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Review

The Effects of Water-Deficit Stress on *Cannabis sativa* L. Development and Production of Secondary Metabolites: A Review

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Abstract: Water-deficit stress is typically viewed as detrimental to agricultural yields. It has been found to enhance secondary metabolite concentrations in certain essential oil-producing plants, including *Cannabis sativa* L. Cannabis is a versatile plant from the Cannabaceae family which is used for its fibers, seeds, and bioactive compounds, including medicinal and recreational cannabinoids. Furthermore, it exhibits significant metabolic shifts under water-deficit stress conditions, which may impact the production of these resources. This review explores the physiological mechanisms underlying the metabolic responses of cannabis to water-deficit stress, focusing on how water-deficit stress could promote the accumulation of secondary metabolites. Water-deficit stress induces metabolic changes in cannabis, leading to secondary metabolite accumulation. Water shortages cause stomatal closure, significantly reducing CO_2 uptake and fixation via the Calvin cycle and leading to an oversupply of $NADPH+H^+$. This oversupply allows metabolic processes to shift toward synthesizing highly reduced compounds, such as secondary metabolites. Overall, the literature suggests that the controlled application of water-deficit stress during cannabis cultivation can enhance cannabinoid quality and yields, offering a practical strategy for optimizing plant productivity while addressing current knowledge gaps in metabolic signaling pathways.

Keywords: drought; irrigation; cannabinoids; induced stress; terpenes

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1. Introduction

Cannabis sativa L. (Cannabaceae) is a multipurpose cultivated crop that is native to Central Asia [1]. There is a consensus that *C. sativa* is certainly of Old-World origin, with some of the earliest indications dating back to about 12,000 years ago [2]. However, there is still some debate about its geographical origin [3,4].

C. sativa is an herbaceous and dioecious flowering plant. Depending on the taxonomic classification, cannabis is frequently viewed as a single species, *C. sativa*, with three varieties, namely *C. sativa* var. sativa, *C. sativa* var. indica, and *C. sativa* var. ruderalis, each with distinct characteristics and uses [5]. However, the three subspecies or varieties interbreed, and their species boundaries are fluid. Therefore, it has been suggested that only a single cannabis species, *C. sativa*, be recognized [6]. The two most common varieties are *C. sativa* var. sativa and *C. sativa* var. indica, which contain relatively high amounts of tetrahydrocannabinol (THC), making them preferred for medicinal and recreational purposes [7]. This influences both their market demand and medicinal applications. In contrast, the less common variety, *C. sativa* var. ruderalis, is the smallest in height and girth and contains relatively lower amounts of THC and other cannabinoids, limiting its direct economic value [7]. However, its autoflowering trait is economically used in breeding programs [8] that improve cultivation efficiency.

Cannabis is usually called "hemp" when used as a source of fiber, "hemp seed" when used as a source of seed oil, and "marijuana" (more commonly spelled "marihuana" in the past) when used as a source of mood-altering substances and therapeutic compounds. Similarly, "hemp" is also used to describe cultivars grown for resin production, which contain high levels of cannabidiol (CBD) and low amounts of THC. Although the terms "hemp" and "marijuana" are likely the most frequently used common names in scientific publications, it is crucial to distinguish between the two while recognizing that they belong to the same species. Specifically, the concentration of delta-9 tetrahydrocannabinol (Δ9-THC) is the primary parameter for distinguishing between them, according to legislative definitions [9].

Cannabis is often cited as a prime example of a crop that initially evolved as a "camp follower" [10]. According to this hypothesis, early humans collected plants for various uses and discarded them in disturbed areas around camps, which are ideal for seed germination. Species classified as "camp followers" typically exhibit vigorous growth and colonization traits, which are key features of weedy plants, including *C. sativa*. As a result, *C. sativa* is exceptionally well suited to this habitat, with its weedy nature facilitating both natural and human-assisted dispersal. This ability to thrive in human-disturbed environments likely facilitated its early cultivation and eventual domestication. Rather than contradicting domestication, the camp follower hypothesis supports a gradual model wherein sustained human association favored traits that led to its cultivation and domestication [10]. Indeed, *C. sativa* is one of the world's oldest crops, being cultivated for at least 6000 years [3]. For centuries, cannabis has been utilized as a source of fiber, food, oil, and medicine, as well as for recreational and religious purposes [11]. These properties likely contributed to early domestication by prehistoric humans. It contains numerous biologically active compounds, such as cannabinoids, terpenoids, flavonoids, and alkaloids [12]. A shared characteristic of all cannabis plants is the presence of cannabinoids, which are sometimes referred to more precisely as "phytocannabinoids" to distinguish them from endocannabinoids, which are found and produced in the human body. While there are only two main endocannabinoids in humans (anandamide and 2-arachidonoylglycerol), there are over 100 different phytocannabinoids in cannabis, which are predominantly generated in the trichome glands that develop in female inflorescences [6]. The medical potential of cannabis plants, particularly phytocannabinoids and their chemical derivatives, has drawn public attention over the past several years [13]. For example, CBD has been widely recognized in treating Parkinson's disease, schizophrenia, pain, anxiety, depression, and other neurological disorders [13], while THC has shown success in the treatment of several serious conditions, such as multiple sclerosis, cancer-related pain, nausea, and appetite loss in AIDS patients [14]. However, to be effective, THC must be administered in sufficient doses at levels which can cause psychoactive side effects [14]. The psychoactive properties of THC are the primary reason the compound and the plants that produce it are still illegal in many places [15]. This makes it difficult for some researchers to study phytocannabinoids for their potential medicinal properties.

Along with the primary metabolites essential for a plant's growth and development, plants also produce secondary metabolites that play crucial roles in plant adaptation and survival under stress conditions [16]. Environmental conditions are one of the best alternatives to breeding for the production and accumulation of cannabinoids in cannabis [17]. Like other medicinal crops, the production of cannabinoids, particularly THC and CBD, is significantly affected by a variety of environmental stresses such as light [17], temperature [17], nutrition [18], heavy metals [19], phytohormones [20], and biotic stresses, including insects and microbial pathogens [21]. In addition to these, plant density [22], plant pruning strategies [23], and harvest timing [24] cultivation practices also play vital roles in shaping cannabinoid profiles. Recent studies have shown that different nitrogen [18,25] and phosphorus levels [26] as well as salinity stress [27] can significantly alter cannabinoid profiles in cannabis. Similarly, water-deficit stress has also been demonstrated to affect the cannabinoid content, often increasing concentrations under moderate stress conditions [28,29]. Hence, applying controlled water-deficit stress can potentially be an effective technique for controlled environment agriculture to boost the production of secondary metabolites in cannabis.

Water-deficit stress refers to a controlled reduction in water availability and is a more appropriate term for indoor controlled environments, growth chambers, and greenhouses, where water limitations are intentionally imposed to study plant responses under specific conditions. Drought, on the other hand, refers to a naturally occurring event where an area experiences below-normal precipitation, either rain or snow, due to climatic conditions [30]. This terminology is most accurately applied to field or outdoor studies, where environmental factors are uncontrolled. Plant physiological and biochemical processes are found to be altered by water-deficit stress, which frequently diminishes biomass and yields due to weakened photosynthesis, nutrient absorption, and cellular expansion [31]. However, it also triggers adaptive responses that accelerate the production of secondary metabolites such as phenolics, flavonoids, alkaloids, terpenoids, and cannabinoids [32]. Controlled water-deficit stress has been demonstrated to boost metabolite accumulation by activating stress-related signaling pathways and redistributing resources from primary growth to protective secondary metabolites [33].

The accumulation of secondary metabolites due to drought and water-deficit stress has been documented in several herbaceous species, but their effects on cannabis secondary metabolism are poorly studied. The increasing medical interest in and economic value of *C. sativa* illustrate the importance of reviewing relevant research on how water-deficit stress affects cannabinoid production in cannabis.

2. Methodology

This review aims to explore the impact of water-deficit stress on the growth, yields, and production of secondary metabolites in cannabis, focusing on the cannabinoid concentration. To gather relevant research, we conducted a narrative search using keyword combinations such as "cannabis cultivation", "water-deficit stress", "drought in *Cannabis sativa*", "water-deficit stress and secondary metabolites", and related terms. Sources were selected from platforms including ResearchGate, Google Scholar, and other academic databases, prioritizing studies that discussed water-deficit conditions and their physiological or biochemical effects on cannabis.

3. Impact of Water-Deficit Stress on Plants

3.1. Overall Plant Growth

Stress may cause various effects on plants, most of which are detrimental to the health and yield of crops. It can influence primary and secondary metabolism, physiology, gene expression, the structure of organs and tissues, and overall total plant growth (Figure 1). The complexity of this response is impacted significantly by the length and severity of stress, the simultaneous presence of multiple stressors, the plant's genotype, and the developmental period at which the stress is applied [34,35]. Abiotic stressors such as an inadequate water content, salt, excessive light, extreme heat or cold, and deregulated nutrient availability can impair plant growth and development [36], which results in significant crop losses globally, making abiotic stressors one of the most consequential issues that agriculture faces today [37] (Figure 1).

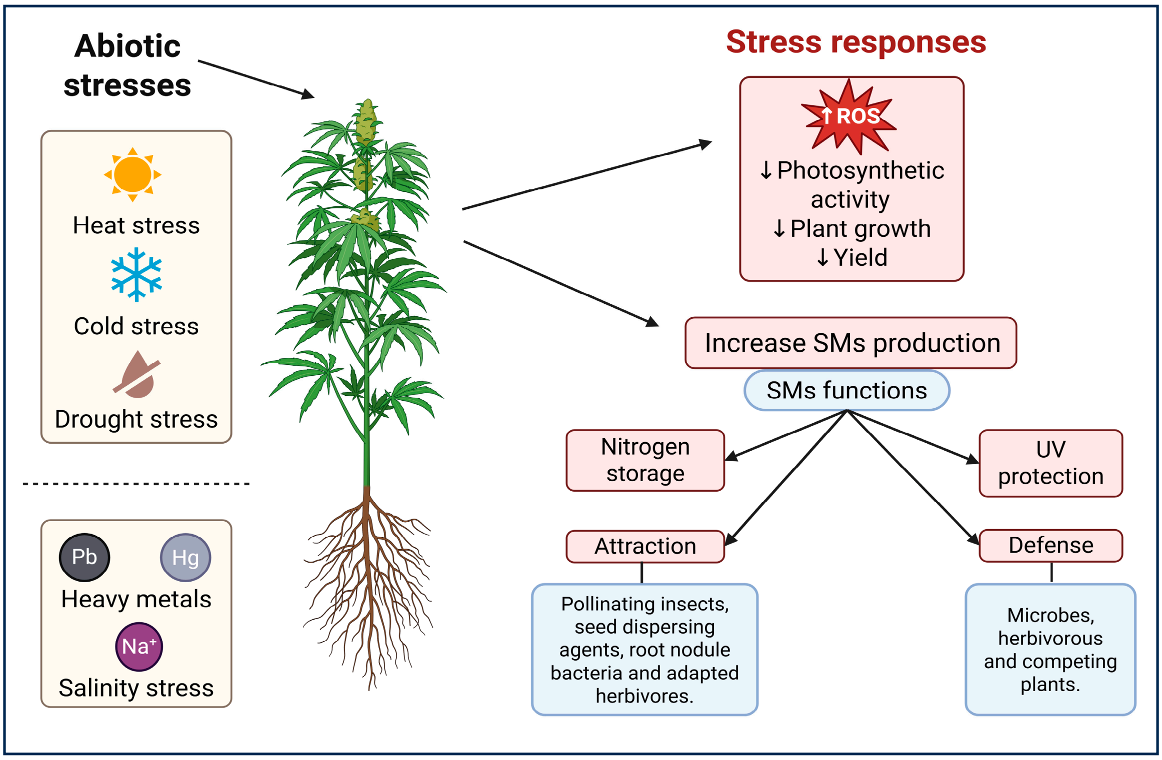

Figure 1. Schematic representation of the impacts of abiotic stress on *Cannabis sativa*. The figure highlights the increase in secondary metabolites (SMs) and their conceptual role in plant responses to water-deficit stress. This illustration synthesizes the general mechanisms of plant physiology, emphasizing the adaptive role of SMs in stress mitigation. Created with Biorender (https://BioRender.com/, accessed on 31 May 2025).

Water-deficit stress and drought are significant abiotic factors influencing both cultivated and wild plant species, eliciting diverse physiological responses often modulated by genetic factors. Plants respond to drought stress through the activation of specific genetic pathways, including the regulation of abscisic acid (ABA) [38] biosynthesis and signaling (NCED and AREB genes), transcription factors like DREB and MYB [39], and stress-responsive proteins such as LEA proteins and antioxidant enzymes (e.g., superoxide dismutase or catalase) [40]. These genetic components help modulate stomatal conductance, osmotic balance, and protection against oxidative stress, thereby enhancing drought tolerance. Understanding these molecular mechanisms provides a foundation for developing drought-resistant cultivars through marker-assisted selection, gene editing, or transcriptome-informed breeding strategies [41].

Drought is defined as a prolonged period of below-normal precipitation, which reduces soil water availability for plant growth and development [42]. Drought typically coincides with high air temperatures, leading to increased plant evapotranspiration, stomatal closure, and reduced photosynthetic activity, ultimately resulting in lower yields. The frequency of drought stress events is rising, driven not only by global temperature increases but also by the overuse of natural resources and soil desertification [42]. While plants may adapt to water-deficit stress situations through various tolerance mechanisms, these adaptations can negatively impact yields as the complex interactions between gene expression and plant physiology come into play.

Plants adapt to drought stress or water-deficit stress by regulating photosynthesis through physiological, biochemical, or other specialized mechanisms. Photosynthesis is highly sensitive to water scarcity and high temperatures [43]. Morales et al. (2020) [44] reviewed the impact of water deficit and high temperatures on the photosynthetic system and plant growth (Figure 1). Drought stress causes water shortages within the plant, affects its nutritional balance, alters the xylem pH, changes farnesyl transferase activity, modifies xylem hydraulic conductance, and reduces the vapor pressure difference between the leaves and the air. These changes lead to stomatal closure in leaves [45]. According to Dias (2010) [46], drought stress-induced immediate responses such as stomatal closure and decreased mesophyll conductance hinder CO_2 diffusion from the atmosphere to the carboxylation sites, thereby reducing photosynthesis. On the other hand, drought causes long-term growth deficits by inhibiting plant cell growth and development, especially in stems and leaves, leading to cytoplasmic water loss, as noted in [47]. This water loss changes the cell volume, vacuole size, turgor pressure sensing, membrane permeability, and intracellular osmotic balance [48]. To differentiate these responses, researchers often monitor early gas exchange, chlorophyll fluorescence as an immediate stress versus biomass accumulation, organ development, and anatomical changes as long-term stress impacts [49]. Reduced growth often occurs following drought stress because of insufficient cell expansion in plants [50]. Turgor pressure is crucial for cell expansion and growth, allowing cells to form specific differentiated regions. When drought causes the turgor pressure to drop below a critical threshold, differentiation and cell expansion halt, leading to decreased plant growth [51]. Additionally, drought stress reduces nutritional absorption, where water scarcity decreases potassium levels, particularly in leaves, which affects stomatal movement and the turgidity of guard cells. Consequently, this reduces photosynthesis and diminishes plant biomass production [52]. Drought stress can be mitigated through precision irrigation [53], the use of stress-responsive biostimulants [54], and the use of drought-tolerant cultivars with improved water use efficiency and root systems [55].

The effects of varying levels of drought stress on *Plantago psyllium* L. (psyllium), *Achillea millefolium* L. (yarrow), *Salvia officinalis* L. (sage), *Calendula officinalis* L. (marigold), and *Matricaria chamomilla* L. (chamomile) led to reduced shoot weights and plant heights compared with non-stressed conditions [56]. Similarly, sunflower (*Helianthus annuus* L.) yields significantly decreased under a 40% field capacity due to reduced cellular division during seed growth and maturation phases, which resulted in lower seed weights and oil weights but not oil concentrations [50]. Previous studies also reported that drought stress shortened the number of days to flowering and ripening in fenugreek [57] and beans [58] and reduced the growing degree days and growth period in thyme [59]. All of these observations are consistent with a reduction in photosynthesis.

3.2. Photosynthesis and Physiology

Drought stress diminishes plant biomass primarily by limiting the photosynthetic capacity through direct and indirect mechanisms. The direct effects comprise stomatal closure, reducing CO_2 transport and resulting in reduced carbon assimilation and excess energy excitation in the chloroplast [60]. This imbalance can produce reactive oxygen species (ROS), causing oxidative stress and damage to mesophyll cells [61] as well as degradation of photosynthetic pigments and efficiency [61]. In addition, biochemical limitations such as reduced Rubisco activity, ATP synthesis, and electron transport under drought stress contribute to lower photosynthesis efficiency and reduced biomass [62], even when stomata are partially open [63], whereas drought can indirectly alter leaf morphology, reduce the leaf area, and impair vascular function, all of which constrain CO_2 transport and water movement, thereby further limiting net photosynthesis [60].

Drought significantly impacts ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco), the enzyme essential for CO_2 fixation, reducing its carboxylation function by approximately 47.5–50%. This inhibition is reversible once drought stress is alleviated [43]. However, repeated droughts can lead to a lasting decline in the Rubisco content, impaired Rubisco activase function, and oxidative modification of the enzymes [64]. Enhancing drought tolerance may involve genetic strategies such as overexpressing Rubisco activase or engineering more stable Rubisco variants [65]. Drought affects various aspects of photosynthesis, including carbon fixation mechanisms such as stomatal aperture and Rubisco activity, as well as light-harvesting processes. During drought conditions, the photosynthetic rate decreases because the acquired light is not fully converted into chemically bound energy. This leads to photoinhibition and reduces the maximal quantum yield of PSII reaction centers (Fv/Fm) [42].

The overall process of photosynthesis is hindered because of Photosystems I and II. This decline in photosystem efficacy is suggested to be related to a general decrease in electron absorption, leading to reduced energy available for carbon dioxide fixation [66]. Excess photons are absorbed by chlorophyll, and when the photosystem's capacity to absorb photons is reduced, it produces ROS. These ROS interfere with various cellular components, diminishing the biological activities of these components [67]. Specifically, ROS can cause oxidation-induced damage to DNA, lipids, cell membranes, and cell walls [68]. During drought stress, the reduced capacity of photosystems to absorb photons prevents the efficient production of NADPH through electron transfer across thylakoid membranes, further exacerbating the stress on the photosynthetic process (Figure 2b) [67]. In alfalfa (*Medicago sativa* L.), under drought stress conditions, there is a reduction in Photosystem II functionality, while Photosystem I mainly remains unaffected [43]. In contrast, in spinach (*Spinacia oleracea* L.), Photosystem II is less severely impacted by drought stress due to a physiological response that slows electron flow to Photosystem II [66]. This differential response corresponds to species-specific regulation of the xanthophyll cycle, non-photochemical quenching (NPQ), and ROS scavenging systems, which collectively limit photooxidative damage by effectively dissipating excess excitation energy and reducing ROS accumulation [69]. These mechanisms offer strategic targets such as enhanced NPQ and stabilized PSII electron transport [70], which can be integrated through advanced breeding and genetic engineering to improve drought resilience.

3.3. Plant Secondary Metabolites

In some medicinal plants, drought stress can paradoxically enhance the production of secondary metabolites, which serve as a survival mechanism against environmental stressors despite the limitations imposed by water availability (Figure 1). Drought stress significantly influences the synthesis of secondary metabolites, which is essential for these plants to thrive and produce valuable natural substances [45]. The generation of ROS under water-deficit stress conditions may have promoted the production of secondary metabolites, thereby modifying the pathways involved in plant cell signal transduction [71]. Typically, water deficits suppress biomass formation (Figure 1), causing the plants to redirect absorbed CO_2 toward synthesizing carbon-based secondary metabolites, which enhances plant defense and survival potential. This redirection disrupts the usual sugar-mediated feedback loop that promotes photosynthesis, increasing the production of secondary metabolites

(Figure 2b) [72]. While this alternation can enhance stress tolerance and increase the metabolite content, it frequently compromises plant growth and yields. However, recent studies suggest that moderate or timed stress applications can be optimized to boost secondary metabolite accumulation without severely compromising the biomass, allowing for a balance between plant survival and economic yield [33].

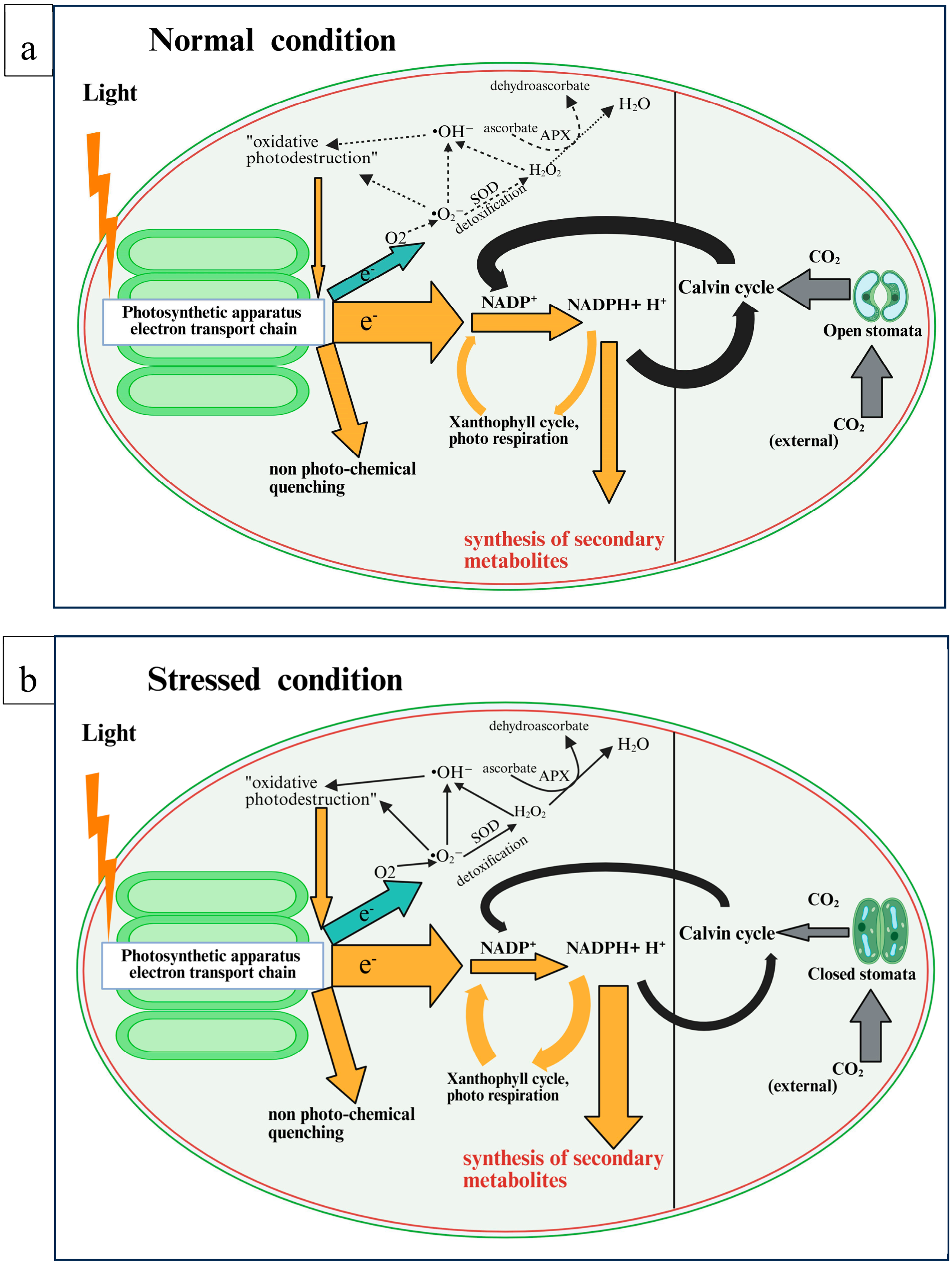

Figure 2. Conceptual model summarizing the mechanisms involved in secondary metabolite biosynthesis in *Cannabis sativa* under (**a**) optimal conditions and (**b**) stressed conditions. Based on physiological principles and the literature, including the work of Selmar & Kleinwachter (2013) [72], this simplified diagram illustrates how an altered redox balance may influence SM production. Created with Biorender (https://BioRender.com, accessed on 10 April 2025).

Figure 2b illustrates that the photosynthetic apparatus absorbs more light energy than is needed to for CO_2 fixation. This excess energy is dissipated through non-photochemical means such as the xanthophyll cycle and photorespiration. These processes help quench excess energy and reoxidize NADPH+H^+. Under optimal water availability conditions, the excess reduction in power does not produce significant amounts of radicals. However, there are noticeable changes in energy fluctuations in plants under drought-stress conditions. The higher diffusion barrier is induced by stomatal closure, which results in low endogenous CO_2 levels. Consequently, in the C_3 cycle, less NADPH+H^+ is used for the fixation and reduction of CO_2, necessitating the release of more energy at the end [73]. The feedback system activates a protective process, including non-photochemical quenching, photorespiration, and the xanthophyll cycle, to help dissipate excess energy. However, when excess energy due to limited CO_2 causes a significant electron transfer to molecular oxygen, the generation of O_2^- ions during photosynthesis produces other ROS, like hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^-). This process, known as the Mehler reaction [74], is also called the water–water cycle [75]. Detoxification of these O_2^- ions is achieved through the stress-induced activation of superoxide dismutase (SOD) and ascorbate peroxidase (APX), which reduces ROS levels (Figure 2b). According to the law of mass action, plants with a higher reduction potential, indicated by a higher ratio of NADPH+H^+ to $NADP^+$, tend to produce more secondary metabolites. However, under normal conditions, due to the co-occurrence of the various dissipation mechanisms, a balance between $NADP^+$ and NADPH+H^+ will be achieved, and the biosynthesis of natural products is reduced (Figure 2a) [72].

Under limited water availability, *Hypericum brasiliense* shows a significant increase in phenolic acids [76]. Water stress also causes a notable rise in sesquiterpene (E) β-caryophyllene levels in two native Iranian subspecies of *Origanum vulgare*, namely *gracile* and *virens* [77]. In *Labisia pumila*, stress conditions increase flavonoid levels, enhancing the plant's therapeutic properties under extreme water deficit conditions [78]. In the Lamiaceae family, the essential oil content declines in *Lavandula latifolia* and *Salvia sclarea*. In contrast, the essential oil content in *Mentha piperita*, *Salvia lavandulifolia*, *Thymus capitatus*, and *Thymus mastichina* increases during drought conditions, which is attributed to a higher density of oil glands from a reduced leaf area [79]. On the other hand, the content of phenolic acids simultaneously improved, while the level of flavonoids decreased in *Achillea pachycephala* [80]. Black cumin trials indicate that drought conditions can elevate commercially valuable compounds, including essential oils [81]. Similarly, *Arabidopsis* plants with elevated flavonol levels due to AtMYB12 overexpression exhibit excellent resistance to salt and drought stress [82]. Additionally, different drought-tolerant plant species were found to have higher concentrations of amino acids such as glycine, asparagine, valine, isoleucine, proline, and leucine compared with drought-sensitive cultivars. Some amino acids, such as proline, glutamine, glutamate, and ornithine, function as osmolytes to enhance stress tolerance in plants like Bermuda grass (*Cynodon dactylon*) and *Arabidopsis thaliana* [83].

4. Impact of Water-Deficit Stress on Cannabis

4.1. Growth and Yield of Cannabis

Environmental stressors such as water-deficit stress, heat stress, and nutrient stress are known to influence plant phenology in *Cannabis sativa* and other species [84], often leading to earlier flowering and a shortened growth cycle as part of the plant's adaptive response [85]. While this strategy may improve survival, it often results in reduced biomass accumulation and smaller reproductive organs, leading to significant declines in overall plant yields. Among various crops, cannabis has gained much attention as it is cultivated for floral biomass and secondary metabolites [86]. Moreover, this response is not uniform across all cannabis cultivars. Photoperiod-sensitive cultivars may have delayed flowering responses under drought or heat stress, while day-neutral cultivars may flower prematurely, hence reducing their productive potential [87].

Several studies have highlighted its agronomic potential under such conditions, demonstrating its resistance to microbial contamination, low pesticide dependence, and ability to grow in contaminated soil, suppress pathogens, and remove heavy metals from soil. Additionally, cannabis positively impacts crop rotation and soil quality, demonstrates resilience to water stress, thrives in diverse climatic conditions, and possesses substantial genetic diversity [88]. Although *Cannabis sativa* can endure dry conditions once established, extended drought stress tends to accelerate early maturity and reduce the growth period [89]. According to Kumar Vijaya (2021) [90], reduced soil moisture altered the cannabis phenology; specifically, the most stressed plants experienced faster flowering and seed maturation than those receiving sufficient water. Previous research has shown that plant morpho-physiological traits, such as the plant height, dry weight, and lateral branches, decrease when plants experience water deficit stress [91]. One study revealed that the cannabis biomass and stem yield decreased by 20% and the stem length dropped by 30% under drought stress compared with adequately hydrated plants [92]. Similarly, Arad (2016) [93] noted significant reductions in plant height, stem diameter, internode length, leaf number, and leaf area in cannabis under drought conditions. Water deficits also reduced the biomass, seed yield, and stem diameter across different cannabis cultivars [87].

In recent years, especially for fiber hemp, the optimal conditions and their dependence on environmental factors such as irradiation, the photoperiod, temperature, and relative humidity, production techniques like plant density, mineral nutrition, irrigation regime, and genetic factors have been intensively investigated [94]. Studies on hemp have shown variable effects on yields under drought stress, with some cultivar strains remaining unaffected while others experience significant yield losses [95]. In fully irrigated conditions where hemp plants were watered at 100% evapotranspiration, significantly higher yields were observed relative to trials with reduced irrigation at 75% of the calculated evapotranspiration [96]. The final yields of the well-watered controls were 43–64% higher than those under drought treatments [96].

Previous research on hemp has examined the effects of water-deficit stress starting in the vegetative stage. Garcia-Tejero et al. (2014) [96] highlighted that prolonged water-deficit stress, applied from early vegetative growth to harvest, led to reduced yields and physiological parameters such as photosynthesis, stomatal conductance, and carbon isotope discrimination. García-Caparrós et al. (2019) [79] reported a significant reduction in plant height and the length of the first internode in cannabis under water-deficit stress. Consistent with these findings, Bahador & Tadayon (2020) [97] observed that cannabis plants subjected to drought stress were shorter in height over a two-year study period. The study attributed the decreased stem diameter to reduced lateral meristem activity, cell proliferation and expansion, and a reduction in epidermal and vascular tissue thickness [98]. Recent research on various cannabis genotypes also confirmed that water deficits lead to decreases in plant height, stem diameter, and internode length [87]. Additional studies have shown that the cannabis cultivars Futura 75 and Black Label experienced reduced growth and yields when the available water in the root zone was limited [92,99]. Conversely, Caplan et al. (2019) [29] found that applying water-deficit stress to medicinal cannabis in the final two weeks of the growing cycle did not adversely affect flower yields. These findings highlight the complex responses of cannabis to water-deficit stress, which can vary depending on the stress's timing, duration, and severity, as well as the specific cultivar, production purpose, and growing conditions.

4.2. Production of Secondary Metabolites of Cannabis

The biological functions of glandular trichomes and their resinous secretion are primarily linked to defense mechanisms against various biotic and abiotic stresses imposed by the environment and herbivores [100]. Therefore, there have been numerous attempts to manage resin accumulation in medical cannabis using stress induction [101]. The production of secondary metabolites in cannabis is influenced by external factors, including light duration, oxygen levels, and harvest timing, particularly during floral maturation [24]. Research has established a connection between water-deficit stress and cannabinoid synthesis in cannabis, as discussed below.

According to Selmar & Kleinwachter (2013) [72], plants experience stomatal closure under drought conditions to conserve water loss, significantly reducing CO_2 uptake. In return, it limits the CO_2 activity of the Calvin cycle, which means less NADPH+H^+ and ATP formed during light-dependent photosynthesis reactions in the thylakoid membranes are used for photosynthetic carbon fixation. Ultimately, large amounts of energy must be dissipated through non-photochemical quenching and effective reoxidation of NADP+H^+ through the xanthophyll cycle and photorespiration (Figure 2b). A key component of NPQ is the xanthophyll cycle, where the pigment violaxanthin is enzymatically converted to antheraxanthin and then zeaxanthin under high light or stress conditions. Zeaxanthin facilitates the safe thermal dissipation of excitation energy in the light-harvesting complexes, thereby protecting PSII from photodamage [70]. Simultaneously, photorespiration serves as a crucial biochemical sink for excess reducing equivalents. When Rubisco catalyzes the oxidation of RuBP, it initiates the photorespiratory pathway involving the chloroplast, peroxisome, and mitochondrion [102]. This process consumes NADPH and ATP to recycle glycolate into 3-phosphoglycerate, helping to re-oxidize NADP+H^+ and relieve redox pressure in the chloroplast [72]. Together, these pathways protect the photosynthetic machinery from oxidative stress and stabilize intracellular energy balance under conditions of limited CO_2 assimilation [72].

However, the excess NADPH+H^+ generated during light reactions causes excess electrons not utilized by $NADP^+$ to be transferred to molecular oxygen, forming highly damaging ROS (Figure 2b). Kleinwächter & Selmar (2014) [73] suggested that plants activate protective mechanisms by activating antioxidant enzymes including SOD and ascorbate peroxidase (APX) to safely dissipate excess energy and prevent ROS damage. This surplus NADPH+H^+ generated during light reactions has been linked to increased levels of THC, tetrahydrocannabinolic acid (THCa), cannabidiolic acid (CBDa), and CBD [29], suggesting that unused NADPH+H^+ might contribute to altered secondary metabolite profiles in cannabis. However, these redox-regulating pathways can be targeted through selective breeding or biostimulants to enhance photoprotection and redox balance, supporting both stress tolerance and secondary metabolite production [70].

It has been demonstrated that the production of cannabinoids, such as THC, CBD, and cannabigerol (CBG), is influenced by simple genetic traits. However, the variability in cannabinoid content is significantly influenced by environmental conditions, including drought stress [103]. Ecological studies have revealed that cannabis plants develop a higher trichome density in arid climates [104]. Additionally, decreased humidity has also been associated with an increased THC content in cannabis [105]. Similar research findings have been reported in non-THC-producing hemp plants, which demonstrated significant cannabinoid production when cultivated in dry regions [106,107]. However, these findings are not entirely conclusive, and further investigation is needed to fully understand how water stress comprehensively affects cannabinoid production.

Minimizing dry weight loss during drought stress is critical for maximizing the production of essential oils and secondary metabolites in *Cannabis sativa* [108]. This species exhibits notable physiological adaptability, adjusting its production of secondary metabolites in response to varying levels of dry conditions. Previous studies have suggested that cannabis cultivated in hotter, drier environments tends to display higher densities of trichomes [104]. Recent research has shown a positive correlation between hemp's accumulation of CBD and its ability to tolerate drought stress in both field and controlled environment experiments [109]. Studies on the effect of drought stress have been documented to increase secondary metabolite accumulation in other crops like *Satureja hortensis* (summer savory) [110]. This indicates a general trend in increased secondary metabolite concentrations under drought stress, which may also apply to *Cannabis sativa*.

Caplan et al. (2019) [29] observed that when cannabis plants were subjected to mild drought stress, it significantly increased the levels of tetrahydrocannabinol acid (THCa), cannabidiolic acid (CBDa), THC, and CBD without reducing the inflorescence dry weight. Similarly, recent research on four medical cannabis varieties has shown that exposure to a wide range of biotic stresses (such as *Golovinomyces spadiceus* and *Manduca sexta*) and abiotic stresses (herbicide treatment, flooding, wound injury, heat, and drought) significantly influences cannabinoid production. The floral parts produced at least 2.5 times more cannabinoids than the leaf tissues under stress conditions [111,112].

However, according to Park et al. (2022) [111], cannabinoid production at the onset of flowering was found to be negatively correlated with herbivory, extreme heat, and drought, whereas mechanical wounding showed no impact. Applying induced water-deficit stress during the early stages of flowering has been observed to significantly alter cannabinoid profiles, with significant increases in CBG alongside reductions of up to 70–80% in THC and CBD accumulation [111]. This suggests that applications of water-deficit stress at the early stages of flowering are likely to disrupt the conversion of cannabigerolic acid (CBGa) into its downstream products, CBDa and THCa; instead, it raises the CBG concentration. The catalytic enzymes, CBDa and THCa synthases, which are responsible for the conversion, may have reduced activities, or their gene expression may have been downregulated, leading to decreased downstream THC and CBD levels while the CBG levels accumulate [111].

Morgan (2023) [113] found that moderate water-deficit stress and drought intensities did not affect the levels of THC or CBD. However, severe drought treatments reduced the concentrations of these cannabinoids due to impaired photosynthesis and carbon fixation. In contrast, the "Nebula" cultivar has shown enhanced production of the primary cannabinoids THCa and THC as well as CBDa and CBD following water-deficit stress initiation, particularly about 5–7 weeks after flowering began [29]. The observed variation in THC and CBD was not only related to water-deficit stress but also the specific cultivar, water-deficit stress timing, and original cannabinoid content. However, the limited research on cannabis cultivation practices has led to gaps in knowledge related to water usage and yield potential [114,115].

5. Conclusions

Water-deficit stress is usually recognized as a negative factor that reduces the plant height, stem diameter, and internode length in crops, ultimately leading to significant yield losses in agriculture. Similar detrimental effects have been seen in different aromatic and medicinal plants, including *Cannabis sativa*. However, recent research revealed a direct relationship between water-deficit stress and plant metabolism. Water-deficit stress, induced directly or indirectly by water shortages, has been shown to enhance the accumulation of secondary metabolites in cannabis, especially cannabinoids. However, the impact of water-deficit stress on cannabis plants can vary based on the cultivar, intensity of the stress, and timing of the stress events, with some studies indicating substantial losses. In contrast, others suggest that late-stage drought stress might not significantly affect flower yields. This variability highlights the need to understand the specific requirements and stress responses of different cannabis cultivar strains to optimize growth and productivity under different growing conditions. Further research is essential to unravel how drought stress can be strategically managed to maximize biomass yields and secondary metabolite production in cannabis under various environmental conditions.

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