# Heat Shock Proteins: Functions And Response Against Heat Stress In Plants

Magaji G. Usman, M. Y. Rafii, M. R. Ismail, M. A. Malek, Mohammad Abdul Latif, Yusuff Oladosu

**Abstract:** Heat stress has significant effect on protein metabolism, including degradation of proteins, inhibition of protein accumulation and induction of certain protein synthesis. It also poses a serious damage to the growth and development of the plant. The ability of the plants to respond to this stress by maintaining protein in their functional conformation as well as preventing the accumulation of non-native proteins are highly important for the cell survival. Heat shock proteins are involved in signaling, translation, host-defence mechanisms, carbohydrate metabolism and amino acid metabolism. In fact, these proteins are now understood to mediate signaling, translation, host-defence mechanisms, carbohydrate metabolism and amino acid metabolism by playing a significant function in controlling the genome and ultimately features that are obvious. Several reviews have reported the tolerance of plants to different abiotic stresses. The topic of enhancing protection mechanisms (including HSPs) to induce heat resistance is very interesting and research in this area has many repercussions for the understanding of heat stress response. However, this review reports Heat Shock Proteins (HSPs) and their function, research progress on the association of HSPs with plant tolerance to heat stress as well as the response of the HSPs under heat stress as an adaptive defence mechanism.

**Keywords:** Heat Stress; Heat Shock Proteins; Crop Plants; Heat Tolerance

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## 1 INTRODUCTION

Heat Shock Proteins (HSPs), or stress proteins, are highly conserved and present in all plants and animals [1]. Some HSPs also referred to as molecular chaperones, play an important role in protein stabilization such as assembling of multi-protein complexes, folding or unfolding of proteins, transport or sorting of proteins into correct compartments at sub-cellular level, control of cell-cycle and signaling, as well as cell protection against stress or apoptosis [2]. In plants, expression pattern of a number of genes modulated in response to various acute environmental changes. This altered pattern result in altered biochemical and physiological activity of the cell and developmental pursuit of the organism [3]. When plants were exposed to high temperatures a new expression pattern was observed by the biosynthesis of HSPs [2]. The heat-shock response in plants is similar to that of other organisms. Trimerization and activation of heat shock factors (HSFs) regulate the induction of heat shock genes [4]. HSFs act in the promoter region of the HSP genes through a well-defined and highly conserved heat shock element (HSE).

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- *Magaji G. Usman is currently pursuing masters degree program in genetics and plant breeding in Dept. of crop science, Faculty of Agriculture, Universiti Putra Malaysia, magajiusman0@gmail.com*
- *M.Y. Rafii: PhD, Institute of Tropical Agriculture Universiti Putra Malaysia PH-+60389381612, mrafii@upm.edu.my*
- *M.A. Malek: PhD, Bangladesh Institute of Nuclear Agriculture, Mymensingh-2202, Bangladesh, malekbina@gmail.com*
- *Mohammad Abdul Latif: PhD, Bangladesh Rice Research Institute, Gazipur-1701, Bangladesh, alatif1965@yahoo.com*
- *M.R. Ismail: PhD, Institute of Tropical Agriculture, Universiti Putra Malaysia, razi@upm.edu.my*
- *Yusuff Oladosu is pursuing his PhD degree program in genetics and plant breeding at Universiti Putra Malaysia Corresponding author: magajiusman0@gmail.com*

HSPs are essential components of cells and developmental processes under normal physiological conditions besides its role in heat stress [5]. Earlier results reveal that most HSPs serve as molecular chaperones [4]. Heat stress is one of the main abiotic stresses and affects the production of various crops [6]. High temperatures alter several metabolic processes reducing photosynthetic activity that results mainly in grain yield losses. Plants response to heat shock leads to changes in the cellular membrane structure, protein metabolism, level of enzymes and photosynthesis activity. It has been reported that high temperature changed the properties of membranes of nucleus, endoplasmic reticulum, mitochondria and chloroplasts of *Oryza sativa* [7]. Lipids in the thylakoid membranes of the chloroplast are very important to improve photosynthesis and hence stress tolerance [8]. Heat stress together with some stresses will cause defence mechanisms such as the clear expression of genes that are expressed under the heat condition but not under favorable conditions [9, 10]. These genes are referred to as either "Heat-shock proteins", "Stress-induced proteins" or "Stress proteins" [2, 11]. Almost all kinds of stresses induce gene expression and synthesis of heat-shock proteins in cells that are subjected to stress [12, 13]. In *Arabidopsis* and some other plant species low temperature, osmotic, salinity, oxidative, desiccation, high intensity irradiations, wounding, and heavy metals stresses were found to induce the synthesis of HSPs [14]. However, stressing agents lead to an immediate block of every important metabolic process including DNA replication, transcription, mRNA export, and translation, until the cells recover [15, 16]. Heat stress – high temperature – affects the metabolism and structure of plants, especially cell membranes and many basic physiological processes such as photosynthesis, respiration, and water relations [17]. On the molecular level, this effect of heat stress reflects the temperature dependence of Michaelis–Menton constant (Km) of every enzyme participating in the process [18]. Membranes and proteins are among the most affected cell components during stress [19, 20]. Plants living in extreme environments require a cell physiology able to compensate for stressful conditions [19]. Changes in these components can alter several processes, such as uptake of water and ions, translocation of solutes, photosynthesis and respiration, and produce inactivation of enzymes,

accumulation of unprocessed peptides and proteolysis. Thus, metabolic damage is produced and growth is, therefore, reduced [21, 22]. One common protective response in most organisms to temperature stress is the induction of genes that code for HSPs [2, 23, 24, 25]. The expression of heat-induced protein is well known to be a vital important adaptive mechanism in this respect [26]. The induction and synthesis of heat-shock proteins due to high temperature exposure are common phenomena in all living organisms from bacteria to human beings [1, 11, 27]. It seems that the synthesis of these proteins is costly energy wise that is reflected on the yield of the organism. Thus, there is the need to shed more light on the various mechanisms on how plants respond to stress, such as heat, and the role they play with regards to stress tolerance [28]. Therefore, this review reports Heat Shock Proteins (HSPs) and their function, research progress on the association of HSPs with plant tolerance to heat stress as well as the response of the HSPs under heat stress as an adaptive defence mechanism.

## 2. Heat Shock Proteins (HSPs)

HSPs can be said to be proteins which are usually expressed when responding to stress conditions [2, 29-35]. HSPs have been studied widely in the fruit fly, *Drosophila melanogaster*, where the idea was first identified. Both at cellular and organismic level exposure, HSPs are highly conserved [2, 31]. For a cell to survive under stress it is quite important to maintain the proteins in their functional conformation and aggregation of non-native proteins should be prevented. There is widespread interest in the cellular mechanisms utilized by an organism to cope with a disruption in homeostasis [36]. Examples at the cellular level include temporary modifications in gene expression to survive changing environments, as well as altering cellular structure and function to deal with more permanent adverse conditions. Plants, as sessile organisms, rely on proteomic plasticity to remodel themselves during periods of developmental change, to endure varying environmental conditions, and to respond to biotic and abiotic stresses. The latter are the basic reason for the loss of crops all over the world, which reduces the average yields of virtually all major crop plants by more than fifty percent [14]. Abiotic stresses usually cause protein dysfunction [28]. Different families of proteins are known to be connected with the ability of the plant to respond to physiological stress either by synthesis, accumulation or reduction [37]. Among other things, these proteins are involved in signaling, carbohydrate metabolism and amino acid metabolism. In fact, proteins are now understood to mediate signaling, translation, host-defence mechanisms, carbohydrate metabolism and amino acid metabolism by playing a significant function in controlling the genome and ultimately features that are obvious such as in xerophytes or coming across stressors directly such as antioxidant enzymes and chaperonins or not directly like a key enzyme in the synthesis of osmolyte [38]. The most studied of these proteins have molecular weights of 100, 90, 70, 60 and 12-40kDa and referred to as HSP100, HSP90, HSP70, HSP60 and sHSPs respectively [39]. There is a difference in the number of HSPs between organisms and even within an organism among the different cell types. To whatever degree, all organisms show the expression of *HSPs* that belongs to the family HSP70 and the molecular weight of the family falls between 68-78kDa [2, 31]. The family of the HSP70, out the

other families of HSPs, has a strong correlation with resistance to heat, either permanent or transient [40-42]. The response of many organisms to elevated temperature has been characterized and described as the Heat Shock Response (HSR) [31]. While it is apparent that the HSR is very common, variations in the nature of the HSR between closely related species have not been well characterized. The HSR in plants has been well characterized primarily in two crop plants, maize and soybean [43-46], cotton [47, 48], and to a lesser extent in a few other systems [49-54] There have been reports on the HSR of a cell culture of a wild species of tomato, *Lycopersicon peruvianum* [55-57] and a recent report on the tissue specific expression of an HSP70 cognate in cultivated tomato [58].

### Classification and the major functions of HSPs

HSPs are generally categorized into 5 evolutionarily conserved families: HSP100, 90, 70, 60, and the small HSPs [59]. Some of the HSPs act as molecular chaperones. Below are the major families/groups:

### The family of HSP70

The family of HSP with molecular weight of 70kDa is wide and acts as molecular chaperones and is virtually found in almost all plant and animal species [60]. The sequence arrangement identity between bacterial and eukaryotic HSP70 identity is around fifty percent, indicating its important and necessary functions in various life forms [60-61]. The organism, eukaryotic, has a quite number of this HSP70 homolog, located in different cell components such as the mitochondrion, chloroplast, ER and cytosol [61]. Regardless of their function in preventing aggregation of proteins and helping again in folding of proteins that are not native in environments that is not favorable, several HSP70 also play a crucial role in housekeeping activities under favorable conditions [61]. Some HSP70 homologues are constitutively expressed in the cytosol of eukaryotic organisms. These homologues are referred to as heat shock cognate 70 (HSC70) [62]. They help to stabilize newly developing proteins being released from ribosome, preventing newly synthesized polypeptide chains from any possible misfolding and aggregation before the expression of the protein is completed [62-63]. A comprehensive analysis of the expression profile of *Arabidopsis thaliana*, HSP70 gene family founded two-twenty-fold induction of 11 HSP70 genes while another two HSP70 genes was expressed and not increased by heat shock treatment [64]. In addition, some members of HSP70 are involved in controlling the biological activity of folded regulatory proteins, and might act as negative repressors of HSF mediated transcription [61]. In addition to its general chaperone functions (i.e. preventing accumulation and assisting in the folding again of proteins that are not native under the conditions of stress), HSP70 also plays a regulatory role in other stress associated gene expression [65]. The interaction suggested between HSP70 and HSP factor is a regulatory mechanism that is negative for HSP factor-mediated activation of transcripts in the HSR [66]. It was suggested that the interaction between HSP70 and HSF prevents the trimerization and binding of HSF to HSE, thereby blocking the transcriptional activation of heat-shock genes by their HSFs [67]. HSP70 is also involved in the modulation of signal transducers such as protein kinase A, protein kinase C and protein phosphatase [68]. In this

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respect, the HSP70 chaperones might play a broad role by participating in modulating the expression of many downstream genes in signal transduction pathways both during stress and under normal growth conditions [69].

### The family of HSP90

HSP90 is one of the most abundant proteins in the cytoplasm, where it constitutes 1–2% of total protein levels [70]. The essential eukaryotic chaperone HSP90 facilitates the maturation of a variety of meta-stable protein substrates, many of which are central regulators of biological circuits. Due to HSP90s central position in numerous pathways regulating growth and development, the chaperone has emerged as a principal focus of investigation in diverse fields [71]. The HSP90s are highly conserved and abundant cytosolic proteins in eukaryotes [72]. Unlike other HSPs, the chaperone activity of the HSP90 is exerted on a number of target substrates or client proteins including steroid hormone receptors, cell cycle kinases, signal transduction pathway components, proteolytic machinery, and microtubule dynamics [73-74]. However, the high abundance of HSP90 compared with that of its client proteins, the high levels of expression in response to stress, and the existence of endoplasmic reticulum (ER), chloroplasts, and mitochondria homologues suggests that this is a very narrow view of the HSP90 cellular activity and further indicates that it may contribute to additional functions in the cytosol and organelles under physiological or stress conditions [75]. HSP90 acts as part of a multi-chaperone machine together with HSP70 and co-operates with a cohort of co-chaperones, including Hip (HSP70 interacting protein), Hop (HSP70/HSP90 organizing protein), p23 and HSP40 [76]. Evidence showed participation of HSP90s in different developmentally, hormonally, and morpho-genetically regulated processes [77]. HSP90 regulates diverse cellular functions and exerts marked effects on normal biology, disease and evolutionary processes [78]. Hsp90s mediate plant abiotic stress signal pathways [79], but again the mechanisms are unclear. An Hsp90-specific inhibitor in the cytoplasm induced the accumulation of heat-induced gene products and improved heat tolerance in *Arabidopsis* [80, 81]. Under normal conditions, Hsp90.2 in the cytoplasm negatively regulates transcription of heat-induced genes by suppression of HSF [80]. Hsp90.2 is instantaneously inactivated under heat shock, and HSF is activated to induce expression of downstream genes containing HSF elements [80]. It was subsequently confirmed that over-expression of Hsp90.2 suppresses HsfA2 transcription, and that HsfA2 is induced under inhibition of Hsp90.2 in order to adapt to oxidative stress [81]. Similarly, an inhibitor of Hsp90 produced by a rhizosphere fungus repressed the growth and development of plants, but enhanced the heat resistance of *Arabidopsis* [82]. These studies show that Hsp90s play important roles in adaptation of plants to stress environments (including heat stress).

### The family of HSP60

This class Hsp60 is called in some of the literatures as chaperonins and it is generally agreed that they are important in assisting plastid proteins such as Rubisco [28]. Some studies pointed out that this class might participate in folding and aggregation of many proteins that were transported to organelles such as chloroplasts and mitochondria [83]. These HSP60 bind different types of proteins after their transcription and before folding to prevent their aggregation [27]. Functionally, plant chaperonins are limited and the general idea is that stromal chaperones (HSP70 and HSP60) are involved in attaining functional conformation of newly imported proteins to the chloroplast [84]. Functional characterization of plant chaperonins is limited. It is generally agreed that they are important in assisting plastid proteins such as Rubisco [61, 85]. It has been reported that a mutated species of *Arabidopsis* chloroplast Cpn60a exhibits defects in chloroplast development and, subsequently, in the proper development of the plant embryo and seedling [86]. Antisense Cpn60b transgenic tobacco plants showed drastic phenotypic alterations, including slow growth, delayed flowering, stunting and leaf chlorosis [87]. Chloroplast Cpn60 is a homologue of the bacterial Hsp60-type chaperone GroEL [88] and [89]. Such chaperones assemble into two stacked heptameric rings, and cooperate with a cochaperone termed Cpn10 (an Hsp10/GroES homologue), which may form heptameric caps at either end of the Cpn60 tetradecamer. Client proteins enter a central cavity in the Cpn60 complex, providing a protected environment in which folding can take place, which is controlled by the nucleotide-dependent cycling of Cpn60 subunits between binding-active and folding-active states [88] and [89]. The role of the Cpn60/Cpn10 chaperonin system in the folding of Rubisco subunits has been well documented [90]. Cpn20 is a chloroplast-specific cochaperone comprising two, tandemly-arranged Cpn10-like units; while in vitro assays have shown that it is a functional homologue of Cpn10, its specific role in vivo remains uncertain [91]. Immunoprecipitation experiments revealed that Cpn60 is in close proximity with Tic110 [92]. This interaction was disrupted in the presence of ATP, while import experiments revealed a transient association of mature, newly-imported proteins with the Cpn60–Tic110 complex, suggesting that Tic110 can recruit Cpn60 in an ATP-dependent manner for the folding of proteins upon their arrival in the stroma. Biochemical data also support the interaction of newly-imported proteins with stromal Hsp70, either before or after the interaction with Cpn60 [93] and [94]. It has been suggested that stromal Hsp70 and Cpn60 act sequentially to assist the maturation of imported proteins; particularly those destined for the thylakoid membranes. Another factor that facilitates the passage of new proteins through the stroma to the thylakoids is cpSRP (*chloroplast Signal Recognition Particle*), the clients of which are light-harvesting chlorophyll-binding proteins. In fact, one of the cpSRP components, a protein termed cpSRP43, was recently reported to have unique chaperone-like properties [95] and [96].

### The family of HSP100

The family of HSP100, also act as molecular chaperones, is among the members of the super family AAA ATPase with a wide range of different functional properties [97-98]. Beside playing a role in protein accumulation and misfolding, the HSP100 family plays a significant position in the disaggregation of proteins and/or degradation. The removal of polypeptides that are not functioning and are potentially harmful as a result of misfolding, accumulation or denaturation is crucial for the maintenance of homeostasis in the cells. Another unique function of this class is the reactivation of aggregated proteins [27] by resolubilization of non-functional protein aggregates and also helping to

degrade irreversibly damaged polypeptides [67 and 99]. HSP100 have been studied in several plant species such as *Arabidopsis*, *Glycine max*, *Nicotiana tabacum*, *Oryza sativa*, maize (*Zea mays*), Lima bean (*Phaseolus lunatus*) and *Triticum sativum* [97, 100, 101]. HSP100 like other molecular chaperones are often expressed in plants, but the environmental stresses such as high and low temperatures, dehydration, high salt or dark-induced etiolating are known to be the agents that induce them and the HSP100 expression is developmental [97, 101, 102]. The work of [103] indicated that in rice HSP100 protein production was correlated with the disappearance of protein granules in yeast cells. It was further shown that the dissolution of electron-dense granules by HSP101 takes place during the post-stress phase, implying a role for HSP100 in the recovery of cell stress. Given the high sequence similarity of *HSP101* with yeast *HSP104* and their conserved functions in thermotolerance, one can reasonably propose that HSP101 in Arabidopsis is also acting to facilitate reactivation of proteins denatured by heat [104]. The finding that HSP101 plays a crucial role in thermotolerance in plants, together with the conserved function of HSP101, suggests that engineering plants to express increased HSP101 may improve survival during periods of acute environmental stress [104]. However, the constitutive HSP100 expression indicates role for heat tolerance.

### The small heat shock protein family (smHSPs)

The family of small heat shock proteins (smHSPs) range in different sizes from 15 to 42 kDa and are characterized by a conserved sequence at their C terminus [105]. The a-crystalline-related smHSPs are ubiquitous in nature, but 20–40kDa smHSPs are unusually abundant in higher plants. Small HSPs are divided into six classes based on their sequence alignments, immunological cross reactivity, and cellular compartmentalization. Three classes (I, II and III) are localized in the cytoplasm or the nucleus and the other three are localized in the chloroplast, the endoplasmic reticulum, and the mitochondria [1, 105]. Although smHSPs' precise functional mechanism is still unclear, *in vivo* studies have shown that smHSPs act as molecular chaperones [106-108]. Plants synthesize significant amounts of smHSPs when exposed to high temperatures [109-111] drought stress [112 and 113], oxidative stress [111 and 114], cold acclimation [115], salts [116], and ABA treatment [108, 113 and 117]. These results suggest that smHSPs play an important part in plant endurance to abiotic stress. Because each smHSPs gene has a unique sequence with the potential for a special function, the unusual abundance of sHSPs (20–40 kDa) in plants could reflect their functional diversity. The smHsps cannot refold non-native proteins, but they can bind to partially folded or denatured substrates proteins, preventing irreversible unfolding or wrong protein aggregation [118]. Recent findings showed that the smHSPs 18.1 isolated from *Pisum sativum*, as well as the sHsps 16.6 from *Synechocystis* sp. PCC6803 under *in vitro* conditions, binds to unfolded proteins and allows further refolding by HSP70/HSP100 complexes [118]. It was noticed that there was a positive qualitative relation between the accumulation of smHSPs in the plastids and thermotolerance of heat shock (from 28 to 40°C) in six divergent *Anthophyta* species, including C3, C4, CAM, monocotyledonous and dicotyledonous species. Similar results were obtained separately with four non *Anthophyta*

species [119]. In another study, [119] indicated that the mitochondrial smHSPs protected NADH: ubiquinone oxidoreductase (complex I) during heat stress in apple fruit of *Pyrus pumila* (P. Mill) K. Koch var. McIntosh. This information might indicate some role of these proteins in adaptation of plants to heat stress. A recent review [120] concluded that there were some indications that smHSPs family plays a significant role in the quality membrane control and hence has the potential contribution in the membrane integrity maintenance especially under the conditions of stress. Liming et al [121] showed that transforming plants with HSP24 from *Trichederma harzianum* was found to confer significantly higher resistance to heat stress when constitutively expressed in *Saccharomyces cerevisia*. Some studies also support that there is a positive correlation between the HSP level in the cell and respective stress tolerance [122,123]. Though it is not very much clear that how HSPs confer heat stress tolerance, a recent investigation focused on the in vivo function of thermo protection, governed by sHSPs, is achieved through its assembly into functional stress granules or heat shock granules [124].

### Induction of HSPs due to heat stress

Heat shock, the stressor that has been studied greatly, together with a wide range of other metabolic stressors is known to cause the synthesis of heat responsive proteins [99]. The HSR causes the enhanced expression of heat stress genes, multi-gene families encoding molecular chaperones [75-61, 69, 120, 125, 126, 127]. The works of [128] showed that HSPs are more expressed *in vivo* and *in vitro* with the increase in temperature for incubation or room temperature respectively. Besides, heat shock proteins expression is reduced at 47°C and ceased at 49°C due to the inability of the cells to survive at higher temperature [129]. During heat shock, at temperatures above 35°C, in tomato, like other plants, very few proteins other than those induced by heat are detected following *in vivo* labeling [128]. They also studied that in addition to the induction of typical HSPs at temperatures approximately 10°C higher than standard growth temperatures, an additional set of heat induced proteins were observed at temperatures 15 to 20°C higher than standard growth temperatures. Persistent heat shock induces persistent HSP synthesis in tomato, until no protein synthesis can be detected. In their analysis of the duration of HSP synthesis in tomato, they investigated the response at two temperatures, 35 and 37°C, the temperatures of induction and of maximal HSP synthesis. Different heat shock proteins have been identified in many crop plants associated with heat stress (Table 1). A more complete identification and comparison of heat responsive proteins in the two leguminous plants contrasting in heat tolerance were achieved through proteomic analysis [130]. They observed that accumulation of HSP70 is higher in *P. chilensis* than in soybean at 20min of treatment at 40°C as well as after 60 and 90min of heat shock, indicating that there is also a better protection and for a longer time against heat shock stress.

### Physiological function of HSPs

HSPs may bind with proteins that are sensitive to heat in a cell under heat shock to protect them from degradation and as well preventing any havoc following precipitation and permanently influencing the viability of the cells [141-142]. Few years back, the studies on protein purification and

function, molecular cloning both *in vitro* and *in vivo* have figure-out clearly the position of HSPs in the sorting of proteins, folding as well as assembly of proteins. As a result HSPs have been called `molecular chaperones`. It is observed that HSPs prevents the cells from the damage effect caused by high temperature [41, 143] Figure 1. The function of any protein is determined by its formation and folding into three dimensional structures [144]. Formation of three dimensional structures requires 50% of principle amino acids sequence [145]. That is why the role of HSPs in the folding of other proteins is important. [66] Indicated that HSPs protect cells from injury and facilitate recovery and survival after a return to normal growth conditions. It has been observed that upon heat stress, the role of HSPs as molecular chaperones is without doubt, their function in non-thermal stress could be different: unfolding of proteins is not the main effect and protection from damage could occur in an alternative way apart from ensuring the maintenance of correct protein structure. It has been concluded that the role of HSPs generally is acting as molecular chaperones by controlling the folding/unfolding and protein accumulation as well as localization and breakdown in both plant and animal species [11, 26, 146-148]. They prevent the irreversible accumulation of other proteins and are involve in the refolding of proteins under heat stress conditions [149].
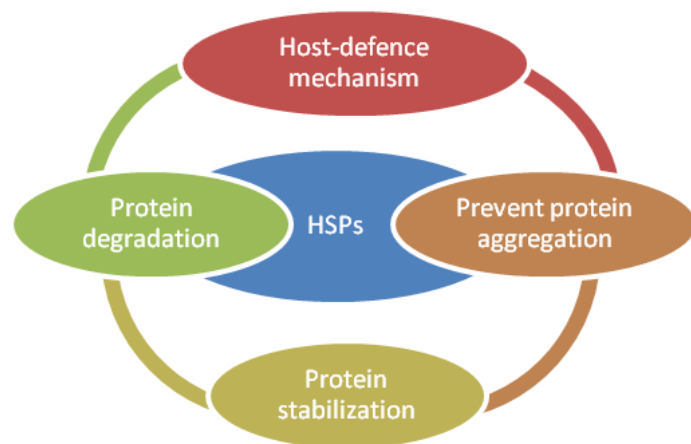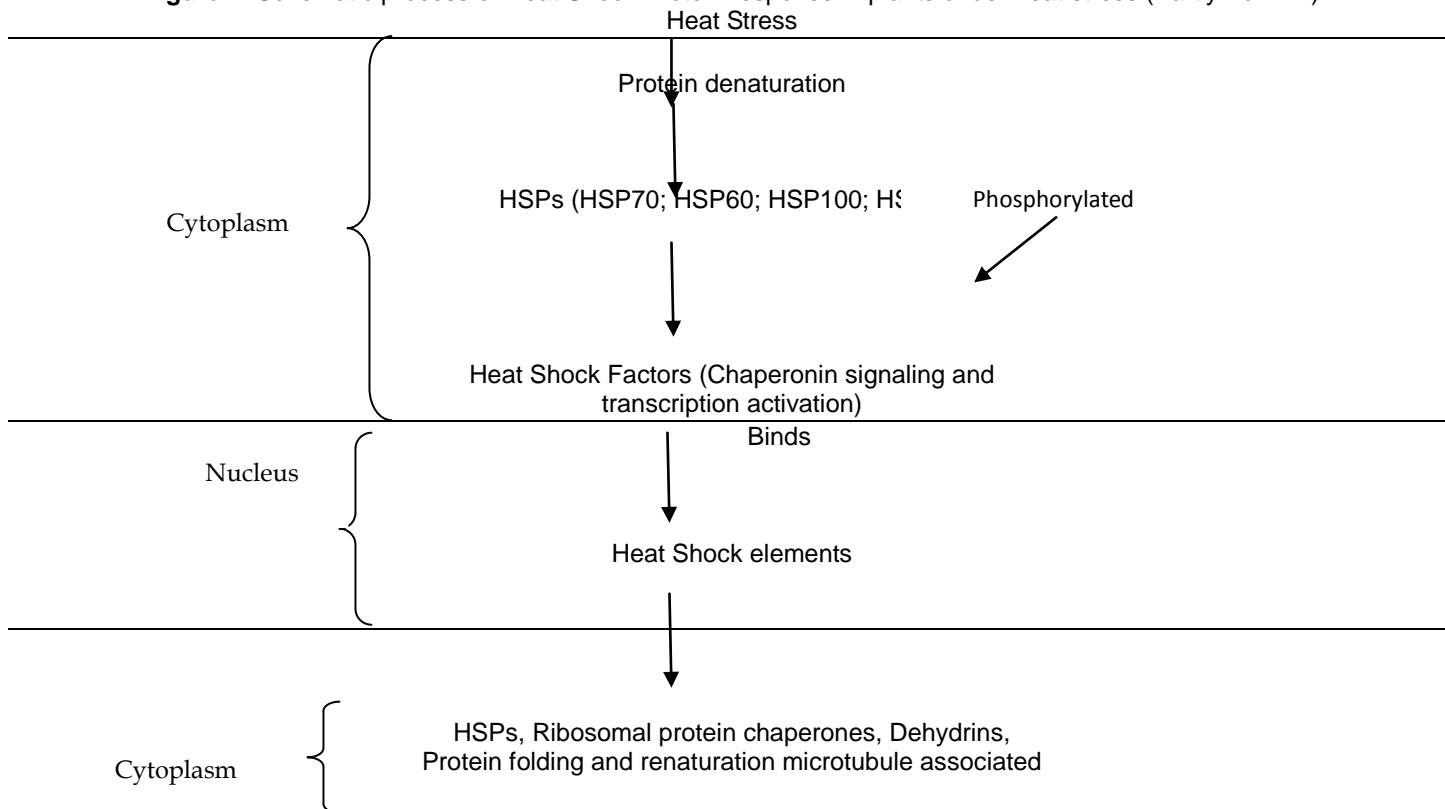


*Figure 1. Shows the function of HSPs under heat stress*

Several evidences now are accumulating showing that HSPs are required to get native structures of monomeric and oligomeric proteins after they have been produced on the ribosomes or after been moved across the membranes [129, 150, 151]. Cells having been subjected to a non-harmful heat shock develop an increased resistance to prolong heat stress subsequently [152-154]. The expression of HSPs group has a relationship with tolerance to heat. They observed that when cell are exposed to heat, proteins synthesis ceased rapidly and it takes five to six hours to recover. On the contrary, [155] indicated that after six to eight hours the development of thermotolerance and induction of protein are completed. Finally, heat tolerance reaches its highest level and the synthesis of HSP is returned to normal.

### Response of HSPs to heat stress in plants
The Heat Shock Response (HSR) in plants and mammals is regulated by a set of highly conserved proteins known as HSPs, and expression of this protein is governed by HSFs

[120]. Interestingly, the number of HSFs in plants far exceeds those found in mammalian cells, most probably to equip plants with the ability to withstand various forms of external stressors at any time during their lifespan. There are 15 known HSFs in *Arabidopsis thaliana* [156] and >21 in *Solanum lycopersicum* (formerly *Lycopersicon esculentum*), and all are thought to play key roles in stress responses [157]. In tomato, only two of these HSFs, HSFA2 and HSFB1, are heat inducible [158], but their expression is controlled by HsfA1, referred to as the master regulator of the HSR [159]. In fact, the interaction of HSFA2 with HSFA1 is imperative for the co-localization of HSFA2 into the nucleus [157]. HSFA2 is seen as the 'work horse' of the stress response and becomes the most dominant HSF during a heat stress [159]. When cells are exposed to various stress conditions, such as heat stress, the HSFs that reside in the cytosol dissociate from the HSP (e.g. HSP70), are activated, and undergo trimerization. These HSF trimers are phosphorylated and translocated to the nucleus where they bind to the HSE, which is located in the promoter region on the HSP genes. The mRNA is then transcribed and translated, which leads to increased levels of HSPs in the cytosol (Figure 2). As such, they function as chaperones of denatured proteins as well as assisting in the translocation and/or degradation of damaged proteins [4]. Within the diverse HSP family, HSP70 is the most widely studied member, and a highly conserved 70kDa protein that plays a key role in the stress response in plants [1] as it does in mammals. HSPs are hypothesized to prevent and/or repair stress induced damage [2]. Exposure to elevated temperatures leads to activation of the cellular HSR, which is conserved throughout all kingdoms of life. The HSR causes the enhanced expression of heat stress genes, multigene families encoding molecular chaperones [61, 69, 99, 125, 126, 127]. Among these, HSP70 is one of the most abundant heat shock proteins in eukaryotic cells. HSP70 binds in an ATP-dependent manner to hydrophobic patches of partially unfolded proteins and prevent protein aggregation [160]. While HSP70s accumulate during heat shock, their constitutively expressed cognates (HSC70) are essential for general cellular functions due to their involvement in the control of protein homeostasis. They assist the folding of nascent polypeptides released from the ribosome [161], sorting of proteins to cell organelles by interaction with mitochondrial and chloroplast protein import complexes [162, 163], and form a link to the ubiquitin-mediated proteasomal degradation pathway [164, 165].

**Figure 2.** Schematic process of Heat Shock Protein response in plants under heat stress (Partly from 17)

Heat Stress

| | |
|---|---|
| Cytoplasm | Protein denaturation |
| | HSPs (HSP70; HSP60; HSP100; HS        Phosphorylated |
| | Heat Shock Factors (Chaperonin signaling and transcription activation) |
| Nucleus | Binds |
| | Heat Shock elements |
| Cytoplasm | HSPs, Ribosomal protein chaperones, Dehydrins, Protein folding and renaturation microtubule associated |

**Table 1.** Expression of heat shock protein major families in some crop plants responding to heat stress

| Major classes of HSP | Crop Species | Responsible Function | References |
|---|---|---|---|
| **HSP100** | Wheat, Tomato, Fescue Arabidopsis, Rice | Facilitate reactivation of proteins denatured by heat | [104, 128, 131, 132] |
| **HSP90** | Maize, Populus, Tomato, Wheat | Acts as part of a multi-chaperone machine together with HSP70 and co-operates with a cohort of co-chaperones | [128, 133, 139, 140] |
| **HSP70** | Wheat, Tomato, Creeping Soybean | chaperone function under heat stress, modulating the expression of many downstream genes in signal transduction pathways during stress | [128, 134, 137] |
| **HSP60** | Maize, bentgrass, Barley, Rye, Wheat, Creeping grass | Participate in folding and aggregation of many proteins | [133, 134, 138] |
| **sHSP** | Barley, Maize, Rice, Wheat, Tomato, Pearl millet, Sorghum | Bind to partially folded or denatured substrates proteins, preventing irreversible unfolding or wrong protein aggregation | [133, 134, 135, 136] |

### Genomic response

In terms of gene expression, the response of plant to heat stress was also studied by analysis of Arabidopsis transcriptomes [166]. Some genes appeared up-regulated. The products of these genes included Hsp100/ClpB (eukaryotic/ Escherichia coli nomenclature), HSP90/HtpG, HSP70/DnaK HSP60/GroEL and small heat shock proteins, confirming proteomic studies. These HSPs are proposed to act as molecular chaperones in protein quality control. Transgenic plants showing a dominant negative variant of heat shock factor 21 suppressed that of Zat12, a water-responsive zinc finger protein required for expression of APX1, and APX1

[167]. Heat shock provokes a rapid reprogramming of gene expression to favor translation of HSPs in which translation factors could play a role. According to [168], they analyzed translation initiation factors in wheat heat-shocked seedlings and during seed development. In general, the expression of HSPs and its factors, HSFs, was induced largely by heat and some other stresses. Presence of Hsps in higher plants was discovered by some researchers in tobacco and soybean using cell culture technique. When soybean was subjected to 40ºC for four hours, ten new proteins were found, but disappeared after 3 h treatment at 28ºC [45]. Studying the gene expression of HSP90 in rice plant (*Oryza sativa*)

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indicated that the HSP87 was present after 2 h of heat shock (from 28 to 45ºC), and its quantity was high and stable even after long heat stress (4 h) and then return to normal conditions i.e condition before stress. According to [128] during heat shock at temperatures above 35ºC, in tomato, like other plants, very few proteins other than those induced by heat are detected following *in vivo* labeling. The transcription levels of all 9 *OsHsp* genes studied were significantly enhanced under heat stress, which showed they may play roles in heat stress [169]. Expression profiles of PtHsp90 genes obtained by RNAseq was carried out by [139], using qRT-PCR of seven selected PtHsp90 genes on three different tissues of *Populus* plant under heat stress.

### Proteomic response

When plants are exposed to high temperatures they synthesize both high molecular mass HSPs (from 60 to 110 kDa) and small HSPs (from 15 to 45 kDa) [170, 171]. With the same unbiased to investigate the responses of abundant and low-abundant proteins of rice leaves upon heat stress [172] performed 2-DE on PEG-fractionated supernatant and pellet samples of rice leaf proteome. A total of 48 differentially expressed proteins in samples taken after 12 or 24 h of heat exposure compared to controls were revealed, 18 of which were HSP (HSP70, dnak-type molecular chaperone BiP, HSP100, Cpn60, small heat shock proteins). Studies carried out by [173] regarding isolation and characterization of relevant HSPs from plant tissues induced in tomato pericarp by thermal treatment, highlighted the presence of two major (HSPC1, HSPC2) and two minor (HSPC3 and HSPC4) class I smHSPs, identified and characterized by using mono specific polyclonal antiserum and MS/MS analysis of tryptic peptides. In this case the authors claimed that smHSPs accumulation is an appropriate parameter for monitoring treatment intensities and consequently for preventing chilling injury. Acoording to [174], they identified a total of 18 proteins as HSPs in the rice leaves studied under heat stress. It is interesting that all of these HSPs were identified from Polyethylene Glycol (PEG) pellet fraction samples, which suggest that PEG pellet fractions may be used as a potential fractionation tool in the analysis of multimeric proteins.

### Tolerant plant response

HSPs are known to be induced not only in response to short-term stress, but their production is a necessary step in plant heat acclimation. It is important to note, in fact, the early production of HSP101 chaperone by plants exposed to heat stress, but there are also many other pathways involved in adaptation to higher temperatures. The studies of HSPs expression made by [175] demonstrated that a better acclimation occurs when plants are gradually exposed to increasing temperatures, without changing parameters suddenly. They also examined clusters of genes whose expression increased during heat stress; in particular, cluster 45 contains 18 HSPs (HSP101, 14 small HSPs and 3 HSP70). Variation in Hsp production among closely related species from thermally contrasting habitats has been observed even when these species are grown and heat stressed under identical conditions [3]. This variation in Hsp production is often correlated with organismal thermotolerance [176]. There are many studies showing quantitative variations for their tolerance degrees among genotypes. The acquisition of thermotolerance appears to depend on not only upon the

synthesis of Hsps but also on their selective cellular localization. Lin et al. [177]. reported that in the soybean seedlings, several Hsps become selectively localized in or associated with nuclei, mitochondria and ribosomes at 40°C, they were absent in other parts. The selective localization of Hsps is temperature dependent. Genotypic variations have been observed for thermo-sensitivity in studies up to date. Heat shock sensitive genotypes synthesized Hsps earlier than tolerant genotypes [178]. Especially very early detected (in a few minutes in heat shock) specific Hsp transcripts might have effect on order of Hsp gene expression and cause different tolerance levels among species [179]. Tolerance to heat shock cannot be controlled by only one gene. The heat shock tolerance is determined by different gene sets in different stages of life cycle and in different tissues. Hsp70 was shown to be causally involved in the capacity to acquire thermotolerance in Arabidopsis and Hsp27 in another thermo-sensitive Arabidopsis mutant. Hsp17 was identified as a factor of acquired thermo tolerance in the study of transgenic cells [180].

## 3. Conclusion and future prospects

HSPs are known to be expressed in plants experiencing high-temperature stress. HSPs have been named as such either due to their expression behavior or based on sequence similarity to other Heat shock protein genes. Their molecular function might be membrane or protein stabilization, but, for now, for most HSPs the molecular function remains to be elucidated. The general observation of the response and induction of heat shock proteins following heat stress suggests that they play a fundamental role in cellular homeostasis. It is possible that HSPs may be involved with the phenomenon of acquired thermotolerance. Heat stress disturbs cellular homeostasis and can lead to severe retardation in growth and development, and even death. Temperature stress can have also a devastating effect on both the plant anabolism and catabolism, initially acting on protein complexes, being the quaternary structure the first folding that is lost during heat stress or heating. One of the side effects is the removal of the connection between pathways, and this involves mostly electron transfer, resulting in the movement of electrons in a high-energy state. Hence, understanding the way plants respond to heat stress is the number one step in the development of thermo tolerant crops, that is crops that are not sensitive to heat. Therefore, further research is needed to explore more opportunities to the better understanding of how plants respond to heat stress. A better knowledge on heat shock proteins is also necessary in order to identify their molecular function and as well their response to heat stress in plants.

**Author Contributions**
*All authors contributed equally to this work.*

**Conflicts of Interest**
The authors declare no conflict of interest.

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