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Research review paper

Role of transgenic plants in agriculture and biopharming

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ABSTRACT

At present, environmental degradation and the consistently growing population are two main problems on the planet earth. Fulfilling the needs of this growing population is quite difficult from the limited arable land available on the globe. Although there are legal, social and political barriers to the utilization of biotechnology, advances in this field have substantially improved agriculture and human life to a great extent. One of the vital tools of biotechnology is genetic engineering (GE) which is used to modify plants, animals and microorganisms according to desired needs. In fact, genetic engineering facilitates the transfer of desired characteristics into other plants which is not possible through conventional plant breeding. A variety of crops have been engineered for enhanced resistance to a multitude of stresses such as herbicides, insecticides, viruses and a combination of biotic and abiotic stresses in different crops including rice, mustard, maize, potato, tomato, etc. Apart from the use of GE in agriculture, it is being extensively employed to modify the plants for enhanced production of vaccines, hormones, etc. Vaccines against certain diseases are certainly available in the market, but most of them are very costly. Developing countries cannot afford the disease control through such cost-intensive vaccines. Alternatively, efforts are being made to produce edible vaccines which are cheap and have many advantages over the commercialized vaccines. Transgenic plants generated for this purpose are capable of expressing recombinant proteins including viral and bacterial antigens and antibodies. Common food plants like banana, tomato, rice, carrot, etc. have been used to produce vaccines against certain diseases like hepatitis B, cholera, HIV, etc. Thus, the up- and down-regulation of desired genes which are used for the modification of plants have a marked role in the improvement of genetic crops. In this review, we have comprehensively discussed the role of genetic engineering in generating transgenic lines/cultivars of different crops with improved nutrient quality, biofuel production, enhanced production of vaccines and antibodies, increased resistance against insects, herbicides, diseases and abiotic stresses as well as the safety measures for their commercialization.

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1. Introduction

Environmental stresses, population explosion and food shortage have caused serious problems to mankind on the globe. The world population is increasing alarmingly and is projected to reach 8.5 billion by 2025. To fulfill the food demand of every individual from limited natural resources is difficult. This, factor has resulted in food deficiency thereby causing malnutrition, which is a serious health problem these days. Producing crops with improved quality and quantity is imperative for growing food demand through sustainable agriculture that could be attained using conventional selection and breeding or through genetic engineering (Ashraf and Akram, 2009). The application and development of biotechnology have led to opportunities and novel possibilities to enhance the qualitative and quantitative traits of organisms (Yamaguchi and Blumwald, 2005; Sun, 2008). Biotechnology for crop improvement has become a sustainable strategy to combat deficiencies in food by enhancing proteins, carbohydrates, lipids, vitamins and micronutrient composition (Zimmermann and Hurrell, 2002; Sun, 2008). Since 1990s, the major emphasis of agricultural biotechnology can be found on traits for improvement in crops related to insect and herbicide resistance, nutritional quality, virus resistance, shelf life, and biofuel production. All these traits involve a number of genes, so crop improvement through genetic engineering is not a simple process. Lack of fundamental knowledge of the molecular biology and genetics of the plant species makes this even more exigent. Transgenic plants have been developed through different genetic engineering techniques but with a number of legal, political and social problems (Ashraf and Akram, 2009). For example, the World Health Organization (WHO) has pinpointed three main concerns with genetically engineered crops, particularly GM food crops, including generation of allergenic foods, incorporation of modified food genes into the human body, and crossing of transgenic plants with non-transgenic conventional plants (http://www.livestrong.com accessed on 20-08-2011). All these factors can pose a threat to food safety. Despite all these barriers, different countries including China, Canada, USA, Brazil and Argentina are now allowing transgenic crop production (James, 2006). Considerable improvement in yield has been achieved by using transgenic approach in a number of crops including wheat, rice, tobacco, brassica, and soybean, etc. (Table 1) and still there is a dire need to generate high yielding and quality transgenic.

Genetically engineered crops appear to play an important role in arbitrating tensions between energy production, environmental protection, and global food supplies (Sexton and Zilberman, 2011). For example, increased global demand for biofuels is placing a great pressure on agricultural systems at a time when traditional sources of yield improvements have been mostly exhausted (Sexton and Zilberman, 2011). Biotechnology embodies a viable option for enhancing capability of biomass-based fuels (Rosegrant, 2008). However, there is a need to estimate the influence of biofuel production on food security due to a substantial change in land use and swap in plantation of agricultural crops. This leads to considerable economic and environmental changes. The energy crisis and climate change need to remove constraints on the expansion of biotechnology,

Table 1
Global area of biotech crops in 2008 by country (million hectares) adopted from C. James, 2010 (With permission).

Country	1996		2008	
	Crop	Total biotech crop area (million ha)	Crop	Total biotech crop area (million ha)
USA	Tomato, cotton, soybean, maize, canola, potato, squash	1.5	Cotton, soybean, maize, canola, potato, squash, papaya, alfalfa, sugarbeet	62.5
Argentina	Soybean	0.1	Soybean, maize, cotton	21.0
Brazil	–	–	Soybean, cotton, maize	15.8
Canada	Canola, maize	0.1	Canola, maize, soybean, sugarbeet	7.6
India	–	–	Cotton	7.6
China	Tobacco, tomato	Trace	Cotton, tomato, poplar, petunia, papaya, sweet pepper	3.8
Paraguay	–	–	Soybean	2.7
South Africa	–	–	Maize, soybean, cotton	1.8
Uruguay	–	–	Soybean, maize	0.7
Philippines	–	–	Maize	0.4
Australia	Cotton	<0.05	Cotton, canola, carnation	0.2
Spain	–	–	Maize	0.1
Mexico	Cotton, tomato	<0.05	Cotton, soybean	0.1
Colombia	–	–	Cotton, carnation	<0.1
Chile	–	–	Maize, soybean, canola	<0.1
Honduras	–	–	Maize	<0.1
Czech republic	–	–	Maize	<0.1
Portugal	–	–	Maize	<0.01
Germany	–	–	Maize	<0.1
Slovakia		–	Maize	<0.1
Romania	–	–	Maize	<0.1
Poland	–	–	Maize	<0.1
Burkina faso	–	–	Cotton	<0.1
Egypt	–	–	Maize	<0.1
Bolvia	–	–	Soybean	0.6
Total	Soybean, maize, tobacco, cotton, canola, tomato and potato	1.7	Soybean, maize, cotton, canola, squash, papaya, alfalfa, carnation, tomato, poplar, petunia, sweet pepper, sugarbeet	125.0

allow the technology to grow, and invest in improving biofuel technologies. There is an evidence that these barriers slow down the growth of agricultural biotechnology relative to its potential (Wolt, 2009; Sexton and Zilberman, 2011). According to an estimate, during 2010, biofuels provided 2.7% of the total world transport fuel (REN21, 2001). Scientists are developing genetically engineered strains of algae, mostly blue green algae (cyanobacteria) to produce fuels. Algae have the ability to produce large amounts of fatty acids, and can be grown without competition with food crops on non arable lands and they require only water and sunlight for optimum growth. Scientists are confident that algal biofuel is better than grass or corn-biofuels in terms of low yields per hectare, food supply and need for extensive processing (The Biology Refugia, 2011).

Although efforts have been made to isolate the genes responsible for tolerance to each of salinity, drought, temperature, insects, pesticides, etc. and transformed into the relatively less tolerant plants to withstand these factors, the complex physiology of stress tolerance, genetic architecture as well as the variation between or within species makes it more difficult to achieve desired success (Garg et al., 2002; Ashraf, 2004; Munis et al., 2010; Ni et al., 2010). Progress in achieving the desired degree of crop stress tolerance has been indeed, slow due to poor knowledge of a myriad of intricate resistance mechanisms operating concurrently at the cellular and whole plant levels (Ashraf, 2004). Thus, considering the considerable intricacy of stress tolerance mechanisms it is not easy to pinpoint one single criterion which could be used for selection of enhanced stress tolerance. Nonetheless, the transfers of beneficial genes in plants are an ultimate goal for overcoming such problems. For example, Horsch et al. (1985) developed the first transgenic tobacco plant expressing foreign phytohormone biosynthetic genes. Since then, transgenic plants of about 100 plant species have been produced which show enhanced resistance to insects and diseases, abiotic stresses etc. In addition, these transformed plants overexpress various traits such as photosynthesis, leaf and seed size, seed yield, number of tillers and floral organs (Brar et al., 1995; Khush and Brar, 1998; Saibo et al., 2009; Suarez et al., 2009; Ashraf et al., 2010; Bhatnagar-Mathur et al., 2010; Cerdeira and Duke, 2010; Wang et al., 2010; Wojas et al., 2010). However, the production of genetically modified plants is increasing day by day around the world. In 1996, only 1.7 Mha of land were under transgenic crops and in 2000 the area increased to 44.2 Mha, and in 2008 to 125 Mha (James, 2008). Around 25 countries are contributing to the production of biotech crops and the major portion is produced by the USA wherein 62.5 Mha are under biotech crops (James, 2010) (Table 1). The major biotech crops cultivated are tomato, wheat, alfalfa, rice, soybean, maize, canola, squash, tobacco, cotton, sugarbeet, petunia, sweet pepper and carnation (Ashraf and Akram, 2009; James, 2010). Other transgenic crops are on the way and they will hit the market soon.

Plant scientists, by employing various genetic engineering techniques, are trying to increase crop production by developing high yielding crops, disease resistant crops (resistant to insects, fungi and bacteria), resistant to abiotic stresses, and crops with high nutritional value and biofuel production. In this review, we have comprehensively discussed the role of genetic engineering in generating transgenic lines/cultivars of different crops with improved yield and nutrient quality, enhanced production of vaccines and antibodies, enhanced resistance against a variety of abiotic and biotic stresses.

2. Modern agriculture — transgenic cultivars/lines

Recently, biotechnology has revolutionized crop improvement by producing GM crops with enhanced availability and utilization of important traits (Icoz and Stotzky, 2008). According to an estimate, the world area of GM crops raised more or less from 1.7–102 million ha i.e. about 60-fold from 1996 to 2006 (James, 2006). Transgenic plants with improved traits have greater advantages as compared to those of wild plants (Jaworski and Cahoon, 2003; Mascia and Flavell, 2004; Ashraf and Akram, 2009), but with a few limitations (Altman, 1999; Krattiger, 2010; Cotter, 2011). In 1970s, scientists were able to manipulate DNA at molecular level and the technology was referred to as genetic engineering. Using this technology, scientists can take specific genes from organisms (bacteria, plants or animals) and introduce them into other organisms. Genetic engineering is now known to everybody and is a routine technology in both basic and applied sciences. First transgenic food available in the market was tomatoes in the US in 1994 (Teisl et al., 2003; http://www.gmo-compass.org/eng/grocery_shopping/fruit_vegetables/15.genetically_modified_tomatoes.html). Later on in 1996, only seven major crops such as soybean, cotton, canola, tomato, potato, maize and squash were used for generating transgenic crops (Table 1). Thereafter, the world area of transgenic crops grew enormously. Development of transgenic biotechnology has promoted the commercialization of genetically modified crops to a great extent (Xia et al., 2010).

In agriculture, yield is a major output and improvement in yield of plants is a major thrust area by counteracting biotic and abiotic environmental cues. Thus, crop cultivars with enhanced yield and stability are required. In this context, a substantial progress has been made in enhancing crop yield worldwide using advanced molecular biology tools. For example, by the introgression of vacuolar Na^+/H^+ antiporter gene *AtNHX1* yield improvement was observed in wheat by 50% (Xu et al., 2004), *Brassica napus* (2.34%) (Zhang et al., 2001) and tobacco (21%) (Wang et al., 2004) under saline conditions. Oh et al. (2009) estimated 16–57% higher grain yield in rice encoding *Oryza sativa AP37* under water deficit conditions. Introgression of Δ^1-pyrroline-5-carboxylate synthetase (*P5CS*) in potato (*Solanum tuberosum*) improved plant growth and tuber yield (21%) of transgenic plants compared with that of non-transformed plants under salinity stress (Hmida-Sayari et al., 2005).

Environmental factors are essential components which affect crop yield to a great extent. The introduction of resistance to heavy metals, salt, cold, and drought into crop plants has become a topic of major economic interest for agriculture. Genetically engineered drought and salt tolerant plants could be used to economically utilize the wastelands that are hit by excessive amount of salts content and low availability of water. In the case of drought, scientists have been able now to uncover some of the extremely intricate mechanisms through which seed from orthodox plants acquires tolerance to desiccation during their final maturation period, when the seed experiences quiescence and its metabolism turns off (Hoekstra et al., 2001; DaMatta, 2004; Oliver et al., 2010). Reviviscent plants, capable of sustaining extreme conditions of desiccation stress, provide another model. Some of the genes associated with tolerance to such extreme conditions of drought have been isolated and characterized (Zhang and Blumwald, 2001; Sunkar et al., 2003; Villalobos et al., 2004; Husaini and Abdin, 2008; Ashraf, 2010; Chen et al., 2010a, 2010b). Similar to these reports, there are several examples showing the success stories of improved tolerance of plants to different abiotic stresses by genetic engineering (Yamaguchi and Blumwald, 2005; Ashraf and Akram, 2009; Ashraf, 2010) (Table 2).

3. Insect and disease resistance

Scientists' endeavors to engineer plants to over-express natural defense against a variety of pests including insects, fungi bacteria etc. also can be deciphered from the literature. *Bacillus thuringiensis* (Bt) insect resistant crops are one of the most astounding achievements in plant transgenic technology. Bt is a potent insecticide which comprises crystal protein endotoxin produced by some strains of soil bacterium *B. thuringiensis* (a soil bacterium). The Bt crystal (cry) insecticidal protein (δ-endotoxin) genes are toxic to lepidopterans (Cohen et al., 2000), dipterans (Andrews et al., 1987) and coleopterans (Herrnstadt et al., 1986). Bt cry protein is non-toxic to

Table 2
Promotion in growth parameters due to altered expression of genes (Adopted from Rojas et al., 2010, with permission).

Gene	Alteration	Phenotype	Reference
Photosynthetic genes			
Phosphoenolpyruvate carboxylase/ pyruvate orthophosphate dikinase	OE	Enhanced stomatal conductance, increased photosynthetic capacity and tiller number	Ku et al., 2007
Cytochrome c6	OE	Higher content of photosynthetic metabolites and increased leaf and root growth	Chida et al., 2007
Rubisco activase	Gene shuffling	More siliques and enhanced vegetative growth	Kurek et al., 2007
Glycolate dehydrogenase/Glyoxylate carboligase/ Tartronic semialdehyde reductase	OE	Improvement of carboxilation/oxygenation ratio, greater biomass and an increase in photosynthesis	Kebeish et al., 2007
Transcription factors			
ARGOS	OE	Plant with larger organs	Hu et al., 2003
AINTEGUMENTA	OE	Increased growth of floral organs	Krizek, 2009
MEGAINTEGUMENTA	LOF	Increased seed size and weight	Schruff et al., 2006
Growth regulating factors 1,3,5	OE	Increased leaf and cotyledon growth	Horiguchi et al., 2005
ANGUSTIFOLIA 3	OE	Increased leaf size	Horiguchi et al., 2005
NAC1	OE	Plants with more abundant roots, larger leaves and thicker stems	Xie et al., 2000
ATAF2	OE	Increased biomass, bigger leaves	Delessert et al., 2005
PEAPOD	POF	Plants with larger leaf and cotyledon laminae	White, 2006
Cell cycle machinery			
Cyclin D2	OE	Increase rate of leaf initiation and accelerated development	Cockcroft et al., 2000
Cyclin D3	OE	Leaves with more but smaller cells	Dewitte et al., 2003
ABAP1	LOF	Larger leaves with more cells	Masuda et al., 2008
CDC27a	OE	Increased growth rate and organ size	Rojas et al., 2009
Hormone metabolism			
AtGA20-oxidase	OE	Promoted growth, biomass production and xylem fiber length	Biemelt et al., 2004
HOG1	LOF	Increments in leaf size and seed yield	Godge et al., 2008
IPT	OE	Increased leaf biomass	Rupp et al., 1999
DASS	OE	Increased plant fresh weight	Chory, 2004
ARF2	LOF	Longer inflorescence stems and larger leaves	Okushima et al., 2005
AVP1	OE	Increment in the number and size of rosette leaves and in root size	Li et al., 2005
microRNAs			
miR396	LOF	Larger leaves with more leaves	Rodriguez et al., 2010
miR319	OE	Larger and crinkled leaves	Palatnik et al., 2003
miR156	OE	Increase in total leaf number on main and side shoots	Chuck et al., 2007

OE—overexpression, LOF—loss of function.

humans and animals, but toxic to insects (BANR, 2000). The first Bt toxin gene was cloned in 1981 (Schnepf and Whiteley, 1981; Jain et al., 2007) and the field trial of transgenic tobacco expressing Bt toxin was performed in 1986. Furthermore, the first GM plant of japonica rice was produced in 1988 and then indica rice in 1990. Subsequently, genetically engineered corn, cotton and tomato were tested under field conditions in different countries and area under Bt crops was 1.2 Mha in 1996 (James, 1997, 2000). Combination of very high transgene expression and improved protein stability resulted in mortality of even Bt-resistant insects (Kota et al., 1999). Today, other insecticidal proteins have been discovered including lectins, protease inhibitors, antibodies, wasp and spider toxins, microbial insecticides and insect peptide hormones (Estruch et al., 1997; Dempsey et al., 1998; Ffrench-Constant and Bowen, 1999; Dinan, 2001; Taniai et al., 2002; Whetstone and Hammock, 2007; Van Damme, 2008). For example, photorhabdus toxin produced by bacterium *Photorhabdus luminescens* represents a potential alternative to Bt for transgenic production. Combined production of photorhabdus toxins and Bt toxins in transgenic crops can be used to combat insect resistance. Recently, a US based company Monsanto with India's Maharashtra Hybrid Seeds Company (Mahyco) has developed Bt eggplant (*Solanum melongena*) by incorporating a crystal gene (*Cry1Ac*) from *B. thuringiensis* (Krattiger, 2010; Cotter, 2011).

Plants are equipped with the natural plant defense system against insects, fungi, bacteria which is provided by the proteinase inhibitors (Jongsma and Bolter, 1997; Larry and Richard, 2002; Kim et al., 2009). The digestive system of many insects possesses trypsin and chymotrypsin (serine-type proteinase like enzymes) for digestion. Proteinase inhibitors have been found to affect growth and development of many insects (Jongsma and Bolter, 1997; Larry and Richard, 2002). The foods from different plants always contain proteinase inhibitors which are usually destroyed by cooking. Thus, transgenic plants expressing proteinase inhibitor genes can be safe (Larry and Richard, 2002). Transfer of proteinase inhibitor genes into other plants will produce insect resistant crops (Larry and Richard, 2002). Various types of proteinase inhibitors have been expressed in rice plants e.g. potato protease inhibitors II, oryzacystatin, cowpea trypsin inhibitors, soybean trypsin inhibitors (Xu et al., 1996; Sharma et al., 2004), trypsin inhibitor (Mochizuki et al., 1999), and barley trypsin inhibitors (Alfonso-Rubi et al., 2003). Brar and Khush (2007) have demonstrated that expression of cowpea trypsin inhibitor (CpTi) improves rice plant resistance against stem borer. Alpha-amylase inhibitor accumulates in plants and defends them against insects. Thus, proteinase inhibitors and α-amylase inhibitors have been found to play a defensive role against insect attack (Ishimoto et al., 1996; Shade et al., 1999; Lawrence and Koundal, 2002; Sivakumar et al., 2006; Mehrabadi et al., 2010). Genes encoding amylase inhibitors, lectins and chitinases also can enhance resistance against insect attack. Expression of α-amylase inhibitor gene in tobacco plants from rye seeds (*Secale cereale*) has developed resistance against *Anthonomus grandis* (cotton

boll weevil) (Dias et al., 2010). The authors came to a conclusion that rye inhibitor is a potential molecular biology tool to generate GM cotton plants with an enhanced resistance to cotton boll weevil.

Lectins, carbohydrate binding proteins occur abundantly in seeds and storage tissues of different plants (Chrispeels and Raikhel, 1991; Kozlov et al., 2006). Lectins have been found to protect the plants against environmental stresses (Joshi et al., 2010). The lectins from snowdrop or garlic were found to be injurious to insects but not to mammals (Rao et al., 1998; Sharma et al., 2000; Li and Romeis, 2009; Fitches et al., 2010). The most important protein examined is the lectin from snowdrop (*Galanthus nivalis* agglutinin; GNA), whose mortality rate is around 80%. It has been reported that GNA affects the metabolic activity of brown plant hopper (BPH), white backed plant hopper (WBPH) and green leafhopper pests of rice (Nagadhara et al., 2003). GM rice plant expressing snowdrop lectin gene (*gna*) showed reduced survival and fecundity of insects, impaired insect development and had an inhibitory effect on BPH feeding (Rao et al., 1998; Tang et al., 2001; Nagadhara et al., 2004; Brar et al., 2009). The *gna* is the first transgene to express insecticidal activity for sap-sucking insects in rice plants. Transgenic potato expressing *gna* gene showed reduced damage to leaves (Bell et al., 2001). Christine et al. (1998) have demonstrated that lectin (arcelin-I) which was obtained from beans is toxic to insect *Zabrotes subfasciatus*. Transgenic plants expressing lectin gene *αai* have been found to safeguard seed from the larvae of *Coleoptera* (Altabella and Chrispeels, 1990). Pea lectin (*P-lec*) genes possess a high level of expression with CaMV35S promoter in transgenic tobacco and can reduce larval biomass of *H. virescens* and leaf damage in GM plants (Boulter et al., 1990). Furthermore, Saha et al. (2006) demonstrated that *Allium sativum* leaf agglutinin (*ASAL*), the garlic lectin gene, possesses the insecticidal activity against BPH and GLH in different crops. For example, expression of *ASAL* gene in rice cv. IR64 induced hopper resistance. The insecticidal property of ASAL is due to the formation of complex between ASAL and receptor molecule (endosymbiotic chaperonin symbionin) present in the gut of the insect. In addition, another gene *Allium cepa* agglutinin (*ACA*) has been reported to show insecticidal property and is employed to control sap sucking insects (Hossain et al., 2006).

Transgenic plants expressing TMV coat protein gene were resistant to TMV infection (Powell-Abel et al., 1986; Koo et al., 2004; Mundembe et al., 2009) and this coat protein mediated resistance is widely used to protect many crops from a large number of viruses (Beachy, 1993; Mundembe et al., 2009). China was the first country to commercialize virus-resistant GM crops with the introduction of virus resistant tobacco in 1992 (James, 1997). After that virus resistant tomato, squash and watermelon plants were produced (Meeusen, 1996). Overexpression of a tomato chitinase gene with a strong gene promoter in oilseed rape resulted in increased resistance to fungal attack (Grison et al., 1996). The plants exhibited increased resistance to the pathogens *Cylindrosporium concentricum* and *Phoma lingam*.

In a study, Cao et al. (1998) used a master-switch gene *NPR1* that regulates expression of a set of pathogenesis-related (PR) genes, to activate a number of PR genes simultaneously. PR genes do not provide enough protection individually but they can work collectively given a long-term resistance against pathogens. The *NPR1* transgenic plants showed increased resistance to bacterial pathogens *Pseudomonas syringae* and the fungal pathogen *Pernospora parasitica*. Recently, Lin et al. (2010) have observed that employing a transgene plant ferrodoxin like protein (PFLP) imparts resistance to plants against bacterial pathogens, e.g. expression of PFLP enhanced the disease resistance in *Arabidopsis*.

Fusarium head blight (FHB) is a disease that adversely affects barley and wheat production. Contamination of food with Fusarium produced trichothecene mycotoxin deoxynivalenol (DON) is a great health risk for humans and animals, because trichothecenes are potent cytotoxins of eukaryotic cells. In this context, Di et al. (2010) have recently demonstrated the expression of an N-terminal fragment of yeast L3 (L3Δ) in wheat which showed reduction in disease severity and improved level of DON in transgenic wheat kernel as compared to non-transgenic wheat plants. Similarly, a disease resistant gene *TuR2* was isolated from cabbage and introduced into mustard through *Agrobacterium* transformation method. The transgenic mustard plants showed high resistance toward (*Turnip mosaic virus*) TuMV as compared to that by the wild mustard plants (Cao et al., 2008).

Trichothecenes play multiple roles in the cell. They particularly inhibit protein synthesis (Grant et al., 1976; McLaughlin et al., 2009; Di et al., 2010). McLaughlin et al. (2009) observed in yeast a critical role of trichothecene mycotoxin (*tcmI*) in the protein synthesis (Grant et al., 1976), which encodes the ribosomal protein L3. Overexpression of *RPL3* gene in transgenic plants induces resistance to trichothecene mycotoxin deoxynivalenol (DON) (McLaughlin et al., 2009). A modified rice *RPL3* cDNA was transformed into tobacco, which resulted in higher regeneration efficiency and viability in the presence of DON in transgenic rice plants (Harris and Gleddie, 2001).

4. Herbicide resistance

The early herbicides were found to be very destructive for most plants and they created undesirable environmental impacts. New chemicals such as glyphosate have been widely recommended for use because glyphosate is environmental-friendly as soil microorganisms are able to degrade it rapidly. By introducing glyphosate tolerance genes into crops, the herbicide can now be applied over the top of crops during the growing season to control weed population more effectively. Plants expressing transformed herbicide tolerance accounted for 71% of all transgenic crops grown worldwide in 1998 and 1999 (James, 1999). Herbicide tolerant soybean, corn, cotton and canola represent the major transgenic products (James, 1999; Liu, 1999) (Table 3). Recently, Gaines et al. (2010) developed herbicide resistant *Amaranthus palmeri* by expressing glyphosate-insensitive herbicide target site gene, 5-enolpyruvylshikimate-3-phosphate synthase (*EPSP*) that is involved in the shikimate cycle wherein it catalyzes the reversible addition of the enolpyruvyl moiety of phosphoenolpyruvate to shikimate 3-phosphate. In the western and central Africa considerable loss of maize was observed by a parasitic weed *Striga hermonthica*. Menkir et al. (2010) incorporated an imidazolinone resistance (IR) *XA17* gene into some maize lines that confers resistance to imazaquin and nicosulfuron herbicides. These IR-maize lines showed resistance to the *Striga hermonthica* weed and the yield loss was minimized to a considerable level. Zang et al. (2009) demonstrated the expression of *bar* gene responsible for resistance to herbicides in sweet potato. Transgenic tobacco expressing a tau class GST isoenzyme GmGSTU4 from soybean is active as glutathione-dependent peroxidase (GPOX) and shows catalytic activity for diphenyl ether herbicide fluorodifen/alachlor (Benekos et al., 2010).

Two approaches have been used to create herbicide tolerant crops: one is to modify the degree of sensitivity of the target enzyme so that the plant sensitivity to the herbicide is inhibited, and the second is to engineer the herbicide-detoxifying pathway into the plant (Simoens and Van Montagu, 1995). Examples of the first approach include glyphosate and acifluorfen tolerance. Transgenic plants tolerant to the herbicide acifluorfen, which inhibits chlorophyll biosynthesis, have been produced through over-expression of the target enzyme involved in chlorophyll biosynthesis (Lermontova and Grimm, 2000). In comparison, resistance to glufosinate and bromoxynil is based on the second approach. By introducing genes that enhance metabolism of these herbicides the active compound is converted to products that are non-toxic to the crop (Haumann, 1997). Similarly, in the case of herbicide Ignite/Basta, the bar resistance gene from *Streptomyces hygroscopicus* was used to detoxify the herbicide.

Table 3
Transgenic plants expressing genes for insect and disease resistance.

Plant	Gene	Resistance to	Reference
Potato	*Cry1Ab*	Potato tuber moth	Kumar et al., 2010
Rice	*Cry1Ab*	Lepidopteron	Qi et al., 2009
Tobacco	Magi6 peptide	*Spodoptera frugiperda*	Hernández-Campuzano et al., 2009
Rice (Indica, Basmati)	*Cry1Ac, Cry2A*	YSB[a]	Bashir et al., 2005
Rice (Indica, Minghuli 63)	*Cry2A*	YSB	Chen et al., 2005
Rice (Indica, Minghuli 63)	*Cry1Ac, Cry2A, Cry9c*	YSB and Asiatic rice borer	Chen et al., 2008
Rice (Elite Vietnamese)	Fused gene, *Cry1Ab-1B* and hybrid Bt gene, *Cry1A/Cry1Ac*	YSB	Ho et al., 2006
Indica Pusa Basmati 1, Japonica, Tainung 67	Potato proteinase inhibitor 2 (Pin 2)	YSB	Bhutani et al., 2006
Indica Basmati 370	*Cry1Ac, Cry2A*	YSB	Riaz et al., 2006
Rice (Korean varieties) P-I, P-II, P-III	*Cry1Ab*	YSB	Kim et al., 2008
Rice (Zhuxian B)	Sbti + GNA	Leaf folder + BPH	Li et al., 2005
Indica rice	*Cry1Ab, Cry1Ac,gna*	YSB	Ramesh et al., 2004
Indica rice	*Cry1Ab, Cry1Ac*	YSB	Alcantara et al., 2004
Indica rice	*Cry1Ac, Cry2A,gna*	Lepidopteron insects	Rahman et al., 2007
Indica rice	Chitinase + β-1,3-glucanase genes	*Rhizoctonia solani*	Sridevi et al., 2008
Rape	*hrf2* gene encoding harpin$_{xooc}$ protein	*Sclerotinia sclerotinorium*	Ma et al., 2008
Tobacco	p35 gene from baculovirus *Autographa californica*	TMV[a]	Wang et al., 2008
Japonica	*Pi-d2*	Rice leaf blast and neck blast	Chen et al., 2010a, 2010b
Tobacco	*GbTLP1*	*Verticillium dahliae*	Munis et al., 2010
Potato	*StPUB17* (UND/PUB/ARM) repeat type gene	*Phytophthora infestans*	Ni et al., 2010
Potato	*RB* resistance gene	*Potato late blight*	Liu et al., 2009
Wheat	Ta-Tlp (thaumatin-like protein gene)	Powdery mildew and *Fusarium* head blight	Xing et al., 2008

[a] YSB = yellow stem borer, TMV = tobacco mosaic virus.

Various transgenic plants expressing the bar gene were produced which include sugarbeet, popular plants, aspen, oilseed rape, tomato, potato, alfalfa and tobacco (De Block, 1990; D'Halluin et al., 1990).

5. Abiotic stress tolerance

Abiotic stresses such as salt, drought, flooding, extreme temperature and oxidative stresses often diminish plant growth and final yield. Agricultural productivity could be increased dramatically if crops were redesigned to better cope with environmental stresses (Table 4). Transgenic regulations of solutes such as mannitol and proline have been used to promote stress tolerance in plants (Hasegawa et al., 2000). Expression of choline oxidase (*codA*) gene increases glycinebetaine production, which helps the cells in osmotic adjustment so that the plant can acclimate under different stresses. Studies with rice confirmed that chloroplast targeting the *codA* gene is a very effective way to enhance tolerance to these abiotic stresses (Alia et al., 1999). Van Camp et al. (1994) demonstrated that over-production of a superoxide dismutase (SOD) gene resulted in increased chilling tolerance in plants. This could be due to the reason that different stress environment (high light intensity, pathogens and cold) produce reactive oxygen species (ROS) which can damage to plants. Antioxidant enzymes such as superoxide dismutase, catalase and peroxidase have the capacity to neutralize the effect of ROS (Hiei et al., 1994; Ahmad et al., 2010a,b). For example, Yang et al. (2009) correlated the enhanced tolerance of *OsMT1a* over-expressing transgenic rice plants to water limited conditions with enhanced APX activity. Cytosolic APX has been found to acclimate the plants to a combination of heat and drought stress (Koussevitzky et al., 2008). Plants with low amount of glutathione were found to be highly sensitive to even low doses of Cd^{2+} due to impaired synthesis of phytochelatin (Xiang et al., 2001). The enhanced production of glutathione reductase (GSH) can be triggered by the stimulation of pathways involved in the metabolism of sulfur and cysteine. Manipulation of GSH biosynthesis has been reported to improve resistance to oxidative stress (Sirko et al., 2004). For example, upon exposure Cd^{2+} exposure of *Arabidopsis* plants, one of the primary responses appearing was the induction of genes involved in sulfur assimilation–reduction and glutathione metabolism in the roots (Herbette et al., 2006). Recently, Sekhar et al. (2011) have reported that transgenic *Escherichia coli* and *Arabidopsis thaliana* overexpressing *CcMT1* gene have shown increased plant biomass and chlorophyll content as well as low content of Cu and Cd metals in roots and shoots compared with wild type plants under metal stress induced by Cu and Cd. In an earlier study, transgenic tobacco plants overexpressing glyoxalase pathway enzymes, suppressed methylglyoxal (MG) (reactive cytotoxic alpha-oxoaldehyde compound) level that increased about 70% in wild type plants under saline conditions. In addition, it increased salinity tolerance and better growth in genetically modified tobacco plants by increasing glutathione (GSH) content, maintaining higher reduced to oxidized glutathione (GSH:GSSG) ratio, and minimizing lipid peroxidation (Yadav et al., 2005). While, observing the constitutive expression of *Osmyb4* rice gene in *A. thaliana* under salinity, drought, temperature (low and high), and oxidative stress by Vannini et al. (2006) found considerable improvement in stress tolerance by regulating vital metabolites as well as ROS scavengers, which indicated that *Osmyb4* gene has an effective role in the stimulation of various integral components of stress signaling pathways.

Vitamin C, also known as ascorbic acid, plays a vital role in collagen biosynthesis and also for the maintenance of the cardiovascular system in humans (Kónya and Ferdinandy, 2006). Like most of the animals, humans are unable to accumulate ascorbic acid. This happens due to a mutation in the gene involved in the ascorbate synthesis (Conklin et al., 2006; Johnson et al., 2008). So, vitamin C is essentially required by the humans from the dietary sources including plants. For example, Hemavathi et al. (2009) developed transgenic potato (*S. tuberosum*) overexpressing strawberry *GalUR* gene. The over-expression of *GalUR* resulted in enhanced tolerance to methyl viologen (MV), mannitol and salinity by increasing chlorophyll pigments and 1.6–2-fold high accumulation of *AsA* in transgenic plants as compared to that in wild type (non-transformed) plants. The levels of AsA in the transgenic potato were significantly associated with enhanced *GalUR* activity. The enzymes pyruvate decarboxylase (Pdc) and alcohol dehydrogenase (Adh) appear to have an important role in anoxia tolerance in plants by improving ethanolic fermentation (Rivoal et al., 1997; Agarwal et al., 2007). During an investigation, Agarwal et al. (2007) observed that rice plants overexpressing *Ospdc1* at early seedling stage showed considerable improvement in root vigor as compared to that of wild-type seedlings under control conditions.

Table 4
Some promising genes that can be expressed in plants for abiotic stress tolerance.

Gene and gene product	Plant	Resistance to	Reference
betA (choline dehydrogenase)	Tobacco	Salinity and low temperature	Holmstrom et al., 2000
BADH1(betaine aldehyde dehydrogenase)	Tomato	Salinity	Jia et al., 2002
EctA, ectB, ectC	Tobacco	Salinity	Nakayama et al., 2000
OstA, OstB (trehalose-6-P synthase, trehalose-6-P phosphatase)	Tobacco Rice	Salt, drought	Garg et al., 2002
TPS and TPP (trehalose synthesis)	Tobacco	Salt and mannitol tolerance	Roosens et al., 2002
TPS and TPP (trehalose synthesis)	Arabidopsis	Drought, salt, temperature	Miranda et al., 2007
TPP1 (trehalose synthesis)	Rice	Salt and cold	Ge et al., 2008
TPS1 (trehalose synthesis)	Alfalfa	Drought, salt, temperature	Suarez et al., 2009
WCOR15 (cold induced gene)	Tobacco	Freezing	Shimamura et al., 2006
AtOAT (ornithine amino transferase)	Rice	Drought and salt	Jang et al., 2003
pdc1 (pyruvate decarboxylase overexpression)	Rice	Submergence tolerance	Minhas and Grover, 1999
pdc1 and pdc2 (Pyruvate decarboxylase overexpression)	Arabidopsis	Hypoxic stress survival	Ismond et al., 2003
ppo (Polyphenol oxidases suppression)	Tomato	Drought	Thipyapong et al., 2004
SAMDC (polyamine synthesis)	Tobacco	Drought, salinity, *Verticillium*, *Fusarium* wilts	Waie and Rajam, 2003
SPDS (spermidine synthase)	Arabidopsis	Salinity	Bagni et al., 2006
P5CS (Δ^1-pyrroline-5-carboxylate synthase)	Tobacco	Salt and drought	Kishor et al., 1995
P5CS (Δ^1-pyrroline-5-carboxylate synthase)	Rice	Salt and drought	Zhu et al., 1998
P5CS (Δ^1-pyrroline-5-carboxylate synthase)	Bean	Drought, salt and cold	Chen et al., 2009
P5CS (Δ^1-pyrroline-5-carboxylate synthase)	Potato	Salt	Hmida-Sayari et al., 2005
P5CS (Δ^1-pyrroline-5-carboxylate synthase)	Wheat	Drought	Vendruscolo et al., 2007
ProDH (proline dehydrogenase)	Arabidopsis	Salt stress	Nanjo et al., 1999
mt1D (Mannitol-1-phosphate dehydrogenase)	Wheat	Salt and osmotic stress	Abede et al., 2003
IMT1 (myo-inositol-*O*-methyl transferase)	Tobacco	Salt and drought	Sheveleva et al., 1997
COD1; COX (choline oxidase)	Arabidopsis Rice Brassica	Salt, cold, light stress	Hayashi et al., 1997; Sakamoto et al., 1998; Huang et al., 2000; Prasad et al., 2000
adc (Polyamine synthesis)	Rice	Drought	Capell et al., 2004
Osm1 to *Osm4* (osmotin protein accumulation)	Strawberry	Salt and drought	Husaini and Abdin, 2008
ME-leaN4 (Lea protein)	Lettuce	Salt	Park et al., 2005
Os LEA3-1 (Lea protein)	Rice	Drought	Xiao et al., 2007
HVA1 (group 3 LEA protein gene)	Mulberry	Salt and drought	Lal et al., 2008
BhLEA1, LEA2 (LEA protein)	Tobacco	Drought	Liu et al., 2009
HAL3 (FMN-binding protein)	Arabidopsis	Salt and osmotic tolerance	Espinosa-Ruiz et al., 1999
HAL1	Arabidopsis	Salt	Ellul et al., 2003
HAL1	watermelon	Salt	Yang et al., 2001
DREB1A	Arabidopsis	Drought, salt and cold tolerance	Kasuga et al., 1999; Liu et al., 1998
OsDREB1A	Arabidopsis	Drought, salt and cold tolerance	Dubouzet et al., 2003
DREB1A (transcription factor)	Paspalum grass	Drought	James et al., 2008
DREB1A (transcription factor)	Tobacco	Salt	Cong et al., 2008
DREB1A, DREB2A (transcription factor)	Arabidopsis	Drought and Cold	Maruyama et al., 2009
OsNAC10 (transcription factor)	Rice	Drought	Jeong et al., 2010
OsSMCP1 (transcription factor)	Arabidopsis	Salt	Yokotani et al., 2009
Osmyb4 (cold induced transcription factor)	Apple	Drought and cold tolerance	Pasquali et al., 2008a, 2008b
A1fin1 (transcription factor)	Alfalfa	Salt	Winicov, 2000
OrbHLH2 (transcription factor)	Arabidopsis	Salt and osmotic stress	Zhou et al., 2009
OsWRKY45 (transcription factor)	Arabidopsis	Drought	Qiu and Yu, 2009
Tsi1 (EREBP/AP2 DNA binding motif)	Tobacco	Salt and pathogen	Park et al., 2001
CBF1 (DREB1B)	Tomato	Drought	Hsieh et al., 2002
CBF4	Arabidopsis	Drought	Haake et al., 2002
ABF3/ABF4	Arabidopsis	Drought	Kang et al., 2002
AtMYC2/AtMYB2	Arabidopsis	Drought	Abe et al., 2003
ZPT2-3 (Cys2/His2-type Zinc-finger protein)	Petunia	Drought	Sugano et al., 2003
CpMYB10	Arabidopsis	Drought and salt	Villalobos et al., 2004
FeSOD (superoxide dismutase)	Tobacco	Salt and oxidative stress	Van Camp et al., 1996
MnSOD	Arabidopsis	Oxidative stress	Wang et al., 2004
MnSOD	Rice	Oxidative stress	Tanaka et al., 1999
Glutathione-S-transferase/glutathione peroxidase	Tobacco	Salt and cold	Roxas et al., 2000
KatE (catalase)	Tobacco	Salt and oxidative stress	Al-Taweel et al., 2007
DHAR1 (dehydroascorbate reductase)	Arabidopsis	Salt tolerance	Ushimaru et al., 2006
AtALDH3 (aldehyde dehydrogenase)	Arabidopsis	Drought, salt and oxidative stress	Sunkar et al., 2003
MsALR (aldose/aldehyde reductase)	Alfalfa	Drought and heavy metal	Oberschall et al., 2000
Ascorbate peroxidise	Tobacco	Drought and salt	Badawi et al., 2004
GlyI and GlyII (glyoxylase)	Tobacco	Salt	Yadav et al., 2005
OsCDPK (calcium dependent protein kinase)	Rice	Drought and salt	Saijo et al., 2000
Cnb1 (calcineurin)	Tobacco	Salt	Pardo et al., 1998
DnaK (heat shock proteins)	Tobacco	Salt	Sugino et al., 1999
AtHsp 17.6A (small heat shock protein)	Arabidopsis	Drought and salt	Sun and Bernard, 2001
AtGSK1	Arabidopsis	Drought and salt	Piao et al., 2001
AtNDPK2 (nucleotide diphosphate kinase)	Arabidopsis	Salt, cold, methyl viologen	Moon et al., 2002
AtNHX1 (vacuolar Na^+/H^+ antiporter)	Tomato	Salt	Zhang and Blumwald, 2001
AtNHX1 (vacuolar Na^+/H^+ antiporter)	Mustard	Salt	Zhang et al., 2001

Table 4 *(continued)*

Gene and gene product	Plant	Resistance to	Reference
AtNHX1 (vacuolar Na^+/H^+ antiporter)	Rice	Salt	Ohta et al., 2002
SOS1 (plasma membrane Na^+/H^+ antiporter)	Arabidopsis	Salt	Shi et al., 2003
AVP1(K^+/Na^+ transport regulation)	Arabidopsis	Drought and salt	Gaxiola et al., 2001
CaXTH3 (xyloglucan endotransglucosylase)	Arabidopsis	Drought and salt	Cho et al., 2006
ZmOPR1 (12-Oxo-phytodienoic acid reductases)	Arabidopsis	Osmotic and salt stress	Gu et al., 2008
SPCP2 (papain-like cysteine protease)	Arabidopsis	Salt and drought	Chen et al., 2010a, 2010b
W6 (ethylene responsive factor gene)	Tobacco	Salt tolerance	Lu et al., 2008
TSRF1 (ethylene responsive factor)	Rice	Drought	Quan et al., 2010
TERF2/LeERF2 (ethylene responsive factor)	Tomato Tobacco	Freezing	Zhang and Huang, 2010
StPUB17 (UND/PUB/ARM) repeat type gene	Potato	Salt	Ni et al., 2010

6. Nutrient rich food

Vitamin A deficiency can adversely affect the eyes as well as it can cause childhood and maternal mortality. Globally, 21% of children have been reported to suffer vitamin A deficiency (Sommer, 2001). In view of a projection, about 800,000 deaths in children and women of reproductive age occur due to vitamin A deficiency (Black, 2003; WHO, 2009). According to another projection, approximately 0.25 to 0.5 million malnourished children in the developing countries become blind each year mainly because of vitamin A deficiency and 50% of which die within a year of becoming blind (WHO, 2008). VAD is found in greater numbers in children and pregnant women. Nutritional deficiency is one of the key challenges of developing countries. In majority of the countries the staple food is rice which is deficient in vitamin A. The expression of vitamin A gene in rice will be an alternative to eradicate this VAD. No technology can overcome such deficiencies, but plant biotechnology tools have been very effective in improving the nutritional levels in some field crops: for example, lysine and threonine in cereals, methionine in leguminous plants, and vitamins A and E in crucifers and rice. Increases in the level of methionine and vitamins in crops to an appreciable level are all due to advanced biotechnological means (Sun, 1999; Ye et al., 2000; Potrykus, 2001). Increasing provitamin A content in rice is a major concern to prevent blindness in children. Rice endosperm lacks provitamin A. Transgenic rice containing four genes isolated from *Narcissus* and *Erwinia* has been obtained (Ye et al., 2000). Some of the stable rice transgenic lines accumulate high amounts of provitamin A, giving the endosperm a yellow color, hence the name golden rice. According to Paine et al. (2005), people who consume 75 g of golden rice per day automatically are prone to have sufficient amount of provitamin A. Golden mustard is also developed by biotechnologists and is rich in provitamin A. In the future, this technology will be beneficial for other variety of potential crops.

According to Panos (1998) there are three generations of GE crops. First generation crops are those which show resistance to environmental stresses such as herbicide resistance, insect resistance, drought resistance, etc. The second generation crops may provide nutrient rich seed for feed, whereas the third generation crops are those which generate biofuels, pharmaceuticals etc. The GE crops which are widely adopted belong to first-generation crops (Tables 2, 3).

GE crops are advantageous in various aspects over non transgenic varieties in terms of higher yield and resistance to biotic and abiotic factors. Producers and biotech companies are generating a lot of profit by adopting GE crops. According to Runge and Ryan (2004) the transgenic crops adoption in the US was 73% for cotton, 70% for canola, 40% for corn and 81% for soybean in 2003.

Another achievement of the transgenic crops is to engineer oil crops that produce good quality industrial lubricant oils. This leads to mitigate the pressure on lubricant sectors for petroleum derived products. Canola oils which are rich in erucic acid are of great use as industrial lubricants. Transgenic plants are also being widely used for the production of pharmaceuticals (biopharming).

7. Molecular pharming

Plant biotechnology entails scientific techniques that can be employed to develop cellular-and molecular-based technologies to improve plant productivity by improving the quality of plant products as well as reducing environment-induced limitations to plant productivity. Plant biotechnology enables plant breeders to bring accurate genetic modifications to yield valuable traits to plants and thereby surpassing all previous expectations. The future of biotechnology is even more promising. The agricultural biotechnology revolution depends on successful and modern research, developmental activities and on a favorable regulatory public and climate approval (Altman, 1999; Huang and Wang, 2002; Icoz and Stotzky, 2008; Jain, 2010). Primarily, agriculture was targeted to improving the production of plant-derived food, in terms of better quantity and quality that is why in the current era, of various agricultural technologies, agricultural biotechnology is the topmost priority area that has received considerable attention (Huang and Wang, 2002; Yamaguchi and Blumwald, 2005; Carpenter, 2010).

In recent years, through plant genetic engineering it has become possible to use genetically engineered plants for the production of therapeutic recombinant proteins, the most important of which are plant-based vaccines (Ma et al., 2003). The interest in producing such proteins in plants comes in part from the problems associated with existing bioreactor systems. Mammalian cell systems are expensive and cannot be easily scaled up, but in contrast, bacterial systems can be scaled up. However, often the recombinant proteins are not properly processed which leads to intracellular precipitation of nonfunctional proteins. On the contrary plant systems can be scaled up allowing amounts of proteins to be purified at the industrial level. In some cases it may be possible to omit purification as plant material containing recombinant enzymes can be added directly to animal feed or industrial process. This plant-based system can benefit both livestock and humans (Pascual, 2007).

For recombinant proteins, plants can serve as a cost-effective production system. Besides this, some plant tissues are the best sites for long-term storing of vaccine antigen without an extensive processing or purification. Selected tissues can be suitable for oral administration, thus minimizing the costs and labor incurred on the delivery of injectable vaccines (Streatfield, 2006). The economics of protein production in plants is complicated. The actual cost will depend on many factors, amongst them are the cost of growing the plant, transport costs and processing and protein purification costs. The costs of proteins produced in plants may significantly reduce the costs of protein production by standard methods.

Two major strategies have been adopted for the production of various proteins in plants: the stable integration approach; and the use of plant viruses as transient vectors. The stable transgene expression approach, in which the transgene is regulated by a strong, constitutive promoter (such as the 35S promoter), is perhaps the most suitable for the bulk production of soluble proteins in leaves, although yields can be low using this approach (Streatfield, 2007). A more

sophisticated approach has been to target gene expression and protein production to specific tissues leading to higher yields. Plant virus capsids have also been used as carriers of recombinant proteins, particularly vaccines (Sainsbury et al., 2010). In one approach, coding sequences for epitopes or proteins have been introduced into the coat protein gene of the virus genome. Another approach that has been used is to construct viral vectors to produce recombinant proteins that are targeted to endoplasmic reticulum for processing. The virus can be replicated in the host plant, and through serial passage enough amount of protein can be generated.

8. Vaccines and antibodies

Infectious diseases are the most dangerous problems in the present world and each year one third of all deaths are caused by the infectious agents. Growth of new pathogens like HIV, hanta virus, hepatitis C virus and SARS has caused hue and cry and the problem is getting more complex day by day. In view of Guzman and Feuerstein (2004) 15% of new cancers (e.g. gastric cancer, hepatocarcinoma and cervical cancer) are due to infectious microorganisms. Vaccination is a sound means of preventing infection and a very cost-efficient method. Today, vaccines are used against both infectious and non-infectious diseases.

Plant genetic engineering technology is now being widely used for "biopharming", or production of pharmaceuticals in plants (Raskin et al., 2002; Walmsley and Arntzen, 2003). Antibodies produced in plants are thought to be particularly suitable for topical immunotherapy. Plants were used as bioreactors to produce antigens induced by plant transgenic vectors, which in turn, produce vaccines for the treatment of various diseases (Tiwari et al., 2009; Rigano et al., 2009). Expressions of antibodies in transgenic plants (plantibodies) have been first shown by Hiatt et al. (1989). After that, experiments were widely carried out for vaccine production using plants as bioreactors. The vaccines produced from transgenic plants have high efficiency in passive immunization of bacterial or viral diseases and are currently under clinical trials (Ko and Koprowski, 2005; Ma et al., 2005). The antigens produced by the transgenic plants are also edible that is why the plant-based vaccine production is gaining market day by day. The production of edible vaccines (a surface protein from Streptococcus) in transgenic tobacco was first reported in 1990 and published as a patent (Mason and Arntzen, 1995).

Many other vaccines, enzymes and a wide range of proteins of pharmaceutical interest have now been produced in plants. Table 5 lists many of these substances. Although active recombinant proteins have been produced, one problem associated by using plants as production system is relatively low product yield and recovery. Despite some difficulties, plants hold out a great promise as a production system for biopharmaceutical proteins.

Different plants have been used for the production of biopharmaceutical proteins which include leafy crops, cereals, legumes, oilseeds, fruits, vegetables, cell cultures, algae, etc. (Twyman et al., 2003; Fischer et al., 2004). In view of Walmsley and Arntzen (2000), some vegetables such as potato, tomato and carrot have been reported to express vaccines. Potato was used as a model plant for the production of oral vaccines (Polkinghorne et al., 2005). After potato, tomato is now used as expression system. Antigen genes encoding HBsAg, HIVgag and rabies capsid proteins have been incorporated into tomato successfully. Proplastids of cultured carrot cells have been shown to express recombinant proteins (Sala et al., 2003a, 2003b; Daniell et al., 2005) and the edible carrot preserved the structural integrity of their target proteins (Muller et al., 2003). Other plants that are being used as production system for the vaccines are lettuce, celery cabbage, and cauliflower, but they show the low expression of vaccine candidates (Koprowski, 2005).

Banana (*Musa paradisiaca*) is one of the earliest fruits used for plant transformation studies (Mason et al., 2002). Expression of foreign proteins (vaccines) in banana with the help of promoter MaExp1 has been demonstrated by Trivedi and Nath (2004). Papaya is another important plant for production of vaccines (Carter and Langridge, 2002). Sciutto et al. (2002) demonstrated the expression of novel synthetic vaccine SPvac. All these examples clearly depict that through this strategy vaccine production can be done on a large scale to assess the possibilities of plant systemic and oral immunization in the near future.

Some plants produce soluble proteins in abundance and are more suitable for oral delivery vaccine production (Streafield et al., 2003; Stoger et al., 2005). Alfalfa (*Medicago sativa*) is propagated through stem cuttings in limited period of time. Alfalfa has high protein content and low levels of secondary metabolites that make it an effective bioreactor for generating recombinant proteins (Dus-Santos et al., 2002). Maize (*Zea mays*) was investigated for producing recombinant antibodies, vaccine candidates and enzymes (Hood, 2002; Hood et al., 2002). Rice (*Oryza sativa*) has also been investigated for expressing some proteins by using constitutive and endosperm-specific promoters (Nicholson et al., 2003). Cereal crops are also used as experimental plants as they contain ample amount of soluble proteins in endosperms which can enhance the antigen concentration and reduce oral doses.

These vaccines derived from transgenic plants have been investigated in preventing infectious diseases in animals. Some vaccines have gone into early phase target animal trials (Lamphear et al., 2004). Production of serum, mucosal antibodies and raising cytokine levels are some of the responses that have been noted in animals with transgenic plant vaccines (Jie and Langridge, 2001; Streatfield and Howard, 2003; Ruhlman et al., 2007; Rawool et al., 2008; Gomez et al., 2010).

9. Viral antigens

Mason et al. (1992) demonstrated that DNA coding for the hepatitis B virus major surface antigen (HBsAg) was incorporated into tobacco plants via *Agrobacterium* transformation. The HBsAg in transgenic tobacco got expressed and retained the capability of self association. The HBsAg isolated from transgenic tobacco was analyzed and found analogous to HBsAg obtained from human serum and recombinant yeast. Plants derived vaccines and commercially available yeast-derived vaccines have shown equivalent immunogenicity in mice (Thanavala et al., 1995; Thanavala and Lugade, 2010). Transgenic potatoes expressing HBsAg were also obtained by Richter et al. (2000) and have been shown to cause high immunogenicity in mice. Kapusta et al. (1999) obtained transgenic lettuce containing expression plasmids for *HBsAg*. This transgenic lettuce was given to three adult volunteers orally but only two showed response to the orally-fed vaccine. Elkholy et al. (2009) demonstrated that expression of recombinant hepatitis B surface antigen (rHBsAg) in banana can be used as edible vaccine against hepatitis B virus (HBV) infection.

Respiratory syncytial virus (RSV) infections cause respiratory tract disease in infancy and early childhood. RSV has the mortality rate 2.5% and no appropriate vaccine is available for its protection so far. For the first time transgenic tomato expressing RSV fusion (F) protein is used as edible vaccine against RSV (Sandhu et al., 2000).

Transgenic tobacco plants expressing *E. coli* heat labile enterotoxin B subunit (LTB) possess the capability of a vaccine or booster vaccine against ETEC (enterotoxigenic *E. coli*) and cholera (Qadri et al., 2005; Svennerholm, 2011). Tacket et al. (1998) for the first time got the successful human trial against ETEC. The human volunteers were given transgenic potato expressing LTB. About 91% of the volunteers developed neutralizing antibodies and 55% showed a mucosal response. Similar results were observed by Arakawa et al. (1998) in potato plants expressing B subunit of the cholera toxin (CTB). An antigen protective against the roundworm *Ascaris suum* (s16) produced as a fusion chimera with CTB showed an As16-specific serum

Table 5
Expression of different antigens/antibodies, proteins in plants.

Recombinant protein	Production system	Reference
Streptococcus mutans surface protein A	Tobacco	Curtiss and Cardineau, 1990
Serum albumin	Tobacco	Peter et al., 1990
Rabies virus glycoprotein	Tomato	McGarvey et al., 1995
α-Amylase	Alfalfa	Austin et al., 1995
Human Protein C	Tobacco	Cramer et al., 1996
Avidin	Maize	Hood et al., 2002
Norwalk virus vaccine	Potato	Tacket et al., 2000
	Tobacco	
Human lactoferin	Potato	Daniell et al., 2001
Human somatotrophin	Tobacco	Jeffrey et al., 2000
Hepatitis B surface antigen	Tobacco	Kong et al., 2001
	Potato	
Cholera Ctox A and Ctox B subunits	Tomato	Sharma et al., 2008
	Potato	Choi et al., 2005
HIV-1	Potato virus X (PVX) coat protein	Marusic et al., 2001
Measles virus vaccine	Tobacco	Webster et al., 2002
Hepatitis B surface antigen	Cherry, tomato	Gao et al., 2003; Thanavala et al., 2005
LT-B (heat-labile toxin B)	Maize kernels	Chikwamba et al., 2003
HRV-VP7(human rotaviruses)	Potato	Yu-Zhang et al., 2003
IgG (hepatitis B virus)	Tobacco	Valdes et al., 2003
Trysin	Maize	Woodard et al., 2003
TetC (Tetanus vaccine antigen)	Tobacco chloroplast	Tregoning et al., 2004
Gastroenteritis virus vaccine	Corn	Lamphear et al., 2004
Bacillus anthracis protective antigen	Tobacco	Watson et al., 2004
LT-B	Corn	Tacket et al., 2004
NVCP (nonvalk virus capsid protein)	Tomato fruit	Zhong et al., 2005
MV-H (measles virus hemagglutinin)	Tobacco	Webster et al., 2005
HIV-1 Tat protein	Tobacco mosaic virus (TMV) to spinach	Karasev et al., 2005
Japanese cedar pollen peptide	Rice	Takagi et al., 2005
Human α_1-antitrypsin	Rice	McDonald et al., 2005
Hepatitis B surface antigen	Banana	Kumar et al., 2005
Pneumonic and bubonic plague	Tomato	Alvarez et al., 2006
Tricosanthin-α from *Trichosanthes kirilowii*	Tobacco	Lei et al., 2006
Foot and mouth virus epitope VP1	Tobacco chloroplasts	Li et al., 2006
Plasmodium yoelii merozoite surface protein 4.5 (PyMSP4/5)	Tobacco	Wang et al., 2008
Mannheimia haemolytic GS60 antigen	Alfalfa	Lee et al., 2008
Recombinant norwalk virus like particles (rNVs)	Tobacco	Santi et al., 2008
Diabetes mellitus	Rice seeds	Xie et al., 2008
Newcastle disease virus (NDV) protein	Potato	Gómez et al., 2008
HIV-1 subtype C p24 protein	Arabidopsis and carrot	Lindh et al., 2009
Hepatitis B surface antigen	Tobacco	Kostrzak et al., 2009
LT-B	Rice	Zhang et al., 2009
Japanese encephalitis virus envelope protein	Tobacco	Appaiahgari et al., 2009
Japanese encephalitis virus envelope protein	Rice	Wang et al., 2009
Hirudin from *Hirudo medicinalis*	Canola	Demain and Vaishnav, 2009
DTP subunit vaccine	Tobacco and carrot cells	Brodzik et al., 2009
Staphylococcus aureus infection	*Chlamydomonas*	Dreesen et al., 2010
LTB	*Peperomia pellucida*	Loc et al., 2010
UreB (urease) protein	Carrot	Zhang et al., 2010
Salmo salar (SasalFN-α1) protein	Potato and rice	Fukuzawa et al., 2010
Rabies virus glycoprotein	Tobacco	Roy et al., 2010
Syncytial virus (RSV)-F protein	Apple	Lau and Korban, 2010
Human cytomegalovirus (HCMV)	*Vicia faba*	Yan et al., 2010

antibody response when administered orally to mice and it caused low lung worm burden (Matsumoto et al., 2009). In addition, pea (*Pisum sativum*) derived vaccine CTB::VP60 pentameric protein protected rabbits against rabbit hemorrhagic disease virus (Mikschofsky et al., 2009). Transgenic tobacco expressing MV-H (measles virus hemagglutinin from Edmonston strain) also developed antibodies in mice 5-folds the level contemplated protective for humans (Huang et al., 2001). After mice, primates have also showed the same results.

Human immunodeficiency virus type 1 (HIV-1) is a dreadful disease worldwide mainly in sub-Saharan Africa. To control this HIV, cheap and effective vaccination is needed. Only plant-based vaccines fulfill this requirement. The expression of HIV-1 antigens in plants has been reported by many workers (Yusibov et al., 1997; Marusic et al., 2001; Zhang et al., 2002; Bogers et al., 2004). Meyers et al. (2008) demonstrated the production of HIV-1 subtype G Gag-derived proteins in *Nicotiana* spp., which develop humoral immune responses in mice that was previously injected with an HIV DNA vaccine.

Pag gene (anthrax protective antigen-PA) has been reported to express a protein in tobacco and is used as a vaccine against anthrax. The expression of PA in transgenic tobacco with lethal factor (LF) was demonstrated by Aziz et al. (2002). Transgenic tomatoes expressing PA cause immunogenecity in mice (Aziz et al., 2005). Kim et al. (2004) expressed cholera toxin B-subunit-anthrax LF conjugate fusion protein in potato for the generation of edible anthrax vaccine.

Human papilloma virus (HPV) causes cervical cancers in women and to get protection from this disease, human papilloma virus vaccine has already been commercialized (Kane et al., 2006; World Health Organization, 2007). Developing countries cannot adopt these vaccines because of their high cost. To provide an alternative for these high cost vaccines, transgenic plants are the best choice in hand as the production system. HPV virus and L1 proteins were generated in transgenic plants like potato, tobacco and the transgenic potato were shown to cause immunization in animals (Santia et al., 2006).

10. Transgenic plants and safety

The production of transgenic cultivars/lines through genetic engineering is a new departure from conventional breeding to modern technology which raises safety concerns. Crops produced through genetic engineering are formally examined critically to ensure that they do not possess non-congenial characteristics before field testing or commercial release. The safety assessment of transgenic plants is a fascinating and challenging intersection of many disciplines including ecology, agronomy and molecular biology which mainly focus on food and environmental safety (Chassy, 2010). Other potent risks considered in the assessment of GM plants particularly for insect or disease resistance traits include environmental consequences on worms, insects, birds, mammals and other organisms. Since 1986, a formal policy namely Coordinated Framework for Regulation of Biotechnology provides a system for evaluating products developed using modern protocols.

The National Institutes of Health (NIH) has devised stringent rules and regulations on the judicious proper use and disposal of GM plants. In addition, other principal agencies to date are the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), the Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) which provide guidelines for the testing and commercial release of GM organisms (Shantharam, 1995; Regaud, 2008). All government regulatory agencies should be fully responsible for ensuring that the GM crops do not harm the environment and human health (Regaud, 2008). A number of problems come across before the release of biotech crops. For example, in 2009, Bt eggplant got approval for its commercialization in India, but still the Indian Government has imposed a moratorium on its release due to the public resentment (Report of the Expert Committee (EC-II) on Bt Brinjal Event EE-1, 2009; The Times of India, February 9, 2010; Jain, 2010). Similarly, government of South Australia has a moratorium on all GM food crops particularly on canola from 2006 to 2008 (Millis, 2006). Monsanto is developing grains to make cooking oils with high omega-3 fatty acids and low saturated fatty acid to safeguard against heart disease. But the Public Affairs Committee for Monsanto has delayed its approval for commercial release. In Canada, agriculture committee debated against approval of GM modified alfalfa varieties. However, in 2008 after a long moratorium, the approval of the commercial cultivation of GM canola in New South Wales has been sanctioned (http://www.dpi.nsw.gov.au/agriculture/field/field-crops/oilseeds/canola/gm).

11. Conclusions and future perspectives

The advent of genetic engineering (GE) and other tools has enabled plant biologists to fight against the prevailing adversaries. The rich sources such as carbohydrates, proteins, oils, minerals, fuels, medicines, dyes, perfumes, flavorings and vitamins are produced by plants. GE modifies the plant to produce reasonable amounts of the earlier-mentioned products. To understand how the overproduction of these biomolecules takes place in plants there is a crucial need to elucidate the underlying mechanisms. GM plants have been generated for their enhanced tolerance to herbicides and pests. Some others have been developed for providing nutritionally rich food and biofuel production. Healthier oils, vegetables and fruits with low calorie sugars and enriched with vitamins are under development. Golden rice is a genetically modified crop. It is rich in provitamin A (β-carotene) and iron. Many parts of the world experience insufficient levels of essential vitamins and minerals such as vitamin A and iron. Golden rice is the promising crop to overcome this problem. Golden rice is being tested these days in India, Vietnam and the Philippines for its ability to effectively produce high levels of vitamin A and iron. High protein potatoes have also been developed in India by transferring a gene from an amaranth plant. Despite the controversies by many countries on transgenic crops agricultural biotechnology has yielded substantial economic benefits. According to a projection by Brookes and Barfoot (2011) the generation of GM crops has allowed to use 393 million kg less pesticides by the growers. This effect has a significant role in reducing greenhouse gas emission which in 2009 was equivalent to removing 7.8 million cars from the roads. Due to the present growing trend of transgenic crops, it is assumed that available transgenic crops in the future could boost crop yield, and the food produced from such crops will be nutritionally rich. Another achievement of plant biologists is that plants are being used for the production of biopharmaceuticals. Valuable proteins are expressed in transgenic plants that can be extracted and processed, which have many advantages over industrial proteins. Though plant-based vaccines have shown promising results, the oral tolerance to plant vaccines is a very important problem that needs in depth research. The genetic engineered plants being used need strict safety evaluation. The plant biotechnologists should keep in mind that the transformants that they are going to develop should be safe enough.

Apart from the success stories in many cases, many concerns are yet to be mitigated before plant based vaccines become a real boom. The world most dangerous diseases like HIV and malaria are very complex diseases. Plant-based vaccines have been found to be very promising in controlling these diseases effectively, but since all these studies have been carried out to a limited scale, so for their effective widespread use, up-scaling of these studies is essential. Furthermore, although a number of vaccines for many diseases are provided by the WHO, there are certain diseases for which the vaccines have to be purchased locally. For example, hepatitis-B/DTP combination vaccines are to be purchased from the local market and the cost of the vaccines is too high. Resultantly, thousands of children are deprived of vaccination and hence at the risk of this preventable disease. To eradicate this problem transgenic plants may provide an excellent expression system and the vaccines can be fed directly to people in the form of edible vegetables, fruits etc. Plants like banana, tomato, potato, spinach, tobacco, rice, corn, etc. are being used to fight diseases like cholera, measles, hepatitis-B, Norwalk virus and rabies virus by inducting immunization edible vaccines. Edible plant vaccines are highly safe as well as cost-effective.

Undoubtedly, there is a consistent increase in the use of genetically modified organisms for food or other essential commodities. The promoters of GM foods claim that they are environment-friendly, have no risk to human health, profitable for farmers as well as well regulated, many people are still of the firm view that GM foods can be injurious to human and animal health, because they have not been properly tested. Also it is not certain what types of long-term effects GM foods can cause. Critics argue that transferring new genes into a food can alter the chemical composition of that food, which may trigger the human body to respond differently to that food, thereby developing allergies or causing long-term toxicity. Furthermore, several GM crops possess antibiotic-resistance genes that could be taken up by bacteria present in the body, thereby increasing bacterial resistance against antibiotics. Thus, every country needs to frame well defined rules and regulations for the utilization of GM organisms, although many developed and some developing countries have already formulated specific regulations.

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