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Original article

Isolation of 6-gingerol and semi-synthesis of 1,4-benzodiazepines derivatives: An in-situ pharmacokinetics properties, molecular docking and molecular dynamics simulation assessments

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ABSTRACT

This paper outlines a methodical approach for isolating 6-gingerol (1a) from *Zingiber officinale Roscoe* rhizomes on a gram-scale, resulting in a product of high purity and significant yield. Further, 6-gingerol (1a) [SSG1] derivatives, including 1-(4-hydroxy-3-methoxyphenyl)decane-3,5-dione (1ab), were synthesized via a semi-synthetic pathway involving DMP-mediated fast oxidation and replication. Subsequently, a new series of 1,4-benzodiazepines (3a-c) was synthesized quantitatively using a basic technique. This synthesis necessitated the interaction of 1ab with various o-phenylenediamine (2a-c) compounds. Spectroscopic methods were employed to characterize the synthesized 1,4-benzodiazepines (3a-c)[SSG2, SSG3 & SSG4]. Despite extensive investments by pharmaceutical companies in traditional drug research and development for diseases like type 2 diabetes (T2D), successful treatments remain elusive. Medication repurposing has gained traction as a strategy to address not only diabetes but also other disorders. Leveraging existing molecular pharmacology data accelerates the development of new medications. This paper underscores the importance of repurposing traditional medicines to combat a range of communicable and non-communicable diseases, offering a promising avenue for therapeutic advancement. Additionally, molecular docking studies suggested that one derivative (SSG2) exhibited stronger binding affinity compared to the reference standards. Overall, the findings of this study highlight the potential of semi-synthetic gingerol derivatives for the development of novel therapeutic agents.

1. Introduction

In recent years, there has been a distinct trend that has evolved with an increasing tendency towards the acceptance of alternative or "natural" therapies for the management of a variety of chronic conditions. Among individuals, there is a widespread notion that herbal or herbal-based therapies are fundamentally seen as safe and reliable alternatives to conventional treatments. This belief is the driving force behind this transition. The rise in popularity of these natural medicines is a reflection of a greater social awareness and preference for holistic approaches to healthcare. In these approaches, the focus is placed on the perceived safety and reliability of herbal interventions in the treatment of chronic health disorders. (Sarvesh et al., 2018) Bioactive compounds, including but not limited to curcumin, quercetin, guggulsterone, among others, play a crucial role in mitigating major chronic illnesses. These compounds, derived from various natural sources, exhibit therapeutic properties that have been linked to their ability to combat inflammation, oxidative stress, and other pathological processes associated with chronic diseases. (B Aggarwal et al., 2011) Natural products (NP) are used for healthcare directly and indirectly, either in raw form or as a finished product. According to ethnopharmacological data, traditional medicines are valuable bioresources that have tremendous therapeutic

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value.(Preethi et al., 2021, Sabarathinam and Vijayakumar, 2021, Priya et al., 2022, Pammi et al., 2023) NP have historically been influential in the discovery of new drugs, especially for the treatment of cancer, metabolic disorders, and infectious diseases. In the process of drug discovery, a bioactive "hit" extract is found through biological screening of "crude" extracts, and it is then further fractionated to isolate the active NP. (Atanasov et al., 2021). Identification of new medicine typically takes 12 years to develop before it is available in clinical practice. It is necessary for a Novel Chemical entity (NCE) to comply with the characteristics of druggability and medicinal chemistry in order for it to have pharmacological effectiveness. These NCEs can be obtained either chemically or by isolating them from natural plant materials. There are numerous examples of new drugs being developed from plant sources. The assumption that active compounds produced from plants that have a history of human usage are more likely to be judged safe is the foundation upon which the research of natural products for the development of novel medications is built.(Katiyar et al., 2012). Ginger (*Zingiber officinale Roscoe*) is a well-known medicinal herb that belongs to the family of Zingiberaceae. Ginger has been on the list of first-line medicine for various illnesses. Ginger is well-known for the antioxidant and anti-inflammatory characteristics that it possesses, both of which help to the slowing down of the ageing process. Followed by ginger can treat a wide range of conditions, including cancer, diabetes mellitus, etc., (Mashhadi et al., 2013) Ginger has generous compounds such as terpenes and Phenolic derivatives such as gingerols. (Mao et al., 2019) Gingerols were found to facilitate insulin-independent glucose absorption by promoting the translocation of the glucose transporter GLUT4 to the plasma membrane surface of muscle cells, in conjunction with slight elevations in the expression of GLUT4 protein overall. (Khandouzi et al., 2015) Most recently, it gingerly got substantial public interest when it was recommended as a natural home cure that may assist against COVID-19, and while this is not an evidence-based application at this time. The addition of a heterocyclic system, such as 1,4-benzodiazepines, to the 6-gingerol structure would grant it unique properties in terms of its multi-faceted actions, including anticancer, antioxidant, and anti-inflammatory effects. The inclusion of the heterocyclic ring enhances 6-gingerol's ability to form hydrogen bonds. (Tardibono and Miller, 2009, Anzini et al., 2011, Sahn et al., 2014, Sampath et al., 2021, Dalsasso et al., 2022, Deng et al., 2022) Our objective is to offer a semi-synthetic method that is both straightforward and practical for the production of 1,4-benzodiazepines. By using 6-gingerol-derived 1-(4-hydroxy-3-methoxyphenyl)decane-3,5-dione, this technique entails the condensation of a variety of o-phenylenediamines, which is then followed by the cyclization of these compounds. (**1ab**). The synthesis of 6-gingerol-semi synthetic compounds that are biologically active is the focus of our work. (**3a-c**). This research breaks new ground in the natural product therapy movement. It focuses on isolating and tweaking ginger's bioactive components, especially 6-gingerol, to create potential new treatments for long-term health issues. Followed by this study introduces a clever method for boosting 6-gingerol's therapeutic power. It involves creating a new group of 1,4-benzodiazepines based on 6-gingerol, which might be even more effective than the natural compound on its own. This research combines traditional methods of extracting and isolating active ingredients from nature with cutting-edge techniques like molecular docking and dynamic simulations. This blend of old and new approaches strengthens the study's findings and makes them more believable. The research tackles a critical need for new ways to manage chronic conditions like diabetes. By showing that the synthesized compounds might bind more strongly to diabetes-related therapeutic targets, the study opens exciting doors for developing alternative treatments. As interest in natural and herbal remedies grows, there's a pressing need to explore and develop alternative treatments for chronic illnesses. This paper addresses this need by proposing a practical approach that taps into the medicinal potential of ginger, a well-known medicinal plant. This study advances the field of drug discovery by investigating the pharmacological properties of natural products and their semi-synthetic variations. By identifying potential lead compounds with enhanced therapeutic properties, the research paves the way for further exploration and development of entirely new medications.

2. Methods and materials

The data for the proton nuclear magnetic resonance (1H NMR) spectrum were obtained with a Bruker BBFO instrument that was operating at 500 MHz. On the other hand, the carbon nuclear magnetic resonance (^{13}C NMR) spectrum was recorded with a Bruker Advance III instrument that was working at 100.64 MHz. The NMR spectra were carried out with $CDCl_3$ performing the role of the solvent. For the purpose of calibration, the 1H NMR chemical shift was compared to tetramethylsilane (TMS, $\delta = 0$ ppm), and deuterated chloroform ($_{CDCl3}$, $\delta =$ 7.26 ppm singlet) serves as the reference. References were made to the 13C NMR spectra using the formula ($CDCl_3$, $\delta = 77.5$ ppm). Through the utilisation of a Bruker A250/D Alpha spectrometer, Fourier-transform infrared spectroscopy (FTIR) spectra were captured within the region of 4000–400 cm^{-1}. The QTOF-ESI source that was purchased from M/S Bruker Daltonik GmbH in Germany was utilised in order to carry out high-resolution mass spectral analysis (HR-MS). Using Thin Layer Chromatography (TLC) using Merck 60 F254 pre-coated silica gel plates with a thickness of 0.2 mm and spot visualisation with a UV light, we were able to monitor the development of the reaction and the isolation of the components. In the process of column chromatography, silica gel with a mesh size ranging from 100 to 200 was used, and hexane and ethyl acetate were used as eluting solvents. No extra purification was performed. Analytical grade chemicals were obtained from Merck, AVRA, and SRL. All of the compounds were purchased. On the basis of ginger that was purchased from a local vegetable shop in the Tiruvallur area of Tamil Nadu, India, the 6-gingerol that was utilised in the research was extracted.

2.1. General procedure for extraction and isolation of 6-gingerol (A) (SSG1) (1a) from ginger

Five kg of fresh rhizomes (*Zingiber officinale*) were purchased from a local vegetable shop and it was authenticated for its species confirmation (specimen code: Z29052403O & PCOG002-ACF) from SIDDHA CENTRAL RESEARCH INSTITUTE (Central Council for Research in Siddha, Chennai, Ministry of AYUSH, Government of India) Anna Govt. Hospital Campus, Arumbakkam, Chennai – 600106. The collected sample was washed with water, slashed into small pieces, and kept for shade drying (3–5 days). After drying completely, ginger (565 g) was powdered and extracted with methanol (MeOH, 5000 mL, 24 h X 3 times) with mechanical stirring at room temperature. Extraction was filtered and concentrated using a rotary evaporator under reduced pressure to obtain crude extract (96.714 g). This natural extract was partitioned with ethyl acetate (EtOAc 50 mL × 5 times) under sonication (5 × 30 mins), the ethyl acetate layer separated, and the solvent was removed to obtain crude ethyl acetate extract (42.6167 g). The ethyl acetate extract was further purified by using column chromatography (ethyl acetate 70 % / hexane 30 %) to yield pure 6-gingerol (**1a**) from the previous data (Tardibono and Miller, 2009).

2.2. General procedure for the synthesis of intermediate (1ab)

1a (3.3969 mmol, 1 eq., dissolved in 35 mL of chloroform), NaHCO3 (13.5876 mmol, 4 eq.), and Dess Martin periodinane (6.7938 mmol, 2 eq.) were all added to a pressure tube that was 30 mL in capacity and was furnished with a magnetic stir bar and a pressure gauge tube. The mixture of the reaction was agitated for a period of five to eight hours while being monitored by TLC until the initial material 1a was no longer present. After that, the reaction mixture was transferred into a separating funnel that had a capacity of 250 mL and contained a mixture of

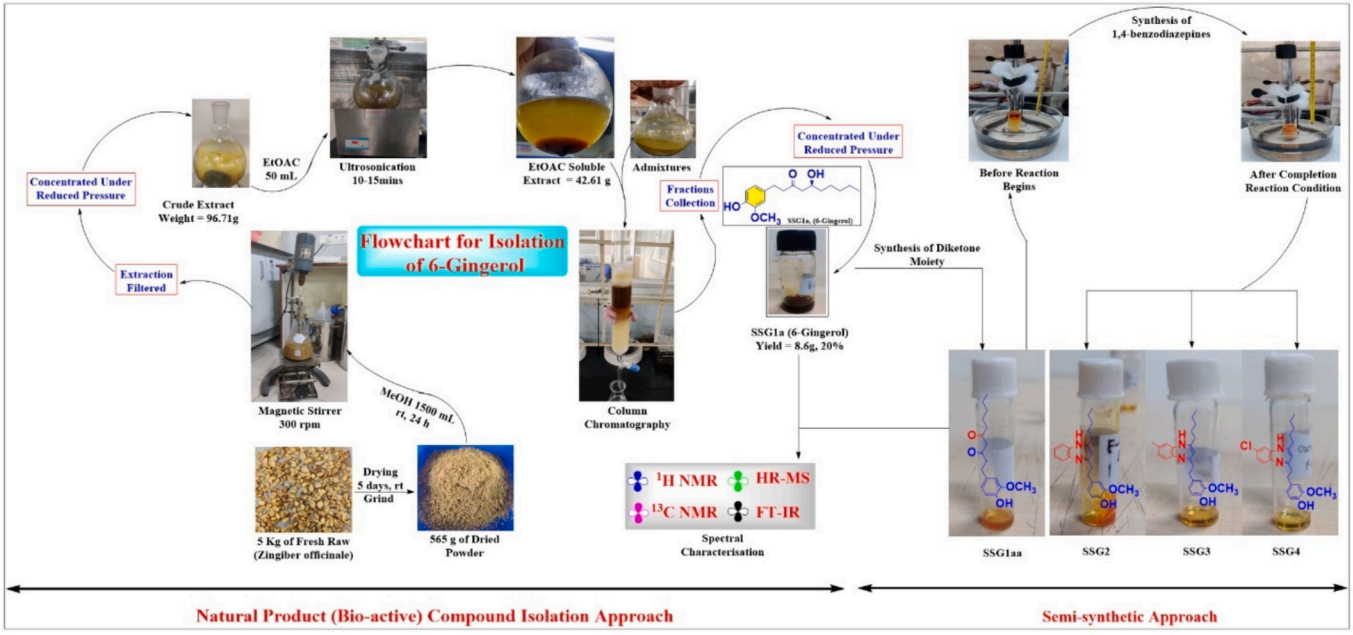


Fig. 1. Schematic diagram of isolation and gingerol derivatives from Ginger.

saturated aqueous NaHCO3 (35 mL) and Na2S2O3 (35 mL) in a ratio of 1:1. The crude reaction mixture was obtained by washing the separated CHCl3 layer with saturated aqueous NaCl (200 mL), drying it on NaSO4, filtering it, and then concentrating it. For the purpose of obtaining the pure product, 1-(4-hydroxy-3-methoxyphenyl)decane-3,5-dione (1ab), the crude reaction mixture was subjected to purification using silica gel column chromatography (ethyl acetate/hexane 10:90).

2.3. General procedure for the synthesis of final process (C) –such as (3a, 3b & 3c) (SSG2, SSG3, and SSG3)

Based on the reaction condition from the previous study (Hamed et al., 2020). A 100 mL pressuring tube equipped with a magnetic stir bar and pressure gauge tube was charged with **1ab** (0.3422 mmol, 1 eq.) dissolved in ethanol 2 mL. During the process of blending, the mixture was stirred at room temperature until a solution that was transparent was created. In addition to 0.15 ml of concentrated hydrochloric acid, o-phenylenediamine (2a) or substrates o-phenylenediamine (2b-c) (1.0268 mmol, three equivalents) were added to the ethanol solution of (1ab). The mixture that was produced proceeded through a process of reflux coupled with continuous stirring for a period of one to three hours, and TLC was utilised to monitor the progression of the reaction. Immediately following the completion of the reaction, the reaction mixture was subjected to concentration by means of a rotary evaporator operating at a relatively low pressure. In order to obtain the pure products (3a-c), the residue that was obtained, which was 3 × 25 mL in volume, was washed with a solution of Na2CO3 at a concentration of 5 %. Subsequently, the crude product was purified using silica gel column chromatography with a mixture of ethyl acetate and hexane at a ratio of 20:80.(Khagar et al., 2023) **The Schematic diagram of isolation and gingerol derivatives from Ginger is depicted in** Fig. 1**.**

2.4. Drug-likeness property estimation

The study further elaborated on the estimation of drug-likeness of the main compound (SSG1) and derived compound (SSG2, SSG3, SSG4) to understand its pharmacological activity. This helps to identify the drug's critical pharmacokinetic attribute. The number of violations indicates the influence of the compound's potential to be novel compound. (Daina et al., 2014, Daina and Zoete, 2016, Daina et al., 2017, Govindaraju and Sabarathinam, 2021, Rupesh et al., 2023, Vaithiyalingam et al., 2023) The Physicochemical properties and Drug-likeness justification of gingerol derivatives are given in Table 1.

Table 1
Physicochemical properties and Drug likeness profile of synthesized compound.

Parameters	SSG1	SSG2	SSG3	SSG4
Formula	C17H26O4	C23H28N2O2	C24H30N2O2	C23H27ClN2O2
Molecular weight	294.39 g/mol	364.48 g/mol	378.51 g/mol	398.93 g/mol
TPSA	66.76 Å^2	53.85 Å^2	53.85 Å^2	53.85 Å^2
Lipinski	Zero violations			

Table 2
Pharmacokinetic Profile of synthesized compounds.

Parameter	SSG1	SSG2	SSG3	SSG4	Unit
Water solubility	−3.164	−5.452	−5.825	−6.048	(log mol/L)
Intestinal absorption (human)	92.416	87.51	87.622	86.164	(% Absorbed)
Skin Permeability	−2.817	−2.721	−2.724	−2.722	(log Kp)
P-glycoprotein substrate	Yes	Yes	Yes	Yes	(Yes/No)
P-glycoprotein I /II inhibitor	No/No	Yes/ Yes	Yes/ Yes	Yes/ Yes	(Yes/No)
VDss (human)	0.524	0.689	0.729	0.687	(log L/kg)
Fraction unbound (human)	0.258	0	0	0	(Fu)
BBB permeability	−0.727	−0.264	−0.262	−0.275	(log B.B.)
CNS permeability	−2.788	−1.829	−1.753	−1.713	(log P.S.)

2.5. Pharmacokinetic parameters estimation

Inadequate safety and pharmacokinetic characteristics pose a serious challenge to drug research due to their high attrition rate. This web-based graph server aids in evaluating the toxicity and ADME characteristics of the substances. (Pires et al., 2015, Sabarathinam and Vijayakumar, 2021, Sabarathinam and Vijayakumar, 2021) Table 2 enlists the ADME characteristics of gingerol derivatives.

Table 3
Toxicity profile of synthesized compounds.

Parameters	SSG1	SSG2	SSG3	SSG4
Mutagenic				
Tumorigenic				
Irritant				
Reproductive effect				
LD50	250 mg/kg	290 mg/kg	290 mg/kg	290 mg/kg

Green alert. Toxic free compound.

2.6. Toxicity profile

The data for toxicity of the gingerol derivatives were collected from admetSAR – 2.0 (http://lmmd.ecust.edu.cn/admetsar2), PkCSM server (http://structure.bioc.cam.ac.uk/pkcsm) and Protox-II server (Drwal et al., 2014, Banerjee et al., 2018, Sabarathinam et al., 2023, Sabarathinam et al., 2023)The toxicity parameters of the synthesized gingerol derivatives is mentioned in Table 3.

2.7. Molecular docking analysis of all derivatives

Protein- ligand docking was performed using CB-Dock. (Cao and Li, 2014, Liu et al., 2020) PDB: This study used the crystal structure of PDB entry 4FFW, which exhibits a resolution of 2.90 Å and non-mutant characteristics, to determine the drug binding affinity of semi-synthesized gingerol derivatives towards the dipeptidyl peptidase inhibitor. This particular structure, with the provided ID, likely represents the crystallographic structure of Dipeptidyl Peptidase IV (DPP4), also known as CD26, in complex with a fragment antigen-binding region (Fab) and the drug sitagliptin. Sitagliptin is a drug belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. It functions by inhibiting the enzymatic activity of DPP4, thereby increasing the levels of GLP-1 and GIP, which stimulate insulin secretion and reduce blood glucose levels. Sitagliptin is commonly used in the treatment of type 2 diabetes mellitus. And PDB:5G5J was chosen to estimate the antidiabetic activity of the semi-synthesized gingerol derivatives. The metformin-bound human CYP3A4 crystal structure, PDB:5G5J, has non-mutant characteristics and a resolution of 2.60 Å. CYP3A4, a key enzyme in drug metabolism, primarily found in the liver, metabolizes a wide range of drugs. Its hydroxylation activity facilitates the conversion of lipophilic compounds into more hydrophilic forms for elimination. Understanding CYP3A4′s structure and function is crucial for predicting drug interactions and individual drug responses. The crystal structure of CYP3A4 bound to metformin (PDB entry 5G5J) provides insights into drug metabolism, particularly in patients receiving metformin for type 2 diabetes. To compare the docking score, two (Sitagliptin & Metformin) were used as positive controls in this study. Computer-aided drug designs help in the identification of suitable and ideal compounds at the time of drug development. (Dhivya et al., 2022, Dhivya et al., 2022, Sivasakthi et al., 2022) (Sabarathinam et al., 2023).

2.8. Molecular dynamic simulation

Using GROMACS 2022.2, a molecular dynamics (MD) simulation was performed. The subsequent procedures were employed which assess the complex's dynamic behavior. Pymol was used to export the ligand–protein complex's three-dimensional (3D) model to the.pdb file format. Protein topology was built using the CHARMM27 force field in pdb2gmx, and ligand topology was produced via the SwissParam server. (Sabarathinam and Ganamurali, 2023, Gnanamurthy et al., 2024).

3. Results

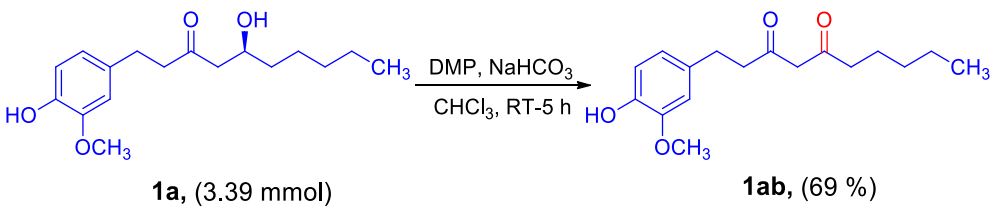
3.1. Extraction and isolation of 6-gingerol from ginger

The simple, robust extraction and isolation method was adopted to obtain (SSG1) in the gram scale. A total of 565 g rhizomes (*Zingiber officinale*) of dried ginger powder (from 5 kg of fresh raw ginger) was extracted with MeOH for (3 days × 24hrs). By ultrasonication, the extract ginger oil (MeOH crude extract) and ethyl acetate soluble portion was taken for silica gel column chromatography and isolated good quantity yield of (SSG1) (8.6 g, 20 %) with high purity, followed by preparing (SSG1) and (SSG2, SSG3 & SSG4). The structure was also confirmed by ^{1}H,^{13}C NMR, FT-IR, and HRMS (ESI) spectrum in the electronic supporting information file (Figure S2, S3, and S11).

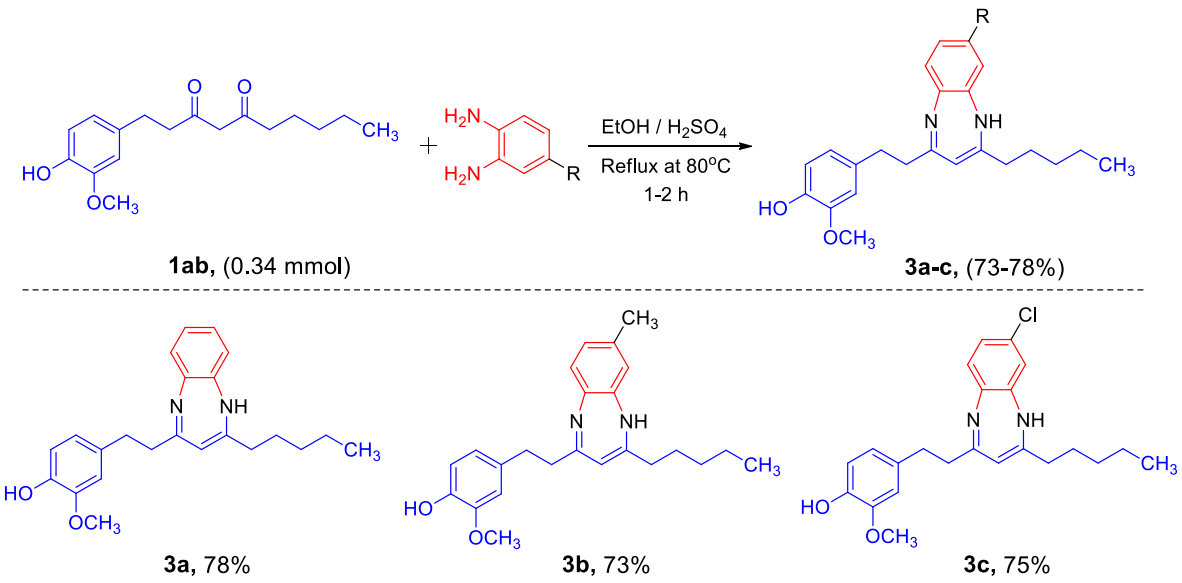
Tamao et al. published the first study on the utilisation of 2-hydroxybenzoic acid (IBX, 1-hydroxy-1,2-benziodoxole-3(1H)-one 1-oxide) for the oxidation of alcohol in the year 1983. (Tamao et al., 1983). According to Kinfe's research from 2019, DMP, also known as Dess-Martin Periodinane, has become increasingly popular in the field of synthetic organic chemistry due to the fact that it has a low level of reactivity. IBX, which is an economically practical and noticeably more stable alternative to DMP, was described by Frigero and Santagostino in 1994. They also demonstrated that IBX might serve as an effective oxidising agent for alcohols in dimethyl sulfoxide (DMSO), as Ballaschk and Kirsch explained in 2019.(Ballaschk and Kirsch, 2019, Kinfe, 2019).

In following years of these breakthroughs, a wide range of benziodoxol oxide derivatives, particularly polymer-supported IBX analogues, have been generated as a means of producing ketone oxidizers that are gentle, resilient, and beneficial for alcohol conversions.(Uyanik and Ishihara, 2009) Due to the high labile nature of β-hydroxy ketone, the direct oxidation compound (**SSG1**) was attempted under DMP reaction condition(Li et al., 2010) The yield of compound **SSG1**, 69 %. It is important to note that 4 equivalents of $NaHCO_3$ are required to perform oxidation. This could be due to the high chelating ability of the 1,3-diketone moiety with the DMP catalyst (Scheme 1). The finally obtained compound (**1ab**) was confirmed by spectroscopic techniques ^{1}H, ^{13}C NMR, FT-IR, and HRMS (ESI) are shown in the supplementary file (Figures S4, S5, and S12).

We prepared 6-gingerol with 1,3-diketone-based 1,4-benzodiazepines; in order to continue this work and create a 6-gingerol derivatives, This is the first report, we synthesized a 1,4-benzodiazepines and the compounds were synthesized by reacting 1-(4-hydroxy-3-methoxyphenyl)decane-3,5-dione (1ab) with different o-phenylenediamine derivatives (2a-c) under reflux condenser for 1–2 h in the presence of a catalytic amount of Conc. H_2SO_4 in ethanol as solvent.(Pramanik and Bhar, 2021) The condensation reaction, followed by cyclization between (**1ab**) and (**2a-c**), began with a nucleophilic addition of diamine to the carbonyl groups, followed by a proton transfer. (**SSG2, SSG3, SSG4**) shown in Scheme 2 with excellent yield. The prepared compounds (**SSG2, SSG3, SSG4**) were produced with a quantitative yield, as shown



Scheme 1. Synthesis of 1,4-benzodiazepines derivative (1ab).



Scheme 2. Synthesis of secondary derivatives (3a, 3b, 3c). from 1-(4-hydroxy-3-methoxyphenyl)decane-3,5-dione (1ab).

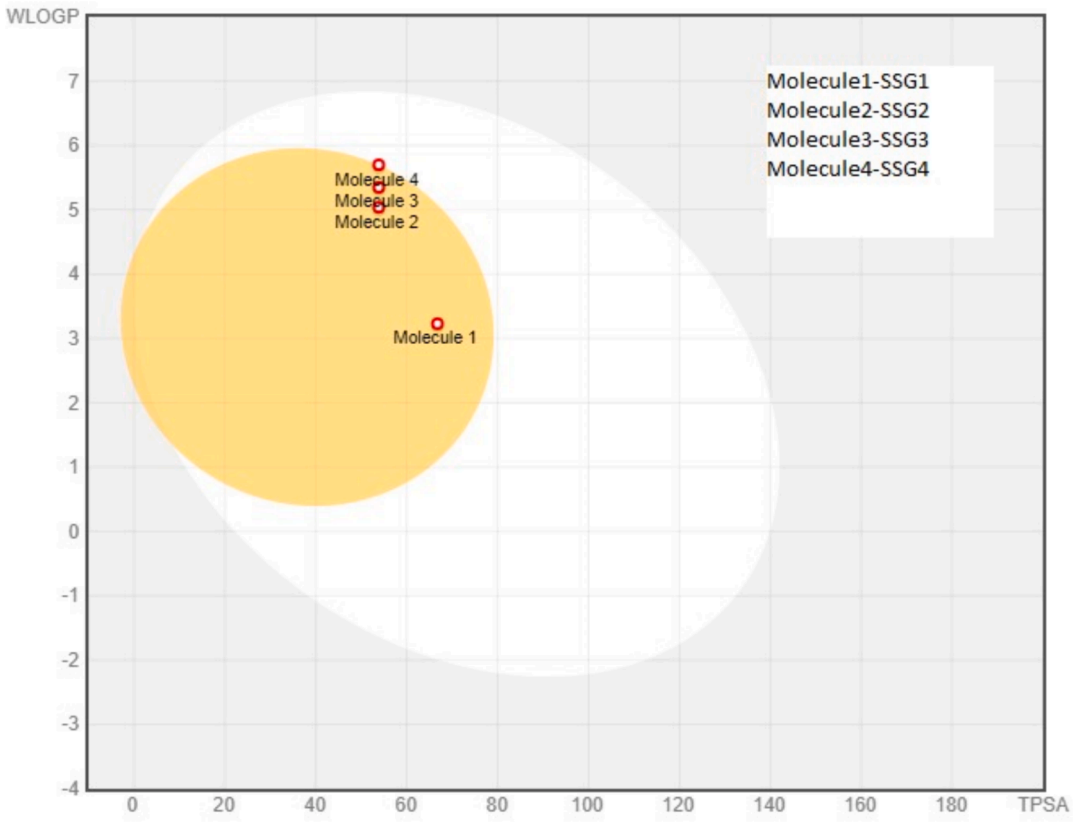


Fig. 2. Boiled egg representation of compound SSG1, SSG2, SSG3 &SSG4.

in the experiment section, and were confirmed by different spectroscopic techniques. Figures S13-S15 show the FT-IR spectra of compounds **(SSG2, SSG3, SSG4)**; the spectra are consistent with the suggested 1,4-benzodiazepines. The compounds were also validated using ^{1}H and ^{13}C NMR Figure S5-S10; however, the vinylic proton of the 1,4-benzodiazepine ring and the diamine hydroxyl proton was not detected.

4. Discussion

The synthesized gingerol derivatives were taken into the next step for the estimation of Pharmacokinetic parameters using the chemical structure. The physicochemical properties and druggability of the molecule solely denote the pharmacokinetic properties of the drug. The druggability of the molecule is often distinguished based on molecular weight, Number of acceptable/donor bonds, and total polar surface area. In this current study, all gingerol derivatives were found to be

Table 4
Molecular docking analysis of Synthesized compound.

PDB: 4FFW Binding Affinity expressed in −Kcal/mol with major amino acid residues				**PDB:5G5J** Binding Affinity expressed in −Kcal/mol with major amino acid residues			
SSG1	**SSG2**	**SSG3**	**SSG4**	**SSG1**	**SSG2**	**SSG3**	**SSG4**
−6.4	**−8.1**	**−8.1**	**−6.7**	**−7.9**	**−10.7**	**−9.7**	**−8.3**
GLU203 GLU204 ARG354 PHE355	GLU203 GLU204 ILE205 PHE206	GLN121 TRP122 THR127 ASN148	ILE344 GLU345 THR346 SER347	TYR53 PHE57 ASP76 ARG106	ILE118 SER119 PHE137 ILE184	TYR53 PHE57 ASP76 ARG105	TYR53 PHE57 ASP76 GLN79
Sitagliptin **−7.6** ARG123 GLU203 GLU204 ILE205				**Metformin** **−5.1** ASP76 GLN79 ARG106 PRO107			

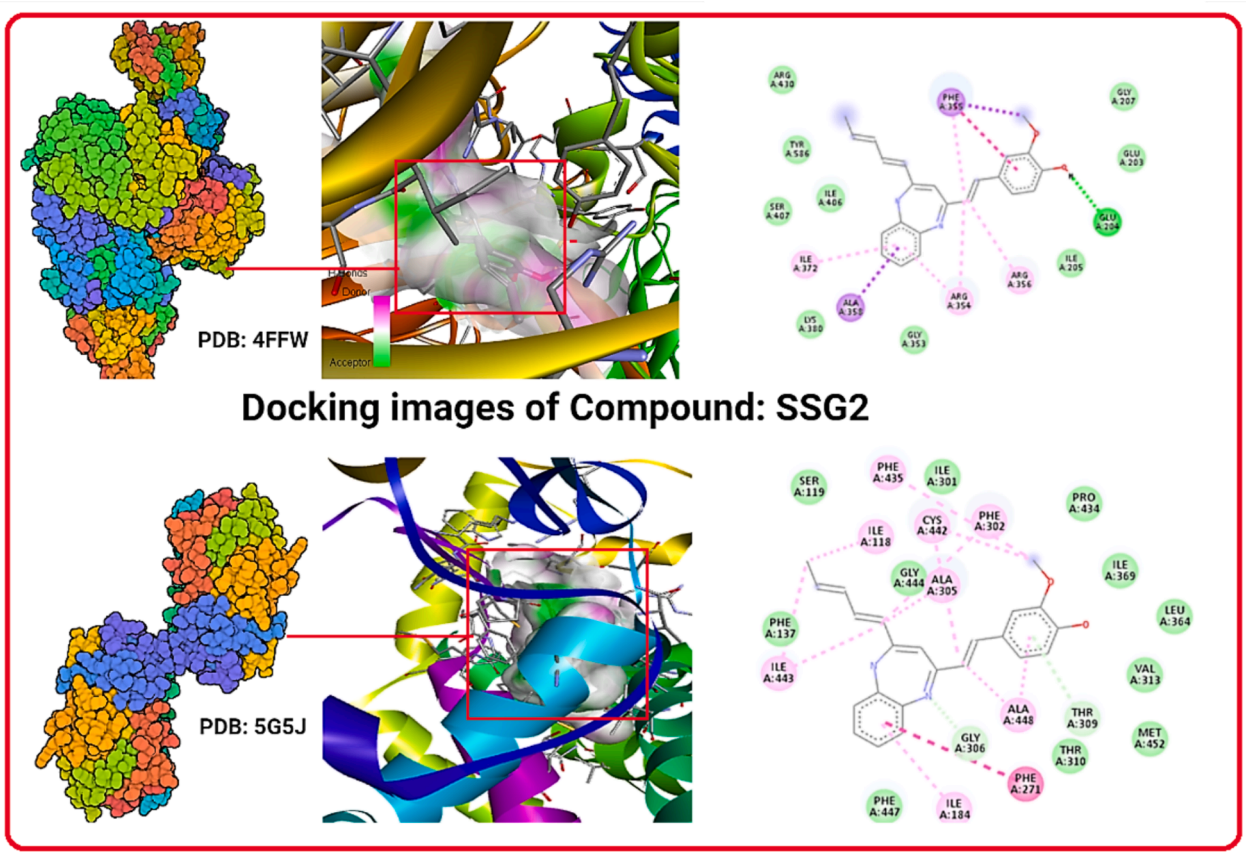


Fig. 3. Images showing the molecular docking of SSG2 with respect to PDB:4FFW and 5G5J.

pharmacologically active. SSG2, SSG3, and SSG4 compounds, on the other hand, demonstrated at least one violation of the Ghose or Muegge rules. The image of the boiled egg symbolizes the passive absorption in the Alimentary system and permeation through the Cerebrovascular barrier. The molecular center in a boiled egg serves as an indicator for the druggability of a novel compound; notably, the yolk delineates a region with a high likelihood of blood–brain barrier (BBB) permeation, while the egg white signifies distinct characteristics conducive to an increased probability of human intestinal absorption (HIA). The molecule is considered as low absorption and BBB penetration if it is identified in the grey region. The bioactivity radar confirms the drug-likeness of the molecule. The pink zone is considered the drug-likeness zone. If the properties of the molecule fall within the pink zone, the molecule will be considered reliable. The Boiled egg justifications are illustrated in Fig. 2. This study investigated the extraction, isolation, and subsequent modification of 6-gingerol, a bioactive compound found in ginger, with the aim of creating novel derivatives with potential therapeutic applications. A simple and efficient method was employed to isolate 6-gingerol (1a) from ginger in high yield (20 %) using a combination of methanol extraction, ultrasonication, and silica gel column chromatography. This approach aligns with previously established methods for gingerol extraction, demonstrating reproducibility and scalability for gram-scale production.(Magdy et al., 2020, Ahmed et al., 2023) Our subsequent reaction between 1,3-diketone (1ab) and various o-phenylenediamine derivatives (2a-c) under reflux conditions yielded the target 1,4-benzodiazepine derivatives (3a-c) in excellent yields. This methodology aligns with the condensation-cyclization reaction. (Teli et al., 2023) Compound SSG3 was identified as hepatotoxic, and all the gingerol derivatives are non-mutantic, tumorigenic, and irritant and have reproductive effects. None of the compounds was detected either as a red alert/orange alert. The multispecies toxicity profile of gingerol derivatives is given in Table 3. The binding affinity of SSG2& SSG3 was found to be slightly higher (−8.1 Kcal/mol) when compared with SSG1 (−6.4 Kcal/mol) and SSG4(−6.7 Kcal/mol) towards PDB: 4FFW.The binding affinity of SSG2 was found to be slightly higher (−10.7 Kcal/mol) when compared with SSG1(−7.9Kcal/mol), SSG3 (−9.7Kcal/mol),

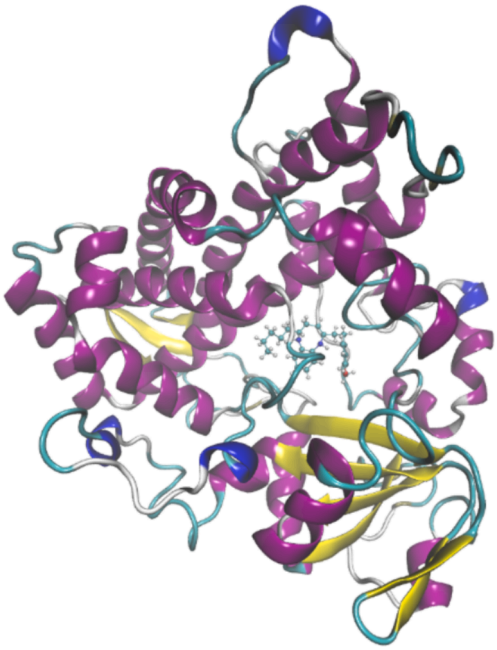


Fig. 4. This graphic depiction provides a visual picture of the protein–ligand complex that includes SSG2 and the CYP3A4 enzyme. The protein is depicted in a cartoon representation, whereas the ligand is provided in CPK (Corey-Pauling-Koltun) representation.

and SSG4(−8.3 Kcal/mol) towards PDB:5G5J. The molecular docking reports confirm that compound SSG2 has stronger binding affinity when compared with the existing reference standard Sitagliptin (−7.6Kcal/mol in PDB:4FFW) and Metformin (−5.1Kcal/mol in PDB:5G5J). The Molecular docking data and molecular docking images are illustrated in Table 4 &Fig. 3. Based on the Docking data, the molecular dynamic simulation is performed for the SSG2 compound toward the (PDB ID: 5G5J) target.

4.1. Molecular dynamic simulations of CYP3A4 enzyme in complex with SSG2

To comprehend the alterations in conformation and assess the interaction between SSG2 and the CYP3A4 enzyme (PDB ID: 5G5J), we conducted a 100 ns molecular dynamics (MD) simulation for the SSG2-CYP3A4 enzyme complex, as depicted in Fig. 4. The simulation underwent scrutiny through the application of diverse statistical metrics throughout the simulation period.

4.2. RMSD analysis

Examining the RMSD provides valuable insights into the structural changes occurring in both the protein and the ligand throughout the simulation. Fig. 5 displays a multiplot illustrating the variation of protein Cα and ligand coordinates during the simulation. Notably, both the ligand and the protein within the complex have reached a stable phase, characterized by RMSD values consistently below 0.25 nm. This stability indicates that the ligand–protein complex remained structurally intact throughout the simulation.

4.3. RMSF analysis

Protein RMSF is a valuable metric for understanding localized fluctuations within the protein chain. Fig. 6 depicts a plot illustrating the variation in protein RMSF (measured in nanometers) across the residue number index. Noteworthy is the observation that the plot reveals minimal fluctuations, with values consistently below 0.45 nm for the protein. Notably, the residues engaged in binding with the ligand exhibit particularly small fluctuations, underscoring the stability of the ligand–protein complex.

4.4. H-bond interaction

Molecular interactions, especially hydrogen bond interactions, are susceptible to disruption under dynamic conditions, as they depend on both distance and angle parameters. In this study, we focused on the analysis of interactions between the ligand and the protein. Fig. 7

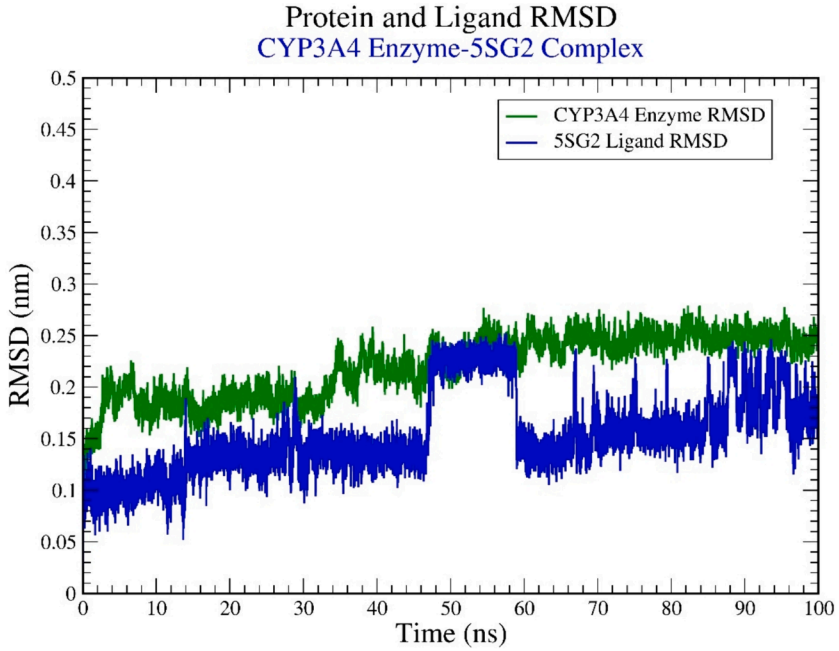


Fig. 5. Here is a graphical representation of the plot depicting protein Cα and ligand RMSD (root mean square deviation) in nanometers versus time (100 ns). In panel (A), the CYP3A4 enzyme protein is represented in green, and in panel (B), the SSG2 ligand is represented in blue.

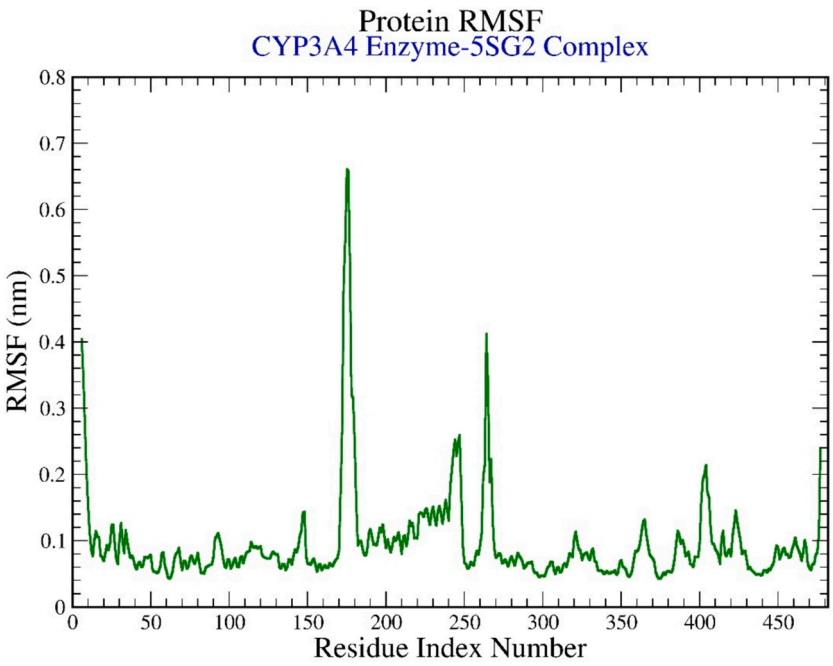


Fig. 6. A graphical representation that illustrates the link between the root mean square fluctuation (RMSF) of the protein, measured in nanometers, and the residue index number of the protein for the SSG2-CYP3A4 enzyme complex.

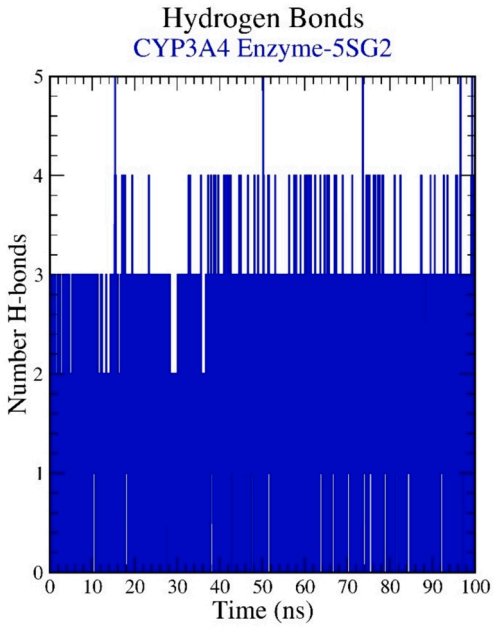


Fig. 7. A graphical depiction that illustrates the number of hydrogen-bond interactions that were formed by SSG2 within the complex with the CYP3A4 enzyme (PDB ID. 5G5J).

illustrates a plot showing the number of hydrogen bonds over time. The plot revealed that SSG2 formed and maintained three stable hydrogen bond contacts while binding to the CYP3A4 enzyme. To further understand these interactions and assess their stability, we calculated the percentage occupancies of specific residues involved in these bonds. Fig. 8 illustrates the histogram depicting the %occupancies of hydrogen bond contacts formed by SSG2 when binding to the CYP3A4 enzyme. The graph highlights SSG2′s capability to establish stable hydrogen bond contacts with residues ARG85 and ARG192, showing occupancies of 45.03 % and 107.34 % (multiple contacts), respectively. In summary,

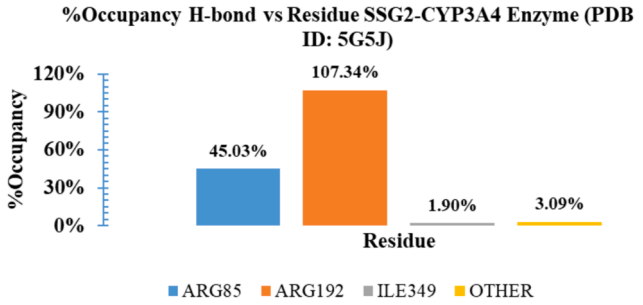


Fig. 8. A histogram that illustrates the distribution of percent occupancies for hydrogen-bond protein–ligand interactions of SSG2 inside the complex with CYP3A4 enzyme (PDB ID: 5G5J).

the data suggests that SSG2 can be deemed an effective ligand for binding with the CYP3A4 enzyme.

A member of the *Zingiberaceae* family, ginger is a strong and aromatic herb that has long been used in traditional medicine to treat a variety of chronic ailments. (Elias Nortaa Kunedeb and Frederick, 2019, Dhivya et al., 2022) For the development of novel drug discovery, NP serves as a solid foundation for physiochemically stable and effective compounds. However, NPS has produced a wide variety of drugs. However, still they are arduous in the stages of synthesis and chemical modification. Biology-oriented synthesis (BIOS) seeks to overcome this limitation by directing the structural simplification of natural products (N.P.s), simplifying their synthesis while retaining biological relevance. (Laraia et al., 2018).

5. Conclusion

In conclusion, this study highlights a methodical approach to isolating and synthesizing 6-gingerol and its derivatives, along with a novel series of 1,4-benzodiazepines with promising yields and purity. By employing spectroscopic methods, the synthesized compounds were thoroughly characterized. The pursuit of repurposing medications, leveraging existing molecular pharmacology data, offers a promising

avenue for addressing challenging diseases like type 2 diabetes and other disorders. This approach accelerates the development of new therapies, holding considerable potential for future pharmaceutical advancements and therapeutic strategies. The ever-increasing popularity of medication repurposing is for the purpose of addressing not just diabetes but also a variety of communicable and non-communicable disorders in which the therapeutic activity of traditional medicines is inadequate. By making use of the molecular pharmacology data that is already available on established therapies, repurposing greatly speeds up the process of developing new medications.

Ethical approval

Not applicable.
Declarations.

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CRediT authorship contribution statement

Mariyappan Vaithiyalingam: . **Ramasamy Mohan Kumar:** . **Prerna Khagar:** Formal analysis, Resources. **Sarvesh Sabarathinam:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yahia Alghazwani:** Funding acquisition, Software, Supervision, Visualization. **Kumarappan Chidambaram:** Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing.

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.sjbs.2024.104048.

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