Spondias mombin: in Silico Screening of 1,2-Benzenedicarboxylic Acid, Butyl 2-Methylpropyl Ester (Fragment of Geraniin) as Anti-Marburg virus agent

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August 16, 2022

Abstract

Background and Purpose Belonging to the family Anacardiaceae, Spondias mombin Linn (SM) has been used in ethnomedicines in the treatment of diseases including viral diseases. This study aims to identify anti-viral volatiles from Geraniin and alcoholic leaf extracts of Spondias mombin Linn as potential anti-Filoviral agent against the Marburg virus (MARV VP35) by the use Gas Chromatographic–Mass Spectrometry (GC-MS) and computer-aided techniques. Experimental Approach We used phytochemical processes and computer aided drug design in the identification (by GC-MS) of anti-viral phytochemical compounds from leaf extracts of S. mombin, constituents of Geraniin and anti-filoviral activity through molecular docking and molecular simulation respectively. Key Results Geranyl benzoate including four (4) antiviral compounds, D-Limonene, p-Cymene, Thymol, L-.alpha.- Terpineol and 1,2-Benzenedicarboxylic acid, butyl -2- methylpropyl ester (1,2BAB-2-MPE) were obtained from fractions of alcoholic SM leaf extracts and 98% pure Geraniin respectively. In silico analysis identified 1,2BAB-2-MPE as the most favourable potential binders MARV VP35 binder characterised by high-affinity interactions binding site residues which favour pocket stability. Conclusions and Implications Our findings, identified Geranyl benzoate compound reported for the first time in ethanolic leaf extracts of SM and 1,2BAB-2-MPE as potential anti-filoviral candidate against Marburg viruses VP35. Our study may provide insights further developed 1,2BAB-2-MPE and /or SM leaf extracts as a therapeutic agent against Marburg viruses

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Data Availability Statement: Data available on request

ABSTRACT

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Experimental Approach

We used phytochemical processes and computer aided drug design in the identification (by GC-MS) of anti-viral phytochemical compounds from leaf extracts of *S. mombin* , constituents of Geraniin and anti-filoviral activity through molecular docking and molecular simulation respectively.

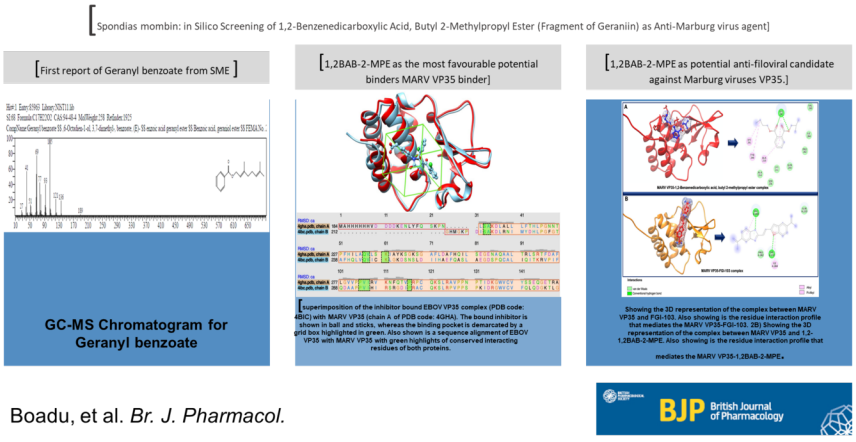
Key Results

Geranyl benzoate including four (4) antiviral compounds, D-Limonene, p-Cymene, Thymol, L-.alpha.- Terpineol and 1,2-Benzenedicarboxylic acid, butyl -2- methylpropyl ester (1,2BAB-2-MPE) were obtained from fractions of alcoholic SM leaf extracts and 98% pure Geraniin respectively. *In silico* analysis identified 1,2BAB-2-MPE as the most favourable potential binders MARV VP35 binder characterised by high-affinity interactions binding site residues which favour pocket stability.

Conclusions and Implications

Our findings, identified Geranyl benzoate compound reported for the first time in ethanolic leaf extracts of SM and 1,2BAB-2-MPE as potential anti-filoviral candidate against Marburg viruses VP35. Our study may provide insights further developed 1,2BAB-2-MPE and /or SM leaf extracts as a therapeutic agent against Marburg viruses

Graphical Abstract



Abbreviations

SM: *Spondias mombin* leaf extract

SME: *Spondias mombin* ethanolic leaf extract

GC-MS: Gas- Chromatography-Mass Spectrometry

1,2BAB-2-MPE: 1,2-Benzenedicarboxylic acid, butyl -2- methylpropyl ester

MARV: Marburg virus

INTRODUCTION

Marburg virus (MARV) belongs to the family Filoviridae. MARV is pathogenic in humans, virulent, enveloped, and linear non-segmented RNA (Cross et al., 2021, Bozhanova et al., 2020, Kuhn et al., 2019, Li et al., 2019, Asad et al., 2020). Marburg virus was reported for the first time in Germany and later in the Democratic Republic of Congo (DRC). Its origin was a bat commonly found in Egypt called *Rousettus aegyptiacus*(Organization, 1978, Pigott et al., 2015, Koch et al., 2020, Schwartz, 2019). The recently reported outbreaks of MARV in DRC resulted in an approximately 81% mortality rate in about 26 months (August 2018 and May 2020) (Batra et al., 2020, Porter et al., 2020, Organization, 2019) (Asad et al., 2020, Kuhn et al., 2019, Nyakarahuka et al., 2019, Batra et al., 2020, Porter et al., 2020, Organization, 2019). The mode of infection of MARV is by direct contact with human blood and body fluids of an infected patient, contaminated objects, uncooked (Moreau et al., 2015), or partially cooked wildlife meat (Batra et al., 2020, Kuhn et al., 2019, Roels et al., 1999, Gałaś, 2014). After infection of MARV in patients, reported symptoms such as fever, sore throat, muscle pain, fatigue, headache and weakness with nausea, diarrhea, stomach pain and haematological irregularities have been observed (Pigott et al., 2015, Nyakarahuka et al., 2019, Uyeki et al., 2016, Kortepeter et al., 2011, Kortepeter et al., 2020, Chertow et al., 2014). The high mortality rate of the Marburg Virus Disease (MVD) has generated research interest to find a possible treatment. Currently, there are no approved FDA drugs for MVD. However, there are few anti-viral drugs such as FGI-103 (Warren et al., 2010), Favipiravir (T-705)(Zhu et al., 2018) and Remdesivir (GS-5734) (Porter et al., 2020) that are being investigated as repurposed drugs (Pruijssers et al., 2020, Choy et al., 2020, Savarino et al., 2003, Dan et al., 2020, Colson et al., 2020, Barlow et al., 2020, Dong et al., 2020, Wang et al., 2020, Awadasseid et al., 2021, Goldman et al., 2021, Beigel et al., 2020, Brauburger et al., 2012).

Some medicinal plants, such as *Spondias mombin Linn*(*S. mombin*), have been reported to have a wide range of anti-viral activity (Mukhtar et al., 2008). In our previous *in silico* study, Geraniin, a compound obtained from *S. mombin* leaf extracts, was reported to be a potential inhibitor candidate of EBOV secreted Glycoprotein (sGP) (Boadu et al., 2021). Geraniin was noted to possess anti-viral properties against Dengue type-2 (DENV-2), Zika (ZIKV), hepatitis B, herpes simplex type 1, and Coxsackie B viruses (Choi et al., 2019, Liu et al., 2016, Yang et al., 2007, Yang et al., 2012, Li et al., 2008, Siqueira et al., 2020, Ahmad et al., 2019, Haddad et al., 2020, Ahmad et al., 2017). Belonging to the family Anacardiaceae (Ayoka et al., 2006), *S. mombin* (SM) has been used in ethnomedicines in the treatment of viral ailments (Agra et al., 2007, Ademola et al., 2005, Amadi et al., 2007, Osuntokun et al., 2018, Shosan et al., 2014). Pharmacologically, leaf extracts of *S. mombin* indicate anti-viral, anti-oxidant, antimicrobial (Ajao et al., 1985), and anti-inflammatory properties (Sabiu et al., 2015, Ishola et al., 2018, Akinmoladun et al., 2015, Corthout et al., 1992, dos Santos Sampaio et al., 2018, Mahmood et al., 1997, Siqueira et al., 2020).

Ethnomedicinally, medicinal plants for decades have been used to manage diseases. However, the lack of proper documentation, standardization, and biosafety poses a significant challenge due to unknown or delayed side effects on patients (Birdi et al., 2006).

Bioactive phytochemical compounds from plants used ethnomedicinally, mostly prepared as crude extracts, have shown various pharmacological properties(Yuan et al., 2016, Anand et al., 2019, Pandey et al., 2008). Hence, to find the rationale for their pharmacological action, several analyses such as Gas- Chromatography-Mass Spectrometry (GC-MS) and computer-aided drug design technology, to mention a few are commonly used to identify possible bioactive drug candidates found in crude extracts of medicinal plants. GC-MS analysis is one of the fastest and accurate techniques and normally requires a small quantity of extract. Identification using GC-MS normally detects terpenes, alcohols and other smaller fragments(Razack et al., 2015, Keskes et al., 2017, Fan et al., 2018, Juszczak et al., 2019). Therefore, in the current study, GC–MS analysis was used to detect and identify antiviral phytochemical compounds obtained from leaf extracts of *S. mombin*and Geraniin; a tannin reported in the literature and our previous research to possess antiviral properties.

Currently, computer-aided techniques are being used in the prediction of drug candidates, from medicinal plant extracts by many pharmaceutical companies to reduce drug failures in the market and the cost of research due to poor pharmacokinetic properties(Fang et al., 2018). Therefore,*in silico* molecular docking, molecular simulation and pharmacokinetic analysis are used to obtain vital information, on predicting the therapeutic-target protein interactions(Bharathi et al., 2014, Lee and Kim, 2019, Sliwoski et al., 2014).

Considering the reported diverse pharmacological properties and broad-spectrum antiviral properties of *S. mombin* and compound it isolate such as Geraniin as well as our previous *in silico* study which identified Geraniin as a potential inhibitor candidate of EBOV secreted Glycoprotein (sGP) (Boadu et al., 2021),*S mombin* phytochemical compounds may be promising targets worth investigating further against other viruses. Hence the present study focused on the detection, identification of antiviral phytochemical compounds from alcoholic leaf extracts of *S mombin* and 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester, a fragment of Geraniin. Subsequently, all antiviral phytochemical compounds identified were subjected to, pharmacokinetics, molecular docking and molecular simulation using *in silico* techniques to investigate a possible anti-Filoviral therapeutic candidate against the Marburg virus (MARV VP35).

2. METHODOLOGY

2.1 Sample collection and identification

Fresh leaves of *S. mombin Linn* were collected from Cape Coast - Ghana and authenticated by the botanist, Mr. Felix Fyn, at the University of Cape Coast Herbarium. A specimen was deposited at the herbarium with voucher number F. AADR002.

2.2 Material and Chemical

All chemicals and solvents utilised in this research work were of analytical reagent grade (AR grade). Geraniin (with certificate of analysis), Dichloromethane methanol and ethanol were purchased from Sigma Aldrich and Merck Millipore, South Africa. Hexane and ethyl acetate were purchased from Associated Chemical Enterprises., South Africa. Whatman filter paper was purchased from Sigma Aldrich, South Africa. Different instruments such as the Rotary evaporator and Soxhlet apparatus (Büchi-Germany), Analytical balance (Lasec, South Africa) were used in the study.

The GC-MS instrument used is Shimadzu GCMS2010-SE with a Zebron ZB-5MSplus 0,25 um, 30 m x 0,25 mm column.

2.3 Extraction and Preliminary Phytochemical screening of leaf powder of *S. mombin L.*

The extraction process was carried out according to standard procedures as indicated by (Harborne, 1998). In brief, 60g of air-dried SM powder was weighed and macerated serially at room temperature for 72 hours until the solvent of extraction was clear. The extraction was performed in triplicates using solvents of increasing polarities. These solvents were from less polar to more; hexane, dichloromethane, ethyl acetate, ethanol and methanol. Extracts of each solvent were bulked together, filtered, concentrated and dried using a rotary evaporator and preserved in the refrigerator (-4 degC) for future phytochemical screening, isolation, purification and characterization. Preliminary qualitative phytochemical analysis was performed on the methanolic extract according to standard procedures reported (Harborne, 1998, Costa et al., 2012a).

2.4 Fractionation of alcoholic crude leaf extract.

All crude extracts and fractions were pooled together, concentrated using a rotatory evaporator to reduce the solvent of extraction. They were then placed in a fume hood at room temperature for several hours till they were completely dry.

To mimic the ethnomedicinal use of leaf extracts of *S. mombin* , dried ethanolic and methanolic crude leaf extracts of *S. mombin*were chosen for fractionation and further analysis (Cos et al., 2006). They were dissolved in 50ml of 50% ethanol solution and transferred into a separating funnel. Liquid-liquid extraction was performed using 100ml, per extraction solvents of n-hexane, Dichloromethane-DCM and Ethyl acetate.

Each extraction was repeated four times. The fractions were stored in an airtight glass container and stored in a refrigerator for further use.

2.5 Identification of phytochemicals from crude leaf extracts and fraction of *S. mombin* using GC-MS.

Our study was to find small molecules that could be docked to Marburg virus protein structure, identify the possible binding site(s) and find novel potential anti-Filoviral properties of the antiviral phytochemicals identified. Hence the use of GC-MS in our characterization of the phytochemicals. We based our characterization of the compounds obtained from the GC-MS chromatograms based on a library database using the name of the compound, molecular weight(g/mol), molecular formula, retention time (minutes) percentage area, physicochemical and pharmacokinetic properties, as well as reported biological activities. The conditions and procedures used in the GC-MS analysis are as follows: samples were analysed using the Shimadzu GCMS2010-SE with a Zebron ZB-5MSplus 0,25 um, 30 m x 0,25 mm column.

Six (6) rinses with Pre and Post-solvent, thereafter it was rinsed two times with the sample. The conditions of the analysis are Plunger Speed(Suction): High, Column Oven Temp. :40.0 degC, Injection Temp. :200.00 degC, Injection Mode :Split, Flow Control Mode :Linear Velocity, Pressure :72.3 kPa, Total Flow :10.9 mL/min, Column Flow :1.32 mL/min, Linear Velocity :41.5 cm/sec, Purge Flow :3.0 mL/min, Split Ratio :5.0, Carrier Gas Saver :ON, Carrier Gas Saver Split Ratio :5.0 and Carrier Gas Saver Time :1.00 min. Interpretation of mass spectrum GC-MS was conducted using the National Institute Standard and Technology (NIST) database, having more than 62,000 patterns.

2.7. Computational Methodology

2.7.1 System preparation

The x-ray crystal structure of the Marburg virus (MARV) VP35 crystal structure was retrieved from the Protein Data Bank (Berman et al., 2002) with code 4GHA (Bale et al., 2012). The retrieved x-ray crystal structure consisted of four chains forming a tetramer and was complexed with the nucleic acid. We deleted all chains, water molecules and nucleic acids except chain A in preparation for molecular docking using UCSF Chimera (Pettersen et al., 2004). Hydrogen atoms were subsequently added and the structure was saved for molecular docking using AutoDock Vina (Trott and Olson, 2010).

2.7.2 Ligand preparation

The two-dimensional (2D) structures of all the isolated phytochemical compounds were constructed using Marvin Sketch (ChemAxon, 2013). The 2D structures were then uploaded onto Avogadro software (Hanwell et al., 2012) to generate the three-dimensional (3D) coordinates of each compound. We used the Avogadro software to minimize the energy and then optimized the compounds using the UFF force field (Rappe et al., 1992). Before molecular docking, the final preparation of each of the compounds was carried out on UCSF Chimera, whereby hydrogen atoms and corresponding Gasteiger charges were added (Gasteiger and Marsili, 1978).

3. RESULTS AND DISCUSSION

3.1 Preliminary Phytochemical Screening

Table 1 presents preliminary phytochemical screening results of*S. mombin* leaf extracts obtained from methanol (SMM). Experiments were performed in triplicates.

The presence of alkaloids, anthraquinones derivatives, terpenoids, saponins, flavonoids and tannins were identified in the leaf extract except for steroids. This result is in line with other authors who have reported the same (Ayoka et al., 2005, Nworu et al., 2007, Igwe et al., 2010, Shittu et al., 2014).

Table 1: Phytochemical screening of methanolic leaf extracts of Spondias mombin.

Class of phytochemicals	Tests	Methanolic leaf extracts of *S. mombin* L.
Alkaloids	Meyer	+
Anthraquinones Derivatives	Borntrager's test	+
Steroids	Liebermann-Burchard test	-
Terpenoids	Liebermann-Burchard test	+
Saponins	Frothing	+
Flavonoids	Sulfuric acid test	+
Tannins	Ferric chloride test	+
Cardiac glucosides	Keller Killian	+

Key: + = present, - =Absent

3.2. Gas Chromatography-Mass Spectrometry analysis of leaf extracts of *S. mombin L and* Geraniin (98% w/w).

GC-MS analysis, assist researchers in identifying the quantitative chemical compositions of extracts, which is helpful in the study of the pharmacological actions of these medicinal extracts (Yamuna et al., 2017). Hence GC-MS analysis of crude and fractionated alcoholic leaf extracts of *S mombin* and Geraniin (98% w/w) was used to identify possible antiviral molecules that may obey Lipinski's rules of five (Lipinski, Lipinski et al., 1997) with references to their molecular size, that can be used to perform *in silico*study.

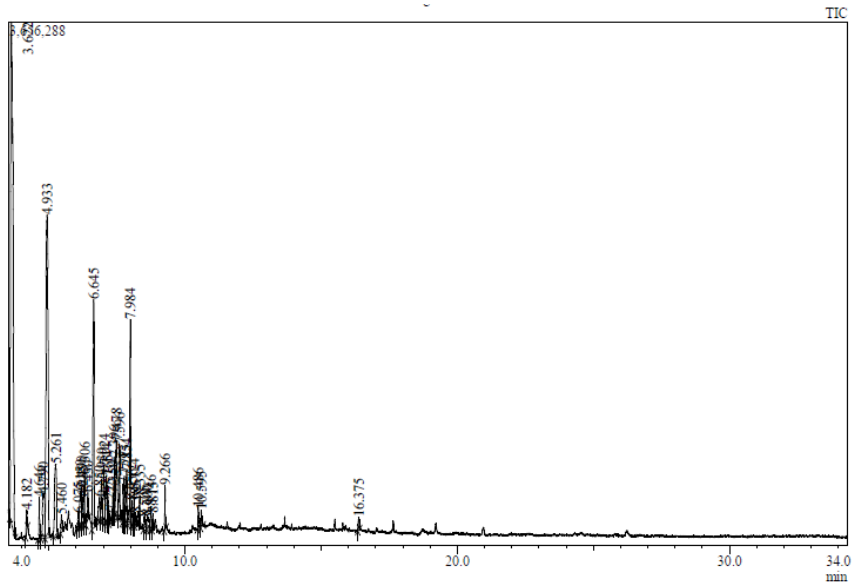


Figure C 1: GC-MS Chromatogram for SME

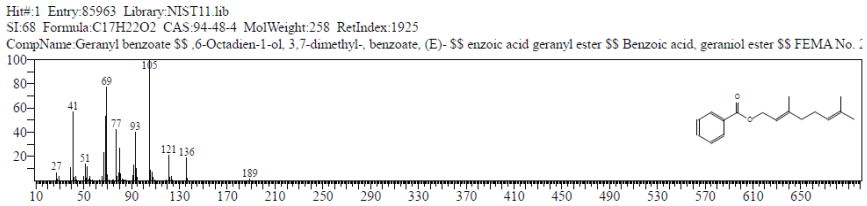


Figure C 2: GC-MS Chromatogram for Geranyl benzoate

GC-MS analysis including chromatograms of all alcoholic leaf extracts of S. *mombin* and Geraniin are presented in the supplementary data (S#). The supplementary Table S1, complimented with Figure C 1, revealed 51 phytochemical compounds from crude ethanolic S. *mombin* leaf extract, which is in contrast with reports by Akanji and co-workers (Akanji, 2020), that identified 25 compounds in SME crude leaf extract. The difference, in conclusion, maybe due to a possible effect of the geographical location of the medicinal plant (Behdad et al., 2020). Geranyl benzoate, as presented in the chromatogram in Figure C 2, was identified in the crude ethanolic extract of S. *mombin* leaf extract. Hence, Geranyl benzoate (1.06 %) is reported for the first time in ethanolic S. *mombin*leaf extract, although it has been reported to have been identified as one of the compounds found in chestnut and highland honey (station 11) (Kanbur et al., 2021).

Geraniin was reported to have been isolated from ethanolic leaf extract of *S. mombin* (Corthout et al., 1991), but was not identified in the GC-MS analysis of our current study, partially due to the method of identification.

The GC-MS analysis as presented in Supplementary Tables S3, S4 and S5. are phytochemicals identified from fractionated ethanolic leaf extract of *S. mombin* with 78, 52 and 12 compounds in SMEH, SMEDCM and SMEEA, respectively. There were three compounds identified to have the highest compositions in SMEH; Toluene (9.56%), n-Nonadecanol-1 (7.46%) and Tetradecane (5.23%). Pharmacologically, Tetradecane is reported to possess anti-microbial, anti-pyretic, anti-helmintic and Tuberculosis effects (Diwan and Malpathak, 2011). Similarly, in SMEDCM, Benzaldehyde, 2-chloro- (9.51%), l-(+)-Ascorbic acid 2,6-dihexadecanoate (7.67%) and Heptadecane (6.30%) were identified to have the highest compositions. Out of these three compounds identified, l-(+)-Ascorbic acid 2,6-dihexadecanoate and Heptadecane were reported by other researchers to possess anti-oxidant and anti-inflammatory (Shyamala and Manikandan, 2019, Dulara et al., 2019).

The SMEEA fraction contained Phytol, acetate (28.48%), 3,7,11,15-Tetramethyl-2-hexadecen-1-ol (20.45%) and Eicosane (19.00%) as the highest percentage compositions. Eicosane has anti-oxidant and anti-inflammatory effects (Godara et al., 2019, Dulara et al., 2019).

Similarly, by GC-MS analysis of fractionated methanolic leaf extracts of*S. mombin* (SMM) as presented in S5, S6, S7 and S8. The extracts SMMH, SMMDCM and SMMEA showed 55, 45 and 40 compounds identified, respectively. The highest percentage composition in the fraction of SMMH is, n-Nonadecanol-1 (18.98%), Toluene (11.46%) and 1-Butene, 2,3,3-trimethyl (5.51%). Similarly, SMMDCM fraction had Diisooctyl phthalate (25.74%), Tetrachloroethylene (23.31%) and Eicosane (16.68%), while SMMEA fraction had, Eicosane (29.23%), Diethyl Phthalate (10.79 %) and 1-Heptacosanol (9.88%). 1-Heptacosanol , has anti-bacterial, anti-oxidant and nematicidal effect (Sultana et al., 2010, Murugan and Iyer, 2014).

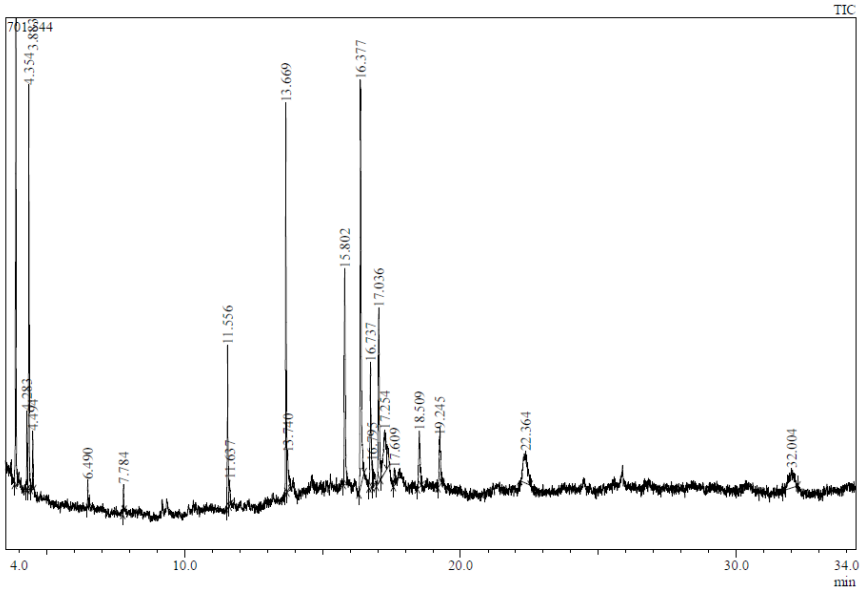


Figure C 3: GC-MS Chromatogram of Geraniin (98% w/w)

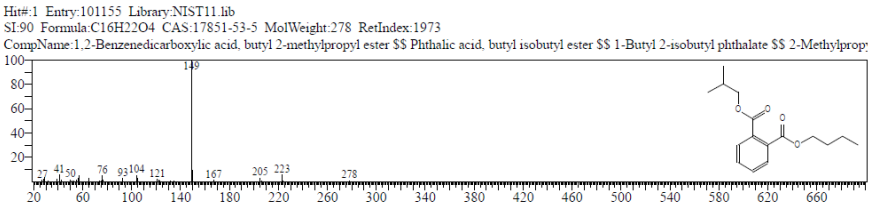


Figure C 4: GC-MS Chromatogram for 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE)

Figure C 3 and Supplementary Table S9, presents, GC-MS fragmentation analysis of Geraniin (98% w/w), revealed 20 compounds with 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE) (18.509%), Phytol, acetate (16.05%) and 3,7,11,15-Tetramethyl-2-hexadecen-1-ol (12.46%) as the compounds with the highest compositions. The compound 3,7,11,15-Tetramethyl-2-hexadecen-1-ol have also been identified in methanolic leaf extracts of the *Annona muricata* and reported to possess cancer-preventive, antimicrobial, anti-inflammatory anti-diuretic and anti-oxidant properties (Shibula and Velavan, 2015). The antiviral compound, 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE) as presented in Figure C 4 below, is reported for the first time as a fragment of Geraniin.

Phytol, acyclic diterpene alcohol was identified as one of the compounds in Geraniin fragments ethanolic crude (SME), SMEH, SMEDCM, SMMH and SMMDCM . Phytol was previously reported by other researchers to exhibit anti-cancer, anti-microbial and anti-oxidant activities (Cos et al., 2006, Costa et al., 2012a, Costa et al., 2012b, Silva et al., 2014) and could be responsible for synergistic pharmacological action of these extracts. Phytol has been reported to be identified in hydroethanolic extracts of*Abutilon indicum* used in the Indian system of medicine (Thakor et al., 2016). Therefore the identification of phytol in the ethanolic extracts is in line with our findings.

Table S 10, presents a similarity table of compounds identified in GC-MS analysis of Geraniin and fractionated alcoholic leaf extracts of*S. mombin* . In the comparative GC-MS analysis of SM leaf extracts and Geraniin fragments, as presented in Table **S 10,** similar compounds such as 1-Tetradecene and n-Nonadecanol-1

found in Geraniin were also identified in all fractionated alcoholic leaf extracts. As previously established in the background literature, Geraniin, found in*S mombin* and other extracts from the plant is known to have several pharmacological activities. This underscores the pharmacological potential of the plant and its compounds. Fragmentation of large molecules to smaller and simpler compounds could increase the drug-likeness, bioactivity, increased bioavailability and decreased toxicity(FA. Olotu *et al.,* 2018). In our previous *in silico* study, Geraniin was identified as a potential anti-Ebola candidate. A pharmacophore model generated from Geraniin, showed that there were three aromatic rings, a hydrophobic ring and several hydrogen donors/acceptors responsible for anti-Ebola activities (Boadu et al., 2021). This model could be a volatile or contaminant of Geraniin. Hence, Geraniin was subjected to GC-MS analysis to identify possible volatile(s) that could be close to the pharmacophore model and to also create uniformity in methodology used in the identification of antiviral phytochemicals in the alcoholic leaf extracts and also to identify the active volatile compound(s) (Chauhan et al., 2014). Twenty (20) fragments of compounds were identified from the chromatogram of Geraniin as indicated in Table S9. Out of the 20 compounds, 1,2-Benzenedicarboxylic acid, butyl 2-methyl propyl ester was the only compound that has been reported in the literature to possess anti-viral and antimicrobial activities (FUNGI, Govindappa et al., 2014). Hence its use in molecular docking in this present study.

Table 2, summarises selected phytochemical compounds from GC-MS analysis of crude and fractionated extracts and Geraniin (98 %w/w) with reported anti-viral properties. It also shows the computed physicochemical descriptors as well as predict Absorption, Distribution, Metabolism, and Excretion (ADME), of the identified anti-viral phytochemicals.

The physicochemical and pharmacokinetic properties in the early days of the inception of drug discovery were normally predicted and the last stage of the drug design process, but it is important to predict ADME properties of the potential drug candidate, to decrease the cost of drug discovery research as ADME, normally contributes to failures of drug molecules of more than 50% (Mandlik et al., 2016).

This study identified a monoterpene, p-Cymene, in the SMM crude and SMEH fractions of *S. mombin* leaf extracts. p-Cymene in literature has been reported to possess anti-viral, anti-oxidant, anti-inflammatory, anti-parasitic, anti-diabetic, anti-fungal, and anti-cancer effects in both *in vivo* and *in vitro* studies of the molecule (Panikar et al., 2021, Balahbib et al., 2021, Sharifi-Rad et al., 2018) In addition, a derivative of p-Cymene known as Thymol with a percentage composition of 0.5% and 0.21% was found in SMM and SMEDCM respectively with reported antimicrobial, anti-inflammatory, anti-oxidant activity (Braga et al., 2006) and anti-viral properties against spike glycoprotein of SARS-CoV-2 (Kulkarni et al., 2020). Furthermore, D-Limonene, another monoterpene, was detected in SMMDCM with a percentage composition of 0.34 %, has been reported to possess anti-SARS-CoV-2 activity *in silico*(Panikar et al., 2021) and antimicrobial properties in vitro (Zahi et al., 2015).

Reported by other authors, L-alpha-Terpineol, a monoterpenoid, is known to exhibit various pharmacological activities such as anti-Covid-19 activity *in silico* (Gul et al., 2020), anticonvulsant, sedative, antinociceptive, and hypotensive effects (Aronsson et al., 2017, Khaleel et al., 2018). We identified L-alpha-Terpineol in both SMMH and SMEH with percentage composition of 0.44% and 1.40%, respectively. The phytochemical L-alpha-Terpineol has been reported to have anti-CoVID-19 properties *in silico* by (Panikar et al., 2021), while its anti-oxidant and disinfectant properties were identified by (Cours, 2020).

In terms of Geraniin (98% w/w), we have reported in our previous*in silico* study to possess anti-Ebola and anti-SARS-CoV-2 properties against EBOV secreted Glycoprotein (sGP) and a possible inhibitor interferes with the functioning of SARS-CoV-2 targets (Boadu et al., 2022, Boadu et al., 2021). During the anti-Ebola study, a pharmacophore model generated showed that three aromatic rings, a hydrophobic ring and several hydrogen donors/acceptors were responsible for ant-Ebola activities, although it violated Lipinski's rule of five (Lipinski, Lipinski et al., 1997).

Table 2 : Summary of identified anti-viral phytochemical compounds from GC-MS analysis of SM crude and fractionated leaf extracts with their reported pharmacological action and computed physicochemical

descriptors as well as predict Absorption, Distribution, Metabolism, and Excretion (ADME), of the identified anti-viral phytochemicals.

No.	*S.mombin* leaf extract(s) & Geraniin to which compound was identified	Name of compound	Molecular weight (g/mol)	Molecular formula	Retention Time (minutes)	Area%	Class of phytochemical	Lipophilicity (LogP)	Water solubility (mg/mL)	human gastrointestinal tract (GIT) absorption	Blood-Brain Barrier (BBB) permeability	Bioavailability score	Hydrogen bond donors/acceptors	Drug likeness (Lipinski)	D
1	SMEH	p-Cymene	134.22	$C_{10}H_{14}$	7.854	1.31	monoterpene	3.99	0.40 mg/mL	Low	Yes	0.55	0	Yes; 1 violation: MLOGP>4.15	No violation: MW<500
2	SMEH	p-Cymene	134.22	$C_{10}H_{14}$	7.854	1.31	monoterpene	3.99	0.40 mg/mL	Low	Yes	0.55	0	Yes; 1 violation: MLOGP>4.15	No violation: MW<500

No.	*S.mombin* leaf extract(s) & Geraniin to which compound was identified	Name of compound	Molecular weight (g/mol)	Molecular formula	Retention Time (minutes)	Area%	Class of phytochemical	Lipophilicity (logP)	Water solubility (mg/mL)	human gastrointestinal tract (GIT) absorption	Blood-Brain Barrier (BBB) permeability	Bioavailability score	Hydrogen bond acceptors	Drug likeness (Lipinski)	D
3	SMEDCM	Thymol	150.22	$C_{10}H_{14}O$	10.595	0.50	monoterpenoid	2.80	0.98 mg/mL	High	Yes	0.55	1	Yes; 0 violation	No vio la- tio M
4	SMMH and SMEH	L-.alpha.-Terpineol	154.25	$C_{10}H_{18}O$	9.337 9.336	0.44 1.40	monoterpenoid	2.58	2.4 mg/mL	High	Yes	0.55	1	Yes; 0 violation	No vio la- tio M

No.	*S.mombin* leaf extract(s) & Geraniin to which compound was identified	Name of compound	Molecular weight (g/mol)	Molecular formula	Retention Time (minutes)	Area%	Class of phytochemical	Lipophilicity (logP)	Water solubility (mg/mL)	human gastrointestinal tract (GIT) absorption	Blood-Brain Barrier (BBB) permeability	Bioavailability score	Hydrogen bond acceptors	Drug likeness (Lipinski)	
5	SMMDCM	D-Limonene	136.23	$C_{10}H_{16}$	7.083	0.34	monoterpene	3.37	negligible	Low	Yes	0.55	0	Yes; 0 violation	No violation MW
6	Geraniin (9.28% w/w)	1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester	278.34	$C_{16}H_{22}O_4$	24.86	18.509	ester	3.62	N/A	High	Yes	0.55	4	Yes; 0 violation	No 2 violation Rot to XL

As shown in **Table 2,** the compound 1,2BAB-2-MPE with anti-viral properties *in vitro* (Gunalan et al., 2014, FUNGI, Govindappa et al., 2014) was identified as part of the Geraniin fragments. The compound 1,2BAB-2-MPE has been reported by GC-MS analysis in leaf extract of *Ocimum americanum L*with antimicrobial properties. Other authors also noted the antimicrobial and anti-viral activities of 1,2BAB-2-MPE. Several anti-viral compounds identified in the crude leaf extracts of SM are; SMDCM – Thymol and SMM- p-Cymene. The fractionated crude leaf extracts contained other anti-viral phytochemicals such as L-.alpha.-Terpineol in SMMH, Limonene in SMMDCM, Thymol and L-.alpha.-Terpineol in SMEH. Thymol, a derivative of Carvacrol, has also been reported to be found in medicinal plants species such as thyme (Kowalczyk et al., 2020); both compounds are reported to inhibit Herpes Simplex Virus Type 1 (Lai et al., 2012, Sharifi-Rad et al., 2017). Thymol and Carvacrol have been said to possess anti-SARS-CoV-2 activities against Mpro both *in silico* and *in vitro* (plaque reduction assay of SARS-CoV-2 viral strain isolated from Egyptian patients) (Seadawy et al., 2020). These anti-viral identified compounds in SM leaf extracts are in line with reports of their anti-viral properties, such as Carvacrol with anti-herpes simplex virus types 1 (HSV-1), anti-SARS-CoV-2, immunomodulatory and anti-inflammatory (Javed et al., 2020). Also, in line with other researchers, it is reported that Carvacrol has anti-HIV, anti-oxidant, anti-bacterial, anti-fungal, anti-cancer, anti-inflammatory, hepatoprotective, spasmolytic and vasorelaxan in both *in vitro* and *in vivo* studies (Suntres et al., 2015, Mediouni et al., 2020). Carvacrol has been reported to have anti-viral activity against herpes simplex virus types 1 (HSV-1), immunomodulatory and anti-inflammatory *in vitro* , SARS-CoV-2 *in silico* study (Suntres et al., 2015, Javed et al., 2020).

The anti-SARS-CoV-2 and anti-oxidants properties have also been reported in the literature for the compound L-.alpha.-Terpineol (Cours, 2020, Panikar et al., 2021). In an *in silico* study, it was observed that p-Cymene impaired SARS-CoV-2 and Influenza A (H1N1) viral replication (Sharifi-Rad et al., 2017), while D-Limonene, although inconclusive, have been reported the same as an anti-SARS-Cov-2 inhibitor in a computer-aided drug design study (Meeran et al., 2020).

3.3 Identifying potential Marburg virus VP35 from anti-viral phytochemical compounds of *Spondias mombin* leaf extracts

Having identified several potential anti-viral compounds from the leaf extracts *Spondias mombin* , we employed molecular modelling techniques, particularly molecular docking, to identify potential MARV VP35 inhibitors from the identified antiviral phytochemical compounds. Molecular docking has been widely used in recent years to identify potential binders to various biological molecules and has also aided in speeding up the design and discovery of novel therapeutic agents at a relatively lower cost (Dar and Mir, 2017, Zoete et al., 2009, Prieto-Martínez et al., 2019).

Therefore, to identify which of the phytochemical compounds in this report would exhibit potency in treating Marburg virus (MARV), molecular docking of each compound into the inhibitor binding domain of MARV VP35 was performed using AutoDock Vina (Trott and Olson, 2010). MARV VP35 is a unique multi-functional protein encoded by all filoviruses. As shown in **Figure 1** , MARV VP35 exhibits a sequence similarity of 42% with Ebola virus (EBOV) VP5 with over 70% sequence similarity in their inhibitor binding domains. VP35 as a crucial protein is implicated in viral pathogenesis, including viral mRNA synthesis and replication of the negative-sense RNA viral genome, whose therapeutic modulation could lead to the discovery of novel anti-filoviral therapeutic agents (Peterson et al., 2006, Martini et al., 1968, Bausch et al., 2003).

In performing the molecular docking, the inhibitor binding domain of MARV VP35 was identified by superimposing the inhibitor bound EBOV VP35 complex (PDB code: 4BIC) with MARV VP35 (PDB code: 4GHA), as shown in**Figure 1** . Using the grid box component of AutoDock Vina, a grid box with centre dimensions; x=13.45, y=33.63, z=31.69 and size dimensions; x=12.67, y=15.97, z=15.19.

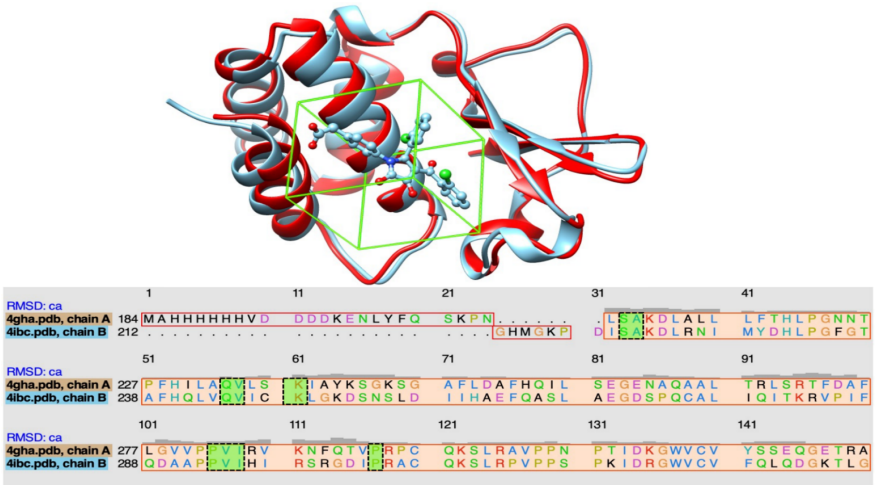


Figure 1 : superimposition of the inhibitor bound EBOV VP35 complex (PDB code: 4BIC) with MARV VP35 (chain A of PDB code: 4GHA). The bound inhibitor is shown in ball and sticks, whereas the binding pocket is demarcated by a grid box highlighted in green. Also shown is a sequence alignment of EBOV VP35 with MARV VP35 with green highlights of conserved interacting residues of both proteins.

Results obtained from molecular docking simulations as presented in**Table 3** provided insights into the possible binding mechanisms of the identified potential MARV VP35 inhibitors based on the interactions

elicited upon binding. The highest negative docking score corresponded with the isolated that exhibited the highest potential binding to MARV VP35. Therefore, as shown in **Table 3** , 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE) with the highest binding affinity of -3.8kcal/mol exhibited the highest binding potential towards MARV VP35 amongst the identified anti-viral phytochemical compounds, whereas D-Limonene showed the least negative binding affinity of -3.1kcal/mol. . As a control, we also performed molecular docking of the known anti-filoviral drug FGI-103 (Warren et al., 2010) in the same active pocket. FGI-103 exhibited a relatively higher negative docking score of -4.1kcal/mol suggesting higher binding affinity than all the identified anti-viral phytochemicals.

Table 3: Tabular representation of docking scores of identified anti-viral phytochemical compounds of *Spondias mombin* against MARV VP35

Anti-viral Compounds	Docking Score (kcal/mol)	Binding residues
FG1-103 (Antifiloviral drug)	-4.1	VAL283, GLN233, PRO282, ILE284
1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE)	-3.8	LYS237, VAL283, ILE284, PRO282, GLN233, LYS211, ALA210, TYR240, LYS241, ALA214, SER236
Geraniin	-3.7	LYS237, VAL283, ILE284, PRO282, GLN50, ALA27, LYS54, GLN233, LYS211, ALA214
P_Cymene	-3.6	GLN50, ALA27, LYS54 GLN233, LYS211, ALA214, SER236
Thymol	-3.5	ILE101, GLN50, ILE47, LYS54, ALA210, TYR240, LYS241
L-alpha-Terpineol	-3.4	GLN50, ALA27, LYS54, PRO282, GLN233
D-Limonene	-3.1	GLN50, ALA27, LYS54, VAL283, ILE284

To establish the mechanism that accounted for the relatively higher potential binding affinity of 1,2BAB-2-MPE, and FGI-103, a molecular visualization of the binding interactions of each compound was determined using the Discovery Studio software (Biovia, 2017). As shown in**Figure 2A,** the potential binding of 1,2BAB-2-MPE is mediated by high-affinity interactions with hydrogen bond interaction with LYS237 and π-alkyl interactions with LYS241, TYR240, and ALA210. In addition to observed van der Waals interactions, these peculiar interactions collectively anchored 1,2BAB-2-MPE to the binding pocket, favoring stability and high-affinity binding.

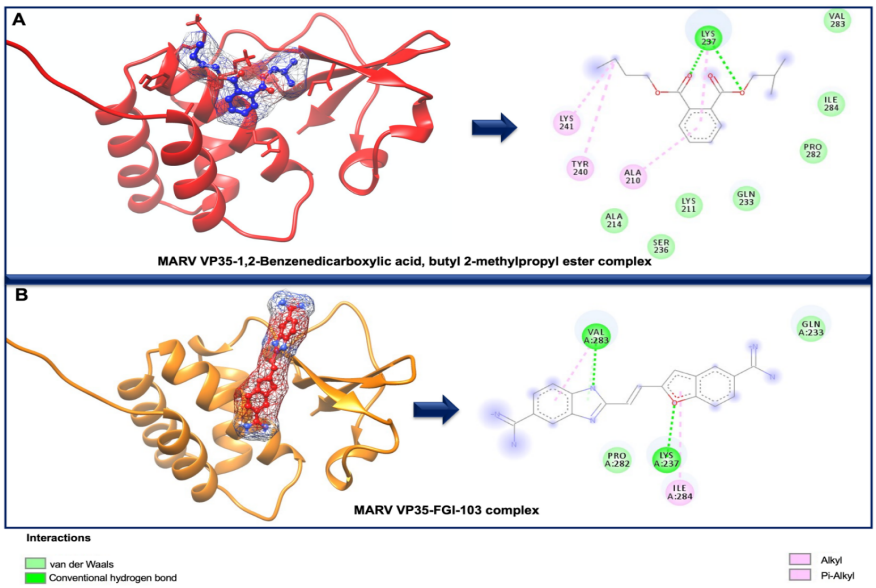


Figure:2 Showing the 3D representation of the complex between MARV VP35 and FGI-103. Also showing is the residue interaction profile that mediates the MARV VP35-FGI-103. **2B)** Showing the 3D representation of the complex between MARV VP35 and 1,2-1,2BAB-2-MPE. Also showing is the residue interaction profile that mediates the MARV VP35-1,2BAB-2-MPE.

The stronger affinity binding of FGI-103 as evidenced by the highest negative docking score of -4.1kcal/mol was mediated by two strong conventional hydrogen bond interactions with VAL283, and LYS237, a π-alkyl interaction with ILE284 in addition to van der Waals interactions with PRO282 and GLN233. As shown in **Figure 2** , the residue LYS237 was observed to engage in conventional hydrogen bond interaction with 1,2BAB-2-MPE and FGI-103, suggesting its cruciality to the therapeutic modulation of MARV VP35 and could therefore guide the future design of novel MARV VP35 inhibitors.

4.0 CONCLUSION:

In conclusion, we reported for the first time, Geranyl benzoate a phytochemical compound identified from leaf extracts of SM. D-Limonene, p-Cymene, Thymol and L-.alpha-Terpineol, were identified as anti-viral compounds from leaf extracts of SM. A phytochemical constituent of Geraniin: 1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester (1,2BAB-2-MPE) has also been reported to have anti-viral activities. The in silico investigation of anti-viral phytochemicals showed that 1,2BAB-2-MPE is a potential anti-filoviral therapeutic candidate against MARV VP35. Further investigations are needed to validate the anti-filoviral therapeutic candidate of 1,2BAB-2-MPE and as a natural supplement or useful for drug formulation in the fight against Marburg viruses.

Nevertheless, more research attempts are craved to isolate, characterize, and assess other phytochemicals from S. mombin Linn leaf extracts to justify their various pharmacological relevance.

5.0 CREDIT AUTHOR STATEMENT

Akwasi Boadu: Conceptualization, Writing- Original draft preparation, Phytochemistry Experimentation (including *in silico* study), Formal analysis and Investigation.

Supervision. and Resources: Rajshekhar Karpoormath and Manimbulu Nlooto

6.0 COMPETING INTERESTS' STATEMENT'

"NON"

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`FIGURES C1-C4, FIGURES 1-2.docx` available at https://authorea.com/users/501738/articles/582065-spondias-mombin-in-silico-screening-of-1-2-benzenedicarboxylic-acid-butyl-2-methylpropyl-ester-fragment-of-geraniin-as-anti-marburg-virus-agent