Recent Advancements in Gibberellic Acid Formulation Techniques and Economics of Use in Agriculture

Avinash Tupe a*, Atul Baravkar a and Ganesh Devkate b

a ADT’s Shardabai Pawar Institute of Pharmaceutical Sciences & Research, Shardenagar, Baramati, Maharashtra, India.
b Shivnagar Vidya Prasarak Mandal’s Institute of Pharmacy, Malegaon (Bk), Baramati, Maharashtra, India.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Gibberellins comprises of a broader family of plant advancement hormones found during the 1930s, which are synthesized by implies of the terpenes course from the geranylgeranyl diphosphate and incorporate a crucial structure formed by an ent-gibberellane tetracyclic skeleton. Among them Gibberellic acid (GA3), which acts as a characteristic plant development controller, especially for stem extending, seed germination, and extended common item degree. It can be gotten from plants, organisms, and microbes. There are as well a couple of reports roughly microalgae GA3 makers. Life forms, especially Gibberella fujikuroi, are favored for GA3 generation through submerged maturing or solid-state development. Various factors may impact its generation, a few of which are related to the control and scale-up of maturing parameters. Particular GA3 items are open on the advertise. They can be found in liquid, powder, tablet, beads and granule dosage forms containing because it were GA3 or a mix of other normal dynamic gibberellins, which can be employed in agriculture, horticulture & floriculture crops.

Keywords: Plant advancement hormones; Gibberella fujikuroi; tetracyclic skeleton.

*Corresponding author: E-mail: avinashptupe@gmail.com;
1. INTRODUCTION

Gibberellic acid (GA3) is connected to crops, plantations, and decorative plants, where it plays a part in seed germination reaction to abiotic stress, natural product development enhancement, stem stretching [1], blossoming [2], the malting of grain [3], and other physiological impacts that happen in its interaction with other phytohormones [4-5]. GA3 could be a diterpenoid carboxylic acid from the gibberellins family that acts as a normal plant growth hormone. It is delivered by plants and a few microbes, such as fungus and tiny creatures. GA3's features related to plant development make it an attractive candidate for use in the agro-industrial sector. Since its discovery, research has focused on improving its synthetic methods, increasing its efficiency, and lowering its cost, which can limit the use of this critical development hormone.

This survey centers on general perspectives of GA3 production through biotechnological forms, the talk approximately the main recuperation options and detailing forms, its market accessibility, and the natural impacts in plants.

1.1 General Chemistry

Gibberellins (GAs) were found in Japan during 1930s when a bunch of researchers and agriculturists started to ponder a disease influencing rice areas [5]. This malady was characterized by temperate stem development, yellowing of the influenced areas, and a low seed production was observed [6]. GA3 is a white crystalline powder with a melting point of around 233–235 °C that is soluble in liquor, acetone, ethyl acetate, and butyl acetate, and it is sparingly soluble in petroleum ether, benzene, and chloroform [6]. The solubility of GA3 in water is poor, at only 5 g L1. It decomposes quickly at extremely high temperatures, in alkaline pH, and in aqueous solutions, with a half-life of 14 days at 20 °C and 2 days at 50 °C [7-8]. The lack of stability is due to a C1–C2 double bond in the molecule's chemical structure, which makes it more reactive [9]. (Fig.1a). GA3 also possesses the double bond at C1-C2 and has same lacks the stability due to the presence of double bond. The most stable of the three GAs is GA4 (Fig. 1b). The removal of the γ-lactone ring has also been linked to the biological inactivation of GA3 [10] and as a result, the existence of the γ-lactone ring and the C1–C2 double bond in the GA3 structure is essential for its biological activity. GA3 hydrolysis to gibberellonic acid can occur in aqueous solutions in a solely chemical process; however, GA3 can be metabolised during C-limitation [11] in the presence of microbes. Different GA3 breakdown products can be generated depending on the temperature, reaction duration, and pH of the solution, resulting from changes in the molecule's structure, and its "gibberellin-like" biological activity can be diminished or completely lost the metabolic products are as shown in (Fig.2).

1.2 Biosynthesis

Plants and fungi use the terpenes pathway to synthesize GA from geranylgeranyl diphosphate. This path has been thoroughly discussed by several researchers. As a result, GA synthesis will be explored briefly in this review. The stages of GA biosynthesis are as described hereunder [12-14].

![Fig.1. Chemical structures of bioactive gibberellins GA3 (a) Gibberellic acid, GA4 (b) & GA7 (c)](image)

GA3 (C19H22O6, CAS 77-06-5, MM = 346.37) is a tetracyclic dihydroxy-lactone acid that has a C1–C2 double bond, a C10 γ-lactone ring, and also a OH group in C13 (Fig. 1a).
Stage 1: Geranylgeranyl diphosphate conversion to ent-kaurene

Geranylgeranyl diphosphate is made up of four isoprenoid molecules bonded together to produce a 20-carbon linear molecule (GGPP). This molecule is converted to ent-copalyl diphosphate (CPS) by an ent-copalyl diphosphate synthase (CPS), which is then converted into the tetracyclic compound ent-kaurene by an ent-kaurene synthase (KS).

Stage 2: ent-kaurene conversion to GA$_{12}$

Plants’ ent-kaurene oxidase (KO) and fungi’s P450-4 catalyse the successive oxidation of ent-kaurene in C-19 to form ent-kaurenoic acid, which is then converted to GA$_{12}$-aldehyde by an entkaurenoic acid oxidase (KAO) in plants and P450-1 in fungi.

Stage 3: GA$_{12}$ conversion to other GAs

GA$_{12}$-aldehyde is first transformed to GA$_{12}$ in plants, and subsequently to GA$_{9}$ by the action of GA$_{9}$-oxidase, which is responsible for the formation of C19- GAs. In a separate process, GA$_{12}$ is 13-hydroxylated to produce GA$_{53}$, which is then transformed to GA$_{30}$ by the action of C20-oxidase. Then, by adding a 3-beta hydroxyl group to GA$_{30}$ and GA$_{9}$, GA$_{3}$-oxidase transforms them into GA$_{1}$ and GA$_{4}$, respectively. GA$_{3}$ is generated when GA$_{30}$ is converted to GA$_{5}$ by the enzyme GA$_{3}$-oxidase. This stage varies by species and is influenced by environmental factors.

GA$_{12}$-aldehyde is 3 beta-hydroxylated to GA$_{14}$-aldehyde in fungi, which is then oxidised to GA$_{14}$. Through the oxidation of C20, this last one is transformed to GA$_{4}$. GA$_{4}$ is the first bioactive molecule to be generated, and it is desaturated to form GA$_{7}$, which is subsequently 13-hydroxylated to form GA$_{3}$. GA$_{1}$ is created when GA$_{4}$ is 13-hydroxylated.

Plants and fungi use comparable biosynthetic pathways to convert geranylgeranyl diphosphate to ent-kaurene, which is then converted to GA$_{12}$-aldehyde. Because of the order in which the processes of 3-hydroxylation and 13-hydroxylation occur in plants and fungi, the pathways differ from the stage in which GA$_{12}$-aldehyde is converted to other GAs. The biosynthetic pathway of gibberellic acid is as shown in Fig. 3.
Fig. 3. The biosynthesis process for gibberellin (GA) in fungi and plants begins with GGDP (geranylgeranyl diphosphate). In fungus and plants, the first GA created is GA\textsubscript{14} and GA\textsubscript{12}. In fungi, CPS (ent-copalyl diphosphate synthase), KS (ent-kaurene synthase), and P450 (cytochrome P450 oxidoreductase) are involved, while in plants, CPS, KS, KO (ent-kaurenoic acid oxidase), KAO (ent-kaurenoic acid oxidase), and GA oxidase (GA\textsubscript{13ox})

2. FORMULATION ASPECTS OF GIBBERELLIC ACID

GA\textsubscript{3} is found in a variety of commercial formulations, either alone or in combination with GA\textsubscript{2} and GA\textsubscript{7}. They come in a variety of forms, including liquid, soluble powder, wettable powder, tablet, and water-dispersible granular. The Table 1 lists some of the product names that include GA\textsubscript{3} as well as their producers.

The relative lack of stability of GA\textsubscript{3} in the presence of water is connected with liquid formulations, which may result in a short shelf life. Some solvents are used in this way to prevent GAs from degrading, but this could result in combustible formulations that would necessitate extreme caution when packaging, transporting, and storing them. Solid formulations appear to be a safer technique due to the disadvantages of liquid formulations, but they also have some drawbacks, such as dust while pouring, moving, or measuring; the likelihood of creating residues in the tank and plants; and the chance of lump formation [15].

2.1 Liquid Formulations

GA\textsubscript{3} is dissolved in an alcohol solution, such as isopropanol, methanol, or ethanol, at a concentration of around 4\% (w/v) for most commercial products. Some additives and/or adjuvants are also used to boost product stability, target a molecule's protective action, extend shelf life, or increase nutritional components in plants [16-17].

The influence of adjuvants on the stability of cleared GA\textsubscript{3} extract was investigated. Adjuvants extend the shelf life of products by preventing or delaying ingredient degradation and promoting extra properties in the final product, such as high stability. After screening tests revealed that the liquid formulation was defined with ethanol (50 percent v/v) and Tween 20 (2.5 percent), which promoted a better conservation of GA\textsubscript{3} activity in accelerated stability tests, the liquid formulation was defined with ethanol (50 percent v/v) and Tween 20 (2.5 percent). The hormone formulation was subsequently subjected to a temperature of 50\°C for 14 days, with GA\textsubscript{3}
activity remaining at roughly 67 percent. The rapid decline in GA$_3$ activity was most likely caused by its degradation, which was accelerated by the high temperatures utilized in the experiment. When exposed to harsh conditions, such as high temperatures and pH, the GA$_3$ molecule decomposes quickly.

Other chemicals such as gibberellinic acid, isogibberelic acid, and dehydroallo-gibberic acid may occur under these conditions. GA$_3$ isomerization can also occur in weak alkaline conditions. This plant growth hormone has little or no biological function in these forms. In fact, the active biomolecule was put under extreme stress during the accelerated storage test. The goal of this test was to use heat to imitate typical long-term ageing of a formulation. In this test, a loss of up to 5% of the active component ensures a shelf life of at least two years [18]. A long-term stability test or alternative circumstances should be utilized to evaluate the product's shelf life in the event of very sensitive active components [19]. As a result, the long-term stability of the GA$_3$ formulation was tested, and it was found to retain 100% of its activity after 6 months at room temperature. The unformulated extract, on the other hand, lost more than half of its activity and revealed some contamination, which could have contributed to the activity reduction because microbes can metabolise the biomolecule in the absence of carbon sources [20]. These findings are consistent with previous studies that show low GA$_3$ stability in aqueous solutions.

**Table 1. Different types of GA$_3$ products available in the international market and their manufacturers**

| Producers                                | Trademarks                                      | Formulation type |
|------------------------------------------|-------------------------------------------------|------------------|
| Orion Crop Protection                    | PastureGibb®                                    | Liquid           |
| NuFarm Americas                          | GibGro® 4LS                                      |                  |
| Valent BioSciences Corporation           | Progibb® 4%/Rizup® 4SL/Release LC               |                  |
| NuFarm Americas                          | GibGro®                                         | Soluble powder/|
| Ferti                                    | Gibb-gro®                                       | wettable powder  |
| Valent BioSciences Corporation           | Progibb® 2%/Release®/Berelex® 2x                | Tablet           |
| Valent BioSciences Corporation           | Progibb® tablet/Berelex® tablet                  | Soluble granule  |
| Ravensdown                               | Express®                                        |                  |
| Valent BioSciences Corporation           | Progibb® SG/Progibb® 40 SG/Activol® 40SG/Berelex® 40SG/Ryzup® 40SG/Ryzup® SmartGrass 40WSG |      |
| Sum Farm New Zealand Limited             | Gibb-star®                                      |                  |

**Table 2. Excipients employed in solid & liquid GA formulations**

| Category            | Excipients                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| Antioxidants        | Gallate (propyl, octyl and dodecyl), ascorbic acid, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), t-butylhydroquinone (TBHQ) |
| Antifoam            | Silicone emulsions full of silica                                           |
| Encapsulating agents| Gums (arabic, alginate and carrageenan), proteins (whey and milk proteins, gelatin), carbohydrate (maltodextrin, starch, sucrose, glucose, trehalose, pectin) |
| Preservatives       | Sulfur dioxide, benzoic acid, sorbic acid, propionic acid, sodium and potassium salts, nitrite and nitrate of sodium and potassium |
| Surfactants         | Nonionic: ethoxylated esters of sorbitan, fatty acid esters, glucose and sucrose esters, ethoxylated alcohols, ethoxylated alkylphenols, ethoxylated fatty acids Anionic: phosphate esters, sulfate and sulfonated oils, sulfates and sulfonates ethoxylated alkylphenols |
| Diluents (Liquid formulations) | Polyethylene glycol, ethanol, isopropyl alcohol, methyl alcohol, glycerol, propanol, n-butanol, n-amyl alcohol, acetone, methyl butyl ketone, ethyl lactate, n-butyl lactate, and propylene glycol |
| Diluents (solid formulation) | Sorbitol, mannitol, lactose, dextrose, starch, limestone, sucrose, maltose, maltodextrin, and fructose |
| UV protectant       | Benzophenone-3 and ethylhexyl methoxycinnamate                             |
| Anti-caking         | Silica, talc, and limestone                                                 |
| Binder              | Maltodextrin, lecithin and polyvinylpyrrolidone                            |
2.2 Powder Formulations

Some formulations use solvents with high levels of volatile organic compounds that are harmful to the environment in order to overcome solubility difficulties. Isopropyl alcohol and methyl alcohol, for example, have serious drawbacks such as flammability and toxicity, which limit their use in production, packaging, labelling, shipping, and warehousing. The eye and skin are both corroded by tetrahydrofurfuryl alcohol (THFA). Developing soluble powder formulations using GA3, GA4, and GA7 is one technique to tackle the solubility concerns. When mixed with water, these powder formulations dissolve quickly and form genuine solutions. No more mixing or agitation of the tank-mix is required once the solution has formed.

Making a wettable powder is another technique to get around the solubility concerns. A wettable powder formulation is one that is dry and finely milled. The active component is coupled with a finely ground dry carrier, commonly a mineral clay, as well as other additives that improve the powder’s capacity to be suspended in water in this sort of formulation. When the wettable powder is mixed with water, a suspension is created, which is then sprayed on. To avoid the settling of insoluble compositions, the spray liquid must frequently be continually mixed. However, when handling wettable powders and soluble powder formulations, such as pouring, transporting, or measuring them, they tend to produce dust. This dust could be hazardous to human health. Furthermore, powder formulations have a weak wetting ability and solubilize slowly when mixed with water. In a tank-mix, powder formulations take longer to wet, disperse, and solubilize. Due to the formation of lumps or partially solubilized spray solutions, the plant growth regulator will be distributed unevenly in the tank-mix, potentially resulting in lower field performance. Spray tank adjuvants can sometimes generate foam in the spray tank, which can impact the wetting and solubility of wettable and soluble powders. Wettable powder preparations will also leave insoluble residues in the tank and on sprayed foliage and fruit [21].

2.3 Tablet Formulations

A tablet is another sort of agricultural preparation. Tablet formulations are dose delivery systems that have been pre-measured. They’re great for small spaces or for ornamental purpose. Effervescent tablet formulations dissolve in water over a two to ten minute period, depending on the kind and size of the tablet. Tablets, on the other hand, typically contain only 0.1 to 1 gram of active substance per pill. They aren’t well suited to large-scale field activities. Furthermore, effervescent tablets are sensitive to dampness, can be slow to dissolve, and are costly [22].

2.4 Water Dispersible Granules

A water-dispersible granule is another type of agricultural preparation. Wetable granules or dry flowables are other names for water-dispersible granules. This formulation is comparable to a wettable powder, but the active ingredient is in the form of a dispersible granule. The water-dispersible granules are dispersed in water and agitated to form a suspension, ready for spray application. Agricultural chemicals are available in a variety of water-dispersible granular forms [23]. When water-dispersible granules are introduced to aqueous solutions, they generate suspensions. To thoroughly disperse the resultant Suspension, it must be stirred for a length of time. During application, agitation or by-pass recirculation of the tank mix must be maintained. Some common excipients which are employed for the gibberellic acid formulations are enumerated in Table 2.

2.5 GA3 Beads

GA3 beads were tested with ALG and ALG/KEF systems as a potential technique for future crop growth hormone application and controlled release in the field. This is the first time kefiran has been used as a polymeric matrix for GA3 encapsulation has been reported. The GA3 molecule must be protected in order to maintain its biological activity. Encapsulation has been reported as an alternative for protecting plant hormones from environmental conditions, which increases efficiency and promotes controlled release. A promising combination of ALG and KEF for the production of GA3 beads was proposed in this preliminary study.

GA3 encapsulation efficiency was approximately 70% for ALG beads and 60% for ALG/KEF beads, respectively. Another molecule, Celecoxib [24], was encapsulated in ALG beads with an encapsulation efficiency of about 40%. Another study used ALG/KEF beads to encapsulate ciprofloxacin [25] and reported an encapsulation efficiency of 80%. Variations in encapsulation efficiency between different matrices of beads
could be attributed to chemical interactions between each polymer and GA$_3$. When compared to ALG beads, ALG/KEF beads had a lower encapsulation efficiency. Kefiran may be to blame for the decrease in polymer interactions with GA$_3$ because it competes with GA$_3$ for alginate binding. As a result, an inefficient matrix was created in this case.

In aqueous solution, ALG and ALG/KEF beads had a spherical shape with a diameter of about 4 mm and 3.5 mm for the ALG system and ALG/KEF beads, respectively, with or without GA$_3$. SEM was used to examine GA$_3$ beads. The shrinkable matrix observed and the loss of the beads’ spherical morphology are most likely related to the fact that the beads were freeze-dried prior to SEM analysis. When compared to ALG beads, the inclusion of KEF in the bead matrix promoted a smoother surface. Some have reported that KEF could help to stabilise the gel matrix structure. KEF and ALG beads had a porous surface with only a few cracks. There have been no reports of GA$_3$ encapsulation in ALG or ALG/KEF beads up to this point. Kefiran is a promising biopolymer for use as a polymeric matrix due to antibacterial and antifungal properties that could prevent contamination and increase product shelf-life [26].

Because of the carboxylic groups from uronic acids contained in its linear structure, alginate is a biopolymer with a negative charge. When the biopolymer is introduced to a CaCl$_2$ solution, it undergoes a polymerization process. The polymeric matrix is formed when the carboxylic acid groups combine with the Ca$_{2+}$ ions, generating a reversible gel known as a "egg-box" structure. GA$_3$ has carboxylic acid groups in its chemical structure, so it can be incorporated into the polymeric mesh created by ALG and Ca$_{2+}$ ions through the same chemical interaction. There are a few factors to consider when considering future GA$_3$ controlled releases in field applications [27]. Although ALG beads are stable at low pH, they may swell in basic solutions, causing destabilisation and erosion. Furthermore, when monovalent cations and complex anions such as phosphate and citrate are present in the media, calcium alginate gels become unstable. As a result, certain conditions of the medium in which the hormone will be released are critical for ensuring the stability of the beads and a good release of the biomolecule [28]. Changes in the medium’s pH are linked to the release of molecules from alginate beads. This is explained by the effect of pH on the charge of the molecules, which affects the hormone-polymer interactions. The electrostatic interactions between the biopolymers and the hormone could define the release behaviour. As a result, fresh experiments to assess the stability of beads and the release behaviour of GA$_3$ are currently underway in order to explicate these crucial details for future use.

3. ECONOMIC ASPECTS OF GIBBERELLIC ACID

The growing worldwide population’s desire for food has inspired study into how to increase the amount and quality of agricultural produce. GA$_3$ serves a significant economic role as a plant growth regulator because of its wide variety of applications, from crops to fruits, which improves production. GA$_3$ output is estimated to be roughly 100 tonnes per year, with a market worth of US $100 million, with around three-quarters used for plant production and the other quarter for malting [29]. GA$_3$ is used in viticulture all over the world to increase fruit size. However, its use is not restricted to viticulture; some producers have identified more than 40 different crops for which GA preparations can be used to improve quality and value, including fruits, vegetables, and cereals. GA$_3$ is one of the most popular and widely used plant growth regulators (PGR). Its widespread use has the benefit of increasing crop productivity, quality, and value. Due to the high expenses of development and manufacture, only a few companies are still working on PGRs, restricting their widespread application. Herbicides, insecticides, and fungicides continue to be the focus of these companies’ investments. However, as a result of the drive for a more sustainable agriculture, the production and usage of GA$_3$ products is predicted to grow.

4. FUTURE PROSPECTUS

The definition of stable liquid or solid formulations is one of the key obstacles to its deployment. Different GA$_3$ commercial products have been documented and are accessible on the global market, allowing it to be used in a wide range of cultivars. The quest for novel and low-cost GA$_3$ production techniques will undoubtedly expand its applicability, benefiting the quality and productivity of various cultivars all over the world, particularly in India, which is one of the world’s most important agriculture-based economies.

5. CONCLUSION

In view of the different formulation techniques and benefits of the plant growth regulators new
formulations containing Gibberellic acid alone or in combination with other plant growth regulators maintaining its potency and stability can be developed. Novel formulations will increase the applicability and benefit for the quality and productivity in Agriculture.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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