic acid further

highlights the extract's chemical diversity. Several key isoflavones, including 5,7,2',4'-Tetrahydroxy-5'-methoxyisoflavone and 3'-Hydroxyformononetin, were also identified. These metabolites are known to modulate glucose metabolism and enzyme inhibition, supporting the extract's antidiabetic activity. The semi-quantitative composition confirms that flavonoids are the dominant secondary metabolites in the extract. This table serves as strong analytical evidence for the phytochemical richness of *Erythrina subumbrans*.

Table-3: Identified Compounds in *Erythrina subumbrans* Extract Based on LC-MS/MS and Molecular Networking (MN) Analysis

No	RT (min)	m/z measured	MW	Molecular Formula	%Composition	Prediction Compound Name
1	0.87	276.1633	275.3	$C_{16}H_{17}NO_3$	4.86	16-methoxy-5-oxa-10-azatetracyclo[8.7.0.0^{2},^{5}.0^{11},^{15}]heptadeca-1,12-dien-4-one
2	3	409.2031	408.5	$C_{25}H_{28}NO_5$	0.92	Lespedezaflavanone B
3	3.17	258.1188	257.3	$C_{15}H_{15}NO_3$	2.07	Isomixan
4	3.49	391.1217	390.1	$C_{21}H_{18}O_5$	8.26	3-(4'-hydroxy-2,5-dimethoxyphenyl)-3,4-dihydro-2H-1-benzopyran-7-ol
5	3.75	317.0654	316.1	$C_{16}H_{12}O_5$	0.77	6,4'-dihydroxy-2,5-dimethoxybiphenyl
6	3.77	301.1054	300.1	$C_{16}H_{12}O_5$	2.23	5,7,2',4'-Tetrahydroxy-5'-methoxyisoflavone
7	3.95	331.0645	330.1	$C_{17}H_{12}O_5$	3.84	(3S)-3-(2-(4-hydroxy-4-methoxyphenyl)-2-methoxy-3,4-dihydro-2H-1-benzopyran-7-ol
8	4.98	285.0079	284.1	$C_{16}H_{12}O_5$	4.25	(2S)-5,8-dihydroxy-7-methoxy-2-phenyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-4-one
9	5.28	298.2008	297.1	$C_{17}H_{14}O_5$	2.01	3'-Hydroxyformononetin
10	5.99	329.1441	328.1	$C_{22}H_{20}O_7$	3.97	5,7,2'-Trihydroxy-6-methoxy-8-prenylisoflavone
11	6.36	347.111	346.1	$C_{18}H_{18}O_7$	1.84	Erybraedin E
12	6.58	369.111	368.1	$C_{18}H_{18}O_7$	2.37	5,7-dihydroxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydro-1-benzopyran-4-one
13	7.16	331.0881	330.1	$C_{19}H_{14}O_7$	5.31	7,11-dimethoxy-1H,2H,4aH,5H,6H,11bH-[1]benzopyrano[2,3-c]isoquinoline-8-carboxylic acid
14	7.46	331.0891	330.1	$C_{19}H_{14}O_7$	11.35	Tectorigenin
15	7.92	331.0883	330.1	$C_{19}H_{14}O_7$	8.02	5,7-dihydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)chromen-4-one
16	8.84	380.0834	379.1	$C_{20}H_{20}O_8$	3.68	5,7,3'-Trihydroxy-4'-methoxy-5-methylisoflavone
17	10.09	409.2005	384.4	$C_{20}H_{20}O_5$	8.28	Sophoraflavanone B
18	11.89	299.2401	294.2	$C_{19}H_{32}O_5$	5.25	Methyl eleostearate

The confirmed presence of phenolic, flavonoid, and isoflavonoid compounds reinforces prior phytochemical screening and α-glucosidase inhibitory findings. Compounds like Tectorigenin and Sophoraflavanone B have been extensively studied for their potential to inhibit glucose-hydrolyzing enzymes. The detection of Methyl eleostearate (5.25%) suggests additional anti-inflammatory benefits that could enhance the therapeutic profile of the extract. The mass range of most identified metabolites falls between 275 and 390 Da, a size range that favors good membrane permeability and oral bioavailability. This molecular size profile supports the potential for effective absorption and biological activity in vivo. The LC-MS/MS annotation results also provide important structural insights into these compounds. The wide spectrum of chemical structures observed suggests the possibility of synergistic interactions

contributing to the overall bioactivity. Identification of these compounds lays the groundwork for further standardization and formulation development.[34] Taken together, these findings justify the potential of *Erythrina subumbrans* extract as a candidate for antidiabetic and anti-inflammatory herbal therapeutics. The extract's chemical diversity and bioactive compound profile warrant further pharmacological validation and formulation research.

CONCLUSION

The ethanolic extract of *Erythrina subumbrans* leaves exhibited notable alpha-glucosidase inhibitory activity, with an IC_{50} value of 15.98 µg/mL, suggesting its potential as a moderate natural antidiabetic agent. Phytochemical screening confirmed the presence of key bioactive secondary metabolites, including flavonoids, tannins, saponins, and alkaloids, all of which are known for their antidiabetic and antioxidant properties. LC-MS/MS analysis successfully identified 18 bioactive compounds, including several flavonoids and isoflavonoids such as Sophoraflavanone B and 3'-hydroxyformononetin, further reinforcing the pharmacological relevance of the extract. These results provide scientific support for the traditional use of *Erythrina subumbrans* and emphasize its potential as a source of plant-based alpha-glucosidase inhibitors. The diverse chemical composition and demonstrated biological activity make this extract a promising candidate for the development of natural antidiabetic therapies.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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