Review
A Review of Bioactive Compounds and Antioxidant Activity Properties of Piper Species

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Abstract: Antioxidants are compounds that are able to inhibit the negative effects that come from free radicals. The phenomenon of imbalanced antioxidant production and the accumulation of free radicals in cells and tissues can cause oxidative stress. Excessive free radicals that enter the body cannot be warded off by endogenous antioxidant compounds so that the required antioxidant compounds can come from the outside, which helps in the performance of endogenous antioxidants. Antioxidants that come from outside consist of synthetic and natural antioxidants; however, synthetic antioxidants are not an option because they have toxic and carcinogenic effects. Therefore, the use of natural ingredients is an alternative method that is needed to create a new natural antioxidant compound.

Piper species are being considered as possible medicinal plants for the development of new sources of antioxidants. Several studies have been carried out starting from the extract levels, fractions, and compounds of the Piper species, which showed good antioxidant activity.

Currently, some of these plants are being used as ingredients in traditional medicines to treat allergies, toothaches, and coughs. This review examines the distribution, botanical data, pharmacology, especially antioxidant activity, and the compounds contained in five Piper species, namely Piper amalago L., Piper betle L., Piper hispidum Sw., Piper longum L., and Piper umbellatum L.

Keywords: antioxidant; Piper amalago; Piper betle; Piper hispidum; Piper longum; Piper umbellatum

1. Introduction

Antioxidants are molecules that delay or inhibit the oxidation process of unstable molecules and can prevent cell damage caused by free radicals [1,2]. Free radicals are highly reactive, unstable, and short-lived molecules because they have unpaired electrons; therefore, they tend to bind with other molecules to attain stability [3]. Molecules that are attacked become free radicals and can cause cell damage [4]. The overproduction of free radicals and insufficient production of antioxidants may result in oxidative stress [5,6]. Oxidative stress can cause several diseases such as cancer, stroke [7], diabetes, and myocardial infarction [8]. Antioxidants from the body (endogenous) are needed to prevent this condition. However, endogenous antioxidants such as the enzymes Superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GSHPx) cannot scavenge the overproduction of free radicals [9]. Antioxidant compounds from outside the body (exogenous antioxidants) can assist in the function of these enzymes. Natural antioxidants can be a source of compounds that can scavenge free radicals [10]. Several studies have reported that the Piperaceae have good antioxidant activity [11–13].

Piperaceae plants contain more than 10 genera and more than 1500 species [14]. These piper species are scattered in various places, and about 700 species are distributed in...
tropical America, 300 species occur in the Asian tropics, and another 15 species are found in Africa [15]. These plants have been widely used in traditional medicine in China, Indonesia, India, and Korea [16] and have many biological activities such as antifungal [17], antioxidant [18], anti-inflammatory [19], antimicrobial [20], and antidiabetic [21].

Bioactive compounds contained in piper species can be used as a source of new drug targets [22]. The bioactive compounds contained in the seeds, leaves, and stem bark are phenolic, tannins, saponins, alkaloids, flavonoids, glycosides, and terpenoids [23,24]. Amide Alkaloids are a unique compound present in *Piper* species; it is based on most of the compounds containing piper ring (pyridine) or pyrrole ring (pyrrolidine) [25]. Furthermore, some *Piper* species have a typical compound such as open-chain alkamides, cyclohexanamid, aristolactams, and ceramides. The main reason *Piper* species are used as a therapeutic alternative based on natural products is the content of bioactive compounds and various biological activities that have been reported in some of these plants. Therefore, the high content of compounds in *Piper* species can be used as the basis for drug discovery. This review aims to obtain information botany, ethnopharmacology, comprehensive compound with structured studies, and the antioxidant activity properties of five *Piper* species (*Piper amalago* L., *Piper betle* L., *Piper hispidum* Sw., *Piper longum* L., and *Piper umbellatum* L.) (see Supplementary Materials).

2. Distribution, Botanical, Traditional Use, and Pharmacological Properties of Five *Piper* Species

*Piper amalago* L. is a plant spread in Brazil and Mexico. In Brazil, this plant is known by the name of “jaborandi-manso” and, in Mexico, this plant is commonly known as “kw’alaal its” [26]. This plant is included in a type of shrub that can reach a height of 2–7 m, the stem and leaves of which contain volatile oils [27]. *P. amalago* can relieve chest pain, and the leaves have been used in traditional medicine in Central America to treat digestive problems and heal burns, abscesses, boils, and insect bites. Chewed leaves are applied to bleeding cuts [28–31].

*P. amalago* has been used in folk medicine to prevent miscarriage and relieve pain in pregnant women and postpartum [32]. Recently, the aqueous extract from *P. amalago* leaves can help heal wounds on the thumbs of patients with type 2 diabetes mellitus for 15 days [33]. In addition, pharmacological studies have shown that *P. amalago* has biological activities like schistosomicidal [34], antimicrobial [35], anxiolytic [36], and anti-inflammatory [28].

*Piper betle* L., green Betel, is cultivated in Indonesia, East Africa, the Philippines, Malaysia, and India [37,38]. About a hundred varieties of this Betel plant are found worldwide—forty grow in Indonesia and thirty grow in Bangladesh [39]. This plant thrives in areas with an altitude of up to 900 m² and is found in areas with high rainfall and hot and humid climates [40,41].

This plant is an evergreen and perennial plant that has a strong stem at the nodes, heart-shaped leaves that alternate and are 15–20 cm in length, and white catkin, with many small roots [42–44]. The roots can climb with the tip of the shoot and can reach 3–10 m; when young, the stems are light green and marked by short lines; however, when mature, they are sturdy, slightly flat, and the internodes are 12 cm long and 1.2 cm in diameter [39].

In Indonesia, raw Betel leaf is chewed to strengthen teeth and whiten teeth [45,46] while, in Sri Lanka, Betel is used in the traditional treatment of peptic ulcers [47]. Regarding ethnomedicines, this plant has been applied in traditional skin and eye medicine [48]. This plant is also used in other traditional medicines such as for the swelling of the gums, rheumatism, abdominal pain, coughs, colds, bronchial asthma, and constipation. Another purpose of using this plant is for the manufacture of insecticides, fish poisoning, perfumes, and oils [49,50].

*P. betle* leaves have been tested for several activities in vitro, such as antimicrobial [51], antidiabetic [52], neuroprotective [53], and antioxidant [54,55]. Abraham et al. [56] reported
that the ethyl acetate extract of \textit{P. betle} leaves can inhibit the proliferation of MCF-7 cells as a chemotherapy agent for breast cancer treatment.

\textit{Piper hispidum} Sw. is an herbaceous plant that spreads in several tropical and subtropical countries in Central and South America [57]. This plant is known by the names “cordoncillo” (Mexico), “bayuoyo” (Cuba), and “jaborandi” (Brazil) [58,59]. This plant is a shrub that has alternating leaves, green cylindrical stems, and roots with sclereids in the parenchyma [60].

\textit{P. hispidum} is commonly used by Nicaraguans to treat pain and wounds, treat urinary tract infections in Brazil, and regulate menstruation in Peru [61]. The flower parts of this plant are used topically to treat muscle pain. Meanwhile, the leaves of the plant are used by the people of Guatemala to treat female reproductive disorders and treat symptoms of skin leishmaniasis [62]. A decoction of \textit{P. hispidum} leaf tea is useful for the treatment of malaria, and an infusion of \textit{P. hispidum} leaves is combined with \textit{P. aduncum} to treat stomach aches and colds in Jamaica [63]. This plant is popular in Ecuador for treating snakebites, insect bites, thrush, diarrhea, and conjunctivitis [30].

Several in vitro activity tests have been carried out on this plant. \textit{P. hispidum} leaf extract has high antibacterial activity against \textit{Enterococcus faecalis}, \textit{Proteus mirabilis}, and \textit{Candida albicans} bacteria [64]. The activity of this extract against MCF-7 cells showed an agonist or inhibitory effect in the formation of new cancer cells [65]. In addition, the pharmacological activity of \textit{P. hispidum} is antioxidant, insecticidal, antiplasmodial, α-amylase, and antifungal activity [66,67].

\textit{Piper longum} L. is referred to as “long pepper” in Javanese, Indian, and Indonesian. The word pepper comes from Sanskrit which means “pippali” [68]. This plant grows in hot areas in India and in some areas in Indonesia as well as in some subtropical areas such as Sri Lanka, America, and the Middle East [69,70]. This plant belongs to the category of vines with perennial woody roots and has heart-shaped leaves with unisexual flowers. The stems can grow from 0.6 to 0.9 m. The fruits, which grow in fleshy spikes 2.4–3.2 cm long and 5 mm thick, are blunt, oblong, and blackish green [71–73].

\textit{P. longum} fruit is used as a spice after the drying process. It is also used as a remedy for diseases of the digestive tract and respiratory tract. During the middle ages, European and Chinese people used this plant as a spice and for curing various digestive ailments [74]. The most important aspect about this plant is that it was used in the traditional medicine system of the Indian tribes, namely Siddha, Ayurveda, and Unani [75,76]. \textit{P. longum} fruit was used in Ayurveda to treat stomach ailments, leprosy, fever, and parasitic infections, while the roots were used to treat tumors and stomach enlargement [77,78].

Piperine is the main compound in \textit{P. longum} and is used to treat bronchitis, dysentery, and insomnia [79,80]. \textit{P. longum} has properties such as anticancer, antioxidant, anti-inflammatory, immunomodulatory, antiplatelet, analgesic, radioprotective, and antifertility [71,72,81].

\textit{Piper umbellatum} L. is an herbaceous plant commonly known as “cow-foot”. It is native to the tropical rainforests of Africa, Amerika, India, and Nigeria. This plant is spread in all geographical areas in Brazil [82]. This plant thrives in cool, humid places with little light. It also grows in forest areas which usually reach 1.0–2.5 m [83,84]. The leaves form an almost circular shape with a dark-green top color and a grayish color on the underside of the leaf. The petiole is 6.5–30 cm long. This plant has small flowers with a width of 0.5–0.8 mm [85].

\textit{P. umbellatum} is usually used for black soup or food seasoning in Nigeria. According to ethnopharmacology research in Cameroon, the roots of this plant are used to treat infertility and the leaves have been proven to treat anemia, genital infections, menstruation, and kidney disorders [86,87]. In Malaysia, the leaves of this plant are used in fish soup dishes because it is believed to have high nutritional value [88]. Every part of this plant is used for medicine in Brazil, such as constipation, colic, edema, and diarrhea. There have been at least 94 traditional medicines derived from this plant [30,89,90].

Based on a scientific literature study, the ethanol extract of the leaves of \textit{P. umbellatum} has antioxidant [91], antifungal [92], anti-inflammatory [93], and anticancer [94] activity.
da Silva et al. [95] investigated the activity of a hydroethanolic extract from *P. umbellatum* leaves, which was very effective in inhibiting the activity of *Enterococcus faecalis*, *Shigella flexneri*, and *Salmonella typhimurium*, with an MIC value of 12.5 µg/mL.

3. Chemical Composition of Five *Piper* Species

3.1. *Piper amalago* L.

One of the main chemical constituents in *piper* species is an essential oil whose composition depends on the species and its growing habitat. In the *P. amalago*, the dominant compounds contained in the leaf extract of this plant are monoterpenes and sesquiterpenes [96–98]. The most abundant chemical fractions in the leaves of this plant are monoterpene hydrocarbons (33–34%), sesquiterpene hydrocarbons (27–37%), and oxygenated sesquiterpenes (27–31%) [32]. Research conducted by Santos et al. [99] stated that the main chemical components in *P. amalago* are α-cadinol (1) (4.96%), β-cedrene (2) (5.15%), germacrene d-4-ol (3) (5.54%), β-murolene (4) (7.85%), (E)-nerolidol (5) (8.08%), dan β-phellandrene (6) (13.64%). Meanwhile, in research conducted by da Silva Mota et al. [100], α-amorphene (7) (25.7 %), p-cymene (8) (9.4 %), and (E)-methyl geranate (9) (7.8 %) were reported as the major constituents. de Ferraz et al. [97] showed β-caryophyllene (10) (4.69%), δ-elemene (11) (6.82%), zingiberene (12) (11.18%), zingiberone (13) (11.18%), and limonene (14) (20.52%) to be the main compounds. Table 1 shows the chemical composition of *P. amalago* found in the leaves, stem, root, flower, and fruit.

Table 1. The chemical compounds of *P. amalago*.

| Compounds                        | RI | Relative Area (%) |
|----------------------------------|----|-------------------|
|                                 | RICalc [100,101] | RILit [100,101] | Unripe Fruit [101] | Ripe Fruit [101] | Flower [100] | Root [100] | Stem [100] | Leaf [100] |
| Ethyl isovalerate (15)           | 858 | 858               | 2.9               | 0.4               | 0.1           |
| Tricyclene (16)                  | 925 | 926               | 0.1               | 0.1               |
| α-Thujene (17)                   | 929 | 930               | 0.8               | 1.8               |
| α-Pinene (18)                    | 933 | 939               | 0.7               | 3.6               |
| Camphene (19)                    | 951 | 953               | 0.2               | 2.6               |
| Verbenene (20)                   | 967 | 968               | 1.3               | 3.0               |
| Sabinene (21)                    | 974 | 975               | 0.2               | 0.8               |
| β-Pinene (22)                    | 980 | 979               | 1.5               | 3.6               |
| endo-Norborneol (23)             | 985 | 986               | 1.8               | 2.6               |
| β-Myrcene (24)                   | 988 | 991               | 2.4               | 3.9               |
| Pyrazine 2,3,5-trimethyl (25)     | 1000| 1000              | 0.4               | 0.4               |
| δ-Carene (26)                    | 1001| 1002              | 1.1               | 0.4               |
| α-Phellandrene (27)              | 1008| 1005              | 0.7               | 2.2               |
| p-Cymene (8)                     | 1024| 1025              | 0.7               | 2.2               |
| α-Cymene (28)                    | 1025| 1026              | 1.1               | 3.0               |
| Limonone (14)                    | 1029| 1029              | 1.0               | 3.0               |
| β-Phellandrene (6)               | 1032| 1031              | 8.2               | 3.0               |
| 1,8-Cineole (29)                 | 1034| 1033              | 0.3               | 0.9               |
| Acetyl pyridine (30)             | 1034| 1034              | 0.1               | 0.3               |
| (Z)-β-Ocimene (31)               | 1037| 1037              | <0.1              | 3.0               |
| γ-Terpine (32)                   | 1058| 1062              | <0.1              | 0.1               |
| cis-Sabinene hydrate (33)        | 1072| 1068              | <0.1              | 0.2               |
| Benzyl formate (34)              | 1077| 1076              | 0.2               | 1.4               |
| p-Mentha-2,4(8)-diene (35)       | 1087| 1086              | <0.1              | 0.9               |
| Terpinolene (36)                 | 1090| 1089              | 4.6               | 6.0               |
| p-Cymene (37)                    | 1092| 1091              | 3.4               |
| Linalool (38)                    | 1101| 1098              | 2.0               |
| cis-Pinene hydrate (39)          | 1127| 1121              | 0.06              |
| Compounds                              | RI Calc [100,101] | RI Lit [100,101] | Unripe Fruit [101] | Ripe Fruit [101] | Flower [100] | Root [100] | Stem [100] | Leaf [100] |
|----------------------------------------|-------------------|------------------|-------------------|-----------------|--------------|------------|------------|------------|
| Pyrazine 3-methyl-2-isobutyl (40)      | 1137              | 1137             | 0.3               | 0.2             |              |            |            |            |
| cis-β-Terpineol (41)                   | 1145              | 1144             | 0.04              |                 |              |            |            |            |
| Menthol (42)                           | 1173              | 1172             | 1.1               | 0.2             |              |            |            |            |
| Bornol (43)                            | 1175              | 1165             | 0.1               |                 |              |            |            |            |
| 4-Terpineol (44)                       | 1183              | 1177             | 0.3               | 0.2             |              |            |            |            |
| α-Terpineol (45)                       | 1188              | 1189             | 0.2               | 0.5             | 1.3          | 1.2        | 0.1        |            |
| Cryptone (46)                          | 1191              | 1185             | 0.1               | 0.9             |              |            |            |            |
| trans-Dihydro carveol acetate (47)     | 1308              | 1307             | 1.3               | 0.2             |              |            |            |            |
| iso-Verbenol acetate (48)              | 1310              | 1310             | 0.7               | 3.2             | 5.1          |            |            |            |
| (E)-Methyl geranate (49)               | 1325              | 1325             | 1.1               | 1.3             | 2.3          | 7.8        |            |            |
| γ-Elemene (49)                         | 1335              | 1339             | 0.4               | 0.5             |              |            |            |            |
| Presilphiperfol-7-ene (50)             | 1337              | 1337             | 3.3               | 0.4             |              |            |            |            |
| α-Cubebene (51)                        | 1347              | 1351             | 0.2               | 0.1             |              |            |            |            |
| (Z)-β-Damascone (52)                   | 1364              | 1364             | 0.6               | 0.6             | 0.2          |            |            |            |
| Cyclasativene (53)                     | 1371              | 1371             | 0.1               | <0.1            | 1.2          | 0.2        |            |            |
| Longicyclene (54)                      | 1373              | 1374             | 1.2               | 2.2             | 2.1          | 0.2        |            |            |
| α-Copaene (55)                         | 1376              | 1376             | 3.0               | 0.7             |              |            |            |            |
| Silphiperfol-6-ene (56)                | 1379              | 1378             | 13.5              | 2.4             |              |            |            |            |
| β-Bourbonene (57)                      | 1384              | 1384             | 0.2               | 0.2             |              |            |            |            |
| β-Cubebene (58)                        | 1388              | 1390             | 3.3               | 2.5             |              |            |            |            |
| β-Elemene (59)                         | 1390              | 1391             | 0.5               |                 |              |            |            |            |
| Sativene (60)                          | 1392              | 1392             | 1.1               | 0.2             | 0.1          |            |            |            |
| Longifolene (61)                       | 1407              | 1408             | 1.2               | 2.3             | 6.6          | 3.0        |            |            |
| α-Gurjunene (62)                       | 1411              | 1410             | 0.5               |                 | 4.4          | 1.1        |            |            |
| β-Funenebene (63)                      | 1416              | 1415             | 1.3               | 0.3             |              |            |            |            |
| β-Caryophyllene (10)                   | 1420              | 1418             | 2.6               | 2.7             |              |            |            |            |
| β-Cedrene (2)                          | 1421              | 1421             | 0.4               | 1.1             | 0.2          |            |            |            |
| β-Duprezianene (64)                    | 1423              | 1423             | 1.0               | 1.0             | 0.4          |            |            |            |
| β-Copaene (65)                         | 1433              | 1432             | 1.2               |                 | 1.2          | 0.2        |            |            |
| β-Gurjunene (66)                       | 1434              | 1434             | 0.2               |                 | 1.2          | 1.2        | 0.2        |            |
| Aromadendrene (67)                     | 1441              | 1441             | 0.1               | <0.1            | 1.1          | 1.1        | 0.2        |            |
| (Z)-β-Farnesene (68)                   | 1443              | 1443             | 2.4               | 1.4             |              |            |            |            |
| Cedrane (69)                           | 1444              | 1444             | 2.5               |                 | 0.8          |            |            |            |
| epi-β-Santalene (70)                   | 1448              | 1447             | 0.5               |                 |              |            |            |            |
| cis-Muurola-3, 5-diene (71)            | 1450              | 1450             | 1.4               | 1.1             | 0.1          |            |            |            |
| α-Himachalene (72)                     | 1451              | 1451             | 1.6               | 0.5             |              |            |            |            |
| α-Humulene (73)                        | 1456              | 1454             | 1.0               | 0.8             |              |            |            |            |
| α-Patchouline (74)                     | 1457              | 1457             | 3.9               |                 |              |            |            |            |
| allo-Aromadendrene (75)                | 1459              | 1460             | 7.0               |                 | 0.1          |            |            |            |
| Seychellene (76)                       | 1460              | 1460             | <0.1              |                 |              |            |            |            |
| cis-Muurola-4(14),5-diene (77)         | 1468              | 1467             | 0.5               | 2.2             | 1.2          | 0.5        |            |            |
| β-Acoradiene (78)                      | 1471              | 1471             | 1.2               |                 | 1.1          |            |            |            |
| γ-Himachalene (79)                     | 1475              | 1476             | 2.3               |                 |              |            |            |            |
| trans-Cadina-1(6),4-diene (80)         | 1477              | 1477             | 1.3               | 0.3             |              |            |            |            |
| β-Chamigrene (81)                      | 1478              | 1478             | 1.3               | 1.3             |              |            |            |            |
| γ-Muurolene (82)                       | 1479              | 1480             | 2.1               | 0.1             |              |            |            |            |
| α-Amorphene (7)                        | 1485              | 1485             | 2.0               | 14.4            | 23.3         | 25.7       |            |            |
| Germacrene D (83)                      | 1485              | 1485             | 2.0               | 1.0             | 18.5         | 0.2        |            |            |
| trans-Muurola-4(14),5-diene (84)       | 1494              | 1494             | 0.6               | 1.6             | 1.5          | 1.1        |            |            |
| Bicyclogermacrene (85)                 | 1496              | 1496             | 9.1               | 3.0             |              |            |            |            |
| γ-Amorphene (86)                       | 1496              | 1496             | 0.3               |                 | 0.3          |            |            |            |
| Valencene (87)                         | 1497              | 1496             | 0.3               | 1.1             |              |            |            |            |
| α-Muurolene (88)                       | 1501              | 1500             | 1.5               | <0.1            | 0.5          | 1.2        | 1.2        |            |
Table 1. Cont.

| Compounds           | RI Calc [100,101] | RI Lit [100,101] | Unripe Fruit [101] | Ripe Fruit [101] | Flower [100] | Root [100] | Stem [100] | Leaf [100] |
|---------------------|-------------------|------------------|--------------------|------------------|-------------|------------|------------|-----------|
| Epizonarene (89)    | 1502              | 1502             | 0.9                | 0.7              |             |            |            |           |
| Germacrene A (90)   | 1507              | 1503             | 0.9                | 0.7              |             |            |            |           |
| (Z)-α-Bisabolene (91)| 1507             | 1507             | 0.9                | 0.7              |             |            |            |           |
| Cuparene (92)       | 1505              | 1505             | 0.9                | 0.7              |             |            |            |           |
| γ-Cadinene (93)     | 1514              | 1514             | 0.9                | 0.7              |             |            |            |           |
| Myristicin (94)     | 1519              | 1519             | 0.9                | 0.7              |             |            |            |           |
| cis-Calamenene (95) | 1521              | 1521             | 0.9                | 0.7              |             |            |            |           |
| Eugenyl acetate (96)| 1523              | 1523             | 0.9                | 0.7              |             |            |            |           |
| (Z)-α-Bisabolene (97)| 1523             | 1523             | 0.9                | 0.7              |             |            |            |           |
| α-Calamene (98)     | 1542              | 1542             | 0.9                | 0.7              |             |            |            |           |
| α-Elemol (99)       | 1549              | 1550             | 0.9                | 0.7              |             |            |            |           |
| Italicene epoxide (100)| 1549         | 1549             | 0.9                | 0.7              |             |            |            |           |
| (E)-Nerolidol (5)   | 1561              | 1564             | 0.9                | 0.7              |             |            |            |           |
| epi-Longipinanol (101)| 1564           | 1564             | 0.9                | 0.7              |             |            |            |           |
| (Z)-Isoelemicin (102)| 1567            | 1570             | 0.9                | 0.7              |             |            |            |           |
| Germacrene d-4-ol (3)| 1578            | 1578             | 0.9                | 0.7              |             |            |            |           |
| Spathulenol (103)   | 1578              | 1578             | 0.9                | 0.7              |             |            |            |           |
| Caryophyllene oxide (104)| 1583        | 1581             | 0.9                | 0.7              |             |            |            |           |
| Thujopsan-2-β-ol (105)| 1587           | 1587             | 0.9                | 0.7              |             |            |            |           |
| Globulol (106)      | 1588              | 1583             | 0.9                | 0.7              |             |            |            |           |
| Carotol (107)       | 1591              | 1591             | 0.9                | 0.7              |             |            |            |           |
| Guaio1 (108)        | 1600              | 1601             | 0.9                | 0.7              |             |            |            |           |
| 1,10-epi-Cubenol (109)| 1619         | 1619             | 0.9                | 0.7              |             |            |            |           |
| ep-L-Cedrol (110)   | 1619              | 1619             | 0.9                | 0.7              |             |            |            |           |
| Eremoligenol (111)  | 1631              | 1631             | 0.9                | 0.7              |             |            |            |           |
| γ-Eudesmol (112)    | 1632              | 1632             | 0.9                | 0.7              |             |            |            |           |
| α-Acorenol (113)    | 1633              | 1633             | 0.9                | 0.7              |             |            |            |           |
| β-Acorenol (114)    | 1637              | 1637             | 0.9                | 0.7              |             |            |            |           |
| Cubenol (115)       | 1643              | 1643             | 0.9                | 0.7              |             |            |            |           |
| epix-Cadinol (116)  | 1644              | 1640             | 0.9                | 0.7              |             |            |            |           |
| α-Murolol (117)     | 1645              | 1646             | 0.9                | 0.7              |             |            |            |           |
| epix-Murolol (118)  | 1646              | 1641             | 0.9                | 0.7              |             |            |            |           |
| α-Cadinol (1)       | 1658              | 1653             | 0.9                | 0.7              |             |            |            |           |
| neo-Intermedeol (119)| 1661           | 1660             | 0.9                | 0.7              |             |            |            |           |
| Bulnesol (120)      | 1672              | 1672             | 0.9                | 0.7              |             |            |            |           |
| α-Bisabolol (121)   | 1672              | 1683             | 0.9                | 0.7              |             |            |            |           |
| neo-5-Cedranol (122)| 1685              | 1685             | 0.9                | 0.7              |             |            |            |           |
| Oplopanone (123)    | 1737              | 1733             | 0.9                | 0.7              |             |            |            |           |
| Khusinol acetate (124)| 1829            | 1816             | 0.9                | 0.7              |             |            |            |           |

RIcal = Retention indices relative (C₈–C₂₆) and apolar DB-5 column; RILit = Retention indices literature.

3.2. Piper betle L.

Based on proximate analysis, P. betle leaves contain water (85–90%), protein (3–3.5%), minerals (2.3–3.3%), carbohydrate (0.5–6.10%), essential oil (0.08–0.2%), vitamin A (1.9–2.9 mg/100 g), chlorophyll (0.01–0.25%), fiber (0.4–1.0%), calcium (0.2–0.5%) [102]. A preliminary phytochemical analysis of P. betle showed the presence of terpenes, phenols, saponin, alkaloids, amino acids, tannins, flavonoids, and steroids [21,37]. Moreover, the phytochemical analysis performed by Kaveti et al. [103] revealed that the P. betle water extract contains alkaloids, reducing sugars, saponins, tannins, and glycosides. Nowadays, bioactive compounds derived from P. betle have been widely studied using several instruments. 4-ρ-coumaroylquinic acid (125) and 3-ρ-coumaroylquinic acid (126) were identified using the HPLC/Electrospray Ionization Mass Spectrometric (ESI-MS) [104]. Furthermore, compounds such as 4-chromanol (127) (27.81%), phenol 2 methoxy 4-(-2-propenyl) ac-
etate (128) (61.5%), and eugenol (129) (20.37%), using aqueous and ethanol extracts, were identified by gas chromatography–mass spectrometry (GC-MS) [105]. Table 2 shows the compounds that were isolated from *P. betle* using several different types of extraction.

Table 2. List of isolated bioactive compounds identified from leaves extract of *P. betle*.

| Classification | Compounds | Rt. (min.) | Percentage (%) | References |
|----------------|-----------|------------|----------------|------------|
| Chloroform extract was identified using nuclear magnetic resonance (NMR) | 1-n-dodecanyloxy resorcinol (130) | 3.874 | 0.34 | [15] |
| Ethanol extract using ultrasound-assisted extraction | Isoeugenol (131), eugenol (129), hydroxychavicol (132) | 10.150 | 0.09 | [106] |
| Soxhlet extraction | 4-Allyl-1,2-diacetoxybenzene (133), 4-chromanol (127), hydroxychavicol (132), eugenol (129) | 5.403 | 0.10 | [107] |
| Hexane, ethyl acetate, and ethanol extract | Eugenol (129), 4-Allyl-1,2-diacetoxybenzene (133), Benzeneacetic acid (134), eugenol (129), | 5.176 | 1.19 | [108] |
| Crude aqueous extract | hexadecanoic acid (135), octadecanoic acid (136), hydroxychavicol (132) | 4.290 | 0.83 | [109] |

*P. betle* contains 0.08–0.2% essential oil, which is classified as aldehydes, phenylpropanoids, sesquiterpenes, and monoterpenes (Table 3). Table 3 shows GC-MS data on the number of essential oils to *P. betle* compared from two different places, namely Bogor, Indonesia, and Varanasi, India. Major components of *P. betle* essential oil are phenolics such as chavibetol (137) (53.1%), safrole (138) (48.69%), and 2-allyl-6-methoxyphenol (139) (25.96%). Another study found several prime compounds including linalool (38), α-humulene (73), methyl eugenol (140), 1, 8-cineole (29), p-cymene (8), 4-Allyl-2-methoxy-phenolacetate (141), β-caryophyllene (10), α-terpinene (142), and methyl chavicol (143) [48,110,111].

Table 3. List of isolated bioactive compounds identified from leaves extract of *P. betle*.

| Classification | Compounds | Rt. (min.) | Percentage (%) | Rt. (min.) | Percentage (%) |
|----------------|-----------|------------|----------------|------------|----------------|
| Monoterpenes | α-Pinene (18) | 3.874 | 0.34 | 9.6 | 0.09 |
| | Camphene (19) | 4.290 | 0.83 | 10.150 | 0.09 |
| | Limonene (14) | 3.761 | 0.34 | 13.100 | 0.28 |
| | Sabinene (21) | 4.425 | 0.61 | 5.176 | 1.19 |
| | γ-Muurolene (82) | 5.722 | 0.99 | 5.403 | 0.10 |
| | β-Myrcene (24) | 5.043 | 0.15 | 5.922 | 0.99 |
| | α-Phellandrene | 5.846 | 0.23 | 5.846 | 0.15 |
| | (E)-β-Ocimene (144) | 6.467 | 0.23 | 6.548 | 0.71 |
| | α-Terpinene (32) | 6.548 | 0.71 | 6.548 | 0.71 |
| Classification | Compounds | Rt. (min.) | Percentage (%) | Rt. (min.) | Percentage (%) |
|----------------|-----------|------------|----------------|------------|----------------|
| **Sesquiterpenes** | Germacrene D (83) | 21.020 | 0.75 | 34.251 | 2.85 |
| | Germacrene B (145) | | | 34.876 | 0.81 |
| | γ-Muurolene (82) | 20.912 | 2.84 | 33.926 | 1.27 |
| | α-Humulene (73) | 20.269 | 3.03 | 33.01 | 0.68 |
| | β-Caryophyllene (10) | 19.291 | 4.13 | 31.501 | 4.22 |
| | β-Elemene (59) | 18.378 | 0.61 | 30.176 | 0.24 |
| | Ledane (146) | | | 39.001 | 0.18 |
| | Globulol (106) | 40.126 | 0.12 | | |
| | γ-Cadinene (93) | 14.978 | 5.87 | 40.926 | 3.85 |
| | α-Copaene (55) | 17.957 | 0.83 | | |
| | Aromadendrene (67) | 20.442 | 0.07 | | |
| | β-Selinene (147) | 21.225 | 5.52 | | |
| | δ-Cadinene (97) | 22.171 | 0.72 | | |
| | Caryophyllene Epoxide (148) | 23.521 | 0.16 | | |
| **Phenylpropanoids** | Chavicol (149) | 12.517 | 6.64 | 23.275 | 0.55 |
| | Eugenol (129) | 16.461 | 0.17 | 28.851 | 63.39 |
| | Methyl eugenol (140) | | | 30.426 | 0.21 |
| | Acetyl eugenol (150) | 21.522 | 9.62 | 35.826 | 14.05 |
| | Isoeugenol (131) | 9.968 | 0.52 | | |
| | Isoestragole (151) | 17.114 | 20.71 | | |
| | Chavicol acetate (152) | 16.120 | 17.75 | | |
| | Acetyl Isoeugenol (153) | 21.603 | 3.96 | | |
| **Aldehydes** | Decanal (154) | | | 20.975 | 0.18 |
| | Undecanal (155) | | | 30.576 | 0.43 |
| | Phenylacetaldehyde (156) | | | 13.650 | 0.13 |

Rt = Retention Time.

### 3.3. *Piper hispidum* Sw.

Several secondary metabolites contained in *P. hispidum* that have been reported include amides, flavonoids, and butenolides. Recently, two amides have been isolated using the supercritical carbon dioxide method, namely (3Z,5Z)-N-isobutyl-8-(3′,4′-methylenedioxyphenyl)heptadienamide ([157]) and N-[3-(6′-methoxy-3′,4′-methylenedioxyphenyl)-2(Z)-propenoyl]pyrrolidine ([158]) [114]. In another study, Ruiz et al. [115] succeeded in isolating a compound from the leaves of *P. hispidum*, namely piperamine ([159]) and piperine ([160]). The chalcones group of flavonoids was isolated from *P. hispidum*, specifically 2′-hydroxy-3′,4′,6′-tetramethoxychalcone ([161]), 2′-hydroxy-4′,6′-trimethoxychalcone ([162]), and 2′,3-dihydroxy-4′,6′-trimethoxychalcone ([163]) were successfully isolated from the same part of *P. hispidum* [116]. Ruiz et al. [115] successfully isolated and characterized 2′-hydroxy-3′,4′,6′-trimethoxychalcone ([164]) from the leaves extract of *P. hispidum*. Meanwhile, a new compound belonging to the butenolide group that was isolated from *P. hispidum* leaves was 9,10-methylenedioxy-5,6-Z-fadyenolide ([165]) [117].

Most of the essential oils identified from the leaves of *P. hispidum* belong to the monoterpenes and sesquiterpenes groups. *P. hispidum* essential oils also presented phenylpropanoids and alcohols. Table 4 shows GCMS data comparing the essential oil content identified by several researchers.
Table 4. Chemical composition of the essential oils of *P. hispidum*.

| Compounds                              | Content Essential Oil of *P. hispidum* (%) |
|----------------------------------------|-------------------------------------------|
|                                        | [57] | [58] | [64] |
| (E)-3-Hexen-1-ol (166)                 | 1.0  | 0.1  |      |
| α-Thujene (17)                         |      |      |      |
| α-Pinene (18)                          | 6.6  | 1.2  | 15.3 |
| Sabinene (21)                          | 0.3  |      |      |
| β-Pinene (22)                          | 12.0 | 1.1  | 14.8 |
| Sylvestrene (167)                      | 1.7  |      |      |
| (Z)-β-Ocimene (31)                     | 1.4  |      |      |
| *trans*-Sabinene hydrate (168)         | 0.5  |      |      |
| Terpinen-4-ol (169)                    | 0.3  | 1.0  |      |
| *iso*-Dihydrocarveol (170)             | 0.4  |      |      |
| Camphene (19)                          | 0.1  | 0.4  |      |
| 6-Methyl-5-heptene-2-one (171)         | 0.5  |      |      |
| β-Myrce (24)                           |      |      |      |
| α-Phellandrene (27)                    | 1.2  | 0.9  |      |
| δ-Carene (26)                          | 0.5  |      |      |
| α-Terpinene (142)                      |      |      | 6.9  |
| *p*-Cymene (8)                         | 14.0 |      |      |
| β-Phellandrene (6)                     | 1.4  | 0.3  |      |
| γ-Terpinene (32)                       | 30.9 |      |      |
| Terpinolene (36)                       | 7.3  |      |      |
| Verbenene (20)                         |      | 0.5  |      |
| Limonene (14)                          |      | 2.3  |      |
| 1,3,8-*p*-Menthatriene (172)           |      | 0.2  |      |
| (E)-Pinocarveol (173)                  |      | 0.5  |      |
| Aromadendrene (67)                     |      |      | 1.4  |
| δ-Elemene (11)                         | 0.3  |      |      |
| α-Cubebene (51)                        | 0.4  |      |      |
| α-Humulene (73)                        |      | 0.4  | 0.6  |
| β-Elemene (59)                         |      |      | 8.1  |
| α-Copaene (55)                         | 0.9  | 0.5  | 1.8  |
| β-Cubebe (58)                          | 0.5  |      |      |
| α-Gurjunene (62)                       | 1.0  |      |      |
| β-Gurjunene (66)                       |      | 0.8  |      |
| γ-Gurjunene (174)                      |      | 0.4  |      |
| β-Caryophyllene (10)                   |      | 5.3  | 6.2  |
| Khusimene (175)                        |      | 12.1 |      |
| α-neo-Clovene (176)                    | 1.1  |      |      |
| β-Chamigrene (81)                      |      | 1.6  |      |
| (E)-Ocimeneone (177)                   |      | 0.6  |      |
| *cis*-Calamene (95)                    |      | 0.6  |      |
| *cis*-β-Guaiene (178)                  | 1.3  |      |      |
| β-Selinene (147)                       | 1.0  | 8.1  |      |
| β-Bourbonene (57)                      |      |      | 0.5  |
| Valencene (87)                         | 2.0  |      | 0.9  |
| Myrtenol (179)                         |      | 0.6  |      |
| Viridiflore (180)                      | 3.4  |      | 1.0  |
| α-Selinene (181)                       | 3.6  |      | 9.0  |
| Epizonarene (89)                       |      | 0.1  |      |
### Table 4. Cont.

| Compounds                                | Content Essential Oil of *P. hispidum* (%) |
|------------------------------------------|-------------------------------------------|
|                                          | [57] | [58] | [64] |
| γ-Cadinene (93)                          | 13.2 | 0.4  | 0.8  |
| δ-Cadinene (97)                          | 6.3  |      |      |
| α-Murolene (88)                          |      | 0.2  |      |
| Selina-3,7(11)-diene (182)               | 0.6  |      |      |
| Germacrene A (90)                        |      | 0.9  |      |
| Germacrene B (145)                       | 0.3  | 5.2  |      |
| Ledol (183)                              | 8.8  |      |      |
| Globulol (106)                           | 0.7  | 1.2  |      |
| 7-epi-α-selinene (184)                   |      | 0.2  |      |
| Viridifloral (185)                       | 3.0  |      |      |
| 10-epi-Eudesmol (186)                    | 1.1  |      |      |
| β-Eudesmol (187)                         |      | 2.6  |      |
| Hinesol (188)                            | 0.3  |      |      |
| Cubenol (115)                            | 4.2  |      |      |
| Selin-11-en-4-α-ol (189)                 | 1.9  | 2.0  |      |
| epi-α-Cadinol (116)                      |      | 0.5  |      |
| Guaiol acetate (190)                     | 0.6  |      |      |
| Spathulenol (103)                        |      |      | 5.0  |
| Caryophyllene oxide (104)                |      |      | 7.8  |

### 3.4. *Piper Longum* L.

Alkaloids, terpenoids, sterols, and essential oils are chemical compounds isolated from *P. longum*. The plant parts that have been studied to date are fruits, roots, leaves, and seeds [118]. Piperine is the most abundant compound in the fruit of *P. longum*. In addition, several compounds were isolated, including asarinine (191), pellitorine (192), retrofractamide A (193), piperlongumine (194), brachystamide A (195), and longamide A (196) [76,119]. Table 5 shows that there are compounds that have been isolated from several parts of *P. longum*.

### Table 5. Other bioactive compounds of *P. longum* [68,118].

| Compounds               | Part Used | Compounds               | Part Used |
|-------------------------|-----------|-------------------------|-----------|
| Piperrolein B (197)     | Fruit     | Cepharadione B (203)    | Root      |
| Dehydropipernonaline (198)| Fruit     | Cepharadione A (204)    | Root      |
| Rosin (199)             | Fruit     | Methylpiperate (205)    | Fruit     |
| Piperchabaoside A (200) | Fruit     | (+)-Diaeudesmin (206)   | Seed      |
| Sylvatine (201)         | Seed      | Aristolactam (207)      | Root      |
| Sesamin (202)           | Seed      | Piperoctadecalidine (208)| Fruit    |

The essential oils isolated from *P. longum* are shown in Table 6, along with their percentages. Forty-nine compounds representing the total essential oils were identified in the leaf, fruit, stem, and root of *P. longum*. This consisted of monoterpenes, aromatic ester, and sesquiterpenes.
Table 6. Other essential oils’ compositions of *P. longum* [120].

| Compound                        | Content Essential Oil of *P. longum* (%) |
|---------------------------------|-----------------------------------------|
|                                 | Root | Stem | Fruit | Leaf |
| α-Pinene (18)                   | 11.8 | 14.0 | 15.3  | 0.3  |
| Camphene (19)                   | 13.9 | 6.6  | 0.7   |      |
| β-Pinene (22)                   | 26.4 | 34.8 | 43.1  | 1.6  |
| β-Myrcene (24)                  | 1.5  | 1.6  | 1.4   |      |
| α-Phellandrene (27)             | 0.2  | 0.4  |       |      |
| β-Phellandrene (6)              | 1.0  | 0.7  | 1.4   |      |
| Limonene (14)                   | 6.3  | 10.3 | 9.6   | 0.7  |
| 1,8-Cineole (29)                | 0.9  | 0.8  |       |      |
| (E)-β-Ocimene (144)             | 0.7  | 0.6  |       |      |
| (Z)-β-Ocimene (31)              | 0.9  | 0.8  |       |      |
| Terpinolene (36)                | 0.4  | 0.5  |       |      |
| Linalool (38)                   | 0.8  | 1.1  | 1.2   |      |
| 1-Methylhexyl acetate (209)     |      |      | 2.5   | 0.3  |
| 2-Nonanone (210)                |      |      | 1.3   |      |
| α-Terpineol (45)                |      |      | 0.4   | 0.5  |
| Decanal (154)                   |      |      | 0.4   |      |
| Bornyl acetate (211)            | 10.0 | 5.0  | 0.6   |      |
| 2-Undecanone (212)              | 0.8  | 1.0  | 2.9   | 2.0  |
| Tridecane (213)                 | 0.6  | 0.7  |       |      |
| δ-Elemene (11)                  | 5.8  | 1.6  |       |      |
| γ-Elemene (49)                  | 1.4  |      |       |      |
| Terpinyl acetate (214)          | 1.1  | 0.5  |       |      |
| α-Copaene (55)                  |      |      | 0.9   |      |
| β-Cubebene (58)                 |      |      | 2.3   |      |
| β-Elemene (59)                  | 0.1  |      | 1.4   |      |
| Dodecanal (215)                 |      |      | 0.4   |      |
| β-Caryophyllene (10)            | 5.6  | 9.3  | 5.7   | 16.8 |
| cis-β-Guaiene (178)             |      |      | 0.6   |      |
| α-Gurjunene (62)                | 0.8  |      | 2.6   |      |
| α-Humulene (73)                 | 0.4  | 2.3  | 5.8   |      |
| (Z)-α-Farnesene (216)           |      |      | 0.3   |      |
| γ-Muurolene (82)                |      |      | 0.6   |      |
| 1-Pentadecene (217)             | 0.6  |      |       |      |
| 2-Tridecanone (218)             |      |      | 0.9   | 0.4  |
| Pentadecane (219)               | 5.0  | 0.7  | 1.8   |      |
| α-Muurolene (88)                |      |      |       |      |
| β-Patchoulene (220)             | 0.7  | 0.8  |       |      |
| γ-Bisabolene (221)              |      |      | 0.6   |      |
| γ-Cadinene (93)                 |      |      | 0.8   |      |
| (E)-Nerolidol (5)               | 1.0  | 2.2  | 8.8   | 22.5 |
| α-Elemol (99)                   |      |      | 0.6   |      |
| Germacrene A (90)               |      |      | 0.5   |      |
| Caryophyllene oxide (104)       | 1.1  | 0.9  | 2.1   |      |
| δ-Cadinol (222)                 | 0.1  |      | 1.9   |      |
| α-Cadinol (1)                   |      |      | 0.5   |      |
| β-Eudesmol (187)                |      |      | 3.3   |      |
| α-Eudesmol (223)                |      |      | 0.7   |      |
| Heptadecane (224)               | 0.4  |      |       |      |
| 9-Eicosyne (225)                |      |      | 1.5   |      |

3.5. *Piper Umbellatum* L.

In general, the bioactive compounds contained in *P. umbellatum* are alkaloids, flavonoids, sterols, and terpenoids (which are generally found in essential oils). Piperumbellactam A–D (226–229) are each classified as an alkaloid compound, which is a pure compound that has recently been discovered in the branch of plants [121]. Other bioactive compounds in *P. umbellatum* are shown in Table 7. Most of the essential oils belong to the monoterpenes and
sesquiterpenes groups. Table 8 shows that there are forty-eight essential oil compounds that have been isolated from the leaves of *P. umbellatum*.

**Table 7. Chemical constituents of *P. umbellatum*.**

| Compounds                                      | Plant Part       | References |
|------------------------------------------------|------------------|------------|
| *N*-Hydroxyaristolam II (230)                  | Branches         | [121]      |
| Acacetin-7-O-β-D-galactopyranoside (231)       | Branches         | [121]      |
| Rhoifolin (232)                                | Branches         | [121]      |
| Campestrol (233)                               | Aerial parts     | [122]      |
| β-Sitosterol (234)                             | Aerial parts     | [122]      |
| Stigmasterol (235)                             | Aerial parts     | [122]      |
| 4-Nerolylcatechol (236)                        | Roots            | [121]      |
| N-p-Coumaroyl tyramine (237)                   | Branches         | [121]      |
| N-trans-Feruloyl tyramine (238)                | Branches         | [121]      |

**Table 8. List of essential oil of *P. umbellatum* [84].**

| Components                                      | Ria   | Rip   | Percentage (%) |
|------------------------------------------------|-------|-------|----------------|
| α-Pinene (18)                                  | 931   | 1020  | 0.2            |
| 6-Methyl-hept-5-en-2-one (239)                  | 961   | 1344  | 0.1            |
| Sabine (21)                                     | 966   | 1127  | 0.1            |
| β-Pinene (22)                                  | 972   | 1117  | 0.5            |
| β-Myrcene (24)                                 | 981   | 1165  | 0.5            |
| α-Phellandrene (27)                            | 998   | 1171  | 0.2            |
| δ-Carene (26)                                  | 1006  | 1154  | 0.1            |
| p-Cymene (8)                                   | 1012  | 1277  | 0.3            |
| Limonene (14)                                  | 1022  | 1207  | 12.5           |
| 1, 8-Cineole (29)                              | 1022  | 1216  | 0.1            |
| (Z)-β-Ocimene (31)                             | 1025  | 1237  | 0.5            |
| (E)-β-Ocimene (144)                            | 1036  | 1254  | 0.2            |
| γ-Terpine (32)                                 | 1049  | 1250  | 0.1            |
| Octan-1-ol (240)                               | 1052  | 1552  | 0.1            |
| Terpinolene (36)                               | 1079  | 1289  | 0.1            |
| Linalool (38)                                  | 1085  | 1352  | 41.1           |
| Camphor (241)                                  | 1123  | 1527  | 0.1            |
| 4-Terpine (44)                                 | 1163  | 1597  | 0.3            |
| α-Terpine (45)                                 | 1173  | 1703  | 1.1            |
| Nerol (242)                                    | 1207  | 1798  | 0.1            |
| Neral (243)                                    | 1210  | 1676  | 0.2            |
| Geraniol (244)                                 | 1234  | 1842  | 0.1            |
| Safrole (138)                                  | 1263  | 1861  | 0.1            |
| Thymol (245)                                   | 1267  | 2193  | 4.3            |
| α-Copaene (55)                                 | 1377  | 1497  | 0.1            |
| β-Elemene (59)                                 | 1399  | 1595  | 0.5            |
| β-Caryophyllene (10)                           | 1421  | 1605  | 19.3           |
| γ-Elemène (49)                                 | 1429  | 1635  | 0.2            |
| trans-α-Bergamotene (246)                      | 1435  | 1579  | 0.2            |
| (E)-β-Farnesene (247)                          | 1447  | 1669  | 0.2            |
| α-Humulene (73)                                | 1453  | 1676  | 1.3            |
| γ-Murolene (82)                                | 1472  | 1693  | 0.2            |
| Germacrene D (83)                              | 1478  | 1703  | 1.2            |
| β-Selinene (147)                               | 1484  | 1715  | 0.9            |
| Bicyclogermae (85)                             | 1493  | 1728  | 0.9            |
| (E)-α-Farnesene (248)                          | 1496  | 1752  | 1.2            |
| β-Bisabolene (249)                             | 1501  | 1723  | 0.8            |
| β-Sesquiphellandrene (250)                     | 1508  | 1762  | 0.2            |
| β-Cadinene (97)                                | 1516  | 1752  | 0.3            |
| β-Elemol (251)                                 | 1535  | 2071  | 0.3            |
| (E)-Nerol (5)                                  | 1548  | 2045  | 4.3            |
| Caryophyllene oxide (104)                      | 1573  | 1993  | 0.8            |
| Humulene oxide II (252)                        | 1597  | 2050  | 0.1            |
| γ-Eudesmol (112)                               | 1620  | 2176  | 0.1            |
| β-Eudesmol (187)                               | 1632  | 2238  | 0.1            |
| α-Eudesmol (223)                               | 1637  | 2228  | 0.1            |
| (E)-Phytol (255)                               | 2099  | 2613  | 1.8            |

Ria: retention indices measured on apolar (BP-1); Rip: retention indices measured on apolar (BP-20).
4. Antioxidant Properties

The chain of chemical reactions can take place well in life because there is oxygen from the air for the oxidation process, which provides energy in the form of ATP [123]. Furthermore, oxygen can be produced from the oxidation-reduction process in a living organism. This process also takes place in the transfer of electrons from one atom to another atom [124]. However, when the flow of electrons is problematic, it will cause unpaired single electrons to produce free radicals. Free radicals are molecules, ions, or atoms that have unpaired electrons in their outer orbitals; therefore, they are very active and react with other molecules by oxidizing or reducing other atoms. Free radicals are also known as reactive oxygen species (ROS) and reactive nitrogen species (RNS). In the human body, the main source of ROS and RNS is the mitochondria, which are the by-products of aerobic respiration [125,126]. Hydroxyl, superoxide anion, alkoxyl, peroxyl, and nitric oxide are oxygen-centered free radicals. Superoxide radicals and nitric oxide are less reactive than hydroxyl and alkoxyl radicals, which have a half-life of 1 and $10^{-9}$ s, respectively, which are two molecules that are highly reactive and can attack nearby molecules quickly and cause severe damage [127,128]. Briefly, ROS are formed from O$_2$ which activates NADPH oxidase to produce superoxide anion radicals and is further converted to O$_2$ and H$_2$O$_2$ by superoxide dismutase (SOD). However, the presence of increased ROS or excessive pro-oxidants in the body can cause oxidative stress. This also happens due to a lack of antioxidant production in the body [129,130]. Oxidative stress can damage the function of biological cells; therefore, several diseases can occur, such as acute kidney failure, diabetes, atherosclerosis, preeclampsia, and hypertension [131]. Therefore, the rate of increase in ROS needs to be controlled by several preventive mechanisms such as increasing the number of antioxidants and detoxifying enzymes.

Antioxidants are molecules that can neutralize free radicals and can inhibit the oxidation process of other molecules or can be used as reducing agents. The main function of this antioxidant is to end the chain reaction of ROS formation [132]. Antioxidant defense mechanisms can occur in the form of oxidants scavenging, converting toxic free radicals into less toxic initiation, enhancing endogenous antioxidant defense systems, and reducing or preventing free radical production. All of these mechanisms work by protecting the body from oxidative stress [129]. Antioxidants can be produced in the body (endogenous) and come from outside in the form of dietary supplements (exogenous). Endogenous antioxidants or enzymatic antioxidants are the primary defense, while exogenous antioxidants or non-enzymatic antioxidants act as a secondary defense against ROS [133].

Enzymatic antioxidants can protect the body against oxidative attack because of their ability to decompose ROS. Superoxide dismutase (SOD), catalase (CAT), and glutathione Peroxidases (GSHPx) are the main enzymes involved in the defense against ROS [134]. SOD is found in prokaryotic and eukaryotic cells as a major defense against ROS. Iron and manganese are the main prosthetic groups in prokaryotes while copper, zinc, and manganese are present in eukaryotes [135]. The main function of this enzyme is to convert the superoxide radical anion into hydrogen peroxide (H$_2$O$_2$). In mammalian tissue, SOD is divided into three types, namely superoxide dismutase 1 (SOD1), which is found in the cytosol in the form of copper, superoxide dismutase 2 (SOD2), which is found in the mitochondria in the form of manganese, and extracellular superoxide dismutase. Recently, SOD1 is a major antioxidant enzyme in dealing with oxidative stress [136,137]. CAT is a heme enzyme group that catalyzes the breakdown of H$_2$O$_2$ in the water and protects cells against oxidative stress. CAT can transfer oxygen bound with H$_2$O$_2$ to other molecules. The decomposition of H$_2$O$_2$ used the peroxidative activity method (H$_2$O$_2$ + AH$_2$ A + 2H$_2$O) and the catalytic activity mode (2H$_2$O$_2$ + O$_2$ + 2H$_2$O). The breakdown of H$_2$O$_2$ by enzymes depends on the concentration of H$_2$O$_2$ and follows the first-order reaction [133,138,139]. GSHPx containing selenium plays a role in the detoxification mechanism. This enzyme catalyzes the reduction of H$_2$O$_2$ to water or alcohol. The mechanism of action of this enzyme starts from reduced glutathione, which functions as an effective electron donor because the thiol dioxide group becomes a sulfide bond (H$_2$O$_2$ + 2GSH → GS-SG + 2H$_2$O) [140,141].
Exogenous antioxidants are further divided into synthetic antioxidants and natural antioxidants. These antioxidant compounds react with ROS to inhibit or eliminate the activity of these ROS [133]. Synthetic antioxidants interact with ROS through various mechanisms such as the binding of metal ions, deactivating singlet oxygen, converting radical into non-radical species, and absorbing UV radiation. Butylhydroxyanisol (BHA), butylhydroxytoluene (BHT), tert-butylhydroquinone (TBHQ), octyl gallate (OG), and propyl gallate (PG) are examples of synthetic antioxidants [142,143]. BHA is more effective than BHT due to the presence of two butyl groups which exhibit greater steric hindrance to other molecules. BHA is very effective in controlling the oxidation of short-chain fats [144]. When compared with TBHQ, BHA and BHT were less effective in inhibiting ROS activity. This is because the two para-hydroxyl groups in TBHQ are responsible for their antioxidant activity [144]. PG is known as a safe antioxidant because it can protect oil and food and rancidity resulting from the formation of peroxide [145]. Apart from being an antioxidant, PG can stabilize food and cosmetic ingredients. OG is a gallic acid and 1-octanol ester and is used as a food preservative. However, of these antioxidants, BHA and BHT are the most widely used antioxidants in the food industry [146]. The use of synthetic antioxidants has been limited and regulated by the Food and Drug Administration (FDA) because some synthetic antioxidants such as BHA and BHT have toxic and carcinogenic effects [143,147]. Synthetic antioxidants can cause DNA damage and induce premature aging [148]. BHA and BHT, in high doses, can cause adverse reactions such as liver damage, carcinogenesis, urticaria, eye problems, asthma, dermatitis, and angioedema [149]. PG can be added as a food additive to prevent bad odors that occur because it has higher chemical activity and suppresses the initiation of the chain oxidation of unsaturated fatty acids. However, the resulting sampling effect can result in toxicities or mutagenicities [150]. According to a study by Le Coz and Schneider [151], seven people experienced excessive reactions to BHA and BHT, such as headaches, drowsiness, pain radiating to the back, and asthma. Even when BHA and BHT were identified as presenting cross-reactivity with aspirin, twenty-one people experienced intolerance which caused dermatitis. These are some of the reasons that make natural compounds the main choice as natural antioxidants.

Natural antioxidants can strengthen endogenous antioxidant defenses in neutralizing and inhibiting the performance of ROS [152]. The main sources of these natural antioxidants can be found in fruits, leaves, seeds, vegetables, bark, and stems [145]. Phenolic is a secondary metabolite compound produced in various parts of the plant which has strong antioxidant activity. The mechanism of phenolic antioxidant activity includes hydrogen donation, metal ion chelation, singlet oxygen quenching, and free radical scavenging [153]. In addition, flavonoids also play an important role in reducing or preventing the toxicity caused by free radicals. Flavonoids protect the body from oxidative stress [129]. There are many compounds in plants that can inhibit the oxidation process; however, only a few are suitable for consumption due to safety concerns. They should not affect the odor, color, and taste, be easy to apply, stable in storage, must have an LD₅₀ lower than 1000 mg/kg body weight, and must pass mutagenic, teratogenic, and carcinogenic tests. Currently, the development of natural antioxidants continues to be carried out because they have the same benefits as synthetic antioxidants but have no side effects [154,155]. Estévez and Ventanas [156] reported that essential oils from sage and rosemary exhibit antioxidant activity similar to BHT, prompting researchers to develop new raw materials from nature without compromising the quality of the resulting product. Currently, there are several benefits in the development of natural antioxidants such as green tea catechins that can inactivate the free radicals of skin collagen which can slow down skin aging [157], garlic as a plant for cardiovascular disease and cancer [158], and the consumption of red wine is good for atherosclerosis [159].

The determination of antioxidant activity in one sample can be performed with several models of antioxidant activity test methods. Currently, a test procedure has been developed to evaluate antioxidant activity in vitro. Antioxidant activity test methods cannot be compared with each other because they have different target mechanisms; therefore,
each has advantages and disadvantages [160]. The method of determining antioxidant activity is divided into two main groups, namely hydrogen atom transfer (HAT) and single electron transfer (SET) methods. The HAT-based method is used to measure the ability of antioxidants to reduce free radical activity by donating hydrogen, while the SET-based method is used to detect the ability of antioxidants to reduce other compounds including free radicals [161].

SET-based methods are widely used for the in vitro testing of antioxidants. Several SET-based methods are 2,2-Diphenyl-1-picrylhydrazyl radical scavenging (DPPH), ferric ion reducing antioxidant power (FRAP), 2,2-Azinobis 3-ethylbenzthiazoline-6-sulfonic acid radical scavenging (ABTS), cupric ions (Cu²⁺) reducing antioxidant power (CUPRAC), nitric oxide (NO) scavenging, superoxide anion (SA) radical scavenging and hydrogen peroxide (H₂O₂) scavenging assays [143,162].

Table 9 shows the antioxidant activity of the five piper species of the extract and fraction levels; however, compounds that have been isolated from these five plants are still underreported in their antioxidant activity.

Table 9. Antioxidant activity test using several methods on five Piper species.

| Five Piper Species | Sample         | Test Methods Antioxidant IC₅₀ (µg/mL) | References |
|-------------------|----------------|--------------------------------------|------------|
|                   |                | DPPH       | ABTS      | SA         | NO         |            |
| P. amalago        | Ethanol        | 28.09      |           |            |            |            |
| leaves            | Methanol       | 675        | 370       |            |            | [66,163]   |
|                   | Dichloromethane| 327        | 392       |            |            |            |
| P. amalago        | Methanol       | 368        | 351       |            |            | [66]       |
| roots             | Dichloromethane| 371        | 509       |            |            |            |
| P. betle          | Methanol       | 16.33      | 345.7     | 288.3      | 143.3      | [13,40,55,56,160,164] |
| leaves            | Ethyl acetate  | 40         | 48.3      | 52.3       |            |            |
|                   | Hexane         | 23.25      | 79        |            |            |            |
|                   | Aqueous        | 179.5      | 79.3      | 94.3       | 57.7       |            |
|                   | Ethanol        | 151.36     | 6.61      |            |            |            |
| P. hispidum       | Methanol       | 404        | 498       |            |            | [66]       |
| leaves            | Dichloromethane| 391        | 158       |            |            |            |
| P. hispidum       | Methanol       | 317        | 131       |            |            | [66]       |
| roots             | Dichloromethane| 263        | 164       |            |            |            |
| P. longum         | Ethanol        | 50         | 80        |            |            | [165]      |
| seeds             | Chloroform     | 6          | 76        |            |            |            |
|                   | Hexane         | 70         | 80        |            |            |            |
|                   | Ethyl acetate  | 54         | 80        |            |            |            |
|                   | Aqueous        | 19.5       |           |            |            |            |
|                   | Hydroethanol   | 26         |           |            |            |            |
| P. longum         | Methanol       | 149.92     |           |            |            | [166]      |
| leaves            | Ethanol        | 220.3      |           | 52.0       |            | [167,168]  |
|                   | Water          | 89.8       | 238.4     | 482.3      |            |            |
|                   |                | 118.29     | 364.2     | 381.5      |            |            |
| P. umbellatum     | Methanol       | 312        | 423       |            |            | [66]       |
| leaves            | Dichloromethane| 226        | 122       |            |            |            |
| P. umbellatum     | Methanol       | 199        | 228       |            |            | [66]       |
| roots             | Dichloromethane| 19         | 102       |            |            |            |
At the compound level, Tabopda et al. [121] succeeded in isolating Piperumbellactam A–C (226-228) from *P. umbellactam* and tested its antioxidant activity using the DPPH method. Piperumbellactam A, B, and C have very strong antioxidant activity with IC$_{50}$ values of 17.4, 8.1, and 13.7 µM, respectively. Furthermore, Eugenol (129), one of the compounds isolated from *P. betle*, has good antioxidant activity, with an IC$_{50}$ value of 114.34 ± 0.46 g/mL when using the nitric oxide radical method [169].

5. Conclusions

*Piper amalago* L., *Piper betle* L., *Piper hispidum* Sw., *Piper longum* L., and *Piper umbellatum* L. are *Piper* species that have tremendous potential as a new source of natural-based medicines. This can be seen from the traditional use of this plant, which is used for dental and oral care. In addition, the content of extracts, fractions, and secondary metabolites has several biological activities, especially, in several methods, antioxidants. Based on this review, it is hoped that it can become a reference and guide in the development of several activities for the discovery of new drugs based on natural ingredients from this *Piper* species.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/molecules27196774/s1, Figure S1: *P. amalago* leaves and plant; Figure S2. *P. betle* plant and leaves; Figure S3. *P. hispidum* plant and leaves; Figure S4. *P. longum* leaves and mature dried corns; Figure S5. *P. umbellatum* plant and leaf; Figure S6. The structure chemical compound of *P. amalago*; Figure S7. The structure chemical compound of *P. betle*; Figure S8. The structure chemical compound of *P. hispidum*; Figure S9. The structure chemical compound of *P. longum*; Figure S10. The structure chemical compound of *P. umbellatum*; Figure S11. The chemical structure of synthetic antioxidants.

Author Contributions: Conceptualization, D.K. and S.G.T.; methodology, D.K. and S.G.T.; validation, D.K., N.C. and D.L.; formal analysis, S.G.T.; resources, D.K., N.C. and D.L.; data curation, S.G.T.; writing—original draft preparation, S.G.T.; writing—review and editing, S.G.T. and D.K.; visualization, S.G.T. and M.H.S.; supervision, D.K. and M.H.S.; project administration, D.K. and N.C.; funding acquisition, D.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Academic Leadership Grant (ALG) Prof. Dikdik Kurnia, M.Sc., Ph.D., Indonesia (2203/UN6.3.1/PT.00/2022; 20 May 2022).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The study did not report any data.

Acknowledgments: The authors are grateful to Academic Leadership Grant (ALG) and Universitas Padjadjaran for supporting all research facilities.

Conflicts of Interest: The authors declare no conflict of interest.

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