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REVIEW PAPER
PLANT BREEDING & GENETICS

MULTIFUNCTIONAL PLANT'S CALMODULIN IN HEAT SHOCK SIGNAL TRANSDUCTIONAL PATHWAYS

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ABSTRACT
Many diverse types of calcium sensors release owing to varying concentration of Calcium (Stimulus). In plants, CaM (Calmodulin) is the most important calcium sensor. Achievements in designing of complete genomes of different crops have prompted to explicate and classify various CaM binding proteins. Genetic studies on CaM revealed that it contains multiple proteins, unique kinases and transcriptional factors which help the plants in adaptation against heat stress condition. Crop improvement could be only possible by having satisfactory acquaintance on stress tolerance mechanism and a brief knowledge on CaM and its related proteins will be obliging in order to acquire its proper functions in plant growth and developmental pathways under high temperature.

KEYWORDS: Heat shock proteins; calcium; sensor; plants growth; heat stress; Pakistan

INTRODUCTION
Heat stress (abiotic stress) defectively affects growth as well as the productivity of crop plants. Plants have acclimatized certain specialized mechanisms for continued existence against unfavorable environmental conditions. The different ways and mechanisms include anatomical, physiological, biophysical, genetical and reproductive changes which in turn makes the plants to cope with incompatible environmental conditions (IPCC, 2007). Diverse types of genes are said to be induced in the form of special products for upholding the stress tolerance by means of signal transductional pathways (Mahajan and Tuteja, 2005).
Thermo related genes like heat shock enzymes, proteins as well as transcriptional elements provides the significant base to a plant against extreme changes in environmental temperature (Gu *et al*., 2012; Lu *et al*., 2013). The expression of thermo related genes was under the control of different transcriptional elements on which CaM related proteins act in order to provide tolerance (Perochon *et al*., 2011). Heat shock elements are basically transcriptional elements which intimately present in the eukaryotes. A big family of such proteins located in plants viz 25 in *Oryza sativa,* 21 in *Arabidopsis thaliana* and 56 in wheat (Scharf *et al*., 2012; Xue *et al*., 2014).
Calmodulin proposed to be a unique Ca^{+2}-binding proteins among plants, extremely conserved protein intimately designated as diverse regulatory protein having pivotal role in modulation under heat stress condition (Snedden and Fromm, 2001). CaM is multipurpose functional protein being engage in calcium based signals towards mechanical, osmotic, oxidative, xenobiotics, salinity, heavy metals, pathogens, chilling, phytohormones and heat shock stress (Zielinski, 1998; Snedden and Fromm, 2001; Reddy, 2001; Rudd and Franklin-Tong, 2001; Fasano *et al*., 2001; White, 2003).

Heat shock proteins
HS-proteins (Heat shock proteins) intimately involved

in providing protection to various proteins against structural malformation under stress. HS- proteins produced under the influence of different genes and have size about 15-43 kDa (Sun *et al*., 2002; Al-Whaibi *et al*., 2011). Heat shock proteins are proposed to be induced under severe heat stress phase intimately in all organisms (Howarth and Ougham, 1993). Most significant families of heat shock proteins ubiquitous to all organisms are HSP90s, HSP70s and small HSPs exclusively produce only in plants (Jakob and Buchner, 1994). A unique relationship among HS reaction and oxidative stress has been implicated in plants (Gong *et al*., 1997; Lee *et al*., 2000; Larkindale and Knight, 2002).

The induction and expression of heat shock proteins (Hsp) under the control of different signaling elements (Calmodulin or CaM-binding protein kinase or CaM-binding protein phosphatase), CaM designated as an important messenger in heat shock signal transductional pathways as hsp carry out diverse types of functions similar to molecular chaperons. Thermotolrance was upgraded by a special type of hsp protein called 100Hsp in Arabidopsis as well as in maize (Miernyk, 1999; Nollen and Morimoto, 1999; Hartl and Hayer, 2002; Mayer and Bukau, 2005). Production of a novel heat shock protein (HSP26) induces the better photochemical performance in photosystem II against heat stress (Lee *et al*., 2000; Kim *et al*., 2012). HSP26 also reported in maize seedlings under high temperature for stress tolerance (Hu *et al*., 2010). Messengers (Calcium) provide the foundation of signal transductional pathways since; important in diverse developmental as well as in growth processes under abiotic stress conditions (Defalco *et al*., 2010; Hashimoto and Kudla, 2011).

Calcium as a messenger for CaM

Plants exploit the divalent cation (calcium) as a second messenger to evaluate the endogenous and exogenous signals which were produce as a consequence of different cellular responses. A collection of different signals encoded by calcium produced with the help of spatial, temporal Ca^{+2} and also via frequency & amplitude of calcium (Bouche *et al.,* 2005). Ca^{+2} act as an indicator to endow the plants with adaptational pathways. Activation of Ca^{+2} sensors induces the defensive ability in plants to combat against altering environmental conditions. Internal & external signals were the chief basis of raising the Ca^{+2} concentrations inside the cytosol and Ca^{+2} transport system thoroughly involved in sustaining the normal level of Ca^{+2} (Mazars *et al*., 2009). CaM concentration should be 100-200nM inside the cytoplasm whereas its concentration should be in minimolar inside vacuole as well as in cell wall for proper functioning (Hirschi, 2004; Reddy and Reddy, 2004; Rudd and Franklin-Tong, 2001; Mcainsh and Pittman, 2009).

In plants, three types of Ca^{+2} sensors have been reported. Ca^{+2} transport system maintained with the varied level of cystolic Ca^{+2} concentrations owing to internal & external stimulus. Calcium mobility proscribed via different types of Ca^{+2} binding proteins which work as a buffer inside the cytosol. Signals received and decoded by diverse types of Ca^{+2} sensor proteins. Calcium sensor proteins consist of high affinity Ca^{+2} binding motif. These Ca^{+2} binding sites were called EF hand motif (Yang *et al*., 2003).

Calcium has pivotal part as a stimulus in different physiological as well as in environmental processes being most important second messenger in all organisms (Bush, 1995; Reddy *et al*., 2011). Elevation or declination of intracellular calcium level was sensed by four types of calcium sensor (**Fig.1**) which were CDPK (calcium-dependent protein kinases), Calmodulins, Calcineurin B-like proteins and Calmodulin-like proteins (Trewavas *et al*., 2002; Sanders *et al*., 2002). CDPK was the largest sub family of calcium sensor which located in plants as well as in protozoans (Ludwig *et al*., 2004; Ishino *et al*., 2006). The first one Ca^{+2} binding protein was CaM; most common & highly conserved in plants. The second type of Ca^{+2} binding protein was CDPK (calcium dependent protein kinase). Calcium dependent protein kinase consists of EF hand motif as well as catalytic domain.

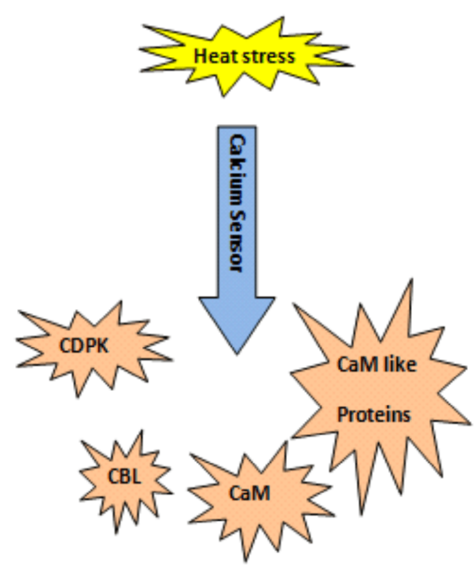

Fig. 1. Calcium sensors under stress

The third Ca^{+2} binding proteins were calcineurin B-like protein (CBL). All such CaM binding elements in turn regulate different growth and developmental process. The CBL also hold EF hand motif & this protein has plant specific Ca^{+2} sensors just like calcineurin B-subunit in animals (Yang *et al*., 2003).

Calcium responsive (sensor) proteins have EF-hands as well as a catalytic region. Movement & mechanisms of calcium sensor proteins was controlled by Ca^{+2} binding EF- hand motif. Among sensor responsive proteins Ca^{+2} –dependent protein kinase (CDPKs), Ca^{+2} or Ca^{+2} CaM-dependent protein kinases (CCaMKs), a few lipid as well as DNA binding proteins, transcriptional elements and some enzymes were included. Calcium sensor proteins encoded via variety of genes and their expression results owing to multiple abiotic stresses (Harper and Harmon, 2005). Application of ATP in Arabidopsis played central role in signaling of stress condition. ATP application intimately induces the calcium level to be increase inside the cytosol while raised calcium level results the activation of AtRBOHC which was responsible for the production of ROS (reactive oxygen species). The enlarged level of ROS induces the calcium intake which in turn stabilizes the AtRBOHC performance under heat stress (Demidchik *et al*., 2009). Expression of various CDPK (calcium dependent protein kinase), DEP (differentially expressed protein), a wide variety of heat shock proteins as well as accumulation of antioxidant enzymes played important role in regulation of lipid peroxidation (thermotolerance) phenomenon by preventing the amassing of H_2O_2 in wheat (Goswami *et al*., 2015).

CaM sub cellular localization

Calmodulin commonly proposed to be located in the vicinity of cytosol but it also present in the peroxisome, endoplasmic reticulum, and nucleus as well as in the matrix outside the intracellular fluid and its magnitude inside the cytosol is 5-40 µM (Zielinski, 1998; Ma *et al*., 1999; Yang and Poovaiah, 2002). In wheat, CaM consentration in stroma of the chloroplast is about 4.08 *u*g/ml mitochondria enclose about 3-7% CaM in matrix region. About -8% CaM is present in liver mitochondria and this CaM is bounded with the surface (Muto, 1982). It was implicated that the location of CaM depends upon proper maintenance of post-translational modifications. Petunia CaM53 granted the confirmation about the implication of calmodulin location. Petunia CaM53 location restricted to the plasma membrane only in the prenylated state whereas un-prenylated Petunia CaM53 present other than plasma membrane (Rodriguez *et al*., 2000).

Structure of calmodulin

CaM characterized by its special conserved configuration (Yang and Poovaiah, 2003). CaM was most common protein and acidic in nature. In plants, CaM consists of 148 amino acids. Analysis of alignment revealed that amino acid sequences among plants and animals were highly conserved and has about more than 70% identity (Reddy, 2001). Ca^{+2} binding domains consisted of 4 EF-hands which usually present in the form of pairs. These EF-hands were inserted in the two different circular areas of the N and C- terminal sites. The N & C-terminal regions were divided from each other with the help of a stiff middle helix **(Fig.2).** This helix was present in the form of dumbbell- shape (Strynadka *et al*., 1989; Snedden and Fromm, 1998; Zielinski, 1998).

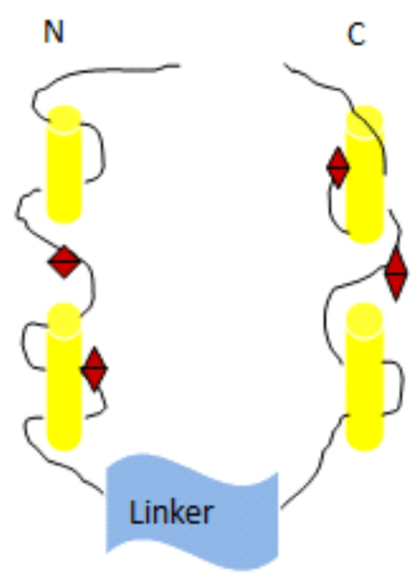

Fig. 2. Calmodulin basic structure

The CML proteins (OsCML4, OsCML5,OsCML6) contains a special cysteine molecule at the primary EF hand while on the other hand lysine molecule present in the OsCML4, OsCML5, OsCML7 OsCML10, OsCML17,OsCML18, and OsCML2. CaM genes of rice also have a high consentrarion of methionine molecule as well (Boonburapong and Buaboocha, 2007). Two major classes of proteins (sensor dependent & sensor responsive) have EF-hands. Sensor dependent inclusively characterized via integrating with other proteins; as these proteins lack functional region as well as enzymatic activity. Among three types of Ca^{+2} sensors proteins, the CaM-like proteins and calcineurin B-like proteins (CBL) belongs from sensor dependent proteins. CaM work collectively with different types of proteins while CBL work with the family of kinase only (Kudla *et al*., 2010). About 243 proteins were present in the rice genome containing EF-hand motif including 37 CaM encoding genes. High level of similarity was observed on the basis of amino acid sequences among the CaM and CML of Arabidopsis thaliana and rice. Three OsCaM genes in both crops carry information for similar type of proteins like CaM 2, 3, 4 and OsCaM 1-1, 1-2, 1-3 (Reddy, 2001).

Mode of action of CaM:

CaM is characterized as a small protein with size of 16-18 KD and consists of two globular domains named as N &C which were joined through a bendable linker. EF hands were attached with both of the globular domains facilitates the attachment of calcium (Chin and Means, 2000; Bouche *et al*., 2005). CaM has an acidic nature therefore it have ability to bind with histones, for better stimulation of a reaction high CaM concentrations required (Polya and Davies, 1982).

Electrostatic reactions have an imperative role in binding of CaM proteins with calcium which was different concept of calmodulin working mechanism under stress conditions (Onions *et al*., 2000).The activation process was termed as auto inhibition; the CaM binding regions were in parallel position (**Fig. 3. I)** or occupy by the enzyme's inhibitory site like CaM kinase (Chin and Means, 2000) .During the activation of oedeme factor which was well-known as anthrax adenylyl cyclase; four different elements of the oedema factor make a special structure in order to identify the particular CaM. Oedema factor binds with the CaM with help of these four elements **(Fig.3.II).** After binding, the helical regions of oedema factor rotate by which loop domains become stabilize and tempt the enzyme to be active and this mechanism falls under remodeling (Drum *et al.,* 2002). Dimmerization resulted owing to binding of two molecules of CaM with two Kb channel regions (potassium channel which are activated by Ca^{+2}) (**Fig. 3. III**).But, now it was proposed that only one molecule of CaM link with 2 peptides of petunia (glutamate decarboxlase) GAD. Dimmerization in petunia by means of single CaM revealed the existence of structural variations of CaM in plants (Yap *et al*., 2003).

CBK a special CaM binding kinase enzyme which control the expression of heat shock proteins via phosphorelation of transcriptional elements which in turn perform function as heat shock regulator (Liu *et al.,* 2007). Calcineurin are Calcium sensor proteins which induces their expression under heat shock. It is a unique serine- threonine type of protein having catalytic subunits (CAN and CNB) which provides special structure for CaM binding (Offenborni *et al*., 2015). The calmodulin/calcium dependent protein kinase (CCaMK) binds with cytosolic Ca^{+2} via CaM-binding domain, three EF-hand motifs and serine/threonine kinase domain (Gleason *et al*., 2006; Tirichine *et al*., 2006; Yang and Poovaiah, *et al*., 2007; Hayashi *et al*., 2010).

Calcium concentration responsible for the induction of several genes under heat shock condition (Braam, 1992; Polisensky and Braam, 1996). Different CaM and CaM related isoform express under heat stress in plants. Under the influence of such CaM genes the CGCGTT region of the promoter commonly known as RSRE (rapid stress-response element) become activated. This CGCGTT region also contain CAMT site which probably perform function in the defensive mechanism under stress (Walley *et al*., 2007; Walley and Dehesh, 2010; Reddy *et al*., 2011). CaM becomes activated in the presence of abscisic acid-responsive elements which were located in the form of CACGTG (Kaplan *et al*., 2006).

CaM binding proteins

Various special CaM binding proteins were analyzed and classified on the foundation of definite properties via novel molecular techniques (**Fig. 2**). About 50 diverse types of CaM binding proteins were reported in all plants (Reddy *et al*., 2002). In plants, about 50 enzymes as well as ion channels were controlled by CaM **(Table 2).** While various CaM modulated proteins are going to be increased and were characterized as Kinases, cytoskeleton proteins(adducing, caldesmon and spectrin), phosphodiesterase, protein phosphatase calcineurin, nitric oxide synthases, notably voltage-gated Ca2+ channels, adenylate cyclases 1 and 8 (Toutenhoofd and Strehler, 2000; Black *et al*.,2004; Bouche *et al*., 2005).

CaM binding proteins belongs to first class of proteins. First class of CaM binding proteins were named as plant-specific CaM-binding proteins. Auxin-responsive SAURs (Small auxin-up RNAs) and pollen-specific MPCBP(maize pollen calmodulin-binding protein) proteins belong to first class of CaM binding protein (Safadi *et al*., 2000). Sencond class of CaM binding proteins has much homology with that of animal's CaM binding proteins (**Fig.4**) However, in plants such proteins showed a few differences with respect to some extra CaM binding regions. The GAD, kinesin and catalase type of proteins belongs to 2^{nd} class of CaM binding proteins (Snedden and Fromm, 2001). Third type CaM binding proteins were reported by Bouche *et al*., 2002. CaM proteins were made up of similar subunits as possess by animals. The CGCG proteins also include in 3^{rd} class of CaM binding proteins. Plants enclose more proportion and unusual CaM binding proteins then from animals (Bouche *et al*., 2002).

The 13 CaM genes reported in tobacco were arranged

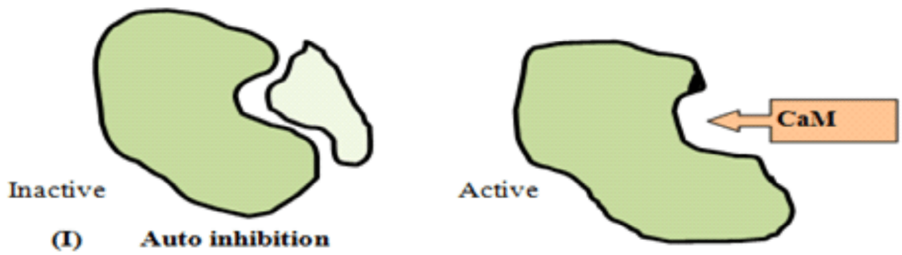

Fig. 3. Mod of action (auto inhibition)

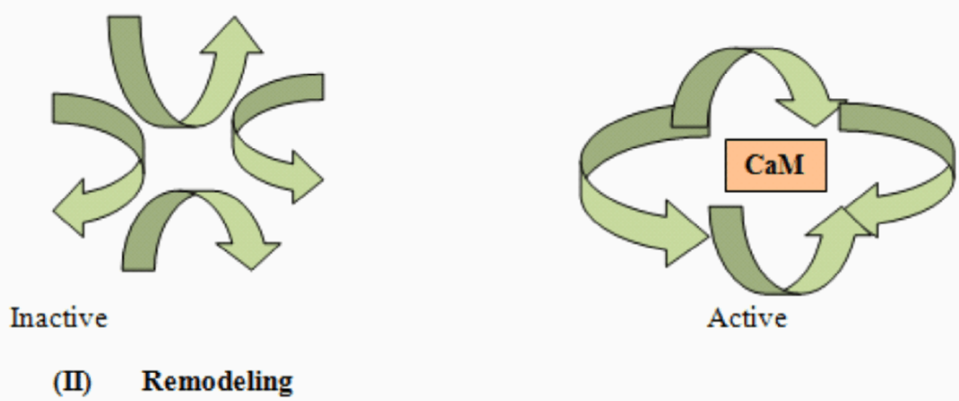

Fig. 3. Mode of action (Remodeling)

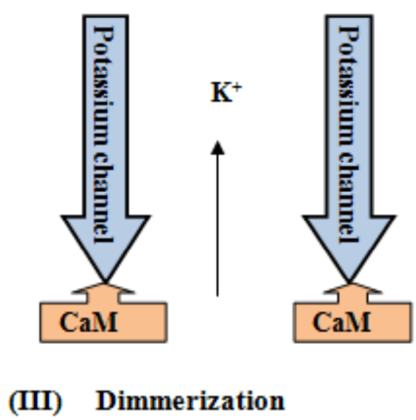

FIG. 3. Mode of action (Dimmerization)

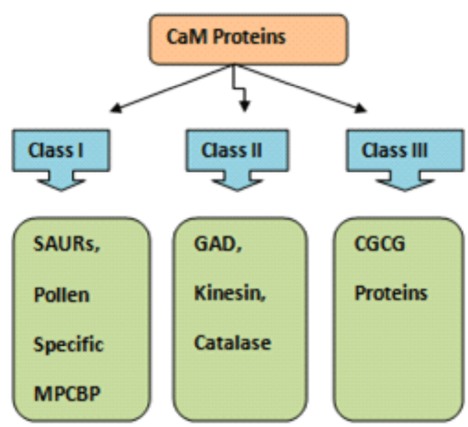

Fig. 4. Types of calmodulin

in three groups on the basis of similarity in amino acid sequences (**Table 1**). The expression of all the CaM binding proteins of tobacco induces owing to TMV (tobacco mosaic virus) via HR (hypersensitive Reaction) (Takabatake *et al*., 2007).

Cyclic nucleotide-gated non- elective cation channel proteins (CNGC) were ascertained in tobacco, barley & Arabidopsis. The cyclic nucleotide-gated non- elective cation channel proteins get hold of CaM-binding properties (Snedden and Fromm, 2001). Apyrase in pea holds the CaM binding characteristic. The function of Apyrase; protein linked with hydrolysis of nucleoside tri- and diphosphates. The pivotal role of apyrase in providing the xenotic resistance against insect pest. Apyrase in other crops also analyzed and ascertained that only a few number of Apyrases in Arabidopsis owned CaM binding properties (Steinebrunner *et al*., 2003). A special type of gene NtER (early ethylene-responsive gene) having imperative function in synthesis of calmodulin binding proteins under heat stress condition (Yang *et al*., 2000).

Table 1. Types of CaM binding proteins in tobacco

TypeI	TypeII	TypeIII
NtCaM1 NtCaM2	NtCaM3 NtCaM4 NtCaM5 NtCaM6 NtCaM7 NtCaM8 NtCaM9 NtCaM10 NtCaM11 NtCaM12	NtCaM13

NtER1gene as well as five other genes were reported in Arabidopsis. The expression of NtER1gene under stress conditions like, salt, wounding, temperature, and hormones (ethylene and abscisic acid) were analyzed. The induction of such genes resulted via signaling elements like salicylic acid, methyl jasmonate and H_2O_2. Entitlement of these six genes as *Arabidopsis thaliana* signal-responsive genes (AtSR1–6). The AtSR1 genes bind with the calmodulin under stress with the help of their specific binding elements. Binding elements enclose specific amphiphilic compounds; endow with binding sites (6 base pair CGCG elements) for calmodulin proteins. These AtSR1 genes have significant function in synthesis of calmodulin (Yang and Poovaiah, 2003). Stimulation of cngcs was analyzed owing to the binding with cyclic nucleotide proteins. Plant ligand gated nonselective cation channels include such diverse cngcs proteins. The ligand gated nonselective cation channels comprise a special CNBD (cyclic nucleotide binding domain) at the carboxyl end of the amino acids chain as the cngcs proteins located inside the cytoplasm. The cngc proteins also act as calmodulin binding regions. The relation among CaM and cyclic nucleotide during the activation of plant cngc channels was analyzed and explicated the presence of a special type of cngc (Atcngc2) in Arabidopsis thaliana. The activation of Atcngc2 results in the production of Atcngc2 CaMBD exposing peptide linkage among proteins (Atcngc2 CaMBD). Peptide linkage amid Atcngc2 and CaMBD depends on the accessibility of calcium concentration inside the cytosol (Hua *et al*., 2003).

CaM binding transcriptional factors

CaM binding transcriptional elements express owing to heat as well as cold stress and these CaM binding transcriptional factors play pivotal role in signal transductional pathways under stress conditions (Mitra, 2015). Calcium signals were modify in the form of transcriptional elements in the presence of CaM (Kudla *et al*., 2010). Six CaM binding transcriptional elements reported in *Arabidopsis thaliana*; all have CG-1 domain on N side which provide binding affinities with the CaM transcriptional elements as well as with ABREs (Abscisic acid-responsive elements). Whereas, C side of transcriptional elements only binds with CaM (Finkler *et al*., 2007).

Effects of CaM on special CaM binding transcriptional factors were explicated. CaM also directs the transcriptional enhancers by way of CaM kinases and phosphatase calcineurin. Many transcriptional

Table 2. CaM binding proteins in different crops:

Protein	Plant	Reference
GAD(Glutamate Decarboxylase)	Arabidopsis thaliana	Snedden and Fromm, 2001
Apyrase	Pea	Hsieh *et al*., 2000
Auxin-induced protein	Maiz	Yang and Poovaiah, 2000
AtSR1	Arabidopsis thaliana	Yang and Poovaiah, 2002
Nuclear protein PCBP	Potato	Safadi *et al*., 2000
Disease resistance gene(MLO)	Rice	Kim *et al*., 2002
Cyclic nucleotide gated cation channels (CNCG)	Tobacco	Leng *et al*., 2002
Vacuolar Ca+2-ATPase	Brassica	Malmstrom *et al*., 2000
Endoplasmic reticulum Ca+2-ATPase(AtACA2)	Arabidopsis thaliana	Hong *et al*., 1999
Plasma membrane calcium(SCA1) and ATPase	Soybean	Chung *et al*., 2000
AAA family CIP111	Arabidopsis thaliana	Zielinski, 2002
Kinesin-like protein	Arabidopsis thaliana	Reddy, 2001
Chimeric Ca+2/CaM-dependent protein kinase	Lily	Sathyanarayanan *et al*.,2000
Diacylglycerol kinase (LeCBDGK)	Tomato	Snedden and Blumwald, 2000
Pollen-specific protein (MPCBP)	Maiz	Safadi *et al*., 2000
Heat shock repressed protein TCP60	Tobacco	Snedden and Fromm, 2001
Chaperonin 10	Arabidopsis	Snedden and Fromm, 2001
CML43	Arabidopsis	Chiasson *et al*., 2005
APR134	Tomato	Chiasson *et al*., 2005

elements of bHLH group have ability to bind with CaM and this approach (CaM) manages their binding affinities with DNA regions (Onions *et al*., 2000). TGA3 (basic leucine zipper transcription element) played incredible role in boosting the binding properties with C or G box in the presence of CaM. Transcriptional factors of Arabidopsis classified into 58 groups. Among these groups some important CaM binding transcriptional elements were like M-type, MIKC, MYB, GRAS, CAMTA, Trihelix, bZIP, NAC, WRKY & CBP60 (Zhang *et al*., 2011).

A special type of DNA binding protein; belongs to CGCG group in plants. Great affinity of DNA at a specific CGCG-box with AtSR1 (transcriptional element of CGCG). The AtSR1 homologe comprise transcription enhancer region along with additional 6 CGCG genes. The induction of additional six genes under environmental and hormonal stimulus which clarify that CGCG genes perform key role during the heat stress period (Reddy *et al*., 2000). A novel type of CaM binding protein which consists on numerous well built PEST motifs in potato tubers. Harper reported another CaM binding protein homolog DRL of yeast TOT4 protein. The TOT4 actually was an extender element responsible for binding with RNA polymeraseII in yeast. The function of DRL is associated with meristem growth & organ development. CaM linked with Ion transporters, channels and membrane proteins (three different types of Ca^{+2}-ATPases). Among three types of Ca^{+2} ATPases one was ACA2 located in endoplasmic reticulum while remaining were ACA4 (vascular membrane) and ACA8 located in the plasma membrane (Harpers, 2001).

Induction of peptidyl prolyl isomerases coding cDNA from the FK506-protien family was analyzed under heat stress. The open reading frame of cDNA; comprise sequences for pep-tidyl prolyl isomerase. This pep-tidyl prolyl isomerase contains three domains of FKBP-12, tetratricopeptide domain and calmodulin-binding elements. The induction of a special type of wFKBP77 domain in wheat plants at 37^{O}C was reported and the comparison among heat-induced isoform; exposed that wFKBP77 have 84% similarity with wFKBP73 and 42% with that of human FKBP59. The wFKBP77 mRNA production was 14 times more at 37^{o}C then at the 25^{o}C. The assembly of wFKBP73 and wFKBP77 proteins provides the indication of heat stress just resembling the different types of heat shock proteins (Kurek *et al*., 1999).

Transcriptional elements which bounds with CaM worked positively as well as negatively in order to provide protection against biotic and abiotic stresses. Some CaM binding transcriptional elements of WRKY gene family involved in positive regulation at early stages of infection whereas same gene family showed opposite response at later stages of infection under pathogen attack (Reddy *et al*., 2011). CAMTAs (calmodulin binding transcriptional factors) played pivotal part in plant protection mechanism against biotic as well as abiotic stresses. Such calmodulin binding transcriptional factors are located inside the nucleus and their expression results owing to damage via stress. Some secondary messengers as well as phytohormones also play important role in the expression of such CaM binding transcriptional elements. Similarly ABA involved in the expression of CAMTA2 and CAMTA4 up to CAMTA6, while ethylene regulates the expression of CAMTA1, CAMTA3 AND CAMTA4. The methyl jasmonate (CAMTA1, CAMTA3), H_2O_2 (CAMTA2, CAMTA3 CAMTA4, CAMTA5, CAMTA6) and salicyclic acid involved in the activation of CAMTA2, CAMTA4, CAMTA6 respectively (Yang and Poovaiah, 2002; Galon *et al*., 2010; Reddy *et al*., 2011).

Functions of CaM

CaM performed its major function only in terms of protection against damages caused by heat stress (Liu *et al*., 2016). Malho *et al*., 2006 reported the assorted functions of CaM; it perform array of functions like, thigmotropism, cell division, cell elongation, photomorphogensis, cell polarity, cell differentiation, cytoplasmic streaming, gravitropism, plant defense and also played core function in stress responses. CaM also played a critical function in feedback of plants alongside drought, salt and water deficiency.

CPK (calmodulin proteins kinases) of wheat played a significant role in resistance against powdery mildew via CPK 1, 2, 3, 4, 7, 10, 12 and 15 (Li *et al*., 2008). CPK of grape vine involved in tolerance against salt stress (Dubrovinaa *et al*., 2013). The expression of OsCDPK (*Oryza sativa* calcium dependent protein kinases) especially OsCDPK7 and OsCDPK13 played significant contribution against cold, drought as well as salt stress (Komatsu *et al*., 2007).

The over expression of CPK4 in *Arabidopsis thaliana* enabled the plant to combat against increasing level of ABA during seedling growth, seed germination, uncontrolled stomatal opening and more above in drought stress (Jiang *et al*., 2013). Mainly CDPK played important role in abiotic stress via regulation of ABA and by limiting the accumulation of ROS (reactive oxygen species) (Das and Pandey, 2010; Asano *et al*., 2012). Expression of some unique CDPK reduces the seedling function in *Arabidopsis thaliana* and provides tolerance by giving the command for metabolite accumulation

(Franz *et al*., 2010). CaM genes and CaM proteins are said to be produce as a result of heat shock. A diverse type of CaM isoform AtCaM3 was present in *Arabidopsis thaliana*. Heat shock factors like AtHSFA were generally induce under AtCaM3 by regulating the activities of AtCBK3 (CaM binding protein kinase) and AtPP7 (protein phosphatase). These heat shock factors played remarkable role in heat shock transfer system (Zhou *et al*., 2009).

Two special CDPK isoforms (AtCPK3 and AtCPK4) which localized in the nucleus and cytosol were repoted in Arabidopsis. Extraction of a special type of CDPK from groundnut; enclose NLS (nuclear localization signal) sequence in the domain area. NLS intimately involved in translocation of CDPK towards nucleus under osmotic stress. A close association of CDPK with the DNA binding proteins was explicated and both involved in scheming the gene expression (Raichaudhuri *et al*., 2006).

CaM has imperative function as transducers for carrying out heat shock signals. An experiment was conducted to analyze the pivotal role of CaM via the three plants of Arabidopsis AtCaM2, AtCaM3 and AtCaM4 respectively. The end results of heat hardening test among individual mutant plants and wild type revealed refusal possessions in their capability to defend against heat stress. A turn down in thermotolrance ability of AtCaM3 mutant at 45^{o}C for 50 min was analyzed and its thermotolrance capability rose by over expression of AtCaM3 mutant genes. The genetic basis of thermotolrance analyzed via real-time quantitative reverse transcription-polymerase chain reaction, Western-blot and electrophoretic mobility-shift assay; exposing the up-regulation of AtCaM3 genes and down regulation in the transgenic mutant plants (Zhang *et al*., 2009).

Oxidative stress resulted owing to continuous exposure of high temperature. The evaluation of Calcium, ethylene, salicylic acid (SA) and abscisic acid (ABA) effects leading to the damages caused by oxidative stress in arabidopsis. Thiobarbituric acid induction intimately raised under high temperature have alarming effect on plant growth. Resistance against oxidative stress induced via mounting the level of calmodulin, calcium, ABA and SA, 1-aminocyclopropane-1-carboxylic acid. Experiments were carried out on mutant plants of Arabidopsis like etr-1 (ir-responsive to ethylene), abi-1 (ir- responsive to ABA) and a transgenic plant having nahG gene. The comparison analysis on the increasing intensity of calcium/CaM performed. The extent of calcium intensity was supplementary in the resistant plants indicating chief role of calcium signals in protection against heat stress ((Larkindale and Knight, 2002).

The significant utility of calmodulin isoforms for resistance under low as well as high temperature was evaluated via 7 calmodulin genes of Arabidopsis. Increased level of GABA observed at both low as well as high temperature stress in the treated and controlled plants of mutant and wild plants. CAM5 and CAM6 genes were responsible for seed germination as well as in avoidance against oxidative stress in the cam5-4 and cam6-1 mutants. At low temperature treatment, the level of GABA production was high which offer the indication that calmodulin have important role in stimulation of GAD (glutamate decarboxylase) as well as also in regulation of GAD along with the other factors also like pH and distribution of metabolites (AL-Quraan *et al*., 2012).

The significant contribution of calmodulin dependent protein kinases (CCaMK) explicated in brassinosteroids (BR) based tolerance against abiotic stress. Elevation in Calcium level in the protoplast observed after treatment with brassinosteroids owing to expression of the genes responsible for the activation of CCaMK in *Zea mays* (*Yan et al*., 2015).

In wheat seedlings, by mounting the concentration of calcium the production of CaM mRNA as well as proteins also goes to highest level at hardening temperature (37^{o}C). The escalating $CaCl_2$ concentration has the positive effect on the amount of synthesis of hsp26 as well as hsp70 genes and by the addition of CaM anti agents like the calcium ion channel blockers LaCl3, calcium ion chelator EGTA, the amount of synthesis of hsp26 and hsp70 reduce. A special type of calmodulin gene CaM1-2 was produced under heat shock treatment which provide the indication of heat stress in wheat plants and stimulate the production of hsp70 and hsp26 (Liu *et al*., 2003).

CaM takes part in ABA signal transduction during drought condition specifically, when plants exposed with PEG strain. ABA assembly draws a parallel relation with the concentration of Ca^{+2} inside the cytosol. The hyper polarization of membrane of guard cell also results owing to escalating level of cytosolic Ca^{+2}. Whereas the intensity of cytosolic Ca^{+2} rise due to the application of ABA (Li *et al*., 2002).

CaM 53 has pivotal function in petunia, an unusual kind of CaM which was in prenylated structure accredited as CaM53 protein. CaM 53 was perceptive by the sugar contents in the cell. When sugar deficit condition occour in the cell then un-prenylated CaM53 moved towards nucleus and perform imperative function; Ca^{+2} sensing channel to find the sugar status in the plant cell (Rodriguez-Concepcion *et al*., 2000). (Rodri *et al*., 1999).

CaM responsible for the activation of glutamate as well as for GABA utilization in order to sustain the growth of plants. The production of GABA (y-aminobutyrate) and carbon dioxide as the of consequence decaroxylation under the control of the GAD (Glutamate decarboxylase). In transgenic tobacco, an extraordinary type of mutant GAD present which was scarce in ability to bind with calmodulin. Some malformations were observed like short stem due to stumpy level of glutamate and elevated level of GABA. The mutant and wild type of tobacco plants were evaluated and observed that EGTA as well as the CaM antagonist trifluoperazine introverted the standard activity of GAD (Baum *et al*., 1996).

CONCLUSION

Calmodulin signaling pathways acknowledged a huge importance in the last few years owing to its great significance in signal transductional pathways; in order to provide tolerance against biotic as well as abiotic environmental stresses. Calmodulin intimately present in plants and animals being a multifunctional conserved protein. Calmodulin consist of many diverse types of proteins and transcriptional factors which need to be more elaborate particularly in terms of site and crop as well in order to meet the future demands to develop tolerant crop varieties. Potentials to achieve the target goals depend upon the precise characterization of the calmodulin sub-families (amount and location) and mode of activation mechanism under specific growth conditions. Available genomic studies in the different crops could be use as a pivotal tool to hasten the research programmes.

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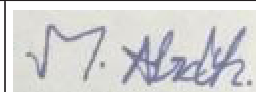
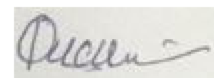
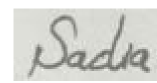
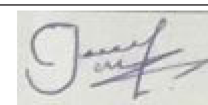
3.	Muhammad Zulkiffal	Helped in write-up the manuscript	
4.	Muhammad Abdullah	Formated the paper	
5.	Qamar Shakil	Proof read the manuscript	
6.	Sadia Kaukab	Compiled the data	
7.	Javed Iqbal	Collected the reivew of literature and provided the technical guidance	
8.	Sajida Habib	Reviewed the manuscript	
9.	Sundas Shahzad	Helped in data collection	
10	Ali Bakhash	Helped in figure work