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Original Article

GC-MS analysis of the active compound in ethanol extracts of white pepper (*Piper nigrum l.*) and pharmacological effects

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ABSTRACT

Pepper (*Piper nigrum L.*) has been utilized since antiquity and is considered the king of spices due to its wide use. This study aims to analyze the active compounds of white pepper through GC-MS and their pharmacological effects. Pepper seeds were extracted using 96% ethanol as solvent by the maceration method. The active compounds in the dry extract were then analyzed by GC-MS. Identification of the active compound was carried out by matching it to the Willey7 Library database. Based on the results chromatogram, is known that there are 127 components of the compound, of which there are 11 main components. Most of the main components are alkaloids and have various pharmacological effects discussed. Piperidine, Caryophyllene, and Ethyl iso-allocholate are some of active compounds in ethanol extract. Ethyl iso-allocholate acts as an anti-inflammatory with a strong affinity for the target protein and also acts as an antiviral for SARS-CoV by inhibiting the attachment of the viral genome to target proteins, namely angiotensin-converting enzyme 2 (ACE2) and main protease (MPro).

1. Introduction

Pepper (*Piper nigrum L.*) has been utilized since antiquity and became a driving force of economics in the 15th and 16th centuries [1], and is considered the king of spices because of its wide use not only to provide and enhance the taste of food but also to be explored related to its active compounds and its wide use in medicine, such as; as an antimicrobial, antioxidant, anticancer, analgesic, anticonvulsant, neuroprotective, hypoglycemic, and hypolipidemic agent [2].

Fruit, peel, and leaf were known to increase the viability of SK-N-SH and SH-SY5Y cells induced with 6-hydroxydopamine (6-OHDA). Pepper is also used in traditional Balinese medicine, either alone or in combination with other ingredients. Pepper is also made into a medicinal formula called *Trikatu* in Indian *ayurvedic* medicine to treat various types of ailments [3, 4].

The extensive use and high economic value of pepper are inseparable from the variety of active compounds so that they can cause a variety of pharmacological effects. In the literature, the main components that are often mentioned are contained in pepper, among them; β-caryophyllene, limonene, β-pinene, α-pinene, δ-3-carene, sabinene, and myrcene[5].

However, the diversity of components of such active compounds may vary due to several things such as; region of origin or growing place, the drying process of extracts such as oven-dry or freeze-dry, the extraction

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process, the long storage time of ground pepper resulted in significant changes in the chemical composition of especially essential oils, as well as pepper varieties such as white or black pepper. Black peppercorns are produced from dark green (ripe) pepper fruits with delicate pepper seeds and a sharp aroma and taste. They will undergo a drying process without removing the outer shell (pericarp). White peppercorns are produced from yellowish-green and red pepper fruits with hard seeds and thinner pericarps. They are produced by removing the outer shell (pericarp) after soaking and drying processes [6, 7].

The diversity of active compounds in pepper can be identified by sensitive methods so that these active compounds can be obtained accurately and quickly. The *gas chromatography-mass spectrometry* (GC-MS) method is a method of separating compounds in the sample to obtain the desired active compound. The GC-MS method is widely used because it has the advantages of high sensitivity and selectiveness. GC-MS analysis can separate mixed compounds and analyze compounds even with very low concentrations [4, 8].

This method combines chromatographic analysis and spectrophotometry. This method is often used for the benefit of analyzing natural materials that have a wide range of complex molecules. The sample analysis process goes through several stages, namely the separation and analysis of the structure of active compounds in the form of smaller molecules. The molecule is known to have pharmacological effects[4, 8].

This study aims to analyze the active compounds of seeds of white pepper through GC-MS and their pharmacological effects. The pharmacological effects of active compounds are traced based on credible and up-to-date sources of publications.

2. Materials and Methods

Pepper seeds (*Piper nigrum* L) were extracted by the maceration method using 96% ethanol as solvent [9]. The pepper seeds were washed and then ground using a blender, then dried for 24 hours. After drying then, filtered with a flour sieve. *Simplicia* was then macerated using 96% ethanol for 48 hours. The products of the maceration were then filtered using filter paper. The filtrate was then concentrated at 45^{o}C using a rotary evaporator to obtain a thick extract.

The thick extract was then dried using freeze-dryer to obtain a dry extract. The active compounds in the dry extract were then analyzed by GC-MS (Shimadzu GC-210 Plus). GC-MS apparatus utilized under the following conditions: HP-5MS UI capillary column (30 m x 0.25 mm x 0.25 m), helium carrier gas with a 1 ml/min flow rate.

The temperature in the GC is regulated by the provisions; injector temperature is 230^{o}C, the initial temperature of the column is 60^{o}C, the rate of temperature rise is 10^{o}C/min, and the final temperature of the oven is 280^{o}C. Identification of the active compound was carried out by matching it to the Willey7 Library database.

3. Results

The active compounds in white pepper were analyzed by looking at the peak area and retention time on the GC-MS chromatogram. Based on the results chromatogram, there are 127 components of the compound (Figure 1), of which there are 11 main components, most of which are alkaloids.

The main component fragmentation can be seen from the peaks in the mass spectrum as presented in Table 1 and Figure 2 to Figure 12. The chromatogram of the compound in Table 1 is the main component of pepper's ethanol extract, each of which has a pharmacological effect.

As shown in Table 1, Piperidine,1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(Z,Z)- and Caryophyllene are two active compounds present in ethanol extract of white pepper with an abundance of peak areas of 9.97% and 6.67%, respectively. The other nine compounds produced area peaks ranging from 0.22% to 2.86%.

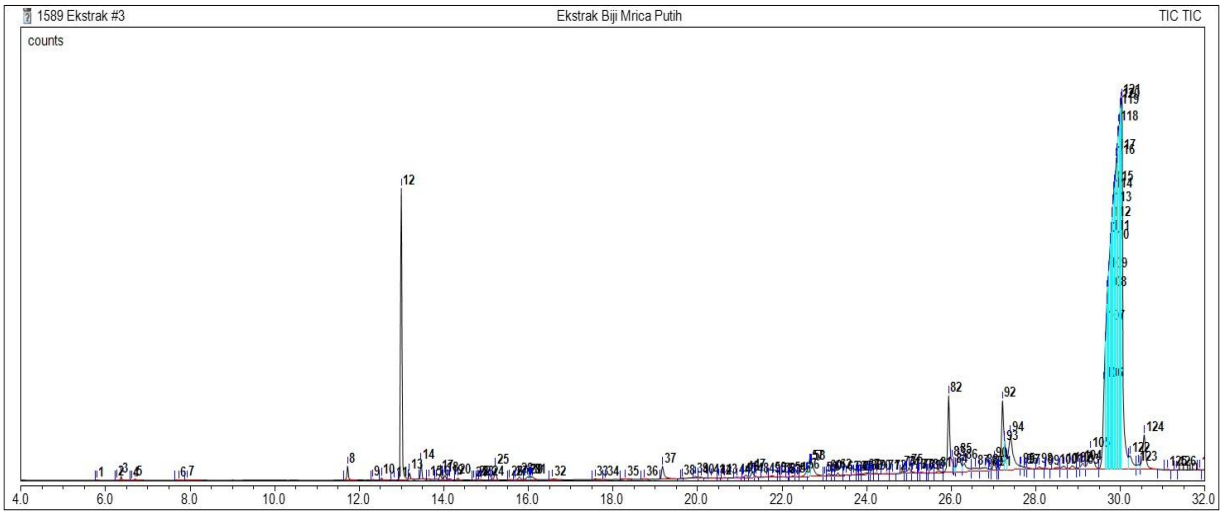

Fig. 1. Chromatogram of Ethanol Extract of Pepper, peak number in Figure According to compounds in Table 2

Table 1. Main Components of Ethanol Extract of White Pepper Seed

Peak	Retention Time	Chemical Components	Area	BM	Molecular Formula
12	12.99	Caryophyllene	6.67	204	$C_{15}H_{24}$
58	22.69	(E) -9-(Benzo[d][1,3] dioxol-5-yl)-1-(piperidine-1-yl)non-8-en-1-one	0.77	343	$C_{21}H_{29}NO_3$
82	25.94	(E)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidine-1-yl)pent-2-en-1-one	2.86	287	$C_{17}H_{21}NO_3$
85	26.18	Piperlonguminine	0.92	273	$C_{16}H_{19}NO_3$
86	26.30	Corynan-17-ol, 18,19-didehydro-10-methoxy-	0.58	326	$C_{20}H_{26}N_2O_2$
93	27.26	Ethyl iso-allocholate	0.52	436	$C_{26}H_{44}O_5$
102	28.87	Methyl glycocholate, 3TMS derivative	0.22	695	$C_{36}H_{69}NO_6Si_3$
105	29.30	Pyrrolidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-, (E,E)-	1.51	271	$C_{16}H_{17}NO_3$
121	30.03	Piperidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(Z,Z)-	9.79	285	$C_{17}H_{19}NO_3$
122	30.23	Piperine	0.92	285	$C_{17}H_{19}NO_3$
124	30.56	(2E,6E)-7-(Benzo[d][1,3] dioxol-5-yl)-1-(piperidine-1-yl) hepta-2,6-dien-1-one	1.84	313	$C_{19}H_{23}NO_3$

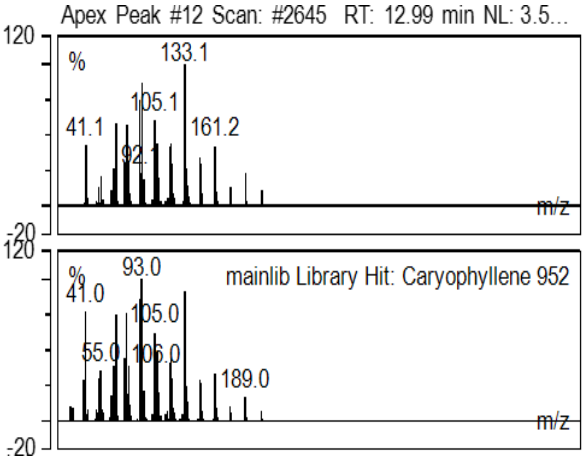

Fig. 2. GC-MS Spectra Massa Caryophyllene

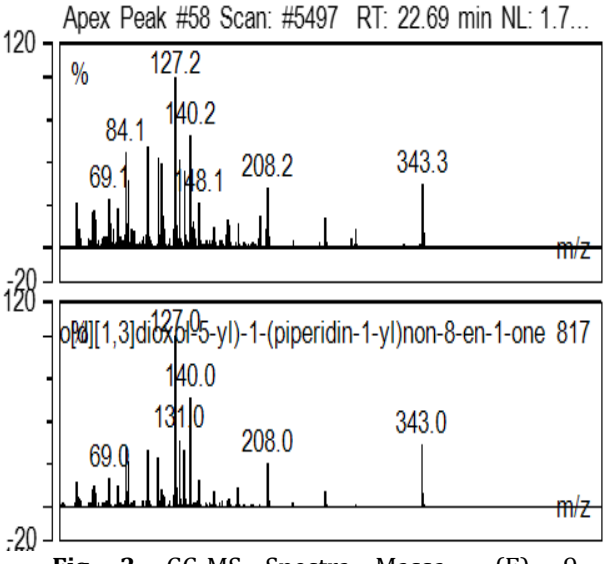

Fig. 3. GC-MS Spectra Massa (E) -9-(Benzo[d][1,3] dioxol-5-yl)-1-(piperidine-1-yl)non-8-en-1-one

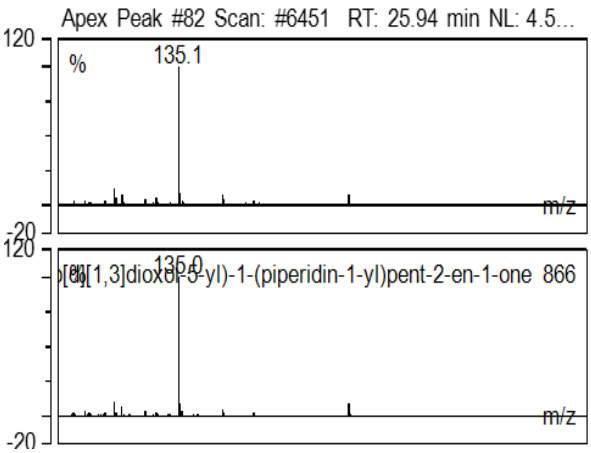

Fig. 4. GC-MS Spectra Massa (E)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidine-1-yl)pent-2-en-1-one

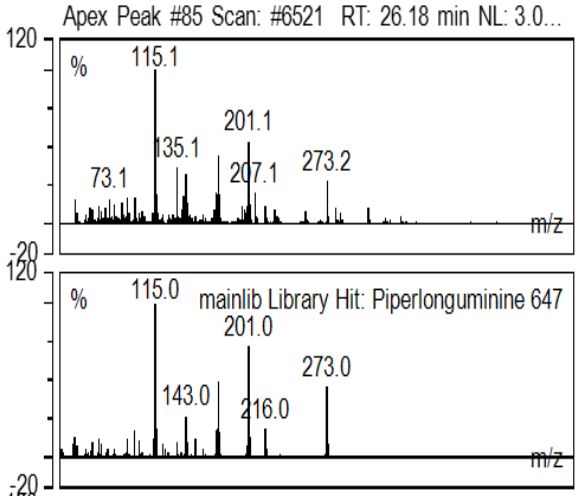

Fig. 5. GC-MS Spectra Massa Piperlonguminine

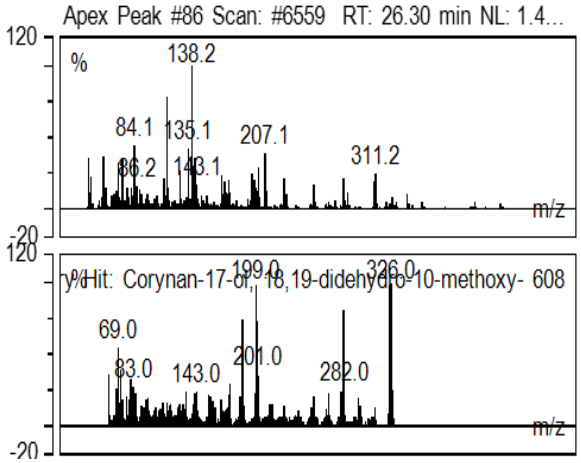

Fig. 6. GC-MS Spectra Massa Corynan-17-ol, 18,19-didehydro-10-methoxy-

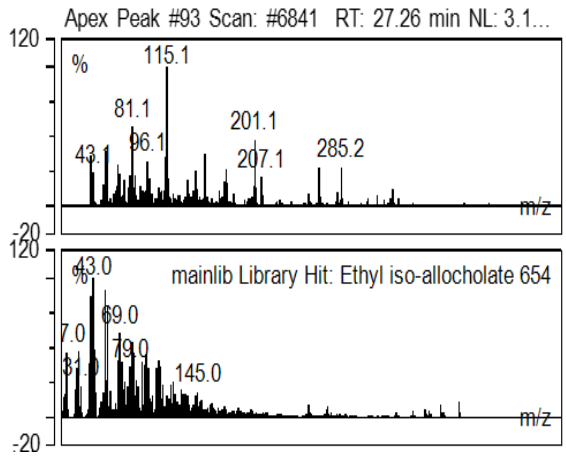

Fig. 7. GC-MS Spectra Massa Ethyl iso-allocholate

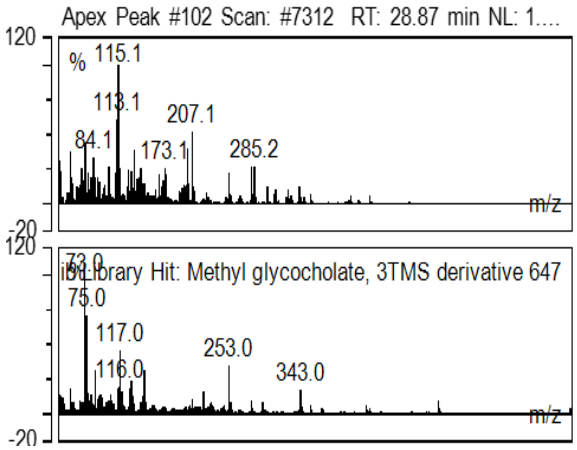

Fig. 8. GC-MS Spectra Massa Methyl glycocholate, 3TMS derivative

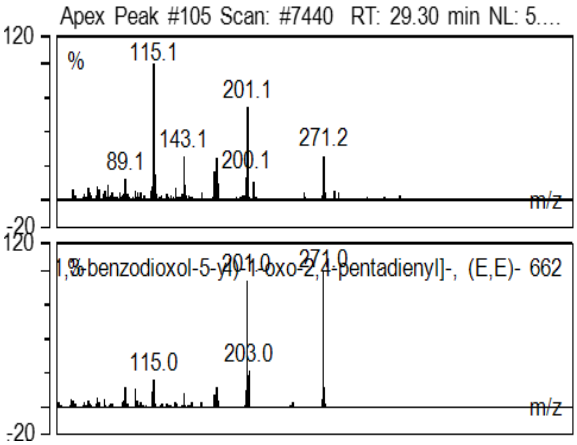

Fig. 9. GC-MS Spectra Massa Pyrrolidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-, (E,E)-

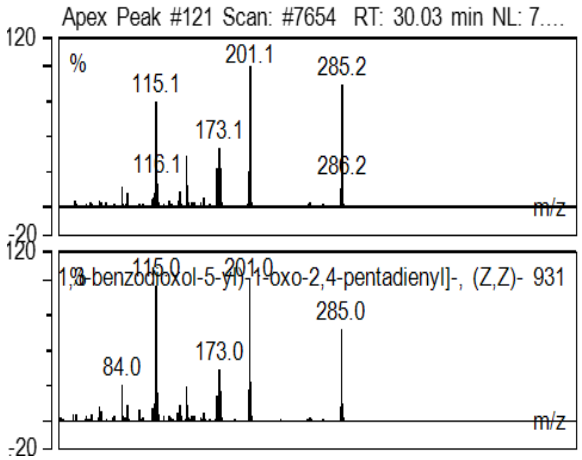

Fig. 10. GC-MS Spectra Massa Piperidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(Z,Z)-

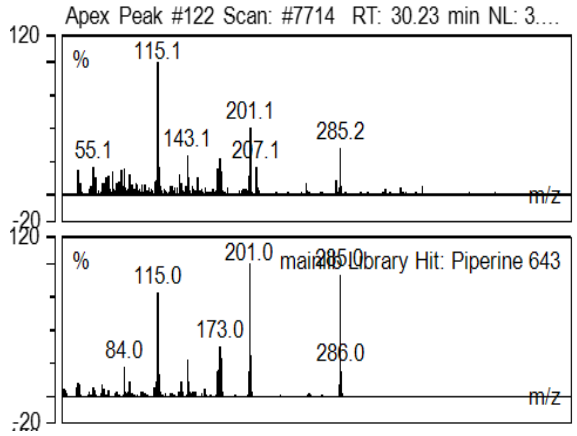

Fig. 11. GC-MS Spectra Massa Piperine

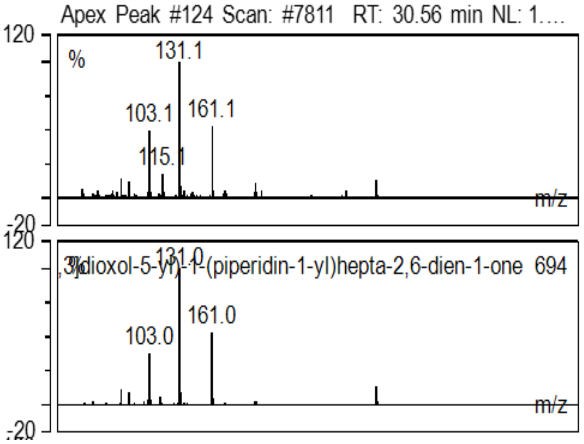

Fig. 12. GC-MS Spectra Massa (2E,6E)-7-(Benzo [d][1,3] dioxol-5-yl)-1-(piperidine-1-yl) hepta-2,6-dien-1-one

4. Discussion

4.1. Caryophyllene

Another name for caryophyllene compounds is (-)-β-caryophyllene or β-caryophyllene which is a natural bicyclic sesquiterpene. In the chromatogram of the caryophyllene compound, it was seen at peak number 12 with a retention time of 12.99 minutes and a relative area reaching 6.67%.

Several studies have revealed that caryophyllene possesses significant pharmacological benefits, including antioxidant, anticancer, cardioprotective, anti-inflammatory, hepatoprotective, nephroprotective, gastroprotective, antimicrobial, and immunomodulator properties [10], can improve wound healing[11], a potential treatment candidate for hyperoxalurate-induced renal problems [12], able to prevent the accumulation of lipids in 3T3-L1 preadipocytes and able to increase glucose absorption in Myotube C2C12 [13].

β--caryophyllene can also eradicate Streptococcus mutans in the oral cavity and block the production of oral biofilms, making it a strong candidate for the prevention of dental caries [14], and improves dental health by inhibiting dental pathogenic bacteria, reducing lipopolysaccharide-induced inflammation, and inhibiting the emission of sulfur gases produced by the bacterium *Porphyromonas gingivalis* [15].

4.2. (E) -9- (Benzo[d][1,3] dioxol-5-yl)-1-(piperidine-1-yl)non-8-en-1-one

Another name for this compound is piperolein B, which belongs to the alkaloid groups. In the chromatogram, this compound appears at peak number 58 with a retention time of 22.69 minutes and a relative area up to 0.77%. Piperolein B is known to have a cytotoxic effect on carcinoma cells [16] and has a hepatoprotective effect on rat primary hepatocyte cell damage induced by D-galactosamine (D-GalN) with IC_{50} reaching 2.9 M [17]. Besides, it is also known to function as a natural larvicide against the moth of *Plutella xylostella* [18].

4.3. (E)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidine-1-yl)pent-2-en-1-one

This compound is also known as piperanine which belongs to the alkaloid group. On the chromatogram, (E)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidine-1-

yl)pent-2-en-1-one seen at peak number 82 with retention time 25.94 minutes, and with relative area up to 2.86%.This compound is also the main component in *Piper longum* fruit [19].

According to a docking-based study, the piperanine ingredient in black pepper is highly effective against COVID-19 and could be utilized to cure the virus [20]. Piperanine is also known to act as a larvacide against mosquito larvae of *Culex quinquefasciatus* with LC_{50} reaching 2.97 ppm [21], and is known to have potential as an inhibitor in preventing corrosion of steel [22].

4.4. Piperlonguminine

Piperlonguminine, which belongs to the alkaloid group, in the chromatogram seen at the peak number 85 with a retention time of 26.18 minutes and with a relative area of 0.92%. Piperlonguminine is known to have antitumor activity [23] and may inhibit AKT/mTOR phosphorylation, hence raising cancer cell levels of reactive oxygen species [24]. In addition, piperlonguminine has the ability to cure severe vascular inflammatory illnesses such as sepsis and septic shock [25], and can repair cell damage in the event of cardiac ischemia/reperfusion by activating aldehyde dehydrogenase to reduce lipid aldehyde concentrations to provide cardiac protection [26].

4.5. Corynan-17-ol, 18,19-didehydro-10-methoxy-

This compound is also known as 10-Methoxycoryn-18-en-17-ol #. On chromatogram, Corynan-17-ol, 18,19-didehydro-10-methoxy-seen at peak number 86 with a retention time of 26.30 minutes and with a relative area of 0.58%. The binding energy value of –5.9 kcal/mol indicates that Corynan-17-ol, 18,19-didehydro-10-methoxy- is a ligand that interacts significantly with the breast cancer protein ErBb2 [27].

4.6. Ethyl iso-allocholate

In the chromatogram, ethyl iso-allocholate compounds were seen at peak number 93 with a retention time of 27.26 minutes and with a relative area of 0.52%. Ethyl iso-allocholate is a steroid derivative that has antimicrobe, anti-inflammatory, diuretic, and anti-asthmatic properties. Ethyl iso-allocholate can also be found in traditional rice, *karungkavuni,* and act as a strong inhibitor of the dihydropteroate synthase enzyme present in bacteria *Escherichia coli*. Ethyl iso-allocholate is also known to be contained in the plant *Phyllanthus nivosus* and acts as an anti-inflammatory with a strong affinity for the target protein, namely caspase-1. *Ipomoea obscura* L also contains ethyl iso-allocholate and is known to have potential as an antiviral for SARS-CoV by inhibiting the attachment of the viral genome to target proteins, namely angiotensin-converting enzyme 2 (ACE2) and main protease (MPro) [28, 29].

4.7. Methyl glycocholate, 3TMS derivative

Methyl glycocholate, 3TMS derivative including terpenoid compounds. On the chromatogram, methyl glycocholate, 3TMS derivative seen at peak number102 with retention time 28.87 minutes and has relative area of 0.22%. Methyl glycocholate, 3TMS derivative has several other names such as; N-[24-Oxo-3alpha,7alpha,12alpha-tris(trimethylsiloxy)-5beta-cholan-24-yl] glycine methyl ester; 57326-16-6; Methyl ((24-oxo-3,7,12-tris[(trimethylsilyl)oxy] cholan-24-yl) amino) acetate#; Glycine,N-[(3.alpha.,5.beta., 7.alpha.,12.alpha.)-24-oxo-3,7,12-tris[(trimethylsilyl)oxy]cholan-24-yl] -, methyl esters.

Methyl glycocholate, 3TMS derivatives can also be identified in green coffee beans which are known to act as antioxidants [30].

4.8. Pyrrolidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-, (E,E)-

Synonyms of this compound are Pyrrolidine, Trichostachine, or Piperyline, which belongs to the alkaloid group. On the chromatogram, Pyrrolidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-, (E,E)- seen at the peak number 105 with retention time 29.30 minutes and has relative area 1.51%. Trichostachine is known to be able to inhibit the quorum sensing system in the bacterium *Chromobacterium violaceum* CV026 so that it has potential as an antibacterial [31]. The quorum sensing system is a signal transduction system that

controls physiological behavior in bacteria. Bacteria produce and secrete small signaling molecules, called autoinducers, outside the cell to recognize population densities and respond to them. The autoinducer spreads to nearby individuals and can eventually induce the production of more autoinducers and can trigger the expression of other desired genes. This system creates positive feedback that causes the population to work in sync. Bacteria can use quorum sensing for purposes such as; bioluminescence, virulence, and biofilm formation [32]. Biofilms are bacterial colonies that attach to surfaces and are encased in a matrix of self-produced polymeric substances. The antibiotic resistance of bacteria in biofilms is greater [33].

Piperyline is also known to induce apoptosis and inhibit preosteoblast adhesion and migration via apoptotic and Src/FAK pathways, thereby suppressing osteoblast differentiation via the osteogenic Smad 1/5/8 and RUNX2 signaling pathways in preosteoblasts, making it useful in the development of modern drugs to treat bone disease [34].

4.9. Piperidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(Z,Z)-

This compound is also known as Chavicine and is an isomer of piperine [35]. On the chromatogram, Piperidine, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(Z,Z)- seen at peak number 121 with retention time 30.03 minutes and has relative area 9.79%. Chavicine is known to have an effect on improving memory, making it a potential candidate for other neurodegenerative disorders [36].

4.10. Piperine

Piperine is a naturally occurring alkaloid compound that is responsible for the spicy taste of pepper [35]. On the chromatogram, piperine appears at peak number 122 with a retention time of 30.23 minutes and a relative area of 0.92%. Piperine possesses antioxidant, anticonvulsant, antibacterial, neuroprotective, larvacidal, antiparasitic, anticancer, and other pharmacological effects [37]. Piperine also has potential as an antidiabetic through its ability to inhibit the activity of α-amylase and α-glucosidase enzymes, thereby reducing blood glucose levels, as well as reducing various types of free radicals to prevent oxidative stress [38].

Based on the bond energy value of –7.0 kcal/mol, molecular docking research demonstrates that piperine is a ligand that interacts strongly with the SARS-CoV-2 nucleocapsid protein; hence, it has potential as an anti-SARS-CoV-2 agent. Piperine is also known to be able to inhibit the quorum sensing system in the bacterium *Chromobacterium violaceum* CV026 with an effective dose of 30 mg/L so that it has potential as an antibacterial [31]. Piperine exhibits anti-proliferative, anti-migratory, and anti-invasive properties in human pancreatic cancer cells, PANC-1 [39]. Piperine has a hepatoprotective effect against D-galactosamine (D-GalN)/lipopolysaccharide-induced damage to rat primary hepatocyte cells (LPS) [17].

4.11. (2E,6E)-7-(Benzo [d][1,3] dioxol-5-yl)-1-(piperidine-1-yl) hepta-2,6-dien-1-one

Synonyms of this compound are pipersintenamide, which belongs to the alkaloid group. On the chromatogram, (2E,6E)-7-(Benzo [d][1,3] dioxol-5-yl)-1-(piperidine-1-yl) hepta-2,6-dien-1-one appears at peak number 124 with retention time 30.56 minutes, and has a relative area 1.84%. Pipersintenamide has also been isolated from *Piper sintenense* and is known to exhibit effective cytotoxicity against cancer cells CCRF-CEM (Acute lymphoblastic leukemia), HL-60 (Acute promyelocytic leukemia), PC-3 (prostate cancer), and HA22T (hepatoma) with fewer than 15% cell survival [40], as well as against P-388, A549, and HT-29 cells [41].

5. Conclusion

In this study, there are 11 main components in the ethanolic extract of pepper (*Piper nigrum* L), mostly alkaloids and active compounds that have various pharmacological effects.

Conflict of interest

The authors declare no conflict of interest

Ethical approval

This article does not contain any studies with human participants or animals performed by any authors.

Authors' Contribution

All authors had an equal role in study design, work, statistical analysis and manuscript writing.

Consent for publications

The author read and proved the final manuscript for publication.

Availability of data and material

All data generated during this study are included in this published article.

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