Importance of Cytochrome P450 gene family from metabolite biosynthesis to stress tolerance: A review

N Laffaru Singpho, J G Sharma
Department of Biotechnology, Delhi Technological University, New Delhi 110042, India
namratalaffarusingpho_2k17/bt/15@dtu.ac.in

Abstract. CYP450 short for Cytochrome P450 is an enzyme superfamily involved in catalysing numerous biochemical reactions. It is known for its involvement in diverse plant processes. CYP450 is widely distributed in the case of eukaryotes and is said to exist in all domains of living organisms including bacteria, plants as well as mammals. The enzyme of this family plays a key role in the oxidative transformation of both endogenous as well as exogenous molecules. The growth and development of the plants are affected by several biotic and abiotic stresses regularly. They downgrade the crop quality and lead to a sharp decline in the productivity of the crop. CYP plays important role in providing protection to plants against these stresses. It does that by taking an active part in various detoxification as well as biosynthetic pathways. The objective of this review is to explore the role of CYP 450 in various metabolite biosynthesis as well as tolerance to various biotic and abiotic stresses in plants. This review aims to provide a framework for further investigation of the CYP450 gene family in plants and will also provide a strong base for the characterization of their diverse role in defence mechanisms against different abiotic and biotic stress and metabolite biosynthesis.

1. Introduction
Cytochrome P450 (CYP450) is a superfamily of enzymes commonly known for its key role in catalyzing various chemical reactions. Its traces have been seen in all domains of organisms. CYP450s are known to be widely distributed in the case of eukaryotes. It was Martin Klingenberg who first reported the CYP450 spectrum in the year 1958. The enzymes of this superfamily are responsible for the oxidative transformation of both exogenous as well as endogenous molecules [66], [23].

In previous studies, with the help of Genome-Wide Analysis, it was found that the Cytochrome P450 genes in the genomes of different organisms range from around 50 to 150. Besides It was also found that the plant Arabidopsis thaliana has 245 Cytochrome P450 [4], 57 Cytochrome P450 in the human genome, 285 Cytochrome P450 in the case of Tartary Buckwheat [96], and 174 Cytochrome P450 in case of Morus notabilis [55](Table 1). CYP450 is a diverse family with more than 35,000 members [66]. When CYP450 was at its initial stages of discovery it was considered to be a pigment rather than an enzyme. It was later found out that the particular pigment displayed vivid characteristics of a heme-protein [74]. Much later it was established that CYP450 were not pigments but enzymes. In CYP450, 450 nm is the wavelength of light the enzyme superfamily can strongly absorb and ‘P’ is short for pigment. CYPs can function in the carbon monoxide binding processes due to the presence of a particular heme group. This particular heme group is involved in the catalysis process in plants. In the case of plants, CYP450 was first identified in the cotton plant [25]. CYP450s are also known for
their important role in the metabolism of numerous pesticides and herbicides. Previous studies show that in the plant *Arabidopsis thaliana*, the P450 gene family vouches for being the 3rd largest gene family. In the case of plants, the molecular mass of the CYP450 gene family lies between 45 to 62kDa [102] with an average mass of approximately 55kDa [22]. Plant growth and development are challenged by numerous stresses daily. They can either be biotic or abiotic. These stresses affect the plants in many ways. They disturb the plant’s physiological processes hence affecting its growth and development. They also downgrade the quality of crops which results in a sharp decline in crop yield. The CYPs are responsible for providing protection against these stresses by taking an active part in numerous biosynthetic as well as detoxification pathways [70]. When in danger, plants tend to produce some specific primary or secondary metabolites as a defense mechanism against various stress caused by insects, pathogens, temperature, weed, or even water. CYP helps in catalyzing the reaction during the biosynthesis of these metabolites and promotes the overall growth and development of plants.

### Table 1  Distribution of CYP450s in different plants

| Plants                          | Total number of CYP450 | Reference |
|---------------------------------|------------------------|-----------|
| *Triticum aestivum* (Wheat)     | 1285                   | [50]      |
| *Gossypium hirsutum* (Cotton)   | 672                    | [57]      |
| *Gossypium arboreum* (Cotton)   | 379                    | -         |
| *Gossypium raimondii* (Cotton)  | 374                    | -         |
| *Sorghum bicolor* (Sorghum)     | 372                    | [68]      |
| *Oryza sativa* (Rice)           | 356                    | -         |
| *Linum usitatissimum* (Flaxseed)| 334                    | [4]       |
| *Glycine max* (Soybean)         | 332                    | -         |
| *Vitis vinifera* (Grapevine)    | 315                    | [67]      |
| *Populus trichocarpa* (Black cottonwood) | 312 | - |
| *Fagopyrum tataricum* (Tartary buckwheat) | 285 | [96] |
| *Brassica oleracea* (Cabbage)   | 279                    | [39]      |
| *Arabidopsis thaliana* (Arabidopsis) | 245 | [4]      |
| *Solanum lycopersicum* L. (Tomato) | 233 | [102]    |
| *Morus notabilis* (Mulberry)    | 174                    | [55]      |
2. Role of CYP in plants
Apart from the role of CYPs in catalyzing various biochemical reactions mentioned earlier, CYP450s are also involved in numerous cellular processes which include growth and development of cell, primary and secondary metabolite biosynthesis as well as xenobiotics detoxification (Figure 1). They also facilitate the regulation of many important processes in a cell that eventually affects plant growth. CYP450s are responsible for the biosynthesis of compounds in numerous metabolic pathways. One example would be the involvement of the CYP706B1 gene in the isoprenoid pathway [53]. This particular hydroxylase is responsible for synthesizing gossypol. Gossypol is a toxic compound present in the cotton plant which makes it more resistant to insect stress due to its toxic nature. They are also responsible for the regulation of plant hormone metabolism. The hormone in turn manages the formation of leaves, stems, and flowers as well as covers the development and maturity of fruits. CYPs are involved in catalyzing secondary metabolites like steroids, flavonoids, glycoside, and many more[42]. These metabolites are in turn responsible for the overall development and growth of the plant. For example, structural genes in secondary metabolites such as flavonoids are often CYP450 genes [9]. Another key function of CYP450 is its important role in the biosynthesis of phytoalexins which is known for being a common plant defense response. Phytoalexins are released by plants during exposure to stress by parasites. They inhibit the growth and further development of parasites during a stressful environment.

3. Distribution of cyp450 in various plants
In plants, Cytochrome P450 is situated in the endoplasmic reticulum, mitochondria, and chloroplast [61]. CYP450 enzyme family is divided into two types i.e. a) A-Type- It consists of CYP71 clan and b) Non-A type- it consists of CYP746, CYP727, CYP711, CYP710, CYP97, CYP86, CYP85, CYP74, CYP72, CYP51[68], [6], [67] (Table 2). In plants, CYP is found in almost all its organs including the shoot, bulbs, hypocotyl, radicle as well as endosperm of germinating seeds. In addition to that in the case of both plants and animals, the spectral properties of CYPs are reported to be somewhat similar with the absorbance ranging from 447-452nm. Moreover, CYPs are also closely related to the biosynthetic pathway of the plant steroid hormone brassinolide (BR) [71]. There are four characteristics regions available that are common for all the P450s i.e. a) I-helix b) K-helix c) Proline-rich membrane hinge and d) “PERF” consensus
I-helix functions in process of oxygen-binding whereas “PERF” consensus ensures the stabilization of the core structure of the heme pocket [30].

In Figure 2 we can see the phylogenetic tree of the CYP450 gene family in different species. The tree includes 6 Arabidopsis thaliana, 2 Saccharomyces cerevisiae, 2 Solanum lycopersicum, 2 Brassica oleracea, 2 Oryza sativa, and 1 Zea mays p450 genes. The analysis was done with the help of a computational biology tool named Mega 6.0 software. The nomenclature system states that the P450 belonging to the same family and same sub-family share around approximately 40% and 55% identity respectively.

|                   |       |     |
|-------------------|-------|-----|
| Nelumbo nucifera  | 172   | [65]|
| Medicago truncatula | 151   | [49]|

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Figure 1 Different functions of CYP450 in plants

Table 2 Classification of CYP450 gene family in plants

| Name of Clan | Name of Family | Name of Sub-family | CYPD, CYPG |
|--------------|----------------|--------------------|------------|
| CYP51        | CYP51          | CYPG, CYP51H       | CYP83, CYP83A, CYP83B |
| CYP71        | CYP71          | CYP71A, CYP71B, CYP71C, CYP71E, CYP71Z | CYP84, CYP84A |
| CYP73        |                | CYP73A             | CYP89, NA |
| CYP75        |                | CYP75A, CYP75B     | CYP92, NA |
| CYP76        |                | CYP76A, CYP76B, CYP76M | CYP93, CYP93A, CYP93B, CYP93C, CYP93E, CYP93G |
| CYP77        |                | CYP77A             | CYP98, CYP98A |
| CYP78        |                | CYP78A             | CYP99, CYP99A |
| CYP79        |                | CYP79A, CYP79B, CYP79D, CYP79F | CYP701, CYP701A |
| CYP80        |                | CYP80A, CYP80G, CYP80B | CYP703, CYP703A |
| CYP81        |                | CYP81A, CYP91B, CYP81D, CYP81A | CYP705, CYP705A |
| CYP82        |                | CYP82              | CYP706, CYP706M |
|              |                |                    | CYP712, NA |
|        |        |        |        |
|--------|--------|--------|--------|
|       |       |        |        |
|       |       |        |        |
|       |       |        |        |
|       |       |        |        |
| CYP719 | CYP719A, CYP719B |       |        |
| CYP723 | NA     |        |        |
| CYP726 | NA     |        |        |
| CYP736 | NA     |        |        |
| CYP72  | CYP72A, CYP72B, CYP72C |       |        |
| CYP709 | CYP709B, CYP709C |       |        |
| CYP714 | CYP714A, CYP714B, CYP714D |       |        |
| CYP715 | NA     |        |        |
| CYP719 | CYP719A, CYP719B |       |        |
| CYP724 | CYP724B |       |        |
| CYP734 | CYP734A |       |        |
| CYP74  | CYP74A, CYP74B, CYP74D |       |        |
| CYP85  | CYP85A |       |        |
| CYP87  | NA     |        |        |
| CYP88  | CYP88A, CYP88D |       |        |
| CYP90  | CYP90A, CYP90B, CYP90C, CYP90D |       |        |
| CYP702 | NA     |        |        |
| CYP707 | CYP707A |       |        |
| CYP85  | CYP85A |       |        |
| CYP87  | NA     |        |        |
| CYP88  | CYP88A, CYP88D |       |        |
| CYP90  | CYP90A, CYP90B, CYP90C, CYP90D |       |        |
| CYP702 | NA     |        |        |
| CYP707 | CYP707A |       |        |
| CYP85  | CYP85A |       |        |
| CYP87  | NA     |        |        |
| CYP88  | CYP88A, CYP88D |       |        |
| CYP90  | CYP90A, CYP90B, CYP90C, CYP90D |       |        |
| CYP702 | NA     |        |        |
| CYP707 | CYP707A |       |        |

(The data given in the table is taken from [20], [42], [60], and [77])
Figure 2 The phylogenetic tree of CYP450 in different species. The given tree includes 6 *Arabidopsis thaliana* P450 genes (CAB78925.1, CAA62082.1, CAA66458.1, CAA16713.1, AAB67854.1 and BAE99066.1), 2 *Saccharomyces cerevisiae* P450 genes (AAB06217.1 and GAX67028.1), 2 *Solanum lycopersicum* P450 genes (BAF41218.1 and BAF41219.1), 2 *Brassica oleracea* P450 genes (DAA64962.1 and DAA64966.1), 2 *Oryza sativa* P450 gene (BCL64962.1 and CAC81901.1) and 1 maize p450 (PLRT03259) gene. It is constructed by MEGA 6.0 software using NJ algorithms with 1000 bootstrap replicates.

4. Metabolite biosynthesis

Members of the CYP450 gene family are known for their diverse roles in core metabolisms. One of the key roles they play is their indirect participation in photosynthesis as well as photo-protection which is closely associated with the growth of plants [60]. Xanthophylls are yellow pigments that are responsible for light–harvesting during the photosynthesis process. CYP genes like CYP97A3 and CYP97C1 actively participates in the biosynthetic pathway of these yellow pigments as they function in catalyzing the process of hydroxylation of beta and gamma rings of carotenoids. CYP genes like CYP86A1, CYP86A2, CYP86A8, and CYP86A33 are responsible for playing a key role in the biosynthesis of cutin and suberin in plants like *Symphytum tuberosum* and *Arabidopsis* [108], [34], [93]. Cutin and suberin are complex biopolymers that are known for protecting plants from certain disturbances including pathogens and UV as they are capable of controlling processes such as water evaporation as well as water transpiration. Cutin majorly consists of glycerol and fatty acids. Suberin on the other hand consists of fatty acid-derived domains. Now, the CYP86 gene family helps in the biosynthesis of these biopolymers as they function in the hydroxylation process of fatty acids which is essentially the most vital component of these compounds.
In plants, members of the CYP450 gene family like CYP93B, CYP93E, and CYP93G are responsible for the secondary metabolites biosynthesis in plants [20]. Additionally, the CYP450 gene family is also considered to be an essential component of auxin biosynthesis in certain plants [5]. Auxins are growth-inducing hormones that function in certain tropic behaviors, root initiation, and also apical dominance [22]. CYP734, CYP724, and CYP90 are involved in the process of glycoalkaloids biosynthesis. The glycoalkaloids are usually known to be toxic to living beings however they are an essential part of the Solanaceae family. In potato plants, CYP74D genes play a vital role in the biosynthesis of antimicrobial compounds such as oxylipins [95]. These antimicrobial compounds are derivatives of fatty acids and are considered useful for overall plant growth. Oxylipins also provides defense against certain stresses in the case of plants. Certain CYP genes like AtCYP97C1 and AtCYP97A3 are responsible for determining the pathway of lutein in the Sorghum plant [43]. Lutein in plants functions in the protection of chlorophyll due to its participation in the absorption and transfer of energy. (Table 3)

| Plant Species | CYP genes | Function of CYP450 | Reference |
|---------------|-----------|--------------------|-----------|
| *Arabidopsis thaliana* | AtCYP72B1, AtCYP72C1 | Modulates signal transduction in this particular plant species | [100] |
| - | CYP79B2, CYP79B3, CYP83 | Biosynthesis of the plant hormone auxin | [5] |
| - | CYP88A, CYP714A | Gibberellin metabolic pathways | [118] |
| - | CYP703A2 | Development of pollen | [62] |
| - | CYP707A | Modulates plant hormone abscisic acid | [59] |
| - | AtCYP74A | Jasmonic acid biosynthesis | [78] |
| - | CYP72A31 | Provides defense against herbicides | [87] |
| *Oryza sativa* | CYP72A31 | Provides defense against herbicides | - |
| *Oryza sativa* | CYP93B, CYP93E, CYP93G | Flavonoid biosynthesis | [20] |
| *Hordeum vulgare* | CYP707A | Modulation of plant hormone abscisic acid | [59] |
| Species                  | Enzyme(s)                        | Function                                                                 | Reference |
|-------------------------|----------------------------------|--------------------------------------------------------------------------|-----------|
| *Sorghum bicolor*       | CYP79                            | Cyanogenic glucosides biosynthesis                                        | [7]       |
| *Sorghum bicolor*       | AtCYP97C1, AtCYP97A3              | Determines the pathway for biosynthesis of lutein                         | [43]      |
| *Ocimum basilicum*      | CYP82D                           | Secondary metabolites biosynthesis                                        | [9]       |
| *Nicotiana rustica*     | CYP51                            | Triterpenes synthesis                                                    | [26]      |
| *Vitis vinifera*        | CYP75                            | Expression of flavonoids in plants                                       | [12]      |
| *Solanum lycopersicum*  | CYP90B3, CYP724B2                | Plant steroid hormone BR (Brassinolide) biosynthetic pathway             | [71]      |
| *Solanum lycopersicum*  | AtCYP90A1, AtCYP90B1              | Increases vegetative growth along with seed production                   | [14]      |
| *Solanum tuberosum*     | CYP74D                           | Synthesis of antimicrobial compound namely oxylipin                      | [95]      |
| *Hordeum vulgare*       | CYP71A11, CYP71AH11, CYP73A1, CYP81B1, CYP81B2, CYP81B2, CYP76B1 | Chlortoluron metabolism                                                 | [70]      |
|                         | CYP96B22                         | Biosynthesis of wax                                                      | [17]      |
| *Gossypium arboreum*    | CYP706B1                         | Modification of isoprenoid pathway                                       | [53]      |
| *Symphytum tuberosum*   | CYP86A33                         | Suberin biosynthesis                                                     | [93]      |
| *Legumes*               | CYP93C                           | Legume specific isoflavonoid biosynthetic pathway                        | [20]      |
| *Land plants*           | CYP93B, CYP93E, CYP93G            | Saponin biosynthesis                                                    | [63]      |
5. ROLE OF CYPs IN DIFFERENT TYPES OF STRESS TOLERANCE IN PLANTS

5.1. Abiotic stress
The stress that facilitates the damaging of plants by the action of certain environmental factors such as availability of water, fluctuations in the salt concentration as well as temperature, increasing metal toxicity, etc. is called Abiotic stress. In plants, it is responsible for the loss of crop yield and decrease in overall productivity. CYP is responsible for protecting plants against various stresses caused by environmental factors (Table 4).

5.1.1. Drought stress. Water or drought stress is the lack of moisture that is considered to be a minimum requirement for the normal growth of an average plant. The main factors responsible for causing drought stress include low rainfall, frequent fluctuation of temperature from low to high or vice-versa, salinity, and many others. Drought stress indirectly affects plant productivity. It leads to reduced cell division in plants. It also disturbs the plant’s stomatal oscillation along with its nutrient and water consumption process. It is known to be one of the most common stresses. The survivability of plants during drought stress depends on the maintenance of cell homeostasis in a water-deficient environment. When under such stress, plants trigger certain hormonal activity as a resistance mechanism. One example of such plant hormone is ABA. ABA plant hormone is responsible for activating multiple stress-responsive genes. During drought stress, this particular hormone gets isomerized into phaseic acid. This process is catalyzed by CYP enzyme CYP707A [119]. In certain plants, CYP genes are responsible for the up-regulation of the water inlet in a water-deficit environment. During drought stress, CYP synthesizes leaf lignin which forms the key structural materials that support tissues of plants and is also responsible for the grain formation [35]. One example of the CYP450 gene family which is involved in the defense mechanism against drought stress is CYP96A8. It is responsible for the biosynthesis of lignin in few plants. In the plant Arabidopsis thaliana, some CYP genes like CYP86A2 showed properties such as reduction of cuticle membrane thickness. This particular property increases the tolerance of plants against stress caused by water deficiency by increasing the water permeability (Xiao et al., 2004).

5.1.2. Salinity stress. Salinity or salt stress is the stress caused due to the abundance of salt in a plant habitat. Similar to drought stress, it also affects the overall plant productivity by affecting the germination of a plant which eventually ends up affecting the crop yield. It is one of the abiotic stresses which hinders the smooth development of plant all over the globe. The major factors causing salinity stress include the use of poor quality water for the purpose of salinization as well as irrigation. High salinity gives rise to several other stresses such as oxidative and water stress. It also leads to nutritional disorders as well as ion toxicity. Other disadvantages of salinity stress include genotoxicity and reduced cell expansion and division. CYP indirectly provides protection to plants against stress caused due to fluctuation in salt concentration by taking an active part in the ABA biosynthesis as the lower is the ABA level; the higher becomes the tolerance against stress caused by salt [38]. Previous studies state that alteration in CYP expression can lead to tolerance against salt stress in the case of plants. Reactive oxygen species (ROS) homeostasis and leaf Na+ exclusion are the two most widely known mechanisms related to this particular stress [115]. CYPs are also known for the regulation of ROS homeostasis resulting in providing salinity tolerance to the plants. For example, in the maize plant, the TaCYP81D5 gene increases the plant’s tolerance to this particular stress by speeding up the activity of ROS scavenging and is also involved in the seedling activity [104].

5.1.3. Heavy metal toxicity. Heavy metal toxicity refers to the oxidative stress plants undergo when they are exposed to heavy metals. Metals have harmful biological effects since they are non-decomposable in nature. Heavy metal includes metals such as Nickel, Zinc, Cobalt, Copper, Thallium, Arsenic, Silver, and others. Heavy metal toxicity damages the cell assemblies of the plant. Among all the heavy metals, five are considered to be most lethal and are treated with utmost care as they have
the highest toxicity. Those five heavy metals are Lead, Mercury, Chromium, Arsenic, and Cadmium [21]. Improper disposal of sewage sludge is one of the causes of heavy metal toxicity [3]. CYPs are responsible for the metabolism of these heavy metals. Due to enhanced metabolism, few CYP genes such as CYP2E1 are capable of withstanding mercury toxicity in certain plants like Medicago sativa. In addition to that, they also function in the secondary metabolites biosynthesis such as alkaloids, flavonoids, etc. [91]. In the maize plant, the CYP88A gene facilitates gibberellin synthesis [32]. Gibberellins are growth hormones that function in the integration of numerous hormone signaling pathways when exposed to heavy metal toxicity stress. A high level of metal toxicity also disturbs the process of photosynthesis in plants. When exposed to heavy metal stress, P450s actively participates in the process of detoxification [97].

5.1.4. Temperature stress. Temperature stress is the increase or decrease in temperature which affects a plant’s biochemical as well as physiological processes. It can either be cold stress (less than 20 degree C) or heat stress (approx. 15 degree C above the optimum temperature). Temperature stress also includes freezing stress i.e. the extreme form of cold stress. Here the temperature is below 0 degree C [89]. Since plants maintain themselves at a constant optimum temperature, change in temperature even for the slightest duration may affect them greatly. Temperature stress in plants leads to certain mishaps such as reduction of stability of cell membrane, poor germination, protein denaturation, rapid unfolding of nucleic acid, yellowing of leaf, and loss of enzyme activity [117]. Heat stress causes protein denaturation by leading to the breakdown of cell proteins in plants. It also affects the permeability of the membrane as extreme heat stress results in the melting of cell walls in the case of plants [101]. They eventually lead to loss of crop yield and a sharp decline in crop productivity. Cold stress in plants results in dehydration and starvation as cold stress affects the rate of uptake of essential nutrients and most importantly water. Various studies have indicated that CYP genes up-regulate under temperature stress. For example, In Lolium perenne, it was found that CYP73A, CYP75B, CYP75A genes were up-regulated due to fluctuations in the temperature [99] and In sorghum up-regulation of CYP99A1 and CYP709C1 genes under temperature stress was seen [15]. In Brassica napus, CYP71A23 is responsible for pollen sterility under temperature stress [83]. In the Arabidopsis plant, the CYP83A1 gene shows a 2-4 fold expression under temperature stress [10].

| Type of stress | Plant | CYP genes | Role of CYP under various abiotic stress | Reference |
|---------------|-------|-----------|----------------------------------------|-----------|
| Drought stress | Sorghum bicolor | CYP71A25, CYP71B2 | CYP up-regulates under drought stress | [41] |
| | Zea mays | CYP96A8 | Biosynthesis of Lignin | [35] |
| | Arabidopsis thaliana | CYP707A1, CYP707A2 | CYP707A1 and CYP707A2 gene is up-regulated under water-deficient condition | [47] |
| | - | CsCYT75B1 | Enhances antioxidant activity | [85] |
| | - | CYP707A | ABA synthesis | [119] |
|                          | Plant Species       | Gene   | Function                                      | Reference |
|--------------------------|---------------------|--------|-----------------------------------------------|-----------|
| **Salinity stress**      |                     |        |                                               |           |
|                          | Citrus sinensis     | CYP75B1| CsCYP75B1 gene up-regulates under drought stress | [108]     |
|                          | Zea mays            | TaCYP81D5 | CYP speeds up the ROS scavenging activity    | [104]     |
|                          | Arabidopsis thaliana| CYP709B3 | AtCYP709B3 exhibit increased expression under salinity stress | [38]     |
|                          | Physcomitrella patens| NA    | Reduces the damaging of cell wall under high salinity stress | [106]     |
|                          | Robinia pseudoacacia| CYP709 | CYP genes showed increased expression when exposed to salinity stress | [110]     |
| **Heavy metal toxicity** | Panax ginseng       | CYP71  | Biosynthesis of secondary metabolites         | [91]      |
|                          | Zea mays            | CYP88A | Gibberellin biosynthesis                      | [32]      |
|                          | Medicago sativa     |        | Phytoremediation                              | [116]     |
|                          | Arabidopsis thaliana| CYP83A1 | CYP exhibits 4-fold expression against Al toxicity   | [29]      |
|                          | Triticum aestivum   | CYP88A | Development of shoot                          | [32]      |
|                          | Oryza sativa        | CYP714A3 | Development of shoot                          | [32]      |
|                          | Pisum sativum       | CYP88A | CYP88A gene showed stunted growth under heavy metal toxicity | [113]     |
Temperatures stress

| Plant              | CYP Gene(s)               | When under heat stress CYP genes up-regulates                                                                 | Reference |
|--------------------|---------------------------|-------------------------------------------------------------------------------------------------------------|-----------|
| Panicum maximum    | CYP71A23                  | When under heat stress CYP genes up-regulates                                                               | [107]     |
| Lolium perenne     | CYP73A, CYP75B, CYP75A    | CYP73A, CYP75B, CYP75A genes are up-regulated under temperature stress                                       | [99]      |
| Arabidopsis thaliana | CYP83A1               | CYP83A1 gene exhibits 2-4 fold expression under heat and cold stress                                        | [10]      |
| Brassica napus     | CYP71A23                  | Pollen sterility                                                                                           | [83]      |
| Sorghum bicolor    | CYP99A1, CYP709C1         | Up-regulation of CYP99A1 and CYP709C1 genes under temperature stress                                       | [15]      |

5.2. Biotic stress

The stress that results in damaging of plants by the actions of living organisms including insects, bacteria, weeds, etc. which disturbs the overall dynamic of plants is called biotic stress. Biotic stresses in plants usually refer to hindrances such as insects, diseases, weeds, etc. These stresses cause deprivation of nutrients and minerals required by the host plant which in some extreme cases also lead to plant death. Apart from disturbing plant growth, biotic stresses are also responsible for affecting the seed quality, rotting of root, and downgrading the crop yield. In plants such as Zea mays and Pisum sativum, CYP genes were found to be up-regulated during the time of wounding [79], [24]. Additionally, the CYP gene i.e. CYP96A15 are also closely involved with a very common structural plant defence mechanism called epicuticular wax biosynthesis. (Table 5)

5.2.1. Disease stress. Disease stress is considered the most prominent out of all these biotic stresses. Fungi are major contributors of disease stress in plants. It is closely followed by plant stress caused by insects. In the Arabidopsis plant, a member of the CYP450 gene family AtCYP76C2 gene results in rapid cell death as a coping response to bacterial stress caused by Pseudomonas syringae as it restricts the further spreading and growth of pathogens [28]. In Capsicum annuum, caCYP1 is a key player as it is known for its involvement in hypersensitive response (HR) to protect the plant from infection by Xanthomonas axonopodis [44]. It is also responsible for the biosynthesis of cutin as well as cyanogenic glucosides [108]. One of the many factions of CYP in plants includes the involvement of CYP93C genes in providing protection against disease stress. This particular gene enhances the intake of isoflavonoids by plants thus facilitating the tolerance against disease stress. CYP450 genes like CYP81E1, CYP81E3, CYP81E7, and CYP93A1 are also considered key players in the isoflavonoids biosynthesis in the case of plants like Medicago truncatula, Glycyrrhiza echinata, Glycine max L and Cicer arietum L [51], [2], [90], [75]. Isoflavonoids in turn provide protection against diseases by increasing dietary intake. In the Arabidopsis plant, CYP71B15 is responsible for the biosynthesis of camalexin and by doing so ensures the protection of plants from disease stress [22] as the secondary
metabolite camalexin discourages the further development of bacterial and fungal pathogens. Camalexins are known for their defence mechanism against a virulent bacterial pathogen namely Pseudomonas syringae. Another example of the involvement of CYP as a defence against pathogens in Arabidopsis is that this plant usually produces phytoalexins as a response to attacks by bacterial pathogens. CYP genes like CYP71B15, CYP71A12, CYP79B3, CYP79B2, and CYP71A13 in the said plant are responsible for the biosynthesis of the previously mentioned aromatic compound camalexin [22]. Hence, helps in the defence mechanism against disease stress.

5.2.2. Insect stress. Insect stress causes physical damage to plants. They also serve as carriers of numerous bacteria and viruses. Insect stress in plants also disturbs important processes such as photosynthesis as insects tend to reduce the surface area of a leaf which is directly related to the rate of photosynthesis. They function in the biosynthesis of xanthophyll. This pigment functions in the light-capturing process during photosynthesis. CYP is responsible for increasing the would-induced defence during the biotic stress environment. In the sorghum plant, CYP71E1 and CYP79A1 catalyse the reaction of conversion on tyrosine, which in turn optimizes pest resistance as well as food safety [5]. Additionally, in few plants like Arabidopsis, CYP450s like CYP86A1 are also known for their function in the biosynthesis of suberin which is a defence mechanism against insect stress [34]. Arabidopsis plants also include CYP PAD3 genes which make the plant resistant to *Myzus persicae* or green peach aphid [81]. The green peach aphids are considered a major threat to plants all around the world due to their ability to work as a vector carrying different plant viruses. Another important role of CYP450 is their involvement in Berberine biosynthesis. Berberines are secondary metabolites that function in providing protection to plants from Plutella xylostella commonly known as the Diamond back moth. This insect is known for its destructive nature and high tolerance to bio-pesticides as well as certain chemicals. Berberine is an alkaloid that is known to be toxic to insects including the diamond back moth. CYP719 genes are responsible for the biosynthesis of this alkaloid in *Coptis japonica* [36]. Hence, they provide defence against insect stress in plants.

5.2.3. Weed stress. Another type of biotic stress includes weeds or undesirable and unprofitable plants. Weed is one of the biotic stresses that the plant faces which yet again challenges its productivity, growth as well as development as there is clear competition for water, minerals, nutrients as well as sunlight between weed and the plant. Weed is a potential threat to crop productivity as they dominate the environment because of their rapid growth criterion. Certain plants such as Sorghum release allelochemicals to inhibit weed growth. CYP71AM1 gene synthesizes these allelochemicals in such plants. It is responsible for catalysing sorgoleone which is an allelochemicals [76]. CYP71C is considered to be vital in the process of biosynthesis of benzoxazinoids namely DIBOA and DIMBOA which are specialized metabolites responsible for inhibiting the weed growth in the case of the wheat plant [69]. Apart from their role in providing defence against weed they also protect the plants from other biotic stresses such as insects and diseases.

| Stress       | Plant                           | CYP genes   | Role of CYP under various biotic stress                                      | Reference |
|--------------|---------------------------------|-------------|--------------------------------------------------------------------------------|-----------|
| Disease stress | *Arabidopsis thaliana*          | AtCYP76C2   | Results in the rapid cell death as a coping response to bacterial stress caused by *Pseudomonas syringae* | [28]      |
| Species                     | Enzyme            | Function                                                                 | Reference |
|----------------------------|-------------------|--------------------------------------------------------------------------|-----------|
| *Arabidopsis thaliana*      | CYP71B15          | Biosynthesis of secondary metabolite camalexin which in turn provide protection against bacterial pathogen *Pseudomonas syringae* | [22]      |
|                            | -                 | Modulates the level of phytoalexins resulting in tolerance against some pathogen | [22]      |
| *Nicotiana benthamiana*     | GmCYP82A3         | High tolerance to gray mold and black shank                              | [111]     |
| *Capsicum annuum*           | CaCYP1            | Involvement in hypersensitive response (HR) to protect plant from infection by *Xanthomonas axonopodis* | [44]      |
| *Triticum aestivum*         | CYP709C3v2        | Tolerance to *Fusarium* head blight                                      | [46]      |
| *Cicer arietum L.*          | CYP81E3           | Biosynthesis of isoflavonoid. Isoflavonoid in turn enhances the dietary intake hence provides protection from diseases. | [75]      |
| *Glycine max L.*            | CYP93A1           | -                                                                        | [90]      |
| *Glycyrrhiza echinata*      | CYP81E1           | -                                                                        | [22]      |
| *Arabidopsis thaliana*      | CYP86A1           | Suberin biosynthesis                                                     | [34]      |
|                            | -                 | Cutin biosynthesis                                                       | [108]     |
|                            | -                 | Protection from *Myzus persicae* commonly known as green peach aphid in the case of *Arabidopsis* plant | [81]      |
| *Nicotiana tobacum*         | Uncharacterized   | Resistance to aphids                                                     | [103]     |
| Insect stress               |                   |                                                                          |           |
| Plant Species          | CYP Gene | Function Description                                                                 | Reference |
|-----------------------|----------|--------------------------------------------------------------------------------------|------------|
| *Oryza sativa*        | CYP704B2 | Anther cutin biosynthesis                                                             | [48]       |
| *Symphytum tuberosum* | CYP77A20, CYP77A19 | Biosynthesis of suberin                                                              | [93]       |
| *Sorghum bicolor*     | CYP71E1, CYP79A1 | Conversion of tyrosine during the biosynthesis of Dhurrin to ensure resistance against pest | [7]        |
| *Coptis japonica*     | CYP719 | CYP functions in Berberine biosynthesis to ensure resistance against Diamond black moth | [36]       |
| Conifers              | CYP720B4 | Biosynthesis of resin acid                                                             | [33]       |
| *Sorghum bicolor*     | CYP71AM1 | Biosynthesis of allelochemicals to suppress the growth of weeds                        | [76]       |
| *Triticum aestivum*   | CYP71C | Biosynthesis of DIBOA, DIMBOA to inhibit further growth of weeds                      | [69]       |
| *Glycine max*         | CYP82A3 | Play important role in the signaling pathways                                          | [111]      |
| *Zea mays*            | NA       | Up-regulation of CYP genes during wounding                                            | [79]       |
| *Pisum sativum*       | NA       | CYP genes get up-regulated during wounding                                             | [24]       |
| *Populus trichocarpa* | CYP79D | Aldoximes biosynthesis                                                                | [37]       |

### 6. Analysis/ Discussion

CYPs are considered vital in a plant’s defence mechanism against different stresses and help in catalysing the reaction during the biosynthesis of primary and secondary metabolites. A CYP first figure out the external stress condition and generates cellular responses accordingly. CYP450 play important role in the biosynthesis of phytoalexins which are released by plants during exposure to stress by parasites. Moreover, CYPs are also involved in important cellular processes like photosynthesis. Xanthophylls are yellow pigments that are responsible for light–harvesting during the photosynthesis process. CYP genes like CYP97A3 and CYP97C1 actively participates in the
biosynthetic pathway of these yellow pigments as they function in catalyzing the process of hydroxylation of beta and gamma rings of carotenoids. In the plant *Arabidopsis thaliana*, CYP86A2 showed properties such as reduction of cuticle membrane thickness which results in the increased tolerance of plants against stress caused by water deficiency by increasing the water permeability. Gibberellins are growth hormones that function in the integration of numerous hormone signaling pathways when exposed to heavy metal toxicity stress. In plants such as maize CYPs facilitates synthesis of these growth hormones. Another important role of CYP450 is their involvement in Berberine biosynthesis. Berberines are secondary metabolites that function in providing protection to plants from *Plutella xylostella* commonly known as the Diamond back moth. This insect is known for its destructive nature and high tolerance to bio-pesticides as well as certain chemicals. Berberine is an alkaloid that is known to be toxic to insects including the diamond back moth.

7. Conclusion
Environmental stresses caused via biotic and abiotic factors often hinder the growth as well as effects the development of plants. Living organisms comprising fungi, bacteria, insects, etc. are often the cause behind biotic stresses. Abiotic and biotic stresses such as these occur due to a mixture of physical as well as environmental factors widely affecting the plants by causing stress thereby reducing plant productivity. However, plants have developed many defense mechanisms against these stresses. In plants, the Cytochrome P450 gene family is responsible for providing protection to plants against multiple abiotic and biotic stresses by actively taking part in numerous detoxification and biosynthetic pathways. They are also responsible for the biosynthesis of numerous compounds to ensure the survival of the plant when exposed to certain stresses. It is expected that factors causing abiotic and biotic stress will increase in the coming future. One example is the rapid increase in Earth’s temperature. It would become a necessity to breed plants that are resistant to these stresses. This study facilitates the characterization of CYP450 in plants to observe its role in metabolite biosynthesis and defense against different stresses in plants. Furthermore, this study will also provide us with a solid foundation for further analysis of the CYP450 gene in numerous plant species in the future. With an increasing amount of genomic information, our knowledge of this specific enzyme will keep on increasing as well. We have previously discussed the diverse functions of CYP450 in plants. Since one of its many functions is its role in generating defense response under stress conditions, increasing our knowledge of this enzyme superfamily will help us develop plants with magnified tolerance to such stresses in the coming future.

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