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Review Article

A Review on Antimalarial Activities of *Aloe* species Extracts

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A B S T R A C T

Among the most prevalent diseases caused by protozoan parasites, the parasites of the genus *Plasmodium* cause malaria. Malaria is transmitted to humans by the infected female anopheles mosquito. Malaria is a vector-borne disease and it continues to have devastating effects on people's lives, especially in developing countries. To control malaria, many popular practices exist to avoid the nuisance of mosquito bites such as fumigation, burning green leaves on the hut's threshold, mosquito coils, insecticide sprays, and repellents. Due to the vast metabolic diversity of plants, natural products may offer relatively cheaper and an easy alternative treatment opportunity to treat malaria. The genus *Aloe* is one of the top medicinal plants that has maintained its popularity over the course of time. *Aloe* in one form or another is a common domestic medicine and is the basis of most pharmaceutical preparations. Various components present in the *Aloe* species have been found effective against many diseases, including malaria. Although most of the antimalarial activities were based on *in vivo* tests, *in vitro* tests were also analyzed by certain researchers. The leaf latex in all *Aloe* species and the isolated compounds displayed antimalarial activity in a dose-independent manner. Considering that natural molecules have acted as natural templates in the development of antimalarial agents, it is encouraged to investigate further analyses into *Aloe* constituents and their values against malaria. It should be followed with phytochemical and pharmacological analyses to give scientific ground to medicinal knowledge and future potential utilization.

Keywords: *Aloe* species, *Aloe* extracts, Malaria, Antimalarial, and Chloroquine

Introduction

Throughout the history of mankind, malaria has been one of the major causes of human illness and death.[1] Among the most prevalent diseases caused by protozoan parasites, malaria is caused by parasites of the genus *Plasmodium* and transmitted to humans by infected female the anophelese mosquito.[2] *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium knowlesi Plasmodium ovale*, and *Plasmodium vivax* are the five parasite species that cause malaria in humans. Among these species, *P. falciparum* causes the most severe form of malaria and hence is responsible for higher mortality rates.[3] Malaria is a vector-borne disease and it continues to have devastating effects on people's lives, especially in developing countries.[4] The estimated number of

malaria deaths stood at 627, 000 of the estimated 241 million cases of malaria in 2020 worldwide.[5] The evidence for man's attempts to fight malaria can be dated back as far as 270 years BC in the ancient Chinese medical records.[6] To control malaria, many popular practices exist to avoid the nuisance of mosquito bites such as fumigation, burning green leaves on the hut's threshold, mosquito coils, insecticide sprays, and repellents. Smoke is a common method of repelling biting mosquitoes that is used throughout the world from ancient times to current.[7] To treat infectious diseases such as malaria, herbal medicine plays a great role. Due to the vast metabolic diversity of plants, natural products may give an alternative opportunity for treatment and a cheap and easy to treat malarial infection. For instance, artemisinin and quinine are antimalarial drugs that were isolated from plants. As a result, it can be generalized that plants have potential as sources of active chemical components used for antimalarial drugs.[8]

Plants are the richest resource of active molecules in traditional systems of medicine and modern medicines. The use of plants and their products as medicines can be traced as far back as the beginning of human civilization.[9] In human history medicinal plants, a source of remedies, are widely used as alternative therapeutic tools for the prevention or treatment of many diseases.[10] The genus *Aloe* is one of the most important medicinal plants that has obtained its popularity from ancient times. *Aloe* plants are used from time immemorial to today. Therefore, they become a popular household remedy exhibiting a range of beneficial health-promoting properties. *Aloe* in one form or another is a common domestic medicine and is the basis of most pharmaceutical preparations.[11] For instance, investigations have led to increased importance of the mostly known *Aloe* species, *A. vera* due to its dependable medicinal properties, and it has been used in the preparation of pharmaceutical products.[12] Combinations of active molecules extracted from Aloe species have been indicated to confer a variety of biological effects with different mechanisms of action.[13] The chemical compositions that have been identified in *Aloe* plants include simple and complex polysaccharides, minerals, vitamins, enzymes, hydrocarbons, fatty acids, indoles, pyrimidines, aldehydes, and ketones, dicarboxylic acids, phenolic compounds, phytosterols, and alkaloids with potential biological and toxicological activities.[14] These components make the *Aloe* species to be known as one of the most important plants to fight various diseases including malaria. In literature, antimalarial activities of specific *Aloe* species have been reported.[2] Therefore, the current work is based on the comprehensive information that shows antimalarial activities of *Aloe* species extracts.

Preparation of *Aloe* extracts

The preparation of *Aloe* extracts has been discussed by authors. The way of preparing extracts is nearly the same. However, the comparative methods are necessary to prepare *Aloe* extracts as well as to isolate the compounds from *Aloe* species. For this reason, selecting mature and healthy parts, not using the oven/sun drying process because it decomposes active constituents are comparative procedures. The leaves of *Aloe* plants are the most used and are heterogeneous and can be divided into three major parts. These are, (i) the majorty consists of structural components of the leaf part, the outer green epidermis; (ii) the part that vascular bundles are placed where the bitter latex or sap is obtained, the outer pulp region below the epidermis; and (iii) the inner leaf pulp, which consists of *Aloe* gel and containing parenchyma cells Figure 1.[15,16]

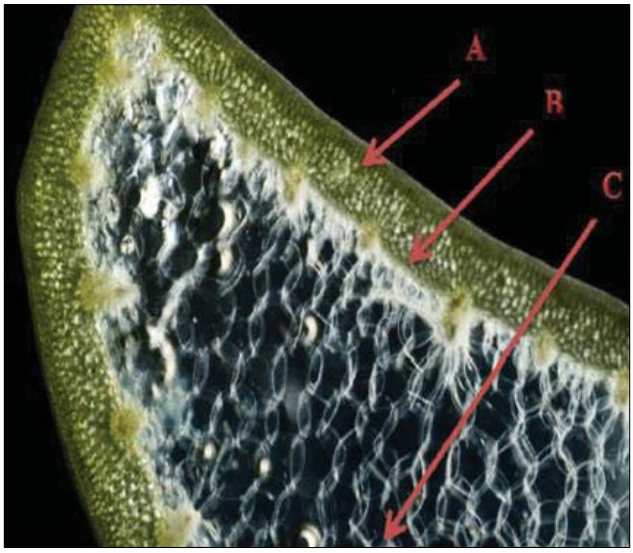

Figure 1.The main parts *Aloe* leaf; A: epidermis (the outer rind); B: the outer leaf pulp, sap/exudate (latex); and C: mesophyll (the inner leaf pulp/gel)[19]

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Figure 2.Separation of the leaf gel of *Aloe fleurentiniorum*[20]

If the three parts of the leaves are needed separately, leaf latex is collected by cutting the leaves transversally near the base and arranging them concentrically around a plate/ container. The latex powder is prepared. The gel of the leaf is prepared by cutting leaves edge and skin with a sharp and sterile knife/ blade Figure 2. Then the gel is chopped into smaller pieces to facilitate the drying process. After that, the gel is powdered to make it ready for the next few steps. The separated skin from latex and gel is also dried and powdered to make it ready for further analysis. Although the drying and powdering process can be different, other parts of the *Aloe* plants like root and flower are also dried and powdered for the further process.[17,18]

Antimalarial Compounds of *Aloe* extracts

The biological properties of *Aloe* such as the treatment of malaria are due to various compounds of *Aloe* extracts, rather than to one single class of compounds.[22] Although leaves are the most used part of the plants, recently some studies have reported that the bioactive roots[17] and flowers[23] of the plant can also be used. Phytochemical analyses shows the presence of flavonoids, alkaloids, terpenoids, saponin, tannin, steroids, glycosides, etc.[24-26] In the phytochemical analysis, the presence or absence of phytochemicals even for one plant is based on basic parameters. (1) Plant parts such as leaf (gel, latex, or skin), root, or flowers, (2) solvent used for extraction (methanol, ethanol, ethyl acetate, chloroform, hexane, etc. or their ratio), and (3) extraction procedures/type (Soxhlet extraction, maceration, or others) Table 1.

Several constituents from various phytochemical classes such as alkaloids, anthrones, anthraquinones, chromones, flavonoids, glycoproteins, naphthalene's, and pyrones have been isolated from different *Aloe* species.[34] These compounds are very active against diseases. In literature, it has been stated that biological activities should be assigned to a synergistic action of the compounds contained therein rather than a single chemical substance.[3] Table 2 shows some of these antimalarial phytoconstituents.

Table 1.Phytochemical screening reports of *Aloe* species

***Aloe* spp.**	**Part of pant**	**Form of Extract**	**Phytochemicals Present**	**Ref.**
A. elegans Todaro	Leaf (Gel)	Methanol extract	Anthraquinones, Flavonoids, Saponins and Tannins	[27]
A.vera	Leaf (Gel)	Ethanolic extract	Tannins, Saponins Phlobatannins, flavonoids, anthraquinones, terpen-oids, steroids, alkaloids, Carbohydrates, Glycosides	[28]
A. gilbertii	Root	CH_2Cl_2:CH_3OH (1:1) extract	alkaloids, anthraquinones, terpen-oids, flavonoids	[25]
A. eleganis	Root	CH_2Cl_2:CH_3OH (1:1) extract	anthraquinones, terpenoids, phenols, saponins, tannins, glycosides	[25]
A. elegans	Leaf (Gel)	Petroleum ether extract	Saponins	[28]
		Ethyl acetate extract	Saponins and glycosides,	
		Ethanol extract	Saponins, tannins, terpenoids, and phenols	
		Distilled water extracts	Saponins and flavonoids	

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A. adigratana Reynolds	Leaf (Gel)	Petroleum ether extract	Alkaloids, Glycosides, Steroids, Carbohydrates, Fixed oils, and fats, Amino acids and proteins	[29]
		Chloroform extract	Flavonoids, Tannins, Terpenoids, Steroids Carbohydrates, Amino acids and proteins	
		Ethyl acetate extract	Glycosides, Terpenoids, Saponins, Amino acids and proteins	
		Ethanol extract	Alkaloids, Alkaloids, Flavonoids, Tannins, Glycosides, Terpenoids Steroids, Carbohydrates, Amino acids and proteins	
A. adigratana Reynolds	Leaf (Gel)	Methanol Extract	Anthraquinones, Flavonoids, Saponins and Tannins	[30]
A. perryi	Flower	Methanol extract	Glycosides, phytosterols, proteins, and amino acids, flavonoids, phenols, and carbohydrates	[31]
A. pulcherrima Gilbert and Sebsebe	Leaf (latex)	Dried latex	Anthraquinones, Flavonoids, Saponins, Glycosides, Tannins, Phenols and Alkaloids	[32]
A. turkanensis	Whole Plant	Aqueous and methanol extracts	Tannins, anthraquinones, terpenoids/steroids, saponins, and alkaloids	[33]

Table 2.The medicinal applications of *Aloe* species toward malaria

Aloe spp.	Part of plant	Name of the isolated compounds	Class of phytochemicals	Ref.
A. percrassa Todaro	Leaf latex	Aloin A/B and microdontin A/B	Anthrone	[36]
A. citrina	Leaf latex	Homonataloin A/B	Anthrone	[37]
A. pulcherrima Gil. and Seb.	Leaf latex	nataloin and 7-hydroxyaloin	Anthrone	[38]
A. debrana Chrstian	Leaf latex	Aloin	Anthrone	[39]
A. debrana Chrstian	Leaf latex	(E)-2-(1-hydroxy-2-methylpropyl)-8-(6'-O-cinnamoyl)-β-D-glucopyranosyl-7-methoxy-5-methylchromone (HCGMM)	Chromone	[39]
A. macrocarpa Todaro	Leaf latex	Aloin and aloinoside	Anthrone	[40]
A. macrocarpa Todaro	Leaf latex	Aloe-emodin	Anthraquinone	[40]
A. otallensis Baker	Leaf latex	Plicataloside	Naphthalene Derivative	[2]
A.pulcherrima	Root	chrysophanol, aloesaponarin I, and aloesaponarin II	Anthraquinones	[41]

The chemical structures of some *Aloe* species phytochemicals components are represented in Table 2 is shown in Figure 3. These bioactive compounds are responsible in *Aloe* species fighting various diseases including malaria.

Antimalarial Activities of *Aloe* extracts

Traditional Therapeutic Effects

There are many natural medicinal herbs and plants, among them, *Aloe* species like *A. vera* possess a vast array of healing benefits. It has been in use for ages as conventional medicine.[8] According to a survey conducted on medicinal plants traditionally used for the treatment of malaria in eastern Ethiopia, *Aloe* species are among the most commonly reported plants.[42] Malaria is one of the diseases that are treated by *Aloe* species traditionally worldwide.[43] Generally, *Aloe* species such as *A. percrassa,*[36] *A. otallensis* B.,[2] *A. macrocarpa* T.,[40] *A. citrina,*[37] *A. debrana*,[39] and *A. dawei*[44] have been used traditionally to treat malaria in

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a different society. The part most used is the leaf of *Aloe* species and it's latex was used. The latex of *A. macrocarpa* and *A. trichosantha* was used while leaf gel and root of *A. gilbertii* to cure malaria traditionally.[45] To treat malaria traditionally people used the plants' parts orally. The fresh exudate, powder of leaf/exudate *Aloe calidophila*, *Aloe gilbertii* Reynolds, *A. macrocarpa*, and *A. pirottae* were used in Ethiopia by incorporating it to other substance like water or without incorporating the plants.[43]

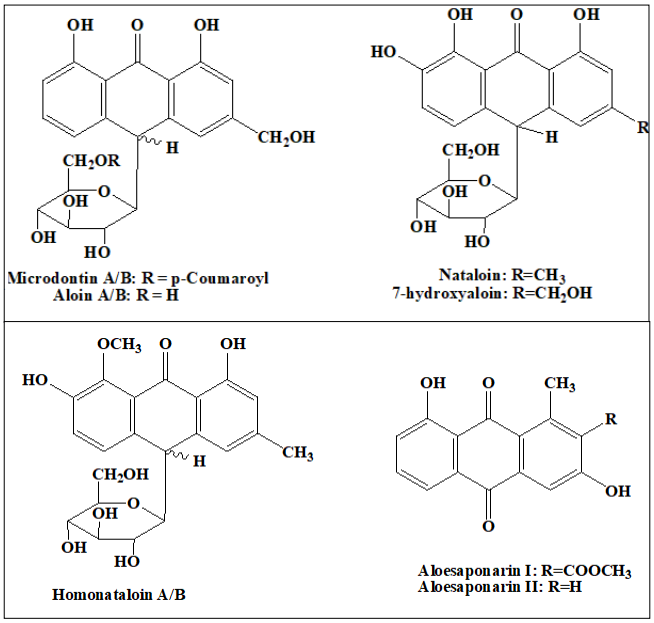

Figure 3.Structures of some antimalarial compounds

Aloe species are not only used to treat malaria but they were also used as a repellent to control mosquitoes and not attack people. One such species is *A. pirottae* which was used by Ethiopians.[46] Therefore *Aloe* has been traditionally used worldwide as a folk remedy for various diseases that have high mortality rates like malaria because of its multiple bioactive constituents which lead to various biological activities. The traditional antimalarial applications of the genus *Aloe* brought the modern analysis of the *Aloe* species for three main reasons: The first reason is to identify the chemical constituents of the *Aloe* species responsible for the treatment of malaria. Secondly, the applications of Aloe species in a scientific way by determining the dosage and toxicity with a clear mechanism of action. Thirdly, once the chemical constituents and scientific way of using the extracts of *Aloe* species have been known, further analysis can take place to synthesize drugs from the *Aloe* species. Therefore, the traditional antimalarial treatment is based on drug delivery.

Modern Therapeutic Effects

In Vitro Antimalarial Activities

Although most of the antimalarial activities were based on *in vivo* tests, *in vitro* tests were analyzed by certain investigators in animals like rat/mice. It is all about the chemical constituents that are used in antimalarial applications. In the literature, the leaves and roots of different *Aloe* species were tested and showed variable antimalarial activities and vitro antimalarial tests of ether leaves extracts of *A. dawei* showed an amazing inhibition of parasite growth against *P. falciparum* comparing the chloroquine diphosphate as a control measure.[47] In the same way, *Aloe perryi* has been studied for its *in vitro* antiplasmodial activity. This resulted in the use of the plant leaf latex in the treatment of malaria.[48] The *in vitro* activity against plasmodium was observed by the aqueous leaf extract as well as isolated compounds of *A. vera*. The compounds, aloe-emodin and aloin which were isolated from *A. vera* leaf extract, possessed dose-dependent antiplasmodial activities in literature.[8]

Different *Aloe* species showed various antimalarial activities. The leaf extracts of *Aloe viridiflora*, *A. wickensii*, *A. speciose*, and *A. suprafoliata* exhibited the most promising antimalarial activity over a single and double cycle of growth, with *A. viridiflora* being the most active. In addition to that, the root of *A. marlothii* showed some greater inhibitory effect which was observed over a double cycle of growth. In comparison to leaf extract which inhibited 18.2% parasite growth over a double cycle of growth, 42.3% inhibitory activity of 50µg mL^{-1} of the root extract was observed in the investigation. It is interesting to note that one of the Aloe active molecules called emodin could inhibit the *in vitro* intra-erythrocytic growth of chloroquine-resistant FCR-3 malaria.

There are methods such as malaria SYBR Green I-based in vitro assay techniques for gauging in-vitro an antiplasmodial activity evaluation of the phytoconstituents against chloroquine-resistant (D6) and -sensitive (W2) strains of *P. falciparum*. Generally, the phytochemicals identified by HPLC and spectroscopic analyses from these *Aloe* species and the reason for the antimalarial activities are mainly anthrones, chromone, flavonoids, coumarines, anthraquinones, and naphthalene derivatives.[42,49]

In Vivo Antimalarial Activities

Most of the antimalarial analyses were done via *in vivo* assays. In the study, *Aloe barbadensis* extracts showed remarkable antimalarial properties. The increases in the concentration of the extracts result in an increase in the antimalarial activities of the extracts. The parasitemia suppressive effect of *Aloe* species such as *A. barbadensis* can be considered hypothetically as a rich source of active components such as anthraquinones and other quinoid molecules that are the characteristic constituents of the *Aloe* genus. When compared to chloroquine which is the standard drug, *A. barbadensis* probably has some intrinsic antimalarial activity from the percentage parasitemia

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inhibition and suppression or clearance due to its active constituents.[50]

Various *Aloe* species extracts and compounds possess genuine antimalarial activity as observed by animal experiments on animals like mice. The latex of *A. debrana* and the compounds that were isolated were (aloin and HCGMM),[39] *A. pulcherrima*, and the isolated compounds (nataloin and 7-hydroxyaloin),[38] *A. percrassa* and isolated compounds (aloin A/B and microdontin A/B),[36] A. megalacantha and TLC isolates,[52] *A. macrocarpa* and the isolated compounds (aloin, aloinoside, and their semi-synthetic derivative aloe-emodin),[40] and *A. citrina* and the isolated compound (homonataloin A/B).[37] Literature states the treatment of *P. berghei* infected animals when treated with leaf latex and isolated compounds of *Aloe* species, have shown dose-dependent weight loss reduction and other signs. However, the treatment by leaf latex and isolates of *A. megalacantha* was observed to reduce malaria caused weight loss and hypothermia. Consequently, it increased the survival time of *Plasmodium berghei* infected animals (mice).[51] Therefore, the cure ability of *Aloe* extracts is considerably greater than the known antimalarial drug itself.[2]

Dosage and Complication

Although *Aloe* species have a crucial role in applications, they are not as safe as the people assume which can cause problems in usage. However, only a few species are extremely toxic and poisonous. Some species such as *A. ferox* are potentially toxic.[14] Hence, it is very important to know and use *Aloe* species by identifying their possible side effects. Hence toxicity assay must be tested before applied it as a therapeutic action, especially for oral administration. The study conducted by the Organization for Economic Cooperation and Development (OECD) guidelines 425[52] reported maximum dose. The dose to 2000mg/kg has been reported by these guide lines as similar to the *Aloe* species.[51] Based on this, the animal under study is observed for toxicity signs such as changes in skin color, tremors, blinking eyes, lacrimation, convulsion, muscle weakness, sedation, salivation, urination, diarrhea, sleep, lethargy, coma, and death in a given period of time.[2,37-40] The extracts and compounds isolated from the *Aloe* species have shown antimalarial activities. The latex of the *Aloe* species has the power to help in the survival of the animal infected by malaria. This is due to the latex which is rich in bioactive compounds. As a result, nataloin, 7-hydroxyaloin, microdontin A/B, aloin A/B, aloin, aloinoside, and aloe-emodin of *A. pulcherrima*, *A. percrassa*, *A. megalacantha,* and *A. macrocarpa* showed good antimlarial activities when compared with a chloroquine treatment regime and well as dosage. In most of *in-vivo* studies, distilled water was used on the mice which was the controlled group.[37,39,41,51]

In the literature, the leaf latex in all *Aloe* species and isolated compounds displayed antimalarial activity in a dose-independent manner. The leaf latex and isolated compounds were prepared at three different doses of 100, 200, and 400 mg/kg of the body infected animal and chloroquine at 25 mg/kg in a volume of 1 mL/100 g body weight of that animal. In all *Aloe* species, the negative control group/distilled water has no suppression effects. The highest percent suppressions are achieved at 200 mg/kg/day is which is 56.2% for *A. pulcherrima* 7-Hdroxyaloin, at 400 mg/kg/day which is 73.6% for *A. percrassa* latex, at 400 mg/kg/day which is 79.6% for A. megalacantha TLC isolate coded AM_3, and at 400 mg/kg/day which is 100% for *A. macrocarpa* aloinoside. The aloinoside of *A. macrocarpa* exhibited a similar chemo suppression effect to chloroquine. This shows that aloinoside is a powerful compound to help treat malaria Table 2. In all *Aloe* species latex and isolates, the mean survival time of animals treated with extracts was longer when compared with vehicle/ negative control groups treated animals. Therefore, mean survival time is another parameter that is commonly used to evaluate the efficacy of antimalarial plant extracts.[53] Although it is not observed in some tests, due to many factors it is interesting to note that latex which has no isolated compounds has strong antimalarial activities. In A. *percrassa*, the tested latex showed a better chemo-supression effect than the individual compounds. Alternatively, the survival mean time activity of latex of *A. pulcherrima*, is longer than the two isolated compounds, nataloin and 7-hydroxyaloin. Generally, these reasons that are explained are that the compounds exert their actions synergistically or there may be other minor components in the latex which have stronger schizonticidal activity as described in the literature.[35]

The other point is to know the symptoms of malaria before using the *Aloe* extracts especially in the traditional treatment because symptoms like fever can be the same for many diseases. It is important to know the symptoms of malaria. Using *Aloe* species as a traditional medicine may generate complication. In addition to this the dosage is another source of complication in traditional usage. In modern times, the need of malarial treatment is obviously important because the parasite is studied or obtained first. Therefore, knowing the symptoms is to get additional information rather than to test whether the symptoms are malarial or not. On the whole, to be familiar with symptoms of malaria is very important for malarial treatment.

Conclusion and Future Avenues

Aloe species have multiple uses, but it has been shown that the most common local use was in the traditional health care system. Based on the indigenous antimalarial effects of *Aloe* plants, the scientific studies, in vitro and in vivo reports confirmed that the leaves and roots of *Aloe*

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plants possessed genuine antimalarial activities which could be attributed to the presence of the active chemical constituents. The studies have demonstrated that the *Aloe* exudates and isolated compounds possess a promising antimalarial activity in a dose-dependent manner, providing the scientific evidence for the conventional use of the plant. Moreover, the activity of the active constituents along with their relative margin of safety merit the use of these compounds as it leads to the development of safer, cost-effective, and more potent alternative drugs for the treatment of malaria.

Considering that natural molecules have acted as natural templates in the development of antimalarial agents, it is imperative to research further analyses into *Aloe* constituents and their values against malaria. It should be followed with phytochemical and pharmacological analyses to give scientific ground to medicinal knowledge and future potential utilization. In most literature, the leaf latex and the compounds isolated from it were used to treat malaria. This shows that the latex is rich in active compounds which is used as antimalarial agents. Therefore, further studies are needed to determine which compound acts as a strong antimalarial agent and if synergistic effects of the compounds are used for antimalarial activities. In addition, it is recommended to test other parts of *Aloe* plants like flowers, leaf gel, leaf skin, etc. against malaria. Further analysis is important to identify the result; in case malarial drugs like chloroquine are incorporated into *Aloe* extracts/ isolated compounds. Although most studies are directed towards the curative effect of the test substances, in-depth pharmacokinetic and pharmacodynamic studies are needed to elucidate their mechanism of action.

Conflict of Interest: None

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