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Antiplasmodial activity of hydroethanol extracts of *Carica papaya* fruit peels and *Citrus aurantifolia* fruits.

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Abstract:

Malaria is a contagious ailment caused by Plasmodium parasites. The antimalarial activity of different parts of *Citrus aurantifolia* and *Carica papaya* except the fruits has been extensively reported. Thus, this study was aimed at evaluating the *in vivo* antiplasmodial effects of crude hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (singly and combined), using the Peters' 4-day suppressive and preventive test in mice. The results of the suppressive study with extracts of *C. papaya*, *C. aurantifolia* and the combined extracts gave % parasitaemia of 29.60 ± 1.14 , 34.40 ± 1.14 and 19.60 ± 1.82 respectively. While in the preventive study, pre-treatment with extracts of *C. papaya*, *C. aurantifolia* and the combined extract caused higher reduction in % parasitemia of 24.00 ± 1.58 , 28.80 ± 2.39 and 16.20 ± 0.84 respectively, when compared with the reduction seen in the suppressive test. Also, treatment in the suppressive test with crude hydroethanol extracts of either plant did not stop reduction in PCV of the mice. However, pre-treatment with hydroethanol extracts of *C. papaya* and the combined extracts prevented a significant ($p < 0.05$) drop in PCV levels. Thus, in this study, all extracts demonstrated varied *in vivo* antiplasmodial activity, with the combined extracts giving the best activity overall. The results have revealed the pharmacological basis and partly explain why the two fruits are used to treat suspected malarial cases by traditional healers. Thus, the combined extract is a potential candidate for new antimalarial drug development.

Keywords: *Citrus aurantifolia*, *Carica papaya*, antiplasmodial, Antimalarials, hydroethanol, % parasitemia.

Introduction

Malaria is a feverish, mosquito-borne disease that is a public global health problem. It is a major disease producing an estimate of 219 million malarial cases that occurred worldwide in 2017 (WHO, 2018). Malaria is caused by diverse species of Plasmodia (Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium falciparum), with Plasmodium falciparum being the most lethal specie, giving the utmost malaria cases worldwide (WHO, 2013). Report by WHO (2015) showed that the vast bulk of deaths (99%) were discovered to be due to *P. falciparum* malaria (Alebie *et al.*, 2017), which also was responsible for the major burden of malaria morbidity in Africa, with 200 million reported cases (92%) in 2017 (WHO, 2018).

The incidence of resistance against the greatest malaria drugs comprising the popular Artemisinin-based Combination Therapy (ACT) by the malaria parasite in some region of the world has aggravated the malarial burden (Cui *et al.*, 2012). Thus, the speedy increase of resistant parasite cases necessitates the urgent need in searching for new active herbal antimalarial compounds. In malaria pervasive countries, traditional herbal medicine has been the most regular choice in malaria treatment. About 1200 plant species known from 160 families has been used in the treatment of malaria (Willcox and Bodeker, 2004).

Citrus aurantifolia (Christm) is of the Rutaceae family, and it is a familiar food and medicinal plant, broadly cultivated all over the world, and virtually all of its parts find potential uses in traditional medicine. The fruits of citrus are rich in a variability of phytonutrients like alkaloids, phenols, flavonoids, tannins and saponins. Phytonutrients are essential in both disease prevention and health promotion (Okwu, 2005). The therapeutic and nutritional properties of citrus fruits are alike owing to their phytonutrient contents (Okwi and Emenike, 2006). These chemicals are able to function as antioxidant and hence can play a significant role in preclusion of wasting diseases like Alzheimer, cancer and Parkinson's disease produced by oxidative stress (Dongmo *et al.*, 2009; Uttara *et al.*, 2009). The phytochemical screening of *C. aurantifolia* has revealed the occurrence of flavonoids, terpenoids, tannins and phenols. The existence of these constituents underlines the medicinal significance of *C. aurantifolia* juice (Chakraborty *et al.*, 2004).

Carica papaya fits in the Caricaceae family, and numerous species of Caricaceae are used as medication against a range of diseases (Mello *et al.*, 2008; Munoz *et al.*, 2000). *C. papaya* is a perennial plant, normally soft-stemmed, unbranched and is able to grow up to about 20m height. It is said to stem from the Caribbean coast in Central America and has found its way into various tropical and subtropical climates over the years (Moussaoui *et al.*, 2001). Various scientific analyses have been done to assess the biological properties of different parts of *C. papaya* (fruits, shoots, rinds, leaves, seeds, latex and roots). The leaves, fruits and latex are traditionally used in parts of the world for the treatment of asthma, diarrhea, rheumatism, fever, hypertension and boils (Zakaria *et al.*, 2006). The leaves have been revealed to encompass various active components like papain, cystatin, chymopapain, α -tocopherol, flavonoids, cyanogenic glucosides, ascorbic acid and glucosinolates (Seigler *et al.*, 2002). Also, the antiplasmodial and antimalarial activity has been mentioned in certain preparations of the plant (Udoh *et al.*, 2005). Similarly, the anti-inflammatory, antifertility and antihelminthic activity of *C. papaya* has been reported (Jyotsna *et al.*, 2016).

Although the antimalarial potentials of several parts of *C. papaya* and *C. aurantifolia* have been widely reported, but not much is seen in the literature about the antimalarial effects of their fruits. Besides, these two fruits are normally mixed together in preparing antimalarial concoction by local healers in the Niger Delta area of Nigeria for the treatment of malaria. Also, combination therapy has steadily replaced treatment with single drug over time due to the increase incidences of drug resistance by the Plasmodium parasites worldwide (Martinelli *et al.*, 2008). The aim of this study was to evaluate the antiplasmodial effects of crude hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (singly and combined).

Materials and methods

Fruits collection and extraction

The fruits (*Citrus aurantifolia* and *Carica papaya*) were procured at a local market (Abraka) and authenticated at the Botany Department of the Delta State University, Abraka. *C. aurantifolia* fruits were processed and extracted as described earlier (Okoro, 2019b). *C. papaya* fruit peels were air dried under shade, pulverized and extracted as described by Okoro (2019a) and kept at 4°C, and reconstituted with distilled water before use.

Animals and parasites

Swiss Albino Mice (fifty mice) of both genders weighing 25 – 30 g were gotten from the Animal house of Anatomy Department, Delta State University, Abraka and were acclimatized for seven days. They were fed with grower's mash (Top Feeds) and water *ad libitum* throughout the experiment. The chloroquine sensitive parasite used (*Plasmodium berghei*, ANKA) was obtained from the National Institute of Medical Research, Yaba Lagos, Nigeria.

Experimental Design

The study was divided into two: Suppressive study, where the antiplasmodial test was done at 0 -3 post inoculation, and Prophylactic study involving treatment (four days) before parasite inoculation. The mice were randomly divided into five groups of five mice each for both studies as follows:

Group A: Mice + 250 mg/kg/day of *C. aurantifolia* fruit extract.

- Group B:** Mice + 250 mg/kg/day of *C. papaya* peels extract.
- Group C:** Mice + 250 mg/kg/day of combined *C. aurantifolia* fruit extract and *C. papaya* peels extract at 1: 1 ratio.
- Group D:** Mice + 10 mg/kg/day of chloroquine phosphate.
- Group E:** Mice + 1 mL/kg/day of distilled water.

Parasite inoculation and suppressive study

Parasite inoculation and the *in vivo* suppressive study (Peter's 1965 test) was done as describe earlier (Okoro, 2019a), using infected mice as donor for non-infected ones.

Prophylactic study

The prophylactic or preventive study was done by first treating animals for four days before parasite inoculation to show if the extracts could prevent infection. Thus, after pretreatment with extracts, the test was done following the Peter's (1965) procedure described earlier (Okoro, 2019a).

At the end of treatment for either suppressive or preventive studies, thin blood smears were taken from each animal and processed for % parasitemia and % reduction of parasitemia as described earlier (Okoro, 2019a). Also, the packed cell volume (PCV) was done following the method described by Gebrehiwot *et al.* (2019).

Data Analysis

Values were expressed: Mean ± standard

deviation. Comparison for statistical significance was done by the one-way ANOVA followed by Turkey's post hoc test using GraphPad Prism (6.0 version) and significant level of $p < 0.05$ was taken.

Results

***In vivo* antiplasmodial effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (Suppressive and Preventive studies)**

Results of the suppressive study with extracts of both plants used either singly or combined showed significant ($p < 0.05$) reduction in % parasitemia of mice in all treated groups when compared with the negative control group (Table 1). The highest level of reduction in parasitemia was seen in the positive control group of mice; while the lowest reduction was shown by the *C. aurantifolia* fruit extract treated mice. Thus, similar observation was seen in the % suppression results, with highest % suppression given by the positive control mice and the least reduction noticed in the mice treated with fruit extract of *C. aurantifolia*.

In the prophylactic or preventive study, pre-treatment with plant extracts either singly or combined and the standard drug caused significant ($p < 0.05$) reduction in % parasitemia when compared with the negative control mice (Table 2). Although, the observation here was similar to that of the suppressive study, but higher reduction in parasitemia was seen in the preventive test relative to the suppressive test.

Table1: The *in vivo* antiplasmodial effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (Suppressive study).

Parameter	A	B	C	D	E
Dose(mg/kg/day)	250	250	250	10	1 mL
% parasitemia	29.60±1.14 ^a	34.40±1.14 ^b	19.60±1.82 ^c	0.97±0.08 ^d	48.80±1.30 ^e
% suppression	39.34	29.51	59.84	98.01	-

*Values expressed as Mean± SD (n = 5). ** Data with different superscripts across rows differ significantly ($p < 0.05$).

Where: Group A= Mice + 250 mg/kg/day of *C. aurantifolia* fruit extract; Group B= Mice + 250 mg/kg/day of *C. papaya* peels extract; Group C= Mice + 250 mg/kg/day of combined *C. aurantifolia* fruit extract and *C. papaya* peels extract at 1: 1 ratio; Group D= Mice + 10 mg/kg/day of chloroquine phosphate; Group E= Mice + 1 mL/kg/day of distilled water.

Table 2: The *in vivo* antiplasmodial effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (Prophylactic study).

Parameter	A	B	C	D	E
Dose(mg/kg/day)	250	250	250	10	1 mL
% parasitemia	24.00±1.58 ^f	28.80±2.39 ^g	16.20±0.84 ^h	0.89±0.13 ⁱ	48.20±1.30 ^j
% suppression	50.21	40.25	66.39	98.15	-

*Values expressed as Mean± SD (n = 5). ** Data with different superscripts across rows differ significantly (p < 0.05).

Where: Group A= Mice + 250 mg/kg/day of *C. aurantifolia* fruit extract; Group B= Mice + 250 mg/kg/day of *C. papaya* peels extract; Group C= Mice + 250 mg/kg/day of combined *C. aurantifolia* fruit extract and *C. papaya* peels extract at 1: 1 ratio; Group D= Mice + 10 mg/kg/day of chloroquine phosphate; Group E= Mice + 1 mL/kg/day of distilled water.

Effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit on packed cell volume (PCV) of mice infected with *P. berghei* (Suppressive and Preventive studies)

Treatment with crude hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit did not stop reduction in PCV of the mice, as there was significant (p< 0.05) reduction of PCV when the levels were compared between day 0 and day 4 (Table 3). Similar observation was seen in the negative control group. However, treatment with either the combined extracts or the standard drug prevented the plasmodia induced reduction in PCV levels of mice between day 0 and day 4. Thus, there was no significant reduction in the PCV levels between the initial and final day in these treated groups (Table 3).

Pre-treatment with hydroethanol extracts of *C. papaya* fruit peels, the combined extracts and the standard drug was observed to prevent a significant drop in PCV levels between day 0 and day 4 (Table 4). While pre-treatment with hydroethanol extracts of *C. aurantifolia* fruit failed to prevent the plasmodia induced reduction in PCV levels between day 0 and day 4, an observation similar to what was seen in the negative control group (Table 4).

Table 3: Effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit on PCV of mice infected with *P. berghei* (Suppressive study)

Day	A	B	C	D	E
Day 0	56.60±1.14 ^m	57.20±0.84 ^o	56.40±1.14 ^q	57.20±0.84 ^r	56.80±0.84 ^s
Day 4	53.80±1.48 ⁿ	51.40±0.89 ^p	55.40±0.89 ^q	56.40±1.52 ^r	46.40±1.14 ^t

*Values expressed as Mean± SD (n = 5). ** Data with different superscripts down the column differ significantly (p < 0.05).

Where: Group A= Mice + 250 mg/kg/day of *C. aurantifolia* fruit extract; Group B= Mice + 250 mg/kg/day of *C. papaya* peels extract; Group C= Mice + 250 mg/kg/day of combined *C. aurantifolia* fruit extract and *C. papaya* peels extract at 1: 1 ratio; Group D= Mice + 10 mg/kg/day of chloroquine phosphate; Group E= Mice + 1 mL/kg/day of distilled water.

Table 4: Effect of hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit on PCV of mice infected with *P. berghei* (Prophylactic study)

Day	A	B	C	D	E
Day 0	56.60±0.55 ^u	57.20±1.30 ^v	56.60±0.89 ^x	57.20±1.30 ^y	57.00±0.71 ^z
Day 4	55.20±1.92 ^u	54.40±1.52 ^w	55.40±1.52 ^x	56.60±1.82 ^y	46.40±2.07 ¹

*Values expressed as Mean± SD (n = 5). ** Data with different superscripts down the column differ significantly (p < 0.05).

Where: Group A= Mice + 250 mg/kg/day of *C. aurantifolia* fruit extract; Group B= Mice + 250 mg/kg/day of *C. papaya* peels extract; Group C= Mice + 250 mg/kg/day of combined *C. aurantifolia* fruit extract and *C. papaya* peels extract at 1: 1 ratio; Group D= Mice + 10 mg/kg/day of chloroquine phosphate; Group E= Mice + 1 mL/kg/day of distilled water.

Discussion

The bulk of the populations of several tropical countries depend on traditional medications (largely from plant sources), because of unavailability/ unaffordability of orthodox medicine (Zirihi *et al.*, 2005; WHO, 2002). The World Health Organization backs the usage of medicinal plants, if they are established to be effective and safe (WHO, 1985). Combination therapy, an approved strategy being used for several multidrug resistance infections like tuberculosis and HIV, is extensively endorsed for malaria treatment (WHO, 2001; White, 1998). Thus, combination therapy has steadily replaced treatment with single drug over time due to the increase incidences of drug resistance by the Plasmodium parasites worldwide (Martinelli *et al.*, 2008). Thus, this study evaluated the antiplasmodial effects of crude hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit (singly and combined). In this study, all extracts demonstrated great *in vivo* antiplasmodial activity, with the combined extracts giving the best activity overall.

The results of the suppressive study with extracts of *C. papaya* and *C. aurantifolia* gave % parasitemia of 29.60±1.14 and 34.40±1.14 respectively, while the combined extracts exhibited even higher reduction (19.60±1.82) than either extracts used singly. But the highest level of reduction in parasitemia was seen in the positive control group of mice. However, there was an observed increase in % parasitemia in the untreated mice, which agrees with earlier report on the effect of the plasmodia on animals

(Okokon *et al.*, 2005).

In the prophylactic or preventive study, pre-treatment with extracts of *C. papaya* and *C. aurantifolia* caused higher reduction in % parasitemia of 24.00±1.58 and 28.80±2.39 respectively, when compared with the reduction seen in the suppressive test. Similarly, a higher reduction in % parasitemia was noticed in the mice pre-treated with the combined extracts of both plants. The observed antiplasmodial action displayed by the *C. papaya* fruit peels agrees with earlier report on the antimalarial activity of *C. papaya* fruit (Zelege *et al.*, 2017). Similarly, the moderate antiplasmodial activity seen in the *C. aurantifolia* fruit extract treated mice agrees with previous report about the antimalarial potential of lime juice (Adegoke *et al.*, 2011).

When two or more drugs/ plant extracts are combined they can generate a synergistic or antagonist results to the malarial causing parasite in mice. The synergistic effect happens when the combination jointly enhances the efficiency of each ingredient. Antagonistic effect appears when a constituent in the combination decreases the activity of another component, causing a reduction in efficacy than the individual dose (Fatmawaty *et al.*, 2017). Thus, the observation in this study about the efficacy of the combined extract over the effects displayed by the individual extract indicates that certain constituents in this combination could have acted synergistically (Berenbaum, 1978).

The presence of flavonoids, phenols, tannins and terpenoids has been reported from the



phytochemical screening of *C. aurantifolia* (Adebayo-Tayo *et al.*, 2016). Similarly, total phenolic content, flavonoids and tannins have been reported from the phytochemical screening of *C. papaya* peels (Martial-Didier *et al.*, 2017). The presence of saponins, flavonoid and steroids has also been reported from the extracts of *C. papaya* peel (Dada *et al.*, 2016). Lydia *et al.* (2016) also reported the presence of Phenols, flavonoids and tannins in *C. papaya* fruit peel. These classes of secondary metabolites reported in extracts of both *C. aurantifolia* and *C. papaya* fruits have also been reported to exhibit antiplasmodial activity in some other plants (Abdulelah and Zainal-Abidin, 2007; Hilou *et al.*, 2006; Asres *et al.*, 2001). Thus, the antiplasmodial activity seen in this study may have resulted from these phytochemicals which might be acting individually or synergistically with one another to have exerted the noticed antimalarial activity.

In the suppressive study, treatment with the crude hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit did not stop the parasitemia induced reduction in PCV of the mice. However, treatment with either the combined extracts or the standard drug prevented the plasmodia induced reduction in PCV levels of mice on day 4 of experiment.

Similarly, in the preventive study, pre-treatment with hydroethanol extracts of *C. papaya* fruit peels, the combined extracts and the standard drug were observed to prevent a significant drop in PCV levels on day 4. While pre-treatment with hydroethanol extracts of *C. aurantifolia* fruit failed to prevent the plasmodia induced reduction in PCV levels on day 4, an observation similar to what was seen in the negative control group. Thus, the trend observed in the PCV levels in the different groups was comparable to what was seen in the % parasitemia tests. The PCV level was measured to assess the efficacy of the extracts in precluding haemolysis arising from parasitaemia level. Malaria infected animals usually suffer from anaemia due to erythrocyte destruction consequent upon malaria multiplication or spleen reticuloendothelial cell action (Chinchilla *et al.*, 1998).

Conclusion

This study has revealed the pharmacological basis and partly explains why the two fruits are used to treat suspected malarial cases in the Niger Delta area of Nigeria. The hydroethanol extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit used singly or combined showed varied antiplasmodial activity, with the combined extract demonstrating the highest activity against the *P. falciparum* (chloroquine resistant strain). Thus, the combined extracts of *C. papaya* fruit peels and *C. aurantifolia* fruit is recommended for further research towards identifying and isolating the active ingredient(s) contained therein.

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