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Screening of the secondary metabolites of the crude extracts of an antiviral herbal formulation using gc-ms/ms and lc-ms/ms

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Abstract

This study describes the screening of secondary metabolites of the n-hexane, methanol, and ethanol extracts and the ethyl acetate layer of the medicinal herb formulation, coded BHA using GC-MS/MS. The formulation was and is still used in the treatment of COVID-19 and other viral respiratory infectious diseases. Additionally, the methanol extract was also analysed using LC-MS/MS. Given its effectiveness and favourable results for COVID-19 patients, BHA has remained one of the most widely used herbal antiviral formulations. The choice of the herbal formulation was due to its effectiveness against COVID-19 and the fact that its constituents were listed on the container. The screening results revealed the presence of a wide range of natural products with different structural features in the herbal formulation extracts, most of which have been reported to possess significant biological and pharmacological qualities, such as anti-tumor, anti-inflammatory, antibacterial, immunomodulatory, antifibrotic, and vasorelaxation effects. A total of 75 compounds were identified, most of which resulted from the GC-MS/MS analyses, whereas the LC-MS/MS detected only 8 compounds. These included flavonoids, coumarins, alkaloids, fatty acids, terpenoids, and many other phenolic compounds. With exception of few compounds, the results revealed some discrepancies from the chemical composition reported for each individual species. These constituents exhibit antioxidant and anti-fibrotic properties, in respiratory ailments, ability to suppress lung inflammation and fibrosis, regulate blood lipid levels, and improve blood flow. The synergistic effects among the constituents of the herbal formulation may account for its efficacy. The screening results corroborate the usefulness and efficacy of the formulation and provide guidance for the safe application of the herbal antiviral formulation as well as the advancement of antiviral drugs that are successful in treating infectious respiratory diseases. Furthermore, the results confirm that herbal medicines with therapeutic capabilities can be used in the treatment of many disorders, including COVID-19.

Keywords: *Anti-inflammatory; Antiviral; Carvacrol; 6,7-Dimethylesculetin; Protobeberine alkaloid;, Zanthoxylum chalybeum*

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Introduction

In an attempt to contain the virus during the COVID-19, a worldwide pandemic, communities in Tanzania and other developing countries relied primarily on herbal medicines (Anand *et al.,* 2021; Oyebode *et al.,* 2016; WHO, 2009, 2019). The reliance resulted from the fact that conventional medicines were unable to treat the pandemic (Mahomoodally, 2013; Antwi-Baffour, 2014; WHO, 2004), and the fact that medicinal

herbs are generally accessible, reasonably priced, and have the potential to be efficacious, unlike mainstream conventional pharmaceuticals that are often expensive and associated with side effects (Ekor, 2014b; Oyebode *et al.,* 2016; WHO, 2004, 2009, 2019). These facts made plant-based drugs the most viable and promising strategy for combating the COVID-19 pandemic.

In efforts to find viable options for the fight against the virus, multiple plant-based extracts and isolated compounds have been tested as part of scientific investigations into possible COVID-19 treatments. Research has verified the protective effect of herbal medicines against respiratory viruses when used as crude extracts or as pure active components (Anand *et al.,* 2021; Khadka *et al.,* 2021; Khan *et al.,* 2021; Mani *et al.,* 2020; Sharanya *et al.,* 2021).

The search for efficacious alternative treatments for the pandemic and other respiratory infectious viral diseases was necessary due to the inability of the existing conventional medications to treat or prevent the illness. Consequently, hundreds of herbs and plant metabolites have been identified, screened, and tested for their antiviral potentials; most of which have demonstrated significant pharmacological utility in preclinical and clinical trials for the treatment or prevention of various viral infections. It has been demonstrated that several plants and isolated compounds with antiviral and immune-boosting properties can affect SARS-CoV-2, the virus that causes COVID-19 (Aini *et al.,* 2022; Ali *et al.,* 2021; Anand *et al.,* 2021; Colunga Biancatelli *et al.,* 2020; Conti *et al.,* 2020; Farmanpour-Kalalagh *et al.,* 2022; Gasmi *et al.,* 2022; Kaul *et al.,* 2021; Lima *et al.,* 2021; Pandey *et al.,* 2021). For instance, in 2020, the island nation of Madagascar announced the discovery of a tea that used traditional Malagasy botanicals, such as *Artemisia*, to treat COVID-19. This tea and pill combination was dubbed COVID-Organics, or CVO (Razanamparany, 2020).

Notwithstanding the vast increase in demand and uses of herbal medicines and the fact that herbal remedies are providing a ray of hope for human health, caution must be taken to avoid harmful side effects emanating from the use of the medicinal herbs due to the fact that some of them may be toxic to humans (Boukandou Mounanga *et al.,* 2015; Dhama *et al.,* 2018; Fatima and Nayeem, 2016; Mensah *et al.,* 2019; Nasri and Shirzad, 2013; Subramanian *et al.,* 2018). This calls for evaluation not of the effectiveness of the therapeutic herbs but also their toxicity. As a result, hundreds of herbs and plant metabolites have been found, examined, and tested for their antiviral properties. Several of these have demonstrated notable therapeutic benefits in the treatment or prevention of different viral infectious illnesses (Dhama *et al.,* 2018).

In addition to being used against SARS-CoV, plants such as *Artemisia annua*, *Isatis indigotica*, *Lindera aggregata*, *Pelargonium sidoides*, *Glychirrhiza* spp., *Sambucus nigra*, *Caesalpinia pulcherrima*, and *Hypericum connatum*, have also been shown to have potent antiviral and immune-boosting properties against different viruses, including zika, ebola, nipah virus, and other highly pathogenic viruses (Akram *et al.,* 2018; Anand *et al.,* 2021; Khan *et al.,* 2021; Li *et al.,* 2005; Mani *et al.,* 2020; Sharanya *et al.,* 2021; Vilhelmova-Ilieva *et al.,* 2020; Wahyuni *et al.,* 2019).

Therefore, along with other drugs currently being tested against COVID-19, plant-based drugs need to be included for speedy development of COVID-19 and other viral infectious diseases treatment (Akram *et al.,* 2018; Anand *et al.,* 2021; Khan *et al.,* 2021; Sharanya *et al.,* 2021; Vilhelmova-Ilieva *et al.,* 2020).

Various studies have reported species like *Nigella sativa*, *Vernonia amygdalina*, *Azadirachta indica*, *Eurycoma longifolia*, *Ocimum sanctum, Withania somnifera, Tinospora cordifolia, Curcuma longa, Zingiber officinalis, Piper nigrum, Nigella sativa, Allium sativum, Hibiscus sabdariffa, Phyllanthus amarus, Alpinia officinarium, Chrysanthemum morifolium, Gardenia sp. Cinnamomum cassia, Vitex trifolia, Avicenna marina* and *Punica granatum,* to have strong antiviral properties against a variety of viruses, including the SARS-CoV-2 virus. Hence, they may be useful as COVID-19 treatment candidates (Akram *et al.,* 2018; Anand *et al.,* 2021; Patel *et al.,* 2021; Saleem *et al.,* 2018; Yashvardhini *et al.,* 2021).

Following the outbreak of COVID-19, several Tanzanian alternative medicine practitioners developed herbal medicine formulations or mixtures that they claimed were able to cure and

overall management of COVID-19 patients. One of the formulations among many, which gave positive results in the treatment and management of COVID-19 patients was BHA, which is made up of five plant species and one type of fungus. The fungus species is *Ganoderma tsugae* Murrill, whereas the plant species include *Adansonia digitata L.*, *Ficus sur* Forssk, *Securidaca longipendiculata* Fresen, *Syzygium cumin* (L.) Skeels, and *Zanthoxylum chalybeum* Engl. This formulation was selected from a variety of other options based on two factors: firstly, it turned out to be among the best performing herbal formulations for the treatment and management of COVID-19 patients. Secondly, the ingredients of the combination were also clearly indicated on the container, information that allowed for more research on each individual species whereas the constituent species of the other formulations were not revealed. A thorough review covering the biological activities, ethnomedicinal applications, and secondary metabolites composition of each individual species in the formation showed the presence of a wide range of compounds belonging to various classes of secondary metabolites with significant biological activities were present (Makangara *et al.,* 2024).

Although Tanzania like many other African countries enormously used the traditional medicines from plants sources, most of the formulations had no known phytochemical ingredients responsible for the claims. This study aimed at bridging the gap between the properties reported in literature for each individual components and those in the formulation by carrying out the screening of the secondary metabolites of three extracts and ethyl acetate layer of the medicinal herbal formulation using GC-MS/MS. In addition, LC-MS/MS analysis of the methanol extract for the formulation's non-volatile ingredients was done. Furthermore, to correlate the chemical composition identified and their corresponding biological or pharmacological properties available in the literature.

Materials and Methods

Sample collection

The light brownish powder sample of the herbal concoction was purchased in Dar es Salaam at the TANHELSO outlet store, located in SIDO House on Bibi Titi Road. The extraction was done at the Department of Chemistry laboratories, University of Dodoma whereas GC-MS/MS and LC-MS/MS analyses were done at the Government Chemist Laboratory Authority (GCLA) laboratories in Dar es Salaam.

Sample preparation

10 g of the dried and pulverized herbal formulation was sequentially soaked in 100 ml of *n*-hexane and methanol for 1 day each, filtered and dried under reduced pressure using a rotary evaporator. The extraction process yielded 0.78 g of yellowish brown and 2.52 g of light brownish oily crude extracts of hexane and methanol, respectively. The obtained 0.78 g of the hexane and 1 g of the methanol crude extracts were reconstituted in 1 ml of dichloromethane and 1 ml methanol, respectively. Furthermore, another 20 g of the sample was soaked in a mixture of ethanol/water (7:3) for 24 hours, filtered and solvent evaporated using rotary evaporator, yielding a total of 8.16 g of a dark brownish oil. The resulting ethanol crude extract was washed with ethyl acetate give 2.45 g of the ethyl acetate layer. 1 g of each of the ethyl acetate layer and ethanol extract were reconstituted in 1 ml of dichloromethane and 1 ml methanol, respectively. 1 µL of each of the reconstituted solutions was drawn and injected in the GC-MS/MS. Identification of the secondary metabolites was done by comparing the spectral data to Mass-hunter and NIST reference databases. Furthermore, 1 µL of the methanol extract was drawn and injected in the LC-MS/MS. The interpretation was done by comparing the spectral data to Mass-hunter and NIST reference databases.

GC-MS/MS Analysis

An Agilent GC-MS Triple Quadrupole 7000D series with electron impact ionization was used for the chemical screening of the four crude extracts. Gas chromatography DB-17MS capillary column of length 30 m x 0.25 mm thickness and helium (purity of 99.999%) as a carrier gas were used for the analysis of samples. 1 µL of each

sample was injected in the GC at a constant flow rate of 1 mL/min. The temperature for ion source was 230 ˚C, while 280 ˚C temperature was for injector. The oven initial temperature was set at 65 ˚C, after 2 min the oven temperature raised to 290 ˚C at the rate of 15 ˚C/min. The temperature was maintained at 290 ˚C for 30 min, before cooling back to 65 ˚C at the rate of 15 ˚C/min. The ionization energy was 70 eV at positive electron ionization. Scan range was from m/z 50-500 range.

LC-MS/MS Analysis

A Thermo Scientific Dionex UltiMate 3000 liquid chromatography pump with OAS autosampler coupled with a Thermo Scientific Q Exactive Orbitrap mass spectrometer with a Thermo Scientific Ion Max source and a heated electrospray (HESI-II) source was used for the analysis and detection of the secondary metabolites. The mobile phases A and B were composed of acetonitrile and 1% formic acid in water, respectively. The column used was a Thermo Scientific Accucore RP-MS, 100 mm x 4.6 mm x (SN: 10508423, LOT: 14358) x 2.6 µm. To increase precursor selection and ion transmission, a single precursor ion was selected in the quadrupole as a mass filter with an isolation width of 2.0 m/z and fragmented in the HCD cell using optimized compound-specific collision energy. The resulting MS/MS product ion spectrum was identified with a resolution of 35,000 (FWHM at 200 m/z) in the Orbitrap detector. The data was processed using Thermo Scientific TraceFinder software. Spectral matching of the spectral data from the MS/MS spectrum with those in the MassHunter and NIST databases were used to identify the secondary metabolites.

Results

This study presents the results of the GC-MS/MS analysis of the therapeutic herbal formula's hexane, ethyl acetate, methanol, and ethanol crude extracts. Additionally, LC-MS/MS analytical data for the methanol extract are also given. Furthermore, the study also reports on the biological activities of some of the identified secondary metabolites. The data from the LC-MS/MS analysis of the methanol extract is as presented in Table 2, while Table 1 displays secondary metabolites found from the GC-MS/MS studies of the medicinal herbal formulation extracts. Each of the identified secondary metabolites is listed in full in the tables along with its chemical formula, name, and measured ion mass-to-charge ratio. Additionally, each of the discovered secondary metabolites has a number, which is displayed in Tables 1 and 2.

Table 1

GC-MS/MS results of the secondary metabolites identified in the extracts of the medicinal herb formulation samples

m/z Ion	Molecular formula	Name	Structure number	Class of compound
126.1	$C_8H_{14}O$	(*E*)-2-Octenal	**1**	Aliphatic aldehyde
144.12	$C_8H_{16}O_2$	Octanoic acid	**2**	Aliphatic carboxylic acid
126.1	$C_8H_{14}O$	Tridecanal	**3**	Aliphatic aldehyde
154.14	$C_{10}H_{18}O$	(*E*)-2-Decenal	**4**	Aliphatic aldehyde
152.12	$C_{10}H_{16}O$	(*E*,*E*)- 2,4-Decadienal	**5**	Aliphatic aldehyde
238.19	$C_{15}H_{26}O_2$	Methyl 3,4-tetradecadienoate	**6**	Aliphatic ester
152.12	$C_{10}H_{16}O$	(*E*,*Z*)- 2,4-Decadienal	**7**	Aliphatic carboxylic acid
282.26	$C_{18}H_{34}O_2$	Oleic acid	**8**	Aliphatic carboxylic acid

m/z Ion	Molecular formula	Name	Structure number	Class of compound
158.13	$C_9H_{18}O_2$	Nonanoic acid	**9**	Aliphatic carboxylic acid
256.24	$C_{16}H_{32}O_2$	*n*-Hexadecanoic acid	**10**	Aliphatic carboxylic acid
280.24	$C_{18}H_{32}O_2$	(9*Z*,12*Z*)-Octadeca-9,12-dienoic acid	**11**	Aliphatic carboxylic acid
298.25	$C_{18}H_{34}O_3$	Ricinoleic acid	**12**	Aliphatic carboxylic acid
284.27	$C_{18}H_{36}O_2$	Octadecanoic acid	**13**	Aliphatic carboxylic acid
198.2	$C_{13}H_{26}O$	2-Tridecanone	**14**	Aliphatic ketone
280.24	$C_{18}H_{32}O_2$	13-Hexyloxacyclotridec-10-en-2-one	**15**	Cyclic carboxylic ester
256.17	$C_{14}H_{24}O_4$	2,2-Dimethyl-6-methylene-1-[3,5-dihydroxy-1-pentenyl]cyclohexan-1-perhydrol	**16**	Aliphatic hydroxy peroxy compound
138.1	$C_9H_{14}O$	Furan, 2-pentyl-	**17**	Furan
98.04	$C_5H_6O_2$	3-Furanmethanol	**18**	Furan alcohol
110.04	$C_6H_6O_2$	5-Methyl furfural	**19**	Furan aldehyde
126.03	$C_6H_6O_3$	5-Hydroxymethylfurfural	**20**	Furan aldehyde
208.15	$C_{13}H_{20}O_2$	3-Hydroxy-3a,6-dimethyl-1,2,3,4,5,5a,6,8-octahydrocyclopenta[h]pentalen-7-one	**21**	Aliphatic ketone
234.16	$C_{15}H_{22}O_2$	Spiro[furan-3(2H),2'-indan]-2-one, 3'a,4,4',5,5',6',7',7'a.beta.-octahydro-3'a.beta.,4'.beta.-dimethyl-4-methylene-, (2'*R*)-	**22**	Sesquiterpene ester
220.18	$C_{15}H_{24}O$	(1*R*,3*E*,7*E*,11*R*)-1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene	**23**	Sesquiterpene epoxide
220.18	$C_{15}H_{24}O$	Humulenol-II	**24**	Oxygenated sesquiterpene
154.14	$C_{10}H_{18}O$	α–Terpineol	**25**	Monoterpenoid alcohol
222.2	$C_{15}H_{26}O$	Drim-7-en-11-ol	**26**	Oxygenated sesquiterpene
220.18	$C_{15}H_{24}O$	2-((2*R*,4aR,8aS)-4a-Methyl-8-methylenedecahydronaphthalen-2-yl)prop-2-en-1-ol	**26**	Oxygenated sesquiterpene

m/z Ion	Molecular formula	Name	Structure number	Class of compound
248.14	$C_{15}H_{20}O_3$	Benzo[e]isobenzofuran-1,4-dione,1,3,4,5,5a,6,7,8,9,9a-decahydro-6,6,9a-trimethyl	**27**	Oxygenated sesquiterpene
220.18	$C_{15}H_{24}O$	Caryophyllene oxide	**28**	Oxygenated sesquiterpene
220.18	$C_{15}H_{24}O$	1,4-Methanoazulen-9-one, decahydro-1,5,5,8a-tetramethyl-, [1*R*-(1.alpha.,3a.beta.,4.alpha.,8 a.beta.)]-	**29**	Oxygenated sesquiterpene
220.18	$C_{15}H_{24}O$	Longifolen aldehyde	**30**	Oxygenated sesquiterpene
220.18	$C_{15}H_{24}O$	Isolongifolene, 9-hydroxy-	**31**	Oxygenated sesquiterpene
220.2	$C_{15}H_{26}O$	Isolongifolol	**32**	Oxygenated sesquiterpene
204.19	$C_{15}H_{24}$	Isocaryophyllene	**33**	Sesquiterpene
238.19	$C_{15}H_{26}O_2$	(3*S*,3a*S*,6*R*,7*R*,9a*S*)-1,1,7-Trimethyldecahydro-3a,7-methanocyclopenta[8]annulene-3,6-diol	**34**	Oxygenated sesquiterpene
222.2	$C_{15}H_{26}O$	Drim-7-en-11-ol	**35**	Oxygenated sesquiterpene
150.1	$C_{10}H_{14}O$	*p*-Cymen-7-ol	**36**	Aromatic terpenoid
150.1	$C_{10}H_{14}O$	Carvacrol	**37**	Aromatic terpenoid
144.04	$C_6H_8O_4$	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	**38**	Pyran derivative
216.15	$C_{15}H_{20}O$	aR-Turmerone	**39**	Phenylpropanoid derivative
164.08	$C_{10}H_{12}O_2$	Eugenol	**40**	Phenylpropanoid
178.06	$C_{10}H_{10}O_3$	Coniferyl aldehyde	**41**	Phenylpropanoid aldehyde
180.08	$C_{10}H_{12}O_3$	(*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol	**42**	Phenylpropanoid
184.07	$C_9H_{12}O_4$	Phenol, 3,4,5-trimethoxy-	**43**	Phenolic compound
132.06	C_9H_8O	Cinnamaldehyde, (*E*)-	**44**	Phenylpropanoid
180.08	$C_{10}H_{12}O_3$	2-Propanone, 1-(4-hydroxy-3-methoxyphenyl)	**45**	Phenylpropanoid ketone
164.08	$C_{10}H_{12}O_2$	Phenol, 2-methoxy-4-(1-propenyl)-	**46**	Phenylpropanoid

m/z Ion	Molecular formula	Name	Structure number	Class of compound
150.07	$C_9H_{10}O_2$	2-Methoxy-4-vinyl-phenol	**47**	Phenolic compound
148.05	$C_9H_8O_2$	2-Propenoic acid, 3-phenyl-	**48**	Phenylpropanoid
122.04	$C_7H_6O_2$	Benzoic acid	**49**	Aromatic carboxylic acid
152.05	$C_8H_8O_3$	Vanillin	**50**	Phenolic compound
168.04	$C_8H_8O_4$	Vanillic acid	**51**	Aromatic carboxylic acid
276.17	$C_{17}H_{24}O_3$	(*E*)-1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one (6-Shogaol)	**52**	Phenylpropanoid derivative
210.09	$C_{11}H_{14}O_4$	*trans*-Sinapyl alcohol	**53**	Phenylpropanoid alcohol
180.8	$C_{10}H_{12}O_3$	Phenol, 4-ethenyl-2,6-dimethoxy-	**54**	Phenolic compound
108.06	C_7H_8O	Benzyl alcohol	**55**	Aromatic alcohol
154.14	$C_{10}H_{18}O$	Chavicol	**56**	Phenylpropanoid
194.09	$C_{11}H_{14}O_3$	2-Butanone, 4-(4-hydroxy-3-methoxyphenyl)- (Zingerone)	**57**	Phenylpropanoid
178.1	$C_{11}H_{14}O_2$	Methyleugenol	**58**	Phenylpropanoid
132.06	C_9H_8O	3-Phenyl-2-propyn-1-ol	**59**	Phenylpropanoid
156.03	C_8H_9ClO	Chloroxylenol	**60**	Phenolic compound
346.19	$C_{24}H_{26}O_2$	(+)-Sesamin	**61**	Lignan
316.13	$C_{22}H_{20}S$	Benzene, 1,1'-[2-methyl-2-(phenylthio)cyclopropylidene]bis-	**62**	Phenolic compound containing sulfur
332.12	$C_{22}H_{20}OS$	(2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide, trans-	**63**	Phenolic compound containing sulfur
268.07	$C_{16}H_{12}O_4$	5-Hydroxy-7-methoxyflavone (Techtochrysin)	**64**	Flavonoid
270.09	$C_{16}H_{14}O_4$	(*S*)- 4H-1-Benzopyran-4-one, 2,3-dihydro-5-hydroxy-7-methoxy-2-phenyl (Pinostrobin)	**65**	Flavonoid
178.06	$C_{10}H_{10}O_3$	(-)-Mellein	**69**	Coumarin
199.06	$C_{12}H_9NO_2$	Dictamnine	**71**	Alkaloid
259.08	$C_{14}H_{13}NO_4$	Furo[2,3-b]quinoline, 4,7,8-trimethoxy- (Skimmianine)	**72**	Furoquinoline alkaloid

Table 2

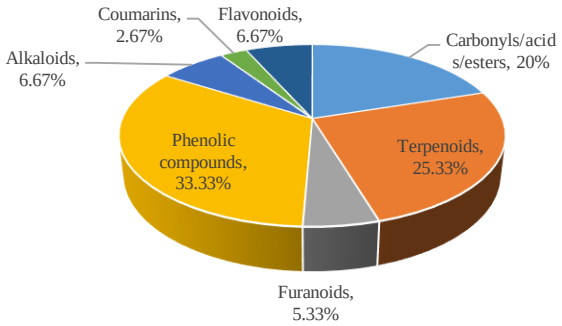
LC-MS/MS analysis results of the methanol extract

m/z Ion	Molecular Formula	Compound Name	Structure number	Class of compound
302.08	$C_{16}H_{14}O_6$	Homoeriodictyol	**66**	Flavonoid
330.07	$C_{17}H_{14}O_7$	3,4′-Dimethoxy-5,7,3′-trihydroxyflavone	**67**	Flavonoid
372.12	$C_{20}H_{20}O_7$	5,6,7,3′4′-Pentamethoxyflavone (Sinensetin)	**68**	Flavonoid
206.06	$C_{11}H_{10}O_4$	6,7-Dimethylesculatin (Scoparone)	**70**	Coumarin
348.12	$C_{21}H_{18}NO_4$	Chelerythrine cation	**73**	Benzophenanthridine alkaloid
352.15	$C_{21}H_{22}NO_4$	Palmatine cation	**74**	Benzophenanthridine alkaloid
338.14	$C_{20}H_{20}NO_4$	Jatrorrhizine cation	**75**	Benzophenanthridine alkaloid

The examinations of the herbal formulation's extracts yielded a total of 75 secondary metabolites, most of which were obtained from the GC-MS/MS analyses. Nine of the secondary metabolites were found by LC-MS/MS analysis; the rest were found by GC-MS/MS analysis. Alkaloids, terpenoids, coumarins, aliphatic and aromatic carboxylic acids, phenylpropanoids, furan derivatives, and other phenolic compounds were the main types of chemicals that were found (Table 1 and 2). The distribution of the secondary metabolites identified is as presented in Figure 1 below.

Figure 1

Percentage composition of the secondary metabolites in the BHA herbal formula extracts



Further analysis of the results revealed that only few identified secondary metabolites in the medicinal herb formulation matched with those reported in literature for the individual species (Makangara *et al.,* 2024). Compounds **61**, **70**, and **73-75** were previously reported from *Zanthoxylum* species whereas none of the detected flavonoids in formulation matched with those reported in literature. *n*-Hexadecanoic acid (**10**), α-terpineol (**25**) and caryophyllene oxide (**28**), were also reported in literature, whereas the rest of the compounds are not reported to occur in the species, however, they have reported to occur in other species.

Table 3 presents the biological activities that have been reported for the identified compounds, including anti-inflammatory, antiviral, antitumor, anticancer, immunomodulatory, antioxidant, vasorelaxant, cardiotonic, antihypertensive, regulation of blood lipids and many other activities.

Table 3

Biological activities reported for the observed secondary metabolites

Compound	Biological activities	References
(*E*)-2-Octenal (**1**)	Antifungal agent	(Luo *et al.,* 2023)
Octanoic acid (**2**)	Epilepsy, kidney failure, digestive disorders, antioxidant, prevention of cognitive decline	(Augustin *et al.,* 2018; Bonetti *et al.,* 2017; Mungali *et al.,* 2020)
(*E*)-2-Decenal (**4**)	Nematicide, alarm pheromone, mutagenic	(Kim *et al.,* 2008; Wu and Yen, 2004)
Oleic acid (**8**)	Antinematodal activity	(Habtemariam, 2019; Zhou *et al.,* 2012)
n-Hexadecanoic acid (**10**)	Anti-Inflammatory, and anti-oxidant activities	(Aparna *et al.,* 2012; Malarvizhi *et al.,* 2015)
2-Pentylfuran (**17**)	Anti-inflammatory, antimicrobial, insect repellent, a flavouring agent, a plant growth stimulator and a bacterial metabolite	(Alizadeh *et al.,* 2020; Cha *et al.,* 2021)
a-Terpineol (**25**)	Antioxidant, antimicrobial, anticancer, anticonvulsant, antiulcer, antihypertensive, anti-nociceptive, anticholesteremic, reliever in neuropathic pain, antidiarrheal, analgesic, and insecticidal activities	(Musterman *et al.,* 2018; Saeed *et al.,* 2023; Sales *et al.,* 2020)
Caryophyllene oxide (**28**)	Analgesic, anti-inflammatory and anticancer activities	(Chavan *et al.,* 2010; Fidyt *et al.,* 2016; Legault and Pichette, 2010)
Longifolen aldehyde (**30**)	Antifungal activity	(Mukai *et al.,* 2018)

Compound	Biological activities	References
Isolongifolene, 9-hydroxy- (**31**)	Antioxidant activity	(Rangasamy and Namasivaya, 2013)
Isocaryophyllene (**33**)	Anti-inflammatory, antibiotic, antioxidant, anticarcinogenic and local anaesthetic activities	(Chavan *et al.,* 2010; Fidyt *et al.,* 2016; Legault and Pichette, 2010)
p-Cymen-7-ol (**36**)	Antifungal, antibacterial, antioxidant, analgesic, antinociceptive, immunomodulatory, vasorelaxant and neuroprotective activities	(Balahbib *et al.,* 2021; Mohammed *et al.,* 2024)
Carvacrol (**37**)	Anti-inflammatory, antibacterial, antioxidant, anticancer, antioxidant potential in respiratory disorders, antifungal, vasorelaxant, and hepatoprotective	(Abbasloo *et al.,* 2023; Cicalău *et al.,* 2021; Imran *et al.,* 2022; Mączka *et al.,* 2023; Magi *et al.,* 2015; Mondal *et al.,* 2021; Morais *et al.,* 2023; Sharifi-Rad *et al.,* 2018)
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- (**38**)	Antimutagenic, antimicrobial, anti-inflammatory, and antioxidant activities	(Rizvi *et al.,* 2023) (Chen *et al.,* 2021; Rizvi *et al.,* 2023; Yu *et al.,* 2013)
aR-Turmerone (**39**)	Anti-inflammatory, anti-oxidant, anticancer and regulates blood sugar levels, treatment of neurodegenerative disorders	(Makaremi *et al.,* 2021; Obulesu, 2021a, 2021c; Razavi and Hosseinzadeh, 2020)
Eugenol (**40**)	Antidiabetic, antimicrobial, anticancer, antioxidant, anti-inflammatory, analgesic, and insecticidal activities	(Habtemariam, 2019; Mbaveng and Kuete, 2017; Nisar *et al.,* 2021; Sharma *et al.,* 2021; Sharma *et al.,* 2020; Tripathi and Mishra, 2016)
Coniferyl aldehyde (**41**)	Antifungal, anti-inflammatory activity	(Wang *et al.,* 2020)
Trimethoxyphenol (**43**)	Antioxidant activity	(Matos *et al.,* 2008)
(*E*)-1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one (6-Shogaol) (**52**)	Anticancer, anti-oxidant, antimicrobial, anti-inflammatory, immunomodulatory, anti-arthritis, antidiabetic, antifungal, and anticancer and anti-allergic to various central nervous system activities	(Arcusa *et al.,* 2022; Bischoff-Kont *et al.,* 2022; Bischoff-Kont and Fürst, 2021; Dasgupta, 2019; Inserra and Brooks, 2017; Mbaveng and Kuete, 2017; Rajini, 2023; Semwal

Compound	Biological activities	References
		et al., 2015; Sheikh *et al.,* 2023; Tao *et al.,* 2023)
Phenol, 4-ethenyl-2,6-dimethoxy- (**54**)	Antioxidative and antimutagenic activities	(Kraljić *et al.,* 2015; Kuwahara *et al.,* 2004; Wang *et al.,* 2014)
4-(4-Hydroxy-3-methoxyphenyl)-2-butanone (Zingerone) (**57**)	Anti-inflammatory, antitumor, antipyretic, gastroprotective, cardiotonic, and antioxidant activities	(Ahmad *et al.,* 2015; Baptista *et al.,* 2022; Daniels *et al.,* 2022; Ekor, 2014a; Srinivasan, 2017)
Methyleugenol (**58**)	Immunostimulatory activity	(Nair *et al.,* 2018; Tan and Nishida, 2012; Tripathi and Mishra, 2016)
(+)-Sesamin (**61**)	Improve blood pressure and blood lipids, prevention of cardiovascular diseases; anti-inflammatory, anti-hypertensive activities	(Correia Alves *et al.,* 2023; Dalibalta *et al.,* 2020; Hadipour *et al.,* 2023; Huang *et al.,* 2023; Majdalawieh *et al.,* 2022; Michailidis *et al.,* 2019; Sharma *et al.,* 2023; Sun *et al.,* 2022)
trans- (2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide (**63**)	Antidiabetic activity	(Deepa *et al.,* 2019)
5-Hydroxy-7-methoxyflavone (Techtochrysin) (**64**)	Antidiabetic, and antioxidant, induce skeletal muscle hypertrophy	(Hasan *et al.,* 2017; Ono *et al.,* 2019; Sarian *et al.,* 2017; Wieczorek *et al.,* 2022)
(*S*)-4H-1-Benzopyran-4-one, 2,3-dihydro-5-hydroxy-7-methoxy-2-phenyl (Pinostrobin) (**65**)	Anti-inflammatory, antioxidant, analgesic, antibacterial, and antitumor activities.	(González *et al.,* 2022; Kaur *et al.,* 2009; Mawa *et al.,* 2019; Raffa *et al.,* 2017; Sun *et al.,* 2020; Wieczorek *et al.,* 2022; Wu *et al.,* 2023; Zhao *et al.,* 2023)
Click or tap here to enter text. Homoeriodictyol (**66**)	Improve memory impairment, antimalarial, antioxidant, anti-inflammatory, antimicrobial, and anticancer properties	(Al-Bzour *et al.,* 2024; Dunstan *et al.,* 2020; Guo *et al.,* 2022; Kuwahara *et al.,* 2004; Melo *et al.,* 2023; Saquib *et al.,* 2020)
5,6,7,3′4′-Pentamethoxyflavone (Sinensetin) (**68**)	Inhibition of □-glucosidase, anticancer, anti-inflammatory, antioxidant, antimicrobial, anti-obesity, anti-dementia and vasorelaxant activities	(Boniface and Ferreira, 2020; Han Jie *et al.,* 2021; Ono *et al.,* 2019; Sung *et al.,* 2012; Yuan *et al.,* 2024; Zhu *et al.,* 2024)

Compound	Biological activities	References
(-)-Mellein (**69**)	Phytotoxic and antifungal, anti-inflammatory and antibacterial activities	(Li *et al.,* 2021; Reveglia *et al.,* 2020; Turker and Gurel, 2005)
6,7-Dimethylesuletin (Scoparone) (**70**)	Anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic and hypolipidemic activities. Treatment of hepatic dysfunction, cholestasis and jaundice	(Cai *et al.,* 2020; Ding *et al.,* 2021; Hui *et al.,* 2020; Kowalczyk *et al.,* 2022; Wang, 2021; Wirasisya and Hohmann, 2023)
Dictamnine (**71**)	Anti-inflammatory and insecticidal activities	(Epifano *et al.,* 2015; Lu *et al.,* 2020; Lv *et al.,* 2015; Sharma *et al.,* 2023; Yao *et al.,* 2020)
Furo[2,3-b]quinoline, 4,7,8-trimethoxy- (Skimmianine) (**72**)	Anticholinesterase, antiviral, antibacterial, antifungal, anti-inflammatory, antioxidant, analgesic, anticonvulsant, cardiotonic and anthelmintic activities	(Bao *et al.,* 2023; Epifano *et al.,* 2015; Mutinda *et al.,* 2023; Ombito *et al.,* 2021; Powder-George, 2023; Son, 2022; Yang *et al.,* 2012; Yao *et al.,* 2020)
Chelerythrine (**73**)	Anti-inflammatory, antiviral and activities, suppressing pulmonary inflammation and fibrosis, prevention of cerebral vasospasm and eryptosis reduction	(Akaberi *et al.,* 2021; Chen *et al.,* 2022; Croley *et al.,* 2023; He *et al.,* 2018; Kang *et al.,* 2022; Liu *et al.,* 2023; Valipour *et al.,* 2021)
Palmatine (**74**)	Anti-cancer, anti-oxidation, anti-inflammatory, neuroprotection, anti-bacterial, anti-viral and regulating blood lipids, antiseizure activity	(Bertoncello and Bonan, 2021; Grabarska *et al.,* 2021; Long *et al.,* 2019; Song *et al.,* 2018; Tarabasz and Kukula-Koch, 2020; Wu *et al.,* 2016; Yan *et al.,* 2017; Zhang *et al.,* 2012)
Jatrorrhizine (**75**)	Anti-inflammatory, antibacterial, antitumor, improvement of blood flow and mitotic activity	(Deng and Wan, 2021; Fu *et al.,* 2023; Long *et al.,* 2019; Rolle *et al.,* 2021; Tarabasz and Kukula-Koch, 2020; Zhong *et al.,* 2022; Zhou *et al.,* 2022)

Discussion

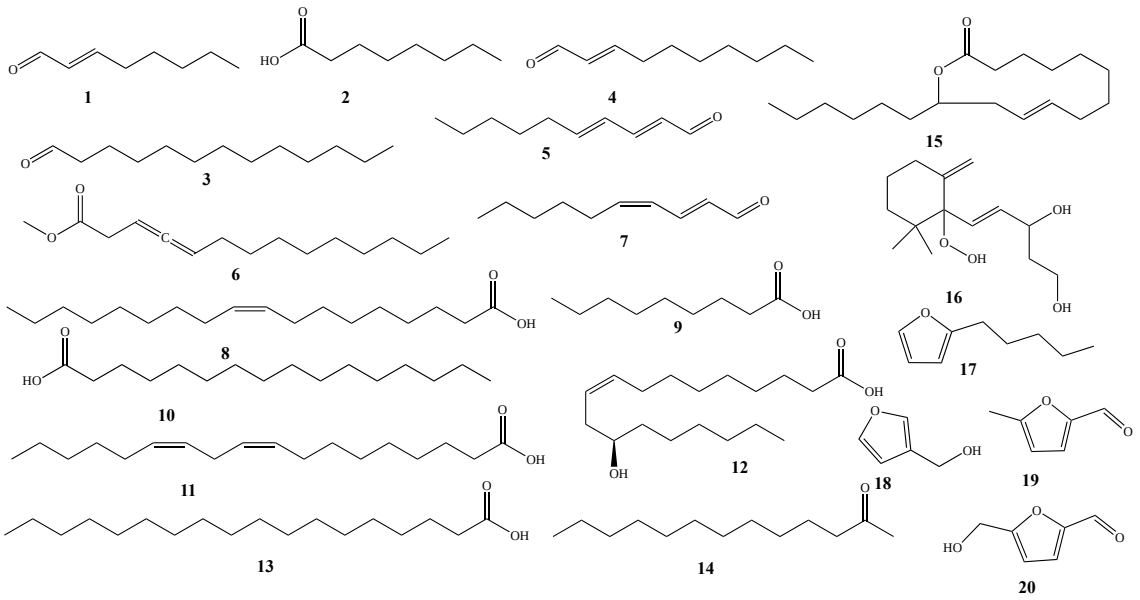
Among the compounds identified by the GC-MS/MS data was a series of aliphatic aldehydes, ketone, carboxylic acids and carboxylic acids esters **1-15** (Table 1; Fig. 2). *n*-Hexadecanoic acid (**10**), one of the carboxylic acids, is reported to have antioxidant and anti-inflammatory properties (Aparna *et al.,* 2012; Malarvizhi *et al.,* 2015). Generally, compounds in this group have been shown to possess antinematodal action, primarily for the fatty acids linoleic and, oleic (Habtemariam, 2019; Zhou *et al.,* 2012).

Terpenoids, primarily monoterpenes and sesquiterpenes, (**21-38**) (Table 1; Fig. 3) were another class that significantly contributed to the secondary metabolites of BHA. The biological

properties reported for the terpenoids include analgesic, anti-inflammatory, antimicrobial, antioxidant, anticarcinogenic, anticonvulsant, antiulcer, antihypertensive, anti-nociceptive, anticholesteremic, relief of neuropathic pain, antidiarrheal, analgesic, and insecticidal effects (Table 3) (Musterman *et al.,* 2018; Saeed *et al.,* 2023; Sales *et al.,* 2020). Among the terpenoids discovered are two aromatic monoterpenes, *p*-cymen-7-ol (**36**) and carvacrol (**37**). Compounds **36** and **37** have antifungal, antibacterial, antioxidant, analgesic, antinociceptive, immunomodulatory, vasorelaxant, and neuroprotective activities. Compound **37** additionally shows antioxidant potential in respiratory illnesses and hepatoprotective properties (Balahbib *et al.,* 2021; de Carvalho *et al.,* 2020; Imran *et al.,* 2022; Mączka *et al.,* 2023; Magi *et al.,* 2015; Mohammed *et al.,* 2024; Mondal *et al.,* 2021; Musterman *et al.,* 2018; Sharifi-Rad *et al.,* 2018; Singh *et al.,* 2021).

Figure 2

Aliphatic carboxylic acids, carbonyl compound and furan derivatives

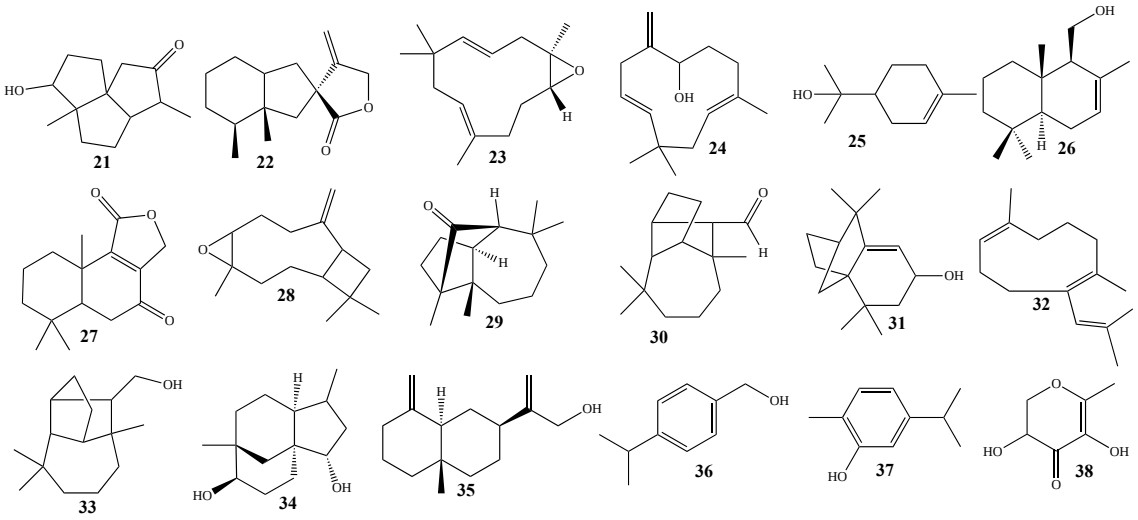


Phenylpropanoids and other phenolic compounds (**39–70**) were another class of secondary metabolites identified from the investigations of the extracts of BHA (Table 1 and 2; Fig. 4 and 5). Potential biological activities of these compounds include antidiabetic, antimicrobial, anticancer, antitumor, antioxidant, anti-inflammatory, analgesic, gastroprotective, cardiotonic, and insecticidal effects; they are also been reported to be used to treat neurodegenerative disorders and stimulate the immune system (Baptista *et al.,* 2022; Correia Alves *et al.,* 2023; Daniels *et al.,* 2022; Habtemariam, 2019; Makaremi *et al.,* 2021; Nisar *et al.,* 2021; Obulesu, 2021a, 2021b; Razavi and Hosseinzadeh, 2020; A. Sharma *et al.,* 2021; M. Sharma *et al.,* 2023; Sung *et al.,* 2012). Among these phenolics, aR-tumerone (**39**), eugenol (**40**), and its derivatives (*E*)-1-(4-hydroxy-3-methoxyphenyl)dec-4-en-3-one (6-Shogaol, **52**), 4-(4-hydroxy-3-methoxyphenyl)-2-butanone (Zingerone, **57**), and methyleugenol (**58**), which are reported to have various biological and pharmacological qualities (Baptista *et al.,* 2022; Correia Alves *et al.,* 2023; Daniels *et al.,* 2022; Habtemariam, 2019; Makaremi *et al.,* 2021; Nisar *et al.,* 2021; Obulesu, 2021a; Razavi and

Hosseinzadeh, 2020; Sharma *et al.,* 2021; Sharma *et al.,* 2020; Sung *et al.,* 2012)

Figure 3

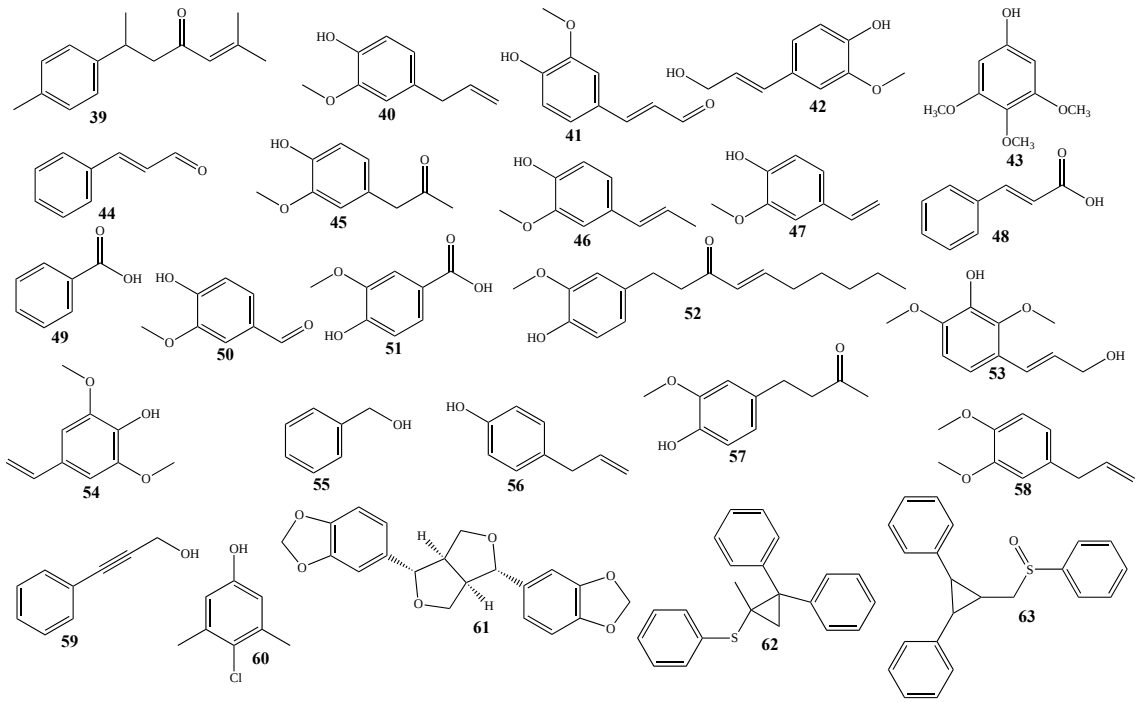
Terpenoids and a pyran derivative



The flavonoids, another significant group of phenolic natural products, were also found in the analyses. These include technochrysin (**64**), (*S*)-4H-1-benzopyran-4-one, 2,3-dihydro-5-hydroxy-7-methoxy-2-phenyl (Pinostrobin, **65**), homoeriodictyol (**66**), 3,4'-dimethoxy-5,7,3'-trihydroxyflavone (3,4'-dimethyl quecrcetin, **67**), and 5,6,7,3'4'-pentamethoxyflavone (Sinensetin, **68**). Pinostrobin (**65**) was the only flavonoid that was found in both studies (Table 1 and 2; Fig. 5). Compounds **66–68** were only detected in LC-MS/MS analysis, while compound **64** was detected in GC-MS/MS. Improvements in memory impairment, antimalarial, antioxidant, anti-inflammatory, antimicrobial, and anticancer activities have been reported for the flavonoids. They have also been shown to inhibit α-glucosidase, exhibit anticancer, anti-obesity, anti-dementia, analgesic, vasorelaxant, and skeletal muscle hypertrophy activities (Table 3) (Al-Bzour *et al.,* 2024; Dunstan *et al.,* 2020; González *et al.,* 2022; Guo *et al.,* 2022; Han Jie *et al.,* 2021; Saquib *et al.,* 2020; Sun *et al.,* 2020; Wieczorek *et al.,* 2022; Wu *et al.,* 2023; Yuan *et al.,* 2024; Zhao *et al.,* 2023; Zhu *et al.,* 2024).

Figure 4

Phenylpropanoids and other phenolic derivatives



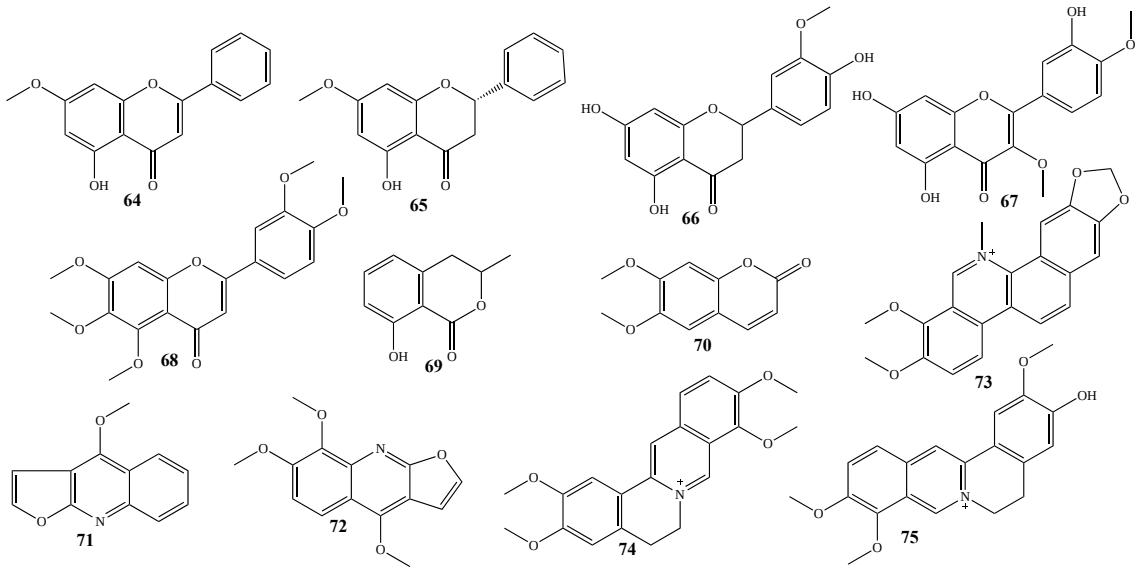
Two coumarins, (-)-mellein (**69**) and 6,7-dimethylesculetin (Scoparone, **70**) were also among the phenolic secondary metabolites of the medicinal herb formulation that were found in this study (Tables 1 and 2). A variety of biological activities, including anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic, and hypolipidemic, have been reported for scoparone (**70**). Scoparone (**70**) was identified in LC-MS/MS analysis of the methanol extract. The compound has also been used to treat cholestasis, jaundice, and liver dysfunction (Cai *et al.,* 2020; Hui *et al.,* 2020; Kowalczyk *et al.,* 2022; Wirasisya and Hohmann, 2023), whereas (-)-mellein is reported to have antifungal, anti-inflammatory and antibacterial activities (Table 3)(Li *et al.,* 2021; Reveglia *et al.,* 2020; Turker and Gurel, 2005). Together with their well-known biological and pharmacological characteristics, the flavonoids (**66–68**) and scoparone (**70**) also have anti-fibrotic and vasorelaxant qualities. The presence of these substances helps to maintain normal and smooth blood flow, preventing the thickening of the lung's air sac walls, and protecting the patient from thrombosis and breathing problems

The alkaloids, dictamnine (**71**), 4,7,8-trimethoxyfuro[2,3-b]quinoline (skimmianine, (**72**), and the protobeberine (benzophenanthridine) alkaloids chelerythrine (**73**), palmatine (**74**) and jatrorrhizine (**75**) were found to be among the secondary metabolites identified in the analyses. Compounds **66–69** and **73–75** were only observed in the LC-MS/MS analysis of the methanol extract (Table 2; Fig. 5). Table 3 shows the biological activities of the alkaloidal constituents of the formulation. Generally, a variety of biological activities have been reported for these compounds, for example, compound **71** is reported to have insecticidal and anti-inflammatory properties (Li *et al.,* 2024; Lu *et*

al., 2020; Lv *et al.,* 2015; Yang *et al.,* 2012), whereas compound **72**, on the other hand, has been reported to demonstrate anticholinesterase, antiviral, antibacterial, antifungal, anti-inflammatory, antioxidant, analgesic, anticonvulsant, cardiotonic, and anthelmintic properties (Li *et al.,* 2024; Lu *et al.,* 2020; Mutinda *et al.,* 2023; Powder-George, 2023; Yang *et al.,* 2012; Yao *et al.,* 2020). Further studies revealed compound **72** to possess *in vitro* antiviral activity against the measles virus (Anywar *et al.,* 2022).

Figure 5

Alkaloids, flavonoids and and coumarins



According to reports, the protobeberine alkaloids (73–75) have beneficial effects on the cardiovascular system in addition to having antibacterial, antidiabetic, anti-inflammatory, antiviral, antiulcer, and antifungal qualities (Mfuh and Larionov, 2015; Mutinda *et al.,* 2023; Nyong *et al.,* 2015; Thawabteh *et al.,* 2019; Volleková *et al.,* 2003).

Chelerythrine (**73**), is reported to have anti-inflammatory and antiviral properties. Furthermore, it suppresses pulmonary inflammation and fibrosis. Additionally, it reduces eryptosis and prevents cerebral vasospasm (Chen *et al.,* 2022; He *et al.,* 2018; Kang *et al.,* 2022; Li *et al.,* 2024; Lu *et al.,* 2020; Valipour *et al.,* 2021). According to reports, palmatine (**74**) has anti-seizure, anti-cancer, anti-oxidant, anti-inflammatory, neuroprotective, anti-bacterial, and antiviral properties. It also regulates blood cholesterol levels (Grabarska *et al.,* 2021; Long *et al.,* 2019; Song *et al.,* 2018; Wu *et al.,* 2016; Yan *et al.,* 2017; Zhang *et al.,* 2012). Jatrorrhizine (**75**) on the other hand has also been shown to display similar activities to those of **73** and **74**, including anti-inflammatory, antibacterial, antitumor, blood flow enhancement, and mitotic activity (Deng and Wan, 2021; Fu *et al.,* 2023; Rolle *et al.,* 2021; Zhong *et al.,* 2022; Zhou *et al.,* 2022).

α-Terpineol (**25**), the lignan (+)-sesamin (**61**), skimmianine (**71**), and the protobeberine alkaloids **72–75,** were previously reported to be isolated from *Zanthoxylum* species, including *Z. chalybeum*, one of the species making up the herbal formulation (Adia *et al.,* 2016; Krohn *et al.,* 2011; Muganga *et al.,* 2014; Okagu *et al.,* 2021; Omosa *et al.,* 2021).

According to the results, the medicinal herb formulation contained a variety of secondary metabolites with a broad range of biological activities of pharmacological significance which

worked synergistically. The presence of these metabolites may have contributed to the effectiveness of the formulation in combating the SARS-CoV-2 virus, which is the cause of COVID-19 and other respiratory infectious viral diseases.

In addition to exhibiting anti-inflammatory, immunomodulatory, antiviral, antioxidant, antibacterial, and other biological properties which have been demonstrated by the majority of the chemicals found in the analyses, carvacrol (**37**) and scoparone (**70)** have also been shown to have anti-fibrotic and antioxidant potentials in respiratory illnesses, respectively (de Carvalho *et al.,* 2020; Hasan *et al.,* 2022; Hui *et al.,* 2020).

One major factor in the development of SARS-CoV-2, which leads to poor outcomes in COVID-19 patients, is lung fibrosis. Thus, the presence of compounds with anti-fibrotic and antioxidant potentials in respiratory illnesses, two biological processes are crucial in the fight against respiratory illnesses (de Carvalho *et al.,* 2020; Hasan *et al.,* 2022; Hui *et al.,* 2020).

Apart from the biological activities mentioned earlier, flavonoids are also known for their ability to relax blood vessels, suppress pulmonary inflammation, manage blood lipid levels and enhance blood flow. These properties are critical in the fight against respiratory infectious viral diseases like COVID-19 and the like because they avert blood thrombosis, which exacerbates patients' conditions. Vasorelaxation allows blood to pass through blood vessels more easily (de Carvalho *et al.,* 2020; Hao and Jiao, 2022; Hui *et al.,* 2020; Peng *et al.,* 2021; Wei *et al.,* 2024; Zhu *et al.,* 2022; Zuo *et al.,* 2024).

In addition to their previously listed actions, chelerythrine (**73**), palmatine (**74**), and jatrorrhizine (**75**), the three benzophenanthridine alkaloids, have also been shown to have the ability to suppress lung inflammation and fibrosis, regulate blood lipids, and enhance blood flow characteristics (Hao and Jiao, 2022; Hasan *et al.,* 2022; Peng *et al.,* 2021; Wei *et al.,* 2024; Zhu *et al.,* 2022; Zuo *et al.,* 2024).

Because pulmonary fibrosis and compromised immune regulation are major contributors to the pathophysiology of COVID-19 and lead to unfavourable outcomes for patients (Hasan *et al.,* 2022; Khan *et al.,* 2021; Nugraha *et al.,* 2020; Sharanya *et al.,* 2021; Zhang and Liu, 2020), the medicinal herbal formulation's efficacy in treating and managing COVID-19 patients can be attributed to the presence of secondary metabolites with antiviral, antioxidant, immunomodulatory, anti-inflammatory, and anti-fibrosis properties. The formulation may have potential applications as a preventive or curative measure for COVID-19 and other viral respiratory infections, as suggested by these data.

Conclusion

These investigations have shown that BHA extracts are rich in biologically active compounds with no mentioned toxicity. The biological characteristics of the previously described secondary metabolites have shown that the therapeutic herbal formulation contained a range of ingredients with almost similar biological effects. Due to the biological activities' synergistic combination effects of the secondary metabolites, the medicinal herb formulation demonstrated more efficacious in treating and managing COVID-19 patients and, consequently, other respiratory infectious viral diseases. The outcomes thus justify the use of the medicinal formulation because the herbal formulation's secondary metabolites in it are effective. The rationale for using the herbal mixture in the fight against respiratory viral infections is further strengthened by the reports of the safety of its constituent secondary metabolites.

Recommendation

Based on the results of this study, LC-MS/MS analyses of the hexane and ethanol extracts and the ethyl acetate layer are required to identify other secondary metabolites. A literature survey of the individual components revealed the presence of a variety of compounds, most of which were not observed in the current study, thus necessitating analyses of the other extracts. Furthermore, there is a necessity of developing the herbal formulation and other formulations with therapeutic potentials into more advanced phases of conventional medications and determining the appropriate dosages for the

herbal formulations. Lastly, using natural products that have therapeutic potential is advised; nevertheless, in order to prevent negative side effects, safety procedures must be taken.

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