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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 used since ancient times 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 (Piper nigrum L) were extracted using 96% ethanol as solvent by the maceration method. GC-MS then analyzed the active compounds in the dry extract. The active compound was identified by matching it to the Willey7 Library database. Based on the results chromatogram, is known that there are 127 components of the combination, of which there are 11 main components. Most of the main components are alkaloids and have various pharmacological effects were discuses.

Keywords: *Pepper (Piper nigrum L)*, GC-MS Analysis, Active Compounds.

Introduction
Pepper*(Piper nigrum L)* has been utilized since ancient times 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 antibacterial, antioxidant, anticancer, analgesic, anticonvulsant, neuroprotective, hypoglycemic, hypolipidemic, and anti-inflammatory properties contribute to its extensive usage in medicine [2]. Both fruit, peel, and leaf were known to increase the viability of SK-N-SH and SH-SY5Y cells induced with 6-hydroxydopamine (6-OHDA) [3].

Pepper is also used in traditional Balinese medicine, alone or in combination with other ingredients [4], [5] Pepper is also made into a medicinal formula called *Trikatu* in Indian *ayurvedic* medicine to treat various ailments [6]. This study aims to analyze the active compounds of seeds of white pepper through GC-MS and their pharmacological effects.

Materials and Methods
Pepper seeds (*Piper nigrum* L) were extracted by the maceration method using 96% ethanol as solvent [7]. The pepper seeds were washed and then ground using a blender, dried for 24 hours, then filtered with a flour sieve. *Simplicia* was then macerated using 96% ethanol for 48 hours. The maceration results were then filtered using molecular sieves. The filtration was then concentrated at a temperature of 45^{o}C using a rotary vacuum evaporator to obtain a thick extract. The thick extract was then dried using freeze-dry to get 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 specified conditions; HP-5MS UI capillary column (30 meters x 0.25-millimeter x 0.25 meter), helium carrier gas with a 1 ml/min flow rate. The provisions regulate the temperature in the GC; 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.

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 is known that 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 ethanol extract of pepper, each of which has a pharmacological effect.

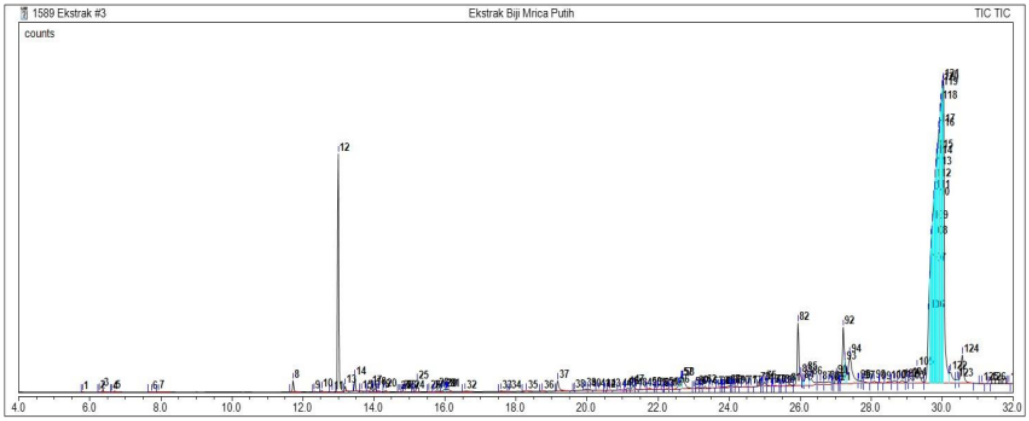

Figure 1. Chromatogram of Ethanol Extract of Pepper, maximum numbers in Figure According to Table 2.

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	$C_{19}H_{23}NO_3$

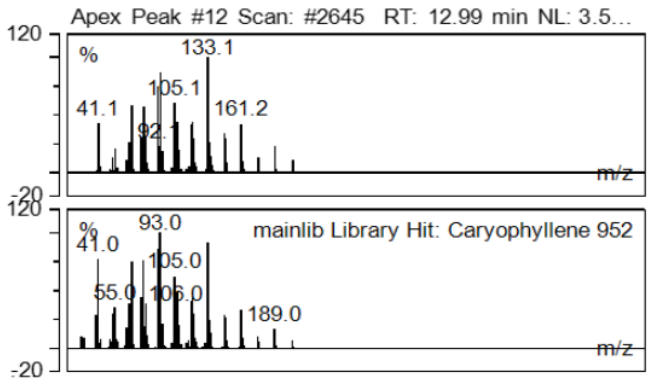

Figure 2. GC-MS Spectra Massa Caryophyllene

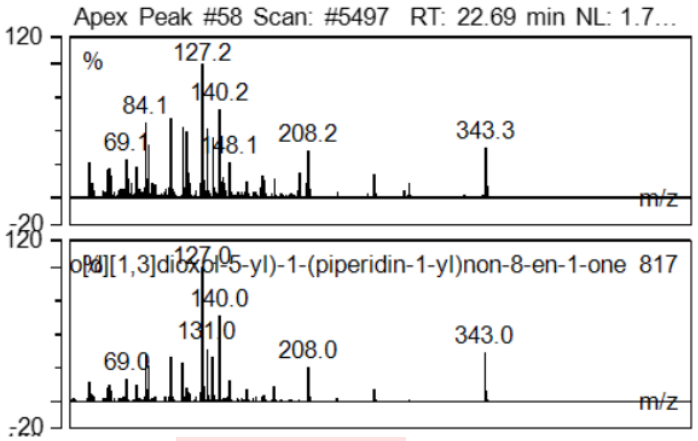

Figure 3. GC-MS Spectra Massa $C_{21}H_{29}NO_3$

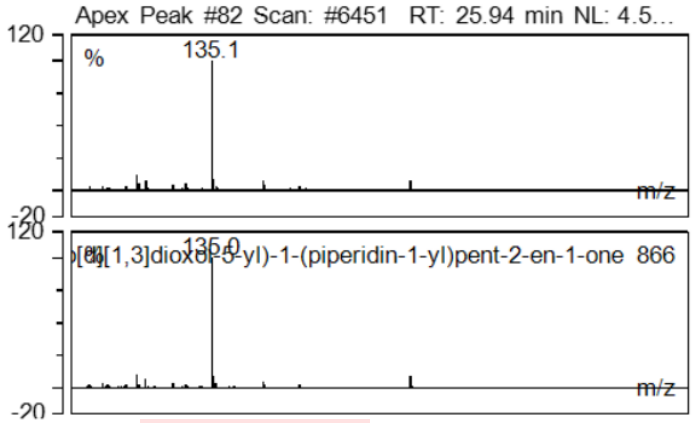

Figure 4. GC-MS Spectra Massa (E) $C_{17}H_{21}NO_3$

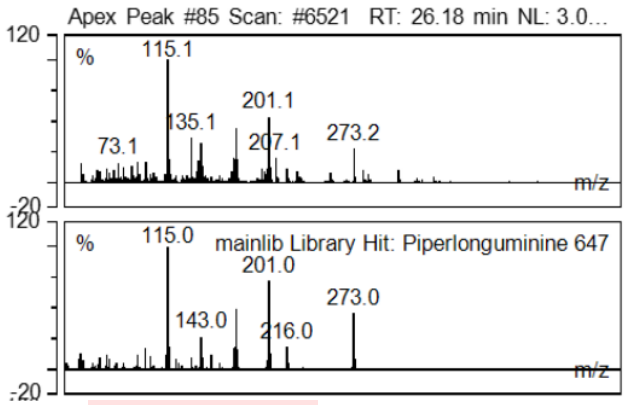

Figure 5. GC-MS Spectra Massa Piperlonguminine

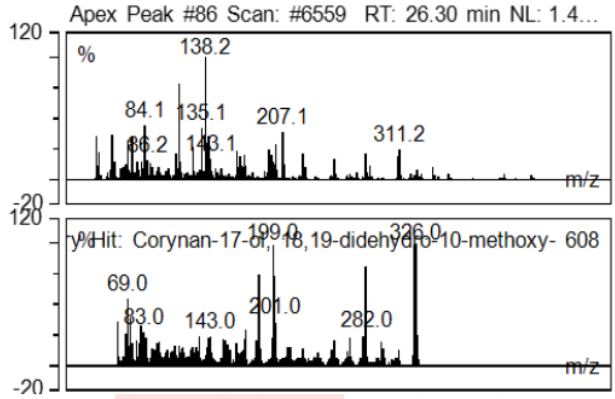

Figure 6. GC-MS Spectra Massa $C_{20}H_{26}N_2O_2$

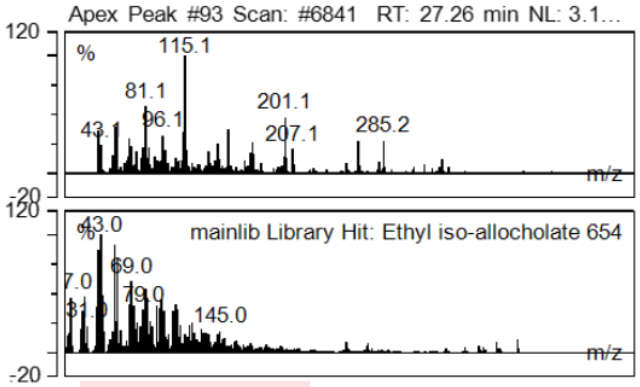

Figure 7. GC-MS Spectra Massa Ethyl iso-allocholate

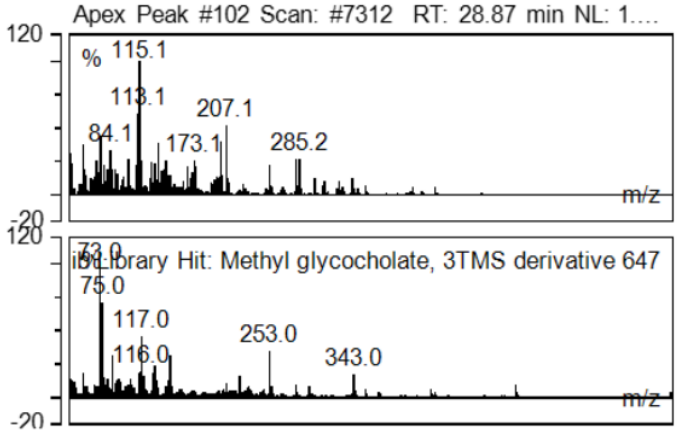

Figure 8. GC-MS Spectra Massa Methyl glycocholate, 3TMS derivative

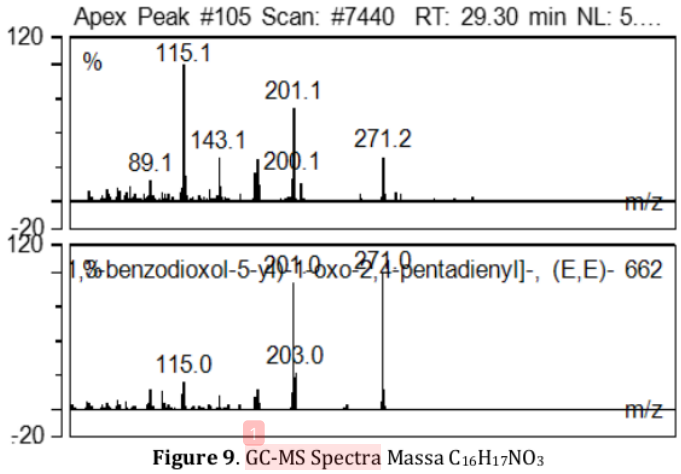

Figure 9. GC-MS Spectra Massa $C_{16}H_{17}NO_3$

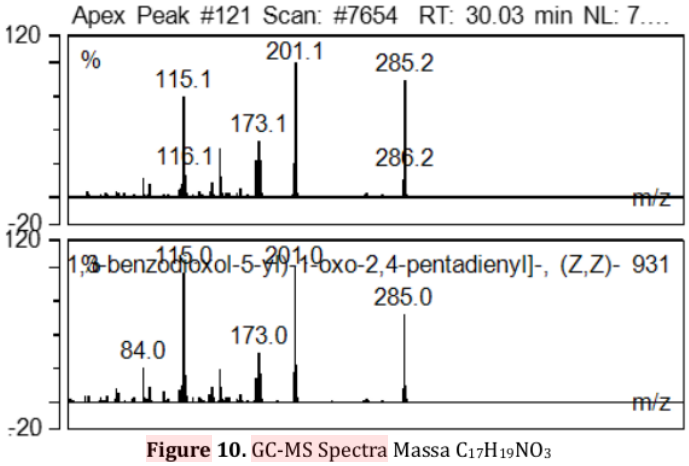

Figure 10. GC-MS Spectra Massa $C_{17}H_{19}NO_3$

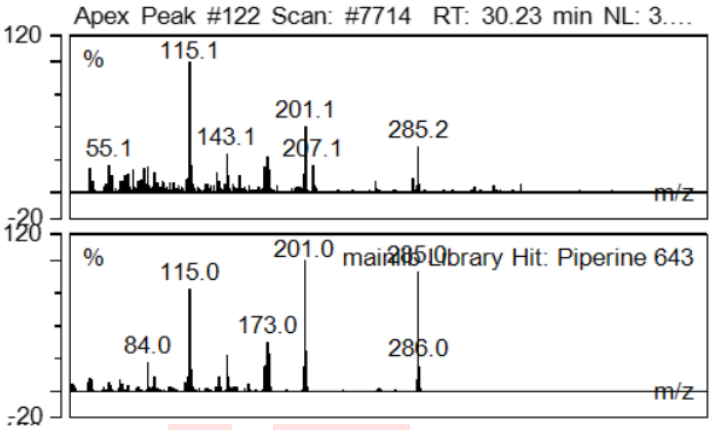

Figure 11. GC-MS Spectra Massa Piperine

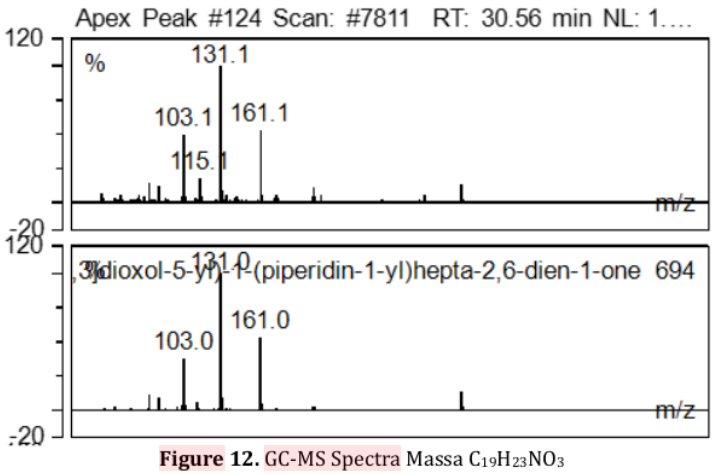

Figure 12. GC-MS Spectra Massa $C_{19}H_{23}NO_3$

Discussion

Caryophyllene

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

Several studies have stated that caryophyllene has significant oxidative, anticancer, cardioprotective, generally pro, anticarcinogenic, nephroprotective, neuroprotective, and antimicrobial properties as well as an immunomodulator [8] and can improve wound healing [9];[10], a reasonable option for treating renal problems caused by hyperoxaluria [11], capable of preventing lipid formation in 3T3-L1 preadipocytes and enhancing glucose absorption in Myotube cells C2C12[12].

β-caryophyllene can also eliminate *Streptococcus mutans* in the oral cavity and inhibit the formation of oral biofilms, so it has the potential to be an acceptable candidate for the prevention of caries [13] 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* [14].

Molecular Formula $C_{21}H_{29}NO_3$

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 [15] and has a hepatoprotective effect on rat primary hepatocyte cell damage induced by D-galactosamine (D-GalN) with IC_{50} reaching 2.9 M [16]. Besides, it is also known to function as a natural larvicide against the moth of *Plutella xylostella* [17].

Molecular Formula $C_{17}H_{21}NO_3$

This compound is also known as piperanine, which belongs to the alkaloid group. On the chromatogram, $C_{17}H_{21}NO_3$ was seen at peak 82 with retention time of 25.94 minutes and relative area up to 2.86%.This compound is also the main component in *Piper longum* fruit [18].

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. [19]. Piperanine is also known to act as a larvacide against mosquito larvae of *Culex quinquefasciatus* with LC_{50} reaching 2.97 ppm [20], and is known to have potential as an inhibitor in preventing corrosion of steel [21].

Piperlonguminine

Piperlonguminine belongs to the alkaloid group, in the chromatogram seen at the peak number 85 with a retention time of 26.18 minutes and a relative area of 0.92%. Piperlonguminine is known to have antitumor activity [22] and can suppress AKT/mTOR phosphorylation, consequently raising cancer cell levels of reactive oxygen species [23]. In addition, piperlonguminine can cure severe vascular inflammatory

illnesses such as sepsis and septic shock. [24], 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 [25].

Molecular Formula $C_{20}H_{26}N_2O_2$

This compound is also known as 10-Methoxycoryn-18-en-17-ol #. On chromatogram, $C_{20}H_{26}N_2O_2$- seen at peak number 86 with a retention time of 26.30 minutes and a relative area of 0.58%. A study based on molecular docking shows that $C_{20}H_{26}N_2O_2$- based on its binding energy value of –5.9 Kcal/mol, is a ligand that strongly interacts with the breast cancer protein ErBb2 [26].

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 with antimicrobe, anti-inflammatory, diuretic, and anti-asthmatic properties [27]. 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* [28]. 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, caspase-1 [29]. *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) [30].

Methyl glycocholate, 3TMS derivative

Methyl glycocholate, 3TMS derivative including terpenoid compounds. On the chromatogram, methyl glycocholate, 3TMS derivative seen at peak number102 with a 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 act as antioxidants [31].

Molecular Formula $C_{16}H_{17}NO_3$

Synonyms of this compound are Pyrrolidine, Trichostachine, or Piperyline, which belongs to the alkaloid group. On the chromatogram, $C_{16}H_{17}NO_3$ is seen at the peak number 105 with a retention time of 29.30 minutes and has a relative area of 1.51%. Trichostachine can inhibit the quorum-sensing system in the bacterium *Chromobacterium violaceum* CV026 so that it has potential as an antibacterial [32]. 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 [33]. Biofilms are communities of bacteria that attach to surfaces and are encased in a matrix of extracellular polymeric compounds created by the bacteria. Biofilm bacteria are more antibiotic-resistant. [34].

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 [35].

Molecular Formula $C_{17}H_{19}NO_3$

This compound, also known as Chavicine, is an isomer of piperine [36]. On the chromatogram, $C_{17}H_{19}NO_3$ is seen at peak number 121 with a retention time of 30.03 minutes and has a relative area of 9.79%. Chavicine is known to have an effect on improving memory, making it a potential candidate for other neurodegenerative disorders [37].

Piperine

Piperine is a naturally occurring alkaloid compound responsible for pepper's spicy taste [36]. 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 [38]. 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 and reducing various types of free radicals to prevent oxidative stress [39].

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 (Choudary, 2020). Piperine is also known 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 [32]. Piperine inhibits the proliferation, migration, and invasion of PANC-1 human pancreatic cancer cells [41]. Piperine also has a hepatoprotective effect on rat primary hepatocyte cell damage induced by D-galactosamine (D-GalN)/lipopolysaccharide (LPS) [16].

Molecular Formula $C_{19}H_{23}NO_3$

Synonyms of this compound are pipersintenamide, which belongs to the alkaloid group. On the chromatogram, $C_{19}H_{23}NO_3$ appears at peak number 124 with a retention time of 30.56 minutes and a relative area of 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 carcinoma), and HA22T (hepatoma) with cell survival of less than 15% [42], as well as against P-388, A549, and HT-29 cells[43].

Conclusion

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

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