A REVIEW ON ASSESSMENT OF ARTEMISININ PRODUCTION UNDER ABIOTIC STRESS

Nafish Ahmad[1], Riyazuddeen Khan[1*], Iffat Zareen Ahmad[2]

[1]Deprtment of Environmental Science, Integral University, Dasauli Kurshi Road, Lucknow, Uttar Pradesh-226026, India

[2]Deprtment of Bioengineering, Integral University, Dasauli Kurshi Road Lucknow, Uttar Pradesh-226026, India

***Corresponding author: Dr. Riyazuddeen Khan**

Email: rkhan@iul.ac.in

Tel: +918887852663

ABSTRACT:

Recently, the growth of the world's population, the loss of arable land, soil erosion and conversion of agricultural land into urban area due to uncontrolled development have all put pressure on crop productivity. *Artemisia annua* is an annual plant native to Asia and Eastern Europe is the primary source of the antimalarial chemical compound artemisinin and it is a sesquiterpene alkaloid found in maximum amounts in the leaves. Although the extracted artemisinin content of *A. annua* is very low (dry weight approximately 0.01 to 1%). The plant stress such as temperature extremes, drought, alkalinity or salinity, UV radiation, and heavy metal have a negative impact on growth and development of plant. The techniques and time in which it is planted and harvested, as well as the weather circumstances, might have an influence on its productivity. However, the abiotic stress factors are utilized in in-vitro conditions to enhance production of artemisinin and other secondary metabolites by regulating the stress genes. The DBR2 gene has been demonstrated to induce a large increase in the amount of artemisinin made in A. annua, which is beneficial to the plant. Elicitation is a technique that has been used a lot in plant cell culture to make more secondary metabolites. This review elaborates the role of different abiotic factors on the production of artemisinin and the plant itself.

Keywords: Artmisinin, secondary metabolite, abiotic stress

Introduction

An annual death toll of over one million people is caused by malaria, a worldwide health issue that affects 300–500 million people (WHO 2016). The presence of multi-drug resistant forms of the Plasmodium falciparum parasites renders it challenging to monitor malaria. Malaria vaccines and synthetic antimalarial medications are presently being researched, but extensive clinical testing is required to determine their effectiveness (Cox 2010). Artemisinin is a chemical compound, a sesquiterpene lactone endoperoxide isolated from *Artemisia annua* that is very efficient against the strains of multi-drug-resistant *Plasmodium* spp., but it is in limited supply and unavailable for the majority of malaria patients (Jing et al. 2009). Though the extracted artemisinin content of *A. annua* is very low (dry weight approximately 0.01 to 1%) for the manufacture of malaria combination medicines, artemisinin and its semi-synthetic artemisinin derivatives (including dihydro-artemisinin, artesunate, artemether, and arteether) are used in conjunction with other artemisinin derivatives (Ro et al. 2006).

In recent years, the growing global population, shrinking arable land, soil degradation and the conversion of agricultural land to urban land due to uncontrolled development and have all contributed to increased pressure on crop productivity. Because of the threat related to climate change, it is projected that this tendency will become much more alarming. All of these discoveries provide a significant challenge to our efforts to ensure food & health security for all humans without further degrading ecology. Another important factor limiting agricultural production is stress, initially described by Hans Selye (1936), as an adverse and environment restrains faced by the plants (Lichtenthaler 1998). The definition of plant stress is, however, quite different from the definition of stress in animals and human beings. Stress is two type one is biotic stress and second is abiotic stress. Abiotic stress which includes water-logging, salinity, drought, freezing, chilling, heat, deficiency of nutrients, and variable light conditions. Abiotic stress can negatively impact plant growth processes and is one of the most common causes of crop failure (Kreps et al. 2002). Abiotic stressors are thought to diminish crop output by more than 50%, according to some reported studies (Rodziewicz et al. 2014). In particular, drought, high salinity, and extreme temperatures are among the most terrible pressures that contemporary on agriculture. When stress was induced in plants, they go through a range of morphological, physiological, molecular and biochemical transformations. Plants have an amazing adaptability towards changed environmental conditions and, depending on the severity of the stress plant adapt in a manner that is appropriate for their survival. There are numerous biological pathways along with the involvement of genes were reported to be involved in tolerance against abiotic stress in various plants. (Yang et al. 2012).

The physiological reactions of plants to stress include abscission of the leaf, wilting of the leaf, leaf region reduction and decreased level of loss of water through transpiration, among other things (Fghire et al. 2015). Low temperatures have a significant impact on the survival of plants as well as their geographical spread. Cold stress is typically responsible for significant crop loss due to deprived plant development and crop efficiency (Browse and Xin 2001). Cold stress also causes dehydration of cells and tissues, as well as crystallization of cellular water, which has the effect of inhibiting plant growth and production. As a result of the decreased membrane conductivity and increased viscosity of water, as well as the inhibition of hydro active stomata closure are the results of water stress induced in plants while electrolyte leakage at low temperatures is reported (Pearce 2001). Up to 45% of the world's farmland is subjected to repeated periods of time when there is insufficient rainfall in areas where 38% of the world's population dwells and approximately 3106 km2 (6%) of the land are mapped on world’s area to be affected by salinity and about 19.5% of irrigated cultivation land were reported to be saline (Volkov 2015). In addition, each year, approximately 1% of the world's agricultural land (2 million hectares) is damaged by salt, resulting in diminished or non-existent crop productivity (Flower 2004). Water constraint, as a result of insufficient rainfall, salinity and cold temperatures, is a prominent abiotic stress experienced by plants especially in their phase of development and growth. According to the 2000 report by FAO World Soil Resources Report, approximately 64% of the world's land area is influenced by drought, whereas 57% is affected by cold, and 6% by salinity, respectively. Addressing the responses by the plant against the abiotic stress has therefore become a significant component of plant research in attempt to ensure food security (Hirayama et al. 2010). Abiotic stresses are interconnected and regulate plant water relationships on a cellular and overall plant level, causing specific and unknown responses that result in a sequence of physiological, morphological, molecular and biochemical changes that adversely impacts plant growth and development. Plants have advanced sophisticated insight, acclimation, and signaling mechanisms to cope with adverse environmental conditions. These processes permit them to tolerate diverse stress conditions, even at the expense of diminished development and productivity (Bailey-Serres, et al. 2019).

Artemisia annua L., a common name for this plant is annual wormwood (Chinese: qngho), sage wort. sweet sagewort and sweet Annie. It is a member of the Asteraceae family and is distinguished by its camphor-like aroma along with bright yellow flowers and fern-like leaves. The majority of research has focused on ways to improve artemisinin production and for that reason it is important to understand the impact of change in climatic conditions on the artemisinin content of plants because the primary and secondary metabolites of plants tend to elevate under stress condition (Ikram and Simonsen 2017). Furthermore, to discover some of the genes that are stress-responsive and could aid in the development of tolerance in plants against stress when subjected to abiotic stressors. The *A. annua* plants when subjected against four different abiotic stresses (drought and water-logging, heavy metals, cold and salt), it was discovered that the content of artemisinin compound was increased in all of the conditions of stress except the drought situation.

1.1Botanical description

A. annua is an annual herb of Asiatic and eastern European origin and is extensively distributed across the temperate region. *Artemisia*, one of the largest genera in the Asteraceae family, is a beneficial group of medicinal and aromatic plants that includes over 300 species that are widely dispersed genera in the world (Garcia 2015). It is thought to have originated in China and can be found largely in the eastern, southern and middle areas of Europe, as well as the middle, northern, and eastern regions of Asia. It is also found in the southern, eastern and middle regions of Asia. In addition to the Mediterranean region, it may be found in North African countries along with Asia in the South and South-Western part, as well as in the Australian continent. It has also gained a substantial presence in both Canada and the United States following its introduction to North America from northern Asia in the 1990s (Simon 1990).

The cultivation of *A. annua* on a wide scale is now only practiced in a few countries, namely Vietnam, Kenya, China and the United Republic of Tanzania. Small-scale farming has been carried out in India as well as in Africa, southern Europe, and South America, among other locations. The majority of *A. annua* harvested for industrial purposes comes from the wild. *A.*

annua can grow to be more than 2.0 m tall, and it is normally single-stemmed with alternate branches. The aromatic leaves ranging in length from 2.5 to 5 cm and are extensively dissected. Flowers and leaves *A. annua* contains biseriate trichomes and filamentous trichomes about 10-celled and 5-celled, respectively. The leaves and aerial components of the plant are often characterized by variation. The borders of the leaves are not complete, but have asymmetrical base. The margin of the leaf's ranges from pale green to dark green, and they have a strong aromatic scent that is slightly bitter in taste (Das 2012).

Table 1 Taxonomical classification of *Artemisia annua*

Kingdom:	Plantae
Phylum:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Asteridae
Order:	Asterales
Family:	Asteraceae
Genus:	Artemisia
Species	Annua
Scientific names: *Artemisia annua* L.	

Fig. 1 *A. annua*, commonly known as sweet worm wood

Vernacular names of *A. annua*

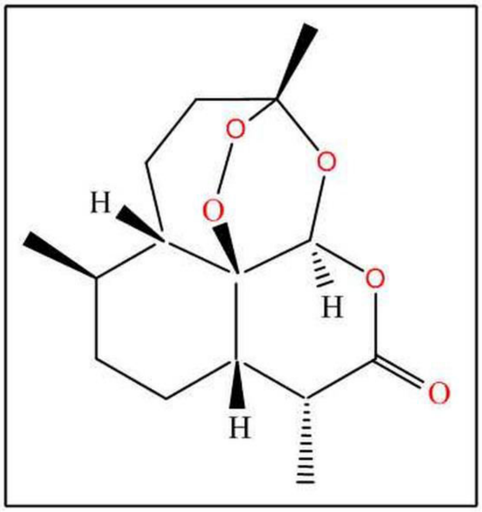
English: sweet wormwood, annual wormwood: **Chinese:** Cao Haozi, Caohao, Cao Qinghao, Chouhao, Jiu Bingcao, Kuhao, Chou Qinghao, Xiyehao, Haozi, San Gengcao, Xiang Sicao, Xianghao, Xiang Qinghao; **Korean:** Chui-ho, Gae-tong-sook, Hwang-hwa-ho; **Japanese:** Kusoninjin; **French:** armoise annuelle; **Vietnamese:** Thanh cao hoa vàng.

The significant chemical elements of *A. annua*

Among the components of *A. annua* chemical composition involves both non-volatile and volatile compounds, while volatile constituents are primarily attributed to essential oils, with the latter accounting for 0.2–0.25% which includes major compounds like 1-camphor, camphene, isoartemisia ketone, β-pinene, β-camphene and β-caryophyllene accounting for around 70% of total essential oil content. The volatile components of *A. annua* also contain other compounds such as camphene hydrate, cuminal, 1,8-cineole and artemisia ketone. Sesquiterpenoids, flavonoids, and coumarins are among the most important non-volatile components, along with content of certain steroids (β-sitosterol and stigmasterol), proteins (β-glucosidase and β-galactosidase). Among the most important chemical constituents of *A. annua* are sesquiterpenoids, which include the artemisinin alkaloids (artemisinin I to artemisinin V), artemisic acid, epoxyarteannuinic acid, artemisinol and artemisilactone. Artemisinin is a sesquiterpene alkaloid that is found in high concentrations in the leaves of *A. annua* (Das 2012).

Artemisinin Biosynthesis by *A. annua*

Artemisinin is a compound that has been the subject of extensive investigation for many years now. There has been some progress in understanding the biosynthesis of the artemisinin and its regulation through the plant of *A. annua*, however, the revelation that the glandular trichomes confine the entire plant's biosynthesis and has allowed for more in-depth regulatory research (Olofsson et al. 2011). Farnesyl diphosphate (FPP), precursor of a C15 sesquiterpenoid is produced by the condensation of one dimethylallyl diphosphate (DMAPP) and two molecules of isopentenyl diphosphate (IPP), that is obtained from the general pathway of terpenoid biosynthesis in the existence of an enzyme farnesyl diphosphate synthase (FPPS/FPS) (Wen and Yu, 2011). Following the findings of Banyai et al. (2010), it was discovered that overexpressing FPS in *A. annua* resulted in the production of artemisinin at higher percentage (Banyai et al. 2010). This supports the notion that FPS, as well as the availability of substrates, serves a factor in the regulation of biosynthesis of the artemisinin compound in a manner that is analogous to that of supplementary sesquiterpene lactones (Simonsen et al. 2013).



Artemisinin

Fig. 2 The primary 2D structure of Artemisinin

Through the processes of carbocation formation and cyclization, the enzyme amorpha-4,11-diene synthase (ADS) generates amorpha-4,11-diene by utilizing FPP (Picaud et al. 2005; Picaud et al. 2006). In the next two phases of oxidation, artemisinic alcohol is produce by hydroxylation of amorpha4,11-diene, which is further oxidized to artemisinic aldehyde in the presence of a cytochrome P450 enzyme called amorphadiene monooxygenase (CYP71AV1) (Wang et al. 2011). Furthermore, the CYP71AV1 enzyme activity has been established in *A. annua* plants by genetically silencing the endogenous gene by the knock-out approach and thus demonstrating that these plants does not synthesize any amorphdiene downstream products as a result of the genetic modification (Czechowski et al. 2016). A dehydrogenase/reductase enzyme, ADH1 (aldehyde dehydrogenase 1) is reported in later studies to be specific for artemisinin alcohol and has been discovered to oxidized the alcohol to the aldehyde. Because of this specificity and significant expression of ADH1 in the glandular trichomes, it is concluded that ADH1 is accountable for the oxidation of artemisinic alcohol and its conversion to artemisinic aldehyde (Olofsson et al. 2011; He et al. 2017). This enzyme, ADH1, which is found in the trichomes are reported to further reduce the artemisinin aldehyde to dihydroartemisinic aldehyde and eventually further oxidized to dihydroartemisinic acid by the enzyme artemisinic aldehyde Δ11 (13) reductase (DBR2), which is also found in the trichomes (Liu et al. 2016). The enzyme ALDH1 is known for its ability to catalyze both the dihydroartemisinic aldehyde oxidation to acid, as well as the conversion of artemisinic aldehyde to acid in plants by the process of oxidation (catalyzed by CYP71AV1) (Teoh et al. 2006; Teoh et al. 2009).

Another enzyme, dihydroartemisinic aldehydereductase (RED1), was identified by Rydén et al. (2010), which produces a “dead-end” molecule namely dihydroartemisinic alcohol from dihydroartemisinic that has an impact on the yield of artemisinin generated. After that, there is a non-enzymatic spontaneous reaction driven by light that converts dihydroartemisinic acid to artemisinin and also involves the conversion of artemisinic acid to arteannuin B (Teoh et al. 2006; Czechowski et al. 2016).

Abiotic factors influencing secondary metabolites

Many environmental conditions (such as extremes of temperature (both high and low), drought, alkaline or salinity, ultraviolet radiation, and pathogen infection) have the potential to be detrimental to plants (**Fig. 3**). Elicitation has been frequently utilized to boost the generation of secondary metabolites in plant cell culture in vitro environment, as well as to promote synthesis of secondary metabolites utilizing de novo pathways. An increasing number of experiments have been carried out in cultures of plant organs, tissues and cells all with varied degrees of success. A variety of elicitors have been tested in order to stimulate secondary metabolite production. An increase in the formation of phenylpropanoids has been observed in response to pathogen attack, ultraviolet radiation, intense light, wounding, nutritional shortages, high temperatures and herbicide treatment. It is also important to note that nutritional stress has an impact on the levels of phenolic chemicals found in plant tissues. In addition, concentration of various secondary products of plant are highly reliant on the growth circumstances and have an influence on the signaling pathways for metabolites biosynthesis that are accountable for the associated natural products aggregation.

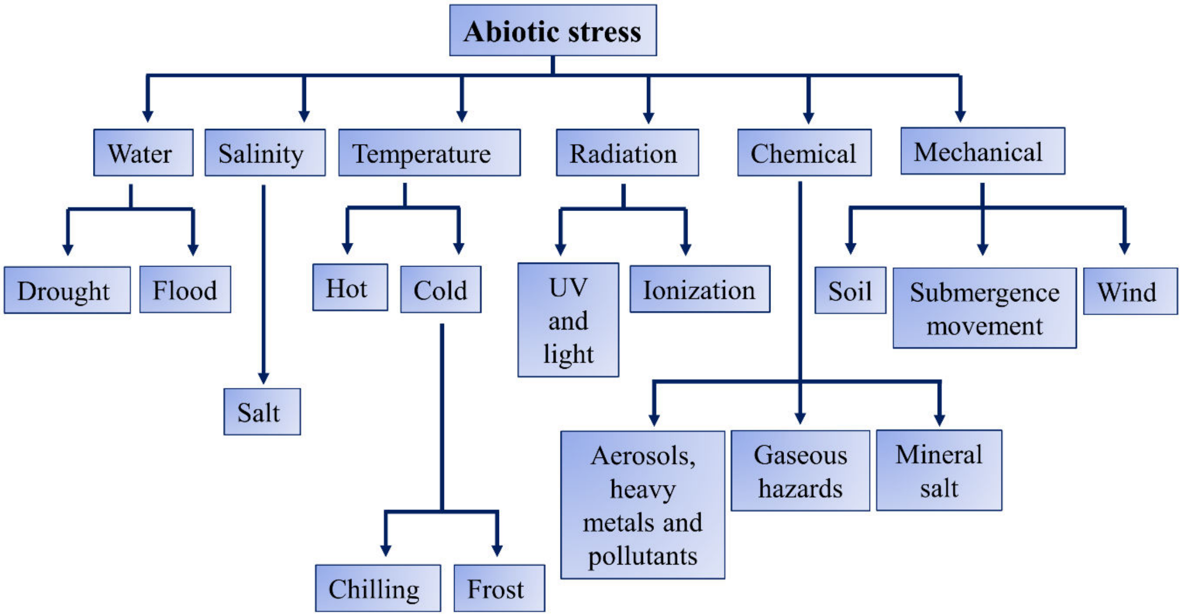


Fig. 3 Several abiotic stress signaling affect plants

When plants are challenged to drought or salt stress, they exhibit a variety of physiological responses. Cellular dehydration is caused by both stresses, which are amplified by the osmotic stress and water loss to the vacuoles from the cytoplasm, which together result in cellular dehydration. Based on the findings of a conversion mechanism of carbon to biomass generation or the synthesis of defensive secondary metabolites that happens when plants are stressed (Akula and Ravishankar 2011). When plants detect stress at the molecular level, they respond by inducing a stress response in the surrounding environment. According to research, secondary metabolites have the ability to protect itself against both biotic and abiotic stress circumstances, including infections. Several studies have demonstrated that phenyl amides are formed in bean and tobacco plants when exposed to abiotic stresses, and that polyamines accumulates dramatically in large amounts, implying the antioxidant function of secondary metabolites. Additional environmental stresses, such as intense light, blue light, ultraviolet (UV), drought, pathogen activity, wounding, as well as sugar and nutritional deficiency, can lead to anthocyanin buildup in plant tissues.

Whereas *A. annua* extracted artemisinin content is exceedingly low (dry weight around 0.01 to 1%), while the market for this medication is expanding in conjunction with the increase in the number of people who are suffering from the disease of malaria. It has been possible to boost artemisinin production using a variety of ways in *A. annua*, constituting the chemical synthesis technique (Avery et al. 1992) including the genetic modification of the genes associated with biosynthesis pathway of artemisinin (Ro et al. 2006). However, the expense of these approaches, as well as the intricate nature of gene regulation and expression in biosynthesis of artemisinin, have resulted in a little success has been recorded. Improved artemisinin production necessitates the development of new approaches that are both less expensive and more convenient. Due to the fact that artemisinin is a type of secondary metabolite (Jorgensen et al. 2005), the climatic conditions, as well as the manner and time in which *A. annua* is planted and harvested, can have an impact on production of artemisinin production (Wallaart et al. 2000).

Stress due to the presence of salt

Because of the dehydration caused by the salt environment, the cell experiences osmotic stress, as a consequence of cytoplasmic water loss and thus leading to decreased vacuolar and cytosolic volumes. Salt stress in plants frequently results in both ionic and osmotic stress, with the accretion or decreased expression of certain secondary metabolites (Mahajan and Tuteja 2005). There is a potential of developing an *A. annua* that is altered for growing in saline circumstances with the goal of achieving agricultural-related technological and economic advantage (Yadav et al. 2017). Some researchers believe that treating *A. annua* plants for one or two months with a salinity stress of 2 to 4 g/L NaCl right before flowering will allow them to accumulate the maximal artemisinin. The influence of salt stress on the growth of plants may be drastically reduced as a result of this, while the accumulation of artemisinin in plants may be significantly increased. It was discovered that the artemisinin content in plants treated with NaCl of about 4 - 6 g/l might be greatly amplified (2 – 3% dry weight) as related to the content in control plants (1% dry weight) (Qian et al. 2007). Two treatments namely S1 (ages of 90 days) and S2 treatment which is administered at age of 120 days, the *Artemisia annua* L. were exposed to distinct treatments with lead acetate (0–500 mM) and NaCl (0–160 mM). In S1 treatments, the plants were tested for photosynthetic rate (Pn), lipid peroxidation rate, yield of artemisinin in leaf samples, chlorophyll content, artemisinin concentration, as well as accumulation of total biomass on after 100, 130, and 160 days of sowing (DAS) and similarly in S2 treatments, the plants were analyzed for the same parameters on 130 and 160 DAS. According to the observations in the *A. annua* plant, both lead and NaCl may induce oxidative stress and the severity of the stress generated by the stressor is proportional to the stressor's concentration in the environment. Consequently, the level of oxidative stress has an effect on the concentration and synthesis of artemisinin. Lead generates more AOS than sodium chloride, subsequently increases the chloroplast destruction and thus resulting decline in the rate of photosynthetic respiration and the accumulation of biomass. Moreover, artemisinin concentrations are amplified at an early stage following treatment. The elevation in artemisinin concentration reported during the initial stages of plant development might be a consequence of activated oxygen species converting its precursors (dihydroartemisinic acid/ artemisinic acid) to artemisinin in response to oxidative stress (Qian et al. 2007).

Drought stress

Stress imposed by abiotic factors such as drought is among the most severe that can have an unfavorable influence on the plant growth and development. It is possible to experience stress due to drought when the volume of accessible water in the soil has been lessened to alarming levels, and when the surrounding environment is contributing to the loss of water on a continuous basis. Xu et al. (2010) discovered that drought stress is produced by a lack of available water, which is frequently accompanied by solar radiation and high temperatures. To safeguard the survival of agricultural crops and the production of sustainable food, stress due to salt and water scarcity are universal concerns (Gossal et al. 2010).

According to the reported analysis by Ghershenzon (1984) and Herms and Mattson (1992), a treatment of 38 hour long moderate water deprivation (WD) has affected artemisinin biosynthesis in the plant that has increased statistically significantly (29%). Under experimental conditions, *Artemisia* spp. plants release considerably more mono and sesquiterpenes than they do under normal conditions. The study discovered this while investigating the implications of an increased temperature and deficiency of water on terpene emissions. Several researchers have discovered that, while a prolonged drought reduced the sesquiterpenes emissions, a mild drought had no effect on the emissions of sesquiterpenes (Marchese et al. 2010). The researchers found that there was no statistically significant relationship between concentration of artemisinin and the applied WD amount for two weeks before harvest, but that there was a trend for concentration of artemisinin to drop with increasing negative potential of water in the field, according to Charles et al. (1993). It's important to remember that although plants under stress accumulate secondary metabolites relatively speedily (Kuc 1995), it's possible that continuous stress will result in a reduction in both accumulation of biomass and content of artemisinin content rather than a rise in artemisinin concentration in the plant.

Ferreira (2007) discovered that the stress caused by a deficiency of potassium leads to a 75% rise in content of artemisinin and a 21% increase in production of artemisinin in Artemis® plants developed from cloned plants when they were exposed to the stress. In light of these observations and conclusions, we may conclude that reasonable percentage of WD can significantly elevated the artemisinin level in leaves, hence supporting the notion that artemisinin is a component of *A. annua* chemical system of protection against both biotic and environmental stressors. For the time being, our findings suggest that artemisinin may be a component of the chemical system that protects *A. annua* from water scarcity in its natural environment. The data also advocated that the deficiency of irrigation (or the lack of rain) few days before the *A. annua* crop is harvested may stimulate a modest water deficit environment, which might result in a significant increase in artemisinin production without a drop in biomass output. In addition, because there will be neither irrigation or rain, the drying process will be quickened, allowing for the start of industrial processing sooner rather than later.

Impact of cold stress

Low temperature is one of the most damaging abiotic stresses that can be imposed on temperate plant species. It is also one of the most difficult to manage. Temperature variations have been adapted by plant species by regulating their metabolism throughout the autumn season, raising their content of a number of cryo-protective compounds in order to boost their cold resistance to the extremes of temperature (Janska et al. 2010). Changes in environmental conditions such as osmotic damage, desiccation, and low temperature can put stress on plants throughout the cryopreservation process, leading to an array or issues with the plants (Janska et al. 2010). Cryoprotectant molecules are produced by temperate plants during the course of their wintering season. Sugar alcohols (inositol, ribitol and sorbitol), soluble sugars (trehalose, raffinose, saccharose and stachyose), and low-molecular-weight nitrogenous compounds are among the molecules that fall into this category (nitrogenous compounds with a molecular weight of less than 100). (Proline, glycine betaine, glycine acetate) Acute cold stress promotes the production of phenolic compounds, which are then integrated into the cell wall as lignin or suberin, depending on the type of cell wall present (Griffith and Yaish 2004). Artemisinin levels in Vietnamese *A. annua* plants increased after a period of night-frost, although levels of dihydroartemisinic acid decreased. This occurrence is consistent with our idea, which was published in Nature Communications, that stress is the driving force behind the conversion of dihydroartemisinic acid to artemisinin. It is hypothesized that high levels of dihydroartemisinic acid are created in response to stressful events (such as night-frost), during which comparatively high levels of $^1O_2$ are produced. As a result of its interaction with reactive oxygen species, dihydroartemisinic acid protects the plant and results in the synthesis of artemisinin, which is a stable end-product (Wallaart et al. 2000)

Heavy metal stress

Excessive amounts of metal ions (europium and lanthanum), as well as oxalate, have an impact on the synthesis of secondary metabolites in the body. Nickel (Ni), a trace metal that is a vital component of the urease enzyme and is required for the development of plant, is classified as a trace element by the World Health Organization (Marschner 1995). With the help of proteomics, Rai et al. (2014) found that *A. annua* has an interactive regulatory network that links secondary and primary metabolism as well as arsenic tolerance in the plant (Rai et al. 2014). Several compounds, including chlormequat (2-chloroethyltrimethylammonium chloride) and triacontanol, have been demonstrated to stimulate the synthesis of artemisinin and herbage in *A. annua*, which has prompted the creation of new breeding procedures (Shukla et al. 1992).

Through a literature survey, it was found that copper promotes the production and accumulation of artemisinin, particularly at concentrations of 20 and 100 mol/, which results in Cd stress causing damage to photosynthetic pigments, although *A. annua*, which is a vigorously developing plant, demonstrated a high tolerance to Cd stress and the addition of appropriate amounts of Cd assisted in the synthesis and accumulation of artemisinin (Li et al. 2012).

The role of light in the production of secondary metabolites

It is generally recognized that light is a physical component that can have an impact on the formation of metabolites. Researchers have established a constructive link between greater intensity of light and higher levels of phenolic compounds. L (Chalker-Scott and Fnchigami, 1989). A possible mechanism by which UV-B exposure increases the quantity of artemisinin and the overexpression of gene DBR2 as a result of DNA hypomethylation caused by UV-B exposure and the stimulation of additional overexpression of the DBR2 gene in *A. annua* has been shown to cause a significant rise in the quantity of artemisinin synthesized, which is beneficial for the plant (Yuan et al. 2015). WRKY-binding sites in the gene promoter as a result of UV-B exposure (Pandey and Pandey-Rai 2015). According to the findings, utilizing Co-60 gamma-rays irradiated sodium alginate in conjunction with phosphorus significantly boosted the yield of dry leaf content, concentration of leaf artemisinin, as well as the overall artemisinin production in a wide range of plants (Aftab et al. 2014). The *A. annua* has shown an increase in the expression of the DBR2 transcript in response to fungal elicitors. Recent research by Yang et al. (2015) suggests that the DBR2 promoter has a key role in the fluctuating expression of the DBR2 gene, as well as the amount of artemisinin present in the environment.

Conclusion

Evidently the stress due to abiotic origin impacted on plant growth and the production of secondary metabolites. Productivity is also influenced by changes in the environment. For example, climate change has an impact on soil microbiota, insects, and on plant productivity, adaptability, and antogeny. Most notably, climate change will have a significant impact on salinity, water availability, and a variety of unfavorable soil conditions, all of which will have a direct impact on plant yields. The utilisation of genetic technologies, as well as the structure and control of secondary metabolism pathways, will provide the foundation for commercial secondary metabolite manufacturing. The rising demand for natural goods for medical reasons, along with poor product yields and plant harvest supply constraints, has reignited interest in large-scale plant cell culture technologies. However, tolerance against stress will be improved as a result of improved understanding of plant responsiveness to abiotic stress, which will be applied in both conventional and modern breeding applications. Furthermore, there have only been a few research conducted on the impact of abiotic stressors on therapeutic plants. Hence this review reports on the responses of the *Artemisia annua* plant to several abiotic stimuli like water-logging/fooding, salt, cold, and drought etc.

The consumption and demand for medicinal plants specially for antimalarial drugs in last 3 years has tremendously increased due to Covid -19. The research on secondary metabolite production under stress condition has potential to cure the global diseases and provide other natural products. The antimalarial chemotherapeutic agents extracted from artimisia and have been produced in increased concentration which are grow in abiotic stress condition.

Statements and Declarations

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