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Research Article

EFFECT OF IRRIGATION INTERVAL ON GROWTH AND ARTEMISININ CONTENT OF WORMWOOD (*Artemisia annua* L.) CHEN YOUNG VARIETY IN SOKOTO

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Abstract: Artemisinin is the main antimalarial compound in *Artemisia annua*, used in the formulation of artemisinin-based combined therapies (ACT) to treat malaria. Artemisinin is largely obtained from *A. annua* plant but the content is very low and its production commercially is not cost effective worldwide. In view of the importance of this phytomolecule and plants being the only source of its production, this study evaluated the effect of irrigation interval on the growth and artemisinin content of *A. annua*. A greenhouse experiment was conducted at Botanical Garden of Usmanu Danfodiyo University Sokoto. The experiment was laid out in completely randomized design with 4 replications. The two factors examined were: (1) irrigation interval at different growth stage and (2) artemisinin content of *A. annua*. Irrigation interval (W) was taken at four levels (W_1, W_2, W_4, and W_6 days interval) while growth stage at three levels: early vegetative stage (EVS), mid vegetative stage (MVS) and late vegetative stage (LVD) and artemisinin were determined and quantified using High Performance Liquid Chromatography (HPLC). The calibration curve was constructed by plotting the peak area against the concentration by the external standard method on five concentration levels of artemisinin standard (5, 10, 15, 20, and 25 µg/ml), with three injections per level. Linear regression was used to establish the calibration curve. Results were calculated using the peak areas with determination coefficient (R^2) of 0.951. Results revealed that W_2 days irrigation interval had significantly ($p<0.05$) affected fresh weight, dry weight, stem diameter and root length during the EVS. At MVS, irrigation interval had no significant ($P>0.05$) effect on plant height and number of branches but significantly reduces stem diameter. During the late vegetative stage (LVD), irrigation intervals have no significant effect on all parameters evaluated. Artemisinin content was not significantly ($P>0.05$) affected by irrigation intervals during the EVS but significantly affected at mid and late vegetative stage and our result demonstrated that prolong mild irrigation interval (W_2) could significantly enhanced artemisinin content in *A. annua*.

Key word: Artemisinin, early vegetative stage (EVS), mid vegetative stage (MVS), late vegetative stage (LVD), High Performance Liquid Chromatography (HPLC).

Introduction

Artemisia annua L. (family Asteraceae), can be found in the temperate regions of the northern hemisphere, in arid and semiarid climates areas. The genus has a great economic importance as medicinal resource, flavouring agent, antibacterial, antifedant and antimalarial activities [IHSAN-UL-HAQ & al. 2012]. *A. annua* is the only planta medical that has been recognized to research and developed as the standards of western medicine research by the WHO in China. It is a famous herb, known for its highest efficiency and lowest toxicity in treating ague [WANG & al. 2011]. It is aromatic annual herbaceous plant [ZANJANI & al. 2012; LIU & al. 2013; MISRA & al. 2013] and belongs to genus *Artemisia* [LIU & al. 2013], family Asteraceae (Compositae) [ZANJANI & al. 2012] and commonly known as sweet

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wormwood or Qinghao [HUANG & al. 2010; EMADI, 2013]. It's the only member of genus *Artemisia* with an annual growth cycle [WILLCOX & al. 2004].

Artemisinin is an effective antimalarial compound that is synthesized in the glandular trichomes of medicinal plant *Artemisia annua* which has saved millions of lives. It is used in the formulation of Artemisinin based combination therapies (ACTs) recommended by the World Health Organization [WHO, 2017] for treatment of uncomplicated malaria caused by the *Plasmodium falciparum* parasite [DUFFY & MUTABINGWA, 2006]. Currently, the supply of ACTs is reliant on the agricultural production of artemisinin. However, plant-based production sometimes cannot meet the global demand due to the low amount of artemisinin produced in *A. annua* leaves (0.1%-2.0% of dry weight). Alternatively, a semi-synthetic system can be used for the production of artemisinin, in which yeast are engineered to synthesize its precursor, artemisinic acid [RO & al. 2006; PADDON & al. 2013]. However, the semi-synthetic production of artemisinin is expensive and thus cannot replace its agricultural production at present [PEPLOW, 2016]. Besides its anti-malarial activity, many other therapeutic effects of artemisinin on diseases such as cancer [EFFERTH, 2006; TIN & al. 2012], tuberculosis [ZHENG & al. 2017], and diabetes [LI & al. 2017] have been reported. The use of the whole Artemisia plant as a malaria therapy was found to be more effective than a comparable dose of pure artemisinin, and was shown to be able to overcome resistance to pure artemisinin in a rodent malaria model and human clinical trial [ELFAWAL & al. 2015; DADDY & al. 2017]. Recently Madagaska's Institute of Applied research has produced Artemisia-containing tonic that supposedly prevent and treat COVID 19 [MWANGI, 2020]. Hence, artemisinin is a potential multi-functional compound and is of high medicinal value. There is a considerable interest in increasing the artemisinin content of *A. annua* and an urgent need to identify other potential method for it production. Despite many malaria cases in savanna region, few or none has been tried to increase the artemisinin content in Savanna region of Nigeria. The research aimed to evaluating the effect of irrigation interval on growth and artemisinin content of *A. annua* in Sokoto.

Material and methods

Collection of plant material and soil

Artemisia annua seeds of Chen Young variety were sourced from Artemisia Programme Unit at the Institute for Agricultural Research (I.A.R) Ahmadu Bello University, Zaria.

Equipment and chemicals

High Performance Liquid Chromatography equipment Soxhlet extraction apparatus, Beakers, Syringe and measuring cylinder etc. Artemisinin standard was purchased from Sigma Aldrech through Bristol Scientific Company. Ethanol, methanol, n-hexane, sodium hydroxide, acetonitrial, and Indole butyric acid and all the solvents used were of analytical-grade.

Experimental design and inducement of irrigation interval

This experiment investigated the effects of irrigation interval on growth and artemisinin content of *A. annua*. Five weeks old seedlings of approximately of the same height (12-15 cm) were selected and subjected to four different watering regimes: control (W_1), mild (W_2), moderate (W_4) and severe (W_6) irrigation interval in completely randomised design (CRD) with four replicate. Soils with mild, moderate and severe irrigation interval were watered once at 2, 4 and 6 days interval respectively and daily as control. Four seedlings (stand) per each experimental unit.

Data were taken at early vegetative stage (EVS), mid vegetative stage (MVS) and late vegetative stage (LVS) after one, two and three-month post irrigation interval respectively. At each stage, plant height, number of branches, fresh weight, dry weight, stem diameter and roots length were determined and Leaves from each stand in the treatment were collected and analyzed. Each treatment was irrigated with one liter of water on it corresponding watering regime throughout the plant developmental stages. At each stage, samples were taken for artemisinin analysis to find out if artemisinin is affected by irrigation interval [YADAV & al. 2014].

Preparation of extracts for soxhlet extraction

Fresh leaves of *A. annua* were dried for two weeks at room temperature, pulverized into powder using mortar and pestle and homogenized. Adopting the method of CHRISTEN & VEUTHEY (2001), 5 g of pulverized sample was extracted with 200 ml of *n*-hexane at 60 °C in Soxhlet apparatus. The hexane was then evaporated under a vacuum and the samples reconstituted in 10 ml acetonitrile then filtered through Whiteman filter paper no.1.

Preparation of standards and high-performance liquid chromatography

Artemisinin solution was obtained by dissolving 10 mlg of artemisinin standard in 100 ml of acetonitrile to form the stock solution and from the stock solution 5 different concentrations of 5, 10, 15, 20 and 25 µg/ml were obtained. Each was run 3 times in HPLC from the results, standard calibration curve was drive. The HPLC analyses were performed with Agilent technologies 1200 series on Eclipse XBD-C18 (4.6 × 150 mm) column and detection was conducted at 214 nm wavelength. The acetonitrile were used as a mobile phase with 0.8 ml/min flow rate [LAPKIN & al. 2009]. Injection column was 10 µL; run time of 20 min at 30 °C.

Calibration curve

The calibration curve was constructed by plotting the peak area against the concentration by external standard method on five levels of concentration of artemisinin standard (5, 10, 15, 20, and 25 µg/ml), with three injections per level. Linear regression was used to establish the calibration curve. Results were calculated using the peak areas and determination coefficient (R^2) of 0.951.

Data analysis

The data obtained were analyzed using one-way analysis of variance with Minitab Statistical Software version 17. Significant means were compared using Turkey simultaneous test at $P<0.05$.

Results

Effect of irrigation interval on the growth of *Artemisia annua* at early, mid and late vegetative stages

The results of irrigation interval on the growth parameters of *A. annua* at early, mid and late stage vegetative stage are presented in Table 1. The results show that Irrigation Interval has no significant ($P>0.05$) effect on plant height and branch number at all the three vegetative stage evaluated. However, irrigation interval significantly affects fresh weight, dry weight and stem diameter at early and mid-vegetative stage while root length was only affected at early vegetative stage with the highest values (23.75 cm) on W_2 days irrigation interval. At mid vegetative stage, irrigation interval significantly reduced stem diameter which is directly

proportional to the severity of the interval and the highest root length was observed at 2 days irrigation interval with (17.00 cm) followed by four days interval (12.50 cm) and then control (11.33 cm). At late vegetative stage, irrigation interval had no significant effect on all the growth parameters evaluated (Table 1).

Effect of irrigation interval on artemisinin content of *Artemisia annua* at early, middle and late vegetative stage

The result on effect of Irrigation Interval at early, mid and late vegetative stage on artemisinin content in *A. annua* is presented in Table 2. The result revealed that irrigation interval had no significant effect (P>0.05) on artemisinin content during the early and late vegetative stage of *A. annua*. However, irrigation interval significantly (P<0.05) affected artemisinin content at mid vegetative stage. The linear calibration curve obtained from High Performance Liquid Chromatography (HPLC) was presented in Figure 1.

Table 1. Effect of irrigation interval on the growth of *A. annua* at early (EVS), mid (MVS), and late (LVS) vegetative stage

Plant growth stage	Irrigation interval	Plant height (cm)	No. Branch	Fresh weight (g)	Dry weight (g)	Stem-diameter (cm)	Root Length (cm)
EVS	W_1	42.75±10.24	49.00±10.42	25.07±4.67^{b}	6.45±1.07^{b}	2.02±0.22^{b}	13.50±1.2^{b}
	W_2	50.75±16.88	50.00±8.30	37.27±6.94^{a}	10.43±3.03^{a}	3.10±0.36^{a}	23.75±3.03^{a}
	W_4	43.50±14.20	39.00±10.14	19.68±2.12^{bc}	5.22±0.43^{b}	1.17±0.22^{c}	12.75±2.01^{b}
	W_6	38.00±14.17	35.00±12.97	11.65±3.03^{c}	4.27±0.60^{b}	1.02±0.22^{c}	11.00±0.82^{b}
MVS	W_1	62.00±7.21	66.00±5.20	21.23±5.20^{ab}	5.133±1.36	1.67±0.37^{a}	11.33±2.31
	W_2	77.50±12.40	67.00±10.83	34.02±10.83^{a}	8.18±4.40	0.95± 0.31^{b}	17.00±4.24
	W_4	76.25±2.50	38.00±4.53	15.93±4.53^{b}	4.37±0.39	0.700±0.14^{b}	12.50±2.38
LVS	W_1	101.00±1.73	83.00±20.20	95.1±70.3	18.63±15.43	2.00±0.20	25.43±4.41
	W_2	129.70±29.0	85.00±27.10	73.0±41.0	28.00±14.38	3.17± 0.40	19.33±5.13
	W_4	119.00±9.54	40.00±10.00	77.50±13.16	20.8±17.60	1.100±0.200	16.00±3.46

Means followed by same superscript in a column are not significantly different (P>00.5).

Table 2. Effect of irrigation interval on artemisinin content in *A. annua* (µg/ml)

Treatment	EVS	MVS	LVS
Daily irrigated (W_1)	5.65 ±1.20^{c}	13.95 ± 5.37^{b}	18.54 ±4.69^{b}
2 days interval (W_2)	5.22 ± 1.62^{c}	10.62 ± 3.91^{b}	16.02 ±3.31^{b}
4 days interval (W_4)	5.96 ± 2.49^{c}	33.60 ±19.6^{a}	33.5 ±17.5^{b}
6 days interval (W_6)	5.99± 2.32^{c}	-	-

EVS: Early vegetative stage. MVS: Mid vegetative stage. LVS: Late vegetative stage
Means followed by same superscript in a column are not significantly different (P>00.5). n=3

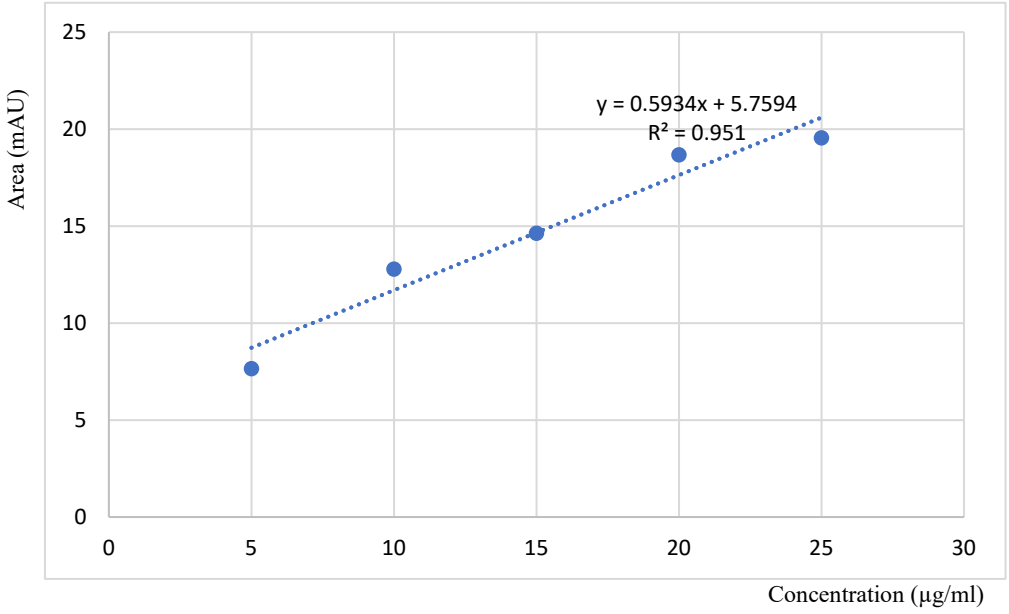

Figure 1. Linear calibration curve for Artemisinin standard

Discussion

The effect of irrigation interval at early vegetative stage on growth parameters of *A. annua* shows that W_2 day's interval has significantly ($p<0.05$) affected the fresh weight, dry weight, stem diameter and root length during the first two month of imposed irrigation interval. This was in agreement with the work of MARCHESE & al. (2010) that treatment of 38 hours water deficit induced the highest foliar biomass accumulation and artemisinin content per plant on dry weight basis, compared with control. Plant height and branch number was also higher at this level, this increase in growth parameters was un-expected because water stress generally decline or seize plant growth and biomass accumulation. This indicate that *Artemisia annua* require moderate moist water environment. Treatments that were watered once after two days interval grow better than any other treatment including control. Plant height decreased with increase in irrigation interval in this irrigation interval order once after two days interval > once after four days interval > once after six days internal. Similarly AZHAR & al. (2011) indicated that plant height, fresh and dry weight of plants was reduced significantly with increasing water stress levels in *Trichyspermum ammi* L. BETTAIEB & al. (2011) reported that *Cuminum cyminum* exposed to water stress caused reduction in growth attributes like plant height, number of branches, fresh and dry matter as well as yield components like number of umbels/plant and umbellets per umbel.

In moderate (W_4 days) and severed (W_6 days) irrigation interval, branch number, fresh weight, stem diameter and root length decrease greatly with increase in irrigation interval imposed. This result agreed with YADAV & al. (2014) who state that water stress significantly affected the plant growth parameters at all four stages of development (early vegetative, mid stage, late vegetative stage and full bloom stage). Irrigation intervals significantly ($p<0.05$)

affect the stem diameter. The extent of decline progressed proportionally to the severity of irrigation interval.

At mid vegetative stage, mild (W_2) irrigation interval greatly influences the plant height and branch number of *A. annua.* Plant height and branch number observed on this treatment was higher than all other treatment including control. Mild irrigation interval was found to significantly increase fresh weight ($P<0.05$). This contradict the result of BRISIBE & al. (2012) who reported that *A. annua* plant that were watered automatically using time controller performed better than those with intermittent periods of water stress and stem diameter is significantly affected by irrigation interval ($P<0.05$) which is directly proportional to the severity of irrigation interval. The highest root length was also observed at mild irrigation interval (17.00 cm) follow by moderate (12.50 cm) and then control (11.33 cm). This is because availability of moisture on the soil surface limits the roots extension. All stands on severe irrigation interval (W_6) die after one month of the imposed irrigation interval in green house which is contrary with our field result that survived for two weeks without water at forestry research farm.

At late vegetative stage, mild irrigation interval (W_2) has a positive influence on plant height, branch number, branch length, dry weight and stem diameter. At this stage, control had the lowest plant height and branch number among the treatment tested following by treatment with four days interval. This result was un-expected because water stress generally affects all plant parameters but the highest plant height and branch number were observed at W_2 treatment. Root length of *A. annua* decreased with increase in irrigation intensity with the highest in control followed by W_2 and W_4 days' interval respectively.

The effect of irrigation interval on artemisinin content of *Artemisia annua* showed a contrasting pattern of artemisinin concentration at all the three stage of development. Our finding revealed that irrigation interval has no significant effect on artemisinin content during early vegetative stage of *A. annua* (one month of imposed irrigation interval). Similar report were made by CHARLES & al. (1993) who found no significant correlation between artemisinin concentration and the water deficit applied for two weeks before harvesting, although there was a trend for artemisinin concentration to decrease with increased negative water potential. However, artemisinin content was significantly ($P<0.05$) affected by irrigation interval at mid vegetative stage. The significant increase in the leaf artemisinin content resulting from the treatment with moderate irrigation interval (W_4 days interval) can be attributed to the decrease in all the growth parameters evaluated on this treatment (plant height, branch number, fresh weight, dry weight, stem diameter and root length while photosynthesis is still occurring. Thus, the excess photo-assimilates not used in growth, were expected to be directed towards artemisinin biosynthesis. Many researchers like; MARCHESE & FIQUIRA, (2005) are on the above opinion. Similar result was reported by MARCHESE & al. (2010) that 38 hours water deficit significantly increase artemisinin content by 29% more than control. This also agrees with HERMS & MATTSON (1992), who reported that terpenes tend to accumulate under moderate water deficit. STAUDT & CHUINE (2005) found that increase in temperature and water deficit had significant effect on mono and sesquiterpenes emissions of *Artemisia* species. However, DUHL & al. (2007) reported that severe drought reduced the emissions of sesquiterpenes.

At late vegetative stage of *Artemisia annua*, artemisinin content was significantly affected by irrigation interval and increase significantly with the advancement in plant developmental stage. They increase in this order EVS>MVS>LVS at control and mild irrigation interval. This was in conformity with the work of YADAV & al. (2014) that artemisinin content

increase with the progression in plant developmental stage. However, *A. annua* plants can tolerate some changes in water availability and temperature without a drastic decrease in artemisinin content. Thus, it is important to note that results in artemisinin content may vary depending on the origin of *A. annua* cultivar and on the regional environmental conditions.

Conclusion and Recommendation

This study concluded that irrigation interval had an effect on both growth and artemisinin content and suggested two days (W_2) irrigation interval for better growth performance and biomass production and four days (W_4) interval for high artemisinin content in *A. annua* at Savannah region of Nigeria.

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