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A critical review on: Significance of floral homeotic *APETALA2* gene in plant system

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ABSTRACT

Flower development is a complex procedure regulated by combinatorial factors, such as transcription factors, peptides, hormones, and small RNAs. One of the important gene determining the floral structure and floral meristem is *APETALA2* (*AP2*) which belongs to a large family of transcription factors. *AP2* contributes stochastically in signaling pathway in flower development and in various bioactive components synthesis. The presence of *GbAP2* transcripts in live fossil *Ginkgo biloba* leaves and female strobili tissue showed that *GbAP2* might be involved directly in leaf and female strobili development, whereas it may possible that *GbAP2* indirectly involved in synthesis of bioactive compounds such as flavonoids, terpenoids, ginkgolides, and organic acids. Gingko or Ginkgo *biloba* is among the most popular plant used in United States. Bioactive compounds isolated from the ginkgo plant are thought to exhibit as antioxidant and antiplatelet activity. Due to the pleotropic nature of *AP2*, it is involved in various tissues such as regulating in floral pattern, stem cell maintenance, floral organ identity, floral meristem, leaves, development of stems, and seed development. *AP2* also regulate number of downstream genes but its own expression is negatively regulated at translational or post-translational levels by *miRNA172* which is a small RNA (22 bp) and binds to complementary region of *AP2* transcript. Mutation in *AP2* showed increases in seed size and seed mass, this property of *AP2* could be used in medicinal plant to enhance the valuable product. Since *AP2* is engaged in various pathways it is essential to compile the functioning in the form of presented manuscript, which discusses the structure and functioning of *AP2*. We likewise explain how *AP2* involved in various expressions and its regulatory mechanism, especially in the plant.

INTRODUCTION

According to the ABCDE model, *APETALA2 (AP2)* gene belongs to Class A gene category primary in *Arabidopsis*, which is responsible for sepal and petal development. It is one of the significant genes responsible to determine the identity of four major floral organs. Any type of alteration in *AP2* gene sequence could cause severe developmental defects, especially homeotic floral organ distortion where petals are replaced by carpels or carpelloids and petals to stamens. In the case of weak *AP2* mutant plant, the leaves were replaced by sepals and petals by antheroid, whereas in strong *AP2* mutant plant, carpelloid-like structures were formed in place of sepals, petals are demised, and the stamen number is reduced. In recent years, scientists pay more focus on RNA interference (RNAi) to characterize the gene function in model and cultivated plants. RNAi is a technique of gene editing which is based on post-transcriptional gene silencing in eukaryotes to modify the phenotypes. Various small interfering RNAs (siRNAs) and micro RNAs (miRNAs) molecules are characterized which involved in gene regulation in plants system at transcriptional as well as translational levels. A *miR172,* 22 bp in length showing similarity with the transcript of a floral homeotic gene *AP2* and regulates its expression pleiotropically. The accumulation of enhanced *miR172* showing the same floral defects as shown in loss-of-function *AP2* mutants. In 2005, two scientists Axtell and Bartel were reported that *miR172* regulates in flowering plants, ferns, and gymnosperms except lycopods and moss (Axtell and Bartel, 2005). Recently in monocotyledons, such as maize, barley, and rice have shown the functioning of *miR172* in differential stage

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transition in flower development (Lauter *et al*., 2005; Nair *et al*., 2010; Zhu and Helliwell, 2011).

During flower development, a cassette of regulatory genes has been revealed, which works collectively to regulate the floral meristem and floral organogenesis. The identification of floral organ is regulating under the influence of consistent homeotic genes. Homeotic genes are the regulatory genes that direct the position and development of particular body segments or structures. *AP2* is one of the important homeotic gene, which governs the determination of floral meristem and floral development. To differentiate the flowering genes, the ABC model was designed which further modified as the ABCDE model of flower development (Colombo *et al*., 1995; Haughn and Somerville, 1988; Pelaz *et al*., 2000). Various combinatorial interaction of homeotic genes involved in flower development. Floral genes based on the ABCDE model are categorized in five different classes, such as A, B, C, D, and E (Bowman *et al*., 1991). Class A genes (*AP1, SQUA*, and *AP2*) control sepal development in whorl 1. Class A genes overlap with Class B genes (*PI* and *AP3*) to promote petal formation in whorl 2. Class B and Class C (*AG*) genes involved in stamen formation in whorl 3, while Class C genes alone promote gynoecium development in whorl 4 (Fig. 1) To sustain the floral structure, Class A (*AP2)* and Class C (*AG)* genes act mutually but in antagonistic fashion. Thus, *AP2* and *AG* gene transcription spatially restricted by the first two whorls and last two whorls, respectively.

AP2 is one of the significant genes known from the decades for governing floral meristematic and floral organ tissue determination (Bowman *et al*., 1989; 1993; Huala and Sussex 1992; Irish and Sussex 1990; Komaki *et al*., 1988; Kunst *et al*., 1989; Schultz and Haughn 1993; Shannon and Meekswagner 1993). The presence of *AP2* transcripts in floral (sepal, petal, anther, ovule, and silique) as well as in vegetative tissues (root, leaf, shoot, and stem) showed the importance of *AP2* gene in reproductive and vegetative tissues (Sharma *et al*., 2017). Since high level of *AP2* protein was observed in vegetative tissue, but still there is no report on any defects in stem or leaf development. Consequently, loss-of-function completely distorts the structure of flower but leaf and root structure seems healthy (Bowman *et al*., 1989). Besides this, it is hypothesized the *AP2* function in stem and leaf may be due to the genetically redundancy in *Arabidopsis* (Okamuro 1997).

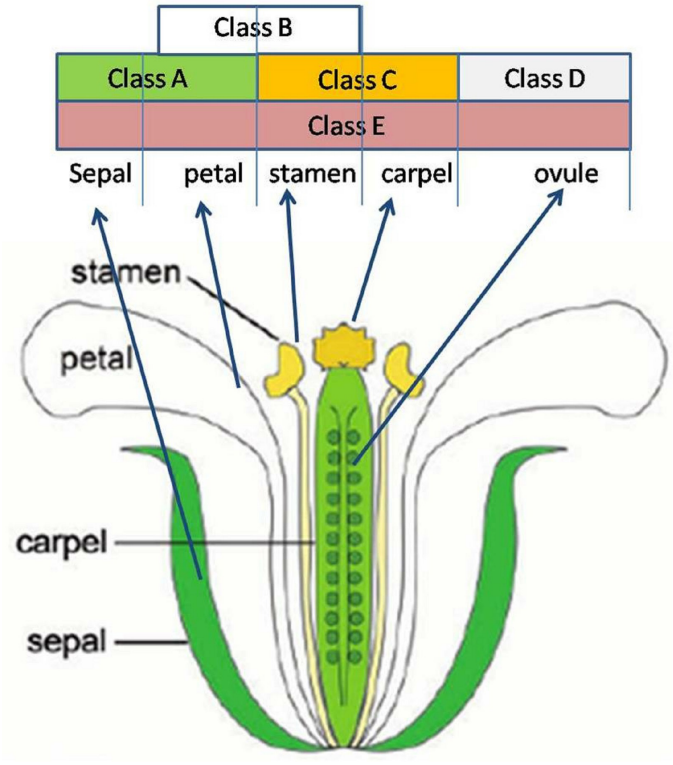

Figure 1. Representation of class A, B, C, D, and E genes with their respective tissue in model flower (modified from Krizek and Fletcher, 2005).

CLASSIFICATION AND STRUCTURAL ORGANIZATION OF *AP2* GENE

Floral homeotic *AP2* gene belongs to *APETALA2/ Ethylene Responsive Factor* super family. The genes belong to this family are involved in primary and secondary metabolism regulation, growth, and development. It also involved in abiotic responses. *AP2* itself is a transcription factor which represents 147, 157, 201, and 148 targets in *Arabidopsis*, rice, wheat, and soya bean, respectively (Nakano *et al*., 2006; Sahu *et al*., 2016; Yant *et al*., 2010; Zhang *et al*., 2008). Respective targets have been divided into three different classes based on the number of *AP2* domains. Class I encodes a functional protein having two *AP2* domains, for example *AP2* (Jofuku *et al*., 1994), *AINTEGUMENTA* (ANT) (Elliott *et al*., 1996; Klucher *et al*., 1996), *Glossy15* (*GL15*) (Moose and Sisco 1996), *SlAP2a* (Karlova *et al*., 2011), *SHAT1*, and *BniAP2*. Class II encodes a functional protein having single *AP2* domain, for example Ethylene-Responsive-element-binding-Factor (*ERFs)* (Ohme-Takagi and Shinshi 1995), It is a mutation caused by transposon element (*TINY)* (Wilson *et al*., 1996), *AtEBP* (Buttner and Singh 1997), and *ABI4* (Finkelstein *et al*., 1998) and a Class III includes Related to ABI3/VP (*RAV)* (Kagaya *et al*., 1999) encodes a protein having one *AP2* associated with B3 DNA-binding domain (Giraudat *et al*., 1992). Some additional sequence conserved in plants genome belonging to the *AP2/ Ethylene-Responsive-element-binding-Factor (ERF)* family known as soloist (Licausi *et al*., 2010; Nakano *et al*., 2006; Zhuang *et al*., 2008).

Since 1994, it is known that transcription start site (TSS) of *AP2* is positioned at 263 bp upstream to the start codon (Jofuku *et al*., 1994). Recently, it is confirmed that *AP2* having multi-TSS site responsible for gene expression (Sharma *et al*., 2017). *AP2* is regulated by nearly 7.5 Kb flanking region located at fifth chromosome in model plant (*Arabidopsis*) with gene id: *AT4G36920*. The structure of *AP2* gene comprised 10 exons and 9 introns with a transcript ranges from 1,300 to 1,500 bp (Fig. 2). *AP2* gene comprised two *AP2* domains, which are essential for *AP2* function. Each *AP2* domain is comprised 68 amino acids, which is evolutionary conserved in plants as *AP2*-like proteins. There were two conserved sequence box within each *AP2* domain.

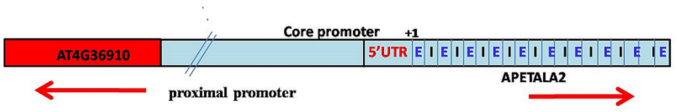

Figure 2. Structure of *AP2* gene with 10 exon–9 intron boundaries with intergenic region and adjacent gene (AT4G36910) in reverse orientation.

The first motif comprised 19–22 basic amino acids and a conserved Tyrosine-Arginine-Glycine motif (Basic amino acids) (YRG) amino acids motif whereas the second motif comprised 42–43 amino acids with 18 amino acids as a core region that forms an amphipathic α-helix, which is essential for *AP2* functioning (Allen *et al*., 1998; Jofuku *et al*., 1994). The *AP2*-like proteins are also characterized by the presence of linker region that is comprised 25–26 highly conserved amino acids and lies between the two *AP2* domains (Allen *et al*., 1998; Jofuku *et al*., 1994).

It was considered that *AP2* domain presents within plant system only (Riechmann and Myerowitz, 1998) but computer-assisted study search that Histidine and Asparagine rich Asparagine-Histidines domain (*HNH)-AP2* class of homing endonucleases were also present in Cyanobacterium (*Trichodesmium erythraeum*) and virus genome (Enterobacteria phage and Bacteriophage Felix) suggesting the horizontal transfer of Asparagine- Histidines domain (*HNH)-AP2* from bacteria to plants. Furthermore, intron-less *AP2*/ Ethylene-Responsive-element-binding-Factor (*ERF)* supports the horizontal gene transfer responsible for *AP2* domain evolved from prokaryotes (Magnani *et al*., 2004; Wessler, 2005; Wuitschick *et al*., 2004).

AP2 itself regulate various downstream gene expression since it belongs to a super family of transcription factors (Yant *et al*., 2010). It suppresses the transcription of *SOC1* and *AGAMOUS* gene expression and promotes the floral repressor *AGL15* and *miR156* expression (Adamczyk et al., 2007, Wu *et al*., 2009). Moreover, *AP2* is also involved at the level of translational regulation by *miR172* (Aukerman and Sakai 2003). *AP2* act pleiotropically and its transcripts have been detected in *Arabidopsis* in several developmental stages of reproductive as well as in vegetative tissue (Jofuku *et al*., 1994; Kinoshita *et al*., 2004; Ripolle *et al*., 2011; Sharma *et al*., 2017). Hybridization experiments also showed the presence of *AP2* transcripts in various tissues, such as leaf, shoot, stem, root, floral meristem, sepals, petals, and seeds (Wollmann *et al*., 2010). An eFP Browser, online software was developed to detect the microarray studies and revealed the *AP2* distribution from vegetative tissue to reproductive tissue (Winter *et al*., 2007) (Fig. 3a and b). *SHAT1* is an *AP2*-like gene which expresses in abscission zone during spikelet development in rice. In addition to this, *Cleistogamy1* (*Cly1*) is an important gene in barley which expresses itself in spike to promotes cleistogamy (Nair *et al*., 2010; Wang *et al*., 2015). *Cly1* is a member of *AP2* gene family, which contains two *AP2* domains and miR172 complementary target sequences (Kim *et al*., 2006). *AP2* gene isolated from several crop showing sequence similarity as shown in Figure 4. In *Arabidopsis,* a single copy is enough for floral development and floral specification; however, it is known in Antirrhinum (Keck *et al*., 2003);

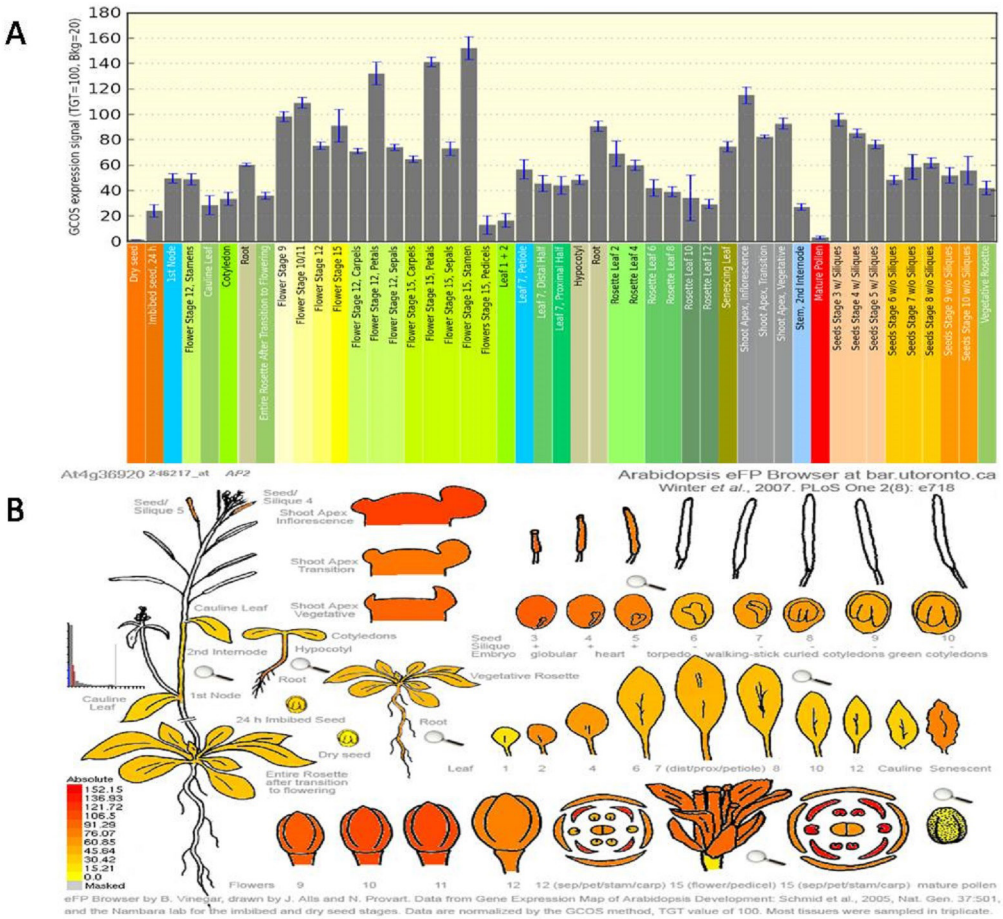

Figure 3. (a) Representation of *AP2* expression in vegetative and reproductive tissues in *Arabidopsis* using eFP Browser online software (b) Representation of level of *AP2* expression in different tissue under different stages of *Arabidopsis* using *in silico*.

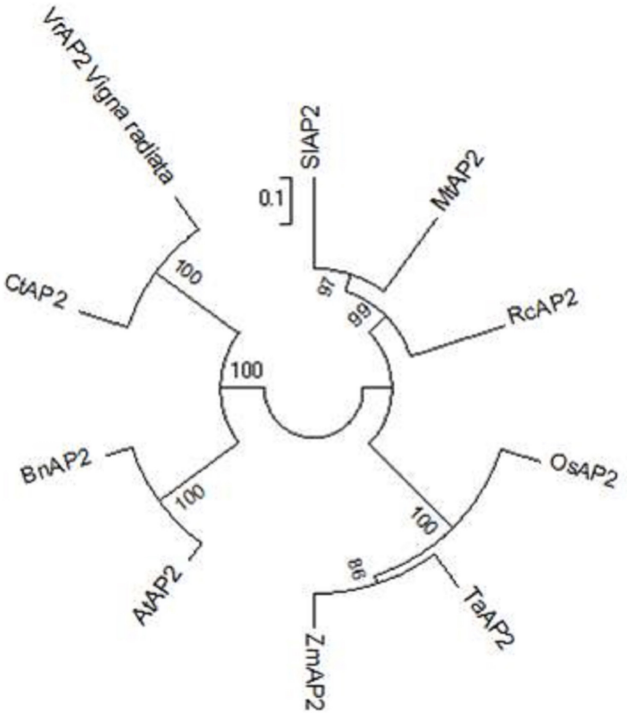

Figure 4. Phylogenetic tree showing relationship of different *AP2* gene family members (At-Arabidopsis thaliana Bn-Brassica nigra Zm-Zea mays Ta-Triticum Aestivum Os- Oriza sativum Sl- solenum lycopercicum Vr-Vigna radiata Rc Ricinus communis) using MEGA 6.0.

Petunia hybrida (Maes *et al*., 2001); *Brassica rapa* (Liu *et al*., 2013) showing two AP2-like genes. *Brassica juncea* which is a tetraploid having three copies of *AP2* (Sharma *et al*., 2018) and tomato (Karlova *et al*., 2011) having five *AP2* copies might be required for flower development.

SIGNIFICANT VALUE OF *AP2* GENE IN PLANT SYSTEM

Several reports are available which reveals that *AP2* play significant role in gene regulation (Jofuku *et al*., 1994; Ripoll *et al*., 2011). Due to the presence of cis-regulatory elements in both directions it is examined that the *AP2* promoter transcribes the genes in both directions hence it is a bidirectional promoter which controls the pleotropic expression in plant developmental biology (Sharma *et al*., 2017). Moreover, the expression of *AP2* is negatively regulated via *miR172*, which is nearly 22 bp in length, highly conserved, and non-coding RNA. Due to sequence-complementary, *miR172* can easily bind to their targets site on *AP2* transcript outside the *AP2* domains. Thus, *AP2* expression is regulated by *miR172* through one of two or both mechanisms (translation inhibition and transcript cleavage) (Chen, 2004; Zhao *et al*., 2007). In *Arabidopsis*, the binding of *miR172* to *AP2* transcripts suppresses its expression (Chen, 2004; Zhu and Helliwell, 2011), whereas in barley *miR172* digest the *AP2* transcripts for negative regulation (Houston *et al*., 2013). The interaction between *miR172* and *AP2* transcripts shows that the *miR172* regulate *AP2* functioning in common bean or *Phaseolus vulgaris* (Nova-Franco *et al*., 2015). Some of the genetic modifications within *miR172* sequences revealed that *AP2-miR172* interaction plays an important role in regulating flowering time in gloxinia plants (Li *et al*., 2019). Expression of

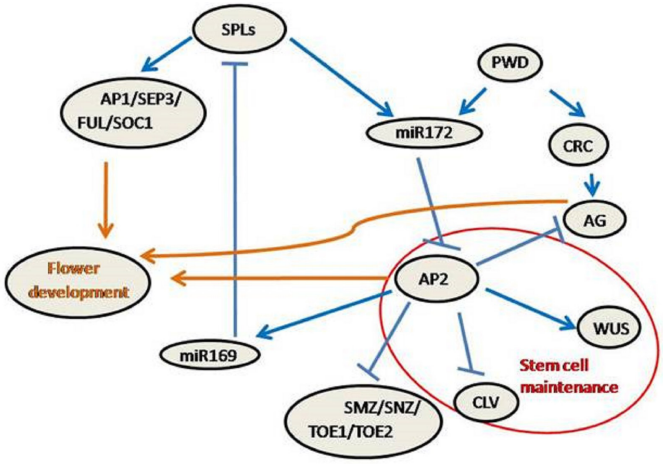

Figure 5. Gene network highlighting the regulatory pathway of *AP2* during stem cell maintenance and flower development.

class A gene, such as *AP2* transcripts, is reduced in transgenics by over-expression of *miR172*, which affects apple fruit weight (Yao *et al*., 2016). Hence, *AP2* shows stochastic interaction between *miR172-AP2*, which is critical for proper floral differentiation and development.

AP2 confers the place and timing of floral organs as well as floral meristem and specification development in plants. It directly promotes the Class C WUSCHEL gene (*WUS)* gene with down regulating the CLAVATA (*CLV)* gene to maintain the stem cell niche in floral meristem. However, *WUS* directly promotes the CLAVATA (*CLV)* gene and CLAVATA (*CLV)* represses the activity of *WUS* for feedback regulation as shown in Figure 5 (Lenhard *et al*., 2001; Wurschum *et al*., 2006). It also observed that ap2 mutant lines induced more hexose/sucrose ratios in seeds as compared with wild-type seeds (Ohto *et al*., 2005). Similarity, loss-of-function of *BnAP2* gene showed defects in shape, structure, development, and size of seeds in *Brassica nigra* (Yan *et al*., 2012) and *RcAP2* gene in *Rosa Chinensis* regulates the number of rose petals (Han *et al*., 2018). Different splice variant of *HvAP2* revealed the differences in size and shape of barley inflorescence (Houston *et al*., 2013). Hence, *AP2* is an essential gene in length of internode in inflorescence, seed size, and seed mass. However, it could be one of the important genes, which regulate the cascade pathway in floral development in medicinal plant. *AP2* transcript in *Arabidopsis* distorts the developmental changes, such as petals to carpels transition and petals to stamens transition in the outer two whorls of flower structure (Table 1). Furthermore, *AP2* regulates replum formation during developing fruit in *Arabidopsis* (Ripoll *et al*., 2011). *SiAP2*, an ortholog of *AP2* in tomato involved in ethylene biosynthetic process to confers the fruit ripening (Chung *et al*., 2010; Rumyana *et al*., 2011).

Ongoing investigation uncovers that the density of grains in barley inflorescence changes as the interaction between alleles of HvAP2 transcript and miR172 differs (Houston *et al*., 2013). Thus, the variation in HvAP2 transcripts and miR172 interaction showed that both are involved in the regulation of size and shape of barley inflorescence. Similarly, in *Phaseolus vulgaris*, legume-rhizobia nitrogen-fixing symbiosis system is also influenced by *miRNA172-AP2-1* complex (Nova-Franco *et al*., 2015).

Table 1. *AP2* mutations observed in different whorl of flower in *Arabidopsis*.

Mutants	Whorl (1) Sepal	Whorl (2) petal	Whorl (3) stamen	Whorl (4) carpel	Reference
***AP2*-1**	Sepal to leaf	Petal to stamen Staminoid petal	Normal	Normal	Bowman *et al*.,1989
***AP2*-2**	Sepal to leaf, carpel and missing	Petal conver ts to stamen or stamenoid petal/missing	Stamen reduced in number	Carpel normal sometimes unfused	Bowman *et al*.,1991
***AP2*-5**	Median sepal to carpel	Petal to stamen	Normal	Normal	Kunst *et al*., 1989
***AP2*-6**	Perianth organ to carpel, perianth organ variably fused	Stamenoid structure fused to perianth	No. of stamen reduced to 3 or 4	Normal	Kunst *et al*., 1989
***AP2*-7**	Perianth reduced to 2-4 organs, median sepal to carpel, lateral sepals reduced/ absent	Lack petals	Stamen fused to perianth, no. of stamen reduced to 1–3	Incomplete fusion of carpels	Kunst *et al*., 1989
***AP2*-8**	Large sepal	Reduced petal	-	-	Bowman *et al*., 1991
***AP2*-9**	Large sepal	Reduced petal/no organ found	Mostly unoccupied	Affected	Bowman *et al*., 1991
***AP2*-11**	Sepal to carpeloid like organ	Petal fails to develop	Number of stamen reduced	Reduced in number	Ohto *et al*., 2005

IMPORTANCE OF *AP2* GENE IN CROP IMPROVEMENT

AP2/ Ethylene-Responsive-element-binding-Factor (ERF) is a super known family, which regulates stress signaling, floral meristem, and floral developmental genes. In rice, over-expression of *OsAP37* and *OsERF71* genes showed more tolerance against drought, which provides more seed yield (Lee *et al*., 2016; Oh *et al*., 2009). OsERF71 is an important gene, which further activates various stress responsive genes, and lignin biosynthesis associated genes causing changes in structure of root. In addition to this, another important *AP2* gene (*EjAP2-1)* characterized from *Eriobotrya japonica* regulates fruit lignification, which is induced by chilling injury (Zeng *et al*., 2015). Due to these biotic and abiotic environmental factors, productivity of crop is severely affected. Over the last decade, it was observed that the *AP2* candidates play an important role in nitrogen use efficiency (NUE) and plant response toward various abiotic factors. Sixteen *AP2* family members were reported as nitrogen deficient responsive genes, which expressed in roots and leaf tissue of rice (Obertello *et al*., 2015; Yang *et al*., 2015). Similarly, finding of more nitrogen responsive genes could be beneficial for biological nitrogen fixation in cereal crops using available sequenced databases. NUE depends upon capability of nitrogen uptake by healthy plants under normal condition, which are utilized by the plant for their optimum growth and development (Bi *et al*., 2009). Due to various factors, the NUE may vary in crop to crop or within the same crop. Furthermore, the stochastic pathways behind nitrogen deficient and nitrogen induced genes may improve the NUE and decreases the unnecessary use of synthetic nitrogen fertilizers for sustainable agriculture.

PHARMACEUTICAL VALUE OF *AP2*

AP2 is a well-known gene for its pleotropic expression in vegetative as well as in reproductive tissues in plant system (Sharma *et al*., 2017). It was found that *AP2* contributes stochastically in signaling pathway of various bioactive compounds synthesis, which has huge importance in pharmaceutical industry (Phukan et al., 2017; Udomsom *et al*., 2016; Xu *et al*., 2016). Total 171 *AP2* members were involved in biosynthesis of bioactive compounds (tanshinone and phenolic acid) characterized from *Salvia miltiorrhiza* which is used in the treatment of cardiovascular disease in Asia, United States, and several European countries and have more pharmaceutical values. Moreover, the medicine exhibits many other activities such as neuroprotective, anti-inflammatory, antioxidant, and strong antidementia (Ji *et al*., 2016; Xu *et al*., 2016). *AP2* transcription factors from *Ophiorrhiza pumila* also regulating camptothecin alkaloid, which is used as an initiator in the synthesis of chemotherapeutic drugs (Udomsom *et al*., 2016). In *Artemisia annua*, *AP2/ERF* transcription factor family were also involved in artimisinin and artemisinic acids biosynthesis, which is commonly used in antimalarial drug and further explored for antiviral, anticancerous and antischistosomal drugs (Afrin *et al*., 2015). In tobacco and *Catharanthus roseus*, one of the *AP2/ ERF* family members (GLYCOALKALOID METABOLISM 9) was involved in regulation of toxic alkaloid production which is considered as antinutritional compounds (Cárdenas *et al*., 2016).

In addition to this, *AP2* mutant showed rapid endosperm growth (Zhang *et al*., 2018), increase in seed size, and seed mass (Ohto *et al*., 2009), this property of *AP2* could be used in medicinal plant using genetic engineering to enhance the valuable product. The novel approach may prove to be beneficial to enhance the inflorescence, seed, and oil production of pharmaceutical important plants.

CONCLUSION

AP2 plays a pivotal role in gene expression regulation of many plant developmental processes. Recently, *miR172-AP2* complex is revealed as an essential regulator in nitrogen-fixing symbiosis and nodulation in legumes. The study could reveal new opportunities in biological nitrogen fixation in cereal crops, which may reduce the gradual use of synthetic nitrogen in agriculture system and improve the NUE. Since the *AP2* influences the seed mass as well as seed size, it could directly control seed mass and seed size and may prove to be beneficial for oil plants and cereals for more inflorescence. Moreover, *AP2* regulate signaling pathway in biosynthesis of tanshinone and phenolic, which is a traditional Chinese medicine and have high pharmaceutical values. During these stochastic processes, several factors are unclear. It seems highly probable that these regulators should further empirically studied to understand the whole processing.

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